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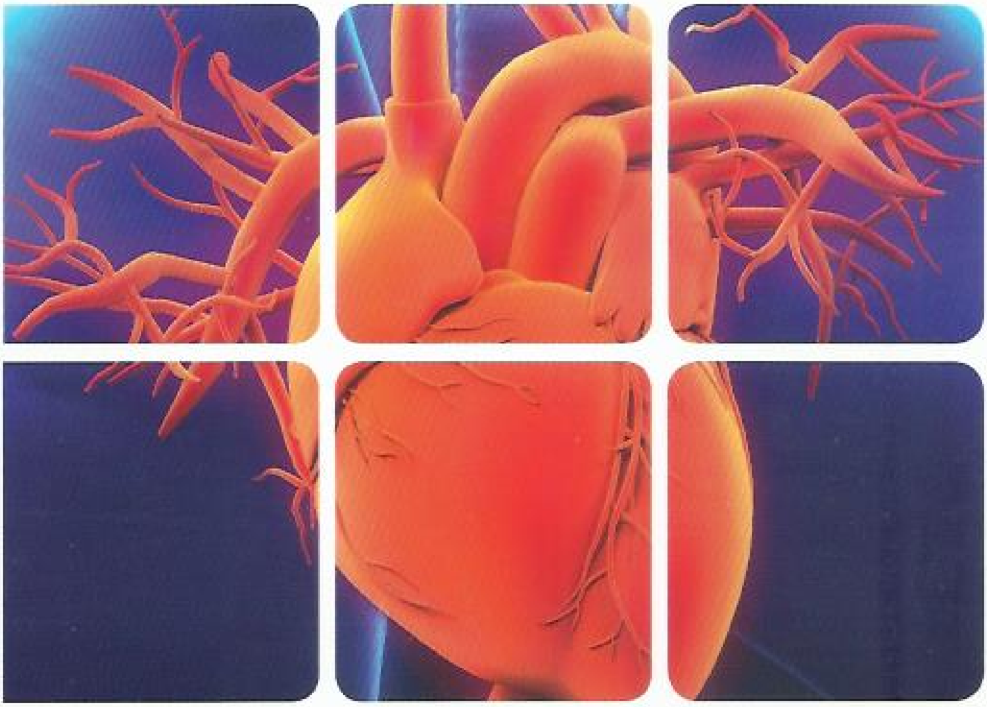

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Welcome to the Cardiovascular Medicine Section of MKSAP 18!

In these pages, you will find updated information on risk assessment in cardiovascular disease, diagnostic testing, coronary artery disease, heart failure, arrhythmias, valvular heart disease, myocardial and pericardial disease, peripheral artery disease, and other clinical challenges. All of these topics are uniquely focused on the needs of generalists and subspecialists *outside* of cardiovascular medicine.

The core content of MKSAP 18 has been developed as in previous editions—all essential information that is newly researched and written in 11 topic areas of internal medicine—created by dozens of leading generalists and subspecialists and guided by certification and recertification requirements, emerging knowledge in the field, and user feedback. MKSAP 18 also contains 1200 all-new peer-reviewed, psychometrically validated, multiple-choice questions (MCQs) for self-assessment and study, including 120 in Cardiovascular Medicine. MKSAP 18 continues to include *High Value Care* (HVC) recommendations, based on the concept of balancing clinical benefit with costs and harms, with associated MCQs illustrating these principles and HVC Key Points called out in the text. Internists practicing in the hospital setting can easily find comprehensive *Hospitalist*-focused content and MCQs, specially designated in blue and with the H symbol.

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On behalf of the many internists who have offered their time and expertise to create the content for MKSAP 18 and the editorial staff who work to bring this material to you in the best possible way, we are honored that you have chosen to use MKSAP 18 and appreciate any feedback about the program you may have. Please feel free to send any comments to mksap_editors@acponline.org.

Sincerely,

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- Improve management of comorbid conditions that can complicate patient care
- Determine when to refer patients for surgery or care by subspecialists
- Pass the ABIM Certification Examination
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Cardiovascular Medicine High Value Care Recommendations

The American College of Physicians, in collaboration with multiple other organizations, is engaged in a worldwide initiative to promote the practice of High Value Care (HVC). The goals of the HVC initiative are to improve health care outcomes by providing care of proven benefit and reducing costs by avoiding unnecessary and even harmful interventions. The initiative comprises several programs that integrate the important concept of health care value (balancing clinical benefit with costs and harms) for a given intervention into a broad range of educational materials to address the needs of trainees, practicing physicians, and patients.

HVC content has been integrated into MKSAP 18 in several important ways. MKSAP 18 includes HVC-identified key points in the text, HVC-focused multiple choice questions, and, for subscribers to MKSAP Digital, an HVC custom quiz. From the text and questions, we have generated the following list of HVC recommendations that meet the definition below of high value care and bring us closer to our goal of improving patient outcomes while conserving finite resources.

High Value Care Recommendation: A recommendation to choose diagnostic and management strategies for patients in specific clinical situations that balance clinical benefit with cost and harms with the goal of improving patient outcomes.

Below are the High Value Care Recommendations for the Cardiovascular Medicine section of MKSAP 18.

- Exercise electrocardiography is the initial stress test in patients who can exercise and have normal findings on a baseline electrocardiogram (see Item 27).
- Stress testing is not routinely recommended in asymptomatic patients with diabetes mellitus to detect subclinical coronary artery disease.
- Coronary artery calcification assessment in asymptomatic patients should be limited to those at intermediate risk in whom reclassification of risk will influence primary prevention therapy.
- Percutaneous coronary intervention in chronic stable angina is reserved for patients with refractory symptoms, high-risk features, or an inability to tolerate medical therapy (see Item 79).
- An ischemia-guided approach is appropriate for low-risk non–ST-elevation acute coronary syndrome (see Item 96).
- Do not use thrombolytic therapy for treatment of non–ST-elevation acute coronary syndromes.
- Do not use statin therapy for secondary prevention of cardiovascular disease in patients on hemodialysis.
- Do not use serial B-type natriuretic peptide measurements to guide heart failure therapy.
- Office follow-up within 1 week of discharge reduces early readmission for heart failure (see Item 83).
- Guideline-directed medical therapy for heart failure with reduced ejection fraction reduces cardiovascular mortality (see Item 114).
- Guideline-directed medical therapy precedes consideration of device therapy for symptomatic heart failure (see Item 28).
- Do not routinely use pulmonary artery catheterization to guide heart failure therapy.
- Low-risk premature ventricular contractions require no intervention.
- Pacemaker implantation is not indicated for asymptomatic first-degree atrioventricular block with bifascicular block (see Item 113).
- Do not perform genetic testing for hypertrophic cardiomyopathy in the absence of an identified mutation in the proband.
- No treatment or follow-up is needed for an asymptomatic patent foramen ovale.
- Treatment of iron deficiency in patients with congenital cyanotic heart disease improves exercise capacity and quality of life (see Item 22).
- Manage uncomplicated ventricular septal defect with periodic clinical follow-up and imaging (see Item 67).
- Do not screen for peripheral artery disease with ankle-brachial index testing in asymptomatic patients without risk factors.
- Primary therapy for asymptomatic peripheral artery disease is risk factor modification (see Item 39).
- Obtain a toe-brachial index in patients with an ankle-brachial index greater than 1.40 to diagnose peripheral artery disease (see Item 24).
- Primary treatment for intermittent claudication is exercise training (see Item 15).
- Benign asymptomatic murmurs do not require investigation (see Item 50).
- Transthoracic echocardiography is indicated for systolic murmurs grade 3/6 or higher, late or holosystolic murmurs, diastolic or continuous murmurs, and murmurs with symptoms (see Item 110).
- Transthoracic echocardiography is the initial imaging modality for suspected infective endocarditis (see Item 95).

Cardiovascular Medicine

Epidemiology and Risk Factors

Overview

Cardiovascular disease (CVD) encompasses many conditions, including coronary artery disease (CAD), heart failure, valvular heart disease, stroke, congenital heart defects, heart rhythm disorders, and sudden cardiac arrest. CVD is the leading cause of death in the United States; however, from 2004 to 2014, the mortality rate attributable to CVD fell approximately 25%, likely as a result of improved primary and secondary prevention. Despite this improvement, CVD was responsible for nearly 31% of all deaths in the United States in 2014 (roughly 800,000 people). Globally, CVD resulted in more than 17.3 million deaths in 2013, representing 31% of all deaths.

More than one in three U.S. adults currently have some form of CVD. Prevalence increases with age, and more than 70% of persons aged 60 to 79 years have CVD. The American Heart Association projects that 44% of the U.S. population will have some form of CVD by 2030. Lifetime risk for CVD is estimated to be one in three for women and two in three for men according to data from the Framingham Heart Study.

Hospitalizations for cardiovascular-related diseases continue to increase. In 2011, heart failure and heart rhythm problems were among the top 10 diagnoses associated with hospital admission in the United States, accounting for approximately 1.7 million hospital stays. The number of inpatient cardiovascular operations and procedures increased 28% to more than 7.5 million from 2000 to 2010. CVD, including stroke, was associated with a cost of $316.6 billion in 2011.

An estimated 5.7 million U.S. adults older than 20 years have a diagnosis of heart failure, a final common pathway for many cardiovascular conditions. The prevalence of heart failure is projected to increase by 46% between 2012 and 2030, and the current annual incidence is 1 in 1000 persons in those older than 65 years. Most patients with heart failure (75%) have a history of hypertension. The overall mortality rate after the diagnosis of heart failure is roughly 50% at 5 years, with about half of those deaths due to cardiovascular causes.

Risk Factors for Cardiovascular Disease

Lifestyle

Cardiovascular risk can be mostly attributed to modifiable risk factors. Very few persons meet the seven metrics of cardiovascular health: optimal lipid, blood pressure, and glucose levels; healthy diet; appropriate energy intake; physical activity; and avoidance of tobacco. Elevated cholesterol levels impart the highest risk for myocardial infarction (MI), followed by current smoking, diabetes mellitus, hypertension, abdominal obesity, no alcohol intake, inadequate exercise, and suboptimal consumption of fruits and vegetables.

Elevations in serum cholesterol levels are associated with increased cardiovascular risk, and reductions in cholesterol levels can reduce overall risk. Thirteen percent of adults older than age 20 years, or 31 million persons, have total cholesterol levels greater than 240 mg/dL (6.22 mmol/L), and 6% of adults are estimated to have undiagnosed hypercholesterolemia. Elevated LDL cholesterol and low HDL cholesterol levels are also independently associated with increased risk for CVD. A 1% reduction in LDL cholesterol level decreases risk for CAD by 1%. Risk for CAD decreases 2% to 3% for every 1% increase in HDL cholesterol level; however, pharmacologic therapies that increase HDL cholesterol levels in patients with acceptable LDL cholesterol levels do not reduce cardiovascular events. Current cholesterol treatment guidelines are based on cardiovascular risk rather than absolute lipid levels. For primary prevention of cardiovascular events, the treatment goal is at least a 50% reduction in LDL cholesterol level in high-risk patients and a 30% to 50% reduction in moderate-risk patients (see MKSAP 18 General Internal Medicine).

Tobacco exposure is a significant risk factor for CVD, including CAD, stroke, and peripheral vascular disease. In 2010, smoking was the second leading risk factor for death in the United States, exceeded only by dietary risks. The prevalence of tobacco use continues to decline; 18.8% of men and 15.1% of women were current smokers in 2014. The percentage of adolescents who smoke tobacco daily has also decreased significantly, from 15.2% in 2003 to 7.8% in 2013. In patients who smoke, overall mortality is increased two to three times, and risk for stroke is increased two to four times. The use of tobacco increases the risk for CAD by 25% in women. Secondhand smoke increases the risk for CVD by 25% to 30%. Smoking cessation substantially reduces cardiovascular risk within 2 years, with risk returning to the level of a nonsmoker after approximately 10 years. Smokers who quit extend their life expectancy by several years. Smoking status should be assessed at every visit, and cessation counseling should be offered to active smokers (see MKSAP 18 General Internal Medicine).

Psychosocial stressors, including depression, anger, and anxiety, are associated with worse cardiovascular

outcomes. Depression has been linked with higher risk for cardiovascular events, and psychosocial stressors also affect the course of treatment and adherence to healthy lifestyles after an event.

Sedentary lifestyle, poor diet, and obesity contribute to increased cardiovascular risk and increase the risk for diabetes. According to the Centers for Disease Control and Prevention, 23.7% of adults report no leisure time physical activity, and only 20.2% of adults meet aerobic and strengthening recommendations. Average fruit and vegetable consumption in the United States is less than 1 cup of fruit daily (recommended is 1.5-2 cups daily) and less than 1.5 cups of vegetables daily (recommended is 2-3 cups daily). On the basis of adherence to 2010 U.S. dietary guidelines, average diet quality is worse in men than in women, in younger adults than in older adults, and in smokers than in nonsmokers. The National Diabetes Prevention Program found that in persons at high risk for diabetes, interventions such as changes in diet, exercise, and moderate weight loss of 5% to 7% reduced the risk for developing diabetes by 58% but did not reduce CVD events.

Genetics

Although CVD risk is mainly attributable to traditional risk factors, additional risk may be caused by other factors, including genetic predisposition. A history of premature CAD (male younger than 55 years, female younger than 65 years) in parents doubles risk for MI in men and increases risk in women by 70%. CVD in a sibling increases risk for CVD by 45%, and stroke in a first-degree relative increases risk for stroke by 50%. A parental history of atrial fibrillation increases odds of this condition by 80%. In addition to genetics, the shared environment (that is, lifestyle) may contribute to increased risk in family members.

Ethnicity

There are significant racial and ethnic differences in the risk and prevalence for CVD in the United States. The prevalence of heart disease, including MI, chest pain, heart failure, and stroke, is highest among Hawaiians and Pacific Islanders (19.1%), followed by American Indians and Alaska Natives (13.7%), non-Hispanic whites (11.1%), blacks (10.3%), Hispanics and Latinos (7.8%), and Asians (6.0%).

Risk factor prevalence varies by ethnicity, location, income, and education level. Prevalence of hypertension (blood pressure ≥130/80 mm Hg) is highest among non-Hispanic black men (59%) and non-Hispanic black women (56%) and lowest among Hispanic men (44%) and non-Hispanic Asian women (36%). In contrast, the risk for diabetes is highest among American Indians and Alaska Natives (15.9%), followed by non-Hispanic blacks (13.2%) and Hispanics (12.8%). Tobacco use is highest among non-Hispanic blacks (19.9%) and lowest among Asian men (13.8%) and Hispanics (13.8%).

Globally, the prevalence of cardiovascular risk factors and subsequent CVD is increasing as a result of changes in eating habits, tobacco use, and lifestyle factors.

KEY POINT

- Risk for cardiovascular disease is mostly attributed to modifiable risk factors, including dyslipidemia, smoking, diabetes mellitus, hypertension, obesity, inadequate exercise, and diet.

Calculating Cardiovascular Risk

Cardiovascular risk scores and calculators can be used to assess a patient's future risk for major cardiovascular events and to identify which interventions are most effective for prevention. Traditionally, the Framingham risk score, which includes age, systolic blood pressure, total cholesterol level, HDL cholesterol level, smoking status, and presence of diabetes, was used to estimate the 10-year risk for a major coronary heart disease event (MI or coronary death). The Framingham risk score classifies a 10-year risk for coronary heart disease of less than 10% as low risk, 10% to 20% as intermediate risk, and greater than 20% as high risk (considered a CVD risk equivalent). A limitation of the Framingham risk score is its underestimation of risk in women and minority populations. The Reynolds risk score, which was developed in an effort to create a more accurate risk assessment tool, is a sex-specific score for both men and women that includes family history and high-sensitivity C-reactive protein level.

The American College of Cardiology/American Heart Association (ACC/AHA) Pooled Cohort Equations are a risk assessment instrument derived from several community-based cohorts that included large minority populations in addition to the cohort included in the Framingham Heart Study. The Pooled Cohort Equations include the cardiovascular endpoints of MI, angina, ischemic or hemorrhagic stroke, transient ischemic attack, claudication, and heart failure. The ACC/AHA CVD risk calculator based on the Pooled Cohort Equations (available at http://tools.acc.org/ASCVD-Risk-Estimator/) may be used to identify persons at risk for the development of CVD who would benefit from preventive measures, including statin therapy. The risk calculator can also be used to risk-stratify patients with diabetes to determine the appropriate intensity of statin therapy. However, there are concerns that the Pooled Cohort Equations overestimate risk in certain populations, including women and some minorities.

The ACC/AHA and U.S. Preventive Services Task Force do not recommend routinely using several previously considered cardiovascular risk factors, including a history of premature cardiovascular disease in a first-degree relative, elevated lifetime ASCVD risk, and LDL cholesterol level of 160 mg/dL (4.14 mmol/L) or higher, for cardiovascular risk calculation. Other nontraditional risk factors,

such as high-sensitivity C-reactive protein level of 2 mg/L or greater, coronary artery calcium score of 300 or higher or in the 75th percentile or greater, and ankle-brachial index below 0.90, have been associated with an increased risk of cardiovascular events; however, the value of these measurements, and whether they should affect treatment decisions, is unclear.

KEY POINT

- The American College of Cardiology/American Heart Association Pooled Cohort Equations are used to identify persons at risk for the development of cardiovascular disease who would benefit from preventive measures, including statin therapy.

Specific Risk Groups

Hypertension

Hypertension, defined as a blood pressure of 130/80 mm Hg or higher, affects approximately 46% of individuals aged 20 years and older. Before age 45 years, the prevalence of hypertension is higher in men than in women; however, after age 65 years, the prevalence is higher in women than in men. The population attributable risk of hypertension for first MI is 18%. Among the modifiable risk factors, hypertension is the leading cause of death in women. Treatment of hypertension reduces risk for stroke, heart failure, and kidney disease.

Women

Although mortality from CVD has decreased in the past decade, the death rate remains higher in women than in men. CVD remains the leading cause of death in women, resulting in more deaths than caused by cancer, diabetes, and kidney disease combined. In 2013, heart disease caused 398,086, or 1 in 3.2, deaths in women. Mortality within the first year after first MI is higher in women (26%) than in men (19%), and younger women are particularly at risk for death. Within 5 years of MI, nearly 50% of women will die, develop heart failure, or have a stroke, compared with 36% of men. Women have a higher risk for stroke than men throughout their lifetime as well.

The prevalence of and risk for CVD are higher in nonwhite women than in white women. Prevalence of acute MI and mortality are highest among black women. Black women also have a higher prevalence of heart disease (7.0%) compared with Hispanic women (5.9%) and white women (4.6%). Hispanic women develop heart disease nearly 10 years earlier than white women. In the past decade, heart disease mortality has increased in Asian Indian women.

Hyperlipidemia, type 2 diabetes, obesity, and tobacco use confer greater risk for CAD in women compared with men. Additional factors associated with increased risk for CVD include depression; preterm labor; and less aggressive management of recognized CVD risk factors, such as hypertension. Significant anatomic obstruction in coronary arteries is less predictive of clinical CAD in women than in men.

Approximately two thirds of women who die of MI have no previous symptoms or have symptoms that were unrecognized as cardiac in origin. Many women have symptoms described as chest discomfort, indigestion, shortness of breath, or unusual fatigue, but less than 50% of women seek medical attention for these symptoms. Because of the atypical presentation of angina, diagnosis and treatment in women are delayed when compared with men.

Treatments and outcomes also differ between men and women. After an acute coronary syndrome, women undergo fewer interventions, have more complications, and have higher unadjusted mortality. Women with non-ST-elevation MI have worse outcomes, with higher rates of bleeding, heart failure, shock, kidney failure, stroke, and reinfarction.

Obesity and Metabolic Syndrome

In the United States, 33.1% of adults older than 20 years are overweight (BMI, 25-29.9), 35.7% are obese (BMI >30), and 6.3% are extremely obese (BMI >40). Rates are increased in nonwhite adults. Obesity may increase the risk for CVD events, even in the absence of metabolic risk factors.

Metabolic syndrome is characterized by the presence of at least three of the following conditions: elevated glucose level, central obesity, low HDL cholesterol level, elevated triglyceride level, and elevated blood pressure. The hallmark feature of metabolic syndrome is glucose intolerance. Approximately 23% of adults older than 20 years meet the criteria for metabolic syndrome, but the prevalence varies considerably among different ethnicities. The highest prevalence is among Mexican American men (35%) and lowest among non-Mexican American black men (19%). Metabolic syndrome is associated with increased risk for CVD, with risk increasing as the number of component conditions increases. The cardiovascular risk associated with metabolic syndrome also appears to be higher among women.

Diabetes Mellitus

Diabetes has been diagnosed in approximately 23.4 million U.S. adults, and an estimated 7.6 million U.S. adults have undiagnosed diabetes. The prevalence of diabetes and prediabetes is increasing among adolescents aged 12 to 19 years and in those older than 65 years. Additionally, diabetes prevalence is disproportionately higher in nonwhite ethnic groups, including African Americans and Hispanics/Latinos.

Diabetes increases cardiovascular risk, especially in women, and is considered a CVD risk equivalent. Persons with diabetes have a two to four times increased risk for CVD; 68% of those with diabetes eventually die of heart disease, and 16% die of stroke. In persons with diabetes, the risk for stroke is increased 1.8- to 6-fold. Additionally, CAD is more extensive in persons with diabetes, and the incidence of multivessel disease is increased. Patients with diabetes are more

likely to have undiagnosed CAD and have worse outcomes when hospitalized for other CVDs, such as heart failure. Undiagnosed diabetes may be recognized at the time of an acute event, such as MI.

Aggressive treatment of cardiovascular risk factors, such as elevated cholesterol levels, is associated with reduced cardiovascular risk in patients with diabetes. Early recognition and treatment are important in reducing the burden of CVD and the morbidity and mortality associated with diabetes.

Systemic Inflammatory Conditions

The prevalence of atherosclerosis is increased and the risk for CVD is higher in patients with systemic inflammatory conditions, such as systemic lupus erythematosus and rheumatoid arthritis. The risk for CAD is nearly 60% higher in patients with rheumatoid arthritis and is doubled in patients with systemic lupus erythematosus. Patients with systemic lupus erythematosus and antiphospholipid antibodies have a higher prevalence of CAD and MI; the relative risk for MI is higher in younger patients with systemic lupus erythematosus than in age-matched controls. The risk for CVD in patients with rheumatoid arthritis increases from twofold at baseline to threefold over 10 years when compared with the general population. The increased risk is likely a result of the inflammatory process, including a prothrombic state, in addition to traditional cardiovascular risk factors.

Chronic Kidney Disease

Chronic kidney disease, defined as reduced estimated glomerular filtration rate, is associated with higher incidence of CVD and worse cardiovascular outcomes. Beyond the risk attributable to traditional risk factors, the risk for cardiovascular events is higher in patients with kidney dysfunction. CVD is the leading cause of death in patients with end-stage kidney disease, and the risk for CVD-related death is 5 to 30 times higher in patients undergoing dialysis than in those with similar risk factors and preserved kidney function. The presence of moderately increased albuminuria (microalbuminuria) independently increases the risk for cardiovascular events.

Despite excessive cardiovascular risk, there is evidence that patients with chronic kidney disease do not receive appropriate preventive therapies, such as statins. Data indicate that patients undergoing hemodialysis do not benefit from secondary prevention with statins.

HIV

Increased survival of patients infected with HIV due to effective antiretroviral therapy has resulted in the increased development of non–AIDS-related complications, including CVD. Patients with HIV have a 1.5 times increased risk for CVD, and cardiovascular mortality is increasing in the HIV-infected population. The increased risk is likely multifactorial, related to antiretroviral therapy–associated dyslipidemia, insulin resistance, medications associated with CVD events (such as protease inhibitors), viral load, and disease-related increases in risk factors (dyslipidemia, diabetes).

KEY POINTS

- Hyperlipidemia, type 2 diabetes mellitus, obesity, and tobacco use confer greater risk for coronary artery disease in women than in men.
- Delayed diagnosis of coronary artery disease in women is often due to the presentation of atypical chest pain.
- Cardiovascular disease risk is increased in patients with diabetes mellitus, systemic inflammatory conditions, HIV, and chronic kidney disease.
- Statin therapy should not be used for secondary prevention of cardiovascular disease in patients on hemodialysis. HVC

Diagnostic Testing in Cardiology

Clinical History and Physical Examination

The clinical history and physical examination are cornerstones in the diagnosis of cardiovascular disease. A careful history that includes symptom characteristics, timing, and duration; factors that exacerbate or relieve symptoms; and functional capacity is critical to ensure a focused and appropriate diagnostic evaluation. Abnormal findings on the cardiovascular examination may also raise suspicion for specific cardiac conditions and guide the selection of tests.

Cardiovascular testing provides both diagnostic and prognostic information, and its use should be guided by symptoms, the pretest likelihood of heart disease, and whether testing results will alter patient management.

Diagnostic Testing for Atherosclerotic Coronary Artery Disease

Diagnostic testing for coronary artery disease (CAD) can be categorized as providing functional and/or anatomic information regarding atherosclerotic disease burden. Functional studies reveal the presence of ischemia (exercise electrocardiography [ECG], single-photon emission CT [SPECT], PET), the extent and severity of ischemia (SPECT, PET), information on coronary blood flow (PET, fractional flow reserve (FFR)–CT), and development of wall motion abnormalities (echocardiography, cardiac magnetic resonance [CMR] imaging). Anatomic information is obtained from invasive angiography, coronary CT angiography (CTA), and coronary artery calcium (CAC) scoring. Cardiac diagnostic testing modalities are summarized in **Table 1**.

TABLE 1. Diagnostic Testing for Coronary Artery Disease

Diagnostic Test	Utility	Advantages	Limitations
Exercise Stress Testing			
Exercise ECG	Initial diagnostic test in most patients suspected of having CAD	Data acquired on exercise capacity, blood pressure and heart rate response, and provoked symptoms	Not useful when baseline ECG is abnormal (LVH, LBBB, paced rhythm, preexcitation, >1-mm ST-segment depression)
Stress echocardiography	Recommended when baseline ECG findings are abnormal or when information on a particular area of myocardium at risk is needed	Exercise data acquired along with imaging for wall motion abnormalities to indicate ischemia Allows evaluation of valve function and pulmonary pressures Relatively portable and less costly than nuclear protocols Entire study is completed in <1 h	Image quality is suboptimal in some patients but can be improved with microbubble transpulmonary contrast Image interpretation is difficult when baseline wall motion abnormalities are present Diagnostic accuracy decreases with single-vessel disease or delayed stress image acquisition
Nuclear SPECT perfusion	Recommended when baseline ECG findings are abnormal or when information on a particular area of myocardium at risk is needed With LBBB, conduction delay in the septum may cause false-positive abnormalities; vasodilator stress can improve the accuracy of perfusion imaging	Gating (image acquisition coordinated with the cardiac cycle); use of higher-energy agents, such as technetium; and techniques used to correct for attenuation provide improved specificity Late reperfusion imaging allows evaluation of myocardial viability if thallium is used	Attenuation artifacts can be caused by breast tissue or diaphragm interference; attenuation correction and software programs can improve image interpretation Radiation exposure
Pharmacologic Stress Testing			
Dobutamine echocardiography	Recommended in patients who cannot exercise or when information on an area of myocardium at risk is needed	Because the patient is supine, images are acquired continuously, allowing the test to be stopped as soon as ischemia is evident	Contraindications are severe baseline hypertension, unstable angina, severe tachyarrhythmias, hypertrophic cardiomyopathy, severe aortic stenosis, and large aortic aneurysm
Vasodilator nuclear perfusion (adenosine, dipyridamole, regadenoson)	Recommended in patients who cannot exercise Minimizes septal abnormalities frequently seen with nuclear perfusion scanning in patients with LBBB	Vasodilator stress testing may minimize effect of β-blockade on perfusion defect size Imaging can be performed sooner after myocardial infarction with vasodilator stress	Contraindications are active bronchospastic airway disease, theophylline use, sick sinus syndrome, hypotension, and high-degree AV block Caffeine must be withheld 12-24 h before the test Adenosine or dipyridamole may cause chest pain, dyspnea, or flushing Radiation exposure
Dobutamine nuclear perfusion	Recommended in patients who cannot exercise and have contraindications to vasodilator stress Recommended when information on an area of myocardium at risk is needed	Has sensitivity and specificity similar to those of exercise or vasodilator perfusion imaging for diagnosis of myocardial ischemia	Contraindications are severe baseline hypertension, unstable angina, severe tachyarrhythmias, hypertrophic cardiomyopathy, severe aortic stenosis, and large aortic aneurysm Radiation exposure
PET/CT	Provides best perfusion images in larger patients Provides data on myocardial perfusion, function, and viability	Study duration is shorter and radiation dose is lower than with conventional nuclear perfusion imaging Absolute myocardial blood flow can be measured Can be combined with CAC scoring	Not widely available More expensive than other imaging modalities Used with pharmacologic stress only (no exercise protocol) Radiation exposure

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TABLE 1. Diagnostic Testing for Coronary Artery Disease *(Continued)*

Diagnostic Test	Utility	Advantages	Limitations
Dobutamine or adenosine CMR imaging	Provides excellent spatial resolution for wall motion abnormalities during dobutamine infusion Identifies perfusion abnormalities during adenosine infusion with gadolinium as contrast agent Provides data on infarction and viability using gadolinium contrast Identifies anomalous coronary artery origin	Accurate test for myocardial ischemia or viability	Some patients experience claustrophobia May be contraindicated in patients with pacemaker, ICD, or other implanted device Gadolinium is contraindicated in patients with kidney failure Sinus rhythm and a slower heart rate are needed for improved image quality Limited availability and expertise
Other Tests			
Coronary angiography	Provides anatomic diagnosis of the presence and severity of CAD	Percutaneous revascularization can be performed after diagnostic study	Invasive Risks of vascular access and radiocontrast exposure (kidney dysfunction, allergy, bleeding) Radiation exposure
CAC scoring	May inform treatment decisions for patients with intermediate 10-year risk for cardiovascular events	CAC scores are predictive of cardiovascular risk in selected patients	Does not provide data on coronary luminal narrowing Radiation exposure
Coronary CT angiography	Identifies anomalous coronary arteries Useful for selected patients with intermediate risk for CAD	Coronary artery vessel lumen and atherosclerotic lesions can be visualized in detail	Requires high-resolution (64-slice) CT instruments Does not provide detailed images of distal vessel anatomy Catheterization will be needed if intervention is planned Ability to quantify lesion severity can be limited by significant calcification Radiation and radiocontrast exposure

AV = atrioventricular; CAC = coronary artery calcium; CAD = coronary artery disease; CMR = cardiac magnetic resonance; ECG = electrocardiography; ICD = implantable cardioverter-defibrillator; LBBB = left bundle branch block; LVH = left ventricular hypertrophy; SPECT = single-photon emission CT.

H Cardiac Stress Testing

Cardiac stress testing is commonly performed to diagnose CAD. Appropriate, cost-effective stress testing is based on the history, physical examination, and pretest probability of CAD, which takes into account age, sex, symptoms, and prevalence of disease. Cardiac stress testing is most effectively used in patients with an intermediate pretest probability of CAD, in whom a positive test result significantly increases disease likelihood and a negative test result significantly decreases likelihood (see Coronary Artery Disease). Performing stress testing in persons with a low likelihood of disease (such as young patients with atypical symptoms) yields a high incidence of false-positive test results, potentially resulting in unnecessary testing, inaccurate diagnoses, and harms. In patients with a high pretest probability of disease, invasive angiography rather than stress testing is appropriate.

Assessment of the patient's functional capacity and ability to exercise is important in determining the most appropriate stress testing. Exercise ECG is recommended as the initial test of choice in patients with normal findings on baseline ECG. If there are baseline ECG abnormalities (such as ST-segment depression >1 mm, left bundle branch block, left ventricular hypertrophy, paced rhythm, or preexcitation), ST segment changes with exercise cannot be used to evaluate for the presence of obstructive CAD; these abnormalities will result in a nondiagnostic ECG stress test. Functional testing with imaging (with exercise or pharmacologic stress) or anatomic assessment with coronary CTA is indicated in these instances.

Stress testing may also be used for risk assessment in patients known or suspected to have CAD. The ability to exercise and, more important, exercise capacity are strong predictors of cardiovascular events. ECG changes, hemodynamic

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response to exercise (blood pressure and heart rate recovery), and other measures (such as the Duke Treadmill Score) also provide prognostic information. Stress imaging studies provide information on the extent and severity of disease, which is helpful for risk assessment.

The decision of whether to withhold cardiac medications, such as nitrates and β-blockers, before stress testing should be individualized. In patients who are undergoing exercise stress testing to diagnose CAD, cardiac medications that impair heart rate response (β-blockers) should be withheld for at least 24 hours before testing because these agents may lead to an inadequate peak heart rate. If the stress test is being performed to evaluate symptoms or determine prognosis in a patient with known CAD, patients should continue their cardioactive medication regimen.

Exercise Electrocardiography

Stress testing should always be performed with exercise, unless exercise is contraindicated or the patient is unable to exercise. Exercise stress testing protocols use treadmill or stationary bicycle ergometry, and each protocol should increase workload in a stepwise manner over a period of 6 to 12 minutes to allow adequate time for development of maximal metabolic demand. A standard Bruce protocol increases the speed and grade of the treadmill every 3 minutes. Achieving 85% of the age-predicted maximal heart rate adequately rules out obstructive CAD; however, patients should exercise until limited by symptoms. Because heart rate and blood pressure are the major determinants of myocardial oxygen demand, achieving a rate pressure product (heart rate × systolic blood pressure) of at least 25,000 is considered an adequate workload and reflects overall left ventricular myocardial performance. Stress testing should be terminated when the patient has exerted maximal effort, requests to stop, or experiences significant angina or other physical symptoms. The test should also be stopped for exertional hypotension, significant hypertension (>200/110 mm Hg), ST-segment elevation or significant ST-segment depression, or ventricular or supraventricular arrhythmias.

Ischemia is defined by the development of horizontal or downsloping ST-segment depression of at least 1 mm occurring 80 milliseconds after the J point on exercise ECG, although ST-segment depression cannot localize ischemia (**Figure 1**). The development of hypotension or lack of blood pressure augmentation during exercise can indicate the presence of significant obstructive disease. Heart rate recovery after cessation of exercise provides incremental prognostic information. A heart rate drop of less than 12/min in the first minute after exercise termination is associated with higher mortality. Functional capacity is also a powerful predictor of outcomes; individuals unable to achieve 5 metabolic equivalents, or the first stage of a Bruce protocol, have higher all-cause mortality. Information obtained from exercise stress testing can be combined with clinical information in risk prediction models. The Duke Treadmill Score incorporates duration of exercise, development of symptoms, and degree of ST-segment depression to calculate 5-year all-cause mortality in patients without CAD.

Stress Testing with Adjunctive Imaging

In patients with obstructive CAD, reduced blood flow and myocardial ischemia lead to a progression of myocardial abnormalities, termed the ischemic cascade. Initially, ischemia induces changes in perfusion, followed by diastolic and (at a later stage) systolic dysfunction, ECG changes, and eventually angina. The addition of imaging studies to ECG stress testing

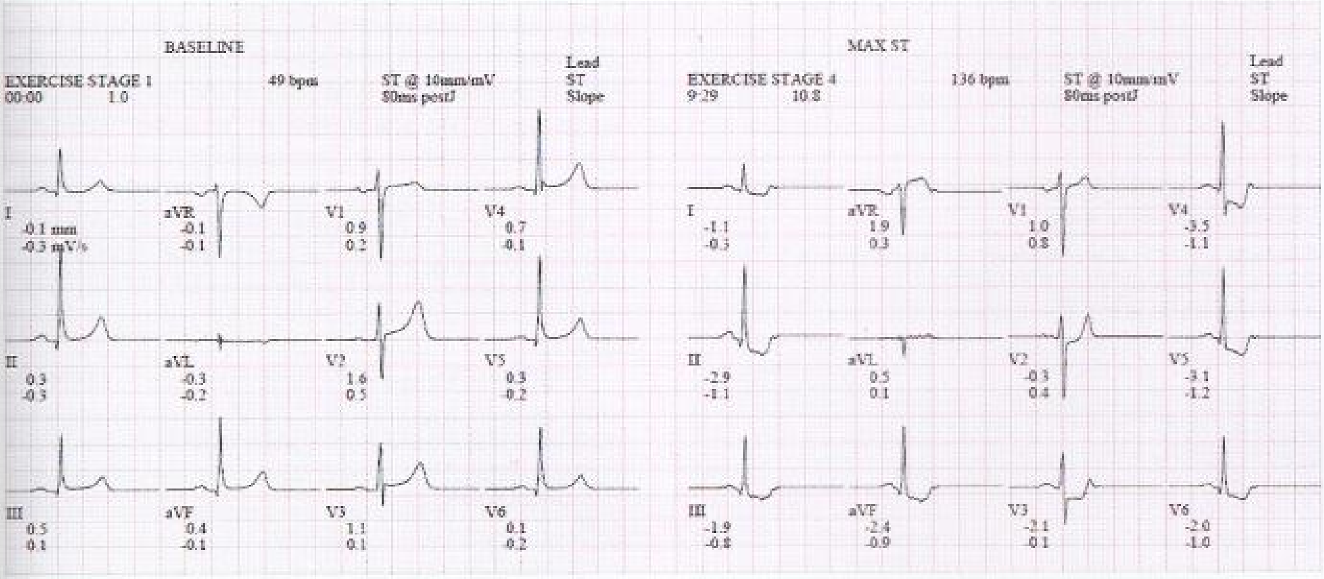

FIGURE 1. Electrocardiogram recorded before (*left*) and during (*right*) exercise stress testing. The presence of 2-mm downsloping ST-segment depressions in leads I, II, III, and aVF, and leads V_3 through V_6, during exercise indicates ischemia.

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increases diagnostic sensitivity by detecting earlier signs of ischemia.

Stress testing with imaging is indicated in patients with an inability to exercise, contraindications to exercise, baseline ECG abnormalities that would preclude interpretation of the exercise ECG, or indeterminate findings on the exercise ECG. Imaging with SPECT, PET, or CMR can be used to detect reduced myocardial perfusion as early evidence of ischemia. Systolic dysfunction, indicated by wall motion abnormalities during stress, can be detected by echocardiography or CMR imaging. Overall, imaging choice should consider characteristics of the patient and modality as well as local availability and expertise (see Table 1).

Stress testing with adjunctive imaging compares wall motion, perfusion, and/or metabolism at baseline and after stress, depending on the modality used (**Table 2**). Exercise is the stress modality of choice. Patients should undergo pharmacologic stress if they are unable to exercise or have contraindications to exercise. Dobutamine, like exercise, increases myocardial oxygen demand and elicits ischemia because of insufficient perfusion to the affected myocardium. Vasodilators, such as dipyridamole, regadenoson, and adenosine, produce hyperemia and a flow disparity between myocardium supplied by unobstructed vessels and myocardium supplied by the stenotic vessel because of the inability of the distal vasculature to dilate. In patients with left bundle branch block undergoing nuclear stress testing, vasodilator-induced stress is preferred to exercise or dobutamine because of the potential for false-positive septal perfusion abnormalities.

TABLE 2. Interpretation of Stress Testing with Imaging Results

Stress SPECT		
At Rest	**After Stressor**	**Interpretation**
Normal	Normal	Normal
Normal	Perfusion defect	Stress-induced myocardial ischemia
Perfusion defect	Perfusion defect	Infarct
Normal	LV dilation	Small or no distinct zone of ischemia, possible balanced ischemia or multivessel CAD
Stress Echocardiography		
At Rest	**After Stressor**	**Interpretation**
Normal	Normal	Normal
Normal	Wall motion abnormality	Stress-induced myocardial ischemia
Regional wall motion abnormalities	Regional wall motion abnormalities	Infarct
Normal	LV dilation	Small or no distinct zone of ischemia, possible balanced ischemia or multivessel CAD

CAD = coronary artery disease; LV = left ventricular; SPECT = single-photon emission CT.

Stress Echocardiography

Exercise stress echocardiography provides information on ischemia, hemodynamic significance of valvular abnormalities, and pulmonary pressures during exercise. Exercise is performed with supine or upright bicycle ergometry, which allows for continuous imaging, or with a treadmill protocol, which requires acquisition of post-stress images within 90 seconds. The development of new wall motion abnormalities indicates ischemia in the visualized territory. Resting wall motion abnormalities that do not change at peak exercise may indicate infarcted or hibernating myocardium (chronic but potentially reversible ischemic dysfunction).

With pharmacologic stress echocardiography, dobutamine is progressively infused (up to 40 µg/kg/min) to achieve 85% of age-predicted maximal heart rate. Atropine is administered if the target heart rate is not achieved. The development of new wall motion abnormalities indicates myocardial ischemia. Dobutamine infusion may also be used in patients with low-gradient aortic stenosis to help differentiate between severe aortic stenosis and pseudostenosis. Patients with reduced systolic function who are able to augment their stroke volume in the setting of severe aortic stenosis may benefit from aortic valve replacement.

Interpretation of stress echocardiography findings is more subjective than with other tests, and the sensitivity of stress echocardiography may be reduced in the setting of baseline wall motion abnormalities, systolic dysfunction, or single-vessel disease.

Nuclear Stress Testing

Nuclear stress testing compares blood flow in the myocardium to diagnose ischemia. In SPECT myocardial perfusion imaging, a radiotracer is injected at rest and at peak exercise/vasodilation, and the radiotracer is taken up by the myocardium relative to blood flow. Rest images are compared with those obtained after exercise or pharmacologic stress. Perfusion defects observed on images obtained after stress indicate flow-limiting CAD (**Figure 2**). Regions with fixed defects can indicate infarcted or hibernating myocardium, and viability assessment can help distinguish between the two. Gated images can provide an assessment of left ventricular systolic function.

SPECT imaging can also quantify the extent and severity of disease, providing additional prognostic information. High-risk features, such as several regions of hypoperfusion, a lack of augmentation or a reduction in post-stress ejection fraction, transient cavity dilatation, and wall motion abnormalities, are associated with a worse prognosis.

Technetium-based myocardial perfusion imaging has higher sensitivity and specificity than thallium-based studies and also provides better image quality. Technetium-based

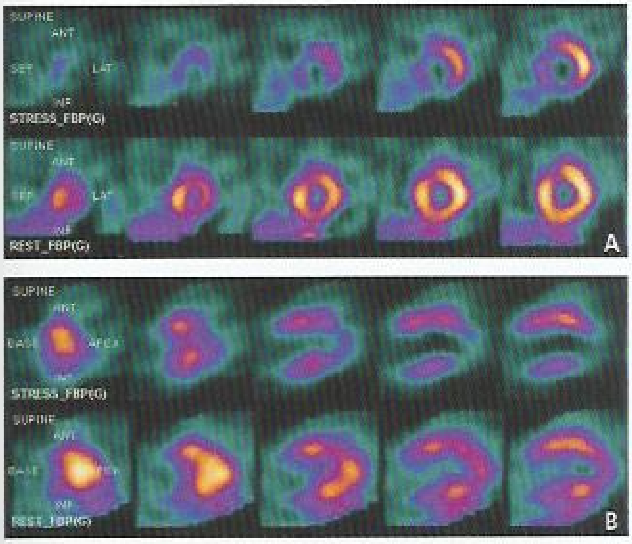


FIGURE 2. Selected images from a nuclear perfusion single-photon emission CT (SPECT) stress study. Short-axis views (*panel A*) of the heart with stress (*top row*) and at rest (*bottom row*) show a radiotracer defect in the septum and inferior wall that is filled on the rest images. Long-axis views (*panel B*) demonstrate an apical filling defect with stress (*top row*) that is perfused on rest images (*bottom row*).

H CONT agents are taken up with blood flow and are bound to the mitochondria, allowing for delayed imaging. In contrast, uptake of thallium requires active metabolism, which can be useful to assess myocardial viability (**Table 3**).

TABLE 3. Interpretation of Myocardial Viability Study Results

SPECT Viability Testing		
Initial Study (at Rest)	**Rest Study Repeated After 4-24 h (with Thallium)**	**Interpretation**
Perfusion defect	Perfusion defect	Fixed defect: infarct, no viability
Perfusion defect	Reperfusion of area	Viable myocardium
PET Viability Testing		
Baseline	**Metabolism**	**Interpretation**
Perfusion defect	Metabolically active	Viable myocardium
Echocardiographic Viability Testing		
Baseline	**Response to Dobutamine**	**Interpretation**
Wall motion abnormality	Low dose: improvement of function Higher dose: worsening of function	Biphasic response indicates viable myocardium

SPECT = single photon emission CT.

Cardiac PET provides excellent diagnostic and prognostic information for patients known or suspected to have CAD. PET provides better temporal and spatial resolution than does SPECT imaging, which is helpful in patients who are obese or who have nondiagnostic SPECT results. CT may be used with PET to provide information on the presence of coronary artery calcification. PET radiotracers have a short half-life, resulting in lower radiation exposure and necessitating the use of vasodilators. Vasodilator stress allows for assessment of peak stress ejection fraction, quantification of absolute myocardial blood flow, and evaluation of myocardial metabolism. The utility of PET imaging in cardiac patients is limited by availability of the technology.

Cardiovascular Magnetic Resonance Imaging

CMR imaging is used with dobutamine to assess development of wall motion abnormalities or with vasodilators to assess perfusion. Right and left systolic function can be assessed with gated imaging. CMR imaging is commonly used to evaluate inflammatory or infiltrative diseases, pericardial diseases, and the extent and severity of infarction. Viability can be determined by evaluating the extent of myocardial fibrosis (nonviable myocardium) within the left ventricular region. CMR imaging is limited by operator expertise, length of time for image acquisition, and availability. H

KEY POINTS

- Cardiac stress testing is best used in patients with an intermediate pretest probability of coronary artery disease.
- In patients undergoing cardiac stress testing, exercise is the preferred stressor because it provides additional prognostic information, including functional capacity and hemodynamic response.
- Stress testing with imaging is indicated in patients with an inability to exercise, contraindications to exercise, baseline electrocardiographic (ECG) abnormalities that would preclude interpretation of exercise ECG results, or indeterminate findings on exercise ECG.

Visualization of the Coronary Anatomy

Anatomic assessment of the coronary arteries can be performed with noninvasive coronary CTA or invasive angiography. Both tests require administration of contrast agents and expose the patient to radiation. CTA interpretation can be limited in cases of extensive calcification and with assessment of distal arteries.

In symptomatic patients with an intermediate risk for CAD, CTA may be helpful in ruling out CAD. In the PROMISE trial, 10,000 symptomatic patients suspected of having CAD were evaluated with an initial strategy of anatomic testing with CTA or functional testing. In patients with an intermediate pretest probability of CAD, the composite cardiovascular event rate was low (<1% per year) in both groups, and outcomes (death, myocardial infarction, hospitalization for

unstable angina, or major procedural complication) at 2 years did not differ between groups.

H Coronary CTA may also play a role in the evaluation of acute chest pain in the emergency department. CTA is appropriate in patients suspected of having an acute aortic syndrome or a coronary embolism. Coronary CTA may be helpful in patients with low or intermediate likelihood of non-ST-elevation acute coronary syndrome who have a low TIMI risk score, negative troponin level, or nonischemic ECG. It may also be useful in patients with an equivocal diagnosis of non-ST-elevation acute coronary syndrome who have an equivocal initial troponin level or single troponin elevation without further symptoms of acute coronary syndrome, or in patients who have ischemic symptoms that resolved hours before undergoing testing. Careful consideration of patient factors and selection of appropriate testing are essential to avoid additional unnecessary testing and the associated costs and potential harms.

Coronary angiography during a cardiac catheterization procedure is an invasive test in which nonionic contrast material is injected into the coronary arteries (or bypass grafts) by using long, thin (<2-mm) catheters. Arterial access is obtained by using the femoral or radial artery, and radiation exposure is required. This test should be considered in patients who have a high pretest probability of obstructive CAD, including symptomatic patients with abnormal findings on noninvasive functional or anatomic testing or with an acute coronary syndrome.

The addition of FFR to invasive angiography and CTA can provide additional functional information, including the hemodynamic significance of a lesion and need for intervention. FFR is the ratio of blood flow distal to the stenosis to blood flow proximal to the stenosis at maximal flow. It is typically measured during cardiac catheterization by placing a pressure wire across the stenosis and inducing conditions of maximal hyperemia, usually with adenosine. FFR-CT is an FDA-approved diagnostic test that provides both anatomic and functional data; it has higher specificity for the diagnosis of obstructive CAD than does CTA alone. Performance of FFR-CT is similar to performance of invasive FFR during angiography. The availability of this test and its delayed interpretation may limit its use in patients with acute symptoms. H

KEY POINT

- Coronary angiography and CT angiography (CTA) provide anatomic information regarding the extent and severity of coronary artery disease; however, the diagnostic value of CTA may be limited in cases of extensive calcification.

Coronary Artery Calcium Scoring

Coronary artery calcification indicates atherosclerosis and may be quantified with electron beam or multidetector CT. Although CAC scoring provides information regarding the burden of disease, it cannot determine the degree of obstruction. CAC measurement has been used for diagnosis and risk assessment in both symptomatic and asymptomatic patients; however, assessment of CAC in asymptomatic patients should be limited to those at intermediate risk (according to the Framingham score) in whom risk reclassification will influence primary prevention therapy.

CAC scores are categorized as follows: 0, no disease; 1 to 99, mild disease; 100 to 399, moderate disease; and above 400, severe disease. These scores should be interpreted in the setting of age, ethnicity, and sex. Specific nomograms and risk calculators, such as the MESA risk calculator (www.mesa-nhlbi.org/MESACHDRisk/MesaRiskScore/RiskScore.aspx), can be used for risk prediction. The absence of CAC is associated with a low risk for cardiovascular events.

KEY POINT

- Assessment of coronary artery calcification in asymptomatic patients should be limited to those at intermediate risk in whom reclassification of risk will influence primary prevention therapy. HVC

Risks of Diagnostic Testing for Coronary Artery Disease

Cardiac diagnostic testing carries risks related to exercise; exposure to pharmacologic stress testing agents, radiation, or contrast agents; and vascular access for invasive procedures. Additionally, inappropriate initial testing may lead to unnecessary downstream testing with added physical and financial costs.

There is a very small risk for myocardial infarction or death (1/2500 patients) in patients undergoing exercise stress testing. Absolute contraindications to exercise include unstable angina or acute myocardial infarction, uncontrolled arrhythmias, decompensated heart failure, acute pulmonary embolism or deep venous thrombosis, acute pericarditis or myocarditis, acute aortic dissection, and severe symptomatic aortic stenosis. Relative contraindications are left main coronary artery stenosis, hypertrophic cardiomyopathy with severe obstruction, electrolyte abnormalities, high-degree atrioventricular block, and significant arrhythmias.

Vasodilator stress agents (most commonly adenosine) are associated with the side effects of chest pain, headache, and flushing. Atrioventricular block and bronchospasm may also occur. Theophylline may be given after the test to reverse these effects. Vasodilator stress testing is contraindicated in patients with reactive airways disease with active wheezing, systolic blood pressure of less than 90 mm Hg, sick sinus syndrome, or high-degree atrioventricular block.

Nuclear stress testing with SPECT and PET, CAC scoring, coronary CTA, and coronary angiography all expose the patient to radiation; however, advances in techniques have resulted in reduction of overall radiation exposure. The level of radiation exposure depends on the procedure, equipment, radiopharmaceutical agent, operator technique, and patient characteristics (such as body size).

Contrast agents used in invasive angiography, coronary CTA, CMR imaging, and echocardiography also pose a risk to the patient. CMR imaging that requires gadolinium contrast may rarely cause nephrogenic systemic fibrosis, particularly in patients with underlying kidney disease. Iodinated contrast material used in CT may result in acute kidney injury. Microbubble contrast agents are used to enhance the endocardial borders in echocardiography and can cause hypersensitivity reactions in rare instances.

Coronary angiography can be complicated by vascular access problems; bleeding complications; coronary artery dissection; aortic dissection; and plaque disruption or thrombus leading to peripheral emboli, stroke, or myocardial infarction. Femoral artery access can be complicated by retroperitoneal hemorrhage, which should be suspected in patients with hypotension, back or flank pain, and/or a drop in hemoglobin level. Pseudoaneurysms at the arterial puncture sites occur more commonly with femoral artery access and may manifest as a large hematoma or new bruit at the access site.

Diagnostic Testing for Structural Heart Disease

Diagnostic testing for structural heart disease should be considered in patients with a suggestive history and physical examination, such as those with a systolic murmur that is grade 3/6 or higher, a late or holosystolic murmur, a diastolic or continuous murmur, or a murmur with accompanying symptoms. Routine imaging of known structural disease is unnecessary unless there is a change in the clinical presentation or examination. A change in functional status in patients with known underlying structural disease warrants evaluation. Imaging modalities to evaluate for structural heart disease are listed in **Table 4**.

The mainstay of noninvasive cardiovascular imaging for structural abnormalities is transthoracic echocardiography (TTE). TTE evaluates right and left ventricular size, thickness, and function, including wall motion abnormalities. It can also be used to obtain information on valvular function (including regurgitation or stenosis), diastolic function, filling pressures, and the pericardium. The presence of an intracardiac shunt can be evaluated with the use of agitated saline contrast. Initial assessment for endocarditis can also be performed with TTE.

Transesophageal echocardiography (TEE) is commonly used to evaluate for the diagnosis of infective endocarditis in patients with a high pretest probability and to assess for complications of endocarditis (such as abscess). TEE may also be used to better visualize valvular pathology, particularly when surgical repair or percutaneous intervention is planned; to evaluate specific structures that cannot be well visualized on TTE (such as prosthetic heart valves) or patients with poor transthoracic imaging; to evaluate acute aortic abnormalities; and to rule out left atrial thrombus before cardioversion (**Figure 3**). TEE requires moderate sedation and placement of the TEE probe in the distal esophagus and stomach. Contraindications include esophageal strictures or active esophageal varices. Esophageal injury, including perforation and bleeding, are potential complications of TEE.

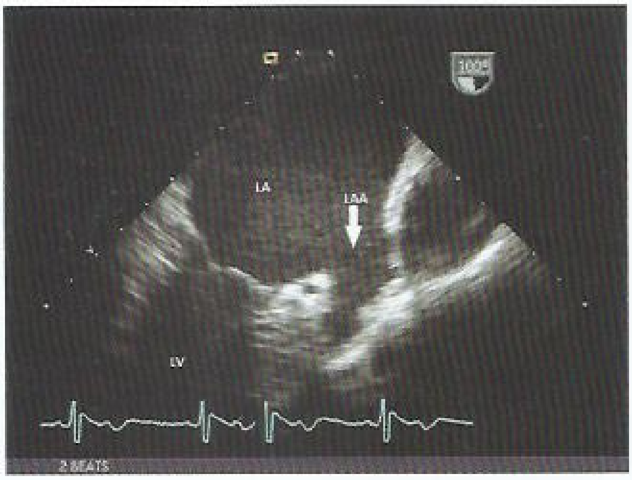


FIGURE 3. Transesophageal echocardiogram. The transducer is posterior to the heart, and the left atrium (LA) and left atrial appendage (LAA, *arrow*) are more easily seen than with transthoracic echocardiography, showing an absence of thrombus in the appendage. LV = left ventricle.

KEY POINTS

- Transthoracic echocardiography is used to evaluate patients with valvular abnormalities, congenital heart disease, pericardial disease, or left or right ventricular dysfunction.
- Transesophageal echocardiography is the most accurate test to evaluate endocarditis, prosthetic valves, and left atrial thrombus.

Diagnostic Testing for Cardiac Arrhythmias

The initial study in patients with a history of palpitations, presyncope, or syncope when an arrhythmia is suspected should be 12-lead resting ECG. The ECG may show evidence of preexcitation, ectopic rhythms, atrioventricular block, or intraventricular conduction delay, providing insight into the cause of the symptoms. Echocardiography should be performed in patients suspected of having structural heart disease.

The intermittent and fleeting nature of arrhythmias can make diagnosis difficult. Diagnostic studies are selected on the basis of the presence and frequency of symptoms and the duration and timing of the recording (**Table 5**). If symptoms occur daily, a 24- or 48-hour ambulatory ECG monitor (Holter monitor) may be used. Infrequent symptomatic events may be captured with an external patient-triggered event recorder if the event lasts long enough for the patient to trigger the device. A looping event recorder captures several seconds of the ECG

TABLE 4. Diagnostic Testing for Structural Heart Disease

Diagnostic Test	Major Indications	Advantages	Limitations
Transthoracic echocardiography	Heart failure Cardiomyopathy Valve disease Congenital heart disease Pulmonary hypertension Aortic disease Pericardial disease	Accurate diagnosis of presence and severity of structural heart disease Quantitation of LV size and function, pulmonary pressures, valve function, and intracardiac shunts Widely available, portable, fast	Operator-dependent data acquisition; interpretation requires expertise Variability in instrumentation Image quality limits diagnosis in some patients (COPD, large body habitus) May require microbubble contrast agents
Transesophageal echocardiography	Endocarditis Prosthetic valve dysfunction Aortic disease Left atrial thrombus	High-quality images, especially of posterior cardiac structures Most accurate test for evaluation of endocarditis, prosthetic valves, and left atrial thrombus	Requires esophageal intubation, typically with conscious sedation
Three-dimensional echocardiography	Mitral valve disease ASD (percutaneous ASD closure)	Improved tomographic imaging Used during cardiac procedures for device placement Improved assessment of LV global/regional systolic function	Adjunct to two-dimensional imaging Limited by availability and expertise
Radionuclide angiography (MUGA)	Evaluation of LV systolic function	Quantitative EF measurements Accurate for serial LVEF measurements (e.g., to evaluate for cardiotoxicity from chemotherapy)	Radiation exposure Provides no data on other cardiac structures
Cardiac catheterization (left and right)	Congenital heart disease Coronary artery disease Valve assessment Shunt assessment	Direct measurement of intracardiac pressures, gradients, and shunts Contrast angiography provides visualization of complex cardiac anatomy Allows percutaneous intervention for structural heart disease	Invasive Radiation and radiocontrast exposure Images not tomographic, limiting evaluation of complex three-dimensional anatomy
Coronary CT angiography	Coronary artery disease Congenital heart disease	Visualization of complex cardiac anatomy High-resolution tomographic images	Invasive Radiation and radiocontrast exposure Image acquisition improved with sinus rhythm and slower heart rate
CMR imaging	Congenital heart disease Aortic disease Myocardial disease (infiltrative disease, myocarditis, hypertrophic cardiomyopathy) RV cardiomyopathy (ARVC) Quantitation of LV mass and function	High-resolution tomographic imaging and blood-flow data Quantitative RV volumes and EF No ionizing radiation or contrast material Enables three-dimensional reconstruction of aortic and coronary anatomy	Limited by availability and expertise Patient claustrophobia May be contraindicated in patients with pacemaker, ICD, or other implanted devices Gadolinium is contraindicated in patients with kidney failure Sinus rhythm and slower heart rate are needed for improved image quality
Chest CT with contrast	Aortic disease Coronary artery disease Cardiac masses Pericardial disease	High-resolution tomographic images Enables three-dimensional reconstruction of vascular structures	Radiation and radiocontrast exposure

ARVC = arrhythmogenic right ventricular cardiomyopathy; ASD = atrial septal defect; CMR = cardiac magnetic resonance; EF = ejection fraction; ICD = implantable cardioverter-defibrillator; LV = left ventricular; LVEF = left ventricular ejection fraction; MUGA = multigated acquisition; RV = right ventricular.

TABLE 5. Diagnostic Testing for Suspected or Known Cardiac Arrhythmias

Diagnostic Test or Device	Indications	Advantages	Limitations
Resting ECG	Initial diagnostic test in all patients	12-lead ECG recorded during the arrhythmia often identifies the specific arrhythmia	Most arrhythmias are intermittent and not recorded on resting ECG
Ambulatory ECG (Holter monitor)	Frequent (at least daily) asymptomatic or symptomatic arrhythmias	Records every heart beat during a 24- or 48-h period for later analysis Patient log allows correlation with symptoms	Not helpful when arrhythmia occurs less frequently ECG leads limit patient activities
Long-term external ECG monitor	Infrequent asymptomatic or symptomatic arrhythmias	Provides continuous rhythm recording for up to 30 days	Adhesive attachment to chest Detection of rhythm abnormalities that are asymptomatic or not clinically significant
Exercise ECG	Arrhythmias provoked by exercise	Allows diagnosis of exercise-related arrhythmias Allows assessment of impact of arrhythmia on blood pressure	Physician supervision needed during testing Most arrhythmias are not exercise related
Patient-triggered event recorder	Infrequent symptomatic arrhythmias that last more than 1-2 min	Small, pocket-sized recorder is held to the chest when symptoms are present Recorded data are transmitted to central monitoring service	Symptomatic arrhythmias must last long enough for patient to activate the device Arrhythmia onset is not recorded Not useful for syncope or extremely brief arrhythmias
Looping event recorder (wearable)	Infrequent, symptomatic, brief arrhythmias Syncope	Continuous ECG signal is recorded (with the previous 30 s to 2 min saved) when the patient activates the recording mode Arrhythmia onset is recorded	ECG leads limit patient activities Device records only when activated by patient
Implantable loop recorder	Very infrequent asymptomatic or symptomatic arrhythmias	Long-term continuous ECG monitoring with patient-triggered or heart rate-triggered episode storage Specific heart rate or QRS parameters can be set to initiate recording of data	Invasive procedure with minor risks Device must be explanted later
Mobile cardiac outpatient telemetry	Continuous outpatient ECG recording for precise quantification or capture of rare arrhythmia	Auto-triggered and patient-triggered capture of arrhythmic events Up to 96 h of retrievable memory	ECG leads limit patient activities Resource intensive
Electrophysiology study	Used for inducing, identifying, and clarifying the mechanism of arrhythmia as well as potential treatment (catheter ablation)	Origin and mechanism of an arrhythmia can be precisely defined	Invasive procedure with some risk Some arrhythmias may not be inducible, particularly if the patient is sedated

ECG = electrocardiography.

signal before the device is triggered; it is useful for syncope or presyncope associated with arrhythmias. A longer-term external ECG monitor or an implanted loop recorder may be warranted in patients with very infrequent events.

Exercise stress testing is also frequently used in patients suspected of having or known to have arrhythmia. Treadmill stress testing is an important tool for evaluating chronotropic response, ischemia, and exercise-induced or adrenergically induced arrhythmia.

Most patients do not require diagnostic electrophysiology testing. Electrophysiology testing may be indicated in patients in whom the diagnosis remains indeterminate or in settings in which catheter-based interventions may be needed to treat refractory arrhythmias.

KEY POINT

- The initial study in patients with a history of palpitations, presyncope, or syncope when an arrhythmia is suspected should be 12-lead resting electrocardiography.

Coronary Artery Disease

Stable Angina Pectoris

Diagnosis and Evaluation

Stable angina pectoris is defined as reproducible angina symptoms (chest pain or pressure) of at least 2 months' duration that are precipitated by exertion or emotional stress and have not appreciably worsened. In contrast, unstable angina is defined by new-onset angina or angina occurring at a relatively low level of exertion, occurring at rest, or accelerating in frequency or severity. Unstable angina is associated with increased short-term risk for acute myocardial infarction (MI). As such, the evaluation of patients with angina should include a focused history, eliciting the duration of symptoms, aggravating and relieving factors, and whether symptoms have worsened. Although angina is classically described as tightness, heaviness, or gripping in the chest, it is important to recognize that classic symptoms may be absent, and some demographic groups (women and patients with diabetes mellitus) may have atypical symptoms, including exertional dyspnea.

The physical examination should include an evaluation of the cardiovascular system and a search for findings suggesting conditions that mimic angina, including heart failure, pulmonary hypertension, valvular heart disease (particularly aortic stenosis), and hypertrophic cardiomyopathy. The first step in diagnostic testing is to determine the pretest probability (or likelihood) of coronary artery disease (CAD) (**Table 6**). Baseline resting electrocardiography (ECG) is required to rule out ongoing ischemia and to guide the choice of stress test (**Figure 4**). The selection of tests for evaluating chest pain is discussed in Diagnostic Testing in Cardiology. Stress testing is most useful in patients with an intermediate probability of CAD; however, when the pretest probability of CAD is high, testing may provide prognostic information. Other diagnoses should be pursued in patients with normal findings on stress testing. If the stress test yields abnormal results, additional evaluation should be considered.

General Approach to Treatment of Stable Angina Pectoris

All patients with angina should receive guideline-directed medical therapy consisting of risk factor modification, cardioprotective medications, and antianginal medications (**Figure 5**). Lifestyle modifications, including regular physical activity, weight loss, tobacco cessation, and dietary changes, should be strongly encouraged, and blood pressure control (with a goal of <130/80 mm Hg) and diabetes management should be emphasized. Cardioprotective medications are indicated in patients with CAD to prevent thrombosis and halt further progression of atherosclerotic plaque. Antianginal medications reduce cardiac workload or increase myocardial oxygen delivery, resulting in decreased angina and improved functional capacity.

Cardioprotective Medications

Aspirin reduces the risk for MI and cardiovascular death in patients with stable angina. Guidelines recommend low-dose aspirin (75-162 mg/d) because it is as effective in preventing MI as high-dose aspirin (325 mg/d) and confers a lower bleeding risk. In aspirin-intolerant patients, clopidogrel, a platelet $P2Y_{12}$ receptor inhibitor, is an acceptable alternative. Neither prasugrel nor ticagrelor has been studied in the context of stable angina, and their role in managing this condition remains to be established.

Lipid-lowering therapy, targeting LDL cholesterol in particular, is indicated to reduce the risk for vascular events and

TABLE 6. Pretest Likelihood of Coronary Artery Disease in Symptomatic Patients According to Age and Sex[a]

	Pretest Likelihood					
	Nonanginal Chest Pain[b]		Atypical Angina[c]		Typical Angina[d]	
Age (y)	Men	Women	Men	Women	Men	Women
30-39	4	2	34	12	76	26
40-49	13	3	51	22	87	55
50-59	20	7	65	31	93	73
60-69	27	14	72	51	94	86

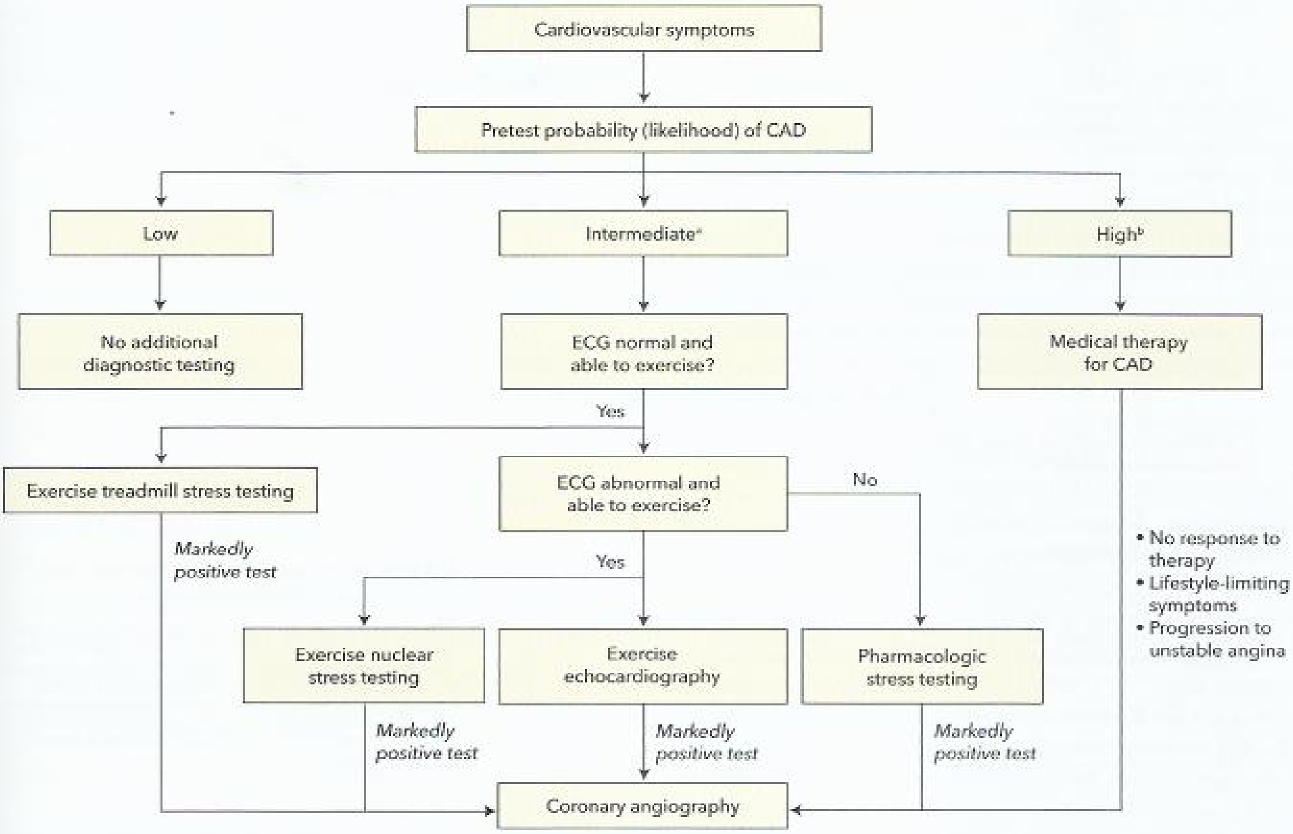
[a]Each value represents the percentage with significant coronary artery disease on catheterization.

[b]Nonanginal chest pain has one or none of the components for typical angina.

[c]Atypical angina has two of the three components for typical angina.

[d]Typical angina has three components: (1) substernal chest pain or discomfort that is (2) provoked by exertion or emotional stress and (3) relieved by rest and/or nitroglycerin.

Reproduced with permission from Fihn SD, Gardin JM, Abrams J, Berra K, Blankenship JC, Dallas AP, et al; American College of Cardiology Foundation. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol. 2012;60:e44-e164. [PMID: 23182125] doi:10.1016/j.jacc.2012.07.013. Copyright 2012, Elsevier.



Stress Test	*Criteria for Markedly Positive Test*
Exercise treadmill	Significant ST-segment ↓ at low work load, ST-segment ↑, hypotension
Exercise nuclear	TID or lung uptake of thallium, ischemia in >2 vascular distributions, EF <35%
Exercise echocardiography	EF <35% at rest, ischemia in >2 vascular distributions, fall in EF with stress

FIGURE 4. Diagnosis of coronary artery disease. CAD = coronary artery disease; ECG = electrocardiography; EF = ejection fraction; TID = transient ischemic dilation.

[a]Intermediate pretest probability (likelihood) is variably defined as between 10% and 90% or between 25% and 75%.

[b]Stress testing in patients with high pretest probability can be used to obtain prognostic information, but the results should not affect the initiation of optimal medical therapy.

progression of underlying CAD. Statin therapy remains the cornerstone of lipid management for secondary prevention, as it has been shown to reduce the risk for MI, death, and stroke. High-intensity statin therapy (atorvastatin, 40-80 mg/d, or rosuvastatin, 20-40 mg/d) decreases LDL cholesterol levels by 50% or more and is preferred to moderate-intensity therapy in patients with no contraindications to its use. In patients who are intolerant of statins (such as those who develop significant myalgia) or who do not achieve adequate LDL cholesterol reduction with statin therapy, it is reasonable to address LDL cholesterol levels with nonstatin medications, including ezetimibe, bile acid sequestrants, fibrates, and proprotein convertase subtilisin/kexin type 9 inhibitors. Management of statin therapy and nonstatin cholesterol-lowering therapy is discussed in MKSAP 18 General Internal Medicine.

ACE inhibitor therapy is indicated in patients with stable angina if there is concomitant diabetes, chronic kidney disease, left ventricular dysfunction (ejection fraction ≤40%), heart failure, or a history of MI. In these populations, ACE inhibitors have additional benefits that are unrelated to CAD, such as preservation of kidney function and improvement in left ventricular function. Angiotensin receptor blockers (ARBs) may be used as an alternative to ACE inhibitors in these same patient populations.

Chelation therapy involves a series of intravenous infusions of ethylene diamine tetra-acetic acid or similar compounds to bind cations (such as calcium) and increase their excretion from the body. There has been no convincing evidence of any benefit with chelation therapy, and it is not recommended for treatment of CAD.

Antianginal Medications

β-Blockers are recommended as first-line agents in patients with stable angina. β-Blockers simultaneously lower heart rate and blood pressure to reduce myocardial oxygen consumption. All β-blockers are equally efficacious in reducing angina, and dosage should be titrated to achieve a resting heart rate

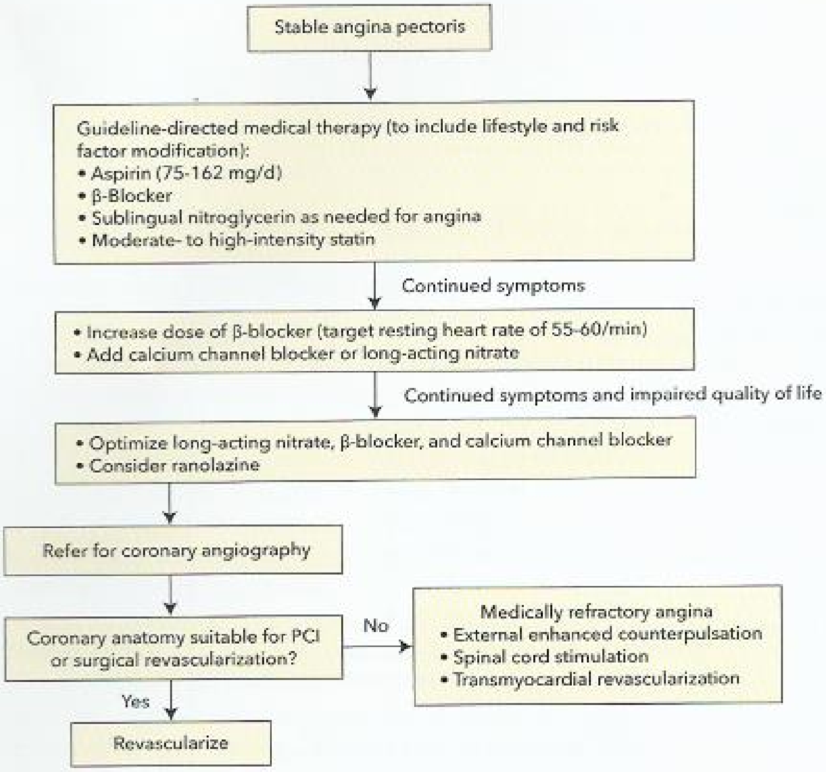


FIGURE 5. Management of stable angina pectoris. PCI = percutaneous coronary intervention.

Recommendations based on Qaseem A, Fihn SD, Dallas P, Williams S, Owens DK, Shekelle P; Clinical Guidelines Committee of the American College of Physicians. Management of stable ischemic heart disease: summary of a clinical practice guideline from the American College of Physicians/American College of Cardiology Foundation/American Heart Association/American Association for Thoracic Surgery/Preventive Cardiovascular Nurses Association/Society of Thoracic Surgeons. Ann Intern Med. 2012;157:735-43. [PMID: 23165665] doi:10.7326/0003-4819-157-10-201211200-00011

between 55/min and 60/min. The choice of β-blocker may depend on other medical conditions, such as concomitant left ventricular dysfunction, kidney dysfunction, lung disease, and significant hypertension. β-Blockers should be used with caution in patients taking nondihydropyridine calcium channel blockers (verapamil, diltiazem) because of additive negative inotropic and chronotropic actions. Caution should also be exercised with these agents in the setting of significant conduction disease on ECG or left ventricular dysfunction. β_1-Selective β-blockers, such as metoprolol, should be used in patients with significant lung disease to avoid worsening respiratory function. Reported side effects include fatigue, lethargy, sleep disturbances, and impotence.

Calcium channel blockers can be useful in patients with symptoms despite β-blocker therapy or in patients intolerant of β-blockers. All calcium channel blockers improve myocardial oxygen delivery by causing coronary vasodilation and reduction in coronary vascular resistance. Additionally, calcium channel blockers can decrease myocardial oxygen consumption through their antihypertensive and negative inotropic effects. The nondihydropyridine calcium channel blockers have negative chronotropic effects and lower heart rate, which can worsen heart failure and increase mortality; therefore, they should not be used in patients with left ventricular dysfunction. Short-acting dihydropyridine formulations, such as short-acting nifedipine, should be avoided because they can paradoxically worsen angina by causing an acute drop in blood pressure, resulting in reflex tachycardia and increased myocardial oxygen demand.

Nitrates cause coronary vasodilation, thereby improving myocardial oxygen delivery. These agents also decrease oxygen consumption by reducing preload, which reduces ventricular wall stress. The beneficial effects may be offset by reflex tachycardia unless β-blockers or calcium channel blockers are used. Short-acting sublingual nitrates should be prescribed to patients with CAD for acute relief of angina. Long-acting nitrates, including isosorbide mononitrate or dinitrate and nitroglycerin patch formulations, provide a constant level of vasodilation throughout the day. A nitrate-free interval of about 12 hours, generally during sleep hours, is needed to avoid development of nitrate tolerance. Side effects include headache, flushing, and hypotension, particularly with rapid-acting formulations. Concomitant use of nitrates and phosphodiesterase 5 inhibitors, such as sildenafil, should be avoided because of the risk for significant hypotension.

Ranolazine decreases angina and modestly increases exercise times in patients with stable angina. It inhibits the late sodium current, which in turn reduces sodium-dependent calcium currents, resulting in reduced wall tension and myocardial oxygen consumption. Ranolazine also has a modest QT-prolonging effect, but no proarrhythmic effect has been directly attributed to ranolazine. The QT interval should be monitored carefully when other QT-prolonging drugs are coadministered. The typical dosage is 1000 mg twice daily; however, the dosage should be reduced to 500 mg twice daily in patients receiving moderate inhibitors of cytochrome P-450 3A4 (verapamil, diltiazem). Ranolazine should not be used in

patients receiving strong inhibitors of cytochrome P-450 3A4 (clarithromycin, itraconazole, ketoconazole, several HIV medications) because serum levels of ranolazine will significantly increase.

KEY POINTS

- Stable angina is characterized by reproducible angina symptoms (chest pain or pressure) that are present for more than 2 months without appreciable worsening and are precipitated by exertion or emotional stress.
- Initial evaluation of a patient with angina should include a focused history, eliciting duration of symptoms, aggravating and relieving factors, and whether symptoms have worsened.
- All patients with coronary artery disease should be counseled on lifestyle modifications, blood pressure control, and management of diabetes mellitus.
- First-line therapy in patients with stable angina includes aspirin (or clopidogrel in aspirin-intolerant patients), statin therapy, and β-blocker therapy.
- ACE inhibitor therapy is indicated in patients with stable angina if there is concomitant left ventricular dysfunction, heart failure, diabetes mellitus, chronic kidney disease, or history of myocardial infarction.

Coronary Revascularization

Decision to Revascularize

Patients with progressive angina symptoms refractory to medical therapy or markedly abnormal stress testing results should be considered for coronary angiography. Before angiography, the risks, benefits, and alternatives to the procedure should be discussed with the patient. It is also important to discuss possible findings and the therapeutic options available after angiography. The goals of revascularization are to improve symptoms of angina and quality of life, prevent future CAD events, and improve survival.

Coronary angiography with fractional flow reserve testing can provide information on the functional significance of angiographically indeterminate lesions (see Diagnostic Testing in Cardiology). Determining the hemodynamic significance of lesions reduces both unnecessary stenting and the need for urgent revascularization. Abnormal fractional flow reserve measures (values <0.80) suggest that a lesion is hemodynamically significant.

Percutaneous Coronary Intervention

Percutaneous coronary intervention (PCI) encompasses several different catheter-based techniques to improve coronary blood flow by relieving coronary obstruction. Initially, PCI was most commonly performed with balloon angioplasty; however, this technique was replaced in the 1990s with bare metal stenting. Currently, most PCI procedures involve drug-eluting stent implantation, which has reduced the risk for in-stent restenosis (the process by which neointimal proliferation within or adjacent to the treated section of coronary artery renarrows the vessel lumen).

Despite advancements in PCI technology, there is no evidence that PCI is superior to guideline-directed medical therapy in the treatment of stable CAD. Specifically, neither the COURAGE trial of patients with stable angina nor the BARI-2D trial of patients with concomitant CAD and diabetes showed any difference in mortality or incidence of MI between treatment strategies. PCI is indicated for the treatment of patients with medically refractory angina, those who are unable to tolerate optimal medical therapy owing to side effects, or those with high-risk features on noninvasive exercise and imaging tests.

Coronary Artery Bypass Graft Surgery

Coronary artery bypass grafting (CABG) is generally recommended for patients with extensive CAD and in certain subsets of patients for whom studies have shown CABG to be superior to PCI or medical therapy. In patients with multivessel CAD, revascularization with CABG results in decreased recurrence of angina, lower rates of MI, and fewer repeat revascularization procedures compared with PCI. Unlike PCI, CABG improves survival in patients with left main or three-vessel CAD and is recommended to reduce mortality in these high-risk patients. Additionally, CABG has an established role in revascularization of patients with diabetes and in those with left ventricular dysfunction. Long-term (10-year) follow-up of the STICH trial demonstrated a survival advantage with CABG compared with medical therapy alone among patients with multivessel CAD and severe left ventricular dysfunction.

After Revascularization

Patients should continue receiving guideline-directed medical therapy following surgical or percutaneous revascularization, although some antianginal therapies may be reduced or discontinued. Aspirin is recommended indefinitely after revascularization. The addition of a $P2Y_{12}$ inhibitor to aspirin therapy, known as dual antiplatelet therapy (DAPT), is also indicated; the recommended duration of DAPT depends on many clinical considerations. Clopidogrel is the only antiplatelet drug that has been studied in combination with aspirin after revascularization of patients with stable CAD. The role of newer antiplatelet agents is unclear at this time.

In patients treated with bare metal stent placement, guidelines recommend a minimum of 1 month of DAPT. Studies of the optimal duration of DAPT after drug-eluting stent implantation have suggested safety and benefits with both shorter (6-month) and longer (30-month) treatment courses. Current guidelines recommend treating patients with stable angina with DAPT for at least 6 months after drug-eluting stent placement, with the option to continue therapy for a longer duration in those with a high risk for thrombosis-related complications (such as depressed left ventricular function, saphenous vein graft stenting, and diabetes) and a favorable bleeding profile. Although guidelines define minimum DAPT duration, the optimal duration should be

individualized according to the patient's risks for thrombotic and bleeding complications.

In patients undergoing CABG for stable CAD, DAPT for 12 months may be reasonable to improve the patency of vein grafts.

KEY POINTS

- Percutaneous coronary intervention may alleviate angina symptoms but does not decrease mortality or risk for myocardial infarction in patients with stable angina.
- Coronary artery bypass graft revascularization is associated with improved survival in patients with multivessel coronary artery disease, diabetes mellitus, or severe left ventricular dysfunction.
- In patients with stable angina who undergo percutaneous coronary intervention, dual antiplatelet therapy should be continued for at least 1 month after bare metal stent implantation and at least 6 months after drug-eluting stent implantation.

Acute Coronary Syndromes

General Considerations

An acute coronary syndrome (ACS) results from acute or subacute disruption in coronary blood flow. Patients present with acute-onset chest pain or an angina equivalent that occurs without a clear precipitant. Unlike stable angina, which involves a gradual narrowing in the coronary artery, an ACS is caused by acute plaque rupture or erosion, often in sections of the coronary artery with mild or moderate stenosis. The presentation depends on the degree of coronary flow impairment.

ACS is classified as ST-elevation myocardial infarction (STEMI) or non–ST-elevation acute coronary syndrome (NSTE-ACS) based on findings on ECG (**Figure 6**). The hallmark ECG features of STEMI are ST-segment elevation of 1 mm or more in two or more contiguous limb or chest leads, excepting leads V_2 and V_3. STEMI is defined as ST-segment elevation of 2 mm or greater in men and 1.5 mm or greater in women in leads V_2 and V_3. Posterior MI typically manifests as ST-segment depression greater than 2 mm in the anterior leads (V_1 through V_4), often with ST-segment elevation in the inferior or lateral leads. New left bundle branch block is considered a STEMI equivalent and potentially reflects an acute left anterior descending artery occlusion.

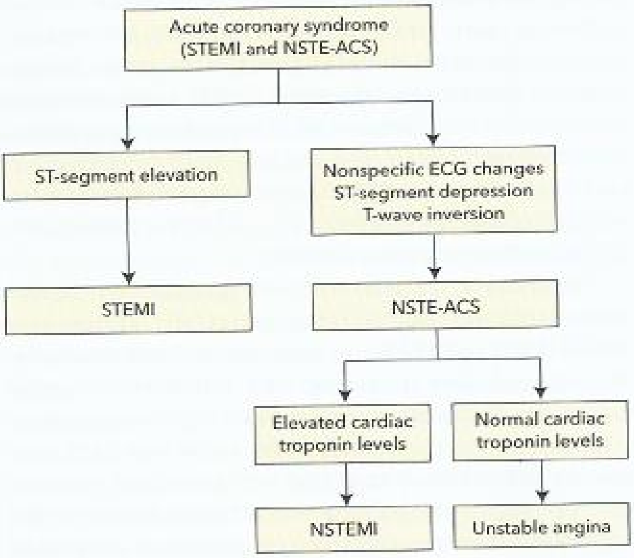


FIGURE 6. Diagnosis of acute coronary syndromes. ECG = electrocardiographic; NSTE-ACS = non-ST-elevation acute coronary syndrome; NSTEMI = non-ST-elevation myocardial infarction; STEMI = ST-elevation myocardial infarction.

NSTE-ACS is further categorized according to the presence of biomarkers of cardiac injury (troponin T or I) in the serum. Non–ST-elevation myocardial infarction (NSTEMI) is defined as a biomarker-positive presentation that does not meet criteria for STEMI. Unstable angina is characterized by new or worsening angina, with or without ECG changes, and without detectable levels of cardiac injury markers. The use of troponin assays has resulted in increased diagnosis of NSTEMI. New high-sensitivity troponin assays can detect cardiac injury with even greater sensitivity and earlier in the setting of ACS than previous tests. Their clinical use may expedite risk stratification in patients with chest pain but may increase detection of non-ACS events and consequent downstream testing.

ST-Elevation Myocardial Infarction

Recognition

The pathogenesis of STEMI typically involves plaque rupture within a coronary artery. The rupture causes platelet adhesion, activation, and aggregation, resulting in a thrombosed coronary artery and acute vessel occlusion. The sudden loss of coronary blood flow leads to transmural ischemia of the myocardium and the ECG manifestation of ST-segment elevation. Because oxygen delivery to the affected artery is acutely and completely obstructed, prompt recognition and initiation of reperfusion therapy are vital (**Figure 7**).

Although the presentation of STEMI is often dramatic and clear, several diagnoses can mimic STEMI. These disease entities need to be distinguished from STEMI to minimize patient harm. Acute pericarditis presents with acute chest pain, albeit pain with a pleuritic and positional nature, and ST-segment elevation. The ST-segment elevation of pericarditis tends to be diffuse and concave; however, it can be easily misinterpreted for STEMI on ECG (**Figure 8**). Pericarditis can also be localized and present with regional ST-segment elevation, such as in the inferior leads. Myopericarditis resulting from viral infections or autoimmune conditions can cause cardiac enzyme release, further confusing the clinical picture. A thorough history and physical examination combined with review of the ECG findings may help differentiate the conditions.

Left ventricular hypertrophy–induced ECG changes may also look similar to ST-segment elevation injury currents; however, these changes are typically concave in appearance. Comparison with previous ECG results is helpful in assessing for acute changes.

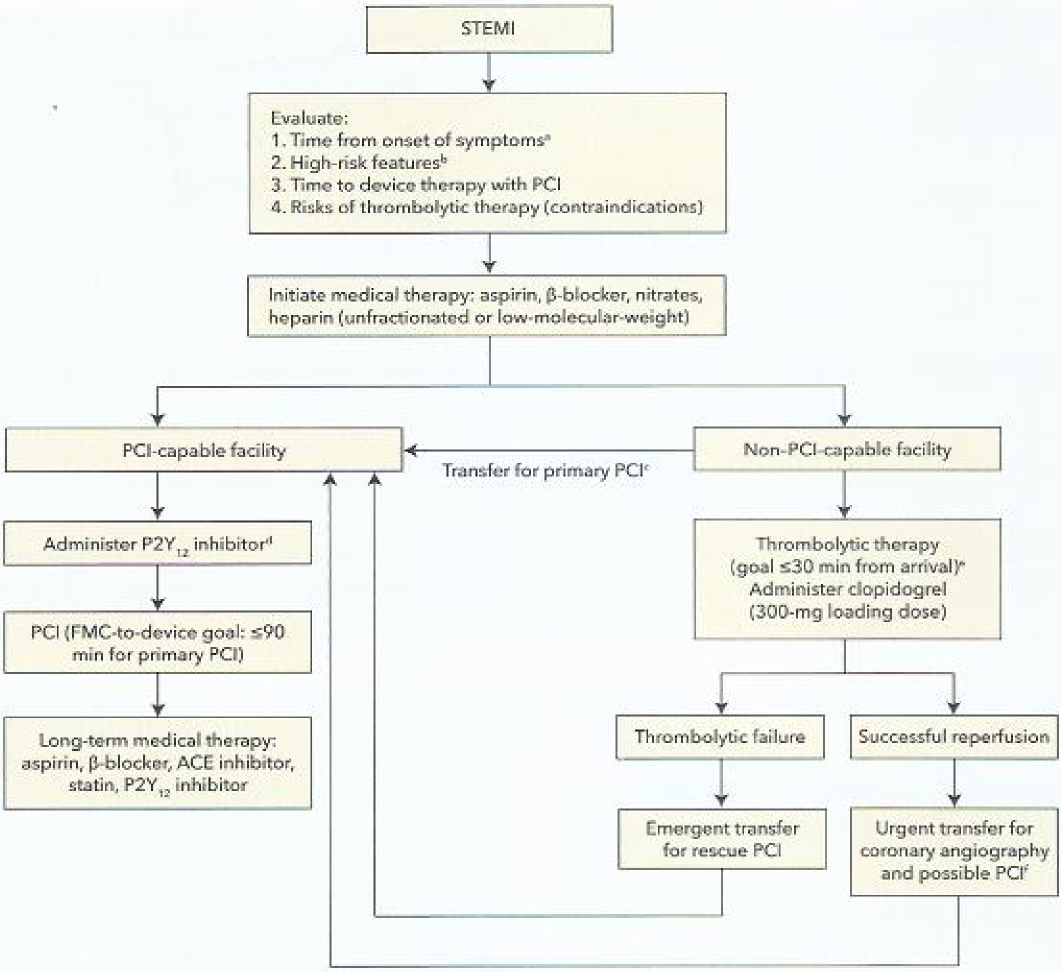


FIGURE 7. Management of ST-elevation myocardial infarction. FMC = first medical contact; PCI = percutaneous coronary intervention; STEMI = ST-elevation myocardial infarction.

[a]If 4 or more hours have elapsed since symptom onset, PCI is preferred.

[b]High risk features, such as cardiogenic shock and heart failure, favor PCI.

[c]FMC to device ("door to balloon") goal for patients being transferred for primary PCI is as soon as possible and ≤120 minutes.

[d]$P2Y_{12}$ inhibitors: clopidogrel, prasugrel, ticagrelor.

[e]Patients with STEMI presenting to a hospital without PCI capabilities and who cannot be transferred to a PCI-capable center and undergo PCI within 120 minutes of FMC ("door-to-balloon time") should be treated with thrombolytic therapy within 30 minutes of hospital presentation ("door-to-needle time") as a systems goal unless thrombolytic therapy is contraindicated.

[f]In patients with successful reperfusion after thrombolytic therapy, it is reasonable to transfer these patients to a PCI-capable center for subsequent coronary angiography. Angiography should not be performed within 2 to 3 hours after thrombolytic administration but is ideally performed within 24 hours.

Recommendations based on O'Gara PT, Kushner FG, Ascheim DD, Casey DE Jr, Chung MK, de Lemos JA, et al; American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2013;127:e362-425. [PMID: 23247304] doi:10.1161/CIR.0b013e3182742cf6

Aortic dissection can cause ST-segment elevation if the dissection involves the left or right coronary artery. In these cases, the ST-segment elevation is due to transmural myocardial ischemia. Aortic dissection is a surgical emergency and must be recognized early because treatment paradigms are drastically different. Diagnostic clues that help differentiate the two conditions include differential blood pressures in the upper extremities and mediastinal widening on chest radiograph with aortic dissection.

Severe hypercalcemia may result in ST-segment elevation that mimics ACS; however, other findings include a short QT interval and flattened T waves.

Reperfusion

Upon STEMI recognition, reperfusion with thrombolytic agents or primary PCI (PPCI) is necessary. PPCI is the preferred method of reperfusion in most cases.

Thrombolytic Therapy

Thrombolytic therapy is recommended for patients with STEMI when symptom onset is within 12 hours and PPCI is not available within 120 minutes of first medical contact. If symptoms began 12 to 24 hours before presentation and there is evidence of hemodynamic instability or significant myocardium at risk

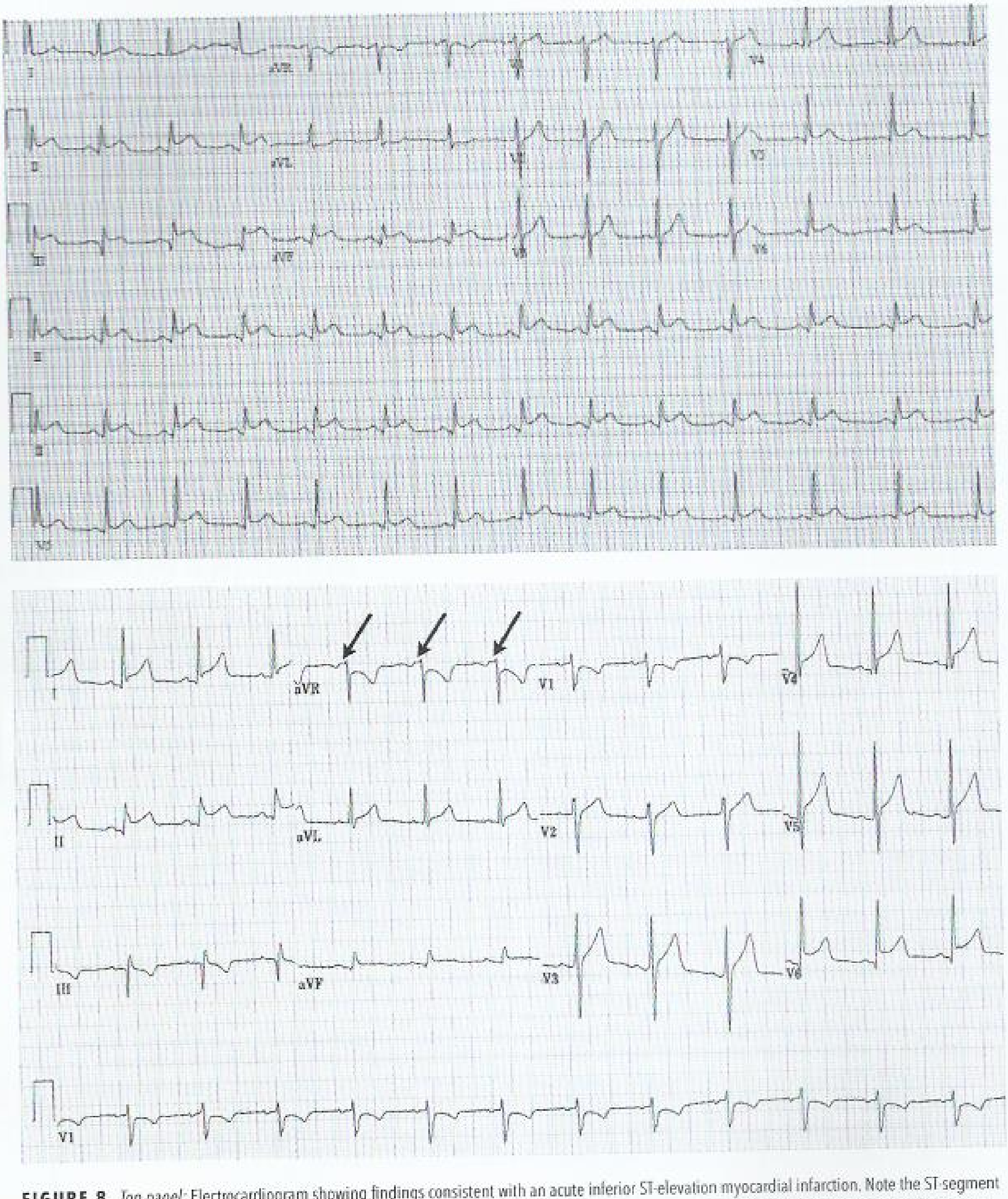


FIGURE 8. *Top panel:* Electrocardiogram showing findings consistent with an acute inferior ST-elevation myocardial infarction. Note the ST-segment elevation isolated to the inferior and lateral precordial leads, which is consistent with a single coronary vascular distribution (that is, the right coronary artery in this case). *Bottom panel:* Electrocardiogram demonstrating acute pericarditis with diffuse ST-segment elevation and slight PR-segment depression (see lead I) and reciprocal PR-segment elevation ("knuckle sign") in lead aVR (*arrows*).

(such as with anterior MI), thrombolytic therapy should be considered. Characteristics of the various thrombolytic agents are presented in **Table 7**.

In addition to thrombolytic therapy, all patients without a specific contraindication should receive a loading dose of aspirin (162-325 mg) as well as intravenous heparin, enoxaparin, or fondaparinux. Clopidogrel loading has been demonstrated to increase rates of vessel patency and is also recommended in this setting.

After thrombolytic therapy is administered, the ECG should be monitored at 60 minutes and 90 minutes to confirm at least 50% improvement in maximal ST segment

TABLE 7. Characteristics of Thrombolytic Agents Commonly Used in the Treatment of ST-Elevation Myocardial Infarction

Characteristic	Streptokinase	Alteplase	Reteplase	Tenecteplase
Dose	1.5 megaunits over 30-60 min	Up to 100 mg in 90 min (based on weight)[a]	10 units × 2 (30 min apart), each over 2 min	30-50 mg based on weight[b]
Bolus administration	No	No	Yes	Yes
Antigenic	Yes	No	No	No
Allergic reactions (hypotension most common)	Yes	No	No	No
Systemic fibrinogen depletion	Marked	Mild	Moderate	Minimal
TIMI flow grade 3	~30%	~50%	~60%	~60%
TIMI flow grade 2/3	~55%	~75%	~83%	~83%
Rate of intracerebral hemorrhage	~0.4%	~0.4%-0.7% (100-mg dose)	~0.8%	~0.9%
Fibrin specificity	None	++	+	+++
Fibrin affinity	None	+++	+	++++
Cost per recommended MI dose (U.S.)[c]	$562.50	$3404.78	$2872.50	$2917.48 for 50 mg

[a]Bolus 15 mg, infusion 0.75 mg/kg × 30 min (maximum 50 mg), then 0.5 mg/kg not to exceed 35 mg over the next 60 min to an overall maximum of 100 mg.

[b]30 mg for weight <60 kg (132 lb), 35 mg for 60-69 kg (132-152 lb), 40 mg for 70-79 kg (154-174 lb), 45 mg for 80-89 kg (176-196 lb), and 50 mg for 90 kg (198 lb) or more.

[c]Department of Health and Human Services, Office of Inspector General. Red Book, 2005. Available at https://oig.hhs.gov/publications/docs/redbook/Red%20Book%202005.pdf.

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elevation. One quarter to one third of patients do not achieve reperfusion, particularly if time from symptom onset to receipt of thrombolytic therapy is delayed. Owing to the potential for thrombolytic failure, patients with STEMI treated with thrombolytic therapy should be subsequently transferred to a PCI-capable hospital. Rescue PCI is associated with improved outcomes compared with conservative management in the event of failed reperfusion. Coronary angiography is generally recommended in all patients before discharge, even after successful thrombolysis. Patients with STEMI who present with heart failure or cardiogenic shock, or who develop these complications after thrombolytic therapy, are a particularly high-risk group (mortality rate >50%) and should be immediately transferred to a PCI-capable center.

Although thrombolytic therapy is potentially life-saving, it carries significant risks, primarily related to bleeding. Intracerebral hemorrhage is the most catastrophic complication of thrombolytic therapy and occurs in approximately 1% of patients. Relative and absolute contraindications to thrombolytic therapy are listed in **Table 8**.

TABLE 8. Contraindications to Thrombolytic Therapy for ST-Elevation Myocardial Infarction

Absolute Contraindications
Any previous intracerebral hemorrhage
Known cerebrovascular lesion (e.g., arteriovenous malformation)
Ischemic stroke within 3 mo
Suspected aortic dissection
Active bleeding or bleeding diathesis (excluding menses)
Significant closed head or facial trauma within 3 mo
Relative Contraindications
History of chronic, severe, poorly controlled hypertension
Severe uncontrolled hypertension on presentation (SBP >180 mm Hg or DBP >110 mm Hg)[a]
History of ischemic stroke (>3 mo), dementia, or known intracranial abnormality
Traumatic or prolonged (>10 min) CPR or major surgery (<3 wk)
Recent (within 2-4 wk) internal bleeding
Noncompressible vascular puncture site
For streptokinase/anistreplase: previous exposure (>5 d) or previous allergic reaction to these agents
Pregnancy
Active peptic ulcer disease
Current use of anticoagulants: the higher the INR, the higher the bleeding risk

CPR = cardiopulmonary resuscitation; DBP = diastolic blood pressure; SBP = systolic blood pressure.

[a]Thrombolytic therapy can be considered if SBP can be reduced to <140 mm Hg and DBP to <90 mm Hg with initial medical therapy.

Primary Percutaneous Coronary Intervention

PPCI refers to the process by which an emergency medical provider activates a team of providers to initiate emergent coronary angiography and PCI in patients with STEMI. Ideally, the time from first medical contact until PCI is less than 90 minutes. The amount of myocardial salvage is directly related to ischemic time; therefore, the quicker the artery can be opened, the better the final outcome. Because the rates of achieving vessel patency are higher and more reliable with

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PPCI than with thrombolysis, PPCI is the preferred method of treating STEMI when the patient presents to a hospital capable of performing PCI or can be transferred from an index hospital to a PCI-capable center quickly (time from first medical contact to PPCI of ≤120 minutes). Once the patient is in the catheterization suite, the initial focus is on quickly restoring flow to the acutely occluded artery. There is ongoing debate as to the timing and potential benefit of PCI of nonculprit vessels.

Patients undergoing PPCI should receive aspirin and heparin before thrombolytic therapy. During the procedure, patients generally receive intravenous heparin (with or without glycoprotein IIb/IIIa blockade) or bivalirudin. Most patients undergo stenting and receive loading doses of additional antiplatelet drugs ($P2Y_{12}$ inhibitors) (**Table 9**). Clopidogrel has historically been the most commonly prescribed $P2Y_{12}$ inhibitor. Compared with clopidogrel, prasugrel is more potent, has a quicker onset of action, and has a lower risk for thrombotic complications; however, prasugrel is also associated with an increased risk for bleeding. Prasugrel should not be used in patients with a history of stroke and those aged 75 years and older, and dosing must be adjusted for those weighing less than 60 kg (132 lb). Ticagrelor, a nonthienopyridine $P2Y_{12}$ inhibitor, also has greater potency and faster onset of platelet inhibition than clopidogrel. In the PLATO trial of patients with ACS, ticagrelor treatment resulted in significantly lower mortality rates compared with clopidogrel. Ticagrelor causes subjective dyspnea in some patients; this symptom is usually self-limited but occasionally causes drug discontinuation.

Medical Therapy

Medical therapies for the treatment of patients with ACS are summarized in **Table 10**.

All patients presenting with STEMI should receive aspirin and anticoagulation therapy. Regardless of the selected reperfusion strategy, patients should also be treated with a $P2Y_{12}$ inhibitor. Clopidogrel is indicated in patients receiving thrombolytic therapy, whereas clopidogrel, prasugrel, and ticagrelor are options for those undergoing PPCI (see Table 9).

β-Blockers decrease myocardial oxygen demand, reduce the incidence of ventricular arrhythmias, and improve long-term survival in patients with STEMI. Current guidelines suggest initiating these drugs within 24 hours of presentation. The COMMIT/CCS-2 trial demonstrated that intravenous metoprolol reduced the early risk for reinfarction and ventricular fibrillation in patients with acute MI but also resulted in a higher rate of cardiogenic shock. β-Blockers should not be given if there is evidence of hypotension, cardiogenic shock, pulmonary congestion, or atrioventricular block. In these cases, β blockers may be withheld initially and introduced once the patient is stabilized.

ACE inhibitors are indicated in most patients with STEMI and particularly in patients with impaired left ventricular function, heart failure, or anterior wall infarction. ARBs may be used if the patient is intolerant of ACE inhibitors. These agents have shown significant early benefit and should be administered within the first 24 hours of presentation, assuming there are no contraindications.

Eplerenone, an aldosterone antagonist, has proved beneficial in patients with STEMI who have an ejection fraction less than or equal to 40% and either heart failure or diabetes; however, the treatment effects were demonstrated only when eplerenone was initiated within 1 week of presentation. Potassium levels must be carefully monitored, particularly in patients with pre-existing kidney dysfunction and those receiving ACE inhibitors or ARBs.

High-intensity statin therapy is indicated in patients with STEMI. Cholesterol levels may be transiently lower around the time of MI, and a low LDL cholesterol level should not dissuade clinicians from prescribing statins.

TABLE 9. $P2Y_{12}$ Inhibitors Used in the Treatment of Patients with Coronary Artery Disease

Drug	Indications	Loading Dose	Maintenance Dose	Adverse Effects	Contraindications
Clopidogrel	Stable CAD treated with PCI ACS	300-600 mg	75 mg/d	Increased bleeding risk	Known allergy to the drug
Ticagrelor	ACS	180 mg	90 mg twice daily[a]	Increased bleeding risk, dyspnea	Known allergy to the drug
Prasugrel	ACS treated with PCI[b]	60 mg	10 mg/d[c]	Increased bleeding risk	Known allergy to the drug, prior transient ischemic attack/stroke, age ≥75 y

ACS = acute coronary syndrome; CAD = coronary artery disease; PCI = percutaneous coronary intervention.

[a]Ticagrelor should be used with aspirin, 81 mg/d.

[b]Prasugrel should not be loaded "upstream" (before catheterization).

[c]Prasugrel, 5 mg/d, should be considered for those weighing less than 60 kg (132 lb) or at moderate to high risk for bleeding (e.g., patients with significant kidney function impairment).

TABLE 10. Medical Therapy for Acute Coronary Syndromes

Medication	Drugs in Class	Dosage	Indications	Comments
Antiplatelet Medications				
Aspirin	N/A	81-162 mg/d	All patients with ACS, unless intolerant or allergic	
Clopidogrel	N/A	75 mg/d	$P2Y_{12}$ inhibitor in combination with aspirin is indicated in all patients after ACS for at least 1 y	Clopidogrel is recommended as an alternative for patients with intolerance or allergy to aspirin
Prasugrel	N/A	5-10 mg/d	$P2Y_{12}$ inhibitor in combination with aspirin is indicated only in patients in whom PCI is performed for at least 1 y	Contraindicated with age >75 y or history of stroke/TIA Dosage adjustment to 5 mg/d should be considered for patients weighing <60 kg (132 lb)
Ticagrelor	N/A	90 mg twice daily	$P2Y_{12}$ inhibitor in combination with aspirin is indicated in all patients after ACS for at least 1 y	More rapid onset of action; does not require first-pass hepatic metabolism; no known genetic polymorphisms Decreased effectiveness with aspirin doses ≥100 mg
Cardioprotective Medications				
β-Blockers	Atenolol, metoprolol, carvedilol, nebivolol	Variable	All patients with prior MI or LV systolic dysfunction	Avoid in patients with cardiogenic shock, hypotension, or conduction disturbances
ACE inhibitors	Benazepril, captopril, enalapril, fosinopril, perindopril, trandolapril, lisinopril, ramipril, quinapril	Variable	All patients with LV systolic dysfunction, hypertension, diabetes mellitus, or kidney disease	Particularly beneficial in patients with anterior MI
Angiotensin receptor blockers	Losartan, valsartan, olmesartan, candesartan, irbesartan, telmisartan	Variable	All patients with LV systolic dysfunction, hypertension, diabetes, or kidney disease who are intolerant of ACE inhibitors	Should not be used in patients already taking an ACE inhibitor
Aldosterone inhibitor	Eplerenone	25-50 mg/d	STEMI patients with LVEF ≤40% and either clinical heart failure or diabetes	Caution is advised in patients with chronic kidney disease or hyperkalemia
High-intensity statin therapy	Atorvastatin Rosuvastatin	40-80 mg/d 20-40 mg/d	For all patients with evidence of coronary artery disease and age ≤75 y	
Moderate-intensity statin therapy	Atorvastatin Rosuvastatin Simvastatin Pravastatin Lovastatin Fluvastatin	10-20 mg/d 5-10 mg/d 20-40 mg/d 40-80 mg/d 40 mg/d 40 mg twice daily	For all patients with evidence of coronary artery disease and age >75 y or otherwise intolerant of high-intensity statin therapy	
Antianginal Medications				
Nitroglycerin	Nitrostat (SL) Nitronal (IV)	0.4 mg every 5 min for a total of three doses Initial IV infusion rate of 5-10 µg/min	As part of multimodality treatment for ongoing chest pain For persistent chest pain following three SL doses and as part of multimodality treatment for heart failure, hypertension	Avoid with SBP <90 mm Hg or ≥30 mm Hg below baseline, bradycardia, tachycardia, RV infarction, PDE-5 inhibitor use within the last 24-48 h, HCM, or severe AS

(Continued on the next page)

TABLE 10. Medical Therapy for Acute Coronary Syndromes *(Continued)*

Medication	Drugs in Class	Dosage	Indications	Comments
Nondihydropyridine calcium channel blockers	Diltiazem, verapamil	Variable	Patients with NSTE-ACS who are intolerant of β-blockers or with angina refractory to nitrates and β-blockers	No benefit in STEMI patients May worsen clinical status with coincidental heart failure or LV dysfunction Avoid with evidence of heart failure, cardiogenic shock, or conduction abnormalities

ACS = acute coronary syndrome; AS = aortic stenosis; HCM = hypertrophic cardiomyopathy; IV = intravenous; LV = left ventricular; LVEF = left ventricular ejection fraction; MI = myocardial infarction; N/A = not applicable; NSTE-ACS = non-ST-elevation acute coronary syndrome; PCI = percutaneous coronary intervention; PDE = phosphodiesterase; RV = right ventricular; SBP = systolic blood pressure; SL = sublingual; STEMI = ST-elevation myocardial infarction; TIA = transient ischemic attack.

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Intravenous nitroglycerin can be used to treat patients with STEMI and hypertension or heart failure; however, there is no role for the routine use of oral nitrates in the convalescent phase of STEMI. Calcium channel blockers and ranolazine also have no role in treating patients with STEMI.

Complications of STEMI

Arrhythmias commonly occur in the peri-infarct setting. Atrial fibrillation, which affects up to 10% to 20% of patients with STEMI, complicates management and may cause hemodynamic instability. Ventricular tachycardia and fibrillation may also occur during MI or after reperfusion. Repetitive and sustained bouts of postinfarct ventricular arrhythmias may warrant consultation with an electrophysiologist, as predischarge implantable cardioverter-defibrillator therapy has a role in treating late arrhythmias complicating STEMI. Routine suppression of ventricular ectopy with antiarrhythmic agents is generally not recommended and is associated with increased risk for ventricular arrhythmias. In particular, accelerated idioventricular rhythm, which commonly arises after reperfusion, is generally benign and transient, requiring no treatment. Atrioventricular blocks, including Wenckebach and complete heart block, may occur after inferior MIs. Temporary transvenous pacemakers are sometimes necessary, but permanent pacing is rarely required. Benign forms of vagally mediated heart block must be differentiated from Mobitz type 2 second-degree atrioventricular block, which is more frequently observed with anterior infarction and damage to the conduction system. Mobitz type 2 block may progress to complete heart block and necessitates permanent pacing.

Cardiogenic shock is a common complication of STEMI. It typically results from a large anterior MI due to severely reduced left ventricular systolic function and carries a mortality rate of 50% to 80%. Patients with cardiogenic shock, particularly those younger than 75 years, have a higher rate of survival if they receive emergent revascularization. In these cases, an intra-aortic balloon pump (IABP) or left ventricular assist device may be implanted temporarily, although limited data support their benefits in cardiogenic shock. Once the patient is stabilized, weening the patient from mechanical and inotropic support and gentle uptitration of afterload-reducing agents, such as captopril, can be attempted. β-Blockers should be avoided initially and can be introduced once the patient is stabilized. Diuretics should be used to treat pulmonary vascular congestion.

Approximately 10% to 20% of cases of anterior STEMI are complicated by left ventricular apical thrombus. Although not supported by rigorous studies, anticoagulation with warfarin is generally recommended for at least 3 months to reduce the risk for systemic embolization.

Rates of mechanical complications after STEMI, including left ventricular free wall rupture, right ventricular infarction, ventricular septal defect (VSD), and acute mitral regurgitation, are low; however, clinicians must be able to recognize these complications, given their highly morbid nature. Free wall rupture produces sudden-onset chest pain or syncope with rapid progression to pulseless electrical activity. It is more common in older adults, women, patients with anterior MI, those receiving anti-inflammatory agents, and patients with a significant delay in receiving reperfusion therapy (>12 hours). Surgery should be considered, but mortality rates, even among those who survive to the operating room, are very high.

Right ventricular infarction, typically indicated by ST-segment elevation in right-sided ECG leads (V_1 and V_4R), can complicate right coronary artery occlusion. It presents with hypotension, elevated jugular venous pressure, and an absence of findings on lung auscultation. Right ventricle pump dysfunction causes inadequate filling of the left ventricle, resulting in shock. Treatments include volume resuscitation and positive inotropes (dobutamine or dopamine) to bridge the right ventricle to recovery, which generally takes 2 to 3 days. Nitrates are contraindicated because they may worsen hypotension by reducing preload.

Acquired VSD from septal wall rupture may complicate inferior or anterior STEMI. With inferior STEMI, the VSD tends to be located in the inferior basal septum, whereas

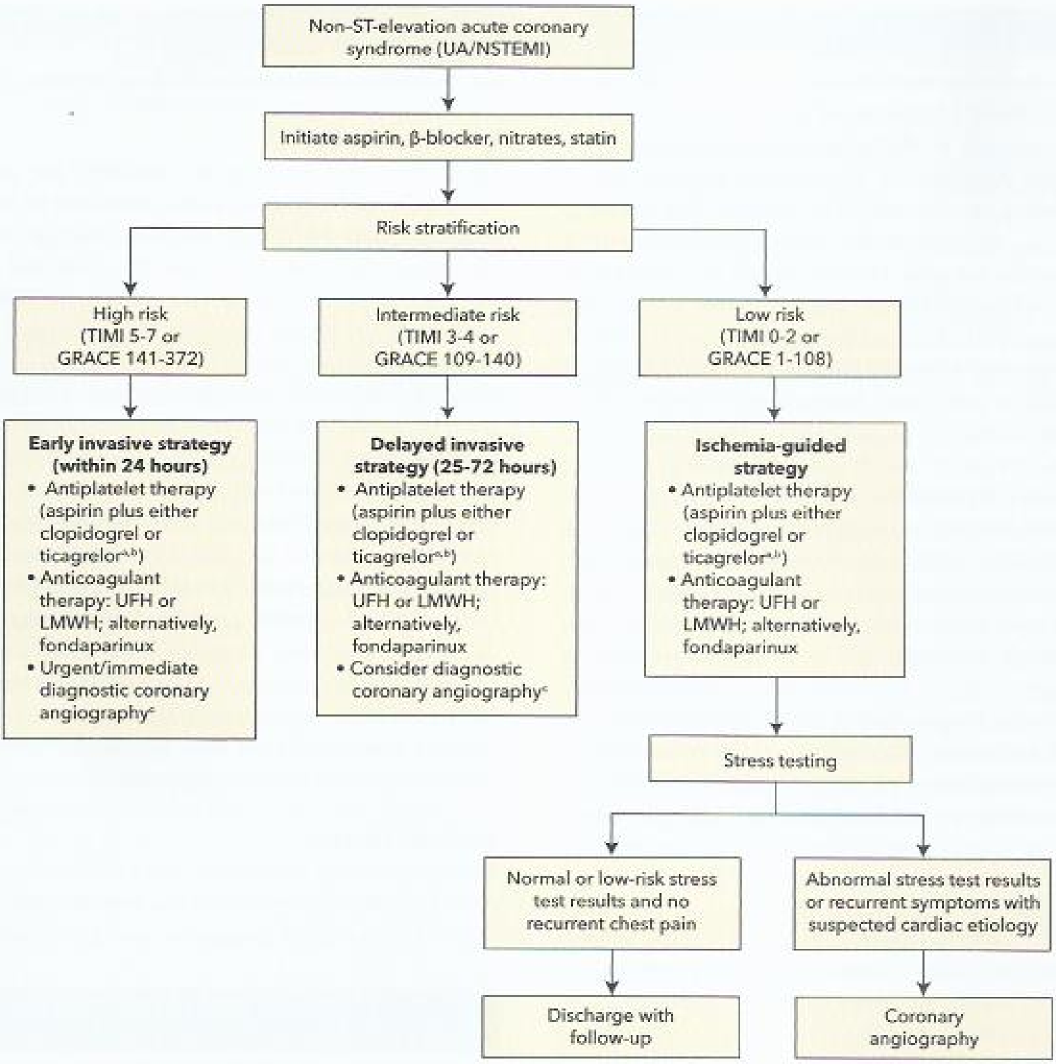

FIGURE 9. Initial management of non-ST-elevation acute coronary syndromes. LMWH = low-molecular-weight heparin; NSTEMI = non-ST-elevation myocardial infarction; UA = unstable angina; UFH = unfractionated heparin.

[a]Clopidogrel or ticagrelor may be dosed at the time of hospital admission and diagnosis of acute coronary syndrome.

[b]If coronary artery bypass grafting is required, clopidogrel or ticagrelor should be stopped, and surgery should be delayed for at least 5 days.

[c]If the decision is made to withhold a $P2Y_{12}$ inhibitor until the time of angiography and a $P2Y_{12}$ inhibitor is desired, clopidogrel, ticagrelor, or prasugrel can be initiated.

Recommendations based on Amsterdam EA, Wenger NK, Brindis RG, Casey DE Jr, Ganiats TG, Holmes DR Jr, et al; ACC/AHA Task Force Members. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014;130:2354-94. [PMID: 25249586] doi:10.1161/CIR.0000000000000133

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treatment of this condition. Notably, thrombolytic therapy is not beneficial in patients with NSTE-ACS and is not recommended. Medical therapies for the treatment of NSTE-ACS are summarized in Table 10.

Antiplatelet Medications

Aspirin (162-325 mg) should be administered at presentation to all patients with definite or likely NSTE-ACS, followed by a daily dose of 81 to 162 mg. Early clopidogrel loading has been recommended in patients with NSTEMI; however, the optimal timing for loading of other oral antiplatelet agents is unclear. Prasugrel loading before coronary angiography is not beneficial. Clopidogrel or ticagrelor therapy is recommended for 1 year after NSTE-ACS presentation, regardless of the treatment strategy. Prasugrel is indicated only in patients treated with PCI. Evidence supports continuing DAPT beyond 1 year in patients at high risk for recurrent vascular events (such as those with depressed left ventricular function, saphenous vein graft stenting, or diabetes) in whom the benefit exceeds the bleeding risk.

The use of intravenous glycoprotein IIb/IIIa inhibitors (eptifibatide, tirofiban) has decreased over the past decade. Although these drugs had been shown to improve outcomes in patients with NSTE-ACS (particularly higher risk and troponin-positive patients), subsequent study demonstrated

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no benefit of upstream glycoprotein IIb/IIIa blockade and an increased risk for bleeding. These agents are generally reserved for use during PCI; however, given the advent of quicker-acting and more potent oral antiplatelet agents, administration of glycoprotein IIb/IIIa inhibitors in the setting of PCI has also significantly declined.

Anticoagulant Medications

Patients with definite NSTE-ACS should undergo anticoagulation. Intravenous unfractionated heparin and subcutaneous enoxaparin are most commonly used. Intravenous heparin is preferred in patients with kidney dysfunction because enoxaparin and similar agents are partially cleared by the kidneys. For patients proceeding to the catheterization laboratory, anticoagulant therapy should be provided until revascularization with PCI or CABG. In medically treated patients, anticoagulation is recommended for at least 48 hours and is generally continued until discharge.

Antianginal Medications

β-Blockers should be administered within 24 hours of NSTE-ACS because these agents reduce ventricular arrhythmias and long-term mortality. β-Blockers are not appropriate for patients with evidence of heart failure or shock at presentation. Likewise, these agents should not be given to patients with bradycardia, heart block, or a PR interval greater than 240 ms on ECG.

Calcium channel blockers are recommended for patients with NSTE-ACS intolerant of β-blocker therapy or in patients with angina symptoms despite therapy with nitrates and β-blockers. The nondihydropyridine calcium channel blockers reduce heart rate, blood pressure, and cardiac contractility, thereby reducing myocardial oxygen demand. However, because of these hemodynamic effects, use of these agents is also contraindicated in the setting of shock, pulmonary edema, or significant conduction disease. Importantly, short-acting dihydropyridine calcium channel blockers are contraindicated, owing to their ability to acutely lower the blood pressure and raise the heart rate.

Nitrates are primarily used to manage angina symptoms in patients with NSTE-ACS. Sublingual nitrates should be administered at presentation to relieve chest pain. For patients with persistent chest pain despite β-blockade, intravenous nitroglycerin can alleviate symptoms, particularly in those with hypertension. Patients receiving nitroglycerin infusions for a prolonged time will often require increased doses due to the development of nitrate tolerance. Nitrates should be avoided in patients who have had recent exposure (within 24-48 hours) to phosphodiesterase type 5 inhibitors such as sildenafil.

Patients with chest pain refractory to antianginal medications should be evaluated for noncardiac causes of chest pain and biomarker elevation, as well as for the possibility of severe underlying CAD or electrocardiographically silent coronary thrombosis.

Lipid-Lowering Medications

Statin therapy reduces mortality and adverse clinical event rates after ACS. High-intensity statin therapy is recommended because it improves outcomes compared with lower-intensity treatment. Initiating statins in the inpatient setting is associated with greater medication adherence. Furthermore, statin preloading before PCI has been associated with lower rates of periprocedural MI.

Invasive Versus Ischemia-Guided Treatment

Immediate invasive treatment (within 2 hours) is recommended for patients with NSTE-ACS who have hemodynamic instability, refractory chest pain, heart failure, or ventricular arrhythmias. In patients with an elevated clinical risk score, significant ST segment deviation, or elevated cardiac biomarkers, cardiac catheterization is usually performed within 24 hours of presentation. The type of revascularization procedure (PCI or CABG) depends on the results of angiography.

An invasive strategy improves the composite clinical endpoint of death, recurrent MI, and repeat hospitalization compared with an ischemia-guided approach in high-risk and troponin-positive patients with NSTE-ACS. An invasive strategy is the favored approach, with the exception of patients with extensive noncardiac comorbid conditions (such as cancer), in whom the clinical benefits of revascularization may be lower, and patients with acute chest pain unlikely to be related to CAD.

With an ischemia-guided treatment strategy, patients undergo noninvasive stress testing before hospital discharge; cardiac catheterization is reserved for patients with active or intermittent ischemia, including those with angina despite medical therapy or evidence of ischemia on stress testing, and patients at very high clinical risk based on risk score. The ischemia-guided approach is appropriate for low-risk patients (TIMI score <2 or GRACE score <109). H

KEY POINTS

- In patients with a non–ST-elevation acute coronary syndrome, initial risk stratification with the TIMI or GRACE risk scores aids in diagnostic and therapeutic decision making.
- Thrombolytic therapy is not indicated in patients with non–ST-elevation acute coronary syndromes. HVC
- The decision to pursue an invasive approach versus an ischemia-guided approach in patients with a non–ST-elevation acute coronary syndrome depends on the patient's risk for clinical events.
- Dual antiplatelet therapy is indicated for at least 1 year after a non–ST-elevation acute coronary syndrome (NSTE-ACS); clopidogrel and ticagrelor may be used in all patients with NSTE-ACS, whereas prasugrel may be used only in patients treated with percutaneous coronary intervention.

H Acute Coronary Syndromes Not Associated with Obstructive Coronary Disease

Elevations in cardiac enzymes, particularly cardiac troponins, coupled with ECG changes provide excellent diagnostic discrimination for ACS. However, conditions not caused by acute coronary plaque rupture can present with similar findings, and treatment of these conditions with antithrombotic agents and revascularization is not beneficial or recommended.

Patients with accelerated hypertension, significant left ventricular hypertrophy, and cardiomyopathies may present with chest pain and elevated cardiac troponin levels caused by elevated left ventricular filling pressures or wall tension rather than plaque rupture. The ECG findings are often abnormal in these patients. Patients with supraventricular tachycardias, which may also dramatically increase the rate-pressure product, often present with chest pain, ST-segment depressions, and elevated cardiac enzyme levels, even if no CAD is present.

Coronary vasospasm is sudden constriction of a coronary artery. It may occur spontaneously or follow use of illicit substances (methamphetamines, cocaine) or prescription drugs (5-fluorouracil, bromocriptine). ECG abnormalities may be nonspecific or mimic STEMI patterns. Coronary vasospasm is a diagnosis of exclusion. Unless the patient has a history of vasospasm, patients often undergo coronary angiography, which may reveal normal findings or slowed coronary flow resulting from microvascular dysfunction. Provocative testing can be performed but is not usually indicated. Patients suspected of having vasospasm (or the related microvascular dysfunction) are usually treated empirically with nitrates and/or calcium channel blockers.

Takotsubo cardiomyopathy, alternatively termed stress cardiomyopathy or apical ballooning syndrome, is a relatively uncommon form of ACS (see Heart Failure). Patients present with acute chest pain, ECG changes (often ST-segment elevations), and elevated cardiac enzyme levels. Takotsubo cardiomyopathy most commonly occurs in women, and there is often, but not always, an antecedent psychological or physical stressor. Patients may initially be diagnosed with STEMI but found to have no significant coronary stenosis at the time of cardiac catheterization. Systolic apical ballooning and notable sparing of the base of the heart on echocardiography or ventriculography are characteristic of this syndrome.

Cardiac syndrome X is a poorly defined condition characterized by anginal chest pain in the presence of angiographically normal coronary arteries or insignificant CAD (<50% stenosis). Cardiac syndrome X is a frequent cause of chest pain syndromes in women, and patients often present without traditional risk factors for CAD. Several hypotheses have been proposed to explain the pathogenesis of this syndrome. One of the most accepted centers on microvascular dysfunction as the cause. Patients may be treated with β-blockers, calcium channel blockers, and nitrates.

Patients with chronic inflammatory muscle diseases or neuromuscular diseases may have elevated levels of cardiac troponin T due to expression of this enzyme in skeletal muscle. The cardiac troponin I level is normal in these cases, which can be helpful in differentiating ACS from these other entities. H

Care After an Acute Coronary Syndrome

All patients with ACS should continue aspirin, preferably 81 mg/d, indefinitely. DAPT is recommended for at least 1 year (see Table 10). There is some evidence for extending DAPT beyond 1 year in stented and medically treated patients; however, the decision to prolong therapy should be individualized, with the risk for bleeding weighed against the risk for thrombosis. Statin therapy should continue indefinitely. β-Blockade and ACE inhibitor therapy should also be continued indefinitely in patients with left ventricular dysfunction; continuation of these medications is reasonable in patients with normal left ventricular function. Guidelines recommend avoiding NSAIDs if possible, owing to the increased cardiovascular risk associated with these drugs. Patients should be referred for cardiac rehabilitation, a medically observed exercise program, to improve functional capacity and risk factor profiles.

Management of Coronary Artery Disease in Special Populations

Women

Clinical Presentation

H Women usually develop ischemic heart disease at an older age than men and more commonly present with stable CAD than an ACS. In women with typical angina symptoms, nonobstructive coronary stenoses are present on coronary angiography in more than 50% of cases, and microvascular dysfunction (endothelium-dependent or endothelium-independent) is thought to be a predominant cause of symptoms in these patients. In women with acute MI, the predominant symptom is chest pain or pressure; however, women can often have atypical symptoms, such as fatigue, dyspnea, nausea, or abdominal symptoms. H

Several unique manifestations of cardiovascular disease, including spontaneous coronary artery dissection, takotsubo cardiomyopathy, and coronary vasospasm, occur primarily in women. Spontaneous coronary artery dissection is a common cause of chest pain among younger women who present with ACS. In many cases, spontaneous coronary artery dissection occurs in the peripartum period and is thought to be caused by hormonal changes, although the true cause is unknown. Given the preponderance of young women with this condition, minimizing radiation exposure and avoiding invasive angiography are recommended. This can typically be achieved with the use of supportive care with or without CT angiography. In severe cases, vessel occlusion causes STEMI and necessitates emergent revascularization.

Evaluation and Treatment

Noninvasive stress testing for the evaluation of CAD symptoms has a lower sensitivity and specificity in women than in men,

and ST segment deviation has a lower reported accuracy in women. Therefore, stress testing with imaging provides better accuracy in women (see Diagnostic Testing in Cardiology). Despite these differences, the same guideline recommendations apply to both women and men.

Reports from observational studies and substudies of randomized controlled trials suggest that women have worse outcomes after STEMI presentation. The cause of these worse outcomes is thought to be delays in recognition of CAD and longer overall ischemic time. Complication rates are also reported to be higher in women who undergo reperfusion therapy for STEMI. The COURAGE trial demonstrated that among patients with stable angina treated with revascularization, women had lower rates of overall mortality and nonfatal MI but a higher rate of complications compared with men. Overall, treatment guidelines do not differ for men and women.

Diabetes Mellitus

Risk and Evaluation

Diabetes has been proposed as a CAD equivalent because age-adjusted risk for CAD events is two- to threefold higher in patients with diabetes. Cardiovascular morbidity and mortality are also significantly higher in this population, especially in patients with type 2 diabetes. Much of the risk has been attributed to the higher incidence of known cardiovascular risk factors; however, evidence suggests that underlying vascular dysfunction may play an important role.

Patients with diabetes may present with atypical cardiac symptoms, such as dyspnea or nausea, requiring a high index of suspicion for CAD during their evaluation. The diagnostic accuracy of noninvasive stress testing in symptomatic patients with diabetes is similar to that in patients without diabetes. Although traditional risk factors for CAD should be aggressively managed in patients with diabetes, screening for CAD in asymptomatic persons is controversial, and routine stress testing is not recommended.

Medical Therapy and Secondary Prevention

Medical therapy for patients with diabetes and CAD includes aggressive risk factor reduction, glucose control, and antianginal therapy. The American College of Cardiology/American Heart Association recommend antihypertensive treatment with a target blood pressure below 130/80 mm Hg in patients with diabetes. In contrast, the American Diabetes Association recommends a systolic blood pressure goal of less than 140 mm Hg and a diastolic blood pressure goal of less than 90 mm Hg for most patients. Lower systolic and diastolic blood pressure targets may be appropriate for individuals at high risk for cardiovascular disease, if they can be achieved without undue treatment burden. ACE inhibitors and ARBs are preferred in the setting of hypertension because of their kidney-protective effects. High-intensity statin therapy is indicated in most patients with diabetes and CAD.

Aspirin is recommended for secondary prevention in all patients with diabetes and CAD. Primary prevention is recommended for patients with diabetes with a 10-year cardiovascular risk greater than 10% or one additional risk factor.

Tight glycemic control reduces microvascular complications; however, it does not reduce the risk for MI. In a recent study, liraglutide, a glucagon-like peptide-1 analogue, was associated with reduced risk for cardiovascular death in patients with type 2 diabetes and high cardiovascular risk. Initial studies suggested thiazolidinediones, specifically rosiglitazone, were associated with an elevated risk for cardiovascular events, although a subsequent clinical trial demonstrated no elevated risk for MI or death. Consequently, the FDA has removed the restriction on rosiglitazone use in patients with type 2 diabetes and CAD. Metformin does not have any cardiovascular effects, but caution should be exercised in patients undergoing coronary angiography, patients who have had an MI, and patients with heart failure because of concern for potentially fatal lactic acidosis.

Invasive Treatment

The choice of revascularization strategy (PCI or CABG) in patients with diabetes is based on many factors, including the severity and extent of CAD, comorbid conditions, and degree of atherosclerotic narrowing of small, distal vessels. Mortality rates are similar between the two procedures; however, CABG is generally preferred because it is associated with lower rates of repeat revascularization. In patients who undergo PCI, drug-eluting stent placement is recommended to reduce the occurrence of target vessel revascularization because of higher rates of restenosis in patients with diabetes.

KEY POINTS

- Stress testing is not routinely recommended in asymptomatic patients with diabetes mellitus to detect subclinical coronary artery disease. HVC
- Coronary artery bypass grafting is the preferred mode of revascularization in patients with diabetes mellitus.

Heart Failure

Pathophysiology of Heart Failure

Heart failure is a clinical syndrome characterized by signs and symptoms of fluid overload and decreased cardiac output. Heart failure can result from systolic or diastolic dysfunction. In cases of systolic dysfunction, multiple causes result in reduced stroke volume and ejection fraction, termed heart failure with reduced ejection fraction (HFrEF). Common causes of HFrEF include coronary artery disease (CAD), myocarditis, valvular heart disease, infiltrative processes, and hypertension. Diastolic dysfunction is usually characterized by a stiffened left ventricle with abnormal relaxation during diastole, resulting in an increase in left

ventricular preload. Ejection fraction classically remains normal in this setting, known as heart failure with preserved ejection fraction (HFpEF). Common causes of HFpEF include hypertension, aging, obesity, diabetes mellitus, and CAD. Often, patients with heart failure have concomitant systolic and diastolic dysfunction. The outcome of both processes is increased left ventricular filling pressures, which are transmitted to the lungs and subsequently to the right ventricle and the body. The increase in pressures causes the classic signs and symptoms of heart failure, including dyspnea, paroxysmal nocturnal dyspnea, orthopnea, peripheral edema, crackles on pulmonary auscultation, elevated jugular venous pressure, and an S_3.

In patients with heart failure, compensatory mechanisms activate to adapt to the reduction in cardiac output and elevated pressures. The heart dilates in response to an increase in preload to improve myocardial contraction (Frank-Starling mechanism). To combat the increase in wall stress that occurs with dilatation and high filling pressures, the myocytes hypertrophy, initially reducing wall stress but eventually leading to reduced left ventricular compliance. These changes improve or maintain stroke volume at first; however, in the long term, they contribute to worsening cardiac function.

Another compensatory mechanism is the upregulation of the renin-angiotensin-aldosterone system to produce angiotensin II and aldosterone. Angiotensin II causes vasoconstriction, which improves blood pressure and stimulates thirst. Aldosterone increases fluid retention by increasing sodium resorption. The adrenergic nervous system is stimulated, resulting in release of epinephrine, norepinephrine, and vasopressin. The hormones cause an increase in heart rate, contractility, and vascular resistance, and vasopressin causes additional water retention. These mechanisms improve blood pressure and forward flow initially; however, over time, they become deleterious. The increase in blood pressure causes an increase in afterload, leading to reduced stroke volume and increased ventricular preload. The increase in volume results in an increase in preload and left ventricular distention, followed by a rise in pulmonary pressures and enlarged heart size owing to both myocyte hypertrophy and elongation. Elevated levels of neurohormones also cause myocyte injury and adversely promote remodeling. The result is a cycle of slowly worsening left ventricular function with decreasing forward flow and increasing pulmonary and right-sided pressures.

KEY POINTS

- Common causes of heart failure with reduced ejection fraction include coronary artery disease, myocarditis, valvular heart disease, infiltrative processes, and hypertension.
- Heart failure with preserved ejection fraction is commonly caused by hypertension, aging, obesity, diabetes mellitus, or coronary artery disease.

Screening and Prevention

Patients at risk for heart failure (such as those with hypertension, diabetes, or vascular disease), but without heart failure symptoms or left ventricular dysfunction, should be screened with B-type natriuretic peptide (BNP) or N-terminal pro-B-type natriuretic peptide (NT-proBNP) measurement, followed by early intervention with appropriate therapy in those with elevated levels. BNP assays are typically used to establish or exclude heart failure as the cause of dyspnea. Small studies have shown that aggressive guideline-based medical therapy in patients with elevated BNP or NT-proBNP levels can help prevent future left ventricular dysfunction or new-onset heart failure. Additional research is needed to identify the effects of screening on mortality as well as the cost-effectiveness of such interventions.

Evidence has shown that heart failure incidence can also be reduced by significantly lowering blood pressure in at-risk patients. The American College of Cardiology (ACC), American Heart Association (AHA), and Heart Failure Society of America recommend targeting an optimal blood pressure of less than 130/80 mm Hg for heart failure prevention.

Diagnosis and Evaluation of Heart Failure

Clinical Evaluation

Clinical evaluation of patients suspected of having heart failure should include a comprehensive history and physical examination, focusing on assessment of fluid and perfusion status. Most patients with heart failure present with volume overload and normal cardiac output. The second most common presentation is low cardiac output with volume overload; rarely, patients have signs and symptoms of low cardiac output without volume overload. Volume overload is associated with crackles, jugular venous distention, peripheral edema, increased abdominal girth (ascites), dyspnea, orthopnea, and paroxysmal nocturnal dyspnea. Patients with heart failure typically develop exertional dyspnea first, followed by orthopnea and paroxysmal nocturnal dyspnea. Elevated jugular venous pressures and orthopnea are most predictive of an elevated pulmonary capillary wedge pressure, which suggests left-sided heart failure. Signs of low cardiac output include low pulse pressure, cool extremities, and reduced cognition. Although worsening kidney or liver function may be a sign of low cardiac output, end-organ dysfunction can also be caused by vascular congestion.

Diagnosis

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Initial diagnostic testing should include electrocardiography to evaluate for ischemia and arrhythmia, chest radiography to exclude pulmonary causes of dyspnea, and a BNP or NT-proBNP assay to establish the presence and severity of heart failure. In patients with dyspnea, BNP can effectively differentiate cardiac from pulmonary causes. BNP levels are

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elevated in patients with increased right or left ventricular filling pressures and systolic or diastolic heart failure (typically >400 pg/mL [400 ng/L]), whereas BNP levels are low to normal in patients with pulmonary disease (typically <100 pg/mL [100 ng/L]). Studies have shown that an elevated BNP level has a sensitivity for heart failure of 95% to 97% and a negative predictive value of 90% to 97%. Between 100 pg/mL and 400 pg/mL (100-400 ng/L), BNP concentrations are neither sensitive nor specific for excluding or confirming the diagnosis of heart failure. Other factors that increase BNP levels include kidney failure, older age, and female sex. BNP levels are reduced in patients with an elevated BMI.

Laboratory assessment should also include a complete blood count, serum electrolytes and kidney function tests, glucose and lipid levels, liver chemistry tests, and serum thyroid-stimulating hormone level. Thyroid-stimulating hormone measurement is indicated to evaluate for occult hypo- or hyperthyroidism as a reversible cause of heart failure. In hyperthyroidism in particular, the predominant manifestation of thyroid dysfunction may be cardiac symptoms, which will abate when the hyperthyroidism is treated.

Echocardiography is the primary diagnostic test in the evaluation of heart failure. An echocardiogram provides information on heart size, systolic and diastolic function, regional wall motion abnormalities, and valvular disease. Findings on echocardiography can provide information on underlying causes of heart failure as well. Regional wall motion abnormalities suggest CAD, and changes in the myocardium can suggest conditions such as cardiac amyloid. Echocardiography may also provide prognostic information, particularly in the setting of severely depressed ejection fraction.

Evaluation for Ischemia

CAD is the leading cause of heart failure in the United States (>50% of patients) and should be considered in all patients with newly diagnosed heart failure. The decision to evaluate for CAD depends on the patient's symptoms and risk factors (family history, male sex, diabetes, hypertension, tobacco use). Additionally, findings on electrocardiography and echocardiography may suggest an ischemic cause for left ventricular dysfunction. Patients with exertional chest pain, history of myocardial infarction, or other symptoms suggesting CAD should undergo further evaluation with stress testing or cardiac catheterization as clinically appropriate (see Diagnostic Testing in Cardiology). Identification of significant CAD is important, as left ventricular dysfunction caused by ischemia may improve or resolve with percutaneous or surgical revascularization. H

Classification

The severity of heart failure is categorized according to the New York Heart Association (NYHA) functional classification (Table 12) and the ACC/AHA heart failure stages (Table 13). Patients can move back and forth between NYHA classes depending on fluid status and progression of heart failure; however, they may only progress in the ACC/AHA stages. Both the patient's functional class and stage affect the choice of therapy.

TABLE 12. New York Heart Association Functional Classification

Class	Description
I	No limitations of physical activity
II	Slight limitation of physical activity
III	Marked limitation of physical activity
IIIA	Symptoms with less than ordinary activity
IIIB	Symptoms with minimal exertion
IV	Unable to carry on any physical activity without symptoms

TABLE 13. American College of Cardiology/American Heart Association Stages of Heart Failure

Stage	Description
Stage A	At risk for heart failure but without structural heart changes (e.g., patients with diabetes mellitus, coronary artery disease, hypertension, or vascular disease)
Stage B	Structural heart disease (e.g., reduced ejection fraction, left ventricular hypertrophy, chamber enlargement) but without heart failure symptoms
Stage C	Structural heart disease with current or prior heart failure symptoms
Stage D	Refractory heart failure requiring advanced intervention (e.g., biventricular pacemaker, left ventricular assist device, transplantation)

Information from Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG, et al. 2009 Focused update incorporated into the ACC/AHA 2005 guidelines for the diagnosis and management of heart failure in adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the International Society for Heart and Lung Transplantation. Circulation. 2009;119:e391-479. [PMID: 19324966] doi:10.1161/CIRCULATIONAHA.109.192065

KEY POINTS

- B-type natriuretic peptide measurement is a sensitive and specific test for the diagnosis of heart failure in patients with dyspnea.
- In patients suspected of having heart failure, echocardiography should be performed to assess ejection fraction and identify possible causes of heart failure.

Medical Therapy for Systolic Heart Failure

The treatment of patients with HFrEF (systolic heart failure) includes treatment of acute exacerbations followed by long-term therapy to decrease morbidity and mortality and improve symptoms in patients with chronic heart failure.

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ACE Inhibitors and Angiotensin Receptor Blockers

ACE inhibitors reduce morbidity and mortality in patients with HFrEF and are the cornerstone of long-term therapy for both symptomatic and asymptomatic patients. ACE inhibitors block the conversion of angiotensin I to angiotensin II, inhibiting the upregulation of the aldosterone pathway. The ATLAS trial examined the effects of low-dose versus high-dose ACE inhibitor therapy (lisinopril) in patients with systolic heart failure and found no difference in overall mortality; however, high-dose lisinopril was associated with a significant reduction in the composite endpoint of mortality and hospitalizations from heart failure and for any cause. On the basis of these results, the general consensus is to uptitrate ACE inhibitors to maximal doses or until the onset of symptomatic hypotension.

The primary adverse effects associated with the use of ACE inhibitors are kidney dysfunction, ACE inhibitor-induced cough, and angioedema. Although ACE inhibitors should be considered in every patient with HFrEF, elevations in creatinine levels may prevent use of maximal doses. Many physicians do not recommend increasing the dosage once the creatinine level rises to 2.5 mg/dL (221 µmol/L) or the estimated glomerular filtration rate falls below 30 mL/min/1.73 m². The estimated glomerular filtration rate should be monitored for decline during uptitration of ACE inhibitor or angiotensin receptor blocker (ARB) therapy and should be rechecked before discontinuation of these drugs, as other conditions or drugs may confound the assessment of kidney function. Hyperkalemia may also result from ACE inhibitor or ARB therapy in patients with pre-existing chronic kidney disease and may require dosage reduction or discontinuation. Development of ACE inhibitor-induced cough is the primary reason to switch a patient from an ACE inhibitor to an ARB. Although fewer data support the use of ARBs in asymptomatic patients with a reduced ejection fraction, there is general consensus that all patients who cannot tolerate ACE inhibitor therapy should receive an ARB. Patients who develop angioedema while taking an ACE inhibitor are often switched to an ARB; however, there are rare reports of ARB-induced angioedema, and patients should be informed of this risk.

Angiotensin Receptor-Neprilysin Inhibitor

The angiotensin receptor-neprilysin inhibitor (ARNI) valsartan-sacubitril belongs to a relatively new drug class that combines an ARB with a neprilysin inhibitor. Neprilysin is a neutral endopeptidase that degrades several vasoactive peptides, including natriuretic peptides and bradykinin. Inhibition of neprilysin increases levels of these substances, leading to enhanced diuresis, natriuresis, and myocardial relaxation. In the PARADIGM-HF trial, patients with symptomatic heart failure (elevated BNP or NT-proBNP level or a heart failure hospitalization within 12 months) and an ejection fraction below 40% were randomly assigned to receive valsartan-sacubitril or the ACE inhibitor enalapril. The patients who received valsartan-sacubitril had a reduction in morbidity and mortality. However, 12% of patients withdrew from the trial during the run-in phase, primarily because of hypotension, kidney dysfunction, cough, and hyperkalemia. During the trial, 16.7% of patients had symptomatic hypotension, and in 4.8% of patients, creatinine level increased to higher than 2.5 mg/dL (221 µmol/L).

Guidelines currently recommend replacing an ACE inhibitor or ARB with valsartan-sacubitril in patients with chronic symptomatic HFrEF who tolerate ACE inhibitor or ARB therapy well. Caution should be used when initiating this drug in patients with hypotension or kidney impairment, and kidney function should be followed closely. Valsartan-sacubitril should not be administered concurrently with an ACE inhibitor or within 36 hours of the last dose of an ACE inhibitor owing to the risk for angioedema.

β-Blockers

β-Blockers should be initiated in all patients with HFrEF. β-Blockers improve remodeling, increase ejection fraction, and reduce hospitalization and mortality when added to ACE inhibitor and diuretic therapy. In contrast to ACE inhibitors, the benefits of β-blocker therapy do not appear to be a class effect, and one of the three agents shown to have a mortality benefit (bisoprolol, carvedilol, and metoprolol succinate) should be used.

β-Blockers are generally well tolerated, but they should be initiated only when the patient is euvolemic or nearly euvolemic. These agents have negative inotropic properties and may exacerbate heart failure in patients with volume overload. Consequently, β-blockers should be initiated at low doses and slowly uptitrated over weeks (not days) until the patient achieves a heart rate of around 60/min or has symptomatic hypotension (**Table 14**). In general, hospitalized patients should be started on β-blocker therapy before discharge. In patients with reactive airways disease or COPD, β-blocker therapy should not be initiated if the patient has bronchospasm or evidence of an exacerbation of pulmonary disease.

Initiating and Managing ACE Inhibitor and β-Blocker Therapy

ACE inhibitors and β-blockers are indicated in all patients with HFrEF. Either drug may be initiated first. Studies have shown that patients receive additive benefit from the second

TABLE 14. Therapeutic Dosages of β-Blockers for Treatment of Heart Failure with Reduced Ejection Fraction

Agent	Target Dosage
Carvedilol	25 mg twice daily (50 mg twice daily if weight >85 kg [187 lb])
Metoprolol succinate	200 mg daily
Bisoprolol	10 mg daily

agent regardless of which agent is started earlier. It is reasonable to select the first agent based on patient factors. For example, a β-blocker should be initiated first in patients with CAD or atrial fibrillation who require heart rate control. Conversely, an ACE inhibitor should be started first in patients with diabetes for the additional renal benefits. Regardless of the agent first initiated, the second drug should be started before the dosage of the first agent is maximized, especially if the patient has low blood pressure or is at risk for hypotension.

Recent guidelines recommend treating to a systolic blood pressure of less than 130/80 mm Hg in patients with HFrEF. Although randomized controlled trials have not specifically evaluated a goal blood pressure in patients with HFrEF, studies have shown that patients with lower blood pressure have fewer adverse cardiovascular events.

Diuretics

Loop diuretics are the mainstay of treatment for volume overload in patients with heart failure because of the increased potency of these agents compared with other diuretics. Of the four loop diuretics, furosemide is most commonly used; however, some studies have shown torsemide to be more effective, which may be attributable to its increased bioavailability and longer half-life. Occasionally, loop and thiazide diuretics are combined to potentiate diuresis. The lowest dosage that achieves euvolemia should be used. The primary side effects include hypokalemia and hypomagnesemia; therefore, electrolyte levels should be monitored.

Digoxin

Digoxin is used in patients with HFrEF and concomitant atrial fibrillation for rate control and in patients who continue to have symptoms of heart failure despite optimal therapy with ACE inhibitor and β-blocker therapies. Digoxin reduces the risk for hospitalization in patients with heart failure, and its discontinuation is associated with worsening heart failure symptoms. Unlike neurohumoral antagonists (including ACE inhibitors, β-blockers, and aldosterone antagonists), digoxin does not improve survival. The use of digoxin in patients with heart failure has decreased over the past 20 years, primarily because of its lack of mortality benefit and the dangerous side effects associated with digoxin toxicity. Digoxin should be managed carefully in patients with impaired kidney function, older adults, and women. It should be dosed to achieve a serum level of less than 1.0 ng/mL (1.28 nmol/L).

Aldosterone Antagonists

Aldosterone antagonists (spironolactone, eplerenone) reduce mortality and heart failure hospitalizations in patients with symptomatic heart failure (NYHA functional class II-IV symptoms) and patients with heart failure after an acute myocardial infarction. Despite their proven efficacy, they are underused, probably because of concerns of hyperkalemia and associated death raised by observational studies of spironolactone. Both drugs require that patients be monitored for hyperkalemia, and these agents should be used carefully in patients with kidney dysfunction. In clinical trials, potassium supplementation was routinely discontinued at the beginning of therapy, and electrolyte measurement was repeated within 1 week of initiation.

Although spironolactone and eplerenone are both effective, their differences may guide drug selection. Spironolactone is a nonspecific antagonist that has antiandrogen and antiprogesterone side effects. It is extensively metabolized in the liver, and the half-life can increase in the setting of hepatic congestion. Eplerenone is a selective antagonist that is metabolized by cytochrome P-450 isoenzyme 3A4 (CYP3A4) and is subject to substantial drug interactions with both inhibitors and inducers of this isoenzyme.

Current guidelines recommend these agents as first-line therapy, along with ACE inhibitors and β-blockers, in patients with symptomatic heart failure. Generally, the doses of both the ACE inhibitor and β-blocker should be uptitrated to maximal levels before spironolactone or eplerenone is added. Aldosterone antagonists should not be considered diuretic therapy, and patients with volume overload will also need to be treated with a loop or thiazide diuretic.

Isosorbide Dinitrate-Hydralazine

Isosorbide dinitrate–hydralazine is superior to placebo in reducing hospitalization but inferior to ACE inhibitors for survival benefit in patients with symptomatic HFrEF. Therefore, this combination should be considered in patients intolerant of ACE inhibitors and ARBs, especially those with chronic kidney disease. In black patients with NYHA functional class III to IV symptoms, isosorbide dinitrate–hydralazine should be used in combination with optimal therapy, including ACE inhibitors, β-blockers, and aldosterone antagonists, to reduce mortality. Headache is a common adverse effect. Because many patients will not adhere to the dosage regimen of three doses daily, clinicians should strongly encourage patients to comply. Nonadherence issues may prompt clinicians to consider switching the patient to once-daily nitrate therapy, but once-daily therapy has not been studied in clinical trials to prove similar efficacy.

Calcium Channel Blockers

The nondihydropyridine calcium channel blockers verapamil and diltiazem both have detrimental effects in patients with systolic heart failure, probably related to negative inotropic effects, and these agents should not be used. Amlodipine and felodipine have shown neither benefit nor harm in patients with heart failure. Therefore, these two drugs are safe but should be used only in patients with hypertension despite therapy with other agents at maximal dosage.

Ivabradine

Ivabradine is a sinoatrial node modulator that selectively inhibits the I_f current in the sinoatrial node, causing a reduction in heart rate. It has no negative inotropic effects. In

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patients with chronic symptomatic heart failure and left ventricular ejection fraction less than or equal to 35% who are in sinus rhythm and taking maximally tolerated doses of a β-blocker, ivabradine reduces heart failure-associated hospitalizations and the combined endpoint of mortality and heart failure hospitalization. Ivabradine has been approved for use in the United States and should be considered for patients who have an elevated heart rate (≥70/min) in sinus rhythm despite maximally tolerated doses of β-blocker therapy. H

KEY POINTS

- Guidelines currently recommend replacing an ACE inhibitor or angiotensin receptor blocker (ARB) with valsartan-sacubitril in patients with chronic symptomatic heart failure with reduced ejection fraction who tolerate ACE inhibitor or ARB therapy well.
- β-Blockers are generally well tolerated in patients with heart failure, but these agents should be initiated only when the patient is euvolemic or nearly euvolemic.
- Ivabradine should be considered for patients with symptomatic heart failure and an ejection fraction less than or equal to 35% who have an elevated heart rate (≥70/min) in sinus rhythm despite maximally tolerated doses of β-blocker therapy.
- Aldosterone antagonists reduce mortality and heart failure hospitalizations in patients with symptomatic heart failure.

H Management of Heart Failure with Preserved Ejection Fraction

The prototypical presentation of HFpEF is an elderly woman with long-standing hypertension associated with left ventricular hypertrophy; however, patients with CAD, diabetes, kidney disease, or other conditions may also present with signs and symptoms of heart failure and a normal ejection fraction. The primary therapies for HFpEF are diuretics to control symptoms of volume overload and antihypertensive agents to target a systolic blood pressure of less than 130 mm Hg in the setting of hypertension. In patients with worsened symptoms of heart failure and atrial fibrillation, restoration of sinus rhythm or rate control may reduce symptoms.

Despite many studies of therapeutic agents, no drug has been shown to reduce morbidity or mortality in patients with HFpEF, which may reflect the heterogeneity of etiology. The recent TOPCAT trial showed no difference in the primary combined endpoint of death, aborted cardiac arrest, or heart failure hospitalization in patients treated with spironolactone compared with those who received a placebo. In retrospective analysis, there was a mortality advantage with use of spironolactone in the United States, whereas in Europe, evidence showed spironolactone to be less effective. However, the clinical characteristics of the enrolled patients were statistically different in these two regions. Some clinicians have suggested that spironolactone should be used routinely for this condition with no other proven treatments; however, spironolactone therapy for HFpEF is not supported by current evidence. H

KEY POINT

- The primary therapies for heart failure with preserved ejection fraction are diuretics to control symptoms of volume overload and antihypertensive agents to target a systolic blood pressure of less than 130 mm Hg.

Device Therapy

H

Implantable Cardioverter-Defibrillator Therapy for Prevention of Sudden Cardiac Death

Arrhythmias are a common cause of death in patients with heart failure, and implantable cardioverter-defibrillators (ICDs) improve survival when used for both primary and secondary prevention of arrhythmias. Current guidelines recommend ICD placement in patients receiving guideline-directed medical therapy who have an ejection fraction less than or equal to 35% and NYHA functional class II or III heart failure symptoms. Patients with class IV symptoms should only undergo ICD placement if they are candidates for heart transplant or left ventricular assist device (LVAD) placement. It is important to reassess both ejection fraction and symptoms after guideline-directed medical therapy (40 days after myocardial infarction, 3 months in all others). Many patients with new-onset heart failure experience substantial improvements in ejection fraction with medical therapy and may not require or benefit from ICD insertion.

Cardiac Resynchronization Therapy

Cardiac resynchronization therapy (CRT), or biventricular pacing, involves traditional pacing of the right ventricular apex and pacing of the left ventricular lateral wall via a lead inserted through the coronary sinus into a lateral cardiac vein. In patients with dyssynchrony (demonstrated in most trials by a widened QRS interval or left bundle branch block [LBBB]), CRT has improved ejection fraction, reduced heart failure symptoms, and reduced mortality. Retrospective analysis of many trials has shown that patients with LBBB are most likely to benefit from CRT. Based on these findings, CRT is indicated in patients with an ejection fraction less than or equal to 35%, NYHA functional class II to IV heart failure symptoms despite guideline-directed medical therapy, sinus rhythm, and LBBB with a QRS complex of 150 ms or greater. Patients with no LBBB but a QRS complex of 150 ms or greater may derive a lesser benefit from CRT. H

KEY POINTS

- Placement of an implantable cardioverter-defibrillator is recommended in patients with heart failure who have an ejection fraction less than or equal to 35% and New York Heart Association functional class II or III symptoms while taking guideline-directed medical therapy.

(Continued)

KEY POINTS *(continued)*

- Cardiac resynchronization therapy is indicated in patients with an ejection fraction less than or equal to 35%, New York Heart Association functional class II to IV heart failure symptoms despite guideline-directed medical therapy, sinus rhythm, and left bundle branch block with a QRS complex of 150 ms or greater.

Assessment of Chronic Heart Failure

Patients with chronic heart failure should be serially assessed for progression of disease in the outpatient setting. Each follow-up visit should include evaluation of current symptoms and functional capacity; assessment of volume status, electrolytes, and kidney function; and review of the patient's medication regimen for adequacy (both appropriate doses and the appropriate medications as heart failure progresses). Of equal or greater importance is repeated patient education, including reminding patients to take their medications as prescribed, measure their weight daily, avoid dietary sodium, watch their fluid intake, and exercise regularly. Patients who appropriately take their medications and avoid sodium and excess fluid intake can greatly improve their functional status.

Sleep disorders frequently occur in patients with heart failure and are often underdiagnosed. Recognizing these disorders and distinguishing between central and obstructive sleep apnea are important for improving quality of life in patients with heart failure and for potentially improving heart failure-related outcomes. Current guidelines support obtaining a formal sleep assessment in patients with symptomatic heart failure (NYHA functional class II-IV) and excessive daytime sleepiness or those who are suspected of having sleep-disordered breathing (see MKSAP 18 Pulmonary and Critical Care Medicine). Treatment with continuous positive airway pressure in patients with obstructive sleep apnea improves sleep quality and reduces the apnea-hypopnea index. In contrast, therapy for central sleep apnea with adaptive servoventilation has been shown to cause harm.

Serial B-Type Natriuretic Peptide Assessment

Measurement of BNP levels is helpful in determining whether dyspnea is related to heart failure or a different cause. For outpatients with chronic heart failure in whom volume status is uncertain on physical examination, BNP level can be useful in diagnosing fluid overload. BNP measurement in patients with stable heart failure also can provide information about prognosis and disease severity. However, serial measurements and treatment based on BNP levels have not been shown to reduce hospitalizations or mortality in patients with heart failure. Currently, BNP measurement should be used to aid in the diagnosis of heart failure and acute volume overload, but it should not be used serially in the inpatient or outpatient setting to guide care.

Echocardiography in Chronic Heart Failure

Echocardiography is the most common method for assessing left ventricular function. For patients with new-onset heart failure, guidelines suggest repeating assessment of left ventricular function after optimization of medical therapy. If the patient's ejection fraction is less than or equal to 35%, the patient may be a candidate for ICD or biventricular pacemaker placement. Current guidelines recommend routine echocardiography every 1 to 2 years in stable patients or when clinical status changes; however, routine echocardiography every 3 to 6 months is not indicated.

Assessing Prognosis

Many prognostic models have been developed to assist in predicting morbidity and mortality in patients with heart failure. These models are usually derived from retrospective analyses of clinical trials or large admission databases. To some extent, the models reflect the unique patient populations enrolled in clinical trials, which tend to have fewer comorbid conditions. Unfortunately, no one tool has been found to be more predictive than the others, and questions remain regarding the utility of these models for the individual patient. It has been suggested that these tools be used in addition to, not in place of, the clinician's judgment for heart failure management.

Clinical indicators associated with worse outcomes in the 1 to 2 years after diagnosis include heart failure hospitalization, poor exercise tolerance, ICD firings, serum sodium level less than 135 mEq/L (135 mmol/L), worsening kidney function, cardiac cachexia, required diuretic doses of more than 1 mg/kg, and symptomatic hypotension necessitating reduction in the dosage of heart failure medications. Heart failure hospitalizations are associated with a mortality rate of 10% to 20% over the next 6 months. In patients with poor prognosis, a frank discussion of advanced therapies, such as LVAD placement or heart transplantation, should occur. For patients who are ineligible for or uninterested in such therapies, end-of-life goals should be discussed, and palliative care or hospice should be considered.

KEY POINTS

- Serial B-type natriuretic peptide measurements should not be used to guide the care of patients with chronic heart failure. **HVC**
- Echocardiography should be performed every 1 to 2 years in stable patients with heart failure or when clinical status changes.

Inpatient Management of Heart Failure

H

Acute Decompensated Heart Failure

Initial management of patients hospitalized for acute decompensated heart failure should focus on identifying the cause of the heart failure exacerbation, determining the patient's

H CONT.

current physiologic state, removing fluid to improve congestion, and optimizing medical therapy before discharge.

Determining the cause of acute heart failure can be challenging. Common causes include fluid overload in the setting of nonadherence to dietary fluid or salt intake recommendations and recurrent ischemia in patients suspected of having ischemic cardiomyopathy. Fluid overload can sometimes be related to an unintentional increase in foods with higher salt content or an inability to tolerate previous levels of fluid and salt intake due to progression of left ventricular dysfunction. Other causes of decompensation include hypertension, concurrent illness, and nonadherence to medication regimens, including but not limited to diuretics. An understanding of the cause of the decompensation may identify opportunities to prevent recurrence.

Patients hospitalized for heart failure should be evaluated for volume overload. Typical symptoms include orthopnea, paroxysmal nocturnal dyspnea, peripheral edema, weight gain, and progressive exertional dyspnea. On physical examination, jugular venous distention is usually present. Patients may have crackles (which are much more likely in acute than chronic heart failure), ascites, or peripheral edema. Perfusion should also be assessed, and patients may be classified as "warm" (adequate perfusion) or "cold" (inadequate perfusion). Signs and symptoms of poor perfusion include cool extremities, a narrow pulse pressure, poor mentation, and worsening kidney function. Intravenous inotropes or other advanced therapies should be considered in patients with signs of poor perfusion to help improve cardiac function.

Diuretic therapy is the principal treatment for patients with decompensated heart failure and fluid overload. A recent study evaluated different strategies for diuresis, including varied diuretic dosages and bolus versus continuous therapy. Administration of high-dose diuretics (2.5 times the outpatient oral daily dosage) was associated with increased diuresis but also transient worsening of kidney function. No differences were observed between bolus and continuous intravenous infusion groups, and length of stay did not differ regardless of the strategy used. Providing effective diuresis is essential and often requires intravenous administration. If the current dosage of loop diuretic is inadequate, increasing the dosage or adding a thiazide diuretic may be considered. Notably, administering low-dose dopamine to improve diuresis and preserve kidney function offers no benefit.

In patients with acute kidney dysfunction at the time of admission, it is still important to treat with diuretic therapy. The most likely cause of the dysfunction is poor kidney perfusion due to vascular congestion, and kidney function will often improve with diuresis. In contrast, withholding ACE inhibitors and aldosterone antagonists may be reasonable until kidney function improves. If a patient receiving diuretic therapy develops worsening kidney function when approaching euvolemia, withholding diuretics for 1 day to allow extravascular fluid to redistribute into the vascular space should be considered. Once euvolemia has been achieved, creatinine often also increases, which may indicate decongestion.

Standard heart failure therapy, including ACE inhibitor or ARB therapy, β-blockers, and aldosterone antagonists, should either be maintained throughout hospitalization or be restarted before discharge. If β-blockers are discontinued upon admission because of signs of low cardiac output, therapy should not be reinitiated until the patient nears euvolemia. If the patient is admitted with volume overload without signs of low cardiac output, β-blocker therapy can usually be maintained at the same or a lower dosage during hospitalization.

BNP level should be measured upon admission and before discharge for prognostic purposes because high levels are linked with increased mortality and rehospitalization. Likewise, patients with BNP levels that fail to decrease during an admission have a higher mortality rate. Serum troponin measurement upon admission can also be used for prognostication; patients with elevated troponin levels have worse clinical outcomes and a higher risk for death. Currently, there are no absolute cutoff values for these biomarkers, and measurement data should be used in combination with clinical judgment in advising the patient with heart failure.

Cardiogenic Shock

Cardiogenic shock is characterized by signs and symptoms of low cardiac output and end-organ compromise, with acute worsening of kidney and liver function. Patients with cardiogenic shock often require intravenous inotropic agents to improve hemodynamic status, including increasing cardiac output and urine output (**Table 15**). Routine use of invasive pulmonary artery catheterization to monitor hemodynamics does not improve survival or reduce future hospitalization in patients with decompensated heart failure. Therefore, pulmonary artery, or "right heart," catheterization should be used only when hemodynamic and volume status is not evident from physical examination findings or other noninvasive tests, or when hemodynamic data may lead to advanced mechanical circulatory support or consideration of heart transplantation.

The use of percutaneous mechanical support during acute exacerbation has greatly increased in the past few years. Intra-aortic balloon pumps, percutaneous ventricular assist devices, and extracorporeal membrane oxygenators can be quickly placed to support the critically ill patient. Treatment by a team composed of a heart failure physician, critical care physician, and cardiac surgeon is suggested to rapidly deploy therapy and care for the patient in the following days. Decisions regarding longer-term options for advanced heart failure (heart transplantation or permanent or "destination" LVAD) are an important aspect in the use of mechanical support in the acute setting. In patients who do not show clinical improvement, there should be daily discussions about treatment options and goals of care, including

TABLE 15. Intravenous Vasoactive Medications Used for Treatment of Cardiogenic Shock

Medication	Mechanism	Inotropy	Vasodilation
Milrinone	Phosphodiesterase inhibition	++	+
Dobutamine	β_1, β_2 Receptor agonism	++	(+) (at low dose) – (vasoconstriction, at high dose)
Nesiritide	Natriuretic peptide receptor agonism	0	++
Sodium nitroprusside	Nitric oxide production	0	++
Nitroglycerin	Nitric oxide production	0	++ (mainly venous)
Vasopressin	Arginine vasopressin receptor (V receptor) agonism	–	– (vasoconstriction)
Dopamine	Dopaminergic receptor (D receptor) agonism β_1 Receptor agonism at intermediate dose α_1 Receptor agonism at high dose	+	– (vasoconstriction, at high dose)
Norepinephrine	α_1, α_2 Receptor agonism greater than β_1 receptor agonism	+	– (vasoconstriction)

Strength of effect: ++ indicates very strong; + indicates strong; (+) indicates weak; 0 indicates neutral; – indicates opposite effect.

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transplantation, permanent device placement, or palliative care or hospice.

Strategies to Prevent Readmission

The first step in preventing heart failure readmission is to treat any reversible causes of the exacerbation. Medication reconciliation before discharge should ensure that the patient is taking the appropriate medications, particularly those that reduce mortality and morbidity in heart failure. Patients should not be discharged until they have achieved euvolemia with diuresis. Patients should be educated on heart failure physiology, the importance of medication and dietary adherence, signs and symptoms of worsening heart failure, and when to contact a physician. Finally, an early follow-up appointment (within 7 days) should be scheduled to review the medication list, assess the patient's volume status and adherence to diet and medications, and reinforce patient education points. H

KEY POINTS

- Management of patients with acute decompensated heart failure focuses on identifying the cause of the heart failure exacerbation, determining the patient's current physiologic state, treating fluid overload, and optimizing medical therapy before discharge.
- In patients hospitalized with acute heart failure, scheduling an early follow-up appointment (within 7 days) to review the medication list, assess the patient's volume status and adherence to diet and medications, and reinforce patient education points reduces the risk for heart failure readmission.
- HVC Routine invasive pulmonary artery catheterization for hemodynamic monitoring is not recommended in patients with decompensated heart failure.

Advanced Refractory Heart Failure

Once heart failure has progressed to ACC/AHA stage D, characterized by persistent severe symptoms despite maximum therapy, advanced treatments should be considered. Cardiac transplantation remains the gold standard therapy for patients with end-stage heart failure. Unfortunately, because of a lack of appropriate donors, fewer than 3000 heart transplantations are performed in the United States each year. Indications for transplantation generally include age younger than 65 to 70 years, no medical contraindications (such as diabetes with end-organ complications, malignancies within 5 years, kidney dysfunction, or other chronic illnesses that will decrease survival), and good social support and adherence. The use of an LVAD as "destination therapy" should be considered for patients who are not transplant candidates. Many patients awaiting transplant also require an LVAD for support until an organ becomes available. Hospice may be considered as an option in shared decision-making discussions.

Mechanical Circulatory Support

In the past 10 years, clinical outcomes of patients with advanced heart failure have markedly improved with the use of LVADs. With newer continuous-flow devices, patients have 1-year survival approximating that of cardiac transplant recipients and substantial improvements in functional capacity and quality of life. Because these devices provide continuous flow, most patients no longer have a palpable pulse, and blood pressure must be measured by Doppler. Typical therapy includes anticoagulation to prevent pump thrombus formation, continued heart failure therapy with ACE inhibitors (or ARBs) and β-blockers, and management of fluid overload with diuretics.

LVADs are associated with important complications related to both the driveline, which passes through the skin and connects the internal pump to a power source, and the

pump itself. Major complications include hemorrhagic and thrombotic strokes; skin infections; pump thrombosis; and gastrointestinal bleeding, which is usually associated with small bowel arteriovenous malformations. Despite these complications, LVADs have been associated with survival of more than 10 years in some patients.

Management of Posttransplant Patients

Most patients who undergo heart transplantation quickly recover physical activity and have normal quality of life, with a mean survival of more than 11 years. The most frequent complication within the first year after transplant is infection. Cytomegalovirus (CMV) infection is common, and patients at moderate risk (CMV-positive donor/CMV-positive recipient) and high risk (CMV-positive donor/CMV-negative recipient) often receive antiviral prophylaxis for 6 months. Incidence of rejection is highest in the first 6 months after transplantation. Because most patients with rejection are asymptomatic, regularly scheduled endomyocardial biopsies are often performed to detect rejection for the first few years after transplant. Severe rejection is characterized by signs of acute heart failure and atrial arrhythmias (typically atrial flutter) or conduction abnormalities. Early complications related to immunosuppressive therapy include hypertension (more than 90% of patients) and diabetes (15%-20% of patients). Long-term complications after transplantation include CAD and an increased incidence of malignancies, including skin cancer (common) and B-cell lymphoma related to immunosuppressive therapy (less common).

When new drugs are added to a transplant patient's medication regimen, careful attention is essential to avoid drug-drug interactions. Cyclosporine and tacrolimus, two agents commonly used for immunosuppression, are metabolized by the CYP3A4 system. Many drugs increase or decrease the metabolism of cyclosporine and tacrolimus, and conversely, these agents may alter the metabolism of other drugs. An extensive list of drugs that can interact through the CYP3A4 isoenzyme can be found at medicine.iupui.edu/clinpharm/ddis.

KEY POINTS

- Patients with severe heart failure symptoms despite maximal medical therapy are candidates for advanced treatment, including placement of a left ventricular assist device and heart transplantation.
- Cardiac transplantation is the gold standard therapy for patients with end-stage heart failure.
- Endomyocardial biopsy should be routinely performed after heart transplantation to diagnose rejection.

Specific Cardiomyopathies

For a discussion of hypertrophic cardiomyopathy and restrictive cardiomyopathy, refer to Myocardial Disease. Peripartum cardiomyopathy is discussed in Pregnancy and Cardiovascular Disease.

Takotsubo Cardiomyopathy

Takotsubo cardiomyopathy, also known as stress cardiomyopathy or apical ballooning syndrome, is a clinical syndrome associated with reduced ejection fraction, elevated cardiac enzyme levels, and signs of ischemia on electrocardiography. It typically occurs in older women and is usually precipitated by a stressful physical or emotional event, such as the death of a loved one, sudden surprise, or other acute stressors. The exact mechanism of takotsubo cardiomyopathy is unknown, but the condition is postulated to result from a reversible toxic effect of very high catecholamine levels on the myocardium. On cardiac imaging, wall motion abnormalities that do not follow a coronary artery territory (typically, apical dyskinesis or ballooning) are often found with preservation of basal wall motion. Because these acute events often resemble an acute coronary syndrome, emergent coronary angiography is often performed and demonstrates nonobstructive CAD. Treatment is largely supportive and is similar to that for other heart failure syndromes (diuretics, ACE inhibitors, β-blockers). Most patients will recover cardiac function over the course of a few weeks to months. As with other forms of new-onset heart failure, repeat echocardiography should be performed in 3 to 6 months to evaluate recovery. If a patient has recovery of function, it is unclear for how long medical therapy should be continued, but most clinicians continue therapy for at least 1 year.

Acute Myocarditis

Myocarditis is a clinical syndrome of acute-onset heart failure. Causes include viral, bacterial, or other infections; toxins; and immunologic syndromes. The classic form is viral in origin and is usually preceded by a typical upper respiratory tract infection caused by adenovirus, echovirus, or coxsackievirus. Although the pathogenesis is not completely understood, it is thought that acute viral infection causes early destruction of the myocytes, followed by an immune response that causes further destruction.

Clinically, patients may be asymptomatic or have a viral prodrome with fever, myalgia, and muscle soreness. Patients may also present with acute heart failure symptoms. Echocardiography is useful to assess for other causes of heart failure. Definitive diagnosis may require cardiac magnetic resonance imaging or endomyocardial biopsy. Anti-inflammatory agents are not of benefit in the treatment of acute myocarditis. Standard therapy for heart failure is recommended. Prognosis depends on the clinical presentation.

Giant Cell Myocarditis

Giant cell myocarditis is an acute and frequently fatal form of myocarditis that typically occurs in younger persons. It is often rapidly progressive and can cause both left and right ventricular dysfunction. Giant cell myocarditis is also associated with

an increased incidence of high-grade atrioventricular block and ventricular arrhythmias. Unlike in acute myocarditis, aggressive immunosuppressive therapy has some benefit and should be initiated in these patients. For this reason, patients with acute heart failure unresponsive to usual care or with accompanying arrhythmias should undergo endomyocardial biopsy for diagnosis. Initial biopsy findings may be negative because of the patchy nature of the inflammation. Patients with giant cell myocarditis often require percutaneous or surgical ventricular support until they recover or need heart transplantation or LVAD placement. If giant cell myocarditis is suspected, prompt transfer to a hospital equipped with mechanical support should be considered because patients can progress from feeling well to moribund within hours.

Tachycardia-Mediated Cardiomyopathy

Tachycardia-mediated cardiomyopathy has been associated with both supraventricular and ventricular arrhythmias. Reversible causes of tachycardia, such as hyperthyroidism, should be ruled out. Importantly, heart rate control improves left ventricular function in these patients. The primary treatments are medications, such as β-blockers, and catheter-directed ablation. In patients with atrial fibrillation associated with rapid ventricular response, there is no evidence that converting to sinus rhythm is more efficacious than controlling the heart rate. In patients with ventricular arrhythmias or frequent premature ventricular contractions, cardiomyopathy is generally thought to develop when the burden of premature ventricular contractions is more than 10,000/day; ablation, especially if the premature ventricular contractions are unifocal, should be considered.

Arrhythmias

Introduction

Arrhythmias are traditionally categorized as supraventricular or ventricular based upon simple electrocardiographic (ECG) findings. Supraventricular arrhythmias originate from the atrium or atrioventricular (AV) node and are characterized by normal-appearing QRS complexes unless complicated by an aberrant ventricular condition. Ventricular arrhythmias originate below the AV node and are characterized by abnormal-appearing and prolonged QRS complexes. Disruptions in rhythm and rate occur in seven basic patterns: early beats, bigeminal beats, grouped beats, pauses, bradycardia, tachycardia, and chaotic rhythms. This section provides an approach to bradycardia and tachycardia and discusses the diagnosis and management of specific rhythm disorders.

Approach to Bradycardia

Clinical Presentation and Evaluation

Bradycardia (heart rate <60/min) may be asymptomatic or associated with symptoms of lightheadedness, syncope, exertional intolerance, dyspnea, and fatigue. It can result from disease in the sinus node, AV node, or His-Purkinje system, or from dysfunction of the autonomic system.

Diagnostic evaluation consists of a thorough history, physical examination, focused laboratory testing (electrolyte levels, thyroid function testing), and resting 12-lead ECG. It is important to identify severe or unstable conduction abnormalities that require urgent intervention. The evaluation should also include investigation for extrinsic and reversible causes of bradycardia, including ischemia, myocarditis, endocarditis, hypothyroidism, electrolyte disturbances, and medication use (especially β-blockers and digoxin). Clues from the history and physical examination may suggest Lyme disease, elevated intracranial pressure, or typhoid as other potential causes of bradycardia. Additional testing may include exercise treadmill testing to assess chronotropic competence and ambulatory ECG monitoring (see Diagnostic Testing in Cardiology).

Sinus Bradycardia

Sinus bradycardia is defined as the presence of sinus rhythm with a heart rate below 60/min. Sinus bradycardia may be appropriate in trained athletes and during sleep. Inappropriate or pathologic sinus bradycardia is most commonly caused by sinus node dysfunction due to age-related myocardial fibrosis. Less commonly, sinus node dysfunction may result from right coronary ischemia; intracranial hypertension; postoperative scarring or fibrosis from cardiothoracic surgery; or infiltrative or inflammatory disorders, such as sarcoidosis. The most common extrinsic cause is medication use.

Atrioventricular Block

AV block may be classified as first degree, second degree, or third degree. First-degree AV block is defined by a delay in AV conduction (PR interval >200 ms). In large cohort studies, first-degree AV block has been associated with an increased risk for atrial fibrillation and all-cause mortality.

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In second-degree AV block, only some P waves conduct to the ventricles. Mobitz type 1 second-degree (Wenckebach) AV block is characterized electrocardiographically by a PR interval that progressively prolongs until a beat is dropped (**Figure 10**). Mobitz type 2 second-degree AV block is typified by ECG findings of grouped beating and progressive shortening of the RR intervals (**Figure 11**). The PR interval does not lengthen in Mobitz type 2 before nonconducted atrial beats. When 2:1 block is present, the Mobitz type cannot be determined. Mobitz type 2 AV block usually occurs below the AV node and has a higher risk for progression to complete heart block.

In third-degree AV block, also termed complete heart block, no P waves conduct to the ventricles. AV dissociation is observed on the ECG (**Figure 12**).

Treatment

In patients with symptomatic bradycardia and hemodynamic distress, atropine should be administered. If atropine is

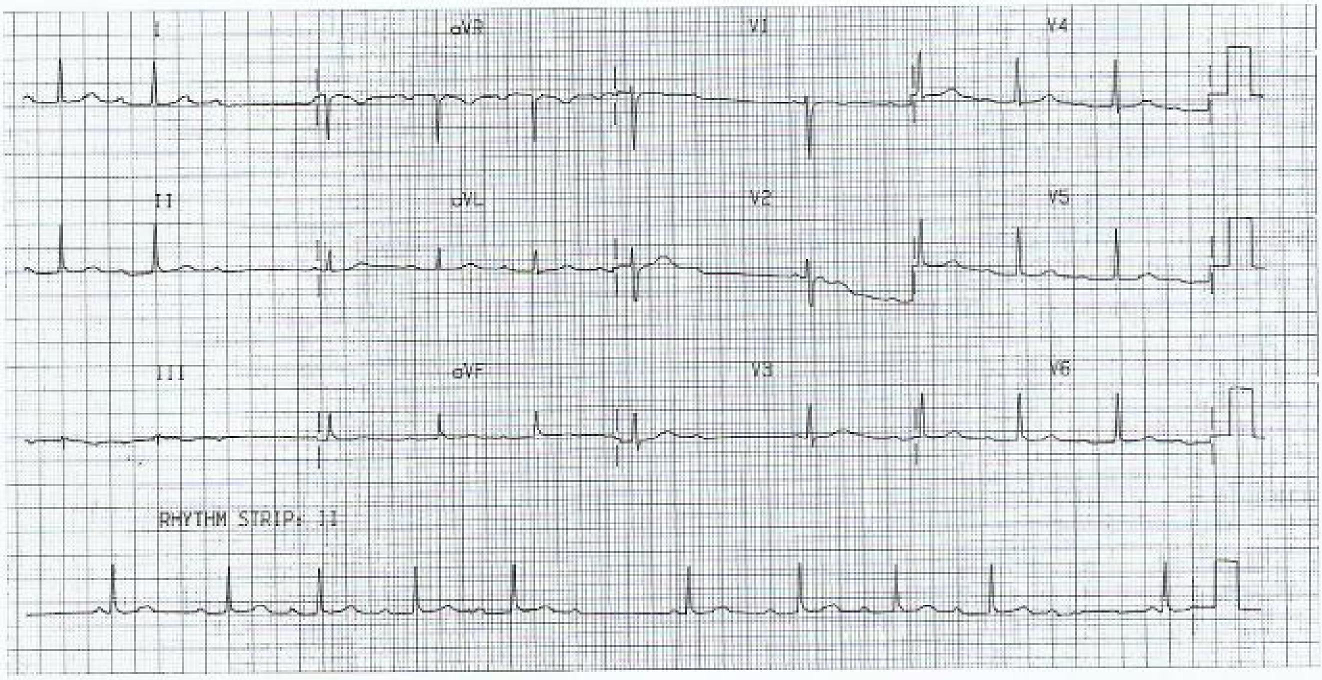

FIGURE 10. Electrocardiogram showing Mobitz type 1 second-degree atrioventricular block (Wenckebach block), which manifests as a progressive prolongation of the PR interval until there is a dropped ventricular beat.

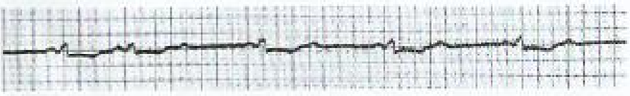

FIGURE 11. Electrocardiogram showing Mobitz type 2 second-degree atrioventricular block. P waves are blocked intermittently, and the PR interval is fixed. Note the wide QRS complexes, which are also more consistent with block below the compact atrioventricular node.

H CONT.

ineffective, dopamine or epinephrine infusions can be given until transcutaneous pacing or a temporary pacing wire (preferred) can be placed. Temporary pacing is indicated in cases of hemodynamically unstable bradycardia or asystole. In some unique circumstances, prophylactic temporary pacing may be considered, including in patients undergoing transcatheter aortic valve replacement with high-risk features for heart block (such as right bundle branch block).

In hemodynamically stable patients, reversible and extrinsic causes of bradycardia should always be addressed before more invasive measures, such as permanent pacing, are considered. Common indications for permanent pacing include the following:

- Symptomatic bradycardia without reversible cause
- Asymptomatic bradycardia with significant pauses (>3 seconds in sinus rhythm) or heart rate less than 40/min
- Atrial fibrillation with pauses of 5 seconds or longer
- Alternating bundle branch block
- Asymptomatic complete heart block or Mobitz type 2 second-degree AV block

The various types of implanted cardiac electronic devices, their functions, and their general indications are reviewed in **Table 16**. Patients with left bundle branch block or right bundle branch block with or without a prolonged PR interval do not require permanent pacing because intraventricular conduction delays have a low risk for progressing to complete heart block (1%-3% per year). H

KEY POINT

- Permanent pacing is indicated for symptomatic bradycardia with no underlying reversible cause and in asymptomatic patients who have atrioventricular and infranodal conduction disturbances that have a high risk for progressing to complete heart block or asystole.

Approach to the Patient with Tachycardia

Clinical Presentation and Evaluation

Patients with tachycardia (heart rate >100/min) may be asymptomatic or experience tachypalpitations, a sensation of skipped beats, lightheadedness or dizziness, chest discomfort, dyspnea, exertional intolerance, fatigue, progressive heart failure, near-syncope, or syncope. In asymptomatic patients, tachycardia may be discovered incidentally during routine ECG, monitoring in the setting of hospitalization, or other medical care.

ECG documentation of tachycardia and correlation with symptoms is the key component of the diagnostic evaluation.

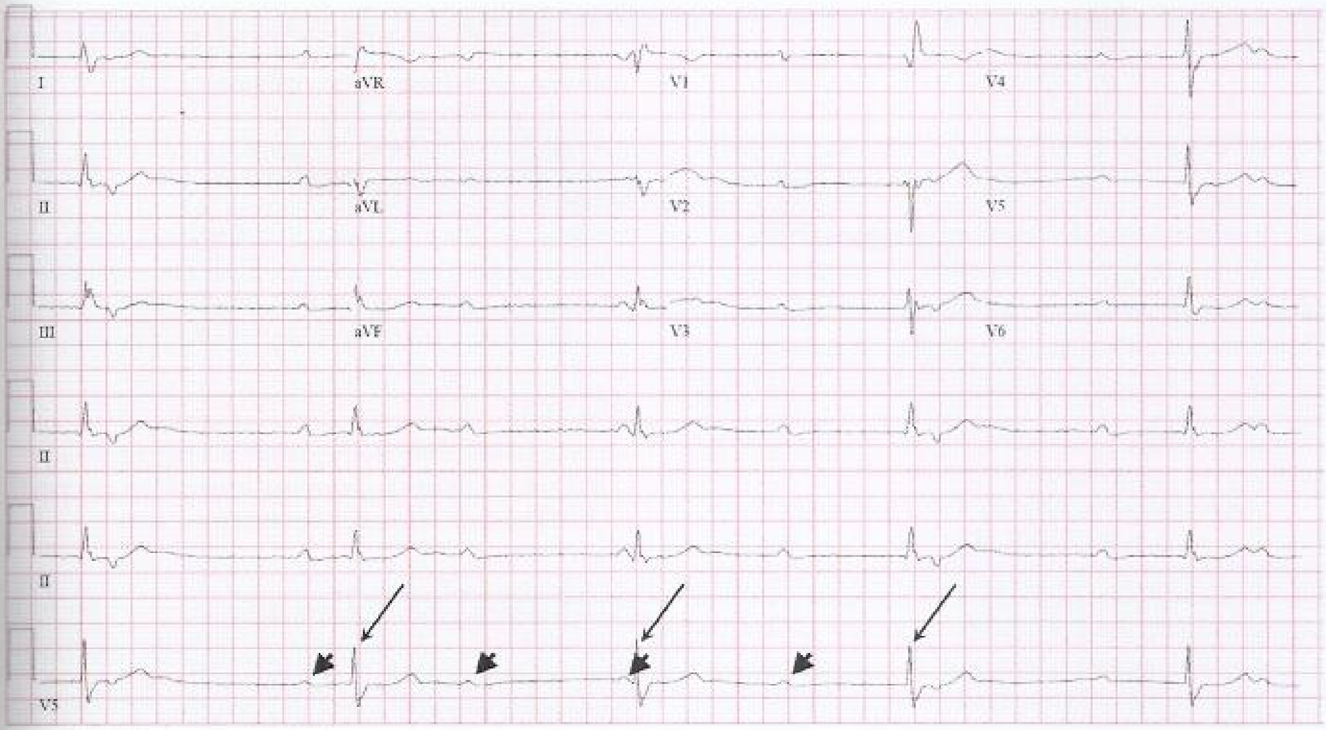

FIGURE 12. In this electrocardiogram, the P waves (*short arrows*) and the QRS complexes (*long arrows*) are not associated with each other, indicating the presence of complete heart block.

TABLE 16. Cardiac Implantable Electronic Devices for Treatment of Cardiac Rhythm Disorders

			Functions		
Device	**Components**	**Indications**	**Pacemaker Function**	**Antitachycardia Pacing**	**Defibrillation**
Transvenous pacemaker	Pulse generator and intravascular leads (single- or dual-chamber)	Sinus node dysfunction, atrioventricular block, nonreversible symptomatic bradycardia	Yes	No	No
Leadless pacemaker	Pulse generator with tines implanted directly into the cardiac chamber; no leads	Atrial fibrillation with bradycardia, paroxysmal sinus node dysfunction (e.g., brief sinus pauses)	Yes (ventricular sensing and pacing only)	No	No
Implantable cardioverter-defibrillator	Defibrillator and intravascular leads (single- or dual-chamber)	Monitoring and treatment of ventricular arrhythmias	Yes	Yes	Yes
Subcutaneous implantable cardioverter-defibrillator	Defibrillator and a single lead that are entirely under the skin (extravascular); no transvenous leads	Monitoring and treatment of ventricular arrhythmias	No	No	Yes
Cardiac resynchronization therapy-pacing (CRT-P)	Pulse generator and intravascular leads, including a pacing lead in the coronary sinus to pace the left ventricle	Restoring electrical synchrony in patients with symptomatic heart failure (left ventricular ejection fraction ≤35% and left bundle branch block)	Yes	No	No
Cardiac resynchronization therapy-defibrillator (CRT-D)	Defibrillator and intravascular leads, including a pacing lead in the coronary sinus to pace the left ventricle	Restoring electrical synchrony between the ventricles in patients with heart failure; monitoring and treating ventricular arrhythmias	Yes	Yes	Yes

After a thorough history and physical examination, a 12-lead ECG should be obtained in all patients with stable tachycardia. A 12-lead ECG recorded during symptoms, although often not possible to obtain, is far superior to most forms of ambulatory monitoring in terms of diagnostic value (see Diagnostic Testing in Cardiology for strategies for selecting an appropriate monitoring device). Thyroid function testing and echocardiography may be considered in selected patients with tachycardia.

Sinus Tachycardia

Sinus tachycardia (sinus rhythm with a heart rate >100/min) is the most common tachycardia and is typically the result of physiologic demand or distress, including exercise, pain, fever, anemia, or anxiety. Diagnostic evaluation and treatment are guided by the underlying cause.

Inappropriate sinus tachycardia (IST) is a disorder characterized by an elevated resting heart rate, with exaggerated increases in heart rate with light activity. The sinus rate typically decreases during sleep, which can be documented with ambulatory ECG monitoring. IST frequently presents in women in their second to fourth decades and appears to be more common in health care professionals. Symptoms vary and can include palpitations, lightheadedness, syncope (or near-syncope), dyspnea, and fatigue. The diagnosis of IST is based on the exclusion of other causes of tachycardia, such as hyperthyroidism, anemia, pheochromocytoma, and structural heart disease. First-line therapy is removal of aggravating factors and exercise therapy. In patients with bothersome and persistent symptoms, pharmacologic therapy with β-blockers, calcium channel blockers, or ivabradine (in refractory cases) can be considered.

Postural orthostatic tachycardia syndrome (POTS) is another condition that often presents with tachycardia. POTS is a form of dysautonomia characterized by orthostatic intolerance and excessive tachycardia, particularly with standing. Diagnostic criteria for POTS include an increase in heart rate of 30/min or more, or an increase to greater than 120/min, within 10 minutes of standing. The diagnosis is often confirmed with tilt-table testing. Behavioral modification, compression stockings, exercise training, and increased fluid intake are important components of therapy. Medical therapy for POTS is highly variable and may include, but is not limited to, β-blockers, fludrocortisone, selective serotonin reuptake inhibitors, midodrine, and pyridostigmine.

Supraventricular Tachycardias

Paroxysmal supraventricular tachycardias (SVTs), including atrioventricular nodal reentrant tachycardia (AVNRT), accessory pathway–mediated tachycardias, and atrial tachycardia, are frequently the cause of palpitations in younger persons. The accessory pathway may result from anterograde conduction, manifesting as a delta wave on ECG or retrograde conduction (so-called concealed accessory pathway). Management of these arrhythmias is discussed later in this chapter.

Other Tachycardias

Older patients with palpitations are more likely to have atrial fibrillation, atrial flutter, or ventricular tachycardia (VT), often due to underlying cardiovascular disease. VT is often associated with hemodynamic compromise; however, some VT can be well tolerated, particularly in patients with normal ventricular function. Evidence of hemodynamic compromise, including syncope, may also be present in patients with atrial tachyarrhythmias. For further discussion of the clinical presentation and management of these conditions, refer to the Atrial Fibrillation, Atrial Flutter, and Ventricular Arrhythmias sections later in the chapter.

KEY POINT

- Sinus tachycardia is the most common tachycardia and is typically the result of physiologic demand or distress, including exercise, pain, fever, anemia, or anxiety.

Antiarrhythmic Drugs

Antiarrhythmic agents are used to treat and suppress arrhythmias. These medications have traditionally been organized according to primary mechanism of action by using the Vaughan-Williams classification system (**Table 17**); however, most antiarrhythmic drugs exert their effects through several mechanisms.

Class I and class III antiarrhythmic drugs are the most effective antiarrhythmic drugs. Class IA agents are indicated for specific conditions (see Table 17). These medications have been associated with ventricular proarrhythmia, sudden death, and increased mortality in patients with coronary artery disease or structural heart disease. Class II agents (β-blockers) and class IV agents (nondihydropyridine calcium channel blockers) are commonly used to inhibit arrhythmia induction and AV conduction in patients with supraventricular or atrial arrhythmias. Class III agents sotalol and dofetilide are used to treat atrial and ventricular arrhythmias. Class III antiarrhythmic therapy should be initiated in an in-patient setting, with regular assessment of the corrected QT (QTc) interval. Ibutilide is an intravenous class III potassium channel blocker that is used for pharmacologic cardioversion of atrial fibrillation.

Amiodarone is among the most effective and commonly used antiarrhythmic drugs. This multichannel blocker is frequently used to treat patients with recurrent VT or atrial fibrillation. Amiodarone has no significant risk for proarrhythmia but is associated with thyroid, liver, lung, and eye toxicities, as well as neurologic side effects. Monitoring thyroid and liver function every 6 months is recommended in patients receiving amiodarone. Patients should also undergo annual pulmonary function testing and ophthalmologic examination. Amiodarone interacts with many drugs, including warfarin, statins, and digoxin. Dronedarone, another multichannel blocker, can be used in patients with intermittent atrial fibrillation and no overt heart failure.

TABLE 17. Antiarrhythmic Medications

Classification	Mechanism of Action	Individual Agents/ Examples	Effects	Use	Side Effects	Contraindications
Class IA	Sodium channel blockade with some potassium channel blockade	Quinidine, procainamide, disopyramide	Decreases speed of depolarization and prolongs repolarization	Preexcited atrial fibrillation (procainamide), Brugada syndrome (quinidine), SVT, atrial fibrillation, ventricular arrhythmias	Anticholinergic effects, including increased heart rate, dry mouth, urinary retention, blurry vision, and constipation Lupus-like syndrome (procainamide)	Ischemic or structural heart disease, second- or third-degree AV block without a pacemaker, prolonged QT interval, advanced kidney impairment
Class IB	Sodium channel blockade	Lidocaine, mexiletine, phenytoin	Decreases speed of depolarization	Ventricular arrhythmias	Headache, dizziness, or other neurologic symptoms Seizures (lidocaine toxicity)	Advanced liver disease
Class IC	Sodium channel blockade	Flecainide, propafenone	Decreases speed of depolarization and shortens repolarization	Atrial fibrillation, SVT, ventricular arrhythmias	Headache, dizziness, or other neurologic symptoms	Ischemic or structural heart disease, sinus node dysfunction, second- or third-degree AV block or bundle branch disease without a pacemaker
Class II	β-Adrenergic blockade	Metoprolol, propranolol, carvedilol, atenolol, bisoprolol	Decreases sympathetic tone; suppresses automaticity, sinoatrial conduction, and AV conduction	Rate control of atrial arrhythmias, SVT, ventricular arrhythmias	Fatigue, drowsiness, dizziness, hair loss, cold hands and feet, depression, erectile dysfunction, bronchospasm	Severe asthma, cardiogenic shock, second- or third-degree AV block, preexcitation
Class III	Potassium channel blockade	Sotalol, dofetilide, ibutilide	Prolongs action potential duration	Atrial fibrillation, atrial flutter, ventricular arrhythmias, pharmacologic cardioversion of atrial fibrillation (ibutilide)	Headache, dizziness, bradycardia, fatigue, dyspnea (sotalol) Headache, dizziness, diarrhea; rarely, torsades de pointes (dofetilide)	CrCl <40 mL/min/1.73 m^2, QTc interval >440 ms, sinus bradycardia <50/min, second- or third-degree AV block without a pacemaker
Class IV	Calcium channel blockade (nondihydropyridines)	Verapamil, diltiazem	Suppresses sinoatrial and AV conduction	SVT, rate control of atrial arrhythmias, triggered arrhythmias (outflow tract VTs)	Dizziness, constipation, dependent edema, nausea	Significant sinus node dysfunction, second- or third-degree AV block without a pacemaker, preexcitation
Multichannel blockers	Several mechanisms, including potassium, sodium, and calcium channel blockade	Amiodarone, dronedarone	Multiple mechanisms, although they act principally by extending repolarization	Atrial arrhythmias, ventricular arrhythmias	Fatigue, dizziness, nausea, vomiting, constipation or diarrhea, tremor	Advanced liver, lung, or thyroid disease (amiodarone) Advanced liver disease, permanent atrial fibrillation, recent decompensated or advanced heart failure (NYHA functional class III-IV) (dronedarone)

(Continued on the next page)

TABLE 17. Antiarrhythmic Medications *(Continued)*

Classification	Mechanism of Action	Individual Agents/ Examples	Effects	Use	Side Effects	Contraindications
Late sodium channel blockers	Late sodium channel blockade	Ranolazine	Shortens action potential duration and prevents calcium overload	Atrial fibrillation, ventricular arrhythmias	Dizziness, nausea, headache, constipation, hypoglycemia	Advanced liver disease, use of strong CYP3A4 inhibitors or inducers
Adenosine receptor agonists	A_1-receptor agonism	Adenosine	Slows or blocks sinoatrial and AV node conduction	Termination of SVT	Flushing, dyspnea, chest pain, hypotension, dizziness, nausea	Severe asthma, cardiac transplantation
Cardiac glycoside	Increases vagal activity	Digoxin	Slows AV node conduction	Rate control of atrial fibrillation	Nausea, vomiting, dizziness, blurry vision and yellow halos, thrombocytopenia	Advanced kidney impairment (requires dose adjustment)

AV = atrioventricular; CrCl = creatinine clearance; CYP3A4 = cytochrome P450 3A4; NYHA = New York Heart Association; QTc = corrected QT; SVT = supraventricular tachycardia; VT = ventricular tachycardia.

Ranolazine, digoxin, and adenosine are excluded from the Vaughan-Williams classification. Ranolazine is used to treat angina and decreases the risk for atrial fibrillation and ventricular arrhythmias. Digoxin is a positive inotropic agent that also increases vagal activity, leading to a lower resting heart rate. It can be used for rate control in patients with atrial fibrillation. Adenosine is used in the acute treatment of arrhythmias to interrupt AV conduction and terminate SVT. Administering adenosine can also help in determining the type of arrhythmia.

Atrial Fibrillation

Atrial fibrillation is defined by the presence of disorganized atrial activity with an irregularly irregular ventricular response on ECG (**Figure 13**). It is the most common

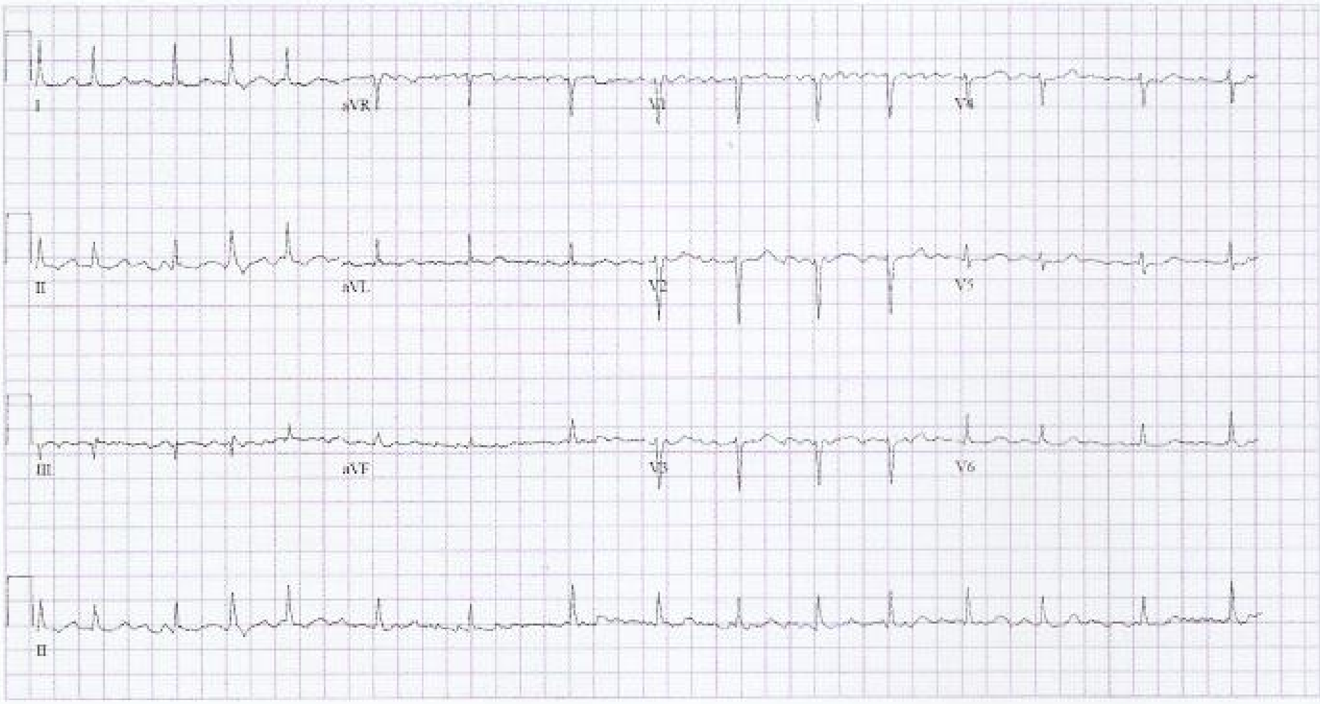

FIGURE 13. Electrocardiogram demonstrating atrial fibrillation. No clear P waves are seen, and the ventricular response is irregular.

sustained arrhythmia, affecting more than 33 million persons worldwide. Lifetime risk for atrial fibrillation is 25% in patients older than 40 years. Incidence is strongly associated with and increases with age. Accordingly, atrial fibrillation is particularly common in the elderly, occurring in 10% of persons older than 80 years. Atrial fibrillation is associated with an increased risk for adverse cardiac events, including a five-fold increased risk for stroke, as well as increased risk for heart failure and dementia. Among patients aged 55 years and older who have a cryptogenic ischemic neurologic event, such as a stroke or transient ischemic attack, occult intermittent atrial fibrillation is thought to be present in up to 25% of cases, and 30-day ambulatory ECG monitoring is indicated for detection.

Atrial fibrillation is usually the result of long-standing risk factors, such as diabetes mellitus, obesity, hypertension, coronary artery disease, heart failure, and obstructive sleep apnea. It may also be caused by reversible or acute physiologic insults, including cardiac surgery, pulmonary embolism, or hyperthyroidism. When there are no identified risk factors, a predisposing genetic background is often present.

Clinical Presentation

H Patients with atrial fibrillation may be asymptomatic or experience palpitations, lightheadedness or dizziness, dyspnea, exercise intolerance, chest pain, near-syncope, or, rarely, syncope. In some cases, atrial fibrillation can lead to hemodynamic compromise, especially in patients with advanced diastolic dysfunction or restrictive cardiomyopathy. Patients with atrial fibrillation uncommonly present with tachycardia-induced cardiomyopathy, characterized by asymptomatic left ventricular dysfunction or overt heart failure. H

Atrial fibrillation is categorized according to its duration. Paroxysmal atrial fibrillation stops spontaneously within 7 days of onset, whereas persistent atrial fibrillation lasts for 7 days or more. Long-standing persistent atrial fibrillation is continuous, with a duration of more than 1 year.

Acute Management

H Immediate cardioversion is indicated in patients with hypotension, acute myocardial ischemia, or decompensated heart failure. R wave synchronization during cardioversion is necessary to avoid an "R-on-T" event and provocation of ventricular fibrillation (VF). H

In stable patients, the primary goals of therapy are to prevent stroke, control heart rate, and minimize or eliminate symptoms. Upon diagnosis, reversible causes must be ruled out. All patients should undergo thyroid function testing to evaluate for hyperthyroidism. Patients with risk factors for or symptoms suggestive of sleep apnea should undergo testing (see MKSAP 18 Pulmonary and Critical Care Medicine). Echocardiography is indicated to evaluate for potential valvular or other structural heart disease. Echocardiography can also be used to assess left atrial size, which helps determine the severity of the underlying atrial myocardial dysfunction. Transesophageal echocardiography is often used before elective (nonemergent) cardioversion to exclude the presence of left atrial thrombus or left atrial appendage thrombus if the patient has not received adequate anticoagulation therapy (3 weeks' duration) before the procedure.

Anticoagulation

H In patients who are not undergoing cardioversion, intravenous anticoagulation is usually unnecessary; however, oral anticoagulation should be initiated if the patient has sufficient risk factors for stroke. The most common method of assessing stroke risk in nonvalvular atrial fibrillation is by calculating the CHA_2DS_2-VASc score (**Table 18**). Patients with valvular atrial fibrillation (mechanical prosthesis or rheumatic mitral stenosis) require oral anticoagulation regardless of the presence or absence of other risk factors.

If cardioversion is planned, the duration of atrial fibrillation guides therapy. Patients with atrial fibrillation with a known duration of less than 48 hours have a low risk for thrombus formation and subsequent stroke, and preprocedural anticoagulation is not needed. In patients in whom the duration of atrial fibrillation is unclear or in whom atrial fibrillation has lasted longer than 48 hours, anticoagulation therapy for 3 weeks is required before cardioversion. In the absence of preprocedural anticoagulation, transesophageal echocardiography can be performed to exclude the presence of

TABLE 18. CHA_2DS_2-VASc Score, Adjusted Stroke Rates, and Antithrombotic Therapy Recommendations

CHA_2DS_2-VASc Score[a]	Incidence of Ischemic Stroke/100 Patient-Years[b]	Antithrombotic Therapy[c]
0	0.2	None
1	0.6	None or aspirin or OAC
2	2.2	OAC
3	3.2	OAC
4	4.8	OAC
5	7.2	OAC
6+	10.3	OAC

OAC = oral anticoagulation.

[a]CHA_2DS_2-VASc scoring (maximum 9 points): One point each is given for heart failure, hypertension, diabetes mellitus, vascular disease (prior myocardial infarction, peripheral artery disease, aortic plaque), female sex, and age 65 to 74 years. Two points each are given for previous stroke/transient ischemic attack/thromboembolic disease and age ≥75 years.

[b]Data from Friberg L, Rosenqvist M, Lip GY. Evaluation of risk stratification schemes for ischaemic stroke and bleeding in 182 678 patients with atrial fibrillation: the Swedish Atrial Fibrillation cohort study. Eur Heart J. 2012;33:1500-10. [PMID: 22246443] doi:10.1093/eurheartj/ehr488

[c]Recommendations from January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC Jr, et al; ACC/AHA Task Force Members. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. Circulation. 2014;130:e199-267. [PMID: 24682347] doi:10.1161/CIR.0000000000000041

H CONT. left atrial appendage thrombus and facilitate urgent cardioversion. Regardless of the duration or nature of atrial fibrillation, all patients who undergo cardioversion must receive anticoagulation therapy for at least 4 weeks following the procedure owing to an increased risk for thromboembolic events after sinus rhythm is restored. H

Cardioversion and Rate Control

Pharmacologic or electrical cardioversion should be pursued in patients with significant symptoms despite rate control. In patients without structural heart disease, class IC agents or ibutilide can be considered for pharmacologic cardioversion. Patients treated with ibutilide should be monitored on telemetry for a minimum of 6 hours or until the QTc returns to baseline, owing to a small risk for torsade de pointes.

Heart rate control is necessary in patients with rapid ventricular rates to improve cardiac function and alleviate symptoms. Acutely, the goal heart rate should be between 60/min and 110/min. Commonly used medications include AV nodal blockers, such as metoprolol or diltiazem. Intravenous or oral administration may be appropriate depending on a patient's symptoms. In patients with left ventricular dysfunction, calcium channel blockers should be avoided. Digoxin can be used as adjunctive therapy to improve rate control, especially in patients with heart failure.

Long-Term Management

Anticoagulation

Arterial thromboembolic events are the most serious complication of atrial fibrillation. In nonvalvular atrial fibrillation patients, the absolute risk for stroke is approximately 4% per year; however, the presence of comorbidities (such as heart failure, hypertension, diabetes, or vascular disease) can increase the risk 15- to 20-fold. Hypertension is associated with an increased risk for both atrial fibrillation and stroke; therefore, blood pressure control is critical in the management of atrial fibrillation.

H Stroke prevention with antithrombotic therapies is dependent on the patient's risk for stroke and risk for bleeding. Although several risk stratification scores are available, current guidelines recommend the use of the CHA_2DS_2-VASc score in patients with nonvalvular atrial fibrillation. Adjusted stroke rates and recommendations for antithrombotic therapy based on the CHA_2DS_2-VASc score are shown in Table 18. Patients with nonvalvular atrial fibrillation who have a CHA_2DS_2-VASc score of 2 or higher should be treated with anticoagulation to prevent stroke. Patients with valvular atrial fibrillation (rheumatic heart disease, mitral stenosis, and valve replacement) should receive warfarin. Non-vitamin K antagonist oral anticoagulants (NOACs) are not approved for use in valvular atrial fibrillation. However, patients with atrial fibrillation and other valvular lesions (aortic valve disease, mitral regurgitation, and tricuspid regurgitation) are eligible for NOAC therapy.

Bleeding scores, such as the ATRIA, HAS-BLED, and ORBIT scores, may be used to identify patients with significant bleeding risk based on patient characteristics, including anemia, hypertension, labile INR, older age, kidney insufficiency, and treatment with antiplatelet medications. Reversible risk factors for bleeding should be addressed in patients receiving anticoagulants. Concomitant antiplatelet therapy should be avoided unless the patient has recent active coronary artery disease (acute coronary syndrome or revascularization within the past year).

Several oral anticoagulants are available for stroke prevention in patients with atrial fibrillation. Vitamin K antagonism with dose-adjusted warfarin is an effective, low-cost therapy; however, warfarin has limitations, including the need for frequent monitoring and adjustment and numerous food and drug interactions. The safety and efficacy of warfarin therapy depend on the time the patient is in the therapeutic range (INR 2-3).

Four NOACs are approved for the prevention of stroke in atrial fibrillation (**Table 19**). Dabigatran, an oral direct thrombin inhibitor, is superior to warfarin for the prevention of ischemic stroke and results in less intracranial bleeding. Patients taking dabigatran have a higher risk for gastrointestinal bleeding relative to warfarin and may experience dyspepsia. Rivaroxaban, a direct factor Xa inhibitor, is noninferior to warfarin in the prevention of stroke or systemic embolism and is associated with less intracranial and fatal bleeding. As with dabigatran, patients taking rivaroxaban have a higher risk for gastrointestinal bleeding compared with those taking warfarin. Apixaban, another oral factor Xa inhibitor, is superior to warfarin for the prevention of stroke and confers less risk for major bleeding, including intracranial bleeding. Edoxaban is noninferior to warfarin for stroke prevention and is associated with less major bleeding. All of the NOACs have shorter half-lives than warfarin; however, there are no quick, readily available serum assays to accurately determine anticoagulant activity. Reversal agents and antidotes continue to be developed for these agents. Andexanet alfa is being evaluated for reversal of factor Xa inhibition, for use in patients treated with rivaroxaban, apixaban, or edoxaban. Idarucizumab is a dabigatran-reversal agent available for emergency invasive or surgical procedures or in cases of uncontrolled or life-threatening bleeding.

Approximately 10% to 25% of patients with atrial fibrillation have contraindications to oral anticoagulation or discontinue therapy for various reasons, including bleeding events. In patients who are at moderate to high risk for stroke (CHA_2DS_2-VASc score ≥3), left atrial appendage occlusion to prevent stroke and systemic thromboembolism can be considered. Occlusion of the left atrial appendage can be achieved percutaneously with a self-expanding device that is implanted in the left atrial appendage or with surgical closure. Left atrial

TABLE 19. Anticoagulants Approved for Stroke Prevention in Atrial Fibrillation

Medication	Frequency	Type of AF	Cautions and Dosing
Warfarin (vitamin K antagonist)	Dosing adjusted to INR	Valvular[a] or nonvalvular	Avoid in pregnancy Caution with idiopathic thrombocytopenic purpura, heparin-induced thrombocytopenia, liver disease, protein C or S deficiency Many drug interactions
Dabigatran (direct thrombin inhibitor)	Twice daily	Nonvalvular	Caution with P-glycoprotein inhibitors Reduce dose with CrCl 15-30 mL/min/1.73 m^2
Rivaroxaban (factor Xa inhibitor)	Once daily	Nonvalvular	Avoid with CrCl <30 mL/min/1.73 m^2, moderate liver impairment, strong P-glycoprotein inhibitors, and strong cytochrome P-450 inducers and inhibitors Reduce dose with CrCl 30-50 mL/min/1.73 m^2
Apixaban (factor Xa inhibitor)	Twice daily	Nonvalvular	Avoid with strong P-glycoprotein inhibitors or strong cytochrome P-450 inducers and inhibitors Reduce dose with two of the following criteria: creatinine ≥1.5 mg/dL 133 (µmol/L), age ≥80 years, or weight ≤60 kg (132 lb)
Edoxaban (factor Xa inhibitor)	Once daily	Nonvalvular	Avoid with strong cytochrome P-450 inducers and inhibitors Reduce dose with CrCl 30-50 mL/min/1.73 m^2, weight ≤60 kg (132 lb), or concomitant use of verapamil or quinidine (potent P-glycoprotein inhibitors)

AF = atrial fibrillation; CrCl = creatinine clearance.

[a]Valvular atrial fibrillation refers to atrial fibrillation in the presence of a mechanical heart valve, rheumatic mitral valve disease, and/or mitral stenosis.

appendage occlusion has a lower risk for intracranial bleeding compared with dose-adjusted warfarin.

Rate Versus Rhythm Control

Studies have not demonstrated that sinus rhythm restoration is superior to rate control alone. Consequently, the decision to initiate a rate or rhythm control strategy is predominantly based on symptoms, patient age, and patient preference. Rate control can be used to manage asymptomatic patients, with a resting heart rate goal of less than 80/min. A goal of less than 110/min may be considered in select patients without left ventricular dysfunction. β-Blockers, calcium channel blockers, and digoxin can be used to control the ventricular rate in patients with atrial fibrillation. Combination therapy may be needed to adequately control heart rate. Aside from resting heart rate assessment, evaluation of the heart rate with activity, such as with a 6-minute walk test, stress test, or 24-hour ambulatory ECG monitoring, should be performed.

A rhythm control strategy can improve quality of life in patients who continue to have symptoms despite adequate rate control. Because the long-term effects of rate control are unknown, rhythm control is often pursued in younger patients (aged <50 years) with minimal symptoms. Rhythm control may require cardioversion in addition to antiarrhythmic therapy. Antiarrhythmic drug selection is guided by the patient's comorbid conditions and safety considerations. Patients with infrequent atrial fibrillation who have no structural heart disease or conduction disease often benefit from a "pill-in-the-pocket" approach. With this strategy, patients take a class IC drug (flecainide or propafenone) at the onset of an episode of atrial fibrillation. These patients should be receiving β-blocker or calcium channel blocker therapy or should take one of these medications before taking the "pill in the pocket." Pill-in-the-pocket therapy should be initiated in a monitored setting to ensure patient safety.

Nonpharmacologic Strategies

Catheter ablation with pulmonary vein isolation is an effective rhythm control therapy in patients with recurrent symptomatic atrial fibrillation despite antiarrhythmic drug therapy. Catheter ablation is most effective in patients without significant left atrial enlargement and multiple comorbid conditions. Seventy percent to 90% of patients with paroxysmal atrial fibrillation are symptom-free 1 year after the procedure; however, success rates vary. Complications include thromboembolism (0.5%-1% risk), tamponade, and vascular complications (such as insertion hematoma, pseudoaneurysm, arteriovenous fistula, and retroperitoneal bleeding). Longer-term complications, such as pulmonary vein stenosis, are uncommon.

AV node ablation is an option in patients with atrial fibrillation who have continued symptomatic tachycardia despite rate and rhythm control therapy. Therapeutic ablation of the

AV node requires implantation of a permanent pacemaker. These patients remain in atrial fibrillation and still require anticoagulation.

KEY POINTS

- Immediate cardioversion to sinus rhythm is indicated in patients with atrial fibrillation who have hypotension, acute myocardial ischemia, or decompensated heart failure, regardless of atrial fibrillation duration.
- Current guidelines recommend calculation of the CHA_2DS_2-VASc score for stroke risk stratification in patients with nonvalvular atrial fibrillation; patients with a CHA_2DS_2-VASc score of 2 or higher should be treated with oral anticoagulation to prevent stroke.
- A rhythm control strategy can improve quality of life in patients with atrial fibrillation who continue to have symptoms despite adequate heart rate control.

Atrial Flutter

Atrial flutter is an organized macro-reentrant tachycardia with discrete regular atrial activity on ECG, usually with a rate of 250/min to 300/min. Typical atrial flutter is characterized electrocardiographically by a sawtooth pattern with inverted flutter waves in leads II, III, and aVF and positive flutter waves in lead V_1 (**Figure 14**). Typical atrial flutter is the result of counterclockwise reentry around the tricuspid annulus. In atypical flutter, the circuit can travel in a clockwise direction or can occur in other locations in the right and left atria. Atypical flutter may occur after ablation or after congenital or valvular cardiac surgery.

Management of atrial flutter is similar to atrial fibrillation management; however, a rhythm control strategy is favored in atrial flutter because rate control may be difficult and often requires high doses of more than one AV nodal blocker. Catheter ablation is the definitive treatment for typical atrial flutter, owing to a very high success rate (>95%) and low complication rate. Oral anticoagulation in patients with atrial flutter is approached in the same manner as in patients with atrial fibrillation. Patients with atrial flutter and sufficient stroke risk (CHA_2DS_2-VASc score ≥2) require oral anticoagulation to prevent stroke and systemic embolism.

KEY POINT

- Catheter ablation is the definitive treatment of typical atrial flutter, owing to a very high success rate (>95%) and low complication rate.

Supraventricular Tachycardias

Clinical Presentation

SVTs are rapid heart rhythms that arise from the atrium or require conduction through the AV node. Atrial fibrillation and atrial flutter are technically SVTs, although the term generally pertains to paroxysmal SVTs. SVTs can affect all age groups but frequently occur in younger patients. Prevalence is higher in women than in men. SVTs usually occur in the

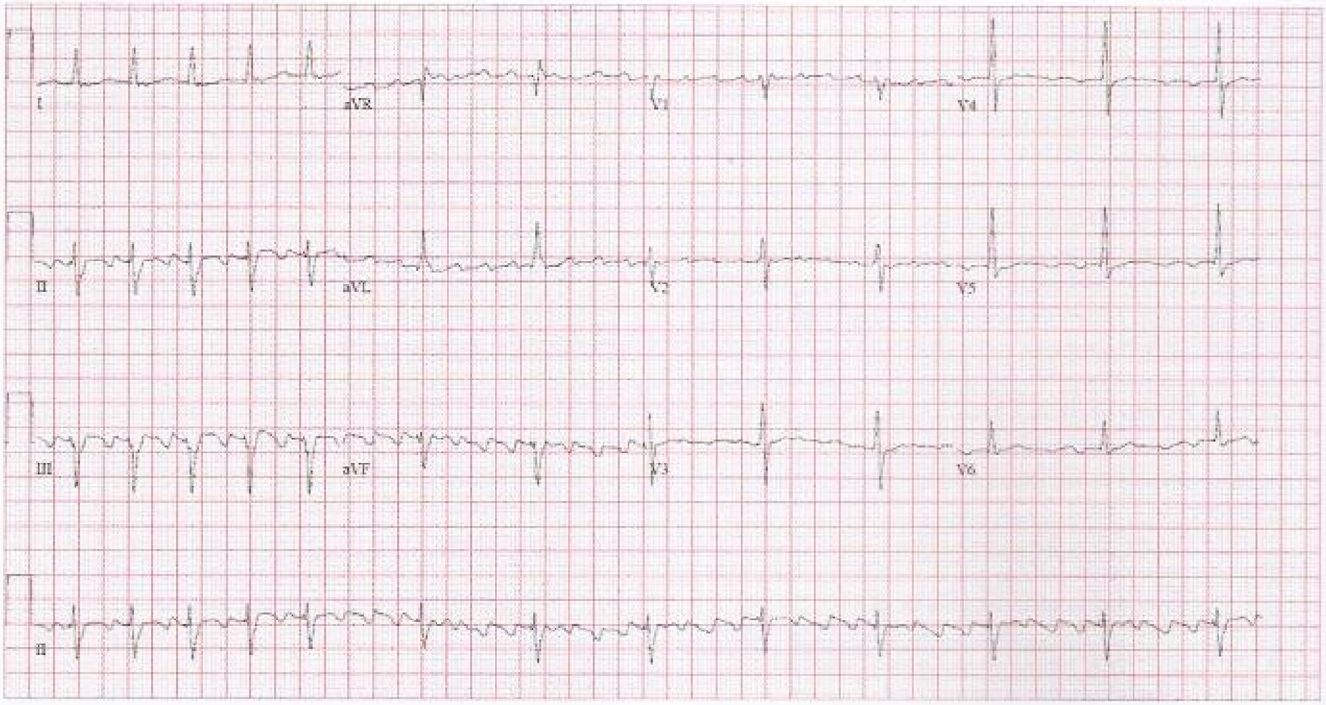

FIGURE 14. In this electrocardiogram demonstrating typical atrial flutter, negatively directed sawtooth waves are seen in the inferior leads, and positive waves are seen in lead V_1. In the bottom rhythm strip, 2:1 and 4:1 conduction patterns are seen.

absence of structural heart disease, although echocardiography should be performed to exclude underlying cardiac dysfunction or structural defects. Patients often have repeated episodes of tachycardia and may report palpitations, a sensation of pounding in the neck, fatigue, lightheadedness, chest discomfort, dyspnea, presyncope, and, less commonly, syncope.

The ECG typically demonstrates a narrow-complex tachycardia; however, wide QRS complexes (>120 ms) may be present in cases of bundle branch block, aberrancy, pacing, or anterograde accessory pathway conduction (antidromic tachycardia). SVTs may be classified electrocardiographically according to the relationship of the P wave and the QRS complex. Short-RP tachycardias (RP interval < PR interval) feature a P wave that closely follows the QRS complex, whereas long-RP tachycardias feature a P wave that is more than half the distance between the RR interval (RP interval > PR interval). Short-RP tachycardias include typical AVNRT, AVRT, and junctional tachycardia. Long-RP tachycardias include atypical AVNRT, sinus tachycardia, and atrial tachycardia.

Vagal maneuvers, including the Valsalva maneuver (bearing down), carotid sinus massage, or facial immersion in cold water, are first-line therapy to restore sinus rhythm in patients with SVT. Adenosine can be used to terminate SVT and simultaneously help diagnose its cause. Tachycardias that terminate with adenosine are typically AV node dependent (AVNRT and AVRT), whereas continued atrial activity (P waves) during AV block is consistent with atrial flutter or atrial tachycardia.

Atrioventricular Nodal Reentrant Tachycardia

AVNRT accounts for two thirds of all cases of SVT, not including cases of atrial fibrillation and flutter. AVNRT is the result of a reentrant circuit within the AV node that uses both the fast and slow pathways. Typical AVNRT involves conduction down the slow pathway and back up to the atrium over the fast pathway (slow-fast). This conduction pattern results in a short RP interval with a retrograde P wave inscribed very close to the QRS complex (**Figure 15**). Atypical AVNRT occurs when the impulse travels down the fast pathway and returns to the atrium via the slow pathway (fast-slow), resulting in a long RP interval.

AVNRT may be terminated with vagal maneuvers or adenosine. AV nodal blocking therapy with β-blockers or calcium channel blockers is used to prevent recurrent AVNRT. In patients with recurrent AVNRT and patients who do not tolerate or prefer to avoid long-term medical therapy, catheter ablation should be considered. Catheter ablation of AVNRT has a high success rate, although it is associated with a 1% risk for injury to the AV node necessitating pacemaker implantation.

Atrioventricular Reciprocating Tachycardia

AVRT is an accessory pathway (bypass tract)-mediated tachycardia that is often observed as preexcitation on ECG (**Figure 16**). Early ventricular activation over the accessory pathway causes shortening of the PR interval, and the initial part of the QRS complex is slurred because of premature ventricular depolarization in the myocardial tissue adjacent to the accessory pathway. In AVRT, the tachycardia can conduct anterograde over the AV node (orthodromic AVRT) or anterograde over the accessory pathway (antidromic AVRT). Orthodromic AVRT is the most

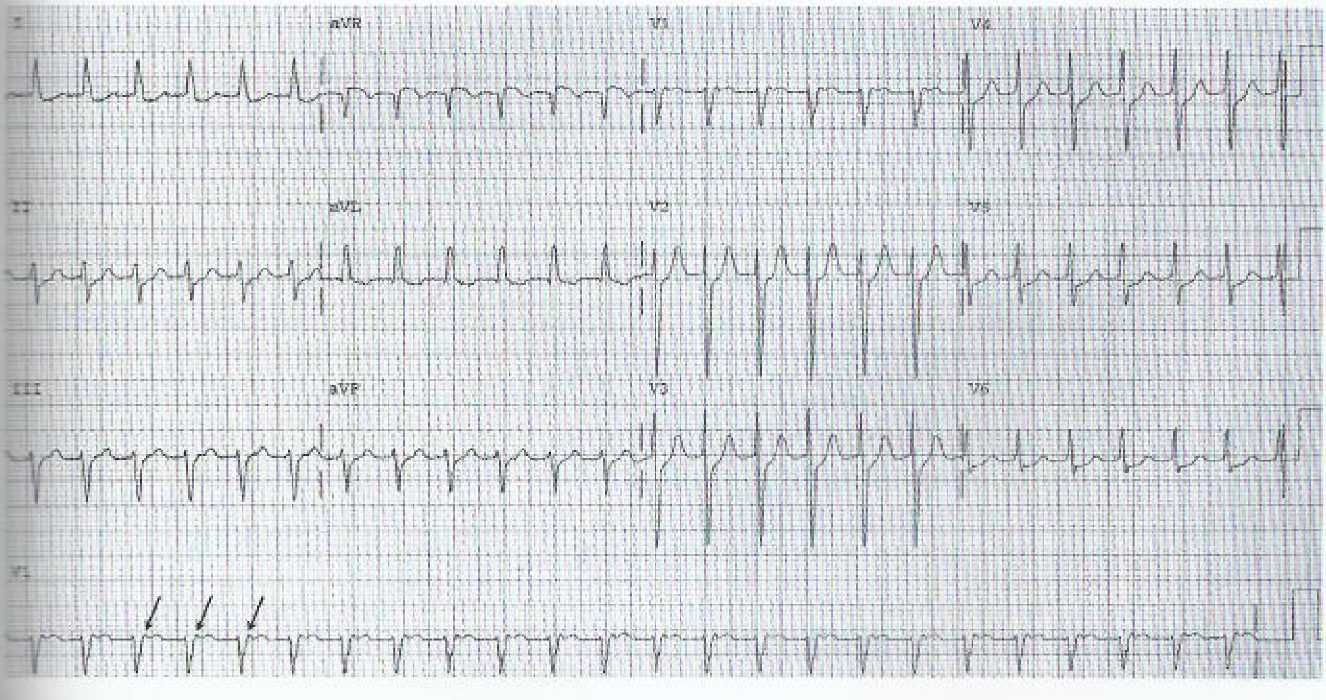

FIGURE 15. Electrocardiogram showing atrioventricular nodal reentrant tachycardia characterized by a short RP interval with a retrograde P wave inscribed very close to the QRS complex, which is best seen in V_1 (appearing as a pseudo r′ wave [*arrows*]).

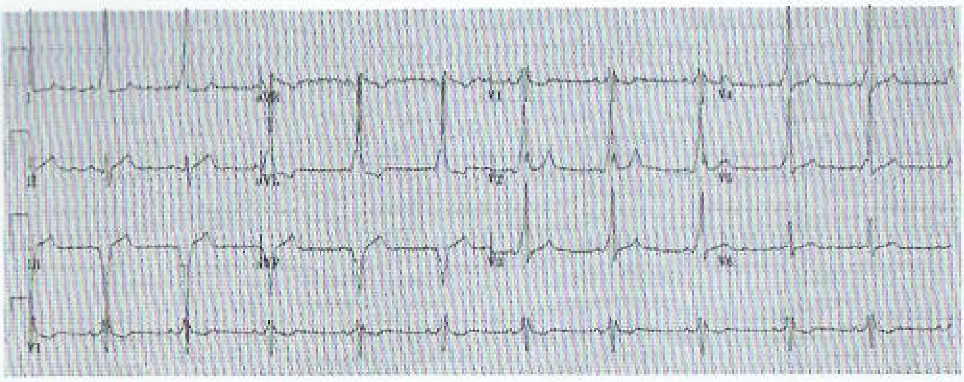

FIGURE 16. Electrocardiogram demonstrating sinus rhythm with preexcitation as indicated by the presence of a delta wave. The slurring of the QRS upstroke represents premature depolarization of the ventricular tissue adjacent to the accessory pathway.

CONT.

common type of AVRT, accounting for more than 90% to 95% of cases. This type of AVRT has a narrow QRS complex, owing to conduction over the AV node and the His-Purkinje system. Antidromic AVRT is characterized by a wide, slurred QRS complex resulting from conduction over the bypass tract and activation of the ventricle without use of the specialized conduction system. Adenosine can be given to terminate orthodromic AVRT; however, adenosine and other AV nodal blockers are contraindicated in cases of antidromic AVRT.

Wolff-Parkinson-White (WPW) syndrome is defined by symptomatic AVRT with evidence of preexcitation on resting ECG (delta wave). It is often seen in patients with Ebstein anomaly. Atrial fibrillation occurs in up to one third of patients with WPW syndrome. Rapid conduction over an accessory pathway in atrial fibrillation can result in VF and sudden cardiac death (SCD), although this occurs in less than 1% of cases of WPW syndrome.

In patients with preexcitation on ECG, stress testing can effectively risk-stratify patients; patients in whom preexcitation is lost during exercise are generally at low risk for ventricular arrhythmia and SCD. Electrophysiology testing is also helpful in determining the risk for SCD and in localizing the pathway to facilitate catheter ablation. Catheter ablation is first-line therapy for patients with WPW syndrome and has a high success rate; however, ablation success is dictated by the location of the bypass tract. Antiarrhythmic therapy is considered second-line therapy. In patients with accessory pathways close to the AV node, antiarrhythmic drug therapy is particularly useful because catheter ablation carries an unacceptable risk for iatrogenic heart block.

In asymptomatic patients with preexcitation on ECG, management is controversial. Invasive testing is generally not required, unless the patient has a high-risk occupation, such as a commercial airline pilot.

Premature Atrial Contractions and Atrial Tachycardia

Premature atrial contractions (PACs) are early isolated beats that arise from the atria. They are exceedingly common, and their frequency increases with age. During ambulatory ECG monitoring, only 1% of persons have no PACs. High PAC burden is associated with increased risk for atrial fibrillation. Symptomatic PACs are typically treated with β-blockers or calcium channel blockers.

Atrial tachycardia can arise in the presence or absence of structural heart disease. β-Blocker or calcium channel blocker therapy is first-line treatment for symptomatic atrial tachycardia. Second-line treatment consists of catheter ablation or antiarrhythmic drug therapy. Ablation success rates are generally lower in patients with atrial tachycardia than in patients with other SVTs.

Multifocal atrial tachycardia is typified by three or more P-wave morphologies and a heart rate greater than 100/min (**Figure 17**). It is usually seen in patients with end-stage COPD.

KEY POINTS

- Vagal maneuvers, including the Valsalva maneuver, carotid sinus massage, or facial immersion in cold water, may restore sinus rhythm in patients with supraventricular tachycardia.
- Patients with recurrent atrioventricular nodal reentrant tachycardia are treated with atrioventricular nodal blocking agents (β-blockers or calcium channel blockers) or catheter ablation.
- First-line therapy for patients with Wolff-Parkinson-White syndrome is catheter ablation; antiarrhythmic therapy is reserved for second-line therapy.

Wide-Complex Tachycardia

A wide-complex tachycardia is any tachycardia with a QRS complex of 120 ms or greater. Differential diagnoses include SVT with aberrancy, preexcited tachycardia (antidromic tachycardia), ventricular paced rhythm, and VT.

In adult patients with structural heart disease, 95% of wide-complex tachycardias are VT. Several important clinical

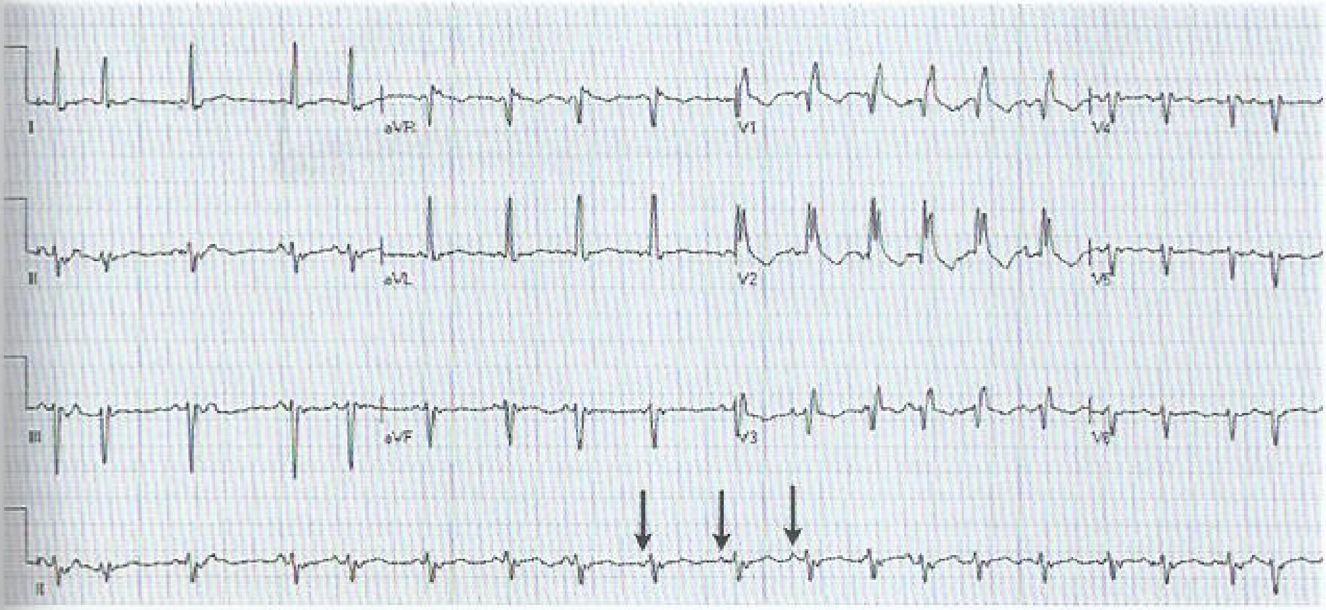

FIGURE 17. Electrocardiogram showing multifocal atrial tachycardia typified by three or more P-wave morphologies (*arrows*).

and ECG features can distinguish VT from other conditions. Wide-complex tachycardias that are positive in lead aVR, have a QRS morphology that is concordant (all predominantly positive or negative) in the precordial leads, have QRS morphology other than typical right or left bundle branch block, and exhibit extreme axis deviation ("northwest" axis) are usually VT. AV dissociation, fusion beats, and capture beats are all highly suggestive of VT (**Figure 18**). When the origin of a wide complex tachycardia cannot be determined, VT should be assumed until expert consultation can be obtained.

Ventricular Arrhythmias

Premature Ventricular Contractions

Premature ventricular contractions (PVCs) occur in up to 75% of healthy persons. Symptoms include palpitations or the

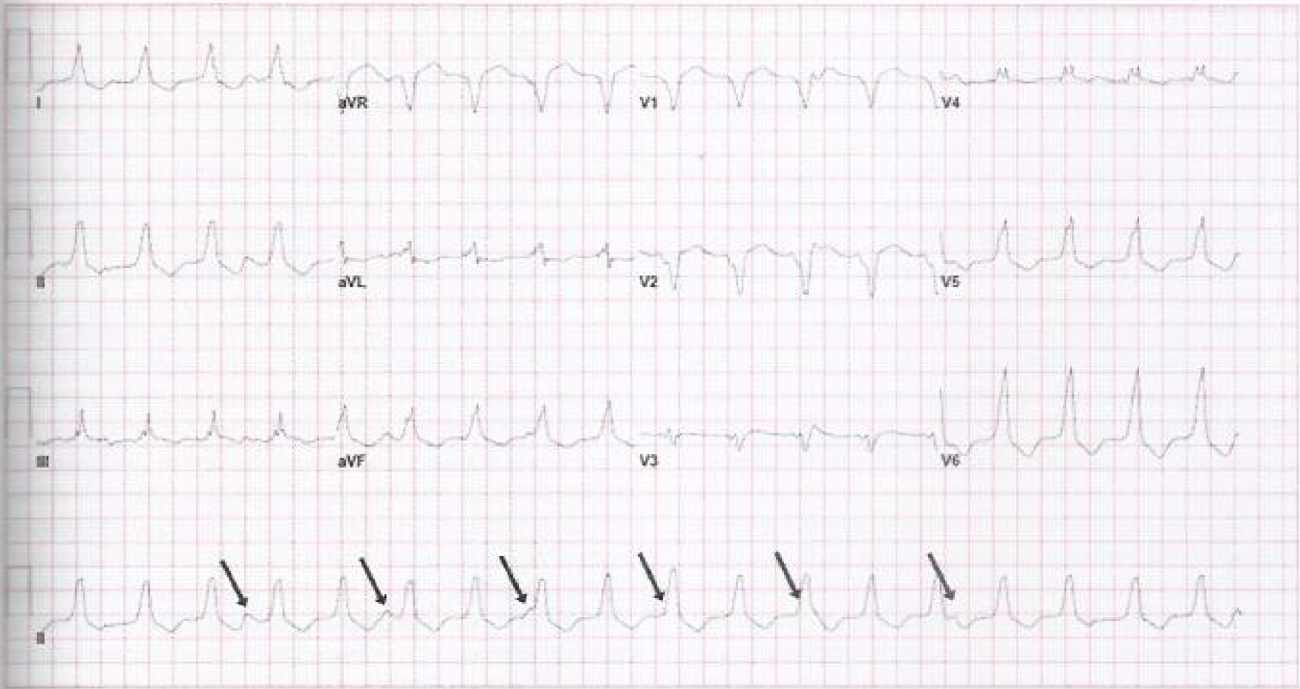

FIGURE 18. Electrocardiogram demonstrating a regular monomorphic wide-complex tachycardia in a left bundle branch block pattern. The presence of atrioventricular dissociation confirms the diagnosis of ventricular tachycardia. The arrows identify nonconducting P waves.

perception of skipped beats. Forceful beats are caused by increased cardiac filling during the pause following the PVC. PVCs are more common in patients with hypertension, left ventricular hypertrophy, previous myocardial infarction, and other forms of structural heart disease, such as nonischemic cardiomyopathy.

In the absence of high-risk features (syncope, a family history of premature SCD, structural heart disease), reassurance is appropriate management. PVCs require treatment when symptoms are bothersome or frequent (>10% of all beats or 10,000 PVCs per day). Tachycardia-induced cardiomyopathy may result from frequent PVCs (see Heart Failure).

First-line treatment for PVC suppression is β-blocker or calcium channel blocker therapy. β-Blockers are preferred in patients with ventricular dysfunction. If PVCs persist despite β-blockade or calcium channel blockade, antiarrhythmic drug therapy may be used. The selection of an antiarrhythmic medication for PVC suppression depends on many factors, including kidney function and comorbid conditions. In young healthy patients without structural heart disease, class IC drugs are usually effective. Amiodarone is most commonly used in patients with structural heat disease, particularly heart failure. Catheter ablation should be considered in patients with continued frequent PVCs despite medical therapy, those who cannot tolerate medical therapy, and patients who develop PVC-related left ventricular dysfunction.

H Ventricular Tachycardia with Structural Heart Disease

In ischemic and nonischemic cardiomyopathy, the presence of myocardial scar tissue facilitates a reentry circuit and the development of VT. VT is usually regular and monomorphic in patients with ventricular scarring. Sustained VT (≥30 seconds) can lead to hypotension, syncope, VF, and cardiac arrest; however, short episodes of VT (nonsustained) or slow sustained VT may be well tolerated or cause no symptoms.

Evaluation with resting ECG, exercise treadmill testing (to provoke arrhythmias), and cardiac imaging (to identify structural heart disease) is indicated in all patients with VT. Patients with ischemic cardiomyopathy who present with VT should be considered for angiography and revascularization if appropriate. Cardiac magnetic resonance imaging clarifies the extent and pattern of myocardial scarring, which can be helpful in refining the cause of the cardiomyopathy and can assist in determining prognosis. For example, patients with a higher burden of myocardial scarring have higher risk for recurrent arrhythmia.

β-Blockers and ACE inhibitors reduce the risk for SCD in patients with prior myocardial infarction and cardiomyopathy. In those with recurrent VT despite β-blocker therapy, antiarrhythmic drug therapy with amiodarone may be considered. Catheter ablation should be considered in patients with recurrent VT despite medical therapy. ICD placement is indicated for secondary prevention of SCD in patients with structural heart disease or cardiomyopathy who have sustained VT/VF, provided that reversible causes have been excluded (such as acute coronary ischemia or cocaine ingestion).

Idiopathic Ventricular Tachycardia

Idiopathic VT (so-called normal heart VT) occurs in the absence of structural heart disease, typically arising from the outflow tracts, fascicles, and papillary muscles. Patients with idiopathic VT usually present with palpitations in the third to fifth decades of life. Episodes of syncope are uncommon. Arrhythmic events are often triggered by stress, emotion, or exercise. These tachycardias are responsive to adenosine.

Calcium channel blockers, especially verapamil, and β-blockers are first-line treatment for idiopathic VT. Catheter ablation can be considered if symptoms continue despite these therapies. ICDs are contraindicated in patients with hemodynamically stable idiopathic VT, owing to the benign prognosis and efficacy of other therapies. H

KEY POINT

- The primary treatment for patients with premature ventricular contractions (PVCs) without high-risk features (syncope, a family history of premature sudden cardiac death, structural heart disease) is reassurance; treatment is reserved for those with bothersome symptoms or frequent PVCs. HVC

Inherited Arrhythmia Syndromes

Patients younger than age 40 years with unexplained SCD, unexplained near drowning, or recurrent exertional syncope, who do not have ischemic or other structural heart disease, should be evaluated for inherited arrhythmia syndromes. Additionally, unexplained premature death (age <35 years) or sudden death in a first-degree family member (age <40 years) should raise suspicion for an inherited arrhythmia syndrome and prompt referral to a cardiovascular specialist, with genetic counseling and genetic testing as indicated by clinical findings. The diagnosis of inherited arrhythmia syndromes can be complicated because of variable penetrance and expressivity of these disorders. Characteristic findings and treatments for these syndromes are reviewed in **Table 20**.

Long QT syndrome is among the most common inherited arrhythmias, affecting between 1 in 1000 and 1 in 5000 persons. Prolongation of the QTc interval has many causes, most of which are acquired, such as medication use, structural heart disease, and electrolyte abnormalities. Drugs that have been implicated in QT prolongation include antiarrhythmic agents, antibiotics (including some macrolides and fluoroquinolones), antipsychotic drugs, and antidepressants. A list of drugs categorized by their potential to cause QT prolongation is available at crediblemeds.org. The presence of a prolonged QTc interval (>440 ms in men and >460 ms in women) alone is insufficient to diagnose long QT syndrome. Diagnosis requires the presence of a QTc interval greater than 500 ms on repeated 12-lead ECGs accompanied by unexplained syncope or ventricular

TABLE 20. Inherited Arrhythmia Syndromes

Disorder	Presenting Symptoms and Characteristic Findings	Treatment[a]
Long QT syndrome	Syncope, QTc interval usually >460 ms, torsades de pointes	β-Blockers, ICD, exercise restriction
Short QT syndrome	Syncope, QT interval <340 ms, atrial fibrillation, VT, VF	ICD in all patients
Brugada syndrome	Syncope, VF, coved ST-segment elevation in early precordial leads (V_1 through V_3)	ICD
Catecholaminergic polymorphic VT	Syncope, polymorphic or bidirectional VT during exercise or emotional distress	β-Blockers, verapamil, flecainide, ICD, exercise abstinence
Early repolarization syndrome	Syncope, inferior and lateral early repolarization on ECG, VF	ICD
ARVC/D	Syncope, palpitations, T-wave inversions in leads V_1 through at least V_3, monomorphic VT, abnormal signal-averaged ECG, frequent PVCs, and abnormal right ventricular size and function on echocardiography or CMR imaging	ICD, β-blockers, antiarrhythmic medications, exercise abstinence

ARVC/D = arrhythmogenic right ventricular cardiomyopathy/dysplasia; CMR = cardiac magnetic resonance; ECG = electrocardiography; ICD = implantable cardioverter-defibrillator; PVC = premature ventricular contraction; QTc = corrected QT; VF = ventricular fibrillation; VT = ventricular tachycardia.

[a]Treatment recommendations for ICDs in inherited arrhythmia syndromes are guided by risk stratification with criteria that are often disease specific. Additionally, antiarrhythmic drugs are often required in several syndromes for recurrent ventricular arrhythmias.

arrhythmia. Patients with a QTc interval greater than 500 ms are at greatest risk for SCD. β-Blockers are first-line therapy; however, patients with cardiac arrest or those who have recurrent events (syncope or VT) refractory to β-blocker therapy are candidates for ICD placement. These patients should not participate in competitive athletics.

Short QT syndrome is a rare and genetically heterogeneous disorder characterized by a short QT interval (QT <340 ms or QTc <350 ms). It is inherited in an autosomal dominant pattern. Patients can present with atrial and ventricular arrhythmias (including atrial fibrillation, polymorphic VT, and VF) and syncope. Patients with short QT syndrome are considered to be at very high risk for SCD; therefore, ICD placement is recommended in all patients.

Brugada syndrome is distinguished by right precordial ECG abnormalities, including ST segment coving (concave or linear downsloping ST segment) in leads V_1 to V_3 with or without right bundle branch block, VF, and cardiac arrest (**Figure 19**). Brugada syndrome has an increased prevalence in men and persons of Asian descent. Arrhythmic events in patients with Brugada syndrome are more common at night during sleep. Abnormalities on ECG can be intermittent and may be elicited by fever or pharmacologic challenge with sodium channel blockade (such as with procainamide infusion). Patients with syncope or ventricular arrhythmia should undergo ICD implantation. Quinidine may be beneficial in patients with recurrent ventricular arrhythmias and/or ICD shocks.

Catecholaminergic polymorphic VT is a rare disorder characterized by intracellular calcium overload, polymorphic ventricular arrhythmias, and cardiac arrest. The arrhythmias are usually triggered by high-adrenergic states, including strong emotion and exercise. These arrhythmias can also be provoked with epinephrine infusion. β Blocker therapy and ICD placement are treatments. Patients with catecholaminergic polymorphic VT should avoid exercise.

Early repolarization syndrome should be strongly suspected in patients with unexplained VF arrest, particularly when provoked during exercise. Early repolarization (J-point elevation) is a common and usually benign ECG finding; however, the presence of inferior and lateral early repolarization of more than 1 mm in a patient with VF and/or cardiac arrest should be considered early repolarization syndrome. ICD implantation is indicated in patients with VF or cardiac arrest.

Hypertrophic cardiomyopathy or arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D) can often present as SCD in young persons. Hypertrophic cardiomyopathy and arrhythmic risk stratification are discussed in Myocardial Disease. Most patients with ARVC/D present between puberty and young adulthood; however, it can also occur in older age. Patients with ARVC/D usually present with frequent ventricular ectopy and/or monomorphic VT, although severe cases can present with heart failure. The diagnosis is established by ECG abnormalities, family history, the presence of arrhythmias, and structural abnormalities of the right ventricle. Cardiac magnetic resonance imaging can demonstrate enlargement (segments of poorly contracting heart muscle), focal aneurysms, and wall motion abnormalities in the right ventricle (hypokinesis). ARVC/D is usually progressive, and patients with ARVC/D should abstain from vigorous exercise. Patients with ARVC/D and cardiac arrest or risk factors (nonsustained VT, inducible VT) should be offered ICD implantation. β-Blockers are first-line therapy for ventricular arrhythmia, although antiarrhythmic

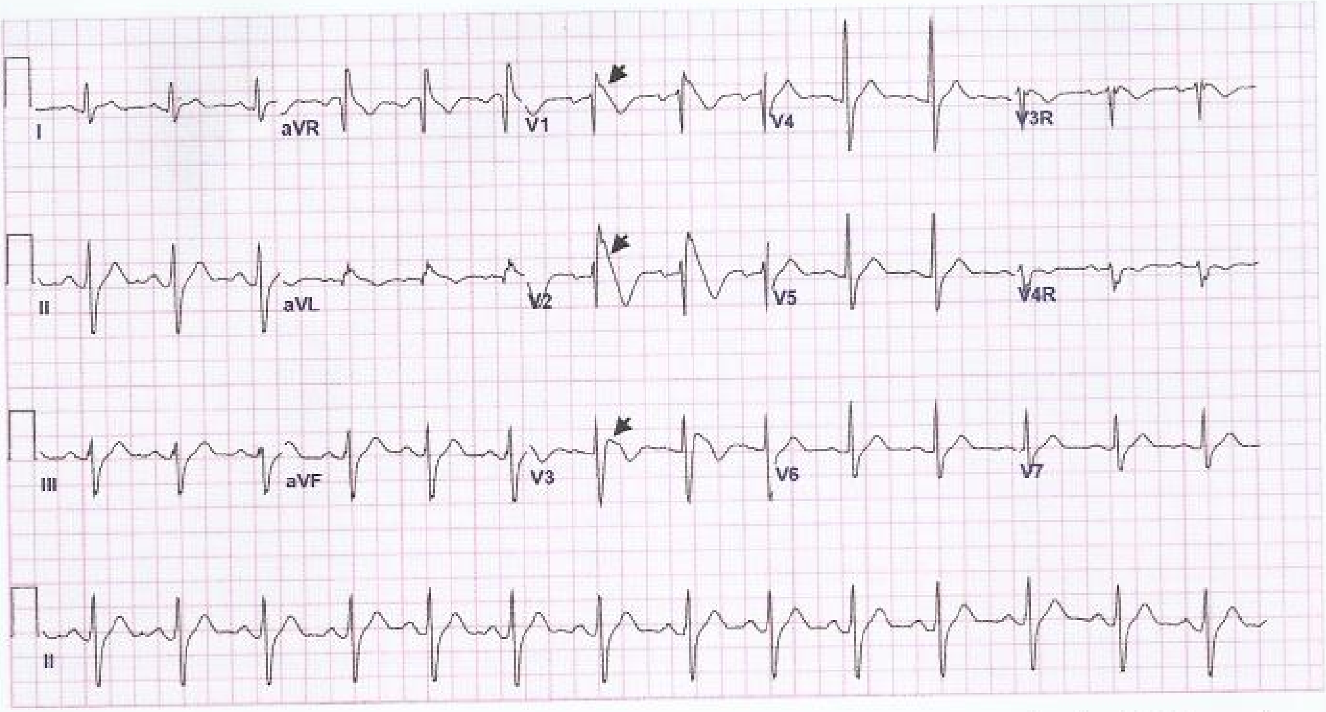

FIGURE 19. Electrocardiogram demonstrating a type 1 Brugada pattern, ≥2 mm J-point elevation, ST-segment coving (concave or linear downsloping ST segment) (*arrowheads*), and T-wave inversions in leads V_1 to V_3.

therapy with sotalol or amiodarone or catheter ablation is often required for recurrent VT.

KEY POINT

- Unexplained premature death (at age <35 years) or sudden death in a first-degree family member should raise suspicion for an inherited arrhythmia syndrome and prompt referral to a cardiovascular specialist.

Sudden Cardiac Arrest

Epidemiology and Risk Factors

SCD is defined as an instantaneous fatal event or collapse within 1 hour of symptom onset in an apparently healthy person. In patients in whom death was unwitnessed, SCD is considered to have occurred if the patient was known to be alive and well within the past 24 hours. VT and VF are the most common causes of SCD.

In the United States, more than 350,000 episodes of SCD occur each year. The annual risk for SCD is 1:1000 in the general population. The highest incidence occurs in patients with pre-existing structural heart disease, although left ventricular function is normal in most patients experiencing SCD. Risk factors include heart failure, diminished left ventricular function, previous myocardial infarction, unexplained syncope, left ventricular hypertrophy, nonsustained ventricular arrhythmia, chronic kidney disease, and sleep apnea. It is important to distinguish between myocardial infarction and SCD when a family history of cardiac disease is obtained.

Acute Management

H

Cardiac arrest necessitates immediate cardiopulmonary resuscitation (CPR) and advanced cardiac life support. Basic life support guidelines emphasize the importance of immediate, rapid, and sustained chest compressions in caring for individuals with cardiac arrest. Following activation of the emergency medical system and request for an automated external defibrillator, the patient's pulse should be checked immediately. Chest compressions should be initiated if no definite pulse is detected within 10 seconds. High-quality CPR (30 compressions and 2 breaths per cycle if no advanced airway is present) includes adequate depression of the lower sternum at a rate of at least 100 compressions per minute with adequate time for chest recoil. Interruptions in chest compressions should be minimized. Once an airway has been secured, breaths should be delivered at a rate of 1 breath per 6 seconds (10/min) to avoid breath stacking and increased thoracic pressure, which impedes cardiac output. Defibrillation should occur as soon as possible in patients with a shockable rhythm because time to defibrillation is an important determinant of the likelihood of survival to hospital discharge.

According to the 2015 American Heart Association advanced cardiovascular life support guidelines, the presence or absence of a shockable rhythm guides management after CPR has been initiated. In patients with asystole or pulseless electrical activity, CPR is continued with reassessment of rhythm status for a shockable rhythm every 2 minutes. Epinephrine should be administered intravenously to increase coronary perfusion. Vasopressin is no longer recommended

H CONT.

because it provides no advantages over epinephrine. Likewise, atropine should not be used for the treatment of asystole or pulseless electrical activity arrest. Any reversible causes (such as tamponade) should be identified and treated.

Patients with VT/VF should be shocked, followed by immediate resumption of CPR and reassessment of the rhythm in 2 minutes. Epinephrine should be administered after the second shock and every 3 to 5 minutes thereafter. Amiodarone should be given as a bolus if VT/VF continues despite three shocks and epinephrine administration. A second dose of amiodarone can be given if VT/VF persists. H

Device Therapy for Prevention of Sudden Death

H

ICDs have demonstrated efficacy in the primary and secondary prevention of SCD. Patients with sustained ventricular arrhythmias (>30 seconds) or cardiac arrest without a reversible cause have a class I recommendation for secondary prevention ICD placement. Patients with heart failure who meet specific criteria should undergo ICD placement for primary prevention (see Heart Failure). Patients with heart failure and interventricular conduction defects (predominantly left bundle branch block) often benefit from cardiac resynchronization therapy or cardiac resynchronization therapy in combination with a defibrillator. H

Patients with ICDs need to avoid strenuous upper extremity exercises, including weight lifting, because of concern for lead stress and subsequent fracture. Inappropriate detection of VT/VF and shocks can result from electromagnetic interference; therefore, patients need to avoid devices that pose risks, such as arc welding equipment and high-voltage machinery. Patients with ICDs who are undergoing invasive procedures or surgery should be evaluated by their electrophysiologist for device reprogramming recommendations.

In the past, ICDs were implanted almost exclusively by using a transvenous approach. New techniques allow for implantation of defibrillators in the lateral chest at the midaxillary line adjacent to the heart with tunneling of the lead under the skin next to the sternum. Subcutaneous defibrillators have several advantages, including reduced risk for device infection.

KEY POINT

- Implantable cardioverter-defibrillators are effective for primary and secondary prevention of sudden cardiac death.

Device Infection

H

Device infections have many different forms, ranging from pocket infections to endocarditis. Most infections are due to *Staphylococcus epidermidis* and *Staphylococcus aureus*. Symptoms of cardiac device infection include fever, chills, malaise, lassitude, and failure to thrive, particularly in the elderly.

Physical examination of the pocket may reveal erythema, swelling, drainage, or wound dehiscence. In patients suspected of having device infection, several blood cultures, an erythrocyte sedimentation rate, and a C-reactive protein level should be obtained. A transesophageal echocardiogram should be obtained to evaluate for intracardiac or lead vegetations. Aspirating the device pocket is never indicated because this can damage the leads or introduce infection in a sterile or uninfected pocket. PET-CT can also identify infection of the device pocket or leads if other testing is inconclusive.

Treatment of cardiac device infection includes complete extraction of all hardware, debridement of the pocket, sustained antibiotic therapy, and reimplantation at a new location after infection has been eradicated. H

Valvular Heart Disease

General Principles

Valvular heart disease (VHD) is characterized by underlying functional or anatomic abnormalities in the cardiac valves that result in regurgitation or stenosis. VHD is common, occurring in approximately 20 million persons in the United States. Although there are congenital forms, VHD is largely age dependent, and 3% to 6% of those aged 65 years and older are affected.

A thorough history and physical examination are essential in evaluating for VHD. Many heart valve lesions are slowly progressive, and patients may unconsciously limit their activity in response to a worsening of underlying VHD. The most common symptom is exertional dyspnea. Other symptoms include angina, syncope, palpitations, lower extremity edema, and ascites, depending on the lesion and severity. Typical physical examination findings for valvular and other cardiac lesions are described in **Table 21**. Twelve-lead electrocardiography, chest radiography, and transthoracic echocardiography (TTE) with two-dimensional imaging may be performed to evaluate for VHD.

For clinical monitoring and timing of intervention, VHD is classified into four stages (A to D), which consider the presence of symptoms, severity of the lesion, ventricular response to the volume or pressure overload caused by the lesion, effect on the pulmonary or systemic circulation, and heart rhythm changes (**Table 22**). Surveillance intervals for echocardiographic evaluation based on disease severity are listed in **Table 23** on page 58.

H

Surgery can be a life-saving intervention in select patients, and surgical risk calculation is a key component of the patient evaluation. Surgical risk is determined through an assessment of the patient's age, morbidities, frailty, and impediments specific to the procedure being considered (for example, prior chest radiation therapy for a sternotomy approach). Risk calculators derived from national databases can assist in estimating risk for morbidity and mortality for various surgical valve procedures. One such calculator, the Society of Thoracic Surgery Adult Cardiac Surgery Risk Calculator, is available at riskcalc.sts.org. Although risk calculators contain many data input fields, it is important to note that frailty and some other important patient and procedural characteristics are not part of these online assessment tools.

TABLE 21. Valvular and Other Cardiac Lesions and Their Associated Examination Findings

Cardiac Condition	Characteristic Murmur	Location	Radiation	Associated Findings	Severity and Pitfalls
Aortic stenosis	Midsystolic; crescendo-decrescendo	RUSB	Right clavicle, carotid, apex	Enlarged, nondisplaced apical impulse; S_4; bicuspid valve without calcification will have systolic ejection click followed by murmur	Severe aortic stenosis findings may include decreased A_2; high-pitched, late-peaking murmur; diminished and delayed carotid upstroke Radiation of murmur down the descending thoracic aorta may mimic mitral regurgitation
Aortic regurgitation	Diastolic; decrescendo	LLSB (valvular) or RLSB (dilated aorta) (heard best sitting and leaning forward)	None	Enlarged, displaced apical impulse; S_3 or S_4; increased pulse pressure; bounding carotid and peripheral pulses	Acute severe regurgitation murmur may be masked by tachycardia and short duration of murmur Severity in chronic regurgitation is difficult to assess by auscultation
Mitral stenosis	Diastolic; low-pitched, decrescendo	Apex (heard best in left lateral decubitus position)	None	Loud S_1; tapping apex beat; opening snap after S_2 if leaflets mobile; irregular pulse if atrial fibrillation present	Interval between S_2 and opening snap is short in severe mitral stenosis Intensity of murmur correlates with transvalvular gradient P_2 may be loud if pulmonary hypertension present
Mitral regurgitation	Systolic; holo-, mid-, or late systolic	Apex	Axilla or back; occasionally anteriorly to precordium	Systolic click in mitral valve prolapse; S_3; apical impulse hyperdynamic and may be displaced if dilated left ventricle; in mitral valve prolapse, Valsalva maneuver moves onset of clicks and murmur closer to S_1; handgrip maneuver increases murmur intensity	Acute severe regurgitation may have soft or no holosystolic murmur, mitral inflow rumble, or S_3
Tricuspid regurgitation	Holosystolic	LLSB	LUSB	Merged and prominent *c* and *v* waves in jugular venous pulse; murmur increases during inspiration	Right ventricular impulse below sternum Pulsatile, enlarged liver with possible ascites Murmur may be high-pitched if associated with severe pulmonary hypertension
Tricuspid stenosis	Diastolic; low-pitched, decrescendo; increased intensity during inspiration	LLSB	None	Elevated central venous pressure with prominent *a* wave, signs of venous congestion (hepatomegaly, ascites, edema)	Low-pitched frequency may be difficult to auscultate, especially at higher heart rate
Pulmonary valve stenosis	Systolic; crescendo-decrescendo	LUSB	Left clavicle	Pulmonic ejection click after S_1 (diminishes with inspiration)	Increased intensity of murmur with late peaking
Pulmonary valve regurgitation	Diastolic; decrescendo	LLSB	None	Loud P_2 if pulmonary hypertension present	Murmur may be minimal or absent if severe due to minimal difference in pulmonary artery and right ventricular diastolic pressures

(Continued on the next page)

TABLE 21. Valvular and Other Cardiac Lesions and Their Associated Examination Findings *(Continued)*

Cardiac Condition	Characteristic Murmur	Location	Radiation	Associated Findings	Severity and Pitfalls
Innocent flow murmur	Midsystolic; grade 1/6 or 2/6 in intensity	RUSB	None	Normal intensity of A_2; normal splitting of S_2; no radiation	May be present in conditions with increased flow (e.g., pregnancy, fever, anemia, hyperthyroidism)
Hypertrophic obstructive cardiomyopathy	Systolic; crescendo-decrescendo	LLSB	None	Enlarged, hyperdynamic apical impulse; bifid carotid impulse with delay; increased intensity during Valsalva maneuver or with squatting to standing	Murmur may not be present in nonobstructive hypertrophic cardiomyopathy
Atrial septal defect	Systolic; crescendo-decrescendo	RUSB	None	Fixed split S_2; right ventricular heave; rarely, tricuspid inflow murmur	May be associated with pulmonary hypertension with increased intensity of P_2, pulmonary valve regurgitation
Ventricular septal defect	Holosystolic	LLSB	None	Palpable thrill; murmur increases with handgrip maneuver, decreases with amyl nitrite	Murmur intensity and duration decrease as pulmonary hypertension develops (Eisenmenger syndrome) Cyanosis if Eisenmenger syndrome develops

A_2 = aortic component of S_2; LLSB = left lower sternal border; LUSB = left upper sternal border; P_2 = pulmonic component of S_2; RLSB = right lower sternal border; RUSB = right upper sternal border.

TABLE 22. Stages of Progression of Valvular Heart Disease

Stage	Definition	Description
A	At risk	Patients with risk factors for development of VHD
B	Progressive	Patients with progressive VHD (mild to moderate severity and asymptomatic)
C	Asymptomatic severe	Asymptomatic patients who have the criteria for severe VHD: C1: Asymptomatic patients with severe VHD in whom the left or right ventricle remains compensated C2: Asymptomatic patients with severe VHD, with decompensation of the left or right ventricle
D	Symptomatic severe	Patients who have developed symptoms as a result of VHD

VHD = valvular heart disease.

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Therefore, a comprehensive, holistic approach is required for determining patient surgical risk and candidacy. Frailty, which is variably defined as a geriatric syndrome characterized by declines in several physiologic systems and processes, portends an increased risk for mortality in patients undergoing surgery and can be measured preoperatively (see MKSAP 18 General Internal Medicine). H

For all patients in whom surgical or interventional therapy is being considered, a multidisciplinary approach with a heart team consisting of cardiologists, surgeons, and interventional cardiologists is recommended. Evaluations in centers with specialized expertise in VHD (for example, a Heart Valve Center of Excellence) is also advised for patients in whom intervention is being considered when (1) there are no symptoms; (2) multiple or complex morbidities are present; or (3) surgical valve repair is favored over valve replacement.

Medical therapy, although often effective for symptom palliation, has not been shown to prevent progression of VHD or improve long-term survival in patients with VHD.

KEY POINTS

- Many heart valve lesions progress slowly, leading patients to unconsciously limit their activity in response; therefore, a careful history and detailed physical examination are essential.
- For all patients with valvular heart disease in whom surgical or interventional therapy is being considered, a multidisciplinary approach with a heart team consisting of cardiologists, surgeons, and interventional cardiologists is recommended.
- Medical therapy, although often effective for symptom palliation, has not been shown to prevent progression of valvular heart disease or improve long-term survival in patients with valvular heart disease.

TABLE 23. Serial Evaluation of Asymptomatic Patients with Left-Sided Valvular Conditions

Factors Considered	Lesion Severity	Frequency of Evaluation
Aortic Stenosis		
Stenosis severity; rate of progression; LV systolic function; ascending aorta dilation if associated with bicuspid aortic valve	At risk (V_{max} <2 m/s)	
	Mild (V_{max} 2.0-2.9 m/s or mean gradient <20 mm Hg)	Clinical evaluation yearly; echo every 3-5 y
	Moderate (V_{max} 3.0-3.9 m/s or mean gradient 20-39 mm Hg)	Clinical evaluation yearly; echo every 1-2 y
	Severe (V_{max} ≥4 m/s or mean gradient ≥40 mm Hg, AVA ≤1.0 cm^2)	Clinical evaluation yearly; echo every 6-12 mo
	Very severe (V_{max} ≥5 m/s or mean gradient ≥60 mm Hg)	Clinical evaluation yearly; echo every 6-12 mo
Aortic Regurgitation		
Regurgitation severity; rate of progression; LV ejection fraction; LV chamber size; ascending aorta dilation if bicuspid aortic valve	Mild (VC <0.3 cm, ERO <0.10 cm^2, RV <30 mL/beat, RF <30%); normal EF	Clinical evaluation yearly; echo every 3-5 y
	Moderate (VC 0.3-0.6 cm, ERO 0.10-0.29 cm^2, RV 30-59 mL/beat, RF 30%-49%)	Clinical evaluation yearly; echo every 1-2 y
	Severe (VC >0.6 cm, ERO >0.3 cm^2, RV ≥60 mL/beat, RF ≥50%)	
	EF ≥50%; LVESD ≤50 mm	Clinical evaluation every 6-12 mo; echo every 6-12 mo, more frequently for dilating LV
	EF <50%; LVESD >50 mm	Clinical evaluation every 6-12 mo; echo every 6-12 mo, more frequently for dilating LV
Mitral Stenosis		
Stenosis severity	Mild and moderate (MVA >1.5 cm^2, diastolic pressure half-time <150 ms)	Clinical evaluation yearly; echo every 3-5 y
	Severe (MVA ≤1.5 cm^2, diastolic pressure half-time ≥150 ms or ≥220 ms with very severe stenosis, PASP >30 mm Hg)	Clinical evaluation yearly; echo every 1-2 y for MVA 1.0-1.5 cm^2, every year for MVA <1.0 cm^2
Mitral Regurgitation		
Regurgitation severity; rate of progression; EF; LV chamber size	At risk (VC <0.3 cm)	Clinical evaluation yearly; echo only if symptomatic
	Mild and moderate (VC <0.7 cm, ERO <0.40 cm^2, RV <60 mL/beat, RF <50%)	Clinical evaluation yearly; echo every 3-5 y for mild severity, every 1-2 y for moderate severity
	Severe (VC ≥0.7 cm, ERO ≥0.4 cm^2, RV ≥60 mL/beat, RF ≥50%)	Clinical evaluation every 6-12 mo; echo every 6-12 mo, more frequently for dilating LV

AVA = aortic valve area; echo = echocardiography; EF = ejection fraction; ERO = effective regurgitant orifice; LV = left ventricular; LVESD = left ventricular end-systolic dimension; MVA = mitral valve area; PASP = pulmonary artery systolic pressure; RF = regurgitant fraction; RV = regurgitant volume; VC = vena contracta width; V_{max} = maximum aortic jet velocity.

Recommendations based on Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP 3rd, Guyton RA, et al; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2014;63:2438-88. [PMID: 24603192] doi:10.1016/j.jacc.2014.02.537

Aortic Stenosis

Clinical Presentation and Evaluation

Aortic stenosis may be congenital, such as in persons with a bicuspid aortic valve, or acquired. The most common cause is degeneration of the valve that occurs with aging; severe lesions occur in approximately 3% of persons aged 65 years and older (**Figure 20**). Other causes include rheumatic disease and chest radiation. Although rheumatic disease of the mitral valve frequently occurs in isolation, rheumatic aortic valve disease almost never occurs without mitral valve involvement. Chest radiation (for example, mantle therapy for non-Hodgkin lymphoma) commonly causes a mixture of both valvular stenosis and regurgitation.

Aortic stenosis results in chronic pressure overload of the left ventricle (LV), leading to concentric LV hypertrophy and myocardial interstitial fibrosis. Diastolic dysfunction follows, with eventual systolic heart failure and pulmonary congestion. Exertional dyspnea, syncope, and angina are the most common presenting symptoms; however, symptoms may not

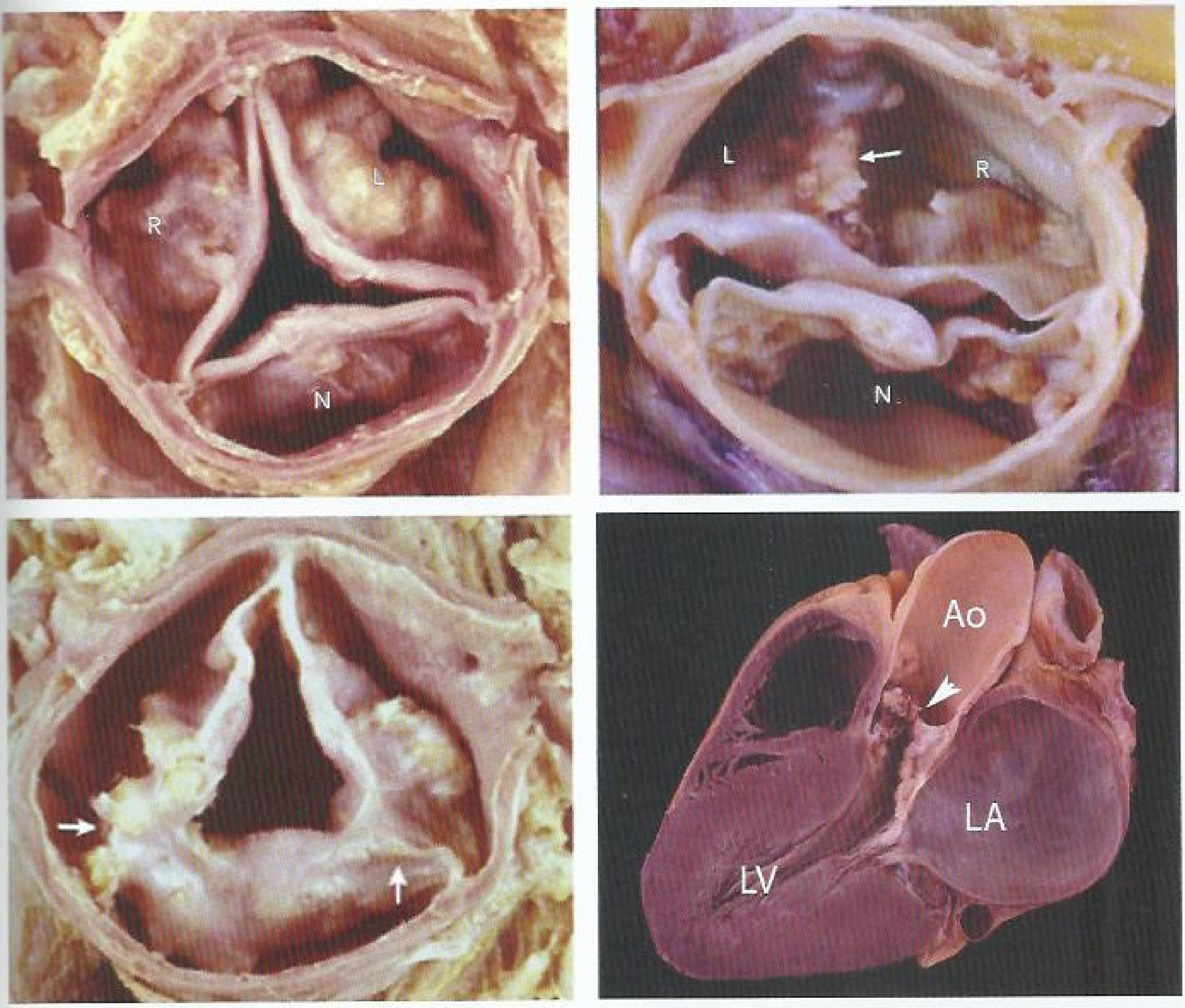

FIGURE 20. Aortic stenosis. Gross specimens showing pathology of degenerative aortic stenosis (*top left panel*), bicuspid aortic stenosis (*top right panel*), and rheumatic aortic disease (*bottom left panel*). The raphe between the left (L) and right (R) aortic cups is fused in this case of bicuspid aortic stenosis (*arrow in top right panel*). Fusion of the commissures is a distinctive feature of rheumatic disease (*arrows in bottom left panel*). Gross specimen showing severe left ventricular (LV) hypertrophy as a result of pressure overload from severe aortic stenosis (*arrowhead in bottom right panel*). Ao = ascending aorta; LA = left atrium; N = noncoronary cusp.

Images courtesy of Dr. William Edwards, Mayo Clinic.

appear until stenosis is severe. The disease typically progresses with a decrease in the aortic valve area of approximately 0.12 cm^2 per year, but the rate depends on patient age, underlying severity of the stenosis, and comorbid conditions, such as kidney failure and hypertension. Among asymptomatic patients with severe aortic stenosis, 75% will die or develop symptoms within 5 years. Once symptoms occur in patients with severe aortic stenosis, life expectancy is generally only 1 to 2 years. Thus, serial evaluation every 6 to 12 months is recommended for patients with severe disease (see Table 23).

In patients with severe aortic stenosis, the characteristic physical findings include a late-peaking systolic murmur, a diminished or absent aortic component of the S_2, and a delay in the carotid upstroke (pulsus tardus) that may be accompanied by a decreased pulse amplitude due to low cardiac output (pulsus parvus). Physical findings that suggest severe aortic stenosis should be promptly evaluated (see Table 21).

The primary imaging modality for the evaluation of aortic stenosis is TTE (**Figure 21**). Echocardiography can determine the cause and severity of aortic stenosis (such as the gradient and valve area) as well as LV function and wall thickness. In some patients, echocardiography may underestimate the severity of aortic stenosis. Further evaluation with cardiac catheterization, during which the cardiac output and the gradient across the aortic valve can be measured, is required when there are discrepancies between the findings on physical

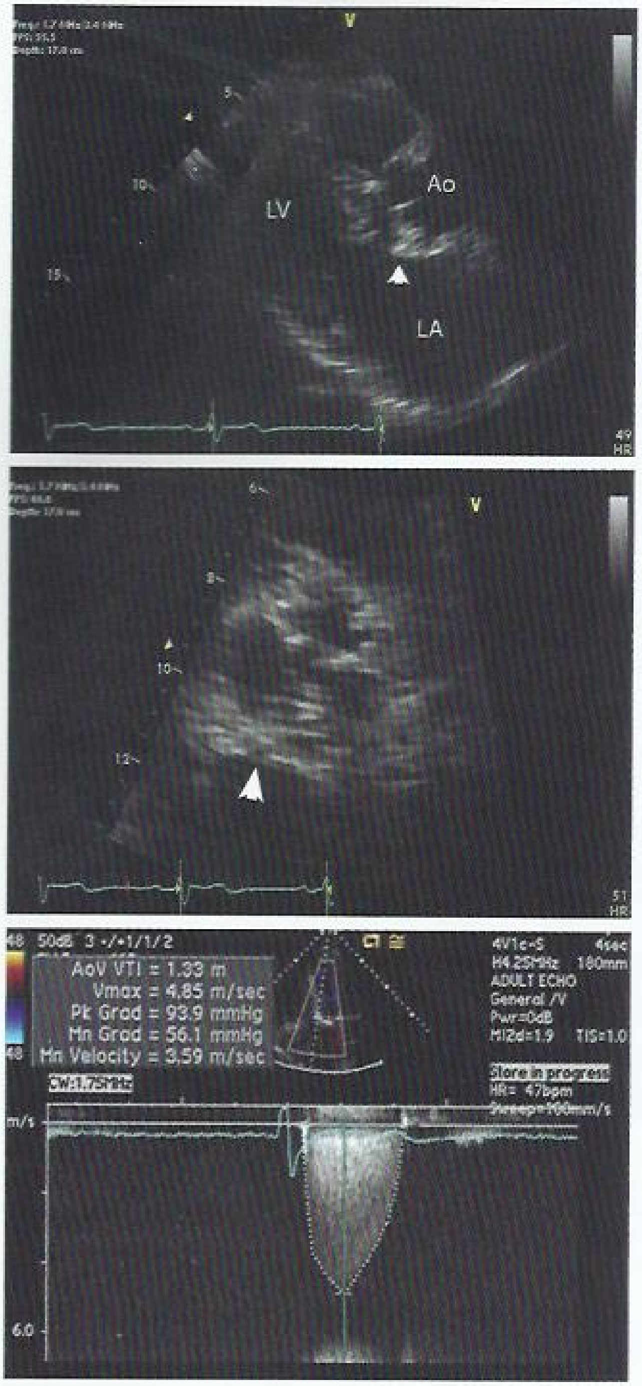

FIGURE 21. Echocardiographic findings in aortic stenosis. Calcific aortic stenosis (*arrowhead*) is present in parasternal long-axis (*top panel*) and short-axis (*middle panel*) views. Left ventricular (LV) hypertrophy is also present. Doppler echocardiogram shows a mean aortic gradient of 56 mm Hg, consistent with severe aortic stenosis (*bottom panel*). Ao = ascending aorta; LA = left atrium.

examination and the echocardiographic results in symptomatic patients being considered for surgery.

Severe aortic stenosis is typically defined by a small valve area (≤1.0 cm²) and either high peak velocity (>4 m/s) or high mean gradient (>40 mm Hg). There are two patient subsets in which severe aortic stenosis may be present with a small valve area and either low velocity or low gradient: patients with severe LV dysfunction and low cardiac output and patients with preserved LV function and paradoxical low-flow, low-gradient aortic stenosis. In the former group, dobutamine echocardiography or an invasive hemodynamic study is needed to distinguish true aortic stenosis from pseudostenosis. With pseudostenosis, dobutamine increases cardiac output and the opening forces on the aortic valve, causing the valve area to increase out of the severe range. With true aortic stenosis, the calculated valve area remains in the severe range with dobutamine administration, and the aortic valve gradient and velocity increase with increased stroke volume. In patients with paradoxical low-flow, low-gradient aortic stenosis, low stroke volume (<35 mL/m²) results from a combination of small LV size and high aortic impedance to flow (hypertension). Determination of lesion severity in paradoxical aortic stenosis requires consideration of the hemodynamics, valve morphology (such as degree of degeneration), presence of LV hypertrophy, and clinical presentation of the patient. In patients with either low-flow, low-gradient severe aortic stenosis or paradoxical low-flow, low-gradient severe aortic stenosis, observational studies have shown improved survival with aortic valve replacement compared with medical therapy.

Management

H Aortic valve replacement is a life-prolonging procedure in patients with severe aortic stenosis. The indications for aortic valve replacement in severe aortic stenosis are (1) the presence of symptoms (such as dyspnea, angina, presyncope, or syncope), (2) LV systolic dysfunction (ejection fraction <50%) in an asymptomatic patient, or (3) a concomitant cardiac surgical procedure for another indication (such as simultaneous coronary artery bypass grafting or ascending aorta surgery). Aortic valve replacement may be considered in asymptomatic patients with abnormal results on supervised exercise testing, such as those with poor exercise tolerance, abnormal electrocardiographic changes, or hypotension during testing.

Aortic valve replacement can be performed with open cardiac surgery (surgical aortic valve replacement [SAVR]) or via transcatheter approach (transcatheter aortic valve replacement [TAVR]) (**Figure 22**). SAVR and TAVR have similar procedural and long-term survival rates, with expected operative mortality rates of 1% to 3%. The choice between surgical and transcatheter interventions is based on the presence of symptoms and the patient's surgical risk, as determined through comprehensive assessment by a multidisciplinary heart team. TAVR is currently indicated for symptomatic patients with trileaflet aortic stenosis who are at intermediate or high surgical risk and who do not have concomitant severe aortic regurgitation. Randomized trials comparing TAVR with SAVR in low-risk patients are ongoing. H

Although the pathophysiology of aortic stenosis is known to be inflammatory, randomized trials of medical therapy, specifically statins, have not found this therapy to be effective in slowing disease progression. For patients with coexistent

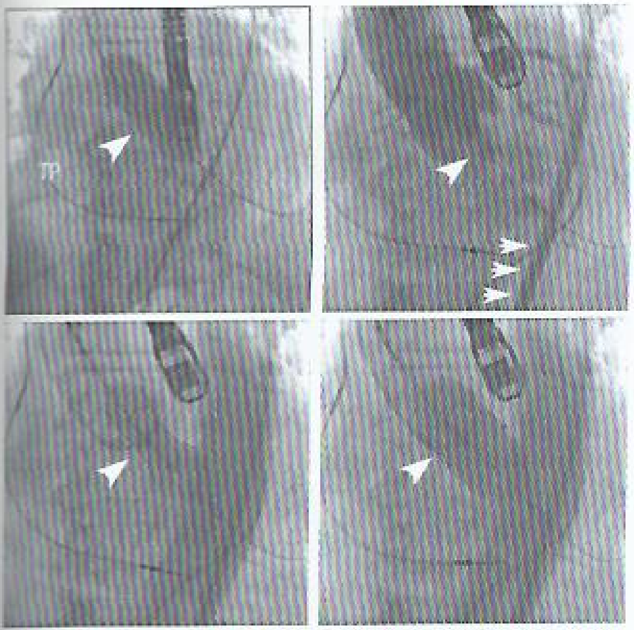

FIGURE 22. Transcatheter aortic valve replacement. *Top left panel:* Balloon aortic valvuloplasty (*arrowhead*) is first performed. *Top right panel:* Using a transfemoral approach (*arrows*), a transcatheter aortic valve (*arrowhead*) is positioned at the aortic annulus using aortography. *Bottom left panel:* The prosthesis (*arrowhead*) is then slowly inflated using rapid pacing from a temporary pacemaker (TP), which creates ventricular standstill. *Bottom right panel:* The prosthesis is fully deployed.

hypertension or heart failure, guideline-directed medical therapy is recommended. Vasodilators should be used with caution in patients with aortic stenosis and heart failure symptoms. In select cases, balloon valvuloplasty may be used to bridge patients to therapy with TAVR or SAVR.

KEY POINTS

- The most common cause of severe aortic stenosis is degeneration of the aortic valve.
- The characteristic physical findings of severe aortic stenosis include a late-peaking systolic murmur, a diminished or absent aortic component of the S_2, and a weak and delayed carotid upstroke.
- Echocardiography is accurate for defining the severity of aortic stenosis in most patients; when there is a discrepancy between the clinical and echocardiographic findings, cardiac catheterization should be considered in patients who are surgical candidates.
- Aortic valve replacement is a life-prolonging intervention in patients with severe aortic stenosis; the patient's surgical risk and the presence of symptoms determine whether aortic valve replacement is performed using open surgery or a transcatheter approach.
- Transcatheter aortic valve replacement is indicated for symptomatic patients with trileaflet aortic stenosis who are at intermediate or high surgical risk and who do not have concomitant severe aortic regurgitation.

Aortic Regurgitation

Clinical Presentation and Evaluation

Aortic regurgitation may be caused by aortic root pathology or intrinsic valve disease and can manifest acutely or chronically. Causes of chronic aortic regurgitation include ascending aortic dilatation and valve abnormalities due to bicuspid disease, calcific degeneration, rheumatic involvement, or chest radiation. Causes of acute aortic regurgitation are endocarditis, blunt chest trauma, iatrogenic causes (such as complications of balloon aortic valvuloplasty), and aortic dissection.

H In chronic aortic regurgitation, volume overload causes progressive LV dilatation and eccentric hypertrophy. Chronic aortic regurgitation may be tolerated for many years but can eventually lead to symptoms, including shortness of breath, fatigue, or angina. Physical findings result from the large stroke volume and LV dilatation and include bounding peripheral pulses, displacement of the LV apex, and a diastolic decrescendo murmur heard either along the right sternal border (suggesting root pathology) or left sternal border (suggesting valve pathology) (see Table 21). The large forward stroke volume can also result in an early-peaking systolic ejection murmur. In patients with acute regurgitation, the abrupt onset of volume overload may not be well tolerated, and these patients can present with acute heart failure or even cardiogenic shock. Additionally, patients with acute regurgitation may not have bounding pulses because stroke volume has not markedly increased, and murmurs may be softer or shorter in duration, owing to the rapid equalization of pressures between the aorta and LV. H

TTE is recommended for the evaluation of aortic regurgitation and LV function. When endocarditis is suspected and transthoracic imaging is suboptimal, transesophageal echocardiography (TEE) is advised. As an alternative, cardiac magnetic resonance (CMR) imaging and invasive angiography also can be used to determine the severity of regurgitation. Criteria for severe aortic regurgitation include a jet width that occupies 65% of the LV outflow tract or more, vena contracta greater than 0.6 cm, holodiastolic flow in the descending aorta, regurgitation volume of 60 mL or more, and effective regurgitant orifice area of 0.3 cm^2 or greater. The LV is also typically dilated in chronic aortic regurgitation. For patients suspected of having an aortic root abnormality, an evaluation with CMR imaging, CT, or TEE is recommended.

Management

H Acute aortic regurgitation due to aortic dissection is a surgical emergency. For other acute causes, the indications for surgery depend on severity, presence of symptoms, and the hemodynamic stability of the patient. In cases of chronic aortic regurgitation, surgery with traditional open aortic valve replacement is advised for patients with symptoms (typically, dyspnea or angina), those with LV dysfunction (ejection fraction <50%), or patients undergoing other cardiac surgery. Surgical treatment of aortic regurgitation is reasonable in cases of significant LV

H CONT. dilatation (end-systolic diameter >50 mm or indexed end-systolic dimension >25 mm/m²). Aortic valve repair without valve replacement may be performed in centers of expertise. Follow-up of asymptomatic patients is based on severity of regurgitation and other factors (see Table 23). H

Medical therapy, preferably with dihydropyridine calcium channel blockers (nifedipine, isradipine, felodipine, nicardipine, nisoldipine, lacidipine, and amlodipine), ACE inhibitors, or angiotensin receptor blockers, is recommended in patients with chronic aortic regurgitation in the setting of hypertension. In the absence of hypertension, medical therapy is appropriate for symptomatic patients who are not surgical candidates.

KEY POINTS

- Characteristic physical findings of chronic aortic regurgitation include bounding peripheral pulses, displacement of the left ventricular apex, and a diastolic decrescendo murmur heard along the right sternal border or left sternal border.
- Emergent surgery is indicated for patients with acute aortic regurgitation due to aortic dissection.
- In cases of chronic aortic regurgitation, surgery with traditional open aortic valve replacement is advised for patients with symptoms, those with left ventricular dysfunction, or patients undergoing other cardiac surgery.
- Medical therapy with dihydropyridine calcium channel blockers, ACE inhibitors, or angiotensin receptor blockers is recommended for patients with aortic regurgitation and hypertension; in the absence of hypertension, medical therapy is appropriate in symptomatic patients who are not surgical candidates.

Bicuspid Aortic Valve Disease

Bicuspid aortic valve disease affects approximately 1% to 2% of the general population. Bicuspid morphology leads to abnormal shear forces and predisposes to early degeneration of the valve, resulting in stenosis in most patients (up to 75%) (see Figure 20) and pure regurgitation in a small minority of patients (2%-10%). Patients with a bicuspid aortic valve typically present with an incidental systolic ejection murmur in adolescence or young adulthood and gradually progress to severe disease in the fifth or sixth decade of life. More than one third of those older than 70 years with severe aortic stenosis have an underlying bicuspid valve.

A bicuspid aortic valve is often accompanied by abnormalities in the aortic arch, independent of the severity of aortic stenosis or regurgitation, and may be associated with aneurysms, dissection, or coarctation. Therefore, in patients with a bicuspid aortic valve, the aortic arch should be examined for aortopathy with CMR imaging, echocardiography, or cardiac CT; serial imaging is indicated if abnormalities are detected. The imaging modality and frequency depend on several factors, including the location and severity of the abnormalities, age of the patient, family history, and candidacy for surgery (see Diseases of the Aorta). Importantly, bicuspid aortic valve disease is heritable, and first-degree relatives should be screened for its presence with echocardiography.

Management of bicuspid aortic valve disease depends on the predominant lesion type (aortic stenosis or regurgitation) and its severity. In patients with a bicuspid valve who are undergoing surgery for severe aortic stenosis or regurgitation, surgical repair of the ascending aorta is advised when the aortic diameter is greater than 4.5 cm. In the absence of surgical indications for a stenotic or regurgitant aortic valve, surgical repair of the ascending aorta or aortic sinuses is advised when the aortic diameter is greater than 5.5 cm or when the diameter is greater than 5.0 cm with additional risk factors for dissection (family history, rate of progression ≥0.5 cm/year).

No medical therapies slow aortic dilatation in patients with aortopathy and a bicuspid aortic valve. Blood pressure should be controlled in patients with concomitant hypertension.

KEY POINTS

- Bicuspid morphology predisposes to early degeneration of the aortic valve, resulting in stenosis in most patients and pure regurgitation in few patients.
- Patients with a bicuspid aortic valve typically present with an incidental systolic ejection murmur in adolescence or young adulthood and gradually progress to severe disease in the fifth or sixth decade of life.
- Management of bicuspid aortic valve disease follows the recommendations for the predominant valve lesion type (aortic stenosis or regurgitation) and severity of the valvular disease.

Mitral Stenosis

Clinical Presentation and Evaluation

The leading cause of mitral stenosis is rheumatic heart disease, which has a higher predilection for women than men (female-to-male ratio of 4:1). Although relatively uncommon in the United States, rheumatic heart disease is frequent in populations with limited access to treatment for streptococcal pharyngitis. Rheumatic heart disease results in fusion of the mitral commissures and, in more advanced forms, calcification of the valve and abnormalities in the subvalvular apparatus (**Figure 23**). Other causes of mitral stenosis are parachute mitral valve, chest radiation, and severe mitral annular calcification. Mitral annular calcification is more common in the elderly and is associated with inflammatory disorders, peripheral artery disease, and chronic kidney disease.

The natural history of mitral stenosis is characterized by a slow progression over decades, with gradual enlargement of the left atrium (LA) and preservation of LV function. Symptoms

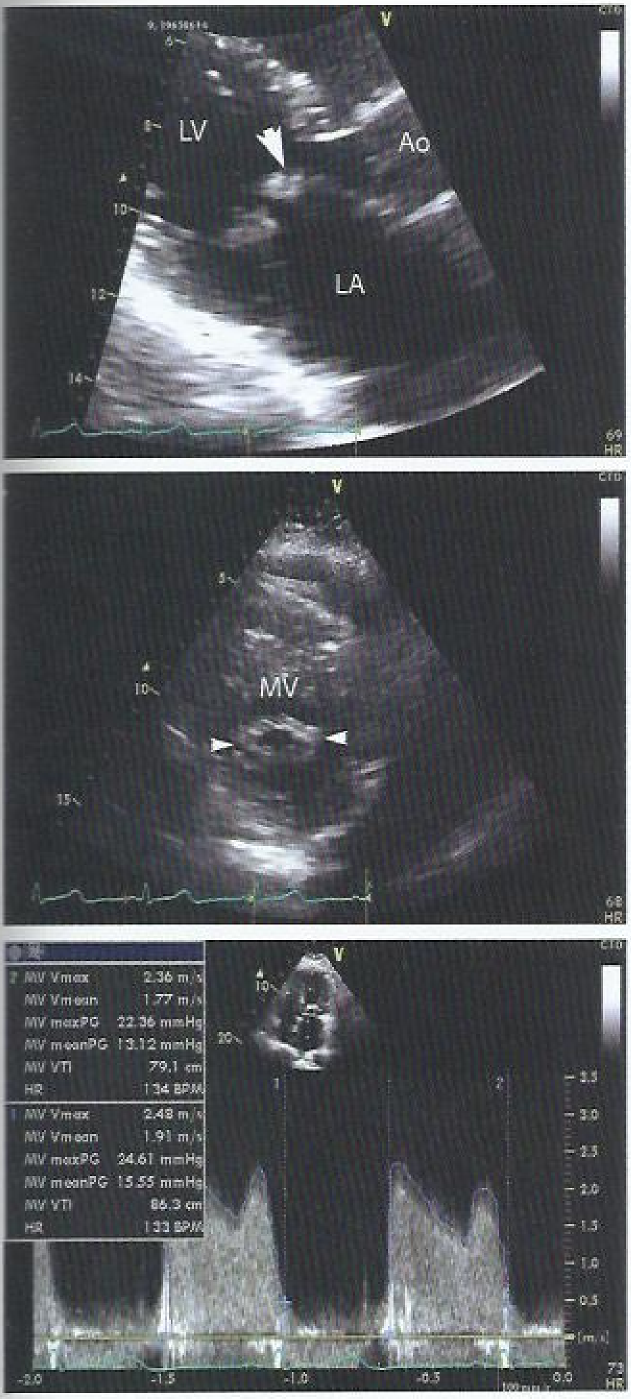

FIGURE 23. Rheumatic mitral stenosis. *Top panel:* Diastolic doming (*arrowhead*) is present with a "hockey stick" deformity from mitral stenosis. *Middle panel:* Commissural fusion (*arrowheads*) of the mitral valve (MV) is present. *Bottom panel:* Doppler echocardiogram showing a mitral gradient of 13 mm Hg, consistent with severe stenosis. Ao = ascending aorta; LA = left atrium; LV = left ventricle.

of mitral stenosis may arise from low cardiac output (fatigue), pulmonary congestion (dyspnea), and pulmonary hypertension with right-sided heart failure (lower extremity edema). Symptoms typically occur with exertion because exercise shortens diastolic filling time and increases the transvalvular flow and diastolic mitral gradient, leading to worsening of LA hypertension. Symptoms may first occur during pregnancy owing to increased blood volume and cardiac output. Patients can also present with systemic embolization, atrial fibrillation, or, in severe cases, hemoptysis. Heart failure is the cause of death in approximately 60% of patients with mitral stenosis, and thromboembolism is the cause in most others.

On physical examination, the findings of mitral stenosis when the valve is pliable include a tapping LV impulse in the precordium, a loud S_1, an increased pulmonic component of S_2, a diastolic opening snap, and a diastolic rumble or low-pitched murmur at the apex (see Table 21). Signs of pulmonary or systemic congestion may be present depending on the severity of the lesion and the patient's volume status.

TTE is highly accurate for assessing mitral stenosis severity, pulmonary pressures, and right ventricular function (see Table 23). Additional imaging or cardiac catheterization is rarely required. Severe mitral stenosis is defined by a mitral valve area of 1.5 cm^2 or less, which usually corresponds to a mean mitral gradient of more than 5 to 10 mm Hg at a normal heart rate. In patients with a discrepancy between the clinical findings and the echocardiographic findings, stress echocardiography with pharmacologic or physical stressors should be pursued to assess the response of the mitral gradient and pulmonary pressures.

Management

The procedure of choice for patients with significant rheumatic mitral stenosis and a pliable mitral valve is percutaneous balloon mitral commissurotomy (PBMC). PBMC is indicated for symptomatic patients with severe mitral stenosis and favorable valve morphology. PBMC may be considered in asymptomatic patients with critical mitral stenosis when the valve area is less than 1.0 cm^2. In patients with LA thrombus, moderate mitral regurgitation, or a severely calcified valve, PBMC should not be performed. In appropriately selected patients, success rates with PBMC are 95%, and complications occur in less than 5% of patients. Surgery for mitral stenosis should be performed in patients with severe symptoms (New York Heart Association functional class III or IV) and a nonpliable valve or concomitantly in patients undergoing other cardiac surgical procedures.

Nearly 50% of patients with mitral stenosis have atrial fibrillation, and without anticoagulation therapy, these patients have a risk for thromboembolism of 20% to 25%. Patients with mitral stenosis and atrial fibrillation should receive warfarin, with a goal INR of 2.0 to 3.0. Other indications for anticoagulation are a history of LA thrombus or systemic embolization. Notably, clinical trials of non–vitamin K antagonist oral anticoagulants in atrial fibrillation excluded patients with mitral stenosis; therefore, the efficacy and safety of these agents in this population have not been demonstrated.

Because the mitral gradient is heavily dependent on transvalvular flow, medical therapy with negative chronotropic agents, diuretics, and long-acting nitrates can be effective for

symptom palliation in patients who are not candidates for interventional or surgical therapy.

KEY POINTS

- Transthoracic echocardiography is highly accurate for assessing the severity of mitral stenosis, pulmonary hypertension, and right ventricular function.
- Percutaneous balloon mitral commissurotomy is indicated for symptomatic patients with severe mitral stenosis and favorable valve morphology.
- Warfarin therapy is recommended for patients with mitral stenosis and a history of atrial fibrillation, left atrial thrombus, or systemic embolization.

Mitral Regurgitation

Clinical Presentation and Evaluation

H Mitral regurgitation may arise from any portion of the complex valve apparatus (such as the leaflets, annulus, chordae, papillary muscles, or LV free walls) and may present acutely or chronically. Causes of acute mitral regurgitation are infective endocarditis, papillary muscle ischemia or rupture, trauma (for example, injury from PBMC), or degenerative disease with chordal rupture and flail leaflet. Chronic mitral regurgitation is classified as primary or secondary. Chronic primary mitral regurgitation relates to processes involving any portion of the mitral annulus. Common causes of primary mitral regurgitation are mitral valve prolapse (also known as myxomatous or degenerative mitral valve disease), radiation therapy, rheumatic disease, and cleft mitral valve. Chronic secondary mitral regurgitation involves causes other than the annulus, such as ventricular dysfunction. H

Mitral regurgitation results in volume overload with LV dilatation and LA hypertension, which may progress and cause pulmonary hypertension and right ventricular failure. In acute mitral regurgitation, heart failure symptoms often occur abruptly because there has not been time for adaptive chamber dilatation, and patients may present with cardiogenic shock. The systolic murmur in acute mitral regurgitation may be brief because of the rapid equalization of LA and LV pressures. Echocardiography with color flow imaging can underestimate the severity of the regurgitation. Thus, when acute mitral regurgitation is suspected, comprehensive assessment to identify the potential causes should be pursued, and additional imaging with TEE should be considered. Aggressive evaluation and accurate diagnosis are crucial for patients with acute mitral regurgitation.

Chronic primary mitral regurgitation is predominantly caused by mitral valve prolapse, which affects approximately 2% of the general population or roughly 500,000 persons in the United States. Echocardiography in patients with chronic primary mitral regurgitation may show a range of abnormalities, including prolapse, gross degeneration of one or both leaflets (Barlow syndrome), or chordal rupture with flail leaflet (**Figure 24**). Barlow syndrome is more common in young adult patients. In patients who are relatively older, fibroelastic deficiency predominates and frequently results in chordal rupture. The mitral valve apparatus is normal in patients with chronic secondary mitral regurgitation (**Figure 25**). In these patients, ventricular dysfunction causes mitral regurgitation through papillary muscle displacement and tethering of the mitral leaflets, which impairs coaptation.

The physical examination in patients with chronic mitral regurgitation is notable for a blowing holosystolic murmur at the apex. In patients with mitral valve prolapse, one or more systolic clicks may precede the murmur, and variation in severity, preload, and afterload can lead to differences in murmur onset (holosystolic, midsystolic, or late systolic). In patients with LV dilatation, the apical impulse may be displaced laterally, and an S_3 may be audible, especially in patients with secondary mitral regurgitation due to LV dysfunction.

H TTE readily assesses the severity of primary mitral regurgitation, with a high degree of accuracy and precision. Severe primary mitral regurgitation is defined by using several parameters; the most common is an effective regurgitant orifice area of 0.4 cm^2 or larger, regurgitant volume of 60 mL or more, or vena contracta of 0.7 cm or larger. In some instances, TEE may be required to further elucidate the mechanism of the mitral regurgitation, particularly when surgical or interventional therapy is planned. TEE may be especially useful in evaluating for acute mitral regurgitation, in which rapid systolic equalization of LV and LA pressures can pose challenges for both the bedside examination and TTE imaging. H

Appropriate follow up of asymptomatic patients with mitral regurgitation is outlined in Table 23.

Management

H Medical therapy and surgical intervention can be life saving in patients with acute severe mitral regurgitation. Vasodilator therapy with a titratable drug, such as nitroprusside, decreases aortic impedance and mitral regurgitation, thereby improving forward cardiac output. An intra-aortic balloon pump can be used to decrease afterload and augment systemic and coronary perfusion pressures. Prompt surgical correction should be considered for all patients with acute severe mitral regurgitation. H

Patients with chronic severe primary mitral regurgitation generally do poorly without surgery, particularly when there are significant symptoms, flail leaflet, or LV dilatation. In one study of 458 patients with asymptomatic severe primary mitral regurgitation, the 5-year survival rate was only 58%. Surgical treatment with repair of the mitral valve is indicated for chronic severe primary mitral regurgitation in (1) symptomatic patients with left ventricular ejection fraction (LVEF) greater than 30%, (2) asymptomatic patients with LV dysfunction (LVEF of 30%-60% and/or LV end-systolic diameter ≥40 mm), or (3) patients undergoing another cardiac surgical procedure. Surgical repair is reasonable in asymptomatic patients with preserved LV function when the expected repair success rate is

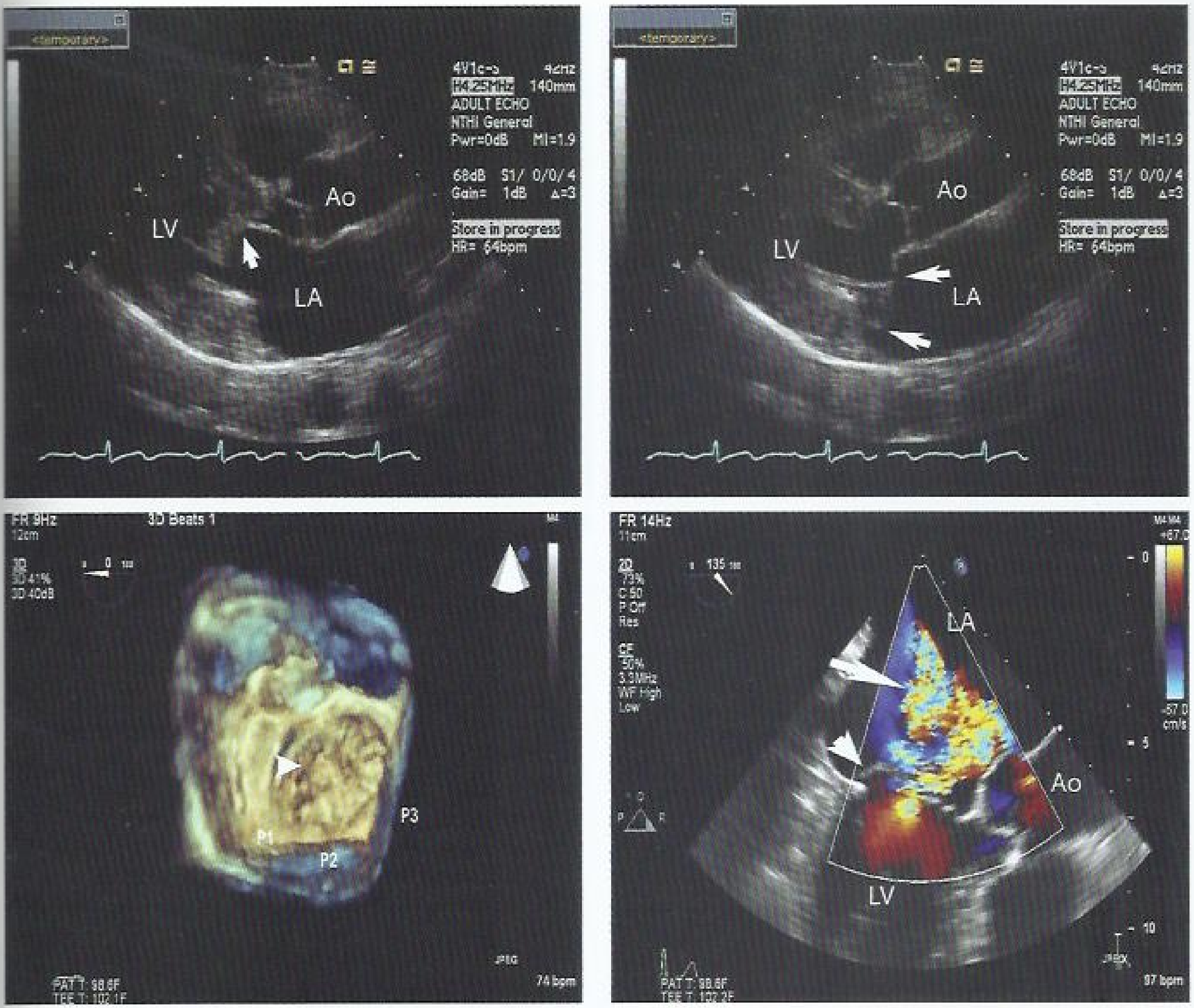

FIGURE 24. Mitral valve prolapse. Echocardiogram showing normal opening of the mitral valve (*arrow, top left panel*), which then prolapses into the left atrium during systole (*arrows, top right panel*). In a different patient with myxomatous degeneration, a flail portion of the posterior mitral valve is present (*bottom panels*); torn chordae are seen (*arrowheads*), leading to severe regurgitation seen on color flow imaging (*arrow, bottom right panel*). Ao = ascending aorta; LA = left atrium; LV = left ventricle.

greater than 95% and the operative risk is less than 1% or when serial imaging studies have demonstrated a progressive increase in LV size or decrease in LVEF. Mitral valve repair should also be considered in asymptomatic patients with chronic severe primary mitral regurgitation who have new-onset atrial fibrillation or pulmonary hypertension (pulmonary artery systolic pressure >50 mm Hg). Surgical repair is preferred over replacement in all patients, and patients should be referred to a surgical center with expertise in valve repair. Medical therapy with vasodilators in patients with primary mitral regurgitation is not beneficial in the absence of symptoms or LV dysfunction.

For patients who are not surgical candidates, mitral valve repair with a catheter-based clip device was approved by the FDA in 2013. The percutaneously delivered clip improves coaptation of the mitral valve leaflets, leading to increased valve closure and a reduction in regurgitation. In selected patients with primary mitral regurgitation, success rates with implantation of the device are approximately 90%, with a procedural mortality of approximately 2%.

In patients with chronic secondary mitral regurgitation, the primary goal of therapy is to address the underlying ventricular dysfunction with guideline-directed medical therapy and, if indicated, cardiac resynchronization therapy (see Heart Failure). Guideline-directed medical therapy for ventricular dysfunction includes ACE inhibitors, angiotensin receptor blockers, an angiotensin receptor-neprilysin inhibitor, β-blockers, diuretics, and/or aldosterone antagonists. Benefits of valve repair or replacement in patients with secondary mitral regurgitation are less certain, although studies have

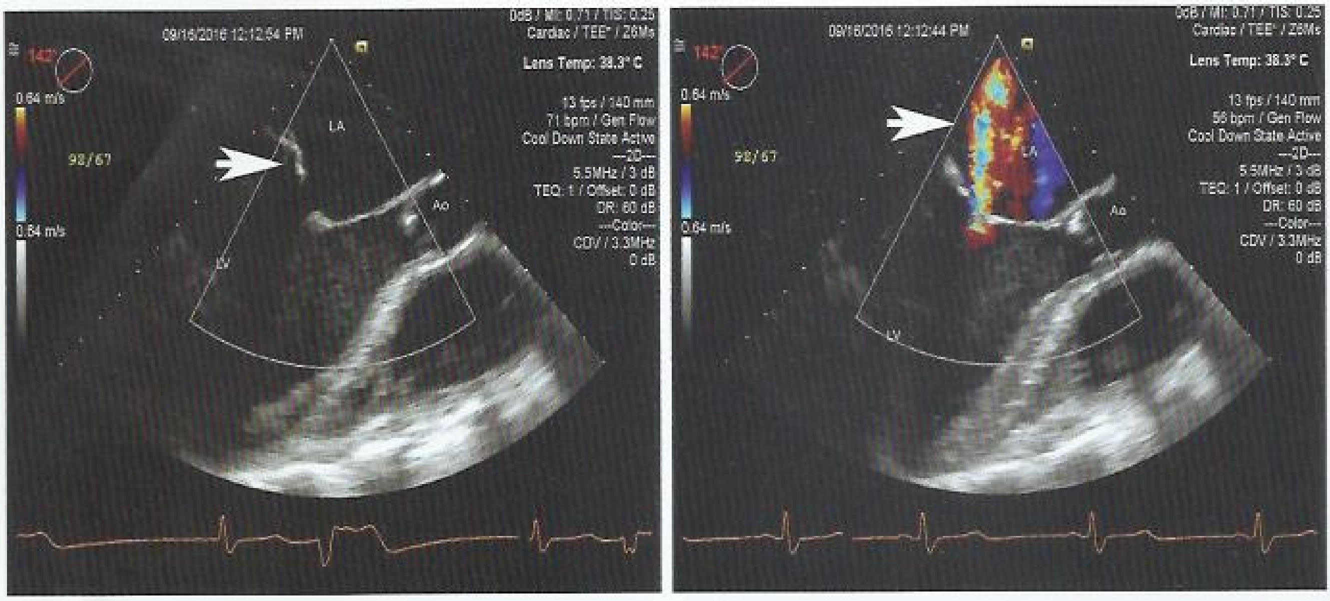

FIGURE 25. Secondary mitral regurgitation in a patient with prior inferior myocardial infarction. Tethering of the posterior leaflet (*arrow*) is present due to the prior infarction and left ventricular remodeling (*left panel*). Mitral regurgitation (*arrow*) is evident on color flow imaging (*right panel*). Ao = ascending aorta; LA = left atrium; LV = left ventricle.

demonstrated favorable LV remodeling after surgery. Surgery for secondary mitral regurgitation is generally advised for those undergoing concomitant cardiac surgical procedures (for example, coronary artery bypass grafting), but mitral regurgitation may recur after repair because of primary LV dysfunction. Trials of transcatheter mitral valve replacement for patients with secondary mitral regurgitation and high surgical risk are ongoing.

KEY POINTS

- Patients with acute mitral regurgitation may present with acute heart failure; these patients may be difficult to diagnose clinically or with echocardiography.
- The most common cause of chronic primary mitral regurgitation is mitral valve prolapse.
- Surgery for chronic severe primary mitral regurgitation is indicated in the presence of symptoms, left ventricular dilatation, or need for concomitant cardiac surgery.
- Surgical repair is preferred over replacement in patients with chronic primary mitral regurgitation, and patients should be referred to a surgical center with expertise to improve the chances of repair.
- Transcatheter mitral valve repair with implantation of a clip device is indicated for patients with chronic primary mitral regurgitation who are at high surgical risk.
- Patients with chronic secondary mitral regurgitation should be treated with guideline-directed medical therapy for ventricular dysfunction, although surgical intervention may be considered for those undergoing concomitant cardiac surgery.

Tricuspid Valve Disease

Tricuspid regurgitation, the most common form of tricuspid valve disease, is frequently functional and clinically asymptomatic. Causes of tricuspid regurgitation include cor pulmonale (or pulmonary hypertension) with right ventricular failure, pacemaker or defibrillator lead placement, trauma, congenital abnormalities, and infective endocarditis. When symptomatic, patients can present with fatigue from low cardiac output and symptoms and signs of right-sided failure, such as elevated jugular venous pulse (a large *c-v* wave), a palpable right ventricular lift, hepatic congestion with pulsatile liver, and peripheral edema. The murmur of tricuspid regurgitation is typically a holosystolic murmur heard along the left sternal border that increases during inspiration due to increased venous return.

Tricuspid regurgitation should be evaluated by TTE, which also allows assessment of right ventricular function and estimation of pulmonary pressures. In patients with tricuspid regurgitation due to pacemaker or defibrillator lead placement, TEE may be required to more clearly evaluate the regurgitant murmur.

Medical therapy with loop diuretics and aldosterone antagonists is effective in improving symptoms of right-sided congestion; however, caution should be exercised to minimize the potential for creating a low-flow state with impaired cardiac output. Surgery is recommended for patients with severe tricuspid regurgitation who are undergoing left-sided valve surgery. Additionally, surgery may be considered in patients with symptomatic tricuspid regurgitation who are unresponsive to medical therapy or have right-sided heart failure.

Tricuspid stenosis is nearly always caused by rheumatic disease. Other causes include radiation therapy, carcinoid

syndrome, and medication use (for example, the ergot agents pergolide or cabergoline). Symptoms of tricuspid stenosis (fatigue, cold skin) are typically overshadowed by those caused by the left-sided abnormalities of coexistent rheumatic mitral disease. Findings on physical examination include those of right-sided congestion (elevated jugular venous pulse, hepatic congestion, peripheral edema) and a diastolic rumble. Surgery for tricuspid stenosis is typically performed in concert with therapy for rheumatic mitral disease.

KEY POINTS

- Loop diuretics and aldosterone antagonists can improve symptoms of right-sided congestion in patients with significant tricuspid regurgitation.
- Tricuspid valve surgery is recommended for patients with severe tricuspid regurgitation undergoing left-sided valve surgery and may be considered in select cases of severe tricuspid regurgitation that are refractory to medical therapy.

Prosthetic Valves

The choice of prosthesis for a patient undergoing surgical valve replacement is complex. Factors to consider are the patient's age, the expected durability of the prosthesis, the surgical risk for reoperation in the event of degeneration, and the ability and willingness of the patient to take warfarin for anticoagulation. The American College of Cardiology/American Heart Association VHD guideline recommends a mechanical valve prosthesis in patients younger than 50 years, bioprosthesis in patients older than 70 years, and either a bioprosthesis or mechanical valve prosthesis in those age 50 to 70 years. However, the final decision on valve type should be reached through a shared decision-making process between the care provider and patient. The patient should thoroughly understand the risks and benefits as well as have decision-making capacity. Additional considerations include the expected durability of bioprostheses (15 years) and that structural deterioration of the valve is more common in younger patients. In those younger than 60 years, approximately 40% of valves have evidence of clinically severe deterioration by 15 years.

Immediately after implantation, all patients should undergo echocardiography to document the baseline hemodynamic performance of the valve, and repeat evaluations should be performed for signs or symptoms of prosthetic dysfunction. Annual evaluation is recommended for all patients with a bioprosthesis beginning at 10 years after surgery. Data on long-term durability of TAVR prostheses are currently limited to a follow-up of 5 years; however, thus far, valve durability is not different from surgical prostheses.

Lifelong warfarin anticoagulation is indicated in all patients with a mechanical valve prosthesis. In recent VHD guidelines, the goal INR for warfarin anticoagulation in patients with a mechanical prosthesis has shifted from a range to a single value. This change was made to minimize the time the patient spends at the low and high ends of a target range because drifting above and below the range can be deleterious. The use of a single-value INR target can pose logistic challenges for testing and warfarin adjustments, and in those instances, recommendations to improve processes and enhance patient understanding and motivation should be considered.

In patients with a mechanical aortic valve prosthesis (bileaflet or current-generation single-tilting disc) with no additional risk factors for thromboembolism (history of embolization, hypercoagulable disorder, LV dysfunction, atrial fibrillation), the goal INR for warfarin anticoagulation is 2.5. In patients with a mechanical aortic valve prosthesis with risk factors for thromboembolism, an older-generation aortic valve prosthesis (ball-in-cage), or any mitral prosthesis, the target INR is 3.0. Because of the risk for valve thrombosis, direct thrombin inhibitors and factor Xa inhibitors should not be used for anticoagulation therapy in patients with a mechanical valve prosthesis. Oral anticoagulation with warfarin should be considered for at least 3 months and as long as 6 months after implantation of a mitral or aortic bioprosthesis. An INR of 2.5 should be targeted in these patients.

Aspirin (75-100 mg/d) is highly recommended in addition to warfarin therapy for patients with a mechanical prosthesis based on the results of randomized trials, which showed reduction in the risk for embolic events, including stroke (1.3% per year versus 4.2% per year; $P < 0.027$) and death (2.8% per year versus 7.4% per year; $P < 0.01$). For all patients with a bioprosthesis, low-dose aspirin is generally recommended.

KEY POINTS

- A shared decision-making process should guide the choice of prosthetic valve type.
- Echocardiographic evaluation of prosthetic valve function is recommended at baseline and in patients with symptoms or signs suggesting prosthetic dysfunction.
- Annual echocardiographic evaluation is recommended for all patients with a bioprosthesis beginning at 10 years after surgery.
- Lifelong warfarin anticoagulation is indicated in all patients with a mechanical valve prosthesis.
- Antiplatelet therapy with low-dose aspirin is strongly recommended for patients with a mechanical prosthesis and is reasonable for patients with a bioprosthesis.

Infective Endocarditis

Diagnosis and Management

Infective endocarditis is a life-threatening disorder that involves native valvular structures or implanted cardiovascular devices. Such devices include cardiac valve prostheses, permanent pacemakers, implanted cardioverter-defibrillators, and occluders for repair of congenital lesions (such as atrial septal defect and ventricular septal defect occluders). Risk factors for

infective endocarditis include advanced age, diabetes mellitus, immunosuppression, injection drug use, congenital heart disease, cardiac transplantation with valvulopathy, and an implanted cardiovascular device. Early diagnosis, targeted antimicrobial therapy, and consideration of early surgical intervention are paramount to the evaluation and treatment of infective endocarditis.

Infective endocarditis is diagnosed with the modified Duke criteria. Definite infective endocarditis requires either pathological confirmation (microorganisms demonstrated by culture or histologic examination of a vegetation, a vegetation that has embolized, or an intracardiac abscess specimen; or a vegetation or intracardiac abscess confirmed by histological examination showing active endocarditis) or clinical criteria consisting of two major criteria, one major criterion plus three minor criteria, or five minor criteria (**Table 24**). Possible infective endocarditis requires one major criterion and one minor criterion, or three minor criteria. Infective endocarditis is excluded when there is a firm alternate diagnosis, resolution of infective endocarditis syndrome with antibiotic therapy for 4 days or less, or no pathological evidence of infective endocarditis at surgery or autopsy with antibiotic therapy for 4 days or less.

Blood cultures are positive in 90% of infective endocarditis cases. In the remaining cases (that is, culture-negative infective endocarditis), serologic testing is required to identify the causative microorganism. For patients with infective endocarditis with a prosthetic valve, the syndrome is classified according to the time from surgery as early (within 60 days), intermediate (60-365 days), and late (>365 days). Early prosthetic valve endocarditis (PVE) is characterized by infection with hospital-acquired microbes, such as *Staphylococcus aureus*. Coagulase-negative staphylococci are the most common microbes in intermediate PVE. Although both *S. aureus* and coagulase-negative staphylococci remain important causes of late PVE, the microbes in late PVE more typically resemble those of native valve endocarditis.

TABLE 24. Major and Minor Criteria Used in the Modified Duke Criteria

Major Criteria
Blood culture positive for infective endocarditis
Typical microorganisms consistent with infective endocarditis from two separate blood cultures: Viridans streptococci, *Streptococcus bovis*, HACEK group (*Haemophilus* spp., *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella* spp., and *Kingella kingae*), *Staphylococcus aureus*; or community-acquired enterococci, in the absence of a primary focus; or
Microorganisms consistent with infective endocarditis from persistently positive blood cultures, defined as follows:
At least two positive cultures of blood samples drawn 12 h apart; or
All of three or a majority of at least four separate cultures of blood (with first and last samples drawn at least 1 h apart)
Single blood culture positive for *Coxiella burnetii* or antiphase I IgG antibody titer >1:800
Evidence of endocardial involvement
Echocardiogram positive for infective endocarditis (TEE recommended in patients with prosthetic valves, rated at least "possible infective endocarditis" by clinical criteria, or complicated infective endocarditis [paravalvular abscess]; TTE as first test in other patients), defined as follows:
Oscillating intracardiac mass on valve or supporting structures, in the path of regurgitant jets, or on implanted material in the absence of an alternative anatomic explanation; or
Abscess; or
New partial dehiscence of prosthetic valve
New valvular regurgitation (worsening or changing of pre-existing murmur not sufficient)
Minor Criteria
Predisposition, predisposing heart condition, or injection drug use
Fever (temperature >38°C [100.4°F])
Vascular phenomena: major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, and Janeway lesions
Immunologic phenomena: glomerulonephritis, Osler nodes, Roth spots, and rheumatoid factor
Microbiologic evidence: positive blood culture but does not meet a major criterion as noted above[a] or serologic evidence of active infection with organism consistent with infective endocarditis

TEE = transesophageal echocardiography; TTE = transthoracic echocardiography.

[a]Excludes single culture positive for coagulase-negative staphylococci and organisms that do not cause endocarditis.

Reproduced with permission from Li JS, Sexton DJ, Mick N, Nettles R, Fowler VG Jr, Ryan T, et al. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. Clin Infect Dis. 2000;30:637. [PMID: 10770721] Copyright 2000, Oxford University Press.

TTE is recommended to identify vegetations and associated hemodynamic derangements (for example, changes in LV function or pulmonary pressures). TEE is recommended in patients with intermediate or high suspicion for infective endocarditis when TTE is not diagnostic (such as with a prosthetic valve), intracardiac device leads are present, or complications such as abscess have developed or are suspected (conduction abnormalities on electrocardiogram or persistent bacteremia despite antibiotic therapy).

Appropriate antimicrobial therapy should be initiated once cultures have been obtained and guidance from sensitivity data and infectious disease consultants has been made available. Empiric antimicrobial therapy may be initiated in high-risk patients (such as those with septic shock) on the basis of patient characteristics, predisposing factors, and epidemiologic factors. For patients with VHD and unexplained fever, antimicrobials should not be administered before several blood cultures are drawn, and all efforts should be made to use targeted therapy when microbiologic results are available.

The decision to pursue surgery for treatment of infective endocarditis is complex and requires a multidisciplinary approach. Early surgery (during hospitalization and before completion of an antimicrobial course) is recommended for patients with (1) symptomatic heart failure and valvular dysfunction; (2) left-sided infective endocarditis caused by fungal infections or highly-resistant organisms; (3) associated complications, such as annular or aortic abscess, destructive penetrating lesions, or heart block; or (4) persistent bacteremia or fevers lasting more than 5 to 7 days despite appropriate antimicrobial therapy. Early surgery is reasonable in patients with recurrent emboli and persistent valve vegetations and may be considered in the presence of a large (>10-mm), left-sided vegetation. When infective endocarditis is associated with a pacemaker or defibrillator, the entire system (generator and leads) must be removed.

Infective endocarditis carries significant risk for morbidity and mortality, with high rates of in-hospital mortality (20%), 1-year mortality (40%), peripheral embolization (23%), stroke (17%), and need for cardiac surgery (48%).

Prophylaxis

Endocarditis prophylaxis is recommended in a specific group of patients before dental procedures that involve manipulation of gingival tissue or the periapical region of the teeth, or perforation of the oral mucosa (**Table 25**). Although endocarditis prophylaxis was previously advised for a broad population, current guidelines now recommend its use only for patients with (1) a history of endocarditis; (2) cardiac transplantation with valve regurgitation due to a structurally abnormal valve; (3) a prosthetic valve; (4) prosthetic material used for cardiac valve repair, including annuloplasty rings and chords; or (5) congenital heart disease, including unrepaired cyanotic disease, repaired lesions with residual defects at the site or adjacent to the site of a prosthetic patch or prosthetic device, or disease that has been repaired with prosthetic material (surgical or catheter-based) within the previous 6 months.

TABLE 25. Prophylactic Infective Endocarditis Regimens for Adults at Highest Risk of an Adverse Outcome Before a Dental Procedure

Situation	Agent	Dosage[a]
Oral	Amoxicillin	2 g
Unable to take oral medication	Ampicillin	2 g IM or IV
	or	
	Cefazolin or ceftriaxone	1 g IM or IV
Allergic to penicillin or ampicillin - oral	Cephalexin[b,c]	2 g
	or	
	Clindamycin	600 mg
	or	
	Azithromycin or clarithromycin	500 mg
Allergic to penicillin or ampicillin and unable to take oral medication	Cefazolin or ceftriaxone	1 g IM or IV
	or	
	Clindamycin	600 mg IM or IV

IM = intramuscular; IV = intravenous.

[a]Regimen consists of a single dose 30 to 60 minutes before the dental procedure, or, if inadvertently not administered, drug may be given up to 2 hours after the procedure.

[b]Or other first- or second-generation oral cephalosporin in equivalent adult dosage.

[c]Cephalosporins should not be used in an individual with a history of anaphylaxis, angioedema, or urticaria with penicillins or ampicillin.

Information from Wilson W, Taubert KA, Gewitz M, Lockhart PB, Baddour LM, Levison M, et al; American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee. Prevention of infective endocarditis: guidelines from the American Heart Association: a guideline from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee, Council on Cardiovascular Disease in the Young, and the Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and the Quality of Care and Outcomes Research Interdisciplinary Working Group. Circulation. 2007;116:1736-54. [PMID: 17446442]

KEY POINTS

- Risk factors for infective endocarditis include advanced age, diabetes mellitus, immunosuppression, injection drug use, congenital heart disease, and an implanted cardiovascular device.
- Early surgery is indicated for patients with acute infective endocarditis presenting with valve stenosis or regurgitation resulting in heart failure; left-sided infective endocarditis caused by fungal or other highly resistant organisms; infective endocarditis complicated by heart block, annular or aortic abscess, or destructive penetrating lesion; and infective endocarditis with persistent bacteremia or fever lasting longer than 5 to 7 days after starting antibiotic therapy.

Myocardial Disease

Hypertrophic Cardiomyopathy

Clinical Presentation

Hypertrophic cardiomyopathy (HCM) is a common autosomal dominant heritable disorder related to mutations in the genes that predominantly encode sarcomeric proteins. It is characterized by the presence of increased left ventricular (LV) wall thickness in the absence of loading conditions or other underlying causes. HCM affects approximately 1 in 500 persons. Most patients with HCM remain asymptomatic and have normal life expectancy; however, certain subsets of patients are more likely to develop symptomatic disease and are at risk for sudden cardiac death (SCD).

The diagnosis of HCM often results from the evaluation of a heart murmur or abnormal electrocardiogram. Symptomatic individuals usually present with signs and symptoms of heart failure or arrhythmias. HCM may be identified within all age groups. In the United States, most index cases present within the third to fourth decade of life.

Symptoms of heart failure may be associated with abnormal LV filling (diastolic dysfunction) or dynamic left ventricular outflow tract (LVOT) obstruction. Diastolic dysfunction is multifactorial, involving increased chamber stiffness related to hypertrophy, progressive fibrosis, and myocardial ischemia due to mismatch of coronary flow and LV mass. Dynamic LVOT obstruction, characterized by asymmetric LV hypertrophy with prominent interventricular septal thickening, is the most classic form of HCM. During ventricular systole, anterior motion of the mitral valve results in early to midsystolic obstruction of the LVOT and subsequent mitral regurgitation related to leaflet malcoaptation ("eject-obstruct-leak" triad). Patients with dynamic obstruction may develop dyspnea, presyncope, or syncope during periods of increased ventricular contractility (exercise) or with decreases in ventricular preload or afterload, all of which may worsen the degree of obstruction.

Arrhythmias may manifest as palpitations, syncope, atrial fibrillation, or SCD. Atrial fibrillation is common in patients with HCM, and risk increases with age. During atrial fibrillation with rapid ventricular response, diastolic filling periods shorten, worsening diastolic dysfunction; reduced LV filling may exacerbate the LVOT gradient. In some cases, SCD may be the initial presentation of HCM.

Evaluation

Physical examination may be normal in patients without LVOT obstruction. The most common finding related to LVOT obstruction is a cardiac murmur, and dynamic maneuvers during examination are helpful in differentiating HCM from fixed valvular obstruction (**Table 26**).

Twelve-lead electrocardiography (ECG) is useful in the evaluation of HCM and reveals abnormal findings in 75% to 95% of affected persons. The most common ECG abnormalities include increased QRS voltage, evidence of left atrial enlargement, LV conduction abnormalities, pathologic Q waves, and significant repolarization abnormalities (**Figure 26**); however, there is substantial interpersonal variability in the degree of abnormalities.

The clinical diagnosis of HCM is most commonly established by transthoracic echocardiography (TTE). Echocardiography demonstrates the magnitude and distribution of hypertrophy, reveals the presence and degree of dynamic LVOT obstruction and mitral regurgitation, and characterizes diastolic LV filling. Doppler echocardiography is the modality of choice for quantifying the LVOT gradient in patients suspected of having HCM. Increasingly, cardiac magnetic resonance (CMR) imaging has also been used for diagnosis, especially when the diagnosis is uncertain despite echocardiography (**Figure 27**). CMR imaging has higher resolution than echocardiography and better defines LV aneurysms and thrombi. When used with intravenous

TABLE 26. Physical Examination Findings of Dynamic Left Ventricular Outflow Tract Obstruction Versus Fixed Valvular Aortic Stenosis

Finding or Maneuver	Hypertrophic Cardiomyopathy with Dynamic LVOT Obstruction	Valvular Aortic Stenosis
Characteristic of murmur	Ejection-quality murmur usually best heard at left lower sternal border; generally does not radiate to the carotid arteries	Ejection-quality murmur usually best heard at right second intercostal space with radiation to the carotid arteries
Carotid impulse	Brisk upstroke; may have two impulses for each ejection (bifid)	Upstroke is often diminished and delayed (parvus et tardus)
Valsalva maneuver	Increase in intensity of murmur during strain phase (+LR = 14)	No change or diminished murmur intensity during strain phase
Position	Increase in intensity of murmur with standing from squat or seated position (+LR = 6.0); decrease in murmur with elevation of legs when supine (+LR = 7.6)	No significant change in intensity of murmur with position
Peripheral pulse after PVC	No change or decrease in intensity of pulse	Increase in intensity of pulse

+LR = positive likelihood ratio; LVOT = left ventricular outflow tract; PVC = premature ventricular contraction.

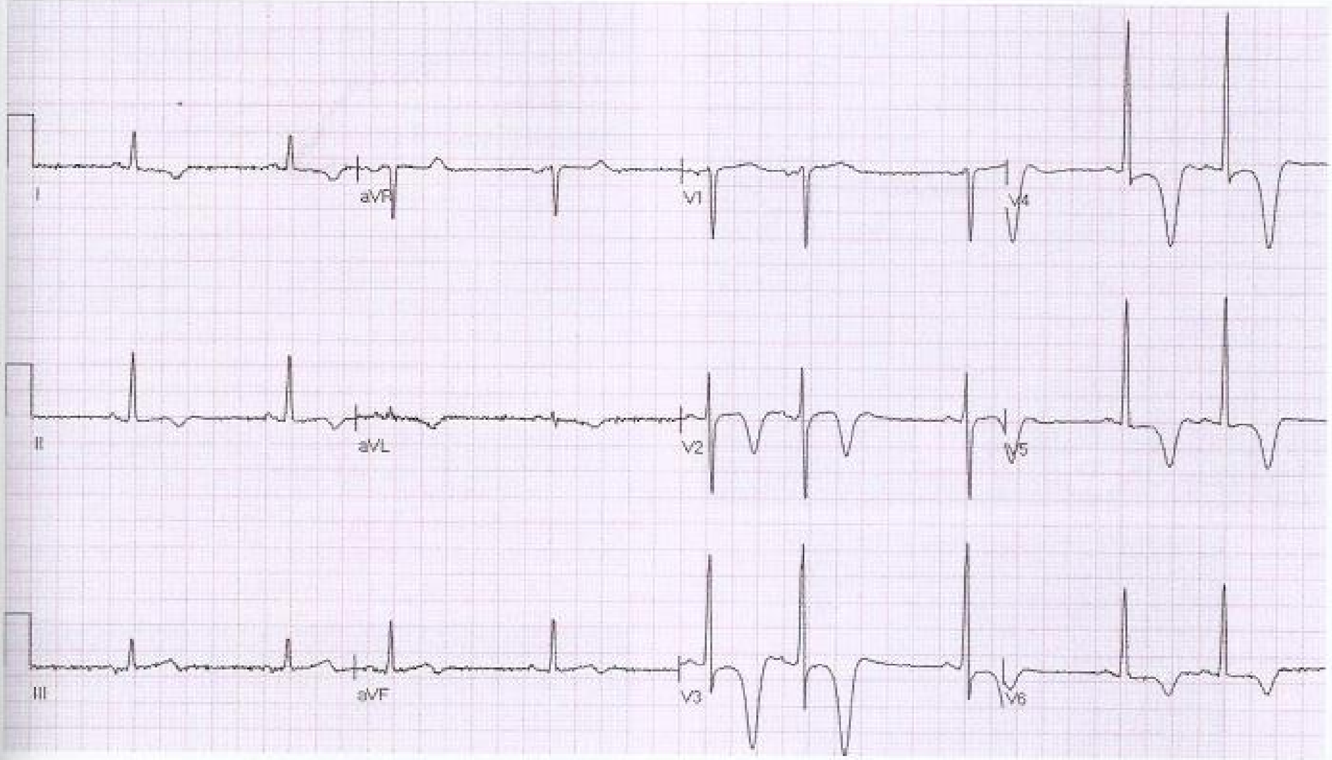

FIGURE 26. Electrocardiogram of a patient with apical hypertrophic cardiomyopathy. There are increased QRS voltage and marked repolarization abnormalities, especially in leads V_2 through V_5.

gadolinium contrast, CMR imaging has the added benefit of demonstrating the volume and distribution of late gadolinium enhancement (LGE), which reflects fibrosis. LGE has been associated with the presence of nonsustained ventricular tachycardia on ambulatory monitoring. Although studies have demonstrated a link between LGE, heart failure death, and cardiovascular death, current guidelines do not support the use of LGE for risk stratification. With more prospective data, the volume of LGE may emerge as a strong independent predictor of SCD.

Upon initial diagnosis of HCM, 24-hour ambulatory ECG monitoring should be performed to evaluate for arrhythmias. The presence of nonsustained ventricular tachycardia identifies patients at higher risk for SCD. Treadmill exercise stress testing is reasonable to determine functional status and to monitor blood pressure response to exercise. Two types of abnormal responses during exercise—a failure to increase systolic pressure more than 20 mm Hg or a drop of 20 mm Hg—may indicate independent risk for SCD. Exercise echocardiography may be useful to demonstrate the response of LVOT obstruction to exercise.

Evaluation for CAD is important in patients with HCM who develop chest discomfort. In patients with a low clinical likelihood of CAD, coronary CT angiography or nuclear myocardial perfusion imaging stress testing is reasonable for risk stratification. In patients at intermediate to high risk for CAD with chest discomfort, coronary angiography is indicated.

HCM must be differentiated from other conditions that may present with increased ventricular wall thickness (**Table 27**). Particularly challenging is the differentiation of HCM from hypertensive heart disease and from the normal and compensatory changes in LV wall thickness seen in competitive athletes. In patients with hypertension, the likelihood of concomitant HCM is increased if LV wall thickness is greater than 25 mm or if dynamic LVOT obstruction is present. In athletes, LV cavity dilatation and normal diastolic filling favor normal physiologic changes, whereas unusual or asymmetric patterns of hypertrophy on echocardiography favor HCM. A brief period of deconditioning demonstrating a decrease in wall thickness favors the athletic heart. When the diagnosis remains unclear, CMR imaging with gadolinium contrast may help with differentiation.

Risk Stratification

Patients with HCM have an annual incidence of cardiovascular death of 1% to 2%, predominantly related to fatal arrhythmia and heart failure. Most arrhythmic deaths are caused by ventricular fibrillation, and all patients with HCM, regardless of the presence of obstruction, should undergo risk stratification for SCD. Prevention with the use of an implantable cardioverter-defibrillator (ICD) is effective in appropriately selected high-risk patients. In patients with one or more established risk factors (**Table 28**), primary prevention with an ICD is indicated. Patients who have experienced SCD or

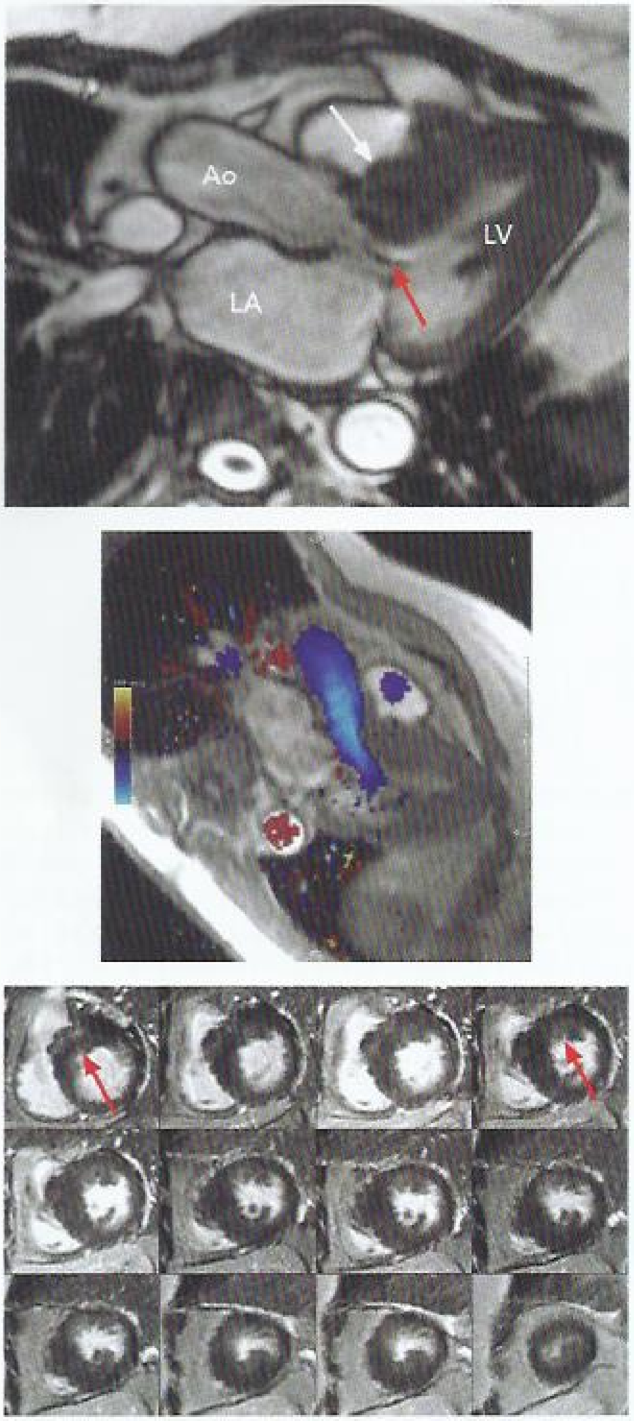

FIGURE 27. Cardiac magnetic resonance images of a patient with hypertrophic cardiomyopathy. *Top panel:* Long-axis image demonstrating marked asymmetric septal hypertrophy (*white arrow*) and systolic anterior motion of the mitral valve narrowing the left ventricular (LV) outflow tract (*red arrow*). *Middle panel:* Long-axis image with velocity flow mapping demonstrating increased flow velocity (lighter blue) originating within the LV outflow tract. *Bottom panel:* Short-axis images demonstrating patchy mid-myocardial late gadolinium enhancement (*red arrows*). Ao = aorta; LA = left atrium.

sustained ventricular tachycardia have an annual recurrent event rate of 10% and should receive an ICD for secondary prevention.

TABLE 27. Conditions with Increased Left Ventricular Wall Thickness

Condition	Clinical Features
Hypertension	Elevated blood pressure
Athletic heart syndrome	No hypertension; normal or supranormal exercise capacity
Amyloidosis	Heart failure, low voltage on electrocardiography, possible neuropathy and/or nephropathy; usually older patients
Fabry disease	Male predominance (X-linked), neuropathic pain, kidney dysfunction, telangiectasias, angiokeratomas; typically young patients
Friedreich ataxia	Ataxia, scoliosis, pes cavus, visual and hearing impairment
Danon disease (*LAMP2* mutation)	Heart failure, mental retardation, skeletal myopathy; young patients

TABLE 28. Risk Factors for Sudden Cardiac Death in Patients with Hypertrophic Cardiomyopathy

Sudden death in a first-degree relative
Maximum left ventricular wall thickness ≥30 mm
Recent, unexplained syncope
Nonsustained ventricular tachycardia (≥3 beats)
Abnormal blood pressure response to exercise[a]
Sustained ventricular tachycardia or resuscitated sudden death event

[a]Defined as a failure to increase by at least 20 mm Hg or a drop of at least 20 mm Hg during effort.

Management

In addition to risk stratification for SCD and ICD therapy, management of HCM includes treatment of symptoms referable to LVOT obstruction, heart failure, and atrial fibrillation.

In patients with obstructive symptoms, such as dyspnea or syncope/near-syncope, lifestyle modification and medical therapy form the basis of management. Patients should be advised to avoid dehydration, excessive alcohol intake, and situational exposures that may result in vasodilation and decreased preload (for example, saunas, hot tubs) because these may provoke greater LVOT obstruction. Patients with probable or unequivocal clinical expression of HCM should not participate in most competitive or recreational sports, with the exception of low-intensity sports. Medical therapy should be initiated with nonvasodilating β-blockers titrated to maximum tolerance; carvedilol, labetalol, and nebivolol should be avoided. Verapamil or diltiazem may be used in patients in whom β-blockers are not tolerated or are contraindicated. Disopyramide, a class IA antiarrhythmic drug with potent negative inotropic activity, may be added if significant symptoms related to LVOT obstruction remain. Diuretics must be

used cautiously and only if symptoms of dyspnea cannot be managed with other therapy. Because of their propensity to exacerbate LVOT obstruction, nitrates and phosphodiesterase type 5 inhibitors should not be used.

Invasive treatment of obstruction with open surgical septal myectomy or catheter-based alcohol septal ablation should be considered in patients who have moderate to severe symptoms of obstruction despite maximal medical therapy with a residual resting or provocable LVOT gradient of 50 mm Hg or greater, or in patients with recurrent syncope not related to arrhythmia. Although both surgical myectomy and alcohol septal ablation reduce the LVOT gradient and symptoms related to LVOT obstruction, appropriate patient selection for each procedure is controversial. Surgical myectomy is associated with a higher likelihood of complete symptom relief and lower rate for repeat procedures, and it may be associated with decreased risk for significant ventricular arrhythmias. Alcohol septal ablation carries a significant risk for atrioventricular block requiring pacemaker implantation, which is higher in older patients. Decisions regarding therapy must be individualized. Septal myectomy is favored in young patients, whereas alcohol septal ablation may be more appropriate for older patients with several comorbid conditions who have increased surgical risk. Outcomes with either procedure are best when the procedure is performed in a center with significant experience in the management of HCM. Surgical myectomy is associated with low operative mortality (0.4%) in such centers.

Atrial fibrillation should be managed with rate control and warfarin anticoagulation, irrespective of the patient's CHA_2DS_2-VASc score. Patients with HCM and atrial fibrillation often remain symptomatic despite rate control, and rhythm control in conjunction with anticoagulation should be considered early (see Arrhythmias). Digoxin should be avoided in patients with atrial fibrillation because the positive inotropic effects may worsen the LVOT gradient.

A small percentage of patients (<5%) will progress to end-stage HCM, manifesting as dilated cardiomyopathy with systolic dysfunction. These patients would appropriately be treated as would those with systolic heart failure (see Heart Failure).

Surveillance

ECG should be performed annually in asymptomatic patients with HCM to screen for changes in rhythm or conduction. Twenty-four hour ambulatory ECG monitoring should be repeated every 1 to 2 years in asymptomatic patients and with the development of symptoms that suggest arrhythmia, such as palpitations or syncope.

Repeat TTE is recommended with any change in clinical status or new cardiac event. In asymptomatic patients, it is reasonable to repeat TTE every 1 to 2 years to assess for mitral regurgitation and changes in LV hypertrophy, function, and degree of obstruction. Although most patients with HCM demonstrate normal LV function, a decrease in LV systolic function is associated with worse outcomes, including death.

Role of Genetic Testing and Counseling

Patients known or suspected to have HCM should undergo an evaluation of familial inheritance and receive genetic counseling. Genetic testing is reasonable in patients who meet the clinical definition of HCM to aid screening of family members, but results must be interpreted carefully. A known sarcomeric mutation may be identified in up to 60% of patients with a family history of HCM; the incidence is lower (20%-30%) in isolated cases. The absence of an identified sarcomeric mutation in the index case does not exclude the diagnosis of HCM. Genetic testing is recommended in first-degree family members if a sarcomeric mutation is identified in the index case. Such testing may disclose genotype-positive persons who do not express clinical features of HCM, and these persons should be followed with clinical examination and serial echocardiography (**Table 29**). In the absence of a pathogenic mutation in the index case, first-degree family members should have ECG and echocardiographic screening for HCM. The use of genetic testing should not be used as the sole determinant for ICD placement for primary prevention.

TABLE 29. Proposed Clinical Screening Strategies with Echocardiography (and 12-Lead ECG) for Detection of HCM with Left Ventricular Hypertrophy in Families[a]

Age <12 y
Optional unless:
Malignant family history of premature death from HCM or other adverse complications
Patient is competitive athlete in an intense training program
Onset of symptoms
Other clinical suspicion of early left ventricular hypertrophy
Age 12 to 18-21 y[b]
Every 12-18 mo
Age >18-21 y
At onset of symptoms or at least every 5 y. More frequent intervals are appropriate in families with a malignant clinical course or late-onset HCM

ECG = electrocardiography; HCM = hypertrophic cardiomyopathy.

[a]When pathologic mutations are not identified or genetic testing is either ambiguous or not performed.

[b]Age range takes into consideration individual variability in achieving physical maturity and in some patients may justify screening at an earlier age. Initial evaluation should occur no later than early pubescence.

Reproduced with permission from Gersh BJ, Maron BJ, Bonow RO, Dearani JA, Fifer MA, Link MS, et al; American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. 2011 ACCF/AHA guideline for the diagnosis and treatment of hypertrophic cardiomyopathy: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Developed in collaboration with the American Association for Thoracic Surgery, American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Failure Society of America, Heart Rhythm Society, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol. 2011;58:e212-60. [PMID: 22075469] doi:10.1016/j.jacc.2011.06.011. Copyright 2011, Elsevier.

KEY POINTS

- Asymmetric septal hypertrophy with dynamic left ventricular outflow tract obstruction represents the classic form of hypertrophic cardiomyopathy.
- Doppler echocardiography is the modality of choice for quantification of the left ventricular outflow tract gradient in patients suspected of having hypertrophic cardiomyopathy.
- Patients with hypertrophic cardiomyopathy who have risk factors for sudden cardiac death should undergo implantable cardioverter-defibrillator placement.
- In patients with hypertrophic cardiomyopathy who have symptoms of left ventricular outflow tract obstruction, nonvasodilating β-blockers are first-line therapy.
- Transthoracic echocardiography should be performed every 1 to 2 years in asymptomatic patients with hypertrophic cardiomyopathy to assess for mitral regurgitation and changes in left ventricular hypertrophy, function, and degree of obstruction.
- HVC Genetic testing is not indicated in first-degree relatives of patients with hypertrophic cardiomyopathy who do not have an identified sarcomeric mutation.

Restrictive Cardiomyopathy

Clinical Presentation and Evaluation

Restrictive cardiomyopathy (RCM) is a rare disorder characterized by abnormally stiff, noncompliant ventricles. RCM was once considered idiopathic; however, increasing evidence suggests that gene mutations in sarcomeric proteins and abnormalities in desmin, an intermediate filament that regulates sarcomere architecture, play an important role in familial and sporadic cases. The sarcomeric protein gene mutations of RCM are similar to or the same as those linked to HCM, raising the possibility that these disorders represent different phenotypic expressions of the same heritable defect.

RCM is characterized histologically by patchy interstitial fibrosis and myocyte disarray, which are also seen in HCM. With increasing interstitial fibrosis, the ventricles stiffen, resulting in increased pressure during normal diastolic filling. Patients may present at any age, usually with symptoms of dyspnea, peripheral edema, and exercise intolerance. Hepatomegaly and ascites may also be present late in the disease course.

The diagnosis of RCM should be suspected in patients when echocardiography demonstrates biatrial enlargement and severe diastolic dysfunction in the setting of normal ventricular size, wall thickness, and systolic function. There is usually evidence of significant pulmonary hypertension, and tricuspid and mitral valve regurgitation are commonly present. Patients with these findings should be referred to a cardiologist for further evaluation.

Primary RCM must be differentiated from other conditions that may present with restrictive physiology. These include fibrosis related to radiation and eosinophilic diseases as well as hemochromatosis, in which wall thickness is typically normal. A complete blood count with manual differential and transferrin saturation are reasonable as part of the evaluation. Infiltrative diseases with increased wall thickness may share restrictive physiology but are considered separate entities. When low ECG voltage accompanies increased wall thickness on echocardiogram, amyloidosis should be considered. Serum protein electrophoresis/urine protein electrophoresis and free light-chain analysis may help identify immunoglobulin light-chain amyloidosis, and technetium-99m cardiac imaging may help identify transthyretin amyloidosis. CMR imaging with gadolinium contrast may help identify and differentiate RCM from other myocardial diseases with restrictive physiology. When the diagnosis remains unclear, endomyocardial biopsy is reasonable to establish a diagnosis.

Differentiating Restrictive Cardiomyopathy from Constrictive Pericarditis

H

Patients with constrictive pericarditis and RCM present with similar symptoms and findings on echocardiography. Differentiating between these two disorders is essential because specific therapies, including surgical pericardiectomy, may relieve symptoms and prolong life in patients with constriction. In patients with previous cardiac surgery, pericarditis, or chest irradiation, constrictive pericarditis should be strongly considered.

On physical examination, patients with constriction and RCM both demonstrate increased jugular venous pressure. Increase in the height of the jugular waveform during inspiration (Kussmaul sign) has been associated more commonly with constriction. Both RCM and constrictive pericarditis may be associated with a diastolic sound. An S_3 gallop is often present in RCM, whereas a pericardial knock can be heard in constrictive pericarditis. Differentiating between these sounds may be very difficult (see Pericardial Disease).

A multimodality approach, including both noninvasive imaging and invasive hemodynamic evaluation, may be required to distinguish RCM from constrictive pericarditis. Clues to the presence of constrictive pericarditis include pericardial calcification on chest radiography or CT, pericardial thickening on CT or CMR imaging, or a B-type natriuretic peptide level below 100 pg/mL (100 ng/L) (usually ≥400 pg/mL [400 ng/L] in patients with RCM). A hallmark feature of constrictive pericarditis is ventricular interdependence, in which total cardiac volume is limited by the rigid pericardium. With ventricular interdependence, increased filling of the right or left ventricle can occur only with reciprocal decreased filling of the other ventricle. Ventricular interdependence may be demonstrated by Doppler echocardiography, CMR imaging, or invasive hemodynamic evaluation; it is not present in patients with RCM. H

Management

There is no specific medical therapy for RCM. Loop diuretics are usually necessary for relief of congestive symptoms, especially in late-stage disease. However, patients with RCM require relatively high filling pressures to maintain cardiac output, and balancing relief of congestion with adequate cardiac output is often challenging. Even small changes in volume may lead to hypoperfusion of the kidneys; therefore, volume status should be monitored carefully.

Atrial fibrillation is a common complication due to left atrial dilatation and elevated pressure. It is poorly tolerated in patients with RCM because of increased heart rate and reduced ventricular filling. Anticoagulation and rate control are indicated, and rhythm control should be considered early in symptomatic patients. Digoxin should be used with caution because it indirectly increases intracellular calcium, which may affect diastolic relaxation.

Survival is poor in patients with RCM, with a 5-year mortality rate of 36% and a 10-year mortality rate of 63%. Cardiovascular mortality is predominantly related to progressive heart failure and arrhythmias. Cardiac transplantation may be considered in selected individuals who remain symptomatic despite maximal therapy. There is no accepted indication for ICD placement for primary prevention in patients with RCM who have preserved systolic function.

KEY POINTS

- Restrictive cardiomyopathy should be suspected in patients when echocardiography demonstrates biatrial enlargement and severe diastolic dysfunction in the setting of normal ventricular size, wall thickness, and systolic function.
- Restrictive cardiomyopathy must be differentiated from constrictive pericarditis because surgical pericardiectomy may relieve symptoms and prolong life in patients with constriction.

Cardiac Tumors

Most cardiac tumors are metastatic. Neoplasms with the highest metastatic potential are melanoma, malignant thymoma, and germ cell tumors. Common tumors with an intermediate risk for cardiac involvement include carcinoma of the lung, stomach, and colon. Therapy is directed at systemic treatment of the underlying neoplasm, with cardiac surgery reserved for patients with obstructive symptoms.

Primary cardiac tumors, which are exceedingly rare, are benign in two thirds of patients. Of the benign tumors, nearly 50% are atrial myxomas. Myxomas may occur in either atria but are most commonly attached to the fossa ovalis within the left atrium (**Figure 28**). Myxomas are usually solitary and discovered at a mean age of 50 years, often after a systemic embolic event. When tumors are multiple, recurrent, or discovered at a young age, they may indicate the Carney complex, which includes the LAMB (lentigines, atrial myxoma, blue nevi) syndrome and the NAME (nevi, atrial myxoma, myxoid neurofibromas, and ephelides) syndrome. The Carney complex is associated with mutations of the *PRKAR1A* gene, which may function as a tumor suppressor gene. Patients with a myxoma may present with constitutional symptoms related to interleukin production, embolic phenomena from tumor fragmentation, or symptoms referable to intracardiac obstruction (dyspnea, syncope). When mitral valvular obstruction is present, auscultatory findings are similar to those of mitral stenosis; however, findings may vary with position or be associated with an early diastolic sound, known as the tumor plop. Surgical removal is indicated to prevent embolic events, as is subsequent surveillance echocardiography for detection of recurrence.

Papillary fibroelastomas usually occur on the surface of the aortic and mitral valves and are commonly discovered in the eighth decade of life. Although most papillary fibroelastomas do not cause symptoms, they may be associated with stroke, transient ischemic attack, and, rarely, coronary embolization with

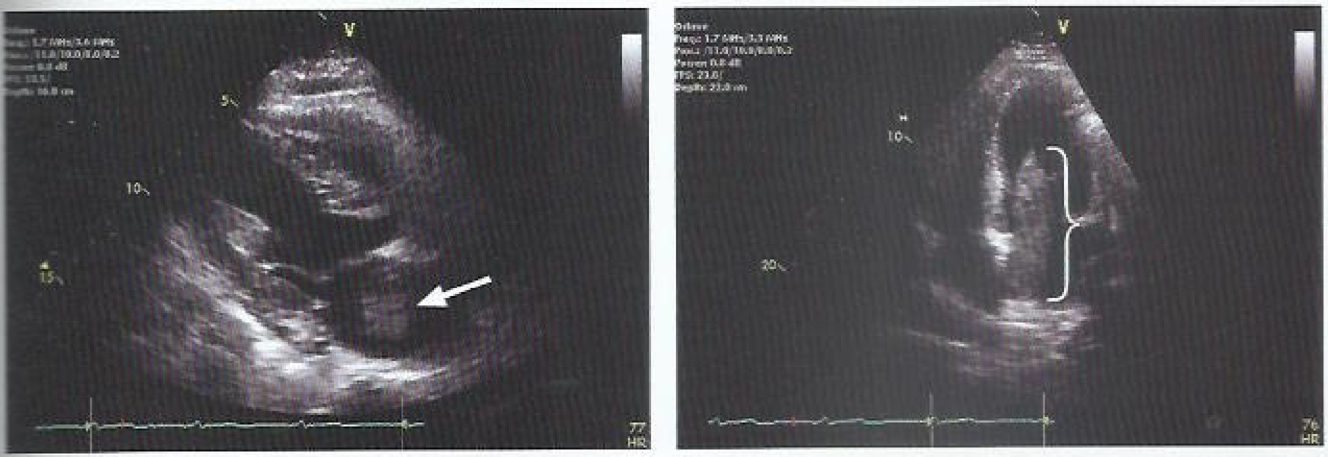

FIGURE 28. Transthoracic echocardiograms demonstrating a left atrial myxoma. *Left panel:* Parasternal long-axis view during ventricular systole showing a large left atrial soft tissue density (arrow). *Right panel:* Apical four-chamber view during diastole demonstrates attachment of the mass to the interatrial septum and prolapse of the mass across the mitral valve.

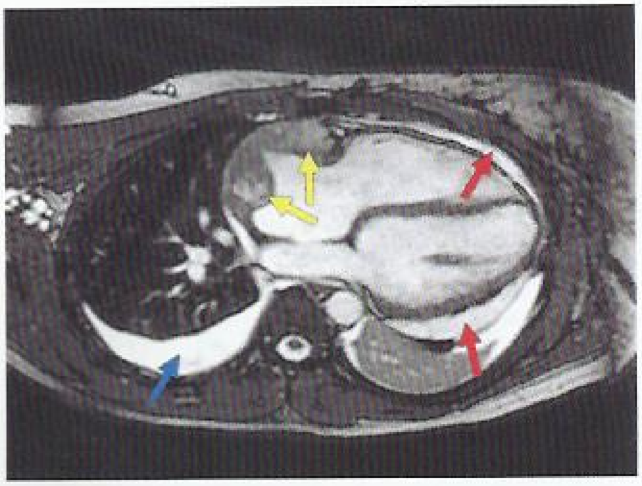

FIGURE 29. Cardiac magnetic resonance image of a patient with an angiosarcoma. A heterogeneous mass (*yellow arrows*) is infiltrating the right atrial wall. A pericardial effusion (*red arrows*) and pleural effusion (*blue arrow*) are also present.

infarction. On echocardiography, these tumors often have a heterogeneous globular shape or a mobile frond-like appearance. Patients with embolic symptoms are treated surgically. There are currently no randomized data comparing surgical therapy with antithrombotic or antiplatelet therapy to prevent embolic events.

Angiosarcomas are the most common primary malignant tumor. Angiosarcomas typically arise in the right atrium and are often associated with pericardial effusion (**Figure 29**). Dyspnea and chest pain are common presenting symptoms. Angiosarcomas are highly vascular tumors, and CT or CMR imaging with contrast may help differentiate an angiosarcoma from a right atrial myxoma. When complete surgical extirpation is possible, survival remains less than 2 years for most patients. With incomplete resection, survival is generally less than 10 months.

KEY POINT

- The primary treatment of atrial myxomas is surgical removal to prevent embolic events.

Pericardial Disease

Acute Pericarditis

Clinical Presentation and Evaluation

Pericarditis is defined as inflammation of the pericardium, the thin fibrous sac surrounding the heart. Pericarditis may be subclinical or present as sharp precordial pain of acute onset. Acute pericarditis has many causes (**Table 30**), but it is most often idiopathic or presumed to be viral in origin.

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Acute pericarditis is diagnosed clinically by the presence of at least two of the following four criteria: chest pain typical for pericarditis, a pericardial friction rub, new electrocardiographic (ECG) changes, or a new pericardial effusion. The chest pain of acute pericarditis is sharp and severe. It is not typically related to exertion and is not relieved with rest or nitroglycerin, unlike anginal pain. The pain is characteristically worse in the supine position and improves with sitting up and leaning forward. These pain features may be related to tension of the pericardium at its sternal and diaphragmatic attachments.

TABLE 30. Causes of Pericardial Disease

Category	Cause
Infectious	
Viral infection	Enterovirus, herpesvirus, adenovirus, parvovirus
Bacterial infection	*Mycobacterium tuberculosis*, *Pneumococcus* spp., *Staphylococcus* spp., *Coxiella burnetii*
Fungal infection	*Histoplasma*, *Aspergillus*, *Blastomyces*, *Candida* spp.
Noninfectious	
Autoimmune diseases	Systemic lupus erythematosus, rheumatoid arthritis, Sjögren syndrome, scleroderma, sarcoidosis, familial Mediterranean fever
Cancer	Metastatic lung cancer, breast cancer, and melanoma; lymphoma and leukemia
Metabolic conditions	Uremia, myxedema
Drug-related causes	Hydralazine, procainamide, minoxidil, all-*trans* retinoic acid
Iatrogenic causes	Cardiac surgery (postpericardiotomy syndrome), coronary perforation during percutaneous intervention, pacemaker lead penetration, radiofrequency ablation
Other	Radiation, aortic dissection, pulmonary arterial hypertension

A pericardial friction rub is frequently present on auscultation. This harsh, scratchy sound classically has three components corresponding to the cardiac cycle during normal sinus rhythm: atrial systole, ventricular systole, and ventricular filling. The three phases of the pericardial friction rub differentiate it from a pleural friction rub, which has two components that are linked to respiration. The rub of pericarditis may also be monophasic or biphasic but is not affected by respiration. Auscultation should be performed during held end-expiration with the patient in the supine position or sitting upright.

The typical ECG feature of acute pericarditis is ST-segment elevation in multiple leads that does not correspond with a single coronary distribution. PR-segment depression in lead II or reciprocal PR-segment elevation in lead aVR may also be present (**Figure 30**). In contrast, ECG findings of acute myocardial infarction are hyperacute T waves, ST-segment elevation consistent with a single coronary distribution, reciprocal ST-segment depression, pathologic Q waves during the evolution of myocardial infarction, and lack of PR-segment change.

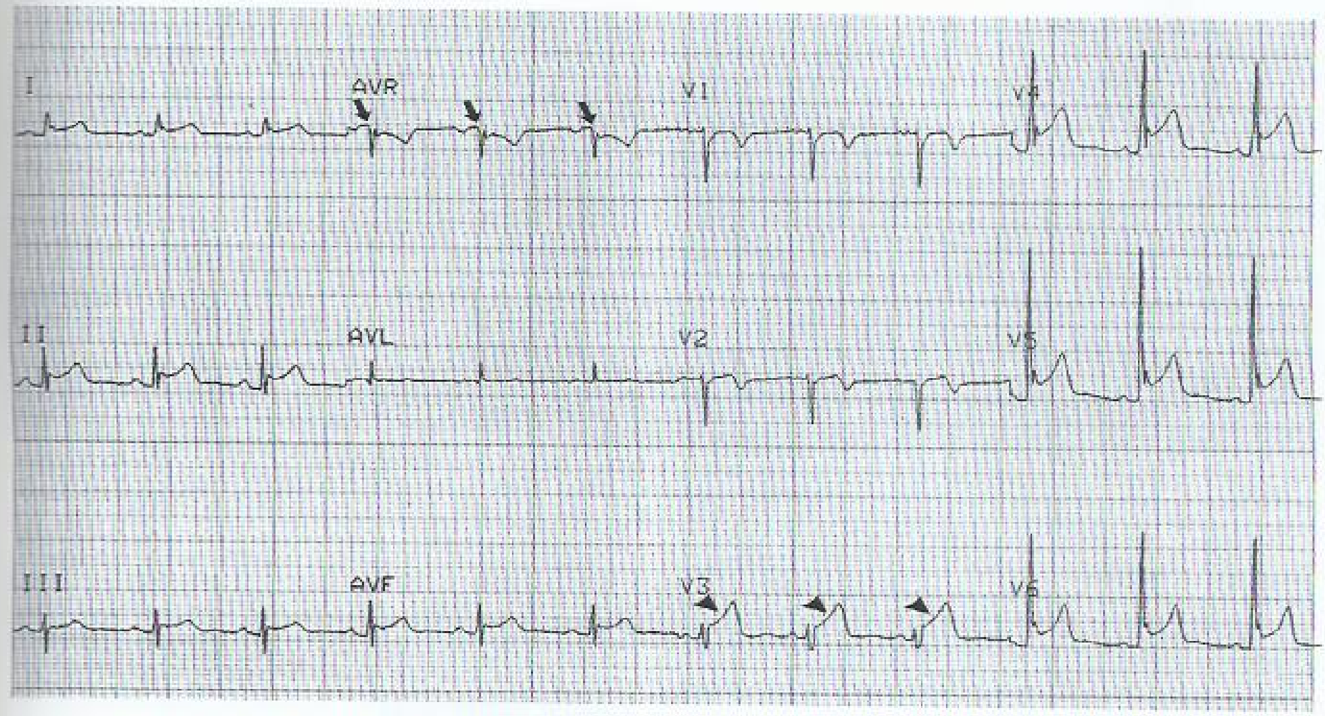

FIGURE 30. Electrocardiographic changes of acute pericarditis. Concave ST-segment elevation is present in most of the leads (*arrowheads*). The PR segment is depressed in all leads except aVR (*arrows*).

Echocardiography should be used to detect a pericardial effusion, although an effusion is not found in all cases of acute pericarditis. When the diagnosis remains uncertain, cardiac magnetic resonance (CMR) imaging with gadolinium intravenous contrast may be used to identify evidence of pericardial inflammation, characterized by pericardial thickening and late gadolinium enhancement (**Figure 31**). Alternatively, gated cardiac CT may also demonstrate pericardial inflammation.

Additional findings that support acute pericarditis may include fever and serologic evidence of inflammation (leukocytosis and elevated erythrocyte sedimentation rate or C-reactive protein [CRP] level). Serum cardiac troponin levels in acute pericarditis are normal or may be slightly elevated if there is a component of myopericarditis.

Although most cases of acute pericarditis are idiopathic, a search for other causes is appropriate (see Table 30). Evaluation includes a thorough history and physical examination, with additional testing based on the suspected cause. Tuberculosis testing should be considered in hospital workers, patients who are incarcerated or residing in chronic care facilities, and patients who are from or have traveled to an endemic area. Treatment of tuberculosis may reduce the risk for reactive pericardial constriction from greater than 80% to less than 10%. Other causes include uremia, chest irradiation, and recent cardiac surgery. Cardiac surgery may be followed by postpericardiotomy syndrome, which is characterized by pericardial inflammation that is likely autoimmune in nature and usually follows a latent period of several weeks. The presentation and treatment of postpericardiotomy syndrome are similar to those of idiopathic pericarditis.

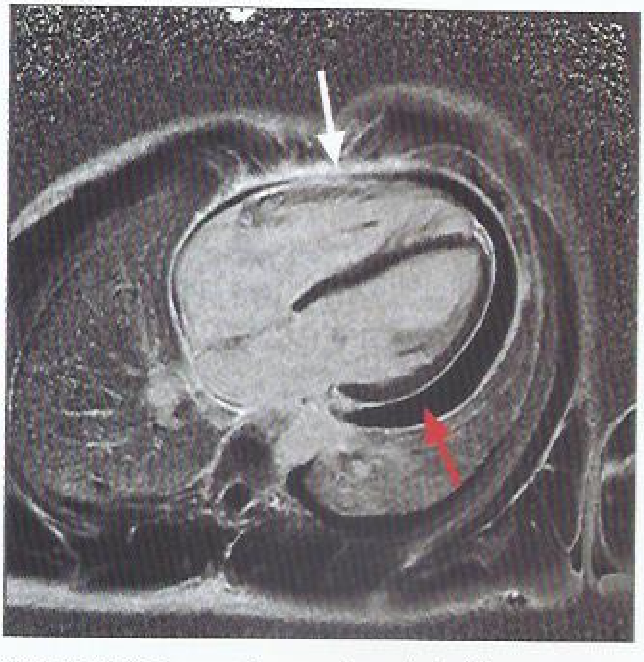

FIGURE 31. Cardiac magnetic resonance image obtained after intravenous administration of gadolinium. A pericardial effusion (*red arrow*) is present, and there is late gadolinium enhancement of the pericardium consistent with inflammation (*white arrow*).

Management

Most patients with acute pericarditis can be managed medically on an outpatient basis; however, patients with acute pericarditis accompanied by high-risk features may require

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hospitalization for treatment and monitoring. Predictors of poor prognosis include temperature higher than 38 °C (100.4 °F), subacute onset, a large pericardial effusion (>20-mm diastolic echo-free space) or tamponade at presentation, oral anticoagulation therapy, or lack of response (no improvement in symptoms and/or inflammatory markers) after 1 week of treatment.

First-line treatment for acute idiopathic pericarditis consists of aspirin (750-1000 mg) or NSAIDs (ibuprofen 600 mg) every 8 hours for 1 to 2 weeks. Colchicine (0.5 mg once or twice daily for 3 months) is recommended as adjunctive therapy to shorten the duration of symptoms and reduce the chances of treatment failure or recurrence. Patients who initially respond to therapy but develop recurrent pericarditis after treatment completion may benefit from a longer course of standard therapy with slow tapering. CRP may be useful as a marker of treatment response, with tapering initiated after the CRP level normalizes. Expert consensus opinion recommends that athletes not return to competitive exercise for 3 months from initial onset and that nonathletes restrict strenuous activity until symptoms resolve.

Some patients with acute pericarditis may develop incessant or chronic pericarditis. Incessant pericarditis has been defined as pericarditis lasting for longer than 4 to 6 weeks but less than 3 months without remission, whereas chronic pericarditis is defined as lasting longer than 3 months. Glucocorticoid therapy is reserved for patients with recurrent, incessant, or chronic pericarditis despite standard therapy (including patients with uremic pericarditis not responsive to intensive dialysis); patients with contraindications to NSAID therapy; and patients with autoimmune-mediated pericarditis. Prednisone should be initiated at a dosage of 0.25 mg/kg to 0.5 mg/kg and continue for 3 months. Tapering should not be initiated until after the first 2 to 4 weeks of therapy or until the CRP level normalizes.

Limited data suggest that the interleukin-1 receptor antagonist anakinra may be an effective therapy for idiopathic recurrent pericarditis that is refractory to standard treatment; however, its role in management is not established. H

KEY POINTS

- Acute pericarditis is diagnosed by the presence of at least two of four criteria: chest pain typical for pericarditis, a pericardial friction rub, new electrocardiographic changes, or a new pericardial effusion.
- First-line treatment for acute idiopathic pericarditis is high-dose aspirin or NSAIDs and adjuvant colchicine therapy.
- Glucocorticoid therapy is reserved for patients with incessant, recurrent, or chronic pericarditis despite standard therapy; patients with contraindications to NSAID therapy; and patients with autoimmune-mediated pericarditis.

Pericardial Effusion and Cardiac Tamponade

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Pericardial Effusion

Pericardial effusion is characterized by an increased amount of fluid in the pericardial cavity. Many patients with pericardial effusion are asymptomatic, and the effusion is discovered incidentally with chest radiography, CT, or echocardiography. In asymptomatic patients, most effusions are idiopathic; however, malignancy, infections, autoimmune disease, hypothyroidism, and iatrogenic causes (medications, anticoagulation therapy) should be considered (see Table 30). In countries where tuberculosis is endemic, more than 60% of effusions are caused by tuberculosis.

If cancer or bacterial infection is strongly suspected, pericardiocentesis should be considered for diagnostic purposes. In patients with a pericardial effusion of unknown cause and elevated inflammatory markers, empiric treatment of pericarditis may be reasonable. Drainage should be considered if large idiopathic effusions are present for more than 3 months because one in three patients progress to cardiac tamponade.

Cardiac Tamponade

Clinical Presentation and Evaluation

Cardiac tamponade occurs when fluid accumulation within the pericardial space compresses the heart and impedes diastolic filling. When fluid accumulates rapidly (such as with trauma, aortic dissection, or invasive cardiac procedures), tamponade may occur at relatively low pericardial volumes. Subacute or chronic processes, such as neoplastic disease or hypothyroidism, may be associated with much larger effusions (several hundred milliliters in volume).

Clinical signs of tamponade include tachycardia, hypotension, muffled heart sounds, and elevation of the jugular venous pulse. The *y* descent of the jugular venous pulse may be absent because passive filling of the ventricles is impeded by the intrapericardial pressure. This finding may be difficult to appreciate, especially in a patient with tachycardia. Pulsus paradoxus represents exaggerated ventricular interdependence and is a key clinical feature of cardiac tamponade. It is characterized by a fall in systolic pressure of greater than 10 mm Hg during inspiration. Pulsus paradoxus is not specific for tamponade and must be interpreted in conjunction with other clinical and echocardiographic features.

The ECG may demonstrate electrical alternans (related to a swinging motion of the heart within the pericardial fluid) or low voltage in patients with tamponade. If the accumulation of fluid has occurred slowly, the cardiac silhouette is typically enlarged on chest radiography.

Echocardiography is an essential tool in the diagnosis of cardiac tamponade because it defines the presence, distribution, and relative volume of pericardial fluid (**Figure 32**). Early diastolic collapse of the right ventricle, late diastolic collapse of the right atrium, and abnormal interventricular septal motion are features associated with cardiac tamponade. Additionally,

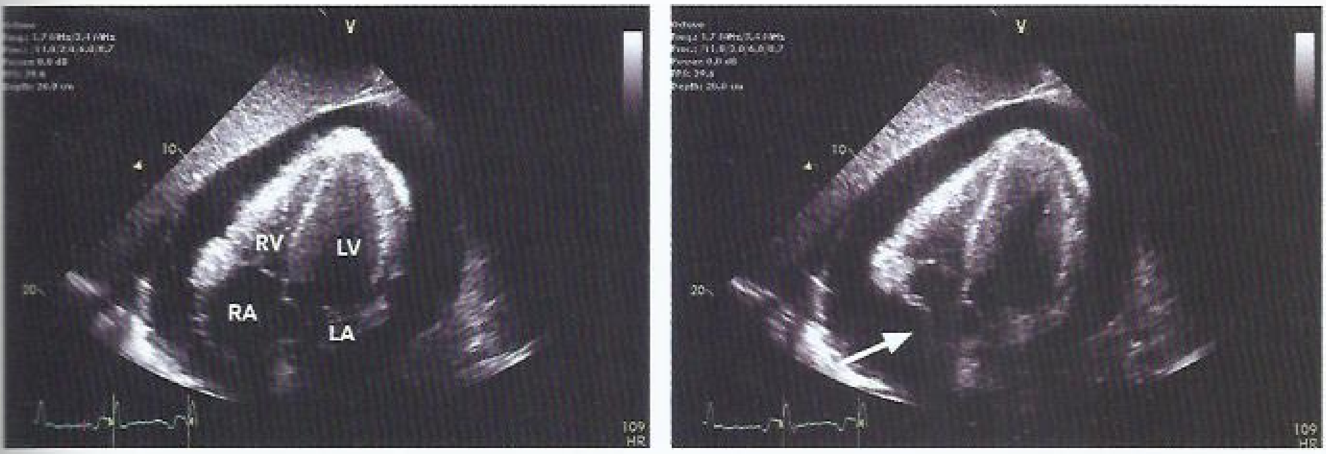

FIGURE 32. Apical four-chamber echocardiogram demonstrating a large circumferential pericardial effusion (*left panel*). Diastolic right atrial collapse (*arrow*) consistent with pericardial tamponade (*right panel*). LA = left atrium; LV = left ventricle; RA = right atrium; RV = right ventricle.

Doppler evaluation may demonstrate a decrease in mitral inflow velocity of more than 25% with inspiration, which is the echocardiographic equivalent of pulsus paradoxus (**Figure 33**).

Cardiac catheterization is rarely necessary for diagnosis. The hemodynamic hallmarks of tamponade include blunting or loss of the *y* descent within the right atrial pressure waveform and elevated and equalized diastolic pressures. The latter reflects the transmitted effect of the intrapericardial pressure. Invasive arterial pressure recordings also show pulsus paradoxus.

Management

Cardiac tamponade is life-threatening, and once a diagnosis is established, fluid removal is required. Drainage is most commonly accomplished with pericardiocentesis, with fluoroscopy or echocardiographic guidance. Surgical therapy via a subxiphoid approach is indicated to drain fluid when pericardiocentesis cannot be performed safely, to obtain pericardial tissue for diagnostic purposes, or to prevent recurrent pericardial effusion by creating a pericardial window (often used in cases of malignant pericardial effusion). In hemodynamically unstable patients, intravenous normal saline is used to stabilize the patient as a temporizing measure or as a bridge to definitive therapy.

After drainage of pericardial fluid, hemodynamic and clinical evaluation may occasionally disclose findings of underlying pericardial constriction, termed effusive constrictive pericarditis. If clinical evaluation and imaging techniques (such as CMR imaging) suggest an active inflammatory process, a course of medical therapy similar to that for acute pericarditis may be considered, and the patient should be re-evaluated before surgery is contemplated.

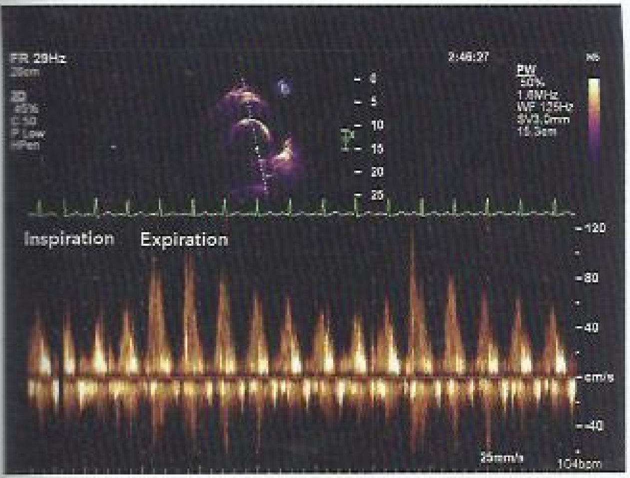

FIGURE 33. Pulsed-wave Doppler evaluation of mitral inflow velocity. A change in the flow between expiration and inspiration of greater than 25% is present, consistent with enhanced ventricular interdependence.

KEY POINTS

- Clinical signs of cardiac tamponade include tachycardia, hypotension, muffled heart sounds, elevation of the jugular venous pulse, and pulsus paradoxus.
- Patients with cardiac tamponade require drainage of pericardial fluid with pericardiocentesis; surgical drainage is indicated when pericardiocentesis cannot be performed safely, pericardial tissue is needed for diagnostic purposes, or a pericardial window is required to prevent recurrent pericardial effusion.

Constrictive Pericarditis

Clinical Presentation and Evaluation

Constrictive pericarditis is characterized by pericardial thickening, fibrosis, and sometimes calcification that impair diastolic filling and limit total cardiac volume. Within developed countries, most cases are viral or idiopathic in origin. Other causes include cardiac surgery, chest irradiation, autoimmune disease, and tuberculosis or other bacterial infection. Tuberculosis remains a major cause of constrictive pericarditis within developing countries.

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Patients with constrictive pericarditis most commonly present with indolent progression of right-sided heart failure symptoms, including peripheral edema, abdominal swelling, and fatigue. Dyspnea and fatigue limit exertion and are caused by increased diastolic pressures and limited ability to augment cardiac output due to the fixed stroke volume.

On physical examination, the jugular veins are distended, with prominent *x* and *y* descents. The height of the waveform does not fall or may increase during inspiration (Kussmaul sign), reflecting the fixed diastolic volume of the right heart. Early diastolic filling is unimpaired or even accentuated and is followed by sudden cessation when total acceptable volume is met, resulting in a high-frequency early diastolic sound (the pericardial knock). Characteristics that may be used to differentiate a pericardial knock from other diastolic sounds are listed in **Table 31**. Pulsus paradoxus is less frequent in constrictive pericarditis than in cardiac tamponade. Peripheral edema, ascites, hepatomegaly, and pleural effusions are common. Muscle wasting may be evident in advanced cases.

Constrictive pericarditis is diagnosed with imaging studies and hemodynamic evaluation. Chest radiography or CT may demonstrate partial or circumferential pericardial calcification, and CT or CMR imaging may demonstrate pericardial thickening (>3 mm). Importantly, constriction may exist in the absence of these findings. In one case series, 18% of cases of hemodynamically proven constrictive pericarditis occurred with normal pericardial thickness. CMR imaging may also demonstrate an inspiratory septal shift, a sign of ventricular interdependence.

TABLE 31. Characteristics of the Common Diastolic Heart Sounds

Diastolic Heart Sound	Condition	Characteristics
Opening snap	Mitral stenosis	High frequency Heard best at the left lower sternal border and the apex Associated with a loud S_1, a loud P_2 with associated pulmonary hypertension, and a low-pitched diastolic rumble at the apex
Pericardial knock	Constrictive pericarditis	High frequency Heard throughout the precordium Earlier than an S_3 Associated with deep *x* and *y* descents in the jugular venous pulse waveform
Tumor plop	Atrial myxoma	Low frequency Heard best at the apex May be positional
S_3	Heart failure	Low frequency Heard best at the apex and the left lateral decubitus position Displaced point of maximal impulse

Transthoracic echocardiography in constrictive pericarditis reveals normal right and left ventricular size and systolic function despite prominent symptoms and examination findings suggestive of heart failure. The echocardiographic finding of dilatation of the inferior vena cava reflects elevated right-sided filling (right atrial) pressure. Myocardial relaxation is impaired in myocardial disease, such as restrictive cardiomyopathy, but is unimpaired or even enhanced in constriction, in which early diastolic filling is rapid and unimpeded. Doppler echocardiography and tissue Doppler velocity are required to differentiate constrictive pericarditis from restrictive cardiomyopathy.

When constrictive pericarditis is suspected but not confirmed by echocardiography, cardiac catheterization can be performed. Invasive hemodynamic findings of constrictive pericarditis include a prominent *y* descent in the right atrial waveform, which corresponds with the dip of the right ventricular dip-and-plateau waveform ("square root sign"). The significant *y* descent and the right ventricular dip both represent unimpeded or rapid early diastolic ventricular filling. As inflow volume reaches the fixed pericardial constraint, pressure rises rapidly until maximum volume is achieved; pressure then remains constant, causing the plateau phase of the square root sign. A more specific finding is ventricular interdependence during simultaneous right and left ventricular systolic pressure measurement. During inspiration, right ventricular inflow is enhanced, and right ventricular systolic pressure rises; however, these changes occur with a concomitant decrease in left ventricular filling and reduction in left ventricular stroke volume and systolic pressure (**Figure 34**). The converse is seen during expiration.

Increased pericardial thickening and impaired distensibility may occur without fibrosis or calcification in the setting of acute or subacute inflammation. In these patients, constriction may be transient and resolve spontaneously. Patients with transient constrictive pericarditis present most commonly with symptoms of right-sided heart failure, although fever and chest pain may indicate the active inflammatory condition. Most cases are idiopathic; other causes include recent cardiac surgery, acute pericarditis, autoimmune disease, or chemotherapy. Systemic markers of inflammation (erythrocyte sedimentation rate and CRP) may be elevated in patients with transient constriction but are generally normal in patients with fixed constriction. Echocardiographic features are similar to those of fixed constriction; however, pericardial effusion is more likely to be present in patients with transient constrictive pericarditis.

Management

Treatment of transient constrictive pericarditis is the same as for acute pericarditis. Treatment with anti-inflammatory agents for 2 to 3 months is reasonable in hemodynamically stable patients before recommending surgical pericardiectomy. Response to therapy is monitored clinically,

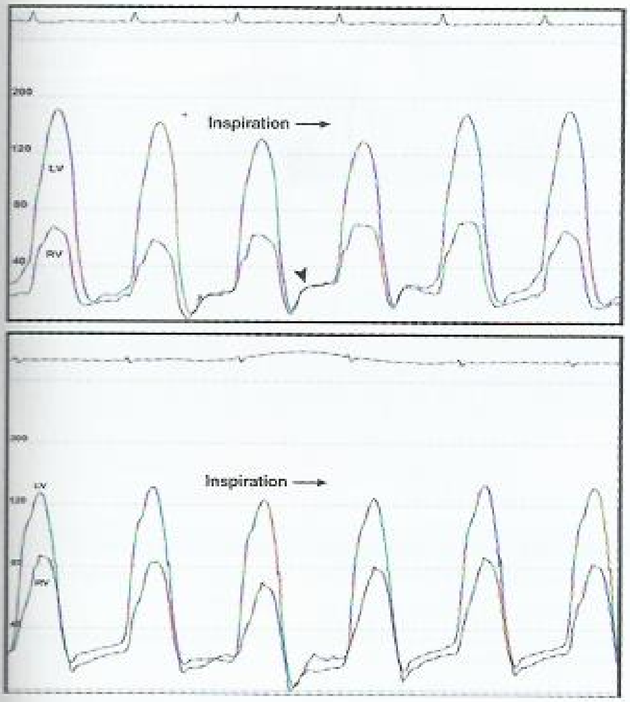

FIGURE 34. Comparison of hemodynamics of constrictive pericarditis versus restrictive cardiomyopathy. In constrictive pericarditis (*top panel*), there is significant enhancement of ventricular interdependence leading to discordance of the left ventricular and right ventricular pressures during respiration. Arrows indicate onset of inspiration and subsequent respective changes in left ventricular and right ventricular systolic pressures. In the top panel, note the diastolic dip and plateau (*arrowhead*), or "square root sign," characteristic of constrictive pericarditis. In restrictive cardiomyopathy (*bottom panel*), there is evidence of early rapid ventricular filling, but the ventricular pressures concordantly rise and fall during respiration. LV = left ventricle; RV = right ventricle.

echocardiographically, and, if initial inflammatory markers are elevated, serologically.

Patients with chronic pericardial constriction should be referred for surgical pericardial stripping (pericardiectomy performed via median sternotomy). In advanced cases, adequate resection of the pericardium may be difficult, leading to incomplete resolution of symptoms. Diuretic therapy to relieve symptoms of congestion may be useful in patients who are not deemed surgical candidates or in whom stripping was incomplete. H

KEY POINTS

- Constrictive pericarditis is characterized by pericardial thickening, fibrosis, and sometimes calcification that impair diastolic filling and limit total cardiac volume.
- Transthoracic echocardiography is the initial diagnostic test for evaluating constrictive pericarditis; however, additional imaging may be required to differentiate constrictive pericarditis from restrictive cardiomyopathy.
- Patients with chronic pericardial constriction should be referred for surgical pericardial stripping (pericardiectomy performed via median sternotomy).

Adult Congenital Heart Disease

Introduction

Medical and surgical advances have resulted in more adults living with congenital heart disease than children with these conditions in North America. All patients with repaired congenital cardiac defects require regular follow-up. In addition to a primary care provider, patients should have an adult congenital heart disease team. Regular care with specialists in adult congenital heart disease is critical for patients born with complex and cyanotic congenital cardiac disease, symptomatic patients, and patients who desire pregnancy. The frequency of follow-up depends on the underlying disorder and patient's status.

Patent Foramen Ovale

The foramen ovale is a passage in the superior portion of the fossa ovalis that allows oxygenated placental blood to transfer to the fetal circulation. It normally closes within the first weeks of life; however, in 25% to 30% of the population, it remains patent (**Figure 35**). A patent foramen ovale (PFO) is usually found incidentally on echocardiography or during evaluation for a cerebrovascular event.

A PFO is typically diagnosed by transesophageal echocardiography (TEE), less commonly by transthoracic echocardiography (TTE). Right-to-left shunting of blood across the PFO is demonstrated by color flow Doppler imaging or by using intravenously injected agitated saline and identifying subsequent transfer of the agitated saline through the PFO from the right atrium to the left atrium. No treatment or follow-up is needed in asymptomatic patients with an incidentally detected PFO.

H Management of patients with a PFO and cryptogenic stroke has been controversial. Antiplatelet therapy has traditionally been used as first-line therapy; however, three randomized trials have shown percutaneous PFO closure to be of benefit in the prevention of a second stroke in select patients. In two of the three trials, PFO closure was combined with

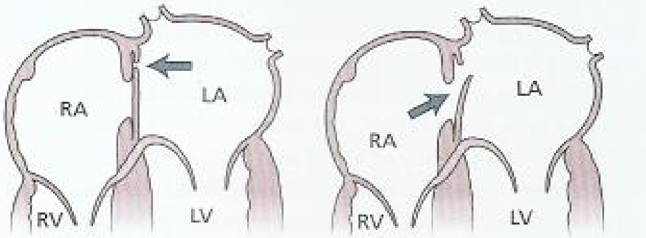

FIGURE 35. Patent foramen ovale. The arrows demonstrate the mechanism of right-to-left shunting through the patent foramen ovale. LA = left atrium; LV = left ventricle; RA = right atrium; RV = right ventricle.

Redrawn from original supplied courtesy of Dr. William D. Edwards, Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN.

H CONT. antiplatelet therapy. Results of these three trials demonstrated a small but statistically significant absolute risk reduction (approximately 1% per year) with closure of the PFO and a low rate of procedural complications (mainly transient atrial fibrillation). Therefore, PFO closure in addition to antiplatelet therapy can be considered in select patients after a thorough evaluation for alternative causes of stroke. Limited data support PFO closure in an effort to decrease the frequency of migraine. Asymptomatic patients require no treatment or follow-up. H

Platypnea-orthodeoxia syndrome is a rare acquired disorder characterized by cyanosis and dyspnea in the upright position as a result of right-to-left shunting across a PFO or, less commonly, through an atrial septal defect. A transient increase in right atrial pressure or change in right atrial anatomy resulting from myocardial infarction, pulmonary embolism, tricuspid regurgitation, or acute right-sided heart failure may precipitate this syndrome. Device closure of the PFO may improve symptoms and oxygen saturation.

H Atrial septal aneurysm is characterized by mobile, redundant atrial septal tissue that is often associated with a PFO. Atrial septal aneurysm with a PFO reportedly increases the risk for stroke compared with a PFO alone. Results of a randomized, open-label trial demonstrated that patients presenting with cryptogenic stroke in the setting of an atrial septal aneurysm with PFO had a lower rate of stroke recurrence when treated with PFO closure combined with antiplatelet therapy than with antiplatelet therapy alone. Rarely, surgical excision and defect closure is considered based on anatomic features. H

KEY POINTS

HVC
- No treatment or follow-up is needed in asymptomatic patients with patent foramen ovale.
- Percutaneous closure of a patent foramen ovale can be considered in select patients with cryptogenic stroke after a thorough evaluation for alternative causes of stroke.

Atrial Septal Defect

Pathophysiology and Genetics

An atrial septal defect (ASD) is a flaw or hole in the atrial septum resulting in a left-to-right shunt with eventual right-sided cardiac chamber dilatation in most patients.

ASDs are generally classified by their location (**Figure 36**). Ostium secundum defects, the most common type of ASDs (75% of cases), are located in the mid portion of the atrial septum and are usually isolated anomalies. Located in the lowest portion of the atrial septum, ostium primum defects (15%-20% of ASDs) are a component of endocardial cushion defects. Associated abnormalities include mitral valve, ventricular septum, and subaortic anomalies. Sinus venosus defects (5%-10% of ASDs) are located near the superior vena cava or, rarely, the inferior vena cava; anomalous pulmonary venous connection

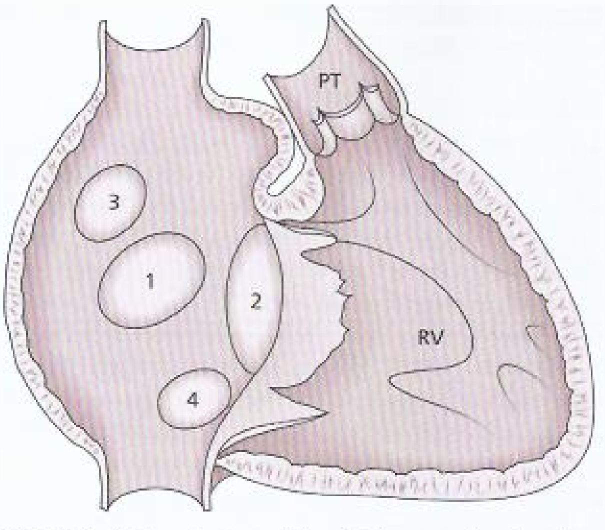

FIGURE 36. Positions of various atrial septal defects viewed from the right side of the heart. (1) Ostium secundum; (2) ostium primum; (3) sinus venosus; (4) coronary sinus. PT = pulmonary trunk; RV = right ventricle.

Redrawn from original supplied courtesy of Dr. William D. Edwards, Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN.

(typically involving the right upper pulmonary vein) is present in more than 90% of patients with this defect. A coronary sinus ASD (<1% of cases) is a communication between the left atrium and the coronary sinus. These defects are commonly associated with a persistent left-sided superior vena cava or complex congenital heart lesions.

ASDs are rarely associated with genetic syndromes. The Holt-Oram syndrome involves bilateral upper extremity abnormalities and congenital heart defects, commonly an ASD. Familial ostium secundum ASDs may be autosomal dominant or linked to chromosome 5. Congenital heart defects are relatively common in patients with Down syndrome; the most frequent abnormalities reported are atrioventricular septal defects, including ostium primum ASD.

Clinical Presentation

ASDs may be suspected in patients with unexplained right heart enlargement or atrial arrhythmias. Atrial fibrillation is a common finding in adults with an ASD. The atrial fibrillation risk decreases but does not normalize after ASD closure. ASD size and associated defects influence the age of presentation; symptoms include fatigue, exertional dyspnea, arrhythmias, and paradoxical embolism. Rarely, patients with pulmonary hypertension (PH) are found to have isolated ASDs.

Clinical findings in patients with an ASD include a parasternal impulse, fixed splitting of the S_2, and a pulmonary outflow murmur. A diastolic flow rumble across the tricuspid valve can occur with a large left-to-right shunt.

Diagnostic Evaluation

The electrocardiographic and radiographic findings in patients with an ASD are presented in **Table 32**.

TABLE 32. Imaging Findings and Late Complications in Adult Congenital Heart Disease

Lesion	ECG and CXR Findings	Late Complications
Patent foramen ovale	Normal	Paradoxical embolism, platypnea-orthodeoxia syndrome
Ostium secundum ASD	ECG: Incomplete RBBB, RA enlargement, right axis deviation CXR: Right heart enlargement, prominent pulmonary artery, increased pulmonary vascularity	Right heart enlargement, atrial fibrillation, PH (rare) Post repair: residual shunt (rare)
Ostium primum ASD	ECG: Left axis deviation, first-degree atrioventricular block CXR: Right heart enlargement, prominent pulmonary artery, increased pulmonary vascularity	Right heart enlargement, atrial fibrillation, mitral regurgitation (from mitral valve cleft), PH (rare) Post repair: residual shunt (rare), mitral regurgitation (from mitral valve cleft), left ventricular outflow tract obstruction
Sinus venosus ASD	ECG: Abnormal P axis CXR: Right heart enlargement, prominent pulmonary artery, increased pulmonary vascularity	Right heart enlargement, atrial fibrillation, PH (rare) Post repair: residual shunt (rare), residual anomalous pulmonary venous connection
Small VSD	Normal	Endocarditis
Large VSD	ECG: RV or RV/LV hypertrophy CXR: RA and RV enlargement, increased pulmonary vascular markings; with PH: prominent central pulmonary arteries, reduced peripheral pulmonary vascular markings	PH with associated RA and RV enlargement, RV hypertrophy, Eisenmenger syndrome Post repair: residual VSD, residual shunt (rare)
Small PDA	Normal	Endocarditis
Large PDA	ECG: LA enlargement, LV hypertrophy; with PH: RV hypertrophy CXR: Cardiomegaly, increased pulmonary vascular markings; calcification of PDA (occasional); with PH: prominent central pulmonary arteries, reduced peripheral pulmonary vascular markings	Endocarditis, right heart failure, PH, Eisenmenger syndrome Post repair: residual shunt (rare)
Pulmonary valve stenosis	ECG: Normal when RV systolic pressure <60 mm Hg; if RV systolic pressure >60 mm Hg: RA enlargement, right axis deviation, RV hypertrophy CXR: Pulmonary artery dilatation, calcification of pulmonary valve (rare); RA enlargement may be noted	Post repair: Severe pulmonary valve regurgitation after pulmonary valvotomy or valvuloplasty
Aortic coarctation	ECG: LV hypertrophy and ST-T wave abnormalities CXR: Dilated ascending aorta, "figure 3 sign" beneath aortic arch, rib notching from collateral vessels	Hypertension (75% of cases), bicuspid aortic valve (>50% of cases), increased risk for aortic aneurysm (ascending or at repair site) and intracranial aneurysm Post repair: Recoarctation, hypertension, aortic aneurysm
Repaired tetralogy of Fallot	ECG: RBBB, increased QRS duration (QRS duration reflects degree of RV dilatation) CXR: Cardiomegaly with pulmonary or tricuspid valve regurgitation; right aortic arch in 25% of cases	Post repair: Increased atrial and ventricular arrhythmia risk, pulmonary valve regurgitation or stenosis; tricuspid regurgitation QRS >180 ms increases risk for ventricular tachycardia and sudden death
Eisenmenger syndrome	ECG: Right axis deviation, RA enlargement, RV hypertrophy CXR: RV dilatation, prominent pulmonary artery, reduced pulmonary vascularity	Right heart failure, hemoptysis, stroke

ASD = atrial septal defect; CXR = chest radiography; ECG = electrocardiography; LA = left atrial; LV = left ventricular; PH = pulmonary hypertension; PDA = patent ductus arteriosus; RA = right atrial; RBBB = right bundle branch block; RV = right ventricular; VSD = ventricular septal defect.

TTE is the preferred imaging modality for identification of ostium secundum and primum ASDs. TTE also measures associated features, such as right-sided cardiac chamber enlargement, tricuspid regurgitation related to annular dilatation, and right ventricular pressure elevation. Agitated saline contrast injection (microcavitation study) in a peripheral vein during TTE may help identify an atrial-level shunt. Sinus venosus and coronary sinus ASDs are less readily diagnosed by TTE in

adults and often require other imaging modalities, such as TEE, cardiac magnetic resonance (CMR) imaging, or CT. CMR imaging and CT are rarely used as the primary imaging modality when an ASD is suspected but can identify anomalous pulmonary veins and quantify right ventricular volume and ejection fraction.

Cardiac catheterization is the only method for accurately calculating pulmonary-to-systemic blood flow ratio (Qp:Qs) but is rarely required for uncomplicated ASDs. Cardiac catheterization may be recommended in patients with an ASD and PH when ASD closure is being considered.

Treatment

The main indications for ASD closure include right-sided cardiac chamber enlargement or symptoms of dyspnea; closure is reasonable for orthodeoxia-platypnea syndrome and also before pacemaker placement because of the increased risk for systemic thromboembolism. In asymptomatic patients with a small ASD and no right heart enlargement, periodic clinical monitoring and echocardiographic imaging are recommended.

Percutaneous device closure is an option for patients with an isolated ostium secundum ASD. Surgical ASD closure is indicated for nonsecundum ASDs, large secundum ASDs, unfavorable anatomy for device closure, and coexistent cardiovascular disease that requires operative intervention, such as coronary artery disease or tricuspid regurgitation.

Patients with an ASD and PH require specialty care; ASD closure may be considered for persistent left-to-right shunting without fixed PH. Medical therapy targeted at PH should also be considered.

Patients with an isolated anomalous pulmonary venous connection may present with clinical findings and TTE features similar to an ASD. Surgical redirection of the pulmonary vein is the only feasible treatment and requires surgical expertise in congenital heart disease.

Patients with small ASDs do not require physical activity limitation. Large left-to-right shunts result in self-limited exercise restriction. Patients with severe PH are advised to avoid isometric or competitive exercise.

Pregnancy is generally well tolerated in patients with an ASD in the absence of PH. The risk for congenital heart disease transmission with a sporadic ASD is estimated to be around 5%. Holt-Oram syndrome is inherited in an autosomal dominant fashion, and other genetic syndromes have variable inheritance; genetic counseling is suggested if a syndrome is suspected.

Follow-up After Atrial Septal Defect Closure

Follow-up is recommended for patients after surgical or percutaneous ASD closure. TTE and clinical assessment are recommended within the first year after closure and then periodically after that. Atrial fibrillation risk persists after closure, and frequency increases related to age at the time of ASD closure. Rare complications after device closure include device migration, erosion into the pericardium or aorta, and sudden death.

KEY POINTS

- Clinical findings in patients with atrial septal defect include a parasternal impulse, fixed splitting of the S_2, and a pulmonary outflow murmur.
- Cardiac catheterization is the only method for accurately calculating pulmonary-to-systemic blood flow ratio but is rarely required for diagnostic purposes other than in patients with an atrial septal defect (ASD) and pulmonary hypertension when ASD closure is being considered.
- The main indications for atrial septal defect (ASD) closure include right-sided cardiac chamber enlargement, symptoms of dyspnea, or atrial arrhythmias; asymptomatic, small ASDs without right heart enlargement can simply be monitored with clinical and echocardiographic surveillance.

Ventricular Septal Defect

Pathophysiology

Ventricular septal defects (VSDs) are defined by their location on the ventricular septum (**Figure 37**). They are common at birth, but many small VSDs close spontaneously, resulting in lower prevalence by adulthood. Perimembranous VSDs are most common (80% of cases) and are usually isolated abnormalities. Muscular VSDs (10% of cases) can be located anywhere in the ventricular septum and often close spontaneously. Subpulmonary VSDs (also called outlet or supracristal

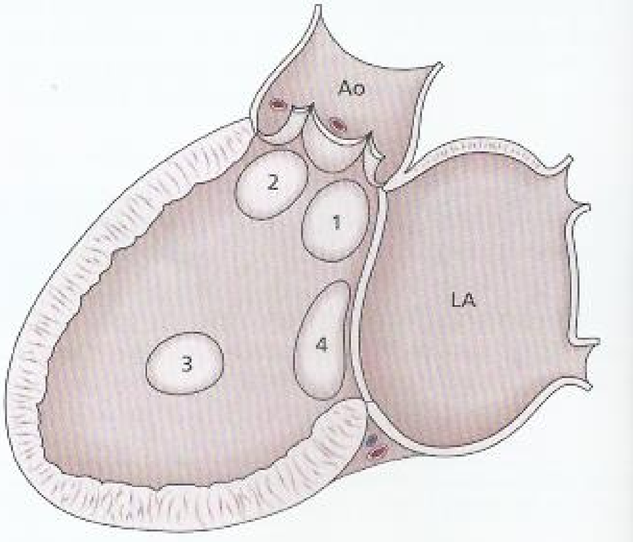

FIGURE 37. Positions of various ventricular septal defects viewed from the left side of the heart. (1) Perimembranous; (2) subpulmonary; (3) muscular; (4) inlet. Ao = aorta; LA = left atrium.

Redrawn from original supplied courtesy of Dr. William D. Edwards, Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN.

VSDs) account for approximately 6% of defects in non-Asians and 33% in Asians and are associated with aortic regurgitation caused by aortic cusp distortion. Inlet VSDs (4% of cases) occur in the superior-posterior portion of the ventricular septum adjacent to the tricuspid valve. They occur as part of the atrioventricular septal defect complex, characteristically seen in patients with Down syndrome.

Clinical Presentation

The presentation of an isolated VSD depends on the VSD size and pulmonary vascular resistance. A small VSD without PH presents with a loud (often palpable) holosystolic murmur located at the left sternal border that may obliterate the S_2. Small VSDs do not cause left heart enlargement or PH.

A VSD with a moderate left-to-right shunt may cause left ventricular volume overload and PH. Patients are asymptomatic for many years but eventually present with heart failure symptoms. A displaced left ventricular apical impulse suggests volume overload. A holosystolic murmur at the left sternal border is noted; the pressure gradient between the ventricles determines the murmur quality and duration. Progressive PH results in shortening of the murmur.

VSDs associated with large left-to-right shunts are usually detected by the presence of a murmur, heart failure, and failure to thrive in infancy. Failure to close the defect early in life usually causes fixed PH within several years with subsequent development of Eisenmenger syndrome (see later discussion) and shunt reversal.

Diagnostic Evaluation

The electrocardiographic and radiographic findings in patients with a VSD are presented in Table 32.

TTE is the imaging modality of choice for identification of VSD location, size, and hemodynamic impact. Rarely, TEE, CMR imaging, or CT is needed to delineate cardiac anatomy when TTE is unsatisfactory. Cardiac catheterization is primarily performed to delineate the Qp:Qs ratio and pulmonary pressures.

Treatment

VSD closure is indicated when the Qp:Qs ratio is 2.0 or greater with evidence of left ventricular volume overload or a history of endocarditis. Most patients are treated surgically, but percutaneous device closure is an option for select VSDs.

VSD closure is not indicated for patients with a small left-to-right shunt and no chamber enlargement or valve disease, but periodic clinical evaluation and imaging are recommended. Large VSDs with shunt reversal (right-to-left shunting) and PH (Eisenmenger syndrome) should not be closed because this causes clinical deterioration owing to reduced cardiac output.

Patients with small VSDs do not require activity restrictions. If the pulmonary artery pressure is greater than 50% of systolic blood pressure, isometric or competitive exercise is discouraged.

Pregnancy in women with VSDs is generally well tolerated in the absence of PH; women with VSDs and associated fixed PH should be counseled to avoid pregnancy.

Follow-up After Ventricular Septal Defect Closure

Residual or recurrent VSD, arrhythmias, PH, endocarditis, and valve regurgitation are recognized complications following VSD closure. Clinical assessment and TTE are recommended within 1 year of VSD closure. Subsequent follow-up frequency depends on clinical and cardiac status.

KEY POINTS

- A small ventricular septal defect without pulmonary hypertension presents with a loud (often palpable) holosystolic murmur located at the left sternal border that may obliterate the S_2.
- Ventricular septal defect closure is indicated when the Qp:Qs ratio is 2.0 or greater with evidence of left ventricular volume overload or in patients with a history of endocarditis.

Patent Ductus Arteriosus

Pathophysiology

A patent ductus arteriosus (PDA) is a persistent fetal connection between the aorta and the pulmonary artery. Prematurity and maternal rubella predispose to a PDA. It may be an isolated abnormality or associated with other congenital cardiac defects.

Clinical Presentation

The typical murmur of a PDA is a continuous "machinery" murmur that envelops the S_2, making it inaudible; the murmur is heard beneath the left clavicle. A tiny PDA is generally asymptomatic and inaudible. Patients with a moderate-sized PDA may present with bounding pulses, a wide pulse pressure, left heart enlargement and dysfunction, and, rarely, clinical heart failure.

A large unrepaired PDA may cause PH with eventual shunt reversal (Eisenmenger syndrome); characteristic features of an Eisenmenger PDA are clubbing and oxygen desaturation affecting the feet but not the hands, owing to desaturated blood reaching the lower extremities preferentially (differential cyanosis).

Diagnostic Evaluation

The electrocardiographic and radiographic findings in patients with a PDA are presented in Table 32.

TTE is the imaging modality of choice for identification of a PDA. The PDA may be difficult to visualize in patients with severe PH owing to equalization of pressures between the aorta and pulmonary artery. In patients with a PDA and PH, cardiac catheterization is used to determine shunt size and

reversibility of PH. Angiography confirms PDA morphology and helps determine whether percutaneous closure is feasible. TEE, CT, and CMR imaging may identify a PDA but are not the primary diagnostic techniques.

Treatment

PDA closure is indicated for left-sided cardiac chamber enlargement in the absence of severe PH. Percutaneous or surgical closure may be performed; referral to a congenital cardiac center for consideration of closure options is recommended.

A tiny PDA requires no intervention. PDA closure is reasonable for small PDAs with previous endocarditis. Moderate-sized PDAs are generally closed percutaneously. Large PDAs with severe PH and shunt reversal should be observed; closure may be detrimental, but medical therapy for PH should be considered.

Patients with a small PDA without PH do not require physical activity restrictions, and women should be able to tolerate pregnancy.

KEY POINTS

- A continuous "machinery" murmur heard beneath the left clavicle that makes the S_2 inaudible is typical for a patent ductus arteriosus.
- Angiography can determine patent ductus arteriosus morphology and whether percutaneous closure is feasible.
- The size of a patent ductus arteriosus (PDA) determines management; a tiny PDA requires no intervention.
- A large patent ductus arteriosus with severe pulmonary hypertension (PH) and shunt reversal should be observed; closure may be detrimental, but medical therapy for PH should be considered.

Pulmonary Valve Stenosis

Pathophysiology

Pulmonary valve stenosis (PS), an autosomal dominant disorder, causes obstruction to right ventricular outflow and is usually an isolated valve lesion. Isolated PS is associated with Noonan syndrome, which includes short stature, variable intellectual capacity, neck webbing, and ocular hypertelorism (abnormally increased distance between the orbits).

Clinical Presentation

Mild and moderate PS is generally asymptomatic. On physical examination, mild PS is characterized by a normal jugular venous waveform and precordial impulse.

Severe PS can cause exertional dyspnea. Right ventricular hypertrophy caused by pressure overload results in a prominent *a* wave on the jugular venous pressure waveform and a palpable right ventricular lift.

Auscultatory findings in PS include a systolic ejection click immediately after the S_1 (which is the only right-sided heart sound to decrease during inspiration), followed by a crescendo-decrescendo murmur. In severe PS, the ejection systolic murmur at the left sternal border increases in intensity and duration, and the pulmonary valve component of S_2 is delayed (splitting of S_2) and eventually disappears. A right ventricular S_4 is often heard in severe PS.

Diagnostic Evaluation

The electrocardiographic and radiographic findings in patients with PS are presented in Table 32.

TTE is the imaging modality of choice for identification of PS. Severe PS is present when the peak gradient is 50 mm Hg or greater. Treatment options depend on valve mobility, calcification, and the effects of obstruction on the right ventricle. PS causes right ventricular hypertrophy. Right ventricular dilatation should prompt a search for an associated lesion, such as pulmonary valve regurgitation or an ASD. TEE, CMR imaging, and CT are not routinely used in patients with PS. Cardiac catheterization is performed when percutaneous intervention for PS is considered.

Treatment

Pulmonary balloon valvuloplasty is the preferred treatment for valvular PS. It is indicated for asymptomatic patients with appropriate pulmonary valve morphology who have a peak Doppler gradient of at least 60 mm Hg or a mean gradient greater than 40 mm Hg and pulmonary valve regurgitation that is less than moderate. Balloon valvuloplasty is also recommended for symptomatic patients with appropriate valve morphology who have a peak Doppler gradient of greater than 50 mm Hg or a mean gradient greater than 30 mm Hg. Surgical intervention is recommended for PS associated with a small annulus, more than moderate pulmonary valve regurgitation, severe subvalvar or supravalvar PS, or another cardiac lesion that requires operative intervention.

Patients with mild and moderate PS (peak gradient <50 mm Hg) do not require exercise restriction. Patients with severe PS should participate only in low-intensity sports.

Pregnancy is generally well tolerated with PS; percutaneous valvotomy has been performed during pregnancy for severe symptomatic PS. Sporadic congenital heart disease recurrence in offspring is rare. Noonan syndrome should be suspected with PS recurrence in offspring.

Follow-up After Pulmonary Valve Stenosis Repair

Patients with previous PS intervention (balloon or surgical) often have severe pulmonary valve regurgitation; thus, long-term clinical and TTE follow-up is recommended. The frequency of follow-up depends on regurgitation severity and impact on the heart.

KEY POINTS

- Auscultation findings in pulmonary valve stenosis include a systolic ejection click immediately after S_1, followed by a crescendo-decrescendo murmur.
- Surgical intervention is recommended for pulmonary valve stenosis (PS) associated with a small annulus, more than moderate pulmonary valve regurgitation, severe subvalvar or supravalvar PS, or another cardiac lesion that requires operative intervention.

Aortic Coarctation

Pathophysiology

Aortic coarctation is a discrete narrowing of the aorta, usually located just beyond the left subclavian artery, causing hypertension proximal and hypotension distal to the narrowing.

Clinical Presentation

Patients with aortic coarctation may present with heart failure early in life. Adults are usually asymptomatic, but exertional leg fatigue or headaches may occur. Upper extremity hypertension and reduced blood pressure and pulse amplitude in the lower extremities cause a radial artery–to–femoral artery pulse delay. A systolic or continuous murmur is heard in the left infraclavicular region or over the back. A murmur from collateral intercostal vessels may also be audible and palpable over the chest wall. Fifty percent of patients with aortic coarctation have a bicuspid aortic valve. Auscultation of the heart may reveal an ejection click, a systolic murmur at the cardiac base, or, sometimes, an S_4.

Turner syndrome, a chromosomal abnormality secondary to partial or total loss of chromosome X, is often associated with congenital cardiac disease, including coarctation. Turner syndrome is characterized by short stature, webbed neck, broad chest, and widely spaced nipples. Aortic coarctation is also associated with aortic and subaortic stenosis, parachute mitral valve (Shone syndrome), ventricular septal defect, and cerebral aneurysms.

Diagnostic Evaluation

The electrocardiographic and radiographic findings in patients with aortic coarctation are presented in Table 32.

The characteristic radiographic features of aortic coarctation include the "figure 3 sign" (**Figure 38**), which is caused by dilatation of the aorta above and below the area of coarctation. Dilatation of intercostal collateral arteries as a result of aortic obstruction may lead to the radiographic appearance of rib notching.

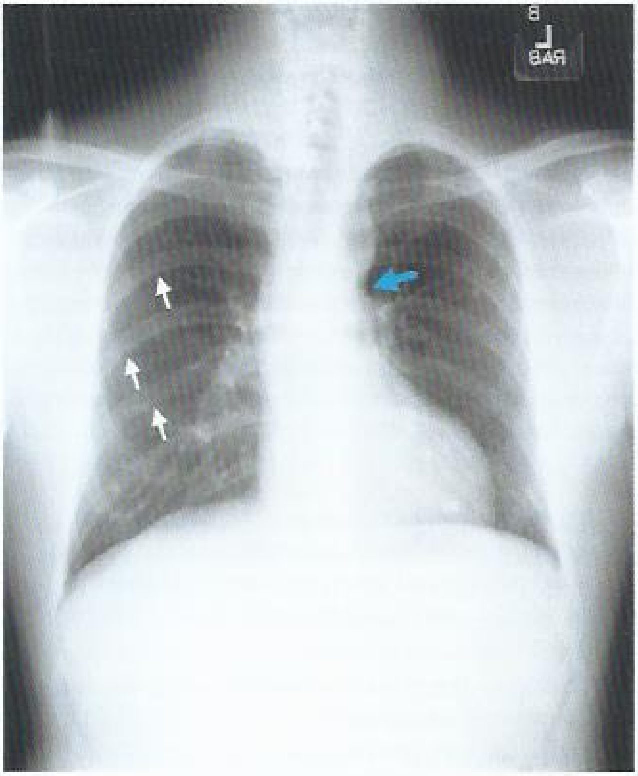

FIGURE 38. Chest radiograph of a patient with aortic coarctation exhibiting the "figure 3 sign," caused by dilatation of the aorta above and below the area of coarctation (*blue arrow*), and rib notching (*white arrows*).

TTE is often the initial diagnostic test in patients suspected of having aortic coarctation; it usually identifies the coarctation and associated features, such as bicuspid aortic valve and left ventricular hypertrophy. CMR imaging and CT are recommended to identify the anatomy, severity, and location of the coarctation; the presence of collateral vessels; and associated abnormalities, such as aortic aneurysm. Cardiac catheterization is primarily used in patients in whom percutaneous intervention is being considered.

Treatment

Severe aortic coarctation is associated with excess morbidity and mortality, including hypertension, coronary artery disease, stroke, aortic dissection, and heart failure. Age at the time of coarctation repair is the most important predictor of long-term survival.

Indications for intervention in patients with coarctation include a systolic peak (peak-to-peak) pressure gradient of 20 mm Hg or greater or radiologic evidence of severe coarctation with collateral flow. Percutaneous or surgical intervention options are available; selection depends on the length, location, and severity of coarctation and the presence of associated cardiovascular lesions.

Physical activity restriction is recommended for patients with severe postintervention residual or unrepaired coarctation, aortic stenosis, or a dilated aorta; these patients should avoid contact sports and isometric exercise.

A comprehensive preconception evaluation is warranted in all patients with coarctation who are considering pregnancy. Pregnancy is reasonable in women with repaired aortic coarctation without significant residua. Women with mild or moderate residua or unoperated coarctation will generally

tolerate pregnancy well but should undergo blood pressure monitoring and cardiovascular evaluation during pregnancy. Pregnancy should be avoided by patients with severe unrepaired coarctation.

Follow-up After Aortic Coarctation Repair

Following coarctation repair, hypertension occurs in up to 75% of patients and should be treated. Additional intervention following repair may be required for bicuspid aortic valve, aortic aneurysm or dissection, recoarctation, coronary artery disease, systolic or diastolic heart failure, or intracranial aneurysm. Regular follow-up should include TTE, periodic aortic imaging, and evaluation by a cardiologist specializing in congenital heart disease.

KEY POINTS

- In patients with aortic coarctation, findings may include upper extremity hypertension and reduced blood pressure and pulse amplitude in the lower extremities, causing a radial artery–to–femoral artery pulse delay.
- The "figure 3 sign" is a characteristic radiographic feature of aortic coarctation.
- Indications for intervention in patients with aortic coarctation include a systolic peak (peak-to-peak) pressure gradient of 20 mm Hg or greater or radiologic evidence of severe coarctation with collateral flow.

Tetralogy of Fallot

Tetralogy of Fallot (TOF) is characterized by a large subaortic VSD, infundibular or valvular PS, aortic override, and right ventricular hypertrophy (**Figure 39**). It is the most common cyanotic congenital cardiac lesion. Repair is usually performed early in life; adults who have not undergone an operation are rarely encountered.

Genetic screening is recommended for all patients with TOF who are planning reproduction. Approximately 15% of patients with TOF have the 22q11.2 chromosome microdeletion (DiGeorge syndrome). When present, congenital heart disease inheritance is approximately 50%, compared with 5% in unaffected patients. TOF is common in persons with Down syndrome.

TOF repair involves VSD patch closure and relief of PS/right ventricular outflow tract obstruction by transannular patch placement; the transannular patch disrupts integrity of the pulmonary valve, causing severe pulmonary valve regurgitation. Severe long-standing pulmonary valve regurgitation causes right heart enlargement, tricuspid regurgitation, exercise limitation, and arrhythmias and is the most common reason for reoperation after TOF repair. Annual congenital cardiology follow-up is recommended for patients with repaired TOF to determine optimal timing for intervention.

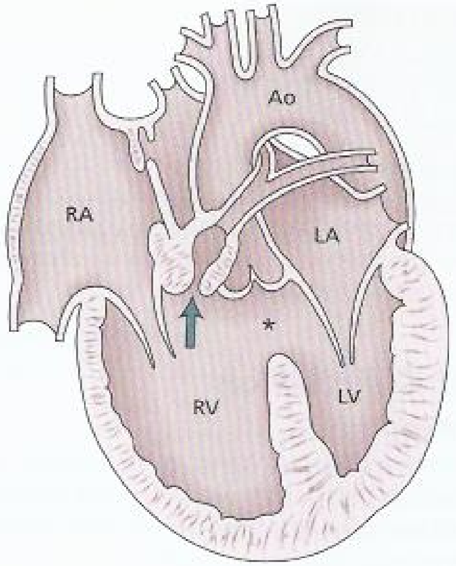

FIGURE 39. Tetralogy of Fallot. A subarterial ventricular septal defect (*asterisk*) and pulmonary stenosis (*arrow*) are associated with secondary aortic override and right ventricular hypertrophy. Ao = aorta; LA = left atrium; LV = left ventricle; RA = right atrium; RV = right ventricle.

Redrawn from original supplied courtesy of Dr. William D. Edwards, Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN.

Diagnostic Evaluation after Repair of Tetralogy of Fallot

The electrocardiographic and radiographic findings in patients with repaired TOF are presented in Table 32.

Symptoms, arrhythmias, or right heart chamber enlargement should prompt a search for severe pulmonary valve regurgitation. Prolongation of the QRS complex reflects the degree of right ventricular dilatation; QRS duration of 180 milliseconds or longer and nonsustained ventricular tachycardia are risk factors for sudden cardiac death.

TTE is the imaging modality of choice for identifying valve dysfunction, residual VSD, left ventricular dysfunction, and aortic dilatation. CMR imaging or CT is preferred for assessment of right ventricular size and function, which helps determine appropriate timing for pulmonary valve replacement. Cardiac catheterization may be required to assess hemodynamics and residual shunts and to delineate coronary artery and pulmonary artery anatomy.

Treatment of Tetralogy of Fallot Residua

Indications for pulmonary valve replacement in patients with repaired TOF and severe pulmonary valve regurgitation include symptoms, decreased exercise tolerance, more than moderate right heart enlargement or dysfunction, arrhythmias, and development of tricuspid regurgitation. Tricuspid valve repair may also be needed. Percutaneous pulmonary valve replacement is possible in select patients with previous TOF surgery.

Physical activity restriction is recommended for patients with repaired TOF and residual sequelae; contact sports and heavy isometric exercise should be avoided.

KEY POINTS

- Genetic screening is recommended for all patients with tetralogy of Fallot who are planning reproduction because the presence of the 22q11.2 chromosome microdeletion (15% of patients) results in congenital heart disease inheritance of approximately 50%.
- Indications for pulmonary valve replacement in patients with repaired tetralogy of Fallot and severe pulmonary valve regurgitation include symptoms, decreased exercise tolerance, more than moderate right heart enlargement or dysfunction, arrhythmias, and development of tricuspid regurgitation.

Adults with Cyanotic Congenital Heart Disease

General Management

Right-to-left cardiac shunts, such as palliated or unrepaired TOF and Eisenmenger syndrome, result in hypoxemia, erythrocytosis, and cyanosis. An increased erythrocyte mass is a compensatory response to improve oxygen transport.

Physical features include digital clubbing and central cyanosis. These patients are predisposed to arthropathy, scoliosis, gallstones, pulmonary hemorrhage or thrombus, paradoxical cerebral emboli or abscess, kidney dysfunction, pheochromocytoma/paraganglioma, and hemostatic problems. Patients with cyanotic congenital heart disease should be evaluated annually by a congenital cardiac specialist.

H Perioperative complications are common in patients with cyanosis, so elective procedures and operations should be performed at specialized multidisciplinary care centers; a congenital cardiac specialist should be consulted when patients are hospitalized. Additional considerations in these patients include antimicrobial prophylaxis for nonsterile procedures; placement of intravenous line filters to prevent paradoxical air embolism; and early ambulation, pneumatic compression devices, and anticoagulation to prevent venous stasis, venous thrombosis, and paradoxical embolism. Venous thromboembolism prophylaxis is especially important in these patients because of the risk for paradoxical embolism if a venous thromboembolism were to occur. H

Most patients with cyanosis have compensated, stable erythrocytosis. Phlebotomy is recommended for patients with symptomatic hyperviscosity (headaches and reduced concentration) with a hemoglobin level greater than 20 g/dL (200 g/L) and hematocrit greater than 65% in the absence of dehydration. Phlebotomy should be performed no more than three times each year and should be followed by fluid administration. Repeated phlebotomies deplete iron stores and cause iron-deficient erythrocytes or microcytosis, increasing the risk for stroke. Short-term iron therapy is administered for iron deficiency in patients with destabilized erythropoiesis.

Maternal and fetal morbidity and mortality increase related to the degree of cyanosis and pulmonary pressures; thus, pregnancy in patients with cyanosis is considered high risk.

Eisenmenger Syndrome

Eisenmenger syndrome is severe PH with cardiac shunt reversal (right to left shunting) caused by a long-standing, unrepaired VSD, PDA, or ASD. TTE evaluation and appropriate intervention has decreased the frequency of Eisenmenger syndrome, but PH related to complex congenital heart disease is increasingly identified.

Conservative medical measures for patients with Eisenmenger syndrome include avoiding iron deficiency, dehydration, acute exposure to excess heat, and moderate or severe strenuous or isometric exercise. Phlebotomy is rarely performed. Additionally, long-term altitude exposure should be avoided or limited because it results in a reduced partial pressure of oxygen. Air travel should be undertaken in pressurized aircrafts; supplemental oxygen may be beneficial with prolonged air travel.

All patients with Eisenmenger syndrome should undergo annual evaluation by a congenital cardiac specialist. Noncardiac surgery should be performed at centers with expertise in the care of patients with complex congenital cardiac disease. Patients with progressive cardiovascular symptoms may benefit from pulmonary vasodilator therapy or, in rare cases, heart and lung transplantation.

Women with Eisenmenger syndrome should be cautioned to avoid pregnancy because of the high risk for maternal mortality.

KEY POINTS

- Phlebotomy is recommended for patients with cyanotic congenital heart disease who have symptomatic hyperviscosity with a hemoglobin level greater than 20 g/dL (200 g/L) and hematocrit greater than 65% in the absence of dehydration; iron deficiency should be avoided.
- Patients with cyanotic congenital heart disease who are undergoing surgery or elective procedures require additional care considerations, including antimicrobial prophylaxis for nonsterile procedures; intravenous line filters to prevent paradoxical air embolism; and early ambulation, pneumatic compression devices, and anticoagulation to prevent venous stasis, venous thrombosis, and paradoxical embolism.
- In patients with Eisenmenger syndrome, air travel should be undertaken in pressurized aircrafts, with supplemental oxygen for prolonged air travel.

Diseases of the Aorta

Introduction

Diseases of the aorta include chronic conditions, such as thoracic and abdominal aortic aneurysms and aortic atheromas,

and potentially life-threatening acute conditions, such as aortic dissection and aneurysm rupture. Once chronic aortic diseases are diagnosed, surveillance and treatment are critical to prevent disease progression, complications, and mortality.

Thoracic Aortic Aneurysm

Thoracic aortic aneurysm (TAA) is defined as an increase in the thoracic aortic diameter of greater than 50% relative to the expected or normal aortic dimension. TAAs may occur at the level of the aortic root, ascending aorta, aortic arch, or descending aorta. They most commonly involve the aortic root and ascending aorta, often forming at the site of aortic atherosclerosis. TAAs are usually the result of cystic medial degeneration and weakening of the aortic wall due to loss of smooth muscle fibers and elastic fiber degeneration.

Common causes of TAA are summarized in **Table 33**. TAAs that occur in patients younger than 50 years are often caused by connective tissue disorders, such as Marfan or Ehlers-Danlos syndrome. Bicuspid aortic valve morphology is also an important risk factor for TAA formation; TAAs occur in approximately 50% of patients with a bicuspid aortic valve. Other risk factors for TAA include age and hypertension.

TAAs are often asymptomatic and are commonly detected by echocardiography during an evaluation of left ventricular function or murmurs. Infrequently, symptoms of hoarseness and dysphagia occur when an aneurysm compresses surrounding structures. Physical examination findings, such as a diastolic heart murmur or wide pulse pressure, are found in the setting of aortic regurgitation, which often occurs in combination with TAA. If the aneurysm ruptures, patients present with severe chest or back pain, sudden shortness of breath, or sudden cardiac death.

TABLE 33. Causes of Thoracic Aortic Aneurysm

Category	Syndrome
Atherosclerosis	
Connective tissue disorders	Marfan syndrome
	Ehlers-Danlos syndrome type IV
	Loeys-Dietz syndrome
Other genetic and/or congenital conditions	Familial thoracic aortic aneurysm and aortic dissection syndrome
	Bicuspid aortic valve
	Turner syndrome
Vasculitis	Takayasu arteritis
	Giant cell arteritis
	Nonspecific (idiopathic) aortitis
	Other autoimmune conditions (Behçet syndrome, systemic lupus erythematosus)
Infectious	Septic embolism
	Direct bacterial inoculation
	Bacterial seeding
	Contiguous infection
	Syphilis
Aortic injury	Prior acute aortic syndrome
	Chest trauma

Screening and Surveillance

Screening for abnormalities of the thoracic aorta with aortic imaging is indicated in asymptomatic patients with genetic conditions (such as Marfan or Ehlers-Danlos syndrome), a bicuspid aortic valve, or a family history of TAA or aortic dissection. Screening is not recommended in other asymptomatic persons.

After TAA is detected, noninvasive imaging is indicated to determine aortic cross-sectional area (**Table 34**). Aortic diameter measurement often varies substantially depending on the type of imaging study used. Care must be taken to measure the dimension perpendicular to the long axis of the aorta because oblique measurements may overestimate the true aortic diameter. The maximum aortic diameter at the site of an aneurysm (measured in cm) is generally used in the criteria for surveillance and treatment.

Because the leading cause of death in patients with TAA is rupture, surveillance and treatment depend on the aneurysm size and risk for rupture. Once the diameter of the aneurysm has grown larger than 5.0 cm, the average growth rate is 0.1 cm/year, and risk for rupture increases. Additional independent risk factors for rupture are a rapid rate of expansion (>0.5 cm/year), the presence of an aneurysm during pregnancy, and previous aortic dissection. Annual surveillance is appropriate in patients with a first-degree relative with a history of familial thoracic aortic aneurysm and aortic dissection.

Transthoracic echocardiography is most commonly used for annual surveillance of TAAs smaller than 5.0 cm in diameter. In patients with previous rapid rate of expansion or in patients with a TAA of 5.0 cm in diameter or larger, more frequent surveillance is often warranted. Patients with rapid expansion of the TAA or aortic dimension of 5.5 cm should undergo additional imaging with CT angiography (CTA) or magnetic resonance angiography (MRA).

In patients with a TAA and a genetic condition (Marfan or Ehlers-Danlos syndrome) or bicuspid aortic valve, it is recommended that repeat assessment occur 6 months after diagnosis to determine the rate of enlargement. Thereafter, annual imaging is recommended if the aortic diameter has been stable and smaller than 4.5 cm. If the aortic diameter is 4.5 cm or larger or the rate of enlargement exceeds 0.5 cm/year, imaging should be performed every 6 months.

Treatment

TAAs with a diameter smaller than 5.0 cm can usually be managed with medical therapy and active surveillance (see Table 34). Medical therapy includes aggressive blood pressure control with a goal blood pressure below 130/80 mm Hg. β-Blockers are the preferred antihypertensive agents in patients with

TABLE 34. Comparison of Thoracic Aortic Imaging Modalities

Modality	Advantages	Disadvantages
Transthoracic echocardiography (TTE)	Good visualization of aortic root/proximal ascending aorta No exposure to radiation or contrast dye Allows definition of valvular pathology, myocardial function, pericardial disease Bedside diagnosis	Requires experienced operator Limited visualization of the distal ascending aorta and aortic arch and branches of the great vessels A negative TTE result does not rule out aortic dissection, and other imaging techniques must be considered
Transesophageal echocardiography (TEE)	TEE has superior imaging quality compared with TTE Excellent visualization of the aorta from its root to the descending aorta No exposure to radiation or contrast dye Allows definition of valvular pathology, myocardial function, pericardial disease Bedside diagnosis	Requires experienced operator Invasive procedure
CT angiography	Visualization of entire aorta and side branches Rapid imaging Multiplanar reconstruction	Exposes patient to radiation, iodinated contrast dye
Magnetic resonance angiography	Visualization of entire aorta and side branches No exposure to radiation or iodinated contrast dye	For acute disease, prolonged image acquisition away from acute care area Contraindicated in patients with implanted pacemaker or defibrillator Gadolinium contrast dye contraindicated in patients with kidney disease
Aortography	Visualization of aortic lumen, side branches, and collaterals Provides exact information on aorta size and shape and any anomalies	Diseases of the aortic wall and thrombus-filled discrete aortic aneurysms may be missed Invasive procedure that requires power injection within the aorta Requires dye load and may be nephrotoxic

TAA. In patients with Marfan syndrome, β-blockers and losartan have been associated with a reduced rate of aneurysm growth.

Once ascending aortic aneurysm size exceeds 5.5 cm in diameter, repair is warranted to prevent the morbidity and mortality associated with aneurysm rupture. In patients with an ascending aorta or aortic root greater than 4.5 cm in diameter who require coronary artery bypass grafting or surgery to repair valve pathology, aortic repair should be performed at the time of cardiac surgery. Current guidelines recommend that all patients with a bicuspid aortic valve and ascending aortic aneurysm undergo aortic repair when the aneurysm exceeds 5.5 cm in diameter, unless there is an indication to repair concomitant coronary artery disease or aortic valve pathology. In patients with Marfan or Ehlers-Danlos syndrome, the American College of Cardiology/American Heart Association guidelines recommend that patients undergo aortic repair at a lower threshold (4.5-5.0 cm).

The aneurysm location, associated aortic valve pathology, and presence of concomitant coronary artery disease all dictate the type of thoracic aortic repair performed. Open surgical repair is indicated for TAAs that involve the aortic root, ascending aorta, and aortic arch. Thoracic endovascular aortic repair (TEVAR) with stent grafting should be used when a descending aortic aneurysm has a diameter greater than 6.0 cm, has exhibited rapid growth (>0.5 cm/year), or has caused end-organ damage, owing to a lower morbidity and shorter hospital stay relative to open repair. TEVAR has the advantage of avoiding an open surgical operation, although complications (stroke, spinal ischemia, aortic graft endoleaks) can occur.

KEY POINTS

- Asymptomatic patients with Marfan or Ehlers-Danlos syndrome, a bicuspid aortic valve, or a family history of thoracic aortic aneurysm or aortic dissection should undergo screening for abnormalities of the thoracic aorta.
- Patients with a thoracic aortic aneurysm smaller than 5.0 cm in diameter should undergo annual echocardiography to monitor aortic aneurysm growth.

(Continued)

KEY POINTS *(continued)*

- In patients with an ascending aortic diameter exceeding 5.5 cm, elective aortic repair is warranted to prevent the morbidity and mortality associated with aneurysm rupture; patients with Marfan or Ehlers-Danlos syndrome should undergo aortic repair at 4.5 to 5.0 cm.
- Thoracic endovascular aortic repair is recommended in patients with a descending aortic aneurysm when the diameter is greater than 6.0 cm, has exhibited rapid growth (>0.5 cm/year), or has caused end-organ damage.

Abdominal Aortic Aneurysm

Abdominal aortic aneurysm (AAA) is defined as an abnormal dilatation of the aorta with an anteroposterior diameter greater than 3.0 cm. Risk factors include male sex (6:1 male-to-female incidence ratio), advanced age, smoking, atherosclerosis, hypertension, and a family history of AAA.

Screening and Surveillance

AAA is most commonly diagnosed incidentally by CTA or abdominal ultrasonography. Approximately 75% of patients with AAA are asymptomatic at the time of diagnosis. Because of the high mortality rate associated with aneurysm rupture, the U.S. Preventive Services Task Force recommends one-time screening with duplex ultrasonography in all men aged 65 to 75 years who have smoked at least 100 cigarettes in their lifetime and selective screening in men in this age group who have never smoked (see MKSAP 18 General Internal Medicine).

Estimated annual risk for aortic rupture according to AAA dimension is shown in **Table 35**. In patients with an AAA diameter of 4.0 cm or less, surveillance with duplex ultrasonography every 2 to 3 years is warranted. In patients with an AAA diameter of 4.1 to 5.4 cm, surveillance with CTA or duplex ultrasonography should be performed every 6 to 12 months. Once the aortic diameter meets the threshold for aortic repair, anatomic imaging tests, such as CTA or MRA, are indicated to determine the exact location of the AAA (suprarenal, juxtarenal, or infrarenal) in planning for repair.

TABLE 35. Annual Rupture Risk of Abdominal Aortic Aneurysm by Diameter

Aneurysm Diameter	Annual Rupture Risk
<4.0 cm	<0.5%
4.0-4.9 cm	0.5%-5%
5.0-5.9 cm	3%-15%
6.0-6.9 cm	10%-20%
7.0-7.9 cm	20%-40%
≥8.0 cm	30%-50%

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Treatment

Medical treatment of AAA involves risk factor reduction to reduce the risk for rupture, cardiovascular morbidity, and overall mortality. Aortic repair should be performed in patients with an AAA diameter of 5.5 cm or larger, in those with rapid expansion in AAA size (>0.5 cm/year), and in patients presenting with symptoms resulting from AAA (abdominal or back pain/tenderness). In patients with an indication for aortic repair, the choice between open surgical repair and endovascular aneurysm repair (EVAR) is driven by the location of the AAA and involvement of the renal and mesenteric arteries. Suprarenal and juxtarenal aneurysms most often necessitate open surgical repair. Patient age, comorbid conditions, and ability to tolerate open surgical repair determine which procedure should be performed in patients with an infrarenal AAA. EVAR is associated with lower short-term (30-day) morbidity and mortality but no significant differences in long-term mortality. Additionally, EVAR is associated with increased need for repeat intervention and significantly higher rates of endoleak, device failure, and postimplantation syndrome (fever, leukocytosis, elevated serum C-reactive protein). These complications necessitate diligent follow-up with noninvasive imaging tests (CTA or ultrasonography) to evaluate the stent graft.

KEY POINTS

- Risk factors for abdominal aortic aneurysm include male sex, increased age, smoking, and family history.
- Aortic repair should be performed in patients with an abdominal aortic aneurysm (AAA) diameter of 5.5 cm or larger, in those with rapid expansion in AAA size, and in patients presenting with symptoms resulting from AAA (abdominal or back pain/tenderness).

Aortic Atheroma

Aortic atherosclerotic plaques commonly occur in patients with evidence of atherosclerosis in other vascular beds. The most frequent complication of aortic atheromas is systemic embolism and stroke. Aortic atheromas greater than 4 mm in diameter or with a mobile component are more likely to be associated with thromboembolism compared with smaller atheromas.

Aortic atheromas are most frequently detected as an incidental finding on imaging studies. The presence of an aortic atheroma represents a coronary artery disease risk equivalent, and patients should be considered for antiplatelet and statin therapies in addition to other risk factor interventions.

KEY POINT

- Patients with an aortic atheroma should be treated with antiplatelet and statin therapies to reduce cardiovascular risk.

Acute Aortic Syndromes

The most common and life-threatening acute aortic syndromes include acute aortic dissection and aortic aneurysm rupture. Additional acute aortic syndromes include intramural aortic hematoma and penetrating atherosclerotic ulcer.

Pathophysiology

Acute aortic dissection involves tearing of the aortic intima, leading to passage of blood from the true lumen of the aorta into a false lumen (**Figure 40**). Dissection of the aorta can propagate in an antegrade or retrograde fashion, mainly due to shear forces. Propagation of the dissection can result in cardiac tamponade; acute aortic regurgitation; compromise of arterial side branches (carotid, mesenteric, renal, or iliac arteries); and underperfusion of organs such as the brain, intestines, or kidneys. Aortic dissections are categorized according to their location of origin by use of the Stanford classification, which describes type A dissections as originating within the ascending aorta or arch and type B dissections as originating distal to the left subclavian artery. Type A aortic dissections require surgical intervention due to risk for rupture and death, whereas type B aortic dissections can often be initially managed with medical stabilization and blood pressure control.

Intramural aortic hematomas result from microtears in the aortic intima and rupture of the vasa vasorum (**Figure 41**). Penetrating atherosclerotic ulcers are caused by erosion of the internal elastic membrane at the site of aortic atherosclerotic plaque, leading to a blood-filled false space within the wall of the aorta (**Figure 42**). Both intramural hematomas and penetrating atherosclerotic ulcers are more common in type B dissections.

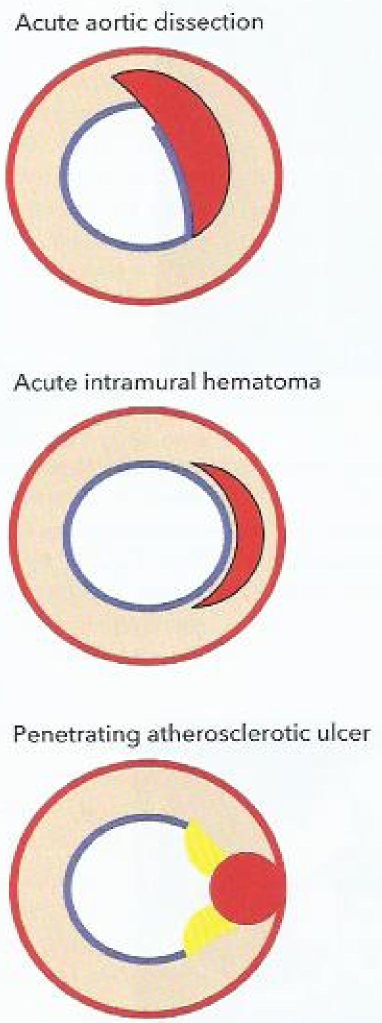

FIGURE 40. Cross-sectional representation of acute aortic syndromes. Acute aortic dissection: interruption of intima (*blue*) with creation of an intimal flap and false lumen formation within the media (*red*). Color flow by Doppler echocardiography or intravenous (IV) contrast by CT is present within the false lumen in the acute phase. Acute intramural hematoma: crescent-shaped hematoma contained within the media without interruption of the intima (*blue*). No color flow by Doppler echocardiography or IV contrast by CT within crescent. Penetrating atherosclerotic ulcer: atheroma (*yellow*) with plaque rupture disrupting intimal integrity; blood pool contained within intima-medial layer (pseudoaneurysm). Color flow by Doppler echocardiography or IV contrast by CT enters the ulcer crater.

Diagnosis and Evaluation

Acute aortic dissection is a medical emergency, and a high index of suspicion is needed for immediate diagnosis and treatment. It classically presents with the sudden onset of chest or back pain that has a tearing or ripping quality; however, not all patients will have this symptom. Patients may present with hypertension, syncope, a murmur of aortic regurgitation, or heart failure in the setting of sudden aortic insufficiency. The findings of asymmetric blood pressures in the upper extremities, asymmetric pulses, or pulsus paradoxus should all raise suspicion for acute aortic dissection.

Abnormalities may be present on chest radiography (widened mediastinum) and electrocardiography (ST-segment depression), but these findings are not diagnostic for acute aortic dissection. In patients with a high likelihood of acute aortic dissection, diagnostic imaging tests should not be delayed based on the results of chest radiography, electrocardiography, or laboratory testing.

Transesophageal echocardiography, CTA, and MRA have similar sensitivity and specificity in patients with acute thoracic aortic disease. Transthoracic echocardiography is often used but is limited by the inability to image the distal ascending aorta, transverse aortic arch, and descending aorta. Compared with CTA or MRA, the primary advantages of transesophageal echocardiography in patients suspected of having aortic dissection include its portability for an unstable patient and the lack of iodinated contrast. With the increased availability of CTA, it has become the primary diagnostic test for acute thoracic aortic disease. Invasive aortography is rarely indicated for the diagnosis of acute disease; however, it is indicated at the time of endovascular repair or when noninvasive testing is contraindicated or cannot be performed.

Treatment

Patients with acute aortic dissection without evidence of cardiogenic shock should be treated with medical therapy to

FIGURE 41. Intramural hematoma demonstrated as a low-attenuation band of hematoma (*arrows*) in the aortic wall on CT images. Axial images at the level of the aortic arch (*top left*), through the mid thorax (*top middle*), and at the level of the superior mesenteric artery with narrowing of the aortic lumen (*top right*). Oblique sagittal reformatted image through the thorax (note band artifact evident without the use of electrocardiographic gating) (*bottom left*). Coronal reformatted image through the abdomen demonstrates the length of the hematoma and an incidental infrarenal aortic aneurysm (*bottom right*).

Reproduced with permission from Hiratzka LF, Bakris GL, Beckman JA, Bersin RM, Carr VF, Casey DE Jr, et al; American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. 2010 ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM guidelines for the diagnosis and management of patients with thoracic aortic disease. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. American Association for Thoracic Surgery, American College of Radiology, American Stroke Association, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of Thoracic Surgeons, and Society for Vascular Medicine. J Am Coll Cardiol. 2010;55:e27-e129. [PMID: 20359588] doi:10.1016/j.jacc.2010.02.015. Copyright 2010, Elsevier.

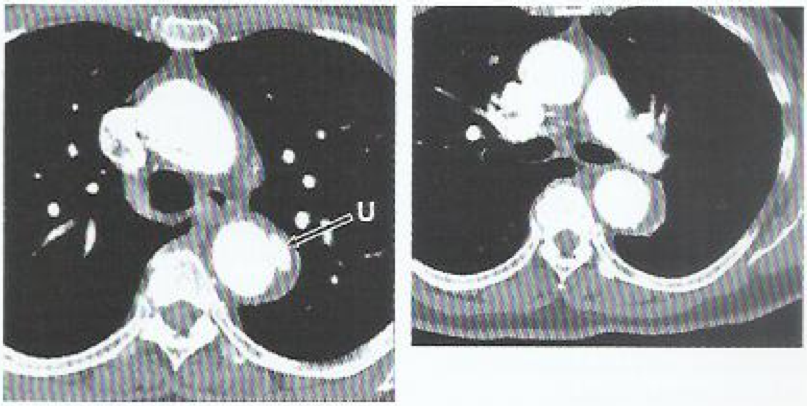

FIGURE 42. Penetrating atherosclerotic ulcer of the proximal descending thoracic aorta. Axial CT images at the level of the aortopulmonary window (*left*) and at the level of the left pulmonary artery (*right*) demonstrate a small penetrating ulcer (*arrow*) that extends beyond the expected confines of the aortic lumen with adjacent intramural hematoma both at the level of the ulcer itself and that extends a few centimeters caudally in the wall of the descending thoracic aorta. U = penetrating ulcer.

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control heart rate and reduce blood pressure. Current guidelines recommend reducing systolic blood pressure to 120 mm Hg or less in the first hour in patients with aortic dissection. Intravenous β-blockers are first-line treatment; for hypertension that does not completely respond to β-blockers, intravenous vasodilators (nitroprusside, nicardipine) should be administered. Pain control is often necessary and is best accomplished with intravenous opioids.

An algorithm for the management of acute ascending aortic dissections is shown in **Figure 43**. Referral for emergency surgery should be considered in all patients with acute aortic dissection and cardiogenic shock, patients with type A aortic dissection, and patients with type A intramural hematoma, given the very high mortality rate associated with these conditions. Decisions regarding concomitant aortic arch reconstruction, aortic valve replacement, branch vessel repair, and/or coronary artery bypass graft surgery or coronary artery reimplantation depend on the anatomy of the aortic dissection, involvement of the aortic valve or branch vessels, and various other patient characteristics.

Patients who present with uncomplicated type B aortic syndromes may be treated with medical therapy initially. TEVAR, when compared with medical therapy, is associated with similar clinical outcomes and improved survival and disease progression measures at 2 years. Patients with type B aortic dissection and refractory chest/back pain or hypertension, rapid aortic expansion, or organ malperfusion should undergo aortic repair.

In patients with an intramural aortic hematoma or penetrating aortic ulcer, treatment choices depend on the location of the hematoma or ulcer, progression to aortic dissection, and evidence of aortic enlargement. Immediate aortic repair is indicated in patients with an ascending aortic intramural hematoma or penetrating aortic ulcer and in those with enlargement or progression of disease after detection. H

KEY POINTS

- Acute aortic dissection classically presents with the sudden onset of ripping or tearing pain in the chest, back, or abdomen.
- Clinical examination findings that increase the index of suspicion for an acute aortic syndrome include pulsus paradoxus, asymmetric blood pressures in the upper extremities, and asymmetric pulses.
- CT angiography is the primary diagnostic test in patients in whom acute thoracic aortic disease is suspected.
- Intravenous β-blockers are first-line treatment to reduce heart rate and control blood pressure in patients with acute aortic dissection without cardiogenic shock.
- Emergency surgery should be considered in all patients with acute aortic dissection and cardiogenic shock, type A aortic dissection, and type A intramural hematoma.

Role of Genetic Testing and Family Screening

Genetic conditions that predispose patients to thoracic aortic aneurysm syndromes include Marfan, Ehlers-Danlos, and Loeys-Dietz syndromes (see Table 33). Clinical findings and a family history of connective tissue disease often lead to genetic testing, for either diagnostic confirmation or screening of family members. Noninvasive imaging of the aorta should be performed if a pathogenic genetic mutation is found, and routine surveillance (initially at 6 months and then annually, if findings are stable) should follow to ensure that the aorta is not rapidly enlarging.

In first-degree relatives of patients with TAA and/or dissection, noninvasive imaging of the aorta should be performed to identify those with asymptomatic disease. In first-degree relatives of patients with a mutant gene (*FBN1, TGFBR1, TGFBR2, COL3A1, MYH11*) and aortic aneurysm and/or dissection, genetic counseling and testing should be performed. Relatives with the genetic mutation should then undergo noninvasive imaging of the aorta.

Peripheral Artery Disease

Epidemiology and Screening

Peripheral artery disease (PAD) is most commonly characterized by narrowing of the aortic bifurcation and arteries of the lower extremities, including the iliac, femoral, popliteal, and tibial arteries. Stenosis in the upper extremity arteries, typically at the origin of the subclavian arteries or at branch points of other major vessels, can also occur. Atherosclerosis is the most common cause. Risk factors for PAD include smoking (current or past), diabetes mellitus, and increasing age. PAD occurs at a later age in women than in men, and because women have a longer lifespan, the overall prevalence of PAD is higher in women. The incidence of PAD begins to increase around age 40 years and rises to approximately 10% at age 70 years.

PAD is considered a coronary heart disease risk equivalent, and both asymptomatic and symptomatic patients with PAD are at increased risk for ischemic events, including myocardial infarction, stroke, and cardiovascular death. Patients with atherosclerotic risk factors (smoking, diabetes, hypertension, dyslipidemia, advanced age) who have atypical limb symptoms (leg weakness, paresthesias), exertional leg discomfort, and/or nonhealing ulcers should undergo initial testing with ankle-brachial index (ABI) measurement. According to guidelines from the American Heart Association and American College of Cardiology, a screening ABI is reasonable in asymptomatic persons with one of the following characteristics that signify increased risk: (1) age 65 years and older, (2) age 50 to 64 years with risk factors for atherosclerosis or family history of PAD, (3) age younger than 50 years with diabetes and one additional risk factor for atherosclerosis, or (4) known atherosclerotic disease in another vascular bed (coronary, carotid, subclavian, renal, or mesenteric artery stenosis, or abdominal aortic aneurysm). The U.S. Preventive Services Task Force

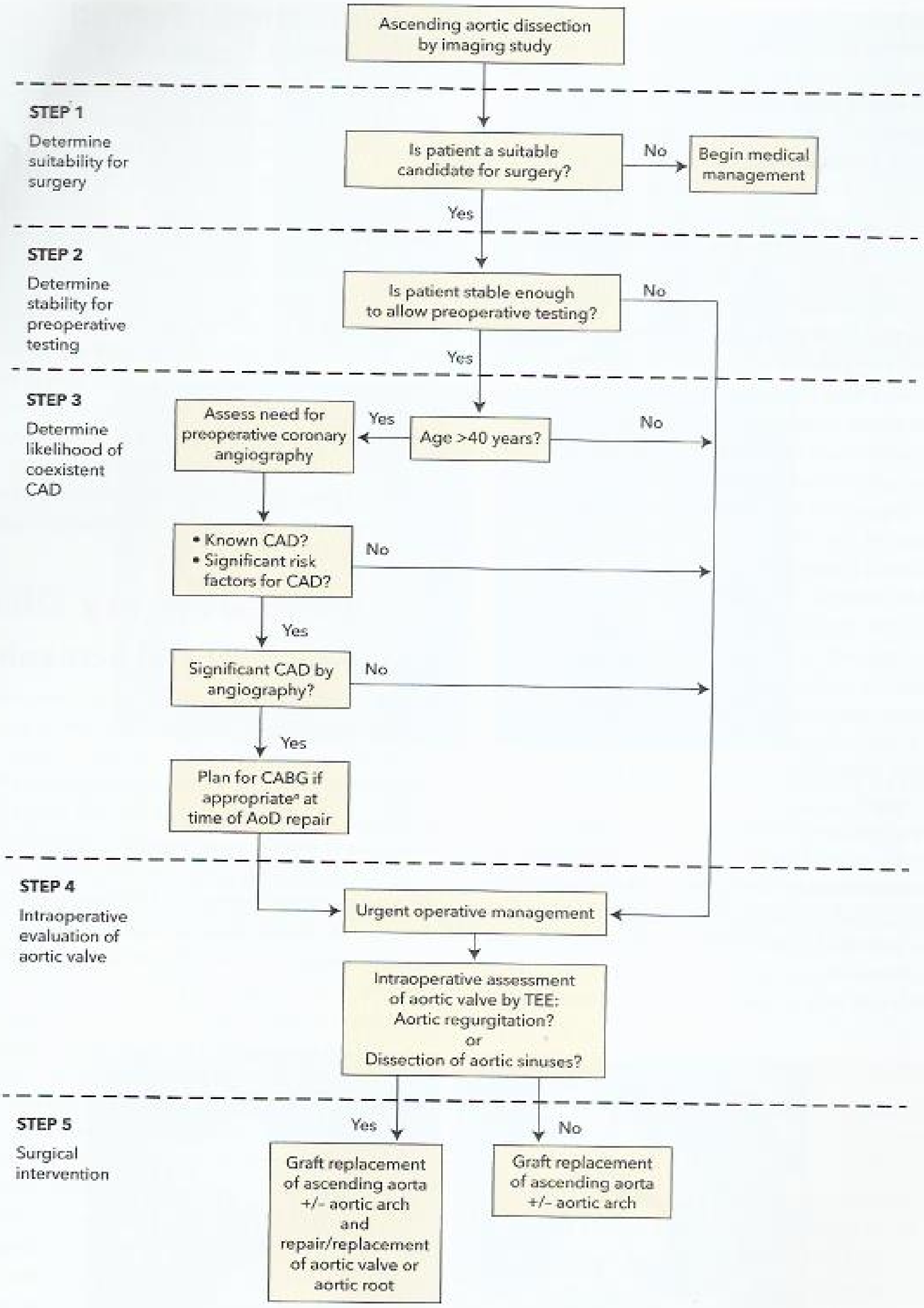

FIGURE 43. Acute surgical management pathway for AoD. AoD = aortic dissection; CABG = coronary artery bypass graft surgery; CAD = coronary artery disease; TEE = transesophageal echocardiography.

[a]Addition of "if appropriate" based on Patel MR, Dehmer GJ, Hirshfeld JW, Smith PK, Spertus JA, American College of Cardiology Foundation Appropriateness Criteria Task Force. ACCF/SCAI/STS/AATS/AHA/ASNC 2009 appropriateness criteria for coronary revascularization: a report by the American College of Cardiology Foundation Appropriateness Criteria Task Force, Society for Cardiovascular Angiography and Interventions, Society of Thoracic Surgeons, American Association for Thoracic Surgery, American Heart Association, and the American Society of Nuclear Cardiology Endorsed by the American Society of Echocardiography, the Heart Failure Society of America, and the Society of Cardiovascular Computed Tomography. J Am Coll Cardiol. 2009;53:530-53. [PMID: 19195618] doi:10.1016/j.jacc.2008.10.005.

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concluded that there is insufficient evidence to support screening for lower extremity PAD with an ABI in all patients, especially those without risk factors for atherosclerotic vascular disease. Measurement of bilateral arm pressures is indicated in asymptomatic and symptomatic patients with atherosclerotic risk factors to assess for upper extremity PAD.

KEY POINTS

- The primary risk factors for peripheral artery disease include cigarette smoking, diabetes mellitus, and advanced age.
- Patients with atypical leg symptoms, exertional leg symptoms, and nonhealing ulcers should undergo ankle-brachial index testing.
- HVC Screening for peripheral artery disease (PAD) with ankle-brachial index testing may be considered in patients at increased risk for PAD; evidence does not support screening asymptomatic patients without risk factors.

Clinical Presentation

Because lower extremity PAD is defined by an abnormal ABI value rather than by symptoms, there is a wide spectrum of clinical manifestations. Patients may present with exertional leg pain relieved by rest (intermittent claudication), atypical exertional leg pain, rest pain, nonhealing wounds, ischemic ulcers, or gangrene. Approximately 25% to 30% of patients with lower extremity PAD present with intermittent claudication, and less than 5% of patients present with critical limb ischemia. Most patients with upper extremity PAD have no symptoms, although patients may present with arm claudication, arm ischemia, or dizziness with arm activity (subclavian steal syndrome).

Patients with intermittent claudication often have reduced exercise capacity and functional status compared with age- and sex-matched controls. Their annual risk for myocardial infarction, stroke, or cardiovascular death is approximately 5% to 7%. Most patients with intermittent claudication have stable symptoms; however, symptoms worsen in approximately 25% of patients, and 10% to 20% of patients will undergo lower extremity revascularization procedures over a period of 5 years.

Critical limb ischemia, the most severe form of PAD, manifests as ischemic rest pain, tissue ulceration, and gangrene. Patients with critical limb ischemia often have reduced exercise capacity and functional status, and these patients have a 30% rate of major amputation and 20% mortality rate within 1 year of diagnosis.

KEY POINTS

- Patients with peripheral artery disease may be asymptomatic or present with intermittent claudication, atypical exertional leg pain, or, rarely, critical limb ischemia.
- Patients with peripheral artery disease have reduced exercise capacity and an elevated risk for cardiovascular morbidity and mortality.

Evaluation

History and Physical Examination

A detailed history, review of symptoms, and physical examination are critical in the evaluation of patients suspected of having vascular disease. Patients should be asked about walking impairment, atypical limb symptoms, intermittent claudication, and ischemic rest pain. In patients with exertional leg symptoms, intermittent claudication should be differentiated from pseudoclaudication (symptoms that arise from spinal stenosis) (**Table 36**). Patients should be questioned about skin breakdown and foot ulcers, and clinicians should educate patients on the importance of foot protection and wearing shoes (specifically, hard-soled shoes) when walking outside the home.

Elements of the physical examination of patients suspected of having PAD are listed in **Table 37**. Vascular examination of patients suspected of having lower extremity PAD should include comprehensive pulse examination, auscultation for bruits, and inspection of the feet for skin and toenail changes. Patients with PAD may exhibit diminished, absent, or asymmetric pulses, and bruits may be heard at or near sites of arterial stenosis. Patients with critical limb ischemia may have decreased temperature or lack of hair growth in the affected extremity, as well as evidence of poor wound healing or active ulceration (typically involving the digits, plantar aspect of the foot, or heel). Clinicians should distinguish between signs of chronic venous disease (leg edema; pigmented, brawny induration of the gaiter zone; ulceration of the shin or ankle) and critical limb ischemia when evaluating patients with leg ulcers because venous leg ulcers are treated differently than ulcerations in patients with critical limb ischemia (see MKSAP 18 Dermatology).

In patients with upper extremity PAD, a characteristic finding on physical examination is a difference in systolic

TABLE 36. Discriminating Claudication from Pseudoclaudication

Characteristic	Claudication	Pseudoclaudication
Nature of discomfort	Cramping, tightness, aching, fatigue	Same as for claudication plus tingling, burning, numbness, weakness
Location of discomfort	Buttock, hip, thigh, calf, foot	Same as for claudication; most often bilateral
Exercise-induced	Yes	Variable
Walking distance at onset of symptoms	Consistent	Variable
Discomfort occurs with standing still	No	Yes
Action for relief	Stand or sit	Sit, flexion at the waist
Time to relief	<5 min	≤30 min

TABLE 37. Physical Examination of Patients for Peripheral Artery Disease
Measure blood pressure in both arms (systolic blood pressure difference >15 mm Hg suggests subclavian stenosis)
Auscultate for presence of arterial bruits (e.g., femoral artery)
Palpate for presence of abdominal aortic aneurysm
Palpate and record pulses (radial, brachial, carotid, femoral, popliteal, posterior tibial, dorsalis pedis)
Evaluate for elevation pallor and dependent rubor
Inspect feet for ulcers, fissures, calluses, tinea, and tendinous xanthoma; evaluate overall skin care

blood pressures between the arms, typically more than 15 mm Hg.

Diagnostic Testing

The most frequently used diagnostic modality to identify lower extremity PAD is measurement of the ABI, which is the ratio of lower extremity to upper extremity systolic blood pressures. ABI measurement is simple, inexpensive, and noninvasive, with a sensitivity and specificity approaching 90%. When undergoing ABI testing, patients should rest for 10 minutes in a supine position before the clinician measures the ankle pressures and brachial pressures with a Doppler machine. Blood pressures should be measured in both arms and in both legs at the dorsalis pedis and posterior tibial ankle locations. To calculate the ABI for each leg, the higher ankle pressure in each leg is divided by the higher brachial artery pressure. In healthy persons, the ankle pressure should be the same as or slightly higher than the brachial pressure; therefore, a normal resting ABI is between 1.00 and 1.40 (**Table 38**). In the presence of atherosclerotic narrowing of the limb arteries, the downstream blood pressure and concomitant ABI value is lower. A resting ABI of 0.90 or less is diagnostic for PAD and correlates with abnormalities seen on imaging of the arterial tree. A resting ABI greater than 1.40 indicates the presence of noncompressible, calcified arteries in the lower extremities and is considered uninterpretable. In patients with an ABI greater than 1.40, a toe-brachial index is used for diagnosis. A toe-brachial index less than 0.70 is diagnostic for PAD.

TABLE 38. Interpretation of the Ankle-Brachial Index

Ankle-Brachial Index	Interpretation
>1.40	Noncompressible (calcified) vessel (uninterpretable result)
1.00-1.40	Normal
0.91-0.99	Borderline
0.41-0.90	Mild to moderate PAD
0.00-0.40	Severe PAD

PAD = peripheral artery disease.

An exercise ABI test is useful when resting ABI values are between 0.91 and 1.40 and the pretest probability of PAD is high. It requires ABI measurements at rest and after treadmill walking or plantar flexion exercises. The American Heart Association has proposed a postexercise ankle pressure decrease of more than 30 mm Hg or a postexercise ABI decrease of more than 20% as a diagnostic criterion for PAD. Other organizations have proposed a postexercise ABI of less than 0.90 and/or a 30-mm Hg drop in ankle pressure after exercise.

Segmental pressure measurements may be performed in a vascular laboratory to localize diseased vessels. This procedure involves pulse volume recordings (measurement of the magnitude and contour of blood pulse volume in the lower extremities) and blood pressure measurements at several locations in the lower extremities (high thigh, low thigh, calf, posterior tibial artery, and dorsalis pedis artery) (**Figure 44**).

Hemodynamic measurements (ABI, toe-brachial index, exercise ABI, and segmental pressure measurements) remain the most commonly used diagnostic tests for patients suspected of having lower extremity PAD. The ABI does not correlate with the patient's perception of symptom severity or functional limitations; however, lower ABI values are associated with higher rates of myocardial infarction, stroke, and death.

Other imaging tests used to delineate the anatomic location and severity of lower extremity PAD include arterial duplex ultrasonography, CT angiography, and magnetic resonance angiography (**Table 39**). These imaging modalities are most often used to plan for endovascular or surgical revascularization procedures. Invasive angiography is often preferred because endovascular revascularization procedures can be performed concurrently.

TABLE 39. Comparison of Imaging Modalities for the Diagnosis of Peripheral Artery Disease

Imaging Modality	Advantages	Limitations
Arterial duplex ultrasonography	Widely available Does not require administration of contrast dye Inexpensive	Limited ability to detect stenoses in the pelvis and in patients with severe calcifications Poor utility for infrapopliteal stenosis
CT angiography	Widely available Useful in defining the severity of PAD Very expensive	Risk for contrast-induced nephropathy
Magnetic resonance angiography	Useful in defining the severity of PAD Very expensive	Contraindicated in patients with implanted pacemakers and defibrillators Risk for nephrogenic systemic fibrosis in patients with severe kidney disease

PAD = peripheral artery disease.

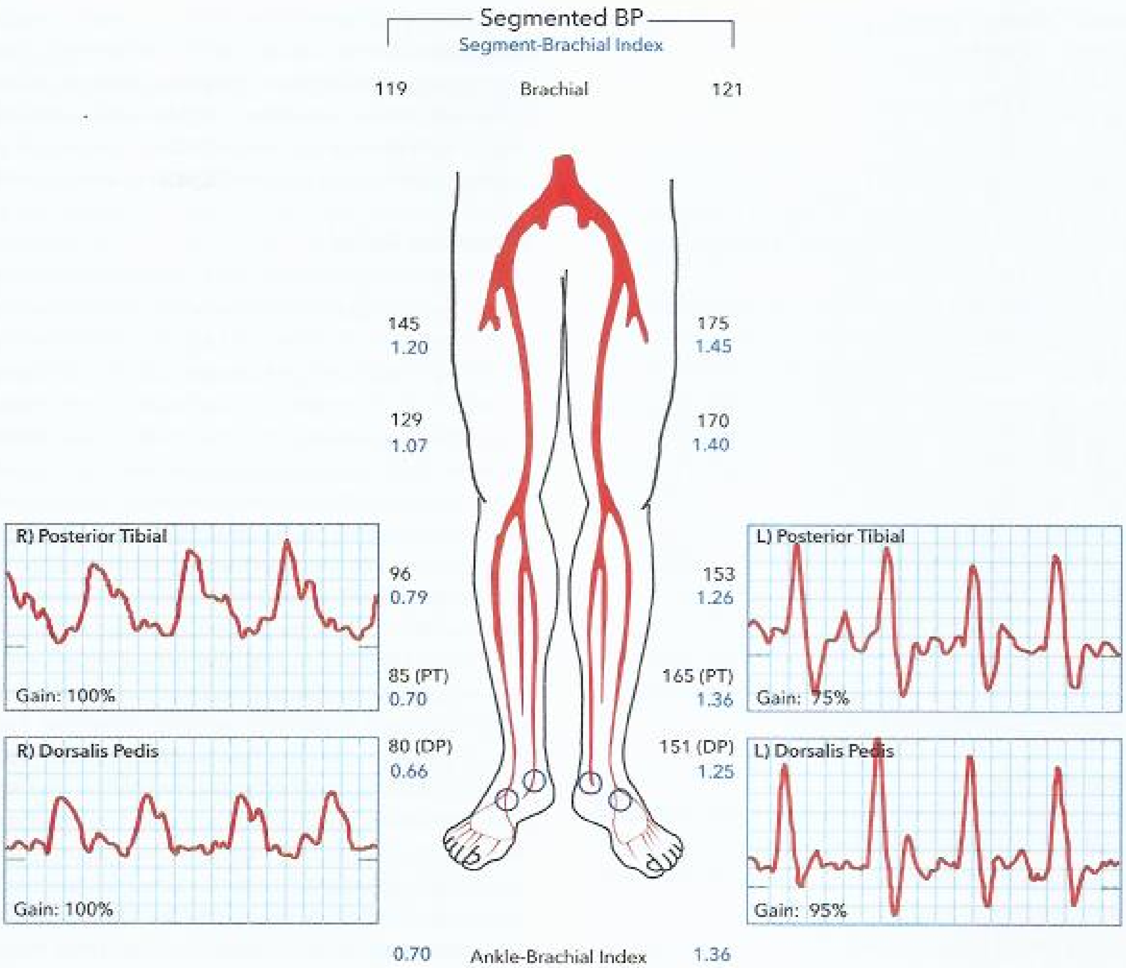

FIGURE 44. A pulse volume recording demonstrating decreased perfusion in the patient's right side. An ankle-brachial index value of 0.70 on the right side is consistent with the diagnosis of mild to moderate peripheral artery disease (ankle-brachial index <0.90). The normal pulse volume recording on the patient's left side has a sharp systolic upstroke and downstroke (the width of the waveform is much narrower compared with the waveform on the right side). When the amplitude of the waveform is significantly blunted and the width is broader, it suggests moderate to severe disease. BP = blood pressure; DP = dorsalis pedis; PT = posterior tibial.

Duplex ultrasonography, CT angiography, and magnetic resonance angiography are also appropriate in patients with upper extremity PAD to confirm the diagnosis and plan for intervention, such as revascularization.

KEY POINTS

- An ankle-brachial index of 0.90 or less indicates peripheral artery disease.
- An ankle-brachial index greater than 1.40 indicates the presence of noncompressible arteries in the lower extremities and is considered uninterpretable; a toe-brachial index is used for diagnosis of peripheral artery disease in these patients.
- Imaging with CT angiography or magnetic resonance angiography is useful to identify the location of stenosis and severity of peripheral artery disease in planning for endovascular or surgical revascularization procedures.

Medical Therapy

Treatment of PAD focuses on reducing cardiovascular risk; improving functional status, quality of life, and claudication symptoms; and preventing tissue loss and amputation.

Cardiovascular Risk Reduction

Cigarette smoking is the most important modifiable risk factor for the development of PAD. Smoking cessation is associated with decreased risk for major amputation, improved patency rates following revascularization, and less disease progression. Smoking cessation is imperative to lower the risk for myocardial infarction and stroke and improve overall survival in patients with PAD.

Diabetes is also a strong risk factor for PAD; however, intensive glucose control has not been demonstrated to reduce macrovascular complications, including myocardial infarction, stroke, or amputation. Regardless, patients with PAD and

diabetes should adhere to American Diabetes Association recommendations on diabetes management, with particular attention to foot care.

Dyslipidemia has a mild effect on the development of PAD. Patients with symptomatic PAD should be treated with high-intensity statin therapy, and patients with PAD who are older than 75 years or intolerant of high-intensity statins should be treated with moderate-intensity statin therapy (see MKSAP 18 General Internal Medicine).

Hypertension also has a mild effect on the development of PAD, and control of blood pressure has been associated with reduction of cardiovascular events in patients with PAD. The 2017 high blood pressure guideline from the American College of Cardiology, the American Heart Association, and nine other organizations recommends a blood pressure target of less than 130/80 mm Hg in patients with PAD. There is no consensus on the antihypertensive therapy of choice in patients with PAD; therefore, thiazide diuretics, ACE inhibitors or angiotensin receptor blockers, and calcium channel blockers remain first-line agents in patients with PAD and hypertension. In patients at high risk for cardiovascular events or with comorbid conditions (such as diabetes), ACE inhibitors are effective in reducing cardiovascular morbidity and mortality.

Antithrombotic Therapy

Current guidelines recommend antiplatelet monotherapy in patients with PAD to reduce risk for myocardial infarction, stroke, and peripheral arterial events. Despite little supporting evidence, aspirin has been recommended by experts as the primary antiplatelet agent in patients with PAD. In patients who are aspirin intolerant, clopidogrel is recommended as an acceptable alternative. There is no compelling evidence for the use of dual antiplatelet therapy with aspirin plus clopidogrel in patients with PAD alone. In the CHARISMA trial, patients with PAD who were treated with aspirin plus clopidogrel had a reduced rate of hospitalization for myocardial infarction and ischemic events, which was mitigated by a higher rate of bleeding.

Evidence from the TRA 2P-TIMI 50 trial demonstrated that vorapaxar, a thrombin receptor antagonist, was associated with improved limb endpoints (specifically, hospitalization for acute limb ischemia) when compared with placebo in patients with PAD. However, most patients in the TRA 2P-TIMI 50 trial were treated with aspirin, and 30% of patients were treated with aspirin plus clopidogrel. Vorapaxar was also associated with an increased risk for moderate or severe bleeding, including intracranial hemorrhage.

In a large secondary prevention study of patients with prior myocardial infarction receiving aspirin therapy, ticagrelor was superior to placebo in reducing the composite endpoint of cardiovascular death, myocardial infarction, or stroke and major adverse limb events in the subset of patients with PAD. Major bleeding was increased in patients randomly assigned to ticagrelor. However, the absolute risk for major bleeding in patients with PAD was lower than in patients without PAD.

There is no evidence that oral anticoagulation with vitamin K antagonists (such as warfarin) is more effective than antiplatelet monotherapy in patients with PAD, and anticoagulant therapy is associated with an increased risk for major bleeding. There is also no evidence that non–vitamin K antagonist oral anticoagulants are superior to antiplatelet agents in patients with PAD.

Symptom Relief

Improving functional status and improving quality of life are critical goals for patients with PAD. In patients who can exercise, supervised exercise training has been associated with improved functional performance and is recommended for patients with intermittent claudication. Systematic reviews comparing supervised exercise with home exercise have reported improvements in maximal walking distance and initial claudication distance that favor supervised exercise; however, no statistically significant differences in quality of life were observed. Despite its effectiveness and safety, supervised exercise training is limited by lack of insurance coverage and unavailability of these programs for patients with claudication.

Medical therapy for patients with intermittent claudication consists of cilostazol, a phosphodiesterase inhibitor with antiplatelet and vasodilator activity. Cilostazol has demonstrated increases in pain-free walking distance and overall walking distance in patients with claudication, and clinical guidelines recommend that patients with claudication be considered for a therapeutic trial of cilostazol. As with other oral phosphodiesterase inhibitors (for example, inotropes such as milrinone), the FDA has placed a black box warning on the use of cilostazol in patients with heart failure. There is no approved pharmacotherapy for patients with critical limb ischemia.

KEY POINTS

- Smoking cessation is essential to reduce cardiovascular risk in patients with peripheral artery disease.
- Antiplatelet monotherapy with aspirin is recommended for patients with peripheral artery disease to reduce the risk for myocardial infarction, stroke, and peripheral arterial events.
- Supervised exercise training is the most effective treatment for improvement of functional status in patients with peripheral artery disease.
- Cilostazol is recommended for patients with intermittent claudication.

Interventional Therapy

Endovascular or surgical revascularization procedures are effective in improving symptoms, increasing functional capacity, and improving wound healing in patients with intermittent claudication or critical limb ischemia. Referral for revascularization is indicated in patients with lifestyle-limiting claudication, rest pain, ulceration, or gangrene, especially if there has been an inadequate response to exercise training, cilostazol, and/or wound

treatment. Patients with critical limb ischemia (ABI <0.40, a flat waveform on pulse volume recording, and low or absent pedal flow on duplex ultrasonography) should be considered for urgent revascularization. Endovascular or surgical revascularization should also be considered in patients with a favorable risk-benefit ratio, which is determined by patient factors (age, frailty, comorbid conditions), anatomic factors (severity and burden of atherosclerotic disease, location of disease in lower extremities), operator expertise, and type of procedure. Revascularization is not recommended in asymptomatic patients.

Endovascular revascularization has dramatically increased in recent years because the procedure is minimally invasive and confers a lower risk for perioperative adverse events compared with surgical revascularization. Endovascular revascularization procedures include balloon angioplasty (standard, cutting, drug-coated), stenting (nitinol [nickel-titanium] bare metal and drug eluting), and atherectomy (laser, orbital, rotational, directional). In patients with isolated iliac disease, endovascular revascularization is favored over surgical revascularization owing to lower morbidity and mortality, high procedural success, and high patency rates over time. Most patients undergo balloon angioplasty and stenting of the iliac arteries, given the significantly higher long-term success rate with stenting compared with angioplasty alone.

In patients with femoral, popliteal, or tibial artery (infrainguinal) disease, the patency rates of endovascular revascularization are not as high as in the iliac arteries. Although infrainguinal disease was traditionally treated with angioplasty alone, the advent of atherectomy devices and nitinol stents has changed management. Recently, FDA-approved drug-coated angioplasty balloons and drug-eluting stents have demonstrated superior efficacy compared with standard angioplasty balloons in these patients.

The use of surgical revascularization has declined in the United States; however, patients with complex anatomy that may limit percutaneous procedural success and long-term patency (for example, long chronic total occlusions, multisegment disease) should still be referred for surgical revascularization. The two most common techniques of surgical revascularization are endarterectomy and surgical bypass.

Hybrid revascularization is the concomitant performance of surgical revascularization and endovascular revascularization in a single setting or finite time frame. Hybrid revascularization has increased in conjunction with the rise in endovascular revascularization; however, there are currently no clinical guideline recommendations for hybrid revascularization.

KEY POINTS

- In patients with life-limiting claudication who have had an inadequate response to exercise or pharmacologic therapy, endovascular or surgical revascularization is indicated.
- Patients with critical limb ischemia should be considered for urgent revascularization.

Acute Limb Ischemia

Acute limb ischemia is an infrequent but life-threatening manifestation of PAD. Classically, patients present with at least one of the "6 Ps": paresthesia, pain, pallor, pulselessness, poikilothermia (coolness), and paralysis. Acute limb ischemia is most commonly caused by acute thrombosis of a lower extremity artery, stent, or bypass graft. Other causes include thromboembolism, vessel dissection (usually occurring periprocedurally), or trauma. The presentation of acute limb ischemia represents a true medical emergency; 10% to 15% of patients undergo amputation during initial hospitalization, and 20% of patients die within 1 year.

Anticoagulation, typically with unfractionated heparin, should be initiated as soon as the diagnosis is suspected. Specialists with expertise in revascularization should be consulted, and diagnostic angiography should be performed immediately to define the anatomic level of occlusion. In addition to surgical and endovascular revascularization options, catheter-directed thrombolysis improves outcomes in patients with acute limb ischemia.

Careful monitoring is required after limb reperfusion because of frequent reocclusion, limb edema, and the possibility of compartment syndrome. Signs and symptoms of compartment syndrome include severe pain, hypoesthesia, and leg weakness. If compartment syndrome occurs, surgical fasciotomy is indicated to prevent irreversible neurologic and soft-tissue damage.

KEY POINTS

- Acute limb ischemia is characterized by at least one of the "6 Ps": paresthesia, pain, pallor, pulselessness, poikilothermia (coolness), and paralysis.
- Patients with acute limb ischemia should receive immediate anticoagulation therapy and diagnostic angiography in preparation for emergent endovascular or surgical revascularization.
- Careful monitoring after limb reperfusion is required because of frequent reocclusion, limb edema, and the possibility of compartment syndrome.

Cardiovascular Disease in Cancer Survivors

Cardiotoxicity of Radiation Therapy to the Thorax

Radiation therapy improves survival in patients with Hodgkin lymphoma, early-stage breast cancer, and other thoracic malignancies. With higher survival rates, cardiovascular disease has emerged as the most common nonmalignant cause of death in patients treated with chest radiation therapy, accounting for 25% of deaths in survivors of Hodgkin lymphoma.

Radiation therapy causes a wide spectrum of cardiac diseases (**Table 40**). Thoracic irradiation damages all cells, including those of the pericardium, myocardium, valves, coronary vasculature, and conduction system, with clinical disease usually presenting two to three decades after treatment. The risk for radiation-induced cardiac injury is further increased in patients who are concomitantly taking anthracyclines or trastuzumab. Recognition of the cardiovascular complications associated with radiation therapy has led to techniques that limit total dosage and field size.

Acute pericarditis is the most common early manifestation of radiotoxicity; however, it is now less common (incidence of 2.5%) because of changes in shielding, divided dosing, and lower cumulative doses. The presentation, diagnosis, and treatment are similar to those of idiopathic acute pericarditis. Chronic or constrictive pericarditis develops in up to 10% to 20% of patients at 5 to 10 years after radiation therapy. Pericardial calcification is not always present radiographically (**Figure 45**). Late constriction can occur in those who have not experienced acute pericarditis.

Radiation therapy also damages the microvasculature, causing endothelial dysfunction and ischemia that result in myocardial fibrosis, diastolic dysfunction, and restrictive physiology. Radiation-induced cardiomyopathy presents similarly to primary restrictive cardiomyopathy. Differentiating cardiomyopathy due to myocardial fibrosis from pericardial constriction is essential because the conditions have different treatments and outcomes.

Although all cardiac valves may be affected by radiation therapy, left-sided involvement predominates. Valvular insufficiency due to tissue retraction is the most common valvular lesion in the first two decades after therapy, with later fibrosis and calcification leading to mixed regurgitation and stenosis.

Radiation therapy results in fibrosis of the conduction system and may lead to sinus node dysfunction, fascicular and bundle branch blocks, and complete heart block. The need for a permanent pacemaker is more common after valve replacement surgery in patients who have received radiation therapy.

Coronary artery disease (CAD) occurs earlier and with increased incidence in patients treated with radiation therapy. Coronary artery lesions are typically ostial, long, smooth, and concentric and have a higher fibrotic content than typical atherosclerotic lesions. The incidence of CAD is increased by traditional risk factors (such as smoking, dyslipidemia, and hypertension), and therapy to address these risk factors is indicated. In-stent restenosis rates with bare metal stents are significantly higher in patients with radiation-induced CAD. There are no data on the outcomes with drug-eluting stents. In patients with radiation-induced CAD, native vessels, including the left internal mammary artery, may be rendered unusable for bypass. The postoperative course may be complicated by radiation-induced lung injury (pleural effusion, prolonged ventilation) and a higher incidence of atrial fibrillation. Limited data are available on outcomes in patients undergoing cardiac surgery for radiation-related valvular or coronary disease.

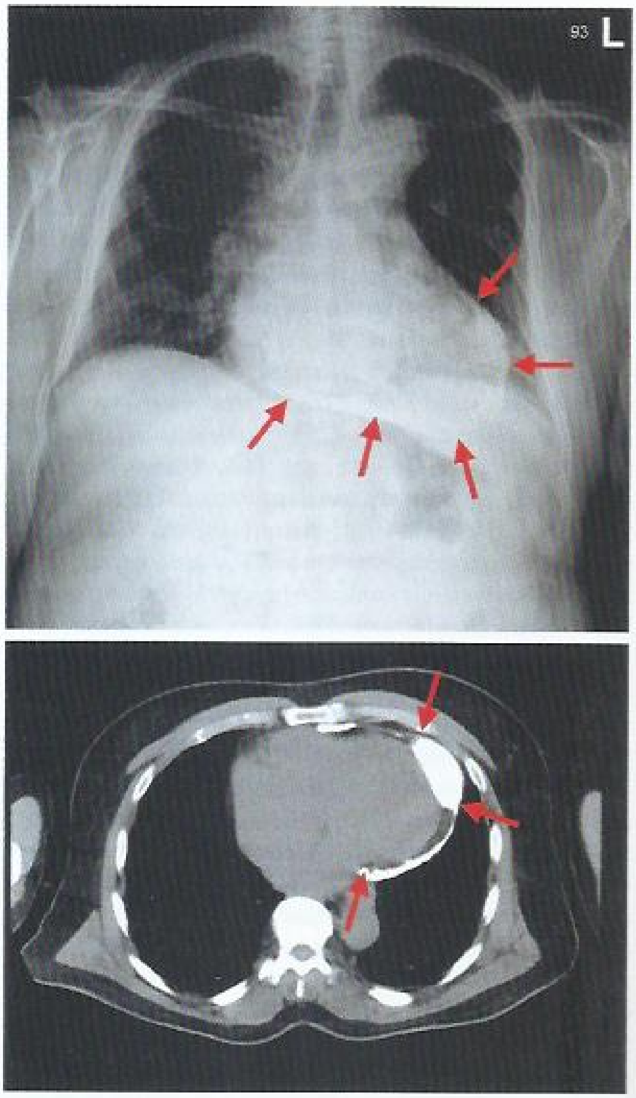

FIGURE 45. Chest radiograph (*top panel*) and chest CT (*bottom panel*) demonstrating pericardial calcification in a patient who received chest radiation therapy for esophageal cancer. Pericardial calcification most often occurs as a circumferential rim but may be incomplete or heterogeneous (*arrows*).

TABLE 40. Cardiovascular Diseases Related to Radiation Therapy
Cardiomyopathy
Conduction defects (atrioventricular block, bundle branch block)
Coronary artery disease
Coronary microvascular injury
Pericardial disease (acute pericarditis, chronic constrictive pericarditis, pericardial effusion)
Peripheral artery disease
Valvular disease

There is no consensus on cardiac testing in asymptomatic patients after chest radiation. Baseline cardiac evaluation that includes echocardiography is reasonable, and several organizations have recommended starting stress echocardiography at 5 to 10 years after completion of therapy or at age 30 years, whichever comes first. The role of serum biomarkers in surveillance is unclear, and their use is not recommended. Routine screening with nuclear medicine testing or coronary CT should be avoided.

Although effective for risk factor reduction, statins, ACE inhibitors, and aldosterone inhibitors have not been proved to prevent radiation-induced cardiovascular disease.

KEY POINTS

- Thoracic irradiation damages all cells, including those of the pericardium, myocardium, valves, coronary vasculature, and conduction system, with clinical disease usually presenting two to three decades after treatment.
- Traditional cardiovascular risk factors, such as smoking, dyslipidemia, and hypertension, should be aggressively managed because of the increased risk for coronary artery disease in patients with a history of chest radiation therapy.

Cardiotoxicity of Chemotherapy

Chemotherapy may result in many types of cardiovascular toxicity (**Table 41**). Two broad categories of chemotherapeutic cardiac injury have been defined based on severity: type I, which is marked by dose-dependent cardiac dysfunction with irreversible ultrastructural necrosis, and type II, which is not dose dependent and is often reversible.

Type I injury is associated with the use of anthracyclines, such as doxorubicin, daunorubicin, and epirubicin. Acute anthracycline toxicity, which can present as heart block, arrhythmias, heart failure, myocarditis, and pericarditis, occurs in less than 1% of patients and may be reversible. Chronic progressive anthracycline toxicity usually presents as dilated cardiomyopathy and is most closely linked with the use of doxorubicin. Chronic progressive toxicity has an early onset (within 1 year of treatment) in 1.6% to 2% of patients and a late onset (after 1 year) in up to 5% of patients. Late-onset chronic progressive toxicity is related to total cumulative dose. In patients with a cumulative anthracycline dose of 550 mg/m^2, the incidence of heart failure is up to 26%, and toxicity may not become clinically evident until 10 to 20 years after treatment. Factors associated with increased risk for anthracycline toxicity include concomitant use of cyclophosphamide, trastuzumab, or paclitaxel; previous chest irradiation; and female sex. Lower risk for cardiotoxicity is associated with epirubicin and idarubicin compared with doxorubicin. Concomitant dexrazoxane reduces the risk for doxorubicin toxicity. Limited data from small studies have shown the angiotensin receptor blocker valsartan may protect against some of the cardiotoxicity of anthracyclines.

TABLE 41. Cardiovascular Toxicities Associated with Chemotherapy

Toxicity	Class	Drug
Left ventricular dysfunction	Anthracyclines	Doxorubicin, epirubicin, idarubicin
	Alkylating agents	Cyclophosphamide, ifosfamide
	Antimicrotubular agents	Paclitaxel, docetaxel
	Monoclonal antibody	Trastuzumab
	Tyrosine kinase inhibitor	Sunitinib
	Proteasome inhibitor	Bortezomib
Ischemia	Antimetabolites	5-Fluorouracil, capecitabine
	Antimicrotubular agents	Paclitaxel, docetaxel
	Monoclonal antibody	Bevacizumab
	Tyrosine kinase inhibitors	Erlotinib, sorafenib
Hypertension	Monoclonal antibody	Bevacizumab
	Tyrosine kinase inhibitors	Sorafenib, sunitinib
Venous thromboembolism	Alkylating agent	Cisplatin
	Angiogenesis inhibitor	Thalidomide
	Tyrosine kinase inhibitor	Erlotinib
Bradycardia	Angiogenesis inhibitor	Thalidomide
	Antimicrotubular agent	Paclitaxel
QT prolongation	Tyrosine kinase inhibitor	Dasatinib
	Histone deacetylase inhibitor	Vorinostat
	Miscellaneous	Arsenic

Type II injury is more commonly associated with molecularly targeted therapy, such as trastuzumab. Trastuzumab toxicity results in left ventricular systolic dysfunction, with symptoms of heart failure in 3% to 7% of patients. It is more common in patients older than 50 years or with concomitant anthracycline use. Patients who demonstrate normalization of left ventricular function after discontinuation of trastuzumab may receive additional therapy.

Multitargeted tyrosine kinase inhibitors and anti–vascular endothelial growth factor antibodies are increasingly being used as targeted molecular therapy. Of the tyrosine kinase inhibitors, sunitinib has been most frequently associated with cardiotoxicity, with up to a 50% incidence of new or worsened hypertension and up to a 15% incidence of decreased left ventricular ejection fraction (LVEF). These effects may be reversible with early recognition. Surveillance with baseline N-terminal proB-type natriuretic peptide measurement and LVEF assessment at baseline, 1 month, and every 3 months thereafter has been advocated for patients taking sunitinib. Not all tyrosine kinase inhibitors carry the same risk for cardiotoxicity. The anti–vascular endothelial growth factor antibody bevacizumab is associated with significant but reversible hypertension.

In patients preparing to receive chemotherapy associated with known cardiotoxicity, an electrocardiogram should be obtained at baseline. Baseline evaluation of LVEF (with echocardiography or multigated acquisition scanning) is important if the associated cardiotoxicity includes left ventricular dysfunction and heart failure. It is reasonable to repeat echocardiography at a total cumulative anthracycline dose of 300 mg/m^2 and before each dose in patients with pre-existent left ventricular dysfunction or those receiving higher cumulative doses. European guidelines suggest that patients receiving trastuzumab should undergo repeat echocardiography every 3 months. In general, cardiovascular consultation should be obtained in asymptomatic patients who demonstrate a decline in LVEF of 10% or more or in patients with symptoms of heart failure associated with a decline in LVEF of 5% or more to a level below 55%. Three-dimensional echocardiographic evaluation of left ventricular volumes may be more accurate in detecting small changes.

In patients with clinical signs or symptoms of cardiac dysfunction, cardiac biomarkers (such as troponin and N-terminal proB-type natriuretic peptide) along with imaging techniques (such as echocardiographically derived global longitudinal strain) may be helpful in identifying early toxicity and guiding individual therapy. At present, treatment of patients with chemotherapy-induced heart failure follows standard paradigms.

KEY POINTS

- Chronic anthracycline toxicity usually presents as irreversible dilated cardiomyopathy.
- Cardiotoxicity from trastuzumab manifests as reversible left ventricular systolic dysfunction.

Pregnancy and Cardiovascular Disease

Cardiovascular Changes During Pregnancy

Knowledge of the cardiovascular changes of pregnancy is necessary to distinguish between normal and pathologic signs and symptoms in the pregnant patient (**Table 42**). During a normal pregnancy, patients develop a relative anemia due to increases in plasma volume and, to a lesser degree, erythrocyte mass. Mean arterial pressure slightly decreases in the setting of reduced systemic vascular resistance and increased heart rate and cardiac output. By the 32nd week of pregnancy, maternal cardiac output peaks at approximately 40% above the prepregnancy level. During delivery, the cardiac output may increase to as much as 80% above the prepregnancy level owing to increased heart rate and blood pressure.

Prepregnancy Evaluation

All women with cardiovascular disease who are anticipating pregnancy should undergo specialized prepregnancy cardiovascular evaluation, high-risk obstetrics consultation, obstetric anesthesia consultation, and, if appropriate, genetic counseling

TABLE 42. Normal Versus Pathologic Signs and Symptoms in Pregnancy

Type of Sign or Symptom	Normal	Pathologic
Pulmonary	Mild dyspnea, dyspnea with exertion	Orthopnea, paroxysmal nocturnal dyspnea, cough, pulmonary edema
Cardiac	No symptoms	Chest pressure, heaviness, or pain
Edema	Mild peripheral edema	More than mild edema
Heart rhythm	Atrial and ventricular premature beats	Atrial fibrillation or flutter, ventricular tachycardia
Heart rate	Heart rate increased by 20%-30%	Heart rate >100/min
Blood pressure	Blood pressure typically is modestly decreased (−10 mm Hg)	Low blood pressure associated with symptoms, high blood pressure (≥140 mm Hg systolic or ≥90 mm Hg diastolic)
Auscultatory	Basal systolic murmur grade 1/6 or 2/6 present in 80% of pregnant women, S_3	Systolic murmur grade ≥3/6, any diastolic murmur, S_4

to evaluate the risks of pregnancy and develop a management plan for labor and the postpartum period. Prepregnancy risk assessment tools include the CARPREG index (**Table 43**), ZAHARA risk score (**Table 44**), and the modified World Health Organization pregnancy risk classification (**Table 45**). All of these tools are used to estimate risk for complications during pregnancy in women with cardiovascular disease.

Pregnancy is contraindicated in patients with ventricular outflow tract obstruction (for example, aortic stenosis or coarctation of aorta) and those with left ventricular systolic dysfunction (ejection fraction <40%) accompanied by New York Heart Association functional class III or IV heart failure symptoms because these conditions confer a high risk for maternal and fetal complications. Women with severe pulmonary hypertension are at high risk for maternal death, with a mortality rate of up to 30%.

KEY POINTS

- Women with cardiovascular disease who are anticipating pregnancy should undergo prepregnancy evaluation with a cardiologist, obstetrician, and anesthesiologist as well as genetic counseling, if appropriate.
- Pregnancy is contraindicated in patients with ventricular outflow tract obstruction and those with left ventricular systolic dysfunction (ejection fraction <40%) accompanied by New York Heart Association functional class III or IV heart failure symptoms.
- Women with severe pulmonary hypertension are at high risk for maternal mortality.

Management of Cardiovascular Disease During Pregnancy

Women with obstructive cardiac lesions may experience symptoms during pregnancy as a result of the increases in blood volume and cardiac output. These patients should be evaluated to determine whether cardiac intervention should be considered before pregnancy. Women with regurgitant valve lesions tend to tolerate pregnancy well.

Vaginal delivery is generally preferred for patients with cardiovascular disease because it results in less blood loss, quicker recovery, and lower risk for thrombosis than does cesarean delivery. Cesarean delivery is recommended for obstetric reasons in women with severe decompensated cardiovascular disease or a markedly dilated aorta. In women receiving warfarin therapy, cesarean delivery is indicated to reduce the risk for fetal intracranial hemorrhage because the fetus is fully anticoagulated.

Peripartum Cardiomyopathy

Peripartum cardiomyopathy is left ventricular systolic dysfunction recognized toward the end of pregnancy or in the months following delivery in the absence of another identifiable cause. Risk factors for peripartum cardiomyopathy include multiparity, age older than 30 years, African descent, multifetal pregnancy, gestational hypertension, preeclampsia, a previous episode of peripartum cardiomyopathy, and therapy with a tocolytic agent.

Death in women with peripartum cardiomyopathy is caused by heart failure, thromboembolic events, and arrhythmias. Most

TABLE 43. Predictors of Maternal Cardiac Events in Women with Congenital or Acquired Cardiac Disease (CARPREG Index)

Risk Factor (Predictor)	Operational Definition
Previous cardiac event or arrhythmia	Heart failure, transient ischemic attack, stroke, arrhythmia
Baseline NYHA functional class III or IV or cyanosis	Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity
Left-sided heart obstruction	Mitral valve area <2 cm²; aortic valve area <1.5 cm² or resting peak left ventricular outflow tract gradient >30 mm Hg
Reduced systemic ventricular systolic function	Ejection fraction <40%

Estimated Risk for Cardiac Events[a]

No. of Predictors	Estimated Risk (%)	Recommendation
0	4	Consider preconception cardiac intervention for specific lesions; increase frequency of follow-up; delivery at community hospital
1	31	Consider preconception cardiac intervention for specific lesions; refer to regional center for ongoing care
>1	69	Consider preconception cardiac intervention for specific lesions; refer to regional center for ongoing care

NYHA = New York Heart Association.

[a]Cardiac events include pulmonary edema, tachyarrhythmia, embolic stroke, and cardiac death.

Data and recommendations from Siu SC, Sermer M, Colman JM, Alvarez AN, Mercier LA, Morton BC, et al; Cardiac Disease in Pregnancy (CARPREG) Investigators. Prospective multicenter study of pregnancy outcomes in women with heart disease. Circulation. 2001;104:515-21. [PMID: 11479246]

TABLE 44. ZAHARA Risk Score Used to Predict Adverse Maternal Cardiac Events

Risk Factor (Predictor)	Risk Score (Points)
Mechanical heart valve	4.25
Severe left heart obstruction (mean gradient >50 mm Hg or aortic valve area <1.0 cm²)	2.5
History of arrhythmias	1.5
History of cardiac medication use before pregnancy	1.5
History of cyanotic heart disease (uncorrected or corrected)	1.0
Moderate to severe pulmonary or systemic atrioventricular valve regurgitation	0.75
Symptomatic heart failure before pregnancy (NYHA functional class ≥II)	0.75

Estimated Risk for Maternal Cardiac Complications[a]

Points	Estimated Risk (%)
0-0.5	2.9
0.51-1.50	7.5
1.51-2.50	17.5
2.51-3.50	43.1
≥3.51	70.0

NYHA = New York Heart Association; ZAHARA = Zwangerschap bij Aangeboren HARtAfwijkingen.

[a]Cardiac complications include clinically significant episodes of arrhythmia or heart failure (episodes requiring treatment with at least a drug prescription), cardiovascular complications (thromboembolic complications, myocardial infarction, and/or cerebrovascular accidents), and endocarditis (including in the first 6 months postpartum).

Data and recommendations from Drenthen W, Boersma E, Balci A, Moons P, Roos-Hesselink JW, Mulder BJ, et al; ZAHARA Investigators. Predictors of pregnancy complications in women with congenital heart disease. Eur Heart J. 2010;31:2124-32. [PMID: 20584777] doi:10.1093/eurheartj/ehq200

women who develop peripartum cardiomyopathy recover fully, as measured by improvement in ejection fraction; however, 13% have major cardiovascular events or persistent severe cardiomyopathy. Studies suggest that the time frame for recovery is 6 months. Prognostic factors that portend a worse outcome include severe left ventricular dysfunction/dilatation or black race.

Women with peripartum cardiomyopathy should be promptly treated with medical therapy, which may include β-blockers, digoxin, hydralazine, nitrates, or diuretics. ACE inhibitors, angiotensin receptor blockers, and aldosterone antagonists are teratogenic and should be avoided until after delivery. Owing to the risk for thromboembolism associated with peripartum cardiomyopathy, anticoagulation is recommended for women with left ventricular ejection fraction below 35%. The choice of anticoagulant (heparin or warfarin) depends on whether the patient is still pregnant and the time since delivery; the decision should be made in consultation with a cardiologist. Duration of anticoagulation is at least 8 weeks, although therapy can be discontinued sooner if the ejection fraction normalizes.

Women with severe refractory heart failure due to peripartum cardiomyopathy should be referred for further evaluation and treatment, including ventricular assist device placement or heart transplantation. Limited evidence from small studies suggests that bromocriptine, which blocks prolactin secretion, improves left ventricular ejection fraction and clinical outcomes when added to peripartum-related heart failure therapy; however, its use is considered investigational.

Because subsequent pregnancy is often associated with recurrent or further reduction of left ventricular function, potentially resulting in clinical deterioration or death, women with a previous episode of peripartum cardiomyopathy with persistent left ventricular dysfunction should be advised to avoid future pregnancy.

Other Cardiovascular Disorders

Women with Marfan syndrome have an increased risk for pregnancy-related aortic dissection. Aortic repair is recommended before pregnancy in women with Marfan syndrome and an aortic diameter of 4.5 cm or greater. Risk factors for dissection during pregnancy in patients with Marfan syndrome with an aortic diameter of less than 4.5 cm include rapid dilatation of the aorta or a personal or family history of aortic dissection. These patients should be counseled to have aortic replacement before pregnancy.

Spontaneous coronary artery dissections may occur during pregnancy or in the postpartum period. Conservative, noninterventional therapy is preferred for most patients. A high index of suspicion is required, as patients presenting with spontaneous coronary artery dissection are generally considered at low risk for acute coronary syndromes.

Cardiovascular Medication Use During Pregnancy

Guidelines for the use of select cardiovascular drugs during pregnancy are outlined in **Table 46**. The FDA formerly used a letter system to categorize drugs by their fetal effects during pregnancy; however, with the implementation of a new pregnancy and lactation labeling rule in 2015, more information is now provided on drug effects in pregnant women, lactating women, and women and men of reproductive potential (see MKSAP 18 General Internal Medicine). Most cardiovascular drugs are not FDA approved for use during pregnancy because of limited safety data. Cardiovascular medications should be used only when needed and at the lowest possible dosage, and the desired therapeutic effect should outweigh the risk.

β-Blocker use during pregnancy or lactation requires periodic fetal and newborn heart rate monitoring because β-blockers cross the placenta and are present in human breast milk. Labetalol is the preferred β-blocker in this setting. Atenolol has been linked to premature delivery and small-for-gestational-age babies; therefore, it is usually avoided during pregnancy.

Adenosine is the drug of choice for treatment of acute symptomatic supraventricular tachycardia during pregnancy. Recurrent episodes of tachycardia are often treated with β-blockers and

TABLE 45. Modified WHO Classification of Pregnancy Risk in Women with Heart Disease

Class	Estimated Risk	Conditions
I	No detectable increased risk for maternal mortality and no/mild increase in morbidity	Uncomplicated small patent ductus arteriosus, mild pulmonary valve stenosis, or mitral valve prolapse Successfully repaired simple lesions (atrial or ventricular septal defect, patent ductus arteriosus, or anomalous pulmonary venous drainage) Isolated atrial or ventricular ectopic beats
II	Small increased risk for maternal mortality	Unrepaired atrial or ventricular septal defect Repaired tetralogy of Fallot Most arrhythmias
II-III	Moderate increase in morbidity	Mild left ventricular impairment Hypertrophic cardiomyopathy Native or bioprosthetic valvular heart disease not considered WHO class I or IV Repaired coarctation Marfan syndrome with aortic dimension <40 mm without aortic dissection Bicuspid aortic valve with ascending aortic diameter <45 mm
III	Significantly increased risk for maternal mortality or severe morbidity	Mechanical valve Systemic right ventricle Fontan circulation[a] Cyanotic heart disease (unrepaired) Other complex congenital heart disease Bicuspid aortic valve with ascending aortic diameter of 45-50 mm Marfan syndrome with aortic diameter of 40-45 mm
IV	Extremely high risk for maternal mortality or severe morbidity; pregnancy is contraindicated	Severe mitral stenosis Symptomatic severe aortic stenosis Bicuspid aortic valve with ascending aortic diameter >50 mm Marfan syndrome with aortic diameter >45 mm Severe systemic ventricular systolic dysfunction (left ventricular ejection fraction <30%, NYHA functional class III-IV) Native severe coarctation Significant pulmonary arterial hypertension of any cause (i.e., pulmonary artery systolic pressure >25 mm Hg at rest or >30 mm Hg with exercise)

NYHA = New York Heart Association; WHO = World Health Organization.

[a]Fontan circulation is a palliative surgical procedure performed for patients with complex congenital heart disease with one functional ventricular chamber. The procedure redirects venous blood directly to the lungs without a pumping chamber in the circulation.

Information from Thorne S, MacGregor A, Nelson-Piercy C. Risks of contraception and pregnancy in heart disease. Heart. 2006;92:1520-5. [PMID: 16973809]

digoxin; sotalol and flecainide have also been safely used. Because of toxicity concerns, amiodarone is rarely used.

ACE inhibitors, angiotensin receptor blockers, and aldosterone antagonists should be avoided during pregnancy because of their associated teratogenicity, although some ACE inhibitors are safe to use while breastfeeding. There is inconclusive evidence on the safety of angiotensin receptor blockers while breastfeeding; thus, these drugs are generally avoided during lactation. Spironolactone is considered compatible with breastfeeding.

The LactMed database (toxnet.nlm.nih.gov/newtoxnet/lactmed.htm) provides information on drugs to which breastfeeding mothers may be exposed, including potential adverse effects and suggested therapeutic alternatives.

Anticoagulation Therapy During Pregnancy

Pregnancy is associated with hypercoagulability, and anticoagulation is often indicated in pregnant patients. **Table 47** lists the indications, recommended regimens, and monitoring parameters for therapy. Prepregnancy counseling is recommended for all women requiring long-term anticoagulation to enable them to make informed decisions regarding anticoagulant preference and to understand the maternal and fetal risks.

TABLE 46. Drugs for Cardiac Disorders in Pregnancy

Drug	Use in Pregnancy	Compatibility with Breastfeeding	Comments
ACE inhibitors			
Captopril, enalapril	No	Yes	Teratogenic in first trimester; cause fetal/neonatal kidney failure with second- or third-trimester exposure; scleroderma renal crisis is only indication
Lisinopril	No	?	Same as above
ARBs	No	?	Teratogenic in first trimester; cause fetal/neonatal kidney failure with second- or third-trimester exposure
Adenosine	Yes	?	No change in fetal heart rate when used for supraventricular tachycardia
Amiodarone	No	No	Fetal hypothyroidism, prematurity
Antiplatelet and anticoagulant agents			
Dipyridamole, clopidogrel	Yes	?	Second-line agent; no evidence of harm in animal clopidogrel studies; no human data
Aspirin (≤81 mg)	Yes	Yes	
NOACs (apixaban, dabigatran, rivaroxaban, edoxaban)	?	?	Pregnancy and lactation should be avoided in NOAC-treated patients; available data do not suggest a high risk for NOAC embryopathy or neonatal complications
β-Blockers			
Atenolol	Yes	No	Second-line agent; low birth weight, intrauterine growth restriction
Esmolol	Yes	?	Second-line agent; more pronounced bradycardia
Labetalol	Yes	Yes	Preferred drug in class
Metoprolol	Yes	Yes	Shortened half-life
Propranolol	Yes	Yes	Second-line agent; intrauterine growth restriction
Sotalol	Yes	?	Second-line agent; insufficient data; reserve use for arrhythmia not responding to alternative agent
Calcium channel blockers			
Diltiazem, verapamil	Yes	Yes	Second-line agent; maternal hypotension with rapid intravenous infusion; used for fetal supraventricular tachycardia
Digoxin	Yes	Yes	Second-line agent; shortened half-life
Disopyramide	Yes	Yes	Second-line agent; case reports of preterm labor
Diuretics	Yes	Yes	Second-line agent; use when needed for maternal volume overload only
Flecainide	Yes	?	Second-line agent; inadequate data but used for fetal arrhythmia; case report of fetal hyperbilirubinemia
Hydralazine	Yes	Yes	Vasodilator of choice
Lidocaine	Yes	Yes	Treatment of choice for ventricular arrhythmias
Sodium nitroprusside	No	No	Potential fetal thiocyanate toxicity
Organic nitrates	Yes	?	No apparent increased risk
Phenytoin	No	Yes	Known teratogenicity and bleeding risk; last resort for arrhythmia
Procainamide	Yes	Yes	Used for fetal arrhythmia
Propafenone	Yes	?	Second-line agent; used for fetal arrhythmia
Quinidine	Yes	Yes	Preferred drug in class; increases digoxin levels

? = unknown; ARB = angiotensin receptor blocker; NOAC = non-vitamin K antagonist oral anticoagulant.

Adapted with permission from Rosene-Montella K, Keely EJ, Lee RV, Barbour LA. Medical Care of the Pregnant Patient. 2nd Edition. Philadelphia, PA: American College of Physicians; 2008. pp 356-357. Copyright 2008, American College of Physicians.

TABLE 47. Anticoagulation Regimens During Pregnancy

Weeks of Gestation	Recommended Regimen
Venous Thromboembolism	
Weeks 6-12	Warfarin (if dose to attain INR 2-3 is ≤5 mg)
	UFH (IV or SQ; aPTT 2 × control)
	Weight-based LMWH
Weeks 13-37	UFH (SQ; aPTT 2 × control)
	Weight-based LMWH
	Warfarin (INR 2-3)
Weeks 37 to term	UFH (IV; aPTT 2 × control)
Atrial Fibrillation	
Weeks 6-12	Warfarin (if dose to attain INR 2-3 is ≤5 mg)
	UFH (IV or SQ; aPTT 2 × control)
	Weight-based LMWH
Weeks 13-37	UFH (SQ; aPTT 2 × control)
	Weight-based LMWH
	Warfarin (INR 2-3)
Weeks 37 to term	UFH (IV; aPTT 2 × control)
Mechanical Valve Prosthesis	
Weeks 6-12	Warfarin dose ≤5 mg for therapeutic INR
	Continue warfarin (class IIa recommendation)
	UFH: IV; aPTT 2 × control (class IIb recommendation)
	Anti-factor Xa adjusted LMWH (class IIb recommendation)
	Warfarin dose >5 mg for therapeutic INR
	UFH: IV; aPTT 2 × control (class IIa recommendation)
	Anti-factor Xa adjusted LMWH (class IIa recommendation)
Weeks 13-37	Warfarin (therapeutic INR)
Weeks 37 to term	UFH (IV; aPTT 2 × control)

aPTT = activated partial thromboplastin time; IV = intravenous; LMWH = low-molecular-weight heparin; SQ = subcutaneous; UFH = unfractionated heparin.

Recommendations from Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP 3rd, Guyton RA, et al; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2014;63:2438-88. [PMID: 24603192] doi:10.1016/j.jacc.2014.02.537 *and* Bates SM, Greer IA, Middeldorp S, Veenstra DL, Prabulos AM, Vandvik PO. VTE, thrombophilia, antithrombotic therapy, and pregnancy: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2012;141:e691S-e736S. [PMID: 22315276] doi:10.1378/chest.11-2300 *and* Furie KL, Kasner SE, Adams RJ, Albers GW, Bush RL, Fagan SC, et al; American Heart Association Stroke Council, Council on Cardiovascular Nursing, Council on Clinical Cardiology, and Interdisciplinary Council on Quality of Care and Outcomes Research. Guidelines for the prevention of stroke in patients with stroke or transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2011;42:227-76. [PMID: 20966421] doi:10.1161/STR.0b013e3181f7d043

Warfarin, unfractionated heparin, and low-molecular-weight heparin can all be used during pregnancy. Careful monitoring and dosage adjustment are indicated for all anticoagulation regimens. It is important to note that warfarin use during the first trimester can cause warfarin embryopathy when the daily dose is greater than 5 mg. Warfarin is stopped before delivery owing to the risk for fetal intracranial hemorrhage if spontaneous labor and vaginal delivery occur while the mother (and thus the fetus) is anticoagulated with warfarin.

Pregnant women with a mechanical valve prosthesis represent a high-risk subset of patients; concerns include valve thrombosis with its associated maternal risks, bleeding, and fetal morbidity and mortality. Warfarin appears to be the safest agent to prevent maternal prosthetic valve thrombosis; however, warfarin poses an increased fetal risk, with possible teratogenicity, miscarriage, and fetal loss due to intracranial hemorrhage. Data suggest that low-molecular-weight heparin and unfractionated heparin are safer for the fetus than warfarin is, but these therapies appear to increase the risk for maternal prosthetic valve thrombosis.

Guidelines from the American College of Cardiology/American Heart Association on the management of anticoagulation during pregnancy in the setting of mechanical valve prosthesis recommend warfarin during the first trimester if the daily dose is 5 mg or less at the time of conception. Intravenous unfractionated heparin or dose-adjusted low-molecular-weight heparin is preferred if the warfarin dose is more than 5 mg daily. During the second and early third trimesters, warfarin therapy is preferred. Intravenous unfractionated heparin is preferred for anticoagulation around the time of delivery in patients with a mechanical valve prosthesis. Weekly monitoring of the anticoagulation level is recommended during pregnancy irrespective of the regimen used, with dosage adjustment as indicated.

Limited data do not suggest a high risk for embryopathy or neonatal complications with exposure to non–vitamin K antagonist oral anticoagulants. However, owing to small case numbers, it is recommended that pregnancy and lactation be avoided in patients receiving non–vitamin K antagonist oral anticoagulants.

KEY POINTS

- Women with peripartum cardiomyopathy should be initially treated with medical therapy, which may include β-blockers, digoxin, hydralazine, nitrates, or diuretics.
- ACE inhibitors, angiotensin receptor blockers, and aldosterone antagonists should be avoided during pregnancy because of their associated teratogenicity.
- In pregnant patients with a mechanical valve prosthesis, warfarin anticoagulation is preferred during the first trimester if the daily dose is 5 mg or less at the time of conception; intravenous unfractionated heparin or dose-adjusted low-molecular-weight heparin is preferred if the warfarin dose is more than 5 mg daily.

Bibliography

Epidemiology and Risk Factors

Centers for Disease Control and Prevention. National Center for Chronic Disease Prevention and Health Promotion. Division of Nutrition, Physical Activity, and Obesity. Data, trends and maps [online]. [Accessed Jan 13, 2017]. URL: https://nccd.cdc.gov/NPAO_DTM/LocationSummary.aspx?statecode=94.

Garcia M, Mulvagh SL, Merz CN, Buring JE, Manson JE. Cardiovascular disease in women: clinical perspectives. Circ Res. 2016;118:1273–93. [PMID: 27081110] doi:10.1161/CIRCRESAHA.116.307547

Goff DC Jr, Lloyd-Jones DM, Bennett G, Coady S, D'Agostino RB Sr, Gibbons R, et al; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2014;63:2935–59. [PMID: 24239921] doi:10.1016/j.jacc.2013.11.005

McSweeney JC, Rosenfeld AG, Abel WM, Braun LT, Burke LE, Daugherty SL, et al; American Heart Association Council on Cardiovascular and Stroke Nursing, Council on Clinical Cardiology, Council on Epidemiology and Prevention, Council on Hypertension, Council on Lifestyle and Cardiometabolic Health, and Council on Quality of Care and Outcomes Research. Preventing and experiencing ischemic heart disease as a woman: state of the science: a scientific statement from the American Heart Association. Circulation. 2016;133:1302–31. [PMID: 26927362] doi:10.1161/CIR.0000000000000381

Mehta LS, Beckie TM, DeVon HA, Grines CL, Krumholz HM, Johnson MN, et al; American Heart Association Cardiovascular Disease in Women and Special Populations Committee of the Council on Clinical Cardiology, Council on Epidemiology and Prevention, Council on Cardiovascular and Stroke Nursing, and Council on Quality of Care and Outcomes Research. Acute myocardial infarction in women: a scientific statement from the American Heart Association. Circulation. 2016;133:916–47. [PMID: 26811316] doi:10.1161/CIR.0000000000000351

Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, et al; Writing Group Members. Heart disease and stroke statistics–2016 update: a report from the American Heart Association. Circulation. 2016;133:e38–360. [PMID: 26673558] doi:10.1161/CIR.0000000000000350

Stein JH, Hsue PY. Inflammation, immune activation, and CVD risk in individuals with HIV infection [Editorial]. JAMA. 2012;308:405–6. [PMID: 22820794] doi:10.1001/jama.2012.8488

Whelton PK, Carey RM, Aronow WS, Casey DE Jr, Collins KJ, Dennison Himmelfarb C, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2017. [PMID: 29146535] doi:10.1016/j.jacc.2017.11.006

Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F, et al; INTERHEART Study Investigators. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. Lancet. 2004;364:937–52. [PMID: 15364185]

Diagnostic Testing in Cardiology

Douglas PS, Garcia MJ, Haines DE, Lai WW, Manning WJ, Patel AR, et al; American College of Cardiology Foundation Appropriate Use Criteria Task Force. ACCF/ASE/AHA/ASNC/HFSA/HRS/SCAI/SCCM/SCCT/SCMR 2011 appropriate use criteria for echocardiography. a report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, American Society of Echocardiography, American Heart Association, American Society of Nuclear Cardiology, Heart Failure Society of America, Heart Rhythm Society, Society for Cardiovascular Angiography and Interventions, Society of Critical Care Medicine, Society of Cardiovascular Computed Tomography, and Society for Cardiovascular Magnetic Resonance Endorsed by the American College of Chest Physicians. J Am Coll Cardiol. 2011;57:1126–66. [PMID: 21349406] doi:10.1016/j.jacc.2010.11.002

Douglas PS, Hoffmann U, Patel MR, Mark DB, Al-Khalidi HR, Cavanaugh B, et al; PROMISE Investigators. Outcomes of anatomical versus functional testing for coronary artery disease. N Engl J Med. 2015;372:1291–300. [PMID: 25773919] doi:10.1056/NEJMoa1415516

Fihn SD, Blankenship JC, Alexander KP, Bittl JA, Byrne JG, Fletcher BJ, et al. 2014 ACC/AHA/AATS/PCNA/SCAI/STS focused update of the guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines, and the American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. Circulation. 2014;130:1749–67. [PMID: 25070666] doi:10.1161/CIR.0000000000000095

Goff DC Jr, Lloyd-Jones DM, Bennett G, Coady S, D'Agostino RB Sr, Gibbons R, et al; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2014;63:2935–59. [PMID: 24239921] doi:10.1016/j.jacc.2013.11.005

Hendel RC, Berman DS, Di Carli MF, Heidenreich PA, Henkin RE, Pellikka PA, et al; American College of Cardiology Foundation Appropriate Use Criteria Task Force. ACCF/ASNC/ACR/AHA/ASE/SCCT/SCMR/SNM 2009 appropriate use criteria for cardiac radionuclide imaging: a report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, the American Society of Nuclear Cardiology, the American College of Radiology, the American Heart Association, the American Society of Echocardiography, the Society of Cardiovascular Computed Tomography, the Society for Cardiovascular Magnetic Resonance, and the Society of Nuclear Medicine. J Am Coll Cardiol. 2009;53:2201–29. [PMID: 19497454] doi:10.1016/j.jacc.2009.02.013

Mark DB, Berman DS, Budoff MJ, Carr JJ, Gerber TC, Hecht HS, et al; American College of Cardiology Foundation Task Force on Expert Consensus Documents. ACCF/ACR/AHA/NASCI/SAIP/SCAI/SCCT 2010 expert consensus document on coronary computed tomographic angiography: a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents. J Am Coll Cardiol. 2010;55:2663–99. [PMID: 20513611] doi:10.1016/j.jacc.2009.11.013

Rybicki FJ, Udelson JE, Peacock WF, Goldhaber SZ, Isselbacher EM, Kazerooni E, et al. 2015 ACR/ACC/AHA/AATS/ACEP/ASNC/NASCI/SAEM/SCCT/SCMR/SCPC/SNMMI/STR/STS appropriate utilization of cardiovascular imaging in emergency department patients with chest pain: a joint document of the American College of Radiology Appropriateness Criteria Committee and the American College of Cardiology Appropriate Use Criteria Task Force. J Am Coll Cardiol. 2016;67:853–79. [PMID: 26809772] doi:10.1016/j.jacc.2015.09.011

Coronary Artery Disease

Amsterdam EA, Wenger NK, Brindis RG, Casey DE Jr, Ganiats TG, Holmes DR Jr, et al; ACC/AHA Task Force Members. 2014 AHA/ACC guideline for the management of patients with non–ST-elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014;130:e344–426. [PMID: 25249585] doi:10.1161/CIR.0000000000000134

Boden WE, O'Rourke RA, Teo KK, Hartigan PM, Maron DJ, Kostuk WJ, et al; COURAGE Trial Research Group. Optimal medical therapy with or without PCI for stable coronary disease. N Engl J Med. 2007;356:1503–16. [PMID: 17387127]

Bonaca MP, Bhatt DL, Cohen M, Steg PG, Storey RF, Jensen EC, et al; PEGASUS-TIMI 54 Steering Committee and Investigators. Long-term use of ticagrelor in patients with prior myocardial infarction. N Engl J Med. 2015;372:1791–800. [PMID: 25773268] doi:10.1056/NEJMoa1500857

Fihn SD, Gardin JM, Abrams J, Berra K, Blankenship JC, Dallas AP, et al; American College of Cardiology Foundation. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol. 2012;60:e44–e164. [PMID: 23182125] doi:10.1016/j.jacc.2012.07.013

Fox CS, Golden SH, Anderson C, Bray GA, Burke LE, de Boer IH, et al; American Heart Association Diabetes Committee of the Council on Lifestyle and Cardiometabolic Health, Council on Clinical Cardiology, Council on Cardiovascular and Stroke Nursing, Council on Cardiovascular Surgery and Anesthesia, Council on Quality of Care and Outcomes Research, and the American Diabetes Association. Update on prevention of cardiovascular disease in adults with type 2 diabetes mellitus in light of recent evidence: a scientific statement from the American Heart Association and the American Diabetes Association. Circulation. 2015;132:691–718. [PMID: 26246173] doi:10.1161/CIR.0000000000000230

Levine GN, Bates ER, Bittl JA, Brindis RG, Fihn SD, Fleisher LA, et al. 2016 ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Thorac Cardiovasc Surg. 2016;152:1243–1275. [PMID: 27751237] doi:10.1016/j.jtcvs.2016.07.044

Levine GN, Bates ER, Blankenship JC, Bailey SR, Bittl JA, Cercek B, et al. 2015 ACC/AHA/SCAI focused update on primary percutaneous coronary intervention for patients with ST-elevation myocardial infarction: an update of the 2011 ACCF/AHA/SCAI guideline for percutaneous coronary

intervention and the 2013 ACCF/AHA guideline for the management of st-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. Circulation. 2016;133:1135-47. [PMID: 26490017] doi:10.1161/CIR.0000000000000336

Marso SP, Daniels GH, Brown-Frandsen K, Kristensen P, Mann JF, Nauck MA, et al; LEADER Steering Committee. Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2016;375:311-22. [PMID: 27295427] doi:10.1056/NEJMoa1603827

Pasupathy S, Air T, Dreyer RP, Tavella R, Beltrame JF. Systematic review of patients presenting with suspected myocardial infarction and nonobstructive coronary arteries. Circulation. 2015;131:861-70. [PMID: 25587100] doi:10.1161/CIRCULATIONAHA.114.011201

Rodriguez F, Mahaffey KW. Management of patients with NSTE ACS: a comparison of the recent AHA/ACC and ESC guidelines. J Am Coll Cardiol. 2016;68:313-21. [PMID: 27417010] doi:10.1016/j.jacc.2016.03.599

Stergiopoulos K, Boden WE, Hartigan P, Möbius Winkler S, Hambrecht R, Hueb W, et al. Percutaneous coronary intervention outcomes in patients with stable obstructive coronary artery disease and myocardial ischemia: a collaborative meta-analysis of contemporary randomized clinical trials. JAMA Intern Med. 2014;174:232-40. [PMID: 24296791] doi:10.1001/jamainternmed.2013.12855

Velazquez EJ, Lee KL, Jones RH, Al-Khalidi HR, Hill JA, Panza JA, et al; STICHES Investigators. Coronary-artery bypass surgery in patients with ischemic cardiomyopathy. N Engl J Med. 2016;374:1511-20. [PMID: 27040723] doi:10.1056/NEJMoa1602001

Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, et al; PLATO Investigators. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med. 2009;361:1045-57. [PMID: 19717846] doi:10.1056/NEJMoa0904327

Whelton PK, Carey RM, Aronow WS, Casey DE Jr, Collins KJ, Dennison Himmelfarb C, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2017. [PMID: 29146535] doi:10.1016/j.jacc.2017.11.006

Heart Failure

Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, et al; Authors/Task Force Members. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2016;37:2129-200. [PMID: 27206819] doi:10.1093/eurheartj/ehw128

Redfield MM. Heart failure with preserved ejection fraction. N Engl J Med. 2016;375:1868-1877. [PMID: 27959663]

Thiele H, Ohman EM, Desch S, Eitel I, de Waha S. Management of cardiogenic shock. Eur Heart J. 2015;36:1223-30. [PMID: 25732762] doi:10.1093/eurheartj/ehv051

Whelton PK, Carey RM, Aronow WS, Casey DE Jr, Collins KJ, Dennison Himmelfarb C, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2017. [PMID: 29146535] doi:10.1016/j.jacc.2017.11.006

Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Drazner MH, et al; American College of Cardiology Foundation. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2013;62:e147-239. [PMID: 23747642] doi:10.1016/j.jacc.2013.05.019

Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Colvin MM, et al. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. Circulation. 2017 Aug 8;136(6):e137-e161. [PMID: 28455343] doi:10.1161/CIR.0000000000000509

Arrhythmias

Conen D, Adam M, Roche F, Barthelemy JC, Felber Dietrich D, Imboden M, et al. Premature atrial contractions in the general population: frequency and risk factors. Circulation. 2012;126:2302-8. [PMID: 23048073] doi:10.1161/CIRCULATIONAHA.112.112300

Cheng S, Keyes MJ, Larson MG, McCabe EL, Newton-Cheh C, Levy D, et al. Long-term outcomes in individuals with prolonged PR interval or first-degree atrioventricular block. JAMA. 2009;301:2571-7. [PMID: 19549974] doi:10.1001/jama.2009.888

Delacrétaz E. Clinical practice. Supraventricular tachycardia. N Engl J Med. 2006;354:1039-51. [PMID: 16525141]

Epstein AE, DiMarco JP, Ellenbogen KA, Estes NA 3rd, Freedman RA, Gettes LS, et al; American College of Cardiology Foundation. 2012 ACCF/AHA/HRS focused update incorporated into the ACCF/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. Circulation. 2013;127:e283-352. [PMID: 23255456] doi:10.1161/CIR.0b013e318276ce9b

Epstein AE, DiMarco JP, Ellenbogen KA, Estes NA 3rd, Freedman RA, Gettes LS, et al; American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the ACC/AHA/NASPE 2002 Guideline Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices). ACC/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the ACC/AHA/NASPE 2002 Guideline Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices): developed in collaboration with the American Association for Thoracic Surgery and Society of Thoracic Surgeons. Circulation. 2008;117:e350-408. [PMID: 18483207] doi:10.1161/CIRCUALTIONAHA.108.189742

Fuster V, Rydén LE, Cannom DS, Crijns HJ, Curtis AB, Ellenbogen KA, et al; American College of Cardiology. ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: full text: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 guidelines for the management of patients with atrial fibrillation) developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. Europace. 2006;8:651-745. [PMID: 16987906]

January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC Jr, et al; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol. 2014;64:e1-76. [PMID: 24685669] doi:10.1016/j.jacc.2014.03.022

Link MS, Berkow LC, Kudenchuk PJ, Halperin HR, Hess EP, Moitra VK, et al. Part 7: Adult Advanced Cardiovascular Life Support: 2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation. 2015;132:S444-64. [PMID: 26472995] doi:10.1161/CIR.0000000000000261

Page RL, Joglar JA, Caldwell MA, Calkins H, Conti JB, Deal BJ, et al. 2015 ACC/AHA/HRS guideline for the management of adult patients with supraventricular tachycardia: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol. 2016;67:e27-e115. [PMID: 26409259] doi:10.1016/j.jacc.2015.08.856

Piccini JP, Fauchier L. Rhythm control in atrial fibrillation. Lancet. 2016;388:829-40. [PMID: 27560278] doi:10.1016/S0140-6736(16)31277-6

Priori SG, Wilde AA, Horie M, Cho Y, Behr ER, Berul C, et al. HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes: document endorsed by HRS, EHRA, and APHRS in May 2013 and by ACCF, AHA, PACES, and AEPC in June 2013. Heart Rhythm. 2013;10:1932-63. [PMID: 24011539] doi:10.1016/j.hrthm.2013.05.014

Zipes DP, Camm AJ, Borggrefe M, Buxton AE, Chaitman B, Fromer M, et al; American College of Cardiology/American Heart Association Task Force. ACC/AHA/ESC 2006 Guidelines for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death: a report of the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines (writing committee to develop Guidelines for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death): developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. Circulation. 2006;114:e385-484. [PMID: 16935995]

Valvular Heart Disease

Desimone DC, Tleyjeh IM, Correa de Sa DD, Anavekar NS, Lahr BD, Sohail MR, et al; Mayo Cardiovascular Infections Study Group. Incidence of infective endocarditis caused by viridans group streptococci before and after publication of the 2007

American Heart Association's endocarditis prevention guidelines. Circulation. 2012;126:60–4. [PMID: 22689929] doi:10.1161/CIRCULATIONAHA.112.095281

Eikelboom JW, Connolly SJ, Brueckmann M, Granger CB, Kappetein AP, Mack MJ, et al; RE-ALIGN Investigators. Dabigatran versus warfarin in patients with mechanical heart valves. N Engl J Med. 2013;369:1206–14. [PMID: 23991661] doi:10.1056/NEJMoa1300615

Holmes DR Jr, Rich JB, Zoghbi WA, Mack MJ. The heart team of cardiovascular care. J Am Coll Cardiol. 2013;61:903–7. [PMID: 23449424] doi:10.1016/j.jacc.2012.08.1034

Li JS, Sexton DJ, Mick N, Nettles R, Fowler VG Jr, Ryan T, et al. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. Clin Infect Dis. 2000;30:633–8. [PMID: 10770721]

Mack MJ, Leon MB, Smith CR, Miller DC, Moses JW, Tuzcu EM, et al; PARTNER 1 trial investigators. 5-year outcomes of transcatheter aortic valve replacement or surgical aortic valve replacement for high surgical risk patients with aortic stenosis (PARTNER 1): a randomised controlled trial. Lancet. 2015;385:2477–84. [PMID: 25788234] doi:10.1016/S0140-6736(15)60308-7

Michelena HI, Khanna AD, Mahoney D, Margaryan E, Topilsky Y, Suri RM, et al. Incidence of aortic complications in patients with bicuspid aortic valves. JAMA. 2011;306:1104–12. [PMID: 21917581] doi:10.1001/jama.2011.1286

Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP 3rd, Fleisher LA, et al. 2017 AHA/ACC focused update of the 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2017;135:e1159–e1195. [PMID: 28298458] doi:10.1161/CIR.0000000000000503

Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP 3rd, Guyton RA, et al; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2014;63:2438–88. [PMID: 24603192] doi:10.1016/j.jacc.2014.02.537

Pibarot P, Dumesnil JG. Low-flow, low-gradient aortic stenosis with normal and depressed left ventricular ejection fraction. J Am Coll Cardiol. 2012;60:1845–53. [PMID: 23062546] doi:10.1016/j.jacc.2012.06.051

Suri RM, Vanoverschelde JL, Grigioni F, Schaff HV, Tribouilloy C, Avierinos JF, et al. Association between early surgical intervention vs watchful waiting and outcomes for mitral regurgitation due to flail mitral valve leaflets. JAMA. 2013;310:609–16. [PMID: 23942679] doi:10.1001/jama.2013.8643

Turpie AG, Gent M, Laupacis A, Latour Y, Gunstensen J, Basile F, et al. A comparison of aspirin with placebo in patients treated with warfarin after heart-valve replacement. N Engl J Med. 1993;329:524–9. [PMID: 8336751]

Myocardial Disease

Ammash NM, Seward JB, Bailey KR, Edwards WD, Tajik AJ. Clinical profile and outcome of idiopathic restrictive cardiomyopathy. Circulation. 2000;101:2490–6. [PMID: 10831523]

Butany J, Nair V, Naseemuddin A, Nair GM, Catton C, Yau T. Cardiac tumours: diagnosis and management. Lancet Oncol. 2005;6:219–28. [PMID: 15811617]

Elliott PM, Anastasakis A, Borger MA, Borggrefe M, Cecchi F, Charron P, et al; Authors/Task Force members. 2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy: the Task Force for the Diagnosis and Management of Hypertrophic Cardiomyopathy of the European Society of Cardiology (ESC). Eur Heart J. 2014;35:2733–79. [PMID: 25173338] doi:10.1093/eurheartj/ehu284

Garcia MJ. Constrictive pericarditis versus restrictive cardiomyopathy? J Am Coll Cardiol. 2016;67:2061–76. [PMID: 27126534] doi:10.1016/j.jacc.2016.01.076

Gersh BJ, Maron BJ, Bonow RO, Dearani JA, Fifer MA, Link MS, et al. 2011 ACCF/AHA guideline for the diagnosis and treatment of hypertrophic cardiomyopathy: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2011;58:2703–38. [PMID: 22075468] doi:10.1016/j.jacc.2011.10.825

Liebregts M, Steggerda RC, Vriesendorp PA, van Velzen H, Schinkel AF, Willems R, et al. Long-term outcome of alcohol septal ablation for obstructive hypertrophic cardiomyopathy in the young and the elderly. JACC Cardiovasc Interv. 2016;9:463–9. [PMID: 26965935] doi:10.1016/j.jcin.2015.11.036

Liebregts M, Vriesendorp PA, Mahmoodi BK, Schinkel AF, Michels M, ten Berg JM. A systematic review and meta-analysis of long-term outcomes after septal reduction therapy in patients with hypertrophic cardiomyopathy. JACC Heart Fail. 2015;3:896–905. [PMID: 26454847] doi:10.1016/j.jchf.2015.06.011

Maron BJ. Hypertrophic cardiomyopathy and other causes of sudden cardiac death in young competitive athletes, with considerations for preparticipation screening and criteria for disqualification. Cardiol Clin. 2007;25:399–414, vi. [PMID: 17961794]

Mogensen J, Kubo T, Duque M, Uribe W, Shaw A, Murphy R, et al. Idiopathic restrictive cardiomyopathy is part of the clinical expression of cardiac troponin I mutations. J Clin Invest. 2003;111:209–16. [PMID: 12531876]

Seward JB, Casaclang-Verzosa G. Infiltrative cardiovascular diseases: cardiomyopathies that look alike. J Am Coll Cardiol. 2010;55:1769–79. [PMID: 20413025] doi:10.1016/j.jacc.2009.12.040

Pericardial Disease

Adler Y, Charron P, Imazio M, Badano L, Barón-Esquivias G, Bogaert J, et al; European Society of Cardiology (ESC). 2015 ESC guidelines for the diagnosis and management of pericardial diseases: The Task Force for the Diagnosis and Management of Pericardial Diseases of the European Society of Cardiology (ESC)Endorsed by: The European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J. 2015;36:2921–64. [PMID: 26320112] doi:10.1093/eurheartj/ehv318

Finetti M, Insalaco A, Cantarini L, Meini A, Breda L, Alessio M, et al. Long-term efficacy of interleukin-1-receptor antagonist (anakinra) in corticosteroid-dependent and colchicine-resistant recurrent pericarditis. J Pediatr. 2014;164:1425–31.e1. [PMID: 24630353] doi:10.1016/j.jpeds.2014.01.065

Haley JH, Tajik AJ, Danielson GK, Schaff HV, Mulvagh SL, Oh JK. Transient constrictive pericarditis: causes and natural history. J Am Coll Cardiol. 2004;43:271–5. [PMID: 14736448]

Imazio M, Brucato A, Maestroni S, Cumetti D, Dominelli A, Natale G, et al. Prevalence of C-reactive protein elevation and time course of normalization in acute pericarditis: implications for the diagnosis, therapy, and prognosis of pericarditis. Circulation. 2011;123:1092–7. [PMID: 21357824] doi:10.1161/CIRCULATIONAHA.110.986372

Klein AL, Abbara S, Agler DA, Appleton CP, Asher CR, Hoit B, et al. American Society of Echocardiography clinical recommendations for multimodality cardiovascular imaging of patients with pericardial disease: endorsed by the Society for Cardiovascular Magnetic Resonance and Society of Cardiovascular Computed Tomography. J Am Soc Echocardiogr. 2013;26:965–1012.e15. [PMID: 23998693] doi:10.1016/j.echo.2013.06.023

Lilly LS. Treatment of acute and recurrent idiopathic pericarditis. Circulation. 2013;127:1723–6. [PMID: 23609551] doi:10.1161/CIRCULATIONAHA.111.066365

Welch TD, Ling LH, Espinosa RE, Anavekar NS, Wiste HJ, Lahr BD, et al. Echocardiographic diagnosis of constrictive pericarditis: Mayo Clinic criteria. Circ Cardiovasc Imaging. 2014;7:526–34. [PMID: 24633783] doi:10.1161/CIRCIMAGING.113.001613

Zurick AO, Bolen MA, Kwon DH, Tan CD, Popovic ZB, Rajeswaran J, et al. Pericardial delayed hyperenhancement with CMR imaging in patients with constrictive pericarditis undergoing surgical pericardiectomy: a case series with histopathological correlation. JACC Cardiovasc Imaging. 2011;4:1180–91. [PMID: 22093269] doi:10.1016/j.jcmg.2011.08.011

Adult Congenital Heart Disease

Kent DM, Dahabreh IJ, Ruthazer R, Furlan AJ, Reisman M, Carroll JD, et al. Device closure of patent foramen ovale after stroke: pooled analysis of completed randomized trials. J Am Coll Cardiol. 2016;67:907–17. [PMID: 26916479] doi:10.1016/j.jacc.2015.12.023

Krieger EV, Leary PJ, Opotowsky AR. Pulmonary hypertension in congenital heart disease: beyond eisenmenger syndrome. Cardiol Clin. 2015;33:599–609, ix. [PMID: 26471823] doi:10.1016/j.ccl.2015.07.003

Mas JL, Derumeaux G, Guillon B, Massardier E, Hosseini H, Mechtouff L, et al; CLOSE Investigators. Patent foramen ovale closure or anticoagulation vs. antiplatelets after stroke. N Engl J Med. 2017;377:1011–1021. [PMID: 28902593] doi:10.1056/NEJMoa1705915

Messé SR, Gronseth G, Kent DM, Kizer JR, Homma S, Rosterman L, et al. Practice advisory: recurrent stroke with patent foramen ovale (update of practice parameter): report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. Neurology. 2016;87:815–21. [PMID: 27466464] doi:10.1212/WNL.0000000000002961

Opotowsky AR, Moko LE, Ginns J, Rosenbaum M, Greutmann M, Aboulhosn J, et al. Pheochromocytoma and paraganglioma in cyanotic congenital heart disease. J Clin Endocrinol Metab. 2015;100:1325–34. [PMID: 25581599] doi:10.1210/jc.2014-3863

Regitz-Zagrosek V, Blomstrom Lundqvist C, Borghi C, Cifkova R, Ferreira R, Foidart JM, et al; European Society of Gynecology (ESG). ESC guidelines on the management of cardiovascular diseases during pregnancy: the Task Force on the Management of Cardiovascular Diseases during Pregnancy of

the European Society of Cardiology (ESC). Eur Heart J. 2011;32:3147–97. [PMID: 21873418] doi:10.1093/eurheartj/ehr218

Saver JL, Carroll JD, Thaler DE, Smalling RW, MacDonald LA, Marks DS, et al; RESPECT Investigators. Long-term outcomes of patent foramen ovale closure or medical therapy after stroke. N Engl J Med. 2017;377:1022–1032. [PMID: 28902590] doi:10.1056/NEJMoa1610057

Søndergaard L, Kasner SE, Rhodes JF, Andersen G, Iversen HK, Nielsen-Kudsk JE, et al; Gore REDUCE Clinical Study Investigators. Patent foramen ovale closure or antiplatelet therapy for cryptogenic stroke. N Engl J Med. 2017;377:1033–1042. [PMID: 28902580] doi:10.1056/NEJMoa1707404

Valente AM, Cook S, Festa P, Ko HH, Krishnamurthy R, Taylor AM, et al. Multimodality imaging guidelines for patients with repaired tetralogy of Fallot: a report from the American Society of Echocardiography: developed in collaboration with the Society for Cardiovascular Magnetic Resonance and the Society for Pediatric Radiology. J Am Soc Echocardiogr. 2014;27:111–41. [PMID: 24468055] doi:10.1016/j.echo.2013.11.009

Van Hare GF, Ackerman MJ, Evangelista JA, Kovacs RJ, Myerburg RJ, Shafer KM, et al; American Heart Association Electrocardiography and Arrhythmias Committee of Council on Clinical Cardiology, Council on Cardiovascular Disease in Young, Council on Cardiovascular and Stroke Nursing, Council on Functional Genomics and Translational Biology, and American College of Cardiology. Eligibility and disqualification recommendations for competitive athletes with cardiovascular abnormalities: task force 4: congenital heart disease: a scientific statement from the American Heart Association and American College of Cardiology. Circulation. 2015;132:e281–91. [PMID: 26621645] doi:10.1161/CIR.0000000000000240

Warnes CA, Williams RG, Bashore TM, Child JS, Connolly HM, Dearani JA, et al; American College of Cardiology. ACC/AHA 2008 guidelines for the management of adults with congenital heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Develop Guidelines on the Management of Adults With Congenital Heart Disease). Developed in Collaboration With the American Society of Echocardiography, Heart Rhythm Society, International Society for Adult Congenital Heart Disease, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol. 2008;52:e143–263. [PMID: 19038677] doi:10.1016/j.jacc.2008.10.001

Diseases of the Aorta

Amarenco P, Cohen A, Hommel M, Moulin T, Leys D, Bousser M-G; French Study of Aortic Plaques in Stroke Group. Atherosclerotic disease of the aortic arch as a risk factor for recurrent ischemic stroke. N Engl J Med. 1996;334:1216–21. [PMID: 8606716]

Chaikof EL, Brewster DC, Dalman RL, Makaroun MS, Illig KA, Sicard GA, et al. SVS practice guidelines for the care of patients with an abdominal aortic aneurysm: executive summary. J Vasc Surg. 2009;50:880–96. [PMID: 19786241] doi:10.1016/j.jvs.2009.07.001

De Bruin JL, Baas AF, Buth J, Prinssen M, Verhoeven EL, Cuypers PW, et al; DREAM Study Group. Long-term outcome of open or endovascular repair of abdominal aortic aneurysm. N Engl J Med. 2010;362:1881–9. [PMID: 20484396] doi:10.1056/NEJMoa0909499

Erbel R, Aboyans V, Boileau C, Bossone E, Bartolomeo RD, Eggebrecht H, et al; ESC Committee for Practice Guidelines. 2014 ESC guidelines on the diagnosis and treatment of aortic diseases: document covering acute and chronic aortic diseases of the thoracic and abdominal aorta of the adult. The Task Force for the Diagnosis and Treatment of Aortic Diseases of the European Society of Cardiology (ESC). Eur Heart J. 2014;35:2873–926. [PMID: 25173340] doi:10.1093/eurheartj/ehu281

Freeman LA, Young PM, Foley TA, Williamson EE, Bruce CJ, Greason KL. CT and MRI assessment of the aortic root and ascending aorta. AJR Am J Roentgenol. 2013;200:W581–92. [PMID: 23701088] doi:10.2214/AJR.12.9531

Greenhalgh RM, Brown LC, Powell JT, Thompson SG, Epstein D, Sculpher MJ; United Kingdom EVAR Trial Investigators. Endovascular versus open repair of abdominal aortic aneurysm. N Engl J Med. 2010;362:1863–71. [PMID: 20382983] doi:10.1056/NEJMoa0909305

Hiratzka LF, Bakris GL, Beckman JA, Bersin RM, Carr VF, Casey DE Jr, et al; American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. 2010 ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM guidelines for the diagnosis and management of patients with thoracic aortic disease. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, American Association for Thoracic Surgery, American College of Radiology,American Stroke Association, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of Thoracic Surgeons, and Society for Vascular Medicine. J Am Coll Cardiol. 2010;55:e27–e129. [PMID: 20359588] doi:10.1016/j.jacc.2010.02.015

Rogers IS, Massaro JM, Truong QA, Mahabadi AA, Kriegel MF, Fox CS, et al. Distribution, determinants, and normal reference values of thoracic and abdominal aortic diameters by computed tomography (from the Framingham Heart Study). Am J Cardiol. 2013;111:1510–6. [PMID: 23497775] doi:10.1016/j.amjcard.2013.01.306

Peripheral Artery Disease

Aboyans V, Criqui MH, Abraham P, Allison MA, Creager MA, Diehm C, et al; American Heart Association Council on Peripheral Vascular Disease. Measurement and interpretation of the ankle-brachial index: a scientific statement from the American Heart Association. Circulation. 2012;126:2890–909. [PMID: 23159553] doi:10.1161/CIR.0b013e318276fbcb

Bonaca MP, Bhatt DL, Storey RF, Steg PG, Cohen M, Kuder J, et al. Ticagrelor for prevention of ischemic events after myocardial infarction in patients with peripheral artery disease. J Am Coll Cardiol. 2016;67:2719–2728. [PMID: 27046162] doi:10.1016/j.jacc.2016.03.524

Creager MA, Kaufman JA, Conte MS. Clinical practice. Acute limb ischemia. N Engl J Med. 2012;366:2198–206. [PMID: 22670905] doi:10.1056/NEJMcp1006054

Gerhard-Herman MD, Gornik HL, Barrett C, Barshes NR, Corriere MA, Drachman DE, et al. 2016 AHA/ACC guideline on the management of patients with lower extremity peripheral artery disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2017;135:e726–e779. [PMID: 27840333] doi:10.1161/CIR.0000000000000471

Morrow DA, Braunwald E, Bonaca MP, Ameriso SF, Dalby AJ, Fish MP, et al; TRA 2P–TIMI 50 Steering Committee and Investigators. Vorapaxar in the secondary prevention of atherothrombotic events. N Engl J Med. 2012;366:1404–13. [PMID: 22443427] doi:10.1056/NEJMoa1200933

Patel MR, Conte MS, Cutlip DE, Dib N, Geraghty P, Gray W, et al. Evaluation and treatment of patients with lower extremity peripheral artery disease: consensus definitions from Peripheral Academic Research Consortium (PARC). J Am Coll Cardiol. 2015;65:931–41. [PMID: 25744011] doi:10.1016/j.jacc.2014.12.036

Whelton PK, Carey RM, Aronow WS, Casey DE Jr, Collins KJ, Dennison Himmelfarb C, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2017. [PMID: 29146535] doi:10.1016/j.jacc.2017.11.006

Cardiovascular Disease in Cancer Survivors

Armenian SH, Lacchetti C, Lenihan D. Prevention and monitoring of cardiac dysfunction in survivors of adult cancers: American Society of Clinical Oncology clinical practice guideline summary. J Oncol Pract. 2017;13:270–275. [PMID: 27922796] doi:10.1200/JOP.2016.018770

Groarke JD, Nguyen PL, Nohria A, Ferrari R, Cheng S, Moslehi J. Cardiovascular complications of radiation therapy for thoracic malignancies: the role for non-invasive imaging for detection of cardiovascular disease. Eur Heart J. 2014;35:612–23. [PMID: 23666251] doi:10.1093/eurheartj/eht114

Hall PS, Harshman LC, Srinivas S, Witteles RM. The frequency and severity of cardiovascular toxicity from targeted therapy in advanced renal cell carcinoma patients. JACC Heart Fail. 2013;1:72–8. [PMID: 24621801] doi:10.1016/j.jchf.2012.09.001

Jaworski C, Mariani JA, Wheeler G, Kaye DM. Cardiac complications of thoracic irradiation. J Am Coll Cardiol. 2013;61:2319–28. [PMID: 23583253] doi:10.1016/j.jacc.2013.01.090

Kongbundansuk S, Hundley WG. Noninvasive imaging of cardiovascular injury related to the treatment of cancer. JACC Cardiovasc Imaging. 2014;7:824–38. [PMID: 25124015] doi:10.1016/j.jcmg.2014.06.007

Lipshultz SE, Rifai N, Dalton VM, Levy DE, Silverman LB, Lipsitz SR, et al. The effect of dexrazoxane on myocardial injury in doxorubicin-treated children with acute lymphoblastic leukemia. N Engl J Med. 2004;351:145–53. [PMID: 15247354]

Mehta LS, Watson KE, Barac A, Beckie TM, Bittner V, Cruz-Flores S, et al; American Heart Association Cardiovascular Disease in Women and Special Populations Committee of the Council on Clinical Cardiology; Council on Cardiovascular and Stroke Nursing; and Council on Quality of Care and Outcomes Research. Cardiovascular disease and breast cancer: where these entities intersect: a scientific statement from the American Heart Association. Circulation. 2018 Feb 1. [Epub ahead of print] [PMID: 29437116] doi: 10.1161/CIR.0000000000000556

Yeh ET, Bickford CL. Cardiovascular complications of cancer therapy: incidence, pathogenesis, diagnosis, and management. J Am Coll Cardiol. 2009;53:2231–47. [PMID: 19520246] doi:10.1016/j.jacc.2009.02.050

Pregnancy and Cardiovascular Disease

Arany Z, Elkayam U. Peripartum cardiomyopathy. Circulation. 2016;133:1397–409. [PMID: 27045128] doi:10.1161/CIRCULATIONAHA.115.020491

Drenthen W, Boersma E, Balci A, Moons P, Roos-Hesselink JW, Mulder BJ, et al; ZAHARA Investigators. Predictors of pregnancy complications in women with congenital heart disease. Eur Heart J. 2010;31:2124–32. [PMID: 20584777] doi:10.1093/eurheartj/ehq200

McNamara DM, Elkayam U, Alharethi R, Damp J, Hsich E, Ewald G, et al; IPAC Investigators. Clinical outcomes for peripartum cardiomyopathy in North America: results of the IPAC Study (Investigations of Pregnancy Associated Cardiomyopathy). J Am Coll Cardiol. 2015;66:905–14. [PMID: 26293760] doi:10.1016/j.jacc.2015.06.1309

Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP 3rd, Guyton RA, et al; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2014;63:2438–88. [PMID: 24603192] doi:10.1016/j.jacc.2014.02.537

Regitz-Zagrosek V, Blomstrom Lundqvist C, Borghi C, Cifkova R, Ferreira R, Foidart JM, et al; European Society of Gynecology (ESG). ESC Guidelines on the management of cardiovascular diseases during pregnancy: the Task Force on the Management of Cardiovascular Diseases during Pregnancy of the European Society of Cardiology (ESC). Eur Heart J. 2011;32:3147–97. [PMID: 21873418] doi:10.1093/eurheartj/ehr218

Tweet MS, Gulati R, Hayes SN. Spontaneous coronary artery dissection. Curr Cardiol Rep. 2016;18:60. [PMID: 27216840] doi:10.1007/s11886-016-0737-6

van Hagen IM, Roos-Hesselink JW, Ruys TP, Merz WM, Goland S, Gabriel H, et al; ROPAC Investigators and the EURObservational Research Programme (EORP) Team*. Pregnancy in women with a mechanical heart valve: data of the European Society of Cardiology Registry of Pregnancy and Cardiac Disease (ROPAC). Circulation. 2015;132:132-42. [PMID: 26100109] doi:10.1161/CIRCULATIONAHA.115.015242

Cardiovascular Medicine Self-Assessment Test

This self-assessment test contains one-best-answer multiple-choice questions. Please read these directions carefully before answering the questions. Answers, critiques, and bibliographies immediately follow these multiple-choice questions. The American College of Physicians (ACP) is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

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Successful completion of the CME activity, which includes participation in the evaluation component, enables the participant to earn up to 30 medical knowledge MOC points in the American Board of Internal Medicine's Maintenance of Certification (MOC) program. It is the CME activity provider's responsibility to submit participant completion information to ACCME for the purpose of granting MOC credit.

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CME credits and MOC points are available from the publication date of July 31, 2018, until July 31, 2021. You may submit your answer sheet or enter your answers online at any time during this period.

Directions

*Each of the numbered items is followed by lettered answers. Select the **ONE** lettered answer that is **BEST** in each case.*

Item 1

A 19-year-old man is evaluated in the emergency department for a 2-week history of abdominal pain and exertional dyspnea. He underwent cardiac transplantation 10 months ago for viral myocarditis. Medications are tacrolimus, prednisone, mycophenolate mofetil, valganciclovir, trimethoprim-sulfamethoxazole, valsartan, calcium-vitamin D supplement, and low-dose aspirin.

On physical examination, vital signs are normal. Neck examination reveals occasional jugular cannon *a* waves with no venous distention. Cardiac examination is significant for an S_3. The remainder of the examination is normal.

An electrocardiogram is shown.

Which of the following tests will most likely establish the diagnosis?

(A) Abdominal CT
(B) Coronary angiography
(C) Echocardiography
(D) Endomyocardial biopsy

Item 2

A 69-year-old man is evaluated in the hospital for four episodes of chest pain at rest in the past 24 hours. Medical history is significant for hyperlipidemia, hypertension, tobacco use, and previous transient ischemic attack. Medications are aspirin, hydrochlorothiazide, atorvastatin, and ramipril.

On physical examination, vital signs are normal. The remainder of the examination is unremarkable.

Laboratory studies are notable for normal serum troponin levels.

An electrocardiogram demonstrates 2-mm ST-segment depressions in leads V_4 through V_6.

Metoprolol, nitrates, clopidogrel, and heparin are initiated.

Which of the following is the most appropriate management?

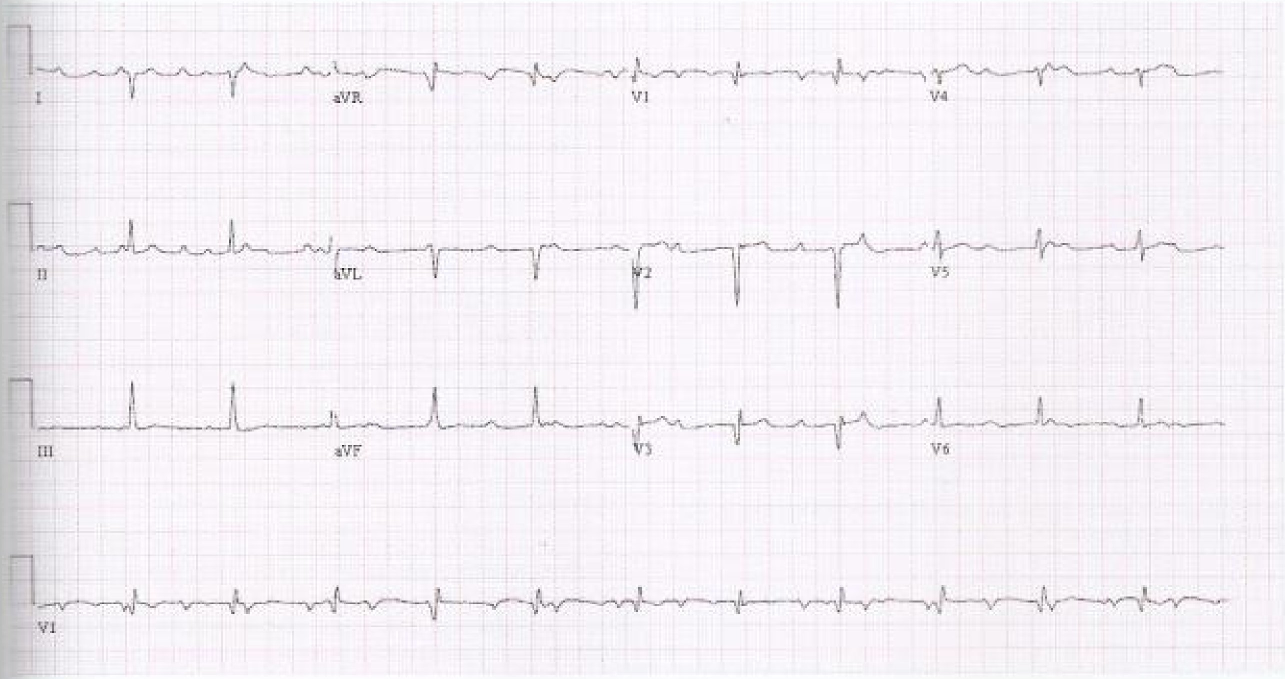
(A) Adenosine nuclear stress testing
(B) Coronary CT angiography
(C) Exercise stress electrocardiography
(D) Urgent angiography

Item 3

A 65-year-old woman is evaluated during a routine examination. She was diagnosed with a cardiac murmur in early adulthood. She is active, healthy, and without symptoms. She takes no medications.

On physical examination, vital signs are normal. A grade 3/6 holosystolic murmur preceded by multiple clicks is present at the apex. Physical findings are otherwise unremarkable.

An echocardiogram demonstrates a left ventricular ejection fraction of 50%. The left ventricle is moderately dilated with an end-systolic dimension of 42 mm. Myxomatous



ITEM 1

degeneration of the mitral valve is present with severe regurgitation due to posterior leaflet prolapse.

Which of the following is the most appropriate next step in management?

(A) Serial clinical and echocardiographic evaluations
(B) Surgical mitral valve repair
(C) Surgical mitral valve replacement
(D) Transcatheter mitral valve repair

Item 4

A 60-year-old woman is evaluated for new onset hypertension. Medical history is significant for metastatic cervical cancer for which she began chemotherapy 2 months ago. She has no history of hypertension. Medications are bevacizumab, cisplatin, paclitaxel, dexamethasone, promethazine, and ranitidine.

On physical examination, temperature is normal, blood pressure is 172/106 mm Hg, pulse rate is 82/min, and respiration rate is 18/min. The remainder of the examination is unremarkable.

Which of the following medications is the most likely cause of this patient's hypertension?

(A) Bevacizumab
(B) Cisplatin
(C) Dexamethasone
(D) Paclitaxel

Item 5

A 52-year-old woman is evaluated in the emergency department for progressive dyspnea. Medical history is notable for aortic stenosis and long-standing hypertension. Family history is unremarkable. Medications are metoprolol and chlorthalidone.

On physical examination, temperature is normal, blood pressure is 190/90 mm Hg in both upper extremities, pulse rate is 80/min and regular, and respiration rate is 22/min. The jugular venous pressure is normal. The apical impulse is displaced and sustained. The S_1 is normal, and the S_2 is soft; an S_4 is noted at the apex. An ejection click is heard at the apex and left sternal border. A systolic ejection murmur is noted along the right sternal border, and a separate systolic murmur is noted under the left clavicle and over the left posterior chest. The femoral pulses are diminished, and the radial artery–to–femoral artery pulse is delayed. No bruits are appreciated in the epigastrium or over the femoral vessels.

A chest radiograph is shown (see top of next column).

In addition to aortic stenosis, which of the following is the most likely diagnosis?

(A) Ascending aortic dissection
(B) Coarctation of the aorta
(C) Essential hypertension
(D) Renovascular hypertension

ITEM 5

Item 6

A 64-year-old man is evaluated in the emergency department for acute right lower leg pain that began 2 days ago. The pain is now severe at rest, and he reports coolness of the right foot. He has a 3-year history of intermittent claudication. He underwent right femoral-popliteal bypass graft surgery for life-limiting claudication 1 year ago. Medical history is otherwise significant for hypertension, hyperlipidemia, and type 2 diabetes mellitus. He quit smoking 4 years ago. Medications are low-dose aspirin, ramipril, hydrochlorothiazide, rosuvastatin, and metformin.

On physical examination, vital signs are normal. The right foot is cool and pale, sensation is intact, and muscle strength is normal. The pedal pulses are not palpable in the right leg. Arterial Doppler ultrasound signals are not detectable over the right dorsalis pedis and right posterior tibial arteries.

Intravenous anticoagulation with heparin is initiated.

Which of the following is the most appropriate management?

(A) Arterial duplex ultrasonography
(B) CT angiography
(C) Emergent right leg amputation
(D) Intravenous recombinant tissue plasminogen activator
(E) Urgent invasive angiography

Item 7

A 75-year-old woman is evaluated during a routine visit. Medical history is significant for hypertension and coronary artery disease with placement of a stent in the mid right coronary artery 5 years ago. She is symptom free. Medications are metoprolol succinate, lisinopril, aspirin, and atorvastatin.

On physical examination, temperature is normal, blood pressure is 130/80 mm Hg, pulse rate is 72/min, and respiration rate is 16/min. BMI is 23. The precordial cadence is irregularly irregular. The remainder of the examination is unremarkable.

An electrocardiogram shows atrial fibrillation.

Which of the following is the most appropriate treatment?

(A) Add clopidogrel
(B) Add oral anticoagulation
(C) Discontinue aspirin and begin clopidogrel and oral anticoagulation
(D) Discontinue aspirin and begin oral anticoagulation
(E) No change in therapy

Item 8

A 55-year-old man is evaluated for chest discomfort of several months' duration. He describes the pain as sporadic left-sided chest heaviness that lasts for several minutes. His chest discomfort is generally but not consistently induced by exercise and is often but not always relieved with rest. He has some associated shortness of breath but no other symptoms. He remains active despite the pain and is able to walk without limitations. Medical history is significant for hypertension treated with amlodipine and hydrochlorothiazide.

On physical examination, vital signs and the remainder of the physical examination are normal.

An electrocardiogram is shown.

Which of the following is the most appropriate management?

(A) Coronary angiography
(B) Coronary artery calcium scoring
(C) Exercise stress echocardiography
(D) Exercise stress electrocardiography
(E) Pharmacologic nuclear stress testing

Item 9

A 48-year-old man is hospitalized for a 6-week history of progressive fatigue, dyspnea on exertion, and vague chest "fullness." He has also had pedal edema for the past 2 weeks. He has no history of incarceration or recent travel and is not immunocompromised.

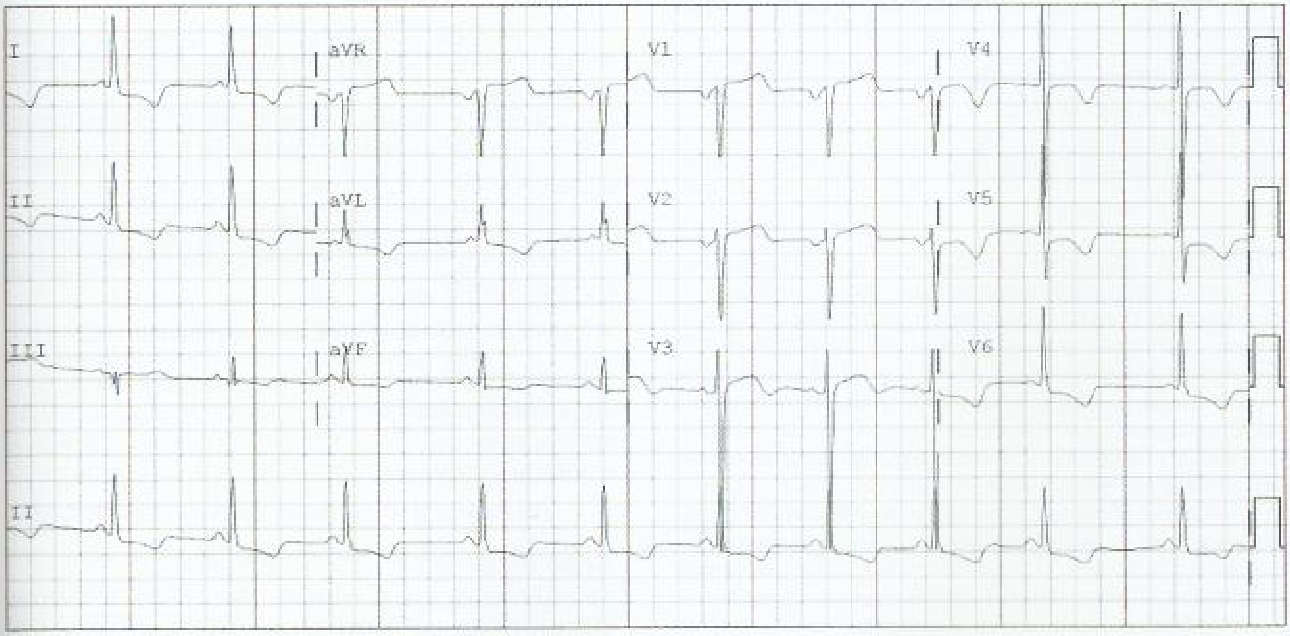
On physical examination, temperature is 37.5 °C (99.5 °F), blood pressure is 132/76 mm Hg with pulsus paradoxus of 16 mm Hg, pulse rate is 100/min, and respiration rate is 16/min. The jugular veins are distended to the angle of the mandible. The lungs are clear to auscultation. No diastolic sound or pericardial friction rub is noted. Hepatomegaly is present. Pitting edema is noted bilaterally at the ankles.

Laboratory studies:

Erythrocyte sedimentation rate	86 mm/h
Leukocyte count	11,000/µL (11×10^9/L) with normal differential
Fourth-generation HIV test	Negative
Antinuclear antibodies	Negative
Interferon-γ release assay	Negative

An electrocardiogram shows sinus tachycardia with a nonspecific ST-T–wave abnormality. A chest radiograph reveals an enlarged cardiac silhouette without pericardial calcification. An echocardiogram shows a moderately sized pericardial effusion. There are diastolic right atrial inversion and a 30% inspiratory reduction in mitral inflow velocity.

Pericardiocentesis reveals an intrapericardial pressure of 16 mm Hg before drainage and 0 to 1 mm Hg after drainage. The right atrial mean pressure and left ventricular end-diastolic pressures before drainage were each 16 mm Hg.



ITEM 8

After pericardiocentesis, there is no change in the intracardiac pressure readings. Pericardial fluid is negative for adenosine deaminase.

Which of the following is the most appropriate management?

(A) Ibuprofen and colchicine
(B) Isoniazid, rifampin, pyrazinamide, and ethambutol
(C) Pericardiectomy
(D) Surgical pericardial window

Item 10

An 80-year-old woman is evaluated for a 6-month history of worsening exertional dyspnea. Two nights ago, she awoke with sudden onset dyspnea that was relieved with ambulation. She has not had chest pain. Medical history is significant for myocardial infarction 8 years ago. She also has a history of left ventricular dysfunction but has been previously well compensated. Her medications are lisinopril, aspirin, metoprolol, and rosuvastatin.

On physical examination, temperature is normal, blood pressure is 95/60 mm Hg, pulse rate is 56/min, and respiration rate is 18/min. The lungs are clear. The carotid upstroke is low in volume. The apical impulse is laterally displaced and enlarged. S_1 is soft; the aortic component of S_2 is diminished. There is no S_3 or S_4. A grade 2/6 mid-peaking systolic murmur is heard throughout the precordium. The remainder of the examination is normal.

An echocardiogram demonstrates a left ventricular ejection fraction of 32%. The aortic valve is slightly calcified. The stroke volume is markedly decreased (23 mL/m²). The mean aortic gradient is 20 mm Hg (consistent with mild to moderate stenosis), and the aortic valve area is calculated to be 0.7 cm² (consistent with severe stenosis).

Which of the following is the most appropriate next step in management?

(A) Aortic valve replacement
(B) Coronary angiography
(C) Dobutamine echocardiography
(D) Switch lisinopril to valsartan-sacubitril

H Item 11

A 75-year-old woman is hospitalized for a 3-week history of progressive exertional dyspnea, increasing peripheral edema, and mental status changes. For the past 4 nights, she has been sleeping in a recliner instead of her bed. She reports no chest pain. She has a 6-year history of ischemic cardiomyopathy, for which she takes low-dose aspirin, furosemide, carvedilol, lisinopril, digoxin, spironolactone, and as-needed metolazone.

On physical examination, the patient is afebrile, blood pressure is 84/52 mm Hg, pulse rate is 118/min, and respiration rate is 28/min. Oxygen saturation is 95% breathing ambient air. She is confused. Jugular venous distention is present. Cardiac examination reveals an S_3. There is ascites on abdominal examination. The extremities are cool, and there is lower extremity edema to the knees.

Laboratory studies:

Alanine aminotransferase	172 U/L
Aspartate aminotransferase	163 U/L
Creatinine	2.9 mg/dL (256.4 µmol/L) (baseline, 1.2 mg/dL [106.1 µmol/L])
Potassium	4.7 mEq/L (4.7 mmol/L)
Sodium	132 mEq/L (132 mmol/L) (baseline, 140 mEq/L [140 mmol/L])
Digoxin	0.3 ng/mL (0.38 nmol/L) (normal range, 0.5-2.0 ng/mL [0.64-2.56 nmol/L])

An electrocardiogram shows no acute changes. An echocardiogram shows a left ventricular ejection fraction of 20%.

Which of the following is the most appropriate initial treatment?

(A) Increase carvedilol
(B) Increase digoxin
(C) Increase lisinopril
(D) Start dobutamine

Item 12

A 78-year-old man is evaluated for palpitations, worsening fatigue, and exercise intolerance. Two months ago, he was diagnosed with atrial flutter and subsequently underwent cardioversion to normal sinus rhythm. Ambulatory electrocardiographic monitoring following cardioversion demonstrated recurrent atrial flutter with an average ventricular rate of 69/min. Medical history is significant for hypertension and coronary artery disease. Medications are warfarin, metoprolol, lisinopril, low-dose aspirin, and atorvastatin.

On physical examination, pulse rate is 73/min and irregular. Other vital signs and findings on physical examination are normal.

Laboratory studies are significant for normal serum thyroid-stimulating hormone and serum N-terminal B-type natriuretic peptide levels.

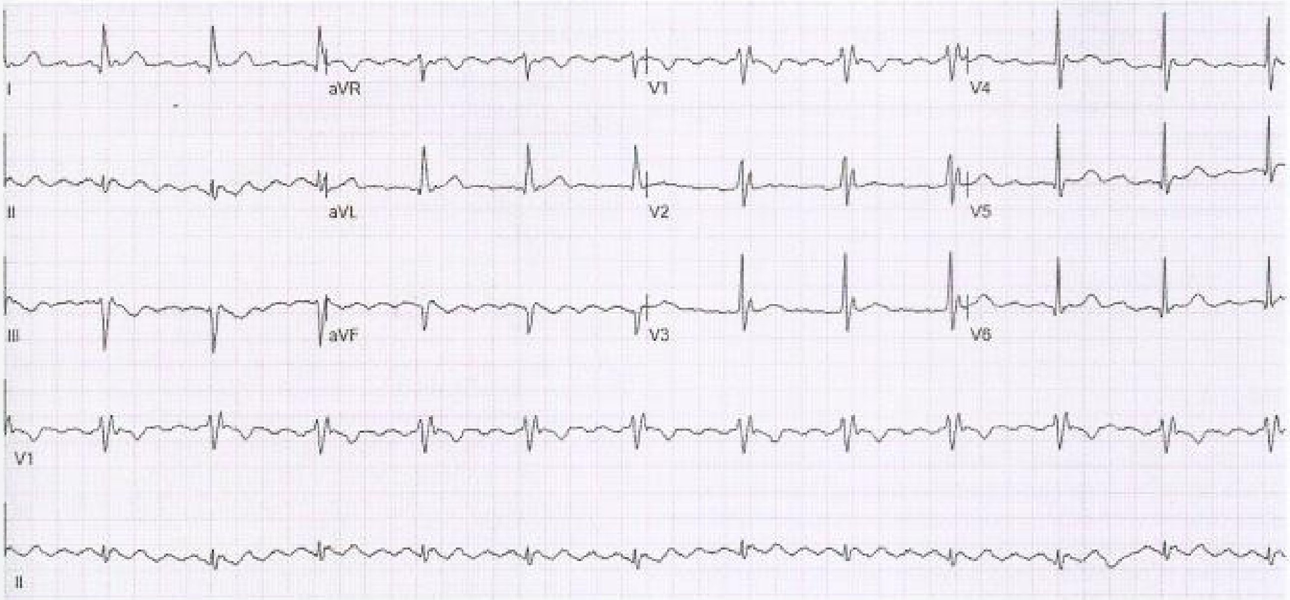
An electrocardiogram is shown (see top of next page). A stress echocardiogram demonstrates normal wall motion at rest and during stress. The left ventricular ejection fraction is greater than 55%.

Which of the following is the most appropriate treatment?

(A) Amiodarone
(B) Cardiac catheterization
(C) Cardioversion
(D) Catheter ablation

Item 13

An 18-year-old man is evaluated for a murmur detected during a college sports physical examination. He reports no symptoms and has no history of cardiac disease. He takes no medications.



ITEM 12

On physical examination, vital signs are normal. He has a normal central venous pressure, waveform, precordial palpation, and S_1. A continuous murmur is heard beneath the left clavicle that envelops the S_2. The remainder of the examination is unremarkable.

Which of the following is the most likely cause of this patient's murmur?

(A) Bicuspid aortic valve with aortic regurgitation
(B) Patent ductus arteriosus
(C) Pulmonary regurgitation
(D) Ventricular septal defect

Item 14

A 48-year-old woman is evaluated for exertional substernal chest pain of several weeks' duration. The chest pain consistently subsides with rest. Medical history is significant for episodic migraine. She has no history of hypertension, hyperlipidemia, or other medical problems. She is a nonsmoker. She takes no medications other than naproxen as needed.

On physical examination, vital signs are normal. Oxygen saturation is 98% breathing ambient air. The remainder of the examination is unremarkable.

An electrocardiogram demonstrates baseline 1.5-mm lateral ST-segment depressions. Nuclear stress testing reveals a mild anterior wall perfusion defect, and a subsequent coronary angiogram demonstrates normal coronary arteries.

Which of the following is the most likely diagnosis?

(A) Acute coronary syndrome with spontaneous recanalization
(B) Cardiac syndrome X
(C) Somatic symptom disorder
(D) Takotsubo cardiomyopathy

Item 15

A 56-year-old woman is evaluated for a 6-month history of progressive left calf discomfort. Her symptoms begin as calf tightness after vigorous walking for two blocks, and discomfort causes her to stop walking after four blocks. The symptoms subside after 5 minutes of rest. She reports no rest pain. Medical history is significant for hypertension and hyperlipidemia. She has a 50-pack-year smoking history, but she quit smoking 6 months ago. Medications are low-dose aspirin, amlodipine, cilostazol, high-intensity rosuvastatin, and losartan.

On physical examination, vital signs are normal. Femoral and popliteal pulses are diminished bilaterally. Pedal pulses are not palpable in the left leg. No skin ulceration is noted. The remainder of the examination is unremarkable.

The ankle-brachial index is 0.68 on the left and 0.86 on the right.

Which of the following is the most appropriate management?

(A) Add clopidogrel
(B) Initiate a supervised exercise program
(C) Obtain a magnetic resonance angiogram
(D) Refer for vascular surgery

Item 16

A 69-year-old man is evaluated during a routine examination. He is asymptomatic. Medical history is significant for hypertension. He has a 50-pack-year smoking history but quit smoking 7 years ago. Medications are aspirin, lisinopril, and amlodipine.

On physical examination, vital signs are normal. A bruit is heard over the abdomen, and a pulsatile mass is present in the epigastrium. The remainder of the examination is unremarkable.

A Duplex ultrasound of the abdomen shows an abdominal aortic aneurysm with transverse diameter of 6.2 cm.

Which of the following is the most appropriate next step in management?

(A) CT angiography of the abdominal aorta and iliac vessels
(B) Endovascular repair
(C) Open surgical repair
(D) Switch amlodipine to metoprolol

Item 17

A 52-year-old man is evaluated during a visit to establish care. He is asymptomatic, but he is seeking advice on how to modify his risk for cardiovascular disease. He drinks one glass of wine with dinner most nights, and he quit smoking 12 years ago. Family history is significant for a myocardial infarction in his father at age 61 years. He takes no medications. The patient is Hispanic.

On physical examination, temperature is normal, blood pressure is 128/76 mm Hg, and pulse rate is 74/min. BMI is 28. The remainder of the physical examination is unremarkable.

Laboratory studies:

Total cholesterol	200 mg/dL (5.18 mmol/L)
HDL cholesterol	30 mg/dL (0.78 mmol/L)
LDL cholesterol	130 mg/dL (3.37 mmol/L)
Triglycerides	200 mg/dL (2.26 mmol/L)

Which of the following risk factors most increases this patient's risk for cardiovascular disease?

(A) Alcohol use
(B) Ethnicity
(C) Family history
(D) Hyperlipidemia
(E) Smoking history

Item 18

A 67 year old man is evaluated during a follow up visit. Medical history is significant for a 7-year history of heart failure with placement of an implantable cardioverter defibrillator 6 years ago. He has New York Heart Association functional class II symptoms and is currently stable. Since his last visit 6 months ago, he has had no changes in medications, symptoms, or other medical issues. Medications are valsartan-sacubitril, carvedilol, furosemide, and spironolactone.

On physical examination, the patient is afebrile, blood pressure is 108/74 mm Hg, and pulse rate is 64/min. He has no jugular venous distention or S_3. No edema is noted.

An echocardiogram obtained 1 year ago demonstrated a left ventricular ejection fraction of 25% and left ventricular end-diastolic diameter of 6.7 cm; these findings are unchanged from 2 years ago.

Heart failure education and the need for diet and medication adherence are reinforced.

Which of the following is the most appropriate testing to perform at this visit?

(A) Echocardiography
(B) 24-Hour ambulatory electrocardiographic monitoring
(C) Serum B-type natriuretic peptide level measurement
(D) Serum electrolyte measurement and kidney function studies

Item 19

A 25-year-old woman is evaluated for intermittent palpitations associated with occasional episodes of shortness of breath and lightheadedness. These episodes last from 30 to 90 minutes. Medical history is notable for a similar episode of symptoms during college that required an emergency department visit; supraventricular tachycardia was diagnosed. She takes no medications.

On physical examination, vital signs are normal. Cardiac examination is normal. The remainder of the physical examination is unremarkable.

A 12-lead electrocardiogram is shown (see top of next page). A resting echocardiogram demonstrates normal left ventricular ejection fraction and a structurally normal heart.

Which of the following is the most appropriate next step in management?

(A) Atenolol
(B) Electrophysiology study
(C) Flecainide
(D) Verapamil

Item 20

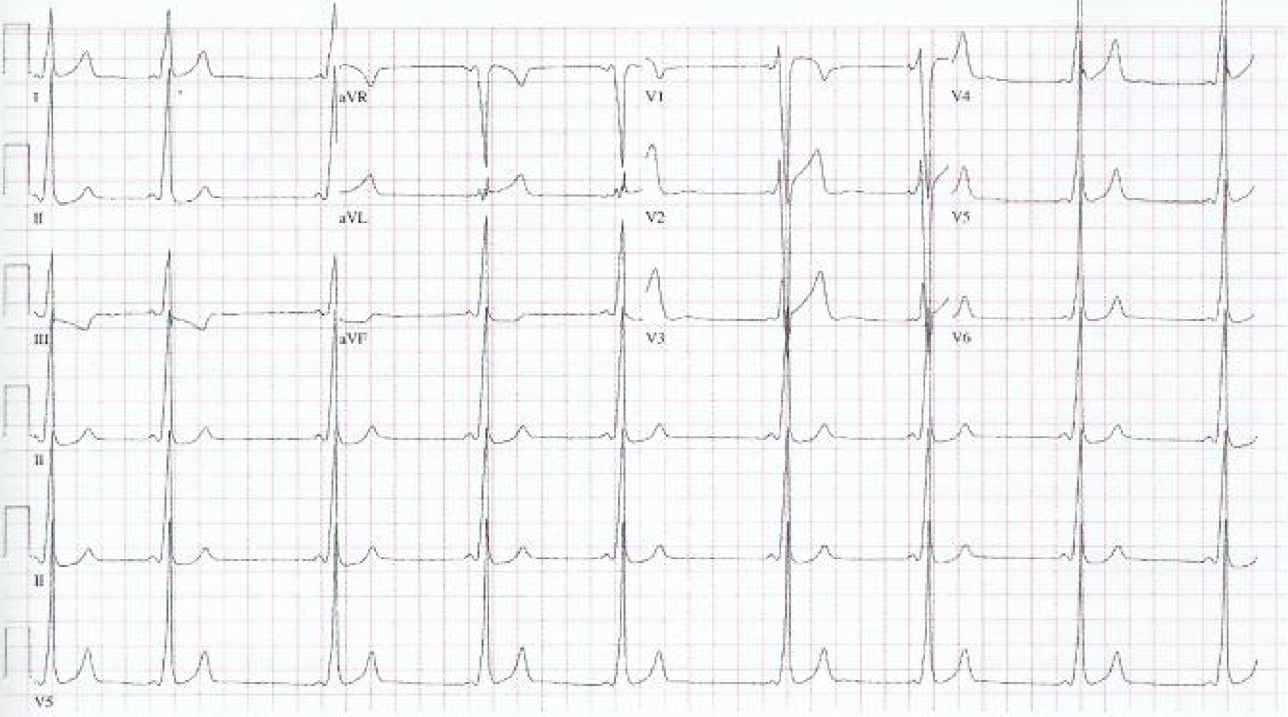
A 26 year old woman is evaluated for a preconception assessment. She has Marfan syndrome. She reports no cardiovascular symptoms. Her only medication is long-acting metoprolol.

On physical examination, blood pressure is 110/60 mm Hg, and pulse rate is 60/min and regular. The patient has facial and skeletal features of Marfan syndrome. The estimated central venous pressure is normal. Cardiac examination reveals a normal apical impulse, normal S_1 and S_2, and a grade 2/6 late-peaking systolic murmur and midsystolic click over the apex. The lungs are clear to auscultation. No edema is noted.

Transthoracic echocardiogram demonstrates a dilated proximal ascending aorta with a dimension of 4.6 cm. No aortic regurgitation is appreciated. Bileaflet mitral valve prolapse is noted with mild mitral regurgitation. The left ventricular size and function are normal. There is no recent echocardiogram for comparison.

Which of the following is the most appropriate management?

(A) Advise against pregnancy
(B) Proceed with mitral valve intervention
(C) Repeat echocardiography in 12 months
(D) Switch metoprolol to losartan



ITEM 19

Item 21

A 62-year-old man is evaluated in the emergency department for a 3-hour history of transient right arm and right leg weakness. His symptoms resolve while in the emergency department. Medical history is otherwise unremarkable, and he takes no medications.

On physical examination, vital signs are normal, and the remainder of the examination is unremarkable.

Laboratory studies are notable for an erythrocyte sedimentation rate of 16 mm/h and LDL cholesterol level of 70 mg/dL (1.81 mmol/L).

A 12-lead electrocardiogram is normal. Carotid duplex ultrasound shows no evidence of hemodynamically significant plaque. CT of the head without contrast demonstrates no evidence of hemorrhage. MRI of the brain reveals a small left internal capsular infarction. A transesophageal echocardiogram is obtained. Representative mid-esophageal four-chamber images at end systole (*top panel*) and end diastole (*bottom panel*) are shown.

Which of the following is the most likely diagnosis?

(A) Bacterial endocarditis
(B) Left atrial myxoma
(C) Nonbacterial thrombotic endocarditis
(D) Papillary fibroelastoma

ITEM 21

Item 22

A 47-year-old woman is evaluated for recent fatigue and dyspnea. She underwent an abdominal hysterectomy for

recurrent severe menorrhagia 3 weeks ago and has had persistent fatigue and exertional dyspnea since the procedure. She has no other symptoms. Medical history is significant for Eisenmenger syndrome related to a ventricular septal defect. Medications are sildenafil and bosentan.

On physical examination, temperature is normal, blood pressure is 98/60 mm Hg, pulse rate is 80/min and regular, and respiration rate is 20/min. The estimated central venous pressure is elevated with a prominent *a* wave. The apical impulse is normal, and a prominent parasternal impulse is noted at the left sternal border. The S_1 is normal, and the S_2 is loud. Digital clubbing and central cyanosis are noted. The abdominal wound is healing well.

Laboratory testing reveals a hemoglobin level of 10.2 g/dL (102 g/L). The hemoglobin level was 15 g/dL (150 g/L) before hysterectomy. One year ago, the hemoglobin level was 18.5 g/dL (185 g/L).

Which of the following is the most appropriate management?

(A) Erythropoietin
(B) Heart-lung transplantation
(C) Intravenous epoprostenol
(D) Short-course iron therapy

H

Item 23

A 48-year-old man is evaluated in the emergency department for epigastric discomfort and nausea that began 45 minutes ago. Medical history is significant for hypertension, tobacco use, and hyperlipidemia. His only medication is atorvastatin.

On physical examination, temperature is normal, blood pressure is 110/60 mm Hg, pulse rate is 90/min, and respiration rate is 18/min. Oxygen saturation is 98% breathing ambient air. The remainder of the physical examination is unremarkable.

Laboratory studies are notable for an elevated initial serum troponin I level.

An electrocardiogram shows 3-mm ST-segment elevations in leads II, III, and aVF. A chest radiograph is normal.

The patient is administered aspirin, clopidogrel, and a bolus of heparin. Transport to the nearest hospital capable of percutaneous coronary intervention would take 4 hours.

Which of the following is the most appropriate management?

(A) Fondaparinux and ticagrelor
(B) Full-dose reteplase
(C) Half-dose reteplase with abciximab
(D) Immediate transfer for primary percutaneous coronary intervention
(E) Nitroprusside

Item 24

A 72-year-old man is evaluated for exertional left calf and foot pain. Three weeks ago, the patient developed an ulcer on the medial aspect of the left great toe. His medical history is significant for coronary artery disease, type 2 diabetes mellitus, hypertension, and hyperlipidemia. Medications are low-dose aspirin, lisinopril, metoprolol, metformin, and atorvastatin.

On physical examination, blood pressure is 155/84 mm; other vital signs are normal. There are no palpable pulses in the left leg. Right femoral, popliteal, and pedal pulses are faint.

Ankle-brachial index testing:

Right systolic brachial pressure	155 mm Hg
Left systolic brachial pressure	145 mm Hg
Left posterior tibialis pressure	255 mm Hg
Left dorsalis pedis pressure	255 mm Hg

Which of the following is the most appropriate diagnostic test to perform next?

(A) Exercise ankle-brachial index
(B) Lower extremity CT angiography
(C) Toe-brachial index
(D) Venous duplex ultrasonography

Item 25

H

A 33-year-old woman was hospitalized 8 days ago for fever and severe dyspnea. Her current symptoms began 1 month ago with chills, malaise, and low-grade fever. She was diagnosed 5 years ago with a bicuspid aortic valve with regurgitation but had been healthy otherwise. On admission, an echocardiogram demonstrated a 12-mm vegetation involving the aortic valve with severe regurgitation and preserved left ventricular function. Blood cultures grew *Staphylococcus aureus* that was sensitive to oxacillin. After 8 days of intravenous antimicrobial therapy, she has continued to be febrile, and her dyspnea has progressed such that she has symptoms at rest.

On physical examination, temperature is 38.1 °C (100.6 °F), blood pressure is 110/60 mm Hg, pulse rate is 96/min, and respiration rate is 23/min. Lung examination demonstrates bilateral crackles. The estimated central venous pressure is 10 cm H_2O. There is a grade 3/6 diastolic decrescendo murmur along the left sternal border. An S_3 is present.

Repeat blood cultures performed yesterday continue to grow *S. aureus* sensitive to oxacillin. An echocardiogram obtained today shows findings similar to those on the initial study done at admission. A transesophageal echocardiogram confirms the valve findings without evidence of additional complications.

Which of the following is the most appropriate next step in management?

(A) Cardiac catheterization
(B) Cardiac valve surgery
(C) Intra-aortic balloon pump placement
(D) Switch oxacillin to vancomycin

Item 26

A 44-year-old man is evaluated in the office during a routine visit. Medical history is significant for HIV diagnosed at age 25 years, hypertension, and hyperlipidemia. He is a current

smoker. Medications are chlorthalidone, tenofovir-emtricitabine, and raltegravir.

On physical examination, the patient is afebrile, and blood pressure is 126/74 mm Hg. Cardiac examination reveals a regular rate and rhythm. S_1 and S_2 are normal; there is an S_4.

Laboratory tests are significant for a fasting plasma glucose level of 98 mg/dL (5.43 mmol/L), a total cholesterol level of 210 mg/dL (5.43 mmol/L), and an HDL cholesterol level of 50 mg/dL (1.29 mmol/L).

An electrocardiogram shows normal sinus rhythm and left ventricular hypertrophy with repolarization abnormalities. A chest radiograph is normal.

To determine his need for statin therapy, his estimated 10-year risk for atherosclerotic cardiovascular disease using the Pooled Cohort Equations will be calculated.

Which of the following risk factors will result in underestimation of the risk for atherosclerotic cardiovascular disease in this patient?

(A) Age
(B) Antihypertensive medication use
(C) Blood pressure
(D) HDL cholesterol level
(E) HIV status

Item 27

A 52-year-old woman is evaluated for a 6-week history of chest pressure. The symptom occurs when she walks up an incline on her daily 2-mile walk and is relieved with rest. She also had chest pressure during a stressful meeting at work last week. She reports no associated symptoms. Medical history is significant for hypertension and hyperlipidemia. Medications are hydrochlorothiazide, lisinopril, and atorvastatin.

On physical examination, vital signs and the remainder of the examination are normal.

An electrocardiogram is normal.

Which of the following is the most appropriate diagnostic test to perform next?

(A) Adenosine single-photon emission CT
(B) Coronary artery calcium scoring
(C) Exercise electrocardiography
(D) Stress echocardiography

Item 28

H

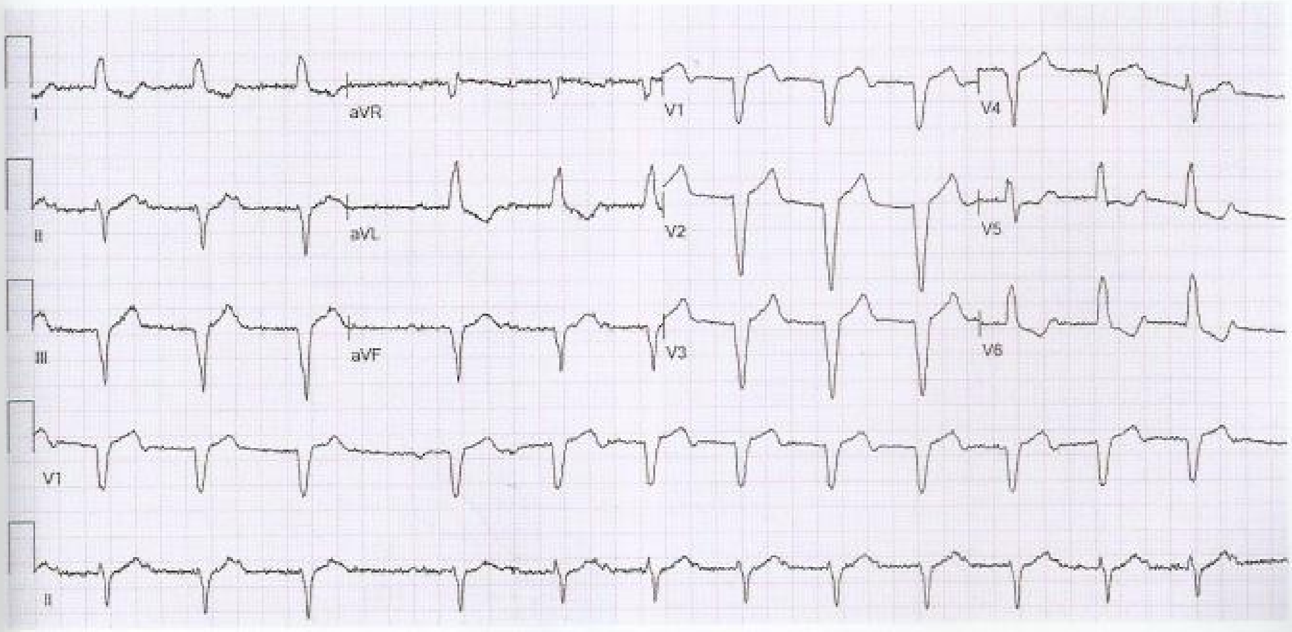
A 72-year old man is evaluated in the hospital for heart failure. In the past month, he has developed progressive dyspnea, such that he cannot walk 50 meters without stopping to catch his breath. He has a history of hypertension and ischemic cardiomyopathy. During the hospitalization, a perfusion imaging study demonstrated no ischemia, and an echocardiogram revealed a left ventricular ejection fraction of 20%. Medications are aspirin, ramipril, isosorbide mononitrate, and furosemide.

On physical examination, the patient is afebrile, blood pressure is 120/68 mm Hg, pulse rate is 73/min, and respiration rate is 22/min. The estimated central venous pressure is 9 cm H_2O. A paradoxical split S_2 and an S_4 are present. Lungs are clear to auscultation.

A 12-lead electrocardiogram is shown.

In addition to diuresis, which of the following is the most appropriate treatment before discharge?

(A) Add carvedilol
(B) Add ivabradine
(C) Cardiac resynchronization therapy
(D) Implantable cardioverter-defibrillator placement



ITEM 28

H

Item 29

A 64-year-old woman is hospitalized for progressive fatigue, dyspnea, orthopnea, and peripheral edema that have been present for the last 18 months. During this time, she has been hospitalized several times for heart failure with preserved ejection fraction. Her medical history is otherwise notable for hypertension. Her current medications are spironolactone, furosemide, and amlodipine.

On physical examination, temperature is normal, blood pressure is 136/84 mm Hg, pulse rate is 90/min, and respiration rate is 16/min. Jugular venous distention is present. Crackles are noted at the bases of both lungs. A loud S_3 is heard at the apex. A grade 2/6 holosystolic murmur is heard at the left lower sternal border and increases in intensity during inspiration. Abdominal ascites and bilateral pitting edema to the knees are present.

Laboratory studies reveal a serum ferritin level of 180 ng/mL (180 µg/L) and a B-type natriuretic peptide level of 560 pg/mL (560 ng/L). Serum protein electrophoresis and urine protein electrophoresis are unremarkable.

Right heart catheterization demonstrates diastolic equalization of pressures at 18 mm Hg. Simultaneous right and left ventricular hemodynamics demonstrate concordant rise and fall of systolic pressures with respiration. Cardiac magnetic resonance imaging with intravenous gadolinium contrast shows a pericardial thickness of 2 mm without enhancement and marked late gadolinium enhancement of the papillary muscle. Echocardiogram shows symmetric left ventricular wall thickness of 11 mm, normal left ventricular cavity size, a left ventricular ejection fraction of 55%, and severe biatrial dilatation. Right ventricular size and function are normal. Tricuspid regurgitation is noted, and the right ventricular systolic pressure is estimated at 72 mm Hg. There is no pericardial effusion.

Which of the following is the most likely diagnosis?

(A) Constrictive pericarditis
(B) Fabry disease
(C) Hemochromatosis
(D) Primary restrictive cardiomyopathy

H

Item 30

A 64-year-old woman is evaluated in the emergency department 4 hours after the abrupt onset of sharp, tearing chest and back pain. Medical history is significant for hyperlipidemia. Her only medication is atorvastatin.

On physical examination, temperature is 36.8 °C (98.2 °F), blood pressure is 173/99 mm Hg, and pulse rate is 90/min. Blood pressure measurements in both arms are equal. The remainder of the physical examination is unremarkable.

CT angiography shows a descending thoracic aortic aneurysm with a maximal diameter of 6.8 cm and aortic dissection originating just distal to the left subclavian artery and extending to just below the diaphragm; there is no involvement of the renal arteries.

Which of the following is the most appropriate initial management?

(A) Immediate endovascular stenting
(B) Immediate open surgical repair
(C) Medical therapy
(D) Repeat CT angiography in 12 hours

Item 31

H

A 58-year-old man is hospitalized for a 1-day history of worsening dyspnea and a 1-month history of increasing weight and peripheral edema. He has a long-standing history of poorly controlled hypertension and stage IV chronic kidney disease. Minoxidil and hydralazine were added to his medical regimen 2 months ago. His other medications are labetalol, a clonidine patch, and furosemide.

On physical examination, he is in distress, with increased work of breathing and diaphoresis. Temperature is normal, blood pressure is 90/60 mm Hg with pulsus paradoxus of 16 mm Hg, pulse rate is 118/min, and respiration rate is 25/min. Oxygen saturation is 90% breathing ambient air. Jugular venous distention is present. Heart sounds are distant, and no pericardial friction rub or murmur is noted. Crackles are noted at the lower quarter of both lung fields. Pitting edema is present to the knees.

Laboratory studies reveal a blood urea nitrogen level of 86 mg/dL (30.7 mmol/L), a serum creatinine level of 5.1 mg/dL (451 µmol/L), and a serum potassium level of 5.0 mEq/L (5.0 mmol/L).

A chest radiograph shows an enlarged cardiac silhouette, prominent pulmonary vasculature, and evidence of pulmonary edema. Echocardiographic findings are compatible with cardiac tamponade.

Which of the following is the most appropriate management?

(A) Hemodialysis
(B) Intravenous nitroglycerin
(C) Pericardiocentesis
(D) Right heart catheterization

Item 32

A 52-year-old woman is evaluated during a follow-up visit. She was discharged from the hospital 3 weeks ago following a small non–ST-elevation myocardial infarction treated with drug-eluting stent placement in the right coronary artery. An echocardiogram obtained during hospitalization showed normal left ventricular function and normal valvular function. Her hospital course was uncomplicated. Since discharge, she has had shortness of breath. Medical history is significant for hyperlipidemia. Medications are aspirin, ticagrelor, lisinopril, metoprolol, and atorvastatin.

On physical examination, vital signs are normal. Oxygen saturation is 99% breathing ambient air. The estimated central venous pressure is normal. Cardiac examination reveals no S_3 or murmurs. The lungs are clear to auscultation.

A chest radiograph is normal. An electrocardiogram is unchanged from those obtained in the hospital.

Which of the following is the most likely cause of this patient's dyspnea?

(A) Heart failure
(B) In-stent restenosis

(C) Stent thrombosis
(D) Ticagrelor-mediated side effect
(E) Ventricular septal rupture

H Item 33

A 68-year-old woman is evaluated in the emergency department for acute-onset dyspnea, palpitations, and chest pain. The symptoms began shortly after her dog was attacked by another dog. She is otherwise healthy and takes no medications.

On physical examination, the patient is afebrile, blood pressure is 150/78 mm Hg, and pulse rate is 88/min. Cardiac examination reveals no evidence of increased central venous pressure. There is no heart murmur, but an S_3 is present. The lungs are clear to auscultation.

Laboratory studies are significant for a serum troponin I level of 5.2 ng/mL (5.2 µg/L).

An electrocardiogram demonstrates sinus rhythm and anterior hyperacute T-wave elevations suggestive of an ST-elevation myocardial infarction. Cardiac catheterization shows normal coronary arteries. Systolic (*left panel*) and diastolic (*right panel*) images from left ventriculography are shown.

Which of the following is the most likely diagnosis?

(A) Acute myocarditis
(B) Giant cell myocarditis
(C) Tachycardia-mediated cardiomyopathy
(D) Takotsubo cardiomyopathy

Item 34

A 52-year-old woman is evaluated for recent-onset exertional dyspnea. Medical history is noncontributory, and she takes no medications.

On physical examination, vital signs are normal. The central venous pressure is elevated with a prominent *a* wave. Apical impulse is normal, and a prominent parasternal impulse is noted at the left sternal border. The S_1 is normal; the S_2 is soft. A grade 4/6 late-peaking systolic murmur is heard at the left sternal border and second left intercostal space. An ejection click is not audible.

Echocardiogram demonstrates doming of the pulmonary valve with stenosis, a peak instantaneous systolic gradient of 65 mm Hg, and a mean systolic gradient of 50 mm Hg. Trivial pulmonary regurgitation is present. The right ventricular size and function are normal, but right ventricular hypertrophy is present. The left heart size and function are normal.

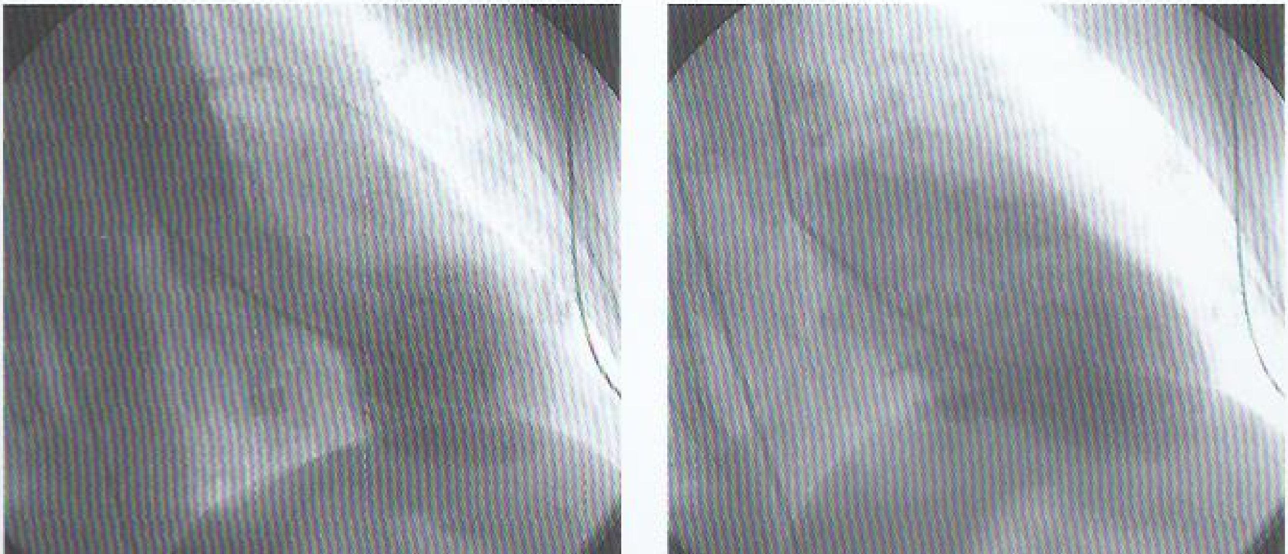
Which of the following is the most appropriate management of this patient?

(A) Endocarditis prophylaxis
(B) Exercise stress testing
(C) Pulmonary balloon valvuloplasty
(D) Pulmonary valve replacement

Item 35

A 60-year-old man is evaluated in the hospital for a 2-day history of intermittent chest pain and dyspnea on exertion. Medical history is significant for type 2 diabetes mellitus, hypertension, hyperlipidemia, COPD, and peripheral neuropathy. His ability to exercise is limited by his COPD. Medications are metformin, simvastatin, low-dose aspirin, lisinopril, amlodipine, and an albuterol-ipratropium inhaler.

On physical examination, temperature is normal, blood pressure is 128/78 mm Hg, pulse rate is 80/min, and respiration rate is 16/min. Oxygen saturation is 94% breathing ambient air. Pulmonary examination reveals expiratory wheezing bilaterally. Heart sounds are distant. No edema is present.



ITEM 33

Serial serum troponin I measurements are negative.

An electrocardiogram demonstrates left ventricular hypertrophy with repolarization abnormalities.

Which of the following is the most appropriate diagnostic test to perform next?

(A) Adenosine single-photon emission CT
(B) Coronary angiography
(C) Coronary CT angiography
(D) Exercise electrocardiography

Item 36

A 35-year-old woman is evaluated for chest discomfort that sometimes occurs at the beginning of exercise but abates completely even though she continues to exercise. She describes the discomfort as sharp in character and notes that it worsens when she breathes in. The pain does not radiate and is not accompanied by other symptoms. She also reports occasionally feeling lightheaded at the end of exercise or as she is "cooling down." She notes that her typical resting heart rate is 49/min. She takes no medications.

On physical examination, pulse rate is 43/min; other vital signs are normal. Oxygen saturation is 99% breathing ambient air. Cardiac examination reveals regular bradycardia. Heart rate varies with respiration. The remainder of the physical examination is normal.

Laboratory studies are significant for normal hemoglobin and serum thyroid-stimulating hormone levels.

A 12-lead electrocardiogram is shown. An echocardiogram demonstrates normal cardiac structure and function.

Which of the following is the most appropriate next step in management?

(A) Chest CT
(B) Coronary angiography
(C) Exercise treadmill stress testing
(D) Pacemaker implantation

Item 37

A 35-year-old woman is evaluated for hypertension. She is at 12 weeks' gestation of her first pregnancy. She reports no symptoms and has no history of hypertension or cardiovascular disease. She has not routinely had her blood pressure checked. Family history is significant for hypertension. Her only medication is a prenatal vitamin.

On physical examination, blood pressure is 166/94 mm Hg in both arms, and pulse rate is 80/min. An S_4 is noted at the apex. There are no murmurs. Pulses are normal throughout. The remainder of the examination is unremarkable.

Serum creatinine level, plasma glucose level, and urinalysis are normal. An ambulatory blood pressure monitor demonstrates an average blood pressure of 162/90 mm Hg.

Which of the following is the most appropriate treatment?

(A) Diet and weight loss alone
(B) Labetalol
(C) Lisinopril
(D) Spironolactone

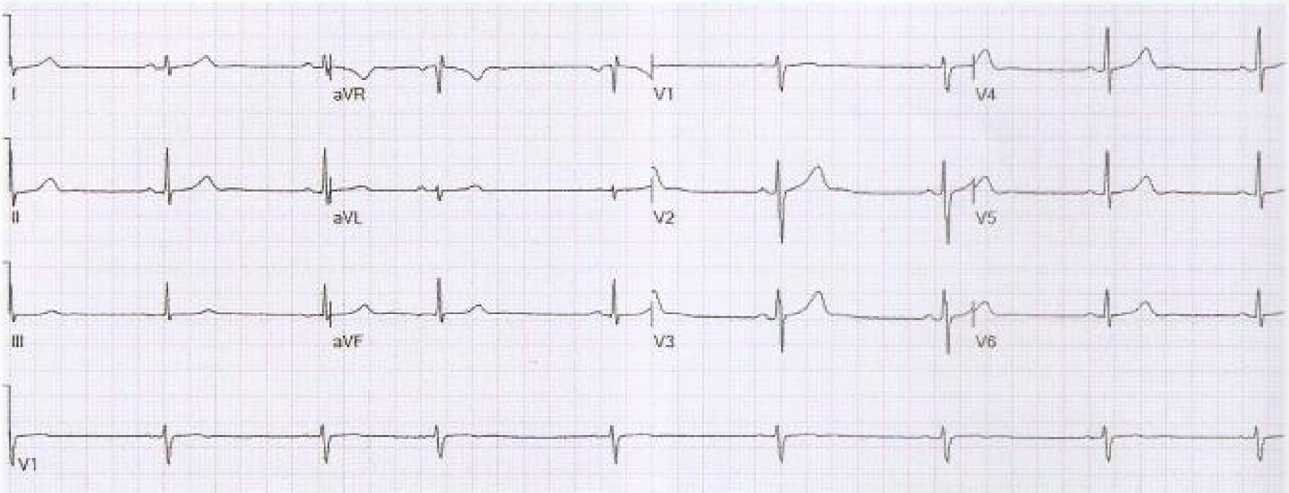
Item 38

A 55-year-old woman is evaluated during a routine examination. Her medical history is significant for mitral regurgitation. She has no history of cardiovascular symptoms. She is moderately active, plays doubles tennis, and occasionally participates in road cycling. She has no other medical problems and takes no medications.

On physical examination, vital signs are normal. Cardiac auscultation reveals a high-pitched midsystolic click and a grade 3/6 late systolic murmur that is loudest at the apex. Standing results in the click-murmur complex increasing in intensity and moving closer to S_1.

An echocardiogram shows severe mitral regurgitation and myxomatous degeneration of the mitral valve. The left ventricular ejection fraction is 65% with normal chamber size.

After discussion regarding early surgical repair versus surveillance, she chooses to defer surgery.



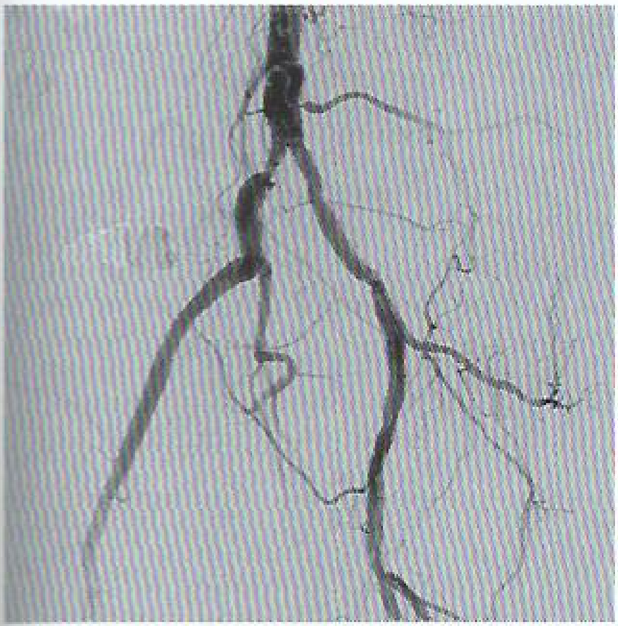
ITEM 36

In the absence of clinical symptoms, which of the following is the most appropriate timing for the next clinical evaluation in this patient?

(A) 3 months
(B) 6 to 12 months
(C) 1 to 2 years
(D) 3 to 5 years

Item 39

A 64-year-old man is evaluated in the office 7 days after discharge from the hospital for non–ST-elevation myocardial infarction. He was treated with percutaneous coronary intervention using a radial artery approach. Right femoral artery access was initially attempted, but the catheter guidewire could not be passed. During the procedure, an abdominal aortogram was obtained (shown). He has not had any symptoms of claudication. Medical history is significant for hyperlipidemia. He is a current smoker with a 40-pack-year history. Medications are low-dose aspirin, ticagrelor, metoprolol, and atorvastatin.



On physical examination, vital signs are stable. The right femoral pulse is faint, and a bruit is heard over the right femoral artery. No foot or toe ulceration is noted.

In addition to aggressive risk factor modification, which of the following is the most appropriate management?

(A) Cilostazol
(B) Cardiac rehabilitation
(C) Endovascular iliac stenting
(D) Vorapaxar

Item 40

An 18-year-old man is evaluated as part of a preparticipation sports examination. He is attending college on a basketball scholarship. He reports no symptoms. Medical history is unremarkable, and he takes no medications.

On physical examination, vital signs are normal. Cardiac examination reveals a brisk carotid upstroke. A grade 3/6 systolic crescendo-decrescendo murmur is heard best along the left sternal border; it decreases with squatting and is more pronounced in the upright position. Lungs are clear to auscultation.

An electrocardiogram shows voltage criteria for left ventricular hypertrophy with abnormal repolarization. An echocardiogram demonstrates asymmetric septal hypertrophy with septal thickness of 18 mm. Systolic anterior motion of the mitral valve is present, and the peak instantaneous left ventricular outflow tract gradient at rest is 30 mm Hg.

Which of the following is the most appropriate management regarding this patient's participation on the basketball team?

(A) Advise the patient that he should not play basketball
(B) Begin β-blocker therapy
(C) Refer for alcohol septal ablation
(D) Refer for implantable cardioverter-defibrillator placement

Item 41 H

An 80-year-old woman was hospitalized for chest pain and findings of a lateral ST-elevation myocardial infarction. She underwent percutaneous coronary intervention of a marginal branch of the left circumflex artery 16 hours after symptom onset. On hospital day 3, her cardiac examination is normal, but 3 hours later, she develops sudden-onset chest pain and loses consciousness. She is found to have pulseless electrical activity. Heart sounds are significantly diminished.

Which of the following is the most likely diagnosis?

(A) Aortic dissection
(B) In-stent restenosis
(C) Ventricular free wall rupture
(D) Ventricular septal defect

Item 42 H

A 64-year-old man is hospitalized for persistent low-grade fever, chest discomfort, and lower extremity edema. He underwent triple coronary artery bypass graft surgery 6 weeks ago. His medical history is otherwise notable for hypertension, hyperlipidemia, and previous smoking. His current medications are aspirin, metoprolol succinate, atorvastatin, lisinopril, and furosemide.

On physical examination, temperature is 37.7 °C (99.8 °F), blood pressure is 136/84 mm Hg, pulse rate is 96/min, and respiration rate is 14/min. Jugular venous distention is noted to the angle of the mandible. Decreased breath sounds and dullness to percussion are noted at the left base. No crackles are noted. A pericardial rub is present. There is no gallop. The liver is enlarged. There is bilateral pitting edema to the mid shin.

H CONT.

Laboratory studies:

Erythrocyte sedimentation rate	76 mm/h
Leukocyte count	12,000/µL (12×10^9/L)
Serum creatinine	1.4 mg/dL (123.8 µmol/L)
Troponin (two samples)	Normal
B-type natriuretic peptide	105 pg/mL (105 ng/L)

A 12-lead electrocardiogram demonstrates normal sinus rhythm with nonspecific ST-T-wave abnormalities. A chest radiograph demonstrates bilateral small pleural effusions. An echocardiogram shows no pericardial effusion. A Doppler echocardiogram shows enhanced ventricular interdependence and dilation of the inferior vena cava. Right heart catheterization demonstrates equalization of diastolic pressures in all heart chambers. Gadolinium-enhanced cardiac magnetic resonance imaging demonstrates increased pericardial thickness and evidence of active pericardial inflammation and edema.

Which of the following is the most likely diagnosis?

(A) Heart failure with preserved ejection fraction
(B) Perioperative graft failure with infarction
(C) Restrictive cardiomyopathy
(D) Transient constrictive pericarditis

Item 43

A 72-year-old woman is evaluated during a routine office visit. She has a 3-year history of heart failure with preserved ejection fraction and a long history of hypertension. She has exertional dyspnea with walking around the house, almost nightly paroxysmal nocturnal dyspnea, and peripheral edema. Cardiac catheterization performed 2 years ago revealed normal coronary arteries. Medications are hydrochlorothiazide and diltiazem.

On physical examination, the patient is afebrile, blood pressure is 136/82 mm Hg, pulse rate is 48/min, and respiration rate is 18/min. There is jugular venous distention. An S_4 is present. Pulmonary examination reveals no wheezes or crackles. Peripheral edema is noted.

Laboratory studies are significant for a serum creatinine level of 1.2 mg/dL (106.1 µmol/L) and a serum sodium level of 139 mEq/L (139 mmol/L).

Which of the following is the most appropriate management?

(A) Add ivabradine
(B) Add valsartan
(C) Discontinue hydrochlorothiazide and diltiazem and start furosemide
(D) Refer for pacemaker placement

Item 44

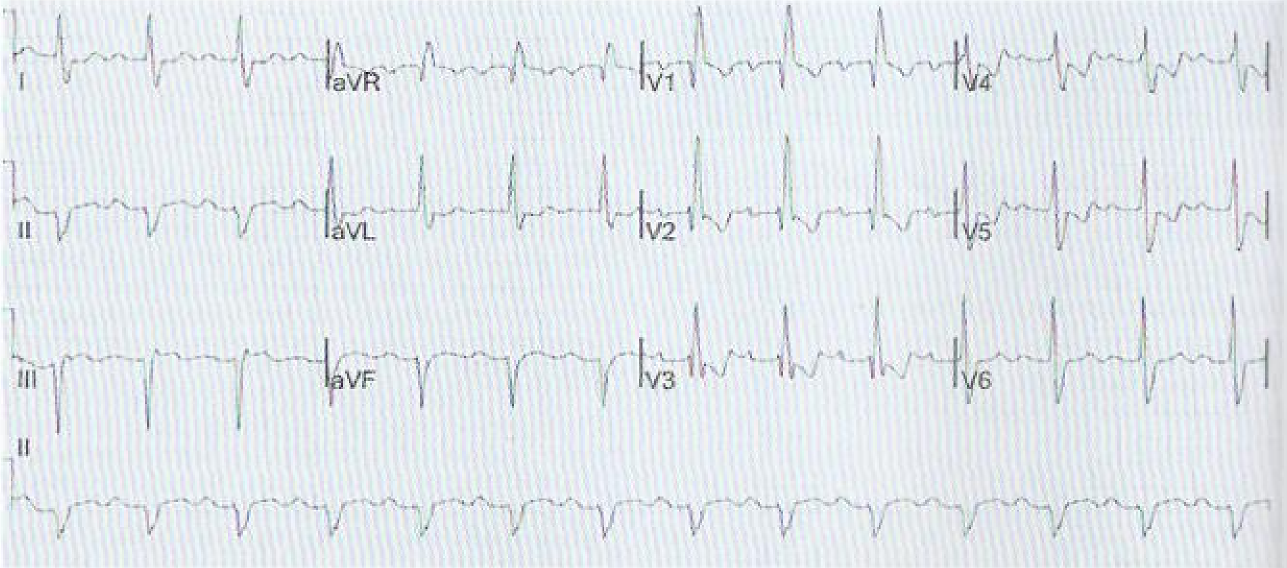
A 47-year-old man is evaluated for gradually progressive exertional dyspnea and two episodes of self-limited atrial fibrillation during the past 6 months. The atrial fibrillation was attributed to alcohol consumption, and no additional testing was performed. Medical history is otherwise noncontributory. He takes no medications.

On physical examination, vital signs are normal. The estimated central venous pressure is elevated. A parasternal impulse is noted at the left sternal border. Persistent splitting of the S_2 is present. A grade 2/6 systolic murmur is heard at the second left intercostal space, with a separate grade 3/6 holosystolic murmur at the apex. The remainder of the examination is normal.

An electrocardiogram is shown.

Which of the following is the most likely diagnosis?

(A) Coronary sinus atrial septal defect (ASD)
(B) Ostium primum ASD
(C) Ostium secundum ASD
(D) Sinus venosus ASD



ITEM 44

Item 45

A 59-year-old man is evaluated during a routine examination. He feels well and has no symptoms. Medical history is significant for hypertension. He does not smoke, and he does not have diabetes mellitus. He is active, performing aerobic exercise for 20 to 30 minutes four times per week. Medications are lisinopril and chlorthalidone.

On physical examination, the patient is afebrile, blood pressure is 122/74 mm Hg, and pulse rate is 76/min. Cardiac examination is unremarkable.

Laboratory studies:

Total cholesterol	169 mg/dL (4.38 mmol/L)
HDL cholesterol	36 mg/dL (0.93 mmol/L)
LDL cholesterol	106 mg/dL (2.75 mmol/L)
Triglycerides	135 mg/dL (1.53 mmol/L)

Which of the following is the most appropriate next step in management?

(A) Begin low-intensity statin therapy
(B) Begin moderate-intensity statin therapy
(C) Begin high-intensity statin therapy
(D) Calculate the 10-year atherosclerotic cardiovascular disease risk
(E) Repeat lipid level measurement in 5 years

Item 46

A 66-year-old man has just received an aortic valve replacement with a mechanical prosthesis. He is otherwise healthy and takes no medications.

On physical examination, vital signs are normal. There is a regular rhythm with a normal S_1, a mechanical S_2, and no murmurs. The remainder of the physical examination is normal.

Which of the following is the most appropriate antithrombotic therapy?

(A) Apixaban
(B) Dabigatran
(C) Warfarin
(D) Warfarin and aspirin
(E) No anticoagulation required

Item 47

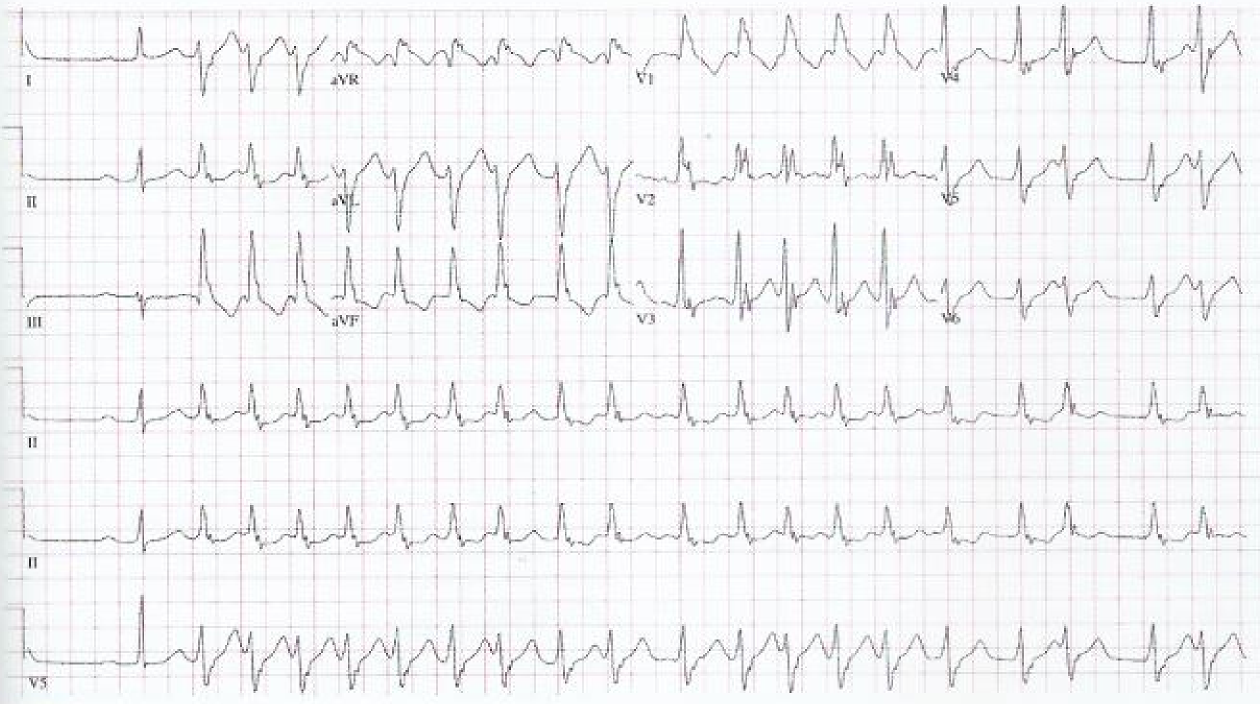
A 79-year-old woman is evaluated in the emergency department for palpitations that have occurred intermittently over the past 48 hours. Medical history is significant for hypertension and hyperlipidemia. Medications are low-dose aspirin, atorvastatin, and lisinopril.

On physical examination, temperature is 36.8 °C (98.2 °F), and blood pressure is 110/74 mm Hg. The resting pulse rate is 110/min with intermittent irregularity. The estimated central venous pressure is normal. Cardiac examination reveals tachycardia with a split S_2. The lung fields are clear. The extremities are warm and well perfused without edema.

An electrocardiogram is shown.

Which of the following is the most appropriate next step in management?

(A) β-Blocker therapy and anticoagulation
(B) Intravenous adenosine
(C) Intravenous procainamide
(D) Urgent cardioversion



ITEM 47

Item 48

A 60-year-old man is evaluated for a 5 month history of exertional chest discomfort that improves with rest. His symptoms have progressively worsened such that he has reduced his activity to a minimum. Medical history is significant for hypertension and hyperlipidemia. Medications are low-dose aspirin, losartan, hydrochlorothiazide, and atorvastatin.

On physical examination, the patient is afebrile, blood pressure is 122/71 mm Hg, and pulse rate is 74/min. Cardiac examination shows a normal S_1 and S_2. A grade 2/6 crescendo-decrescendo systolic murmur is heard best at the upper sternal border with no radiation. Lung examination is normal.

A stress echocardiogram shows 2-mm ST-segment depression at peak stress, normal left ventricular function at rest, normal valvular function, and anterior hypokinesis at peak stress (normal at rest). A 5.4-cm ascending thoracic aortic aneurysm is noted at the level of the sinuses of Valsalva. Coronary angiogram reveals 80% stenosis of the left main coronary artery bifurcation with no significant disease of the left anterior descending, left circumflex, or right coronary arteries.

Which of the following is the most appropriate next step in the patient's management?

(A) Coronary artery bypass graft surgery
(B) Metoprolol and isosorbide mononitrate
(C) Percutaneous coronary intervention
(D) Simultaneous coronary artery bypass graft surgery and aortic repair

H

Item 49

A 37-year-old man is evaluated in the emergency department for right-sided weakness. Medical history is significant for heart failure with placement of a left ventricular assist device 2 years ago. Family history is significant for familial cardiomyopathy. Medications are warfarin, aspirin, lisinopril, carvedilol, and furosemide.

On physical examination, temperature is normal, mean arterial pressure measured by Doppler ultrasonography is 106 mm Hg, pulse rate is 98/min, and respiration rate is 16/min. Oxygen saturation is 94% breathing ambient air. There is no jugular venous distention. Neurologic examination demonstrates global aphasia, right arm paralysis, antigravity movement in the right leg, left gaze preference, and decreased blink response to threat from the right side.

CT of the head shows sulcal effacement and loss of gray-white differentiation in the territory of the left middle cerebral artery.

Which of the following is the most likely cause of this patient's stroke?

(A) Carotid artery stenosis
(B) Cryptogenic stroke
(C) Lacunar infarction
(D) Left ventricular assist device–related thrombosis

Item 50

A 48-year-old woman is evaluated during a new-patient visit. She reports no symptoms. She is fairly sedentary but is trying to become more active by joining the local health club. She has noticed that she is "out of shape" but can cycle on a stationary bike with moderate intensity to the end of her 30-minute workout. Medical history is otherwise unremarkable. She takes no medications.

On physical examination, vital signs are normal. The estimated central venous pressure is 6 cm H_2O. The apical impulse is not palpable. Cardiac examination reveals a grade 2/6 midsystolic murmur localized to the left sternal border without radiation. The murmur does not change with respiration or handgrip but does diminish in intensity with standing. The S_2 is physiologically split. There are no clicks. The lungs are clear to auscultation. Peripheral pulses are normal in volume and contour. No edema is present.

Which of the following is the most appropriate management?

(A) Cardiac magnetic resonance imaging
(B) Transesophageal echocardiography
(C) Transthoracic echocardiography
(D) Routine clinical follow-up without imaging

Item 51

An 81-year-old woman is evaluated following drug-eluting stent placement for stable but disabling angina 1 month ago. After stent placement, she was started on aspirin and clopidogrel. She is currently asymptomatic, and she is interested in minimizing the duration of dual antiplatelet therapy because of her age and comorbid illnesses. Medical history is significant for hyperlipidemia, hypertension, stage 3 chronic kidney disease, and previous peptic ulcer disease. Other medications are lisinopril, metoprolol, atorvastatin, and pantoprazole.

On physical examination, vital signs are normal. Oxygen saturation is 98% breathing ambient air. The remainder of the examination is unremarkable.

Which of the following is the most appropriate management of this patient's antiplatelet therapy?

(A) Discontinue clopidogrel now
(B) Discontinue clopidogrel in 5 months
(C) Discontinue clopidogrel in 11 months
(D) Discontinue clopidogrel and aspirin in 11 months
(E) Discontinue clopidogrel in 29 months

Item 52

H

A 52-year-old woman is evaluated in the hospital for left arm and left leg weakness of 12 hours' duration. She has a 4-month history of progressive dyspnea on exertion, fatigue, low-grade fever, and arthralgia. She takes no medications.

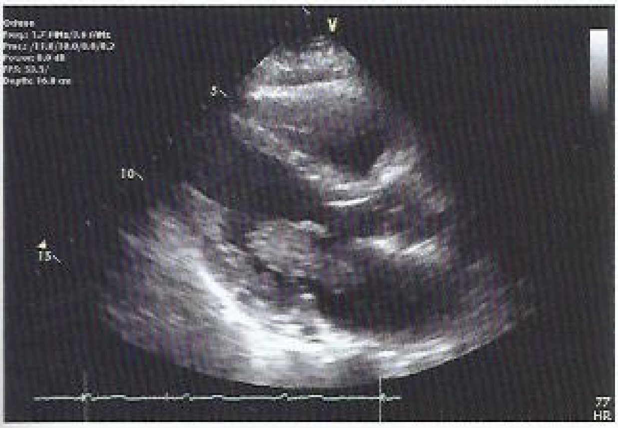
On physical examination, temperature is 38.1 °C (100.5 °F). Other vital signs are normal. On neurologic examination, muscle strength is 4/5 in the left arm and left leg; strength in all other muscle groups is 5/5. Cardiac examination reveals

H CONT.

a loud S_1, a soft diastolic rumble heard at the apex, and an early diastolic sound. The remainder of the examination is normal.

Laboratory studies are significant for an erythrocyte sedimentation rate of 87 mm/h; normocytic, normochromic anemia; and a normal leukocyte count.

An electrocardiogram demonstrates normal sinus rhythm. MRI of the brain reveals multiple small infarcts. An echocardiogram is shown. Left ventricular function is normal.



Which of the following is the most appropriate treatment?

(A) Anticoagulation
(B) Chemotherapy and radiotherapy
(C) Empiric broad-spectrum antibiotic therapy
(D) Percutaenous transesophageal echocardiographic-guided biopsy
(E) Surgical excision

Item 53

A 19-year-old man is evaluated for a heart murmur noted on physical examination. He reports no symptoms. Medical history is noncontributory. He takes no medications.

On physical examination, vital signs are normal. The patient is of short stature with hypertelorism, neck webbing, and a low hairline. The central venous pressure is elevated with a prominent *a* wave. Apical impulse is normal, and a prominent impulse is noted at the left upper sternal border. The S_1 is normal; the S_2 is soft. A grade 4/6 late-peaking systolic murmur is heard best at the left sternal border and second left intercostal space. An ejection click is not audible. The remainder of the examination is unremarkable.

Echocardiogram demonstrates a dysplastic pulmonary valve with a peak instantaneous systolic gradient of 65 mm Hg. Pulmonary regurgitation is moderate. The right ventricular size and function are normal, but right ventricular hypertrophy is present. The left heart size and function are normal.

Which of the following is the most likely genetic disorder responsible for this patient's findings?

(A) Down syndrome
(B) Marfan syndrome
(C) Noonan syndrome
(D) Turner syndrome

Item 54

H

A 51-year-old man is evaluated in the emergency department for an abrupt loss of consciousness while sitting in a restaurant. The event was witnessed, and the patient was noted to shake for several seconds before he regained consciousness. No prodromal symptoms occurred before the episode. After the event, he had no confusion or altered sensorium. Medical history is significant for nonischemic cardiomyopathy. He is slightly limited by shortness of breath during exercise. He has been taking metoprolol succinate and lisinopril for 9 months.

On physical examination, temperature is normal, blood pressure is 134/78 mm Hg, pulse rate is 72/min, and respiration rate is 15/min. Cardiac examination reveals a regular rhythm with intermittent ectopy. The chest is clear to auscultation. The estimated central venous pressure is normal. No edema is present. Carotid massage produces no bradycardia.

Laboratory findings are notable for a negative result on a serum troponin test.

Telemetry in the emergency department demonstrates short runs of nonsustained ventricular tachycardia. A 12-lead electrocardiogram shows premature ventricular contractions. An echocardiogram demonstrates a left ventricular ejection fraction of 25%.

Which of the following is the most appropriate management?

(A) Electroencephalography
(B) Exercise treadmill stress testing
(C) Implantable cardioverter-defibrillator placement
(D) PET of the mediastinum
(E) Tilt-table testing

Item 55

A 45-year-old woman is evaluated for a 12-month history of exertional dyspnea. She experiences shortness of breath during mild exertion, such as house chores and walking on flat surfaces. She describes her symptoms as debilitating, as they have interfered with her activities of daily living. She has not had symptoms at rest, and she has had no palpitations. She takes hydrochlorothiazide for hypertension.

On physical examination, temperature is normal, blood pressure is 112/72 mm Hg, pulse rate is 76/min, and respiration rate is normal. The apical impulse is slightly sustained but not displaced. S_1 is increased. There is an early diastolic sound followed by a soft rumble heard best at the apex. S_2 is normal.

An echocardiogram shows findings consistent with moderate rheumatic mitral stenosis and minimal mitral regurgitation. The mean gradient across the mitral valve is 8 mm Hg, and the mitral valve area is calculated to be 1.8 cm². The mitral valve is pliable. Moderate pulmonary hypertension is present, with an estimated pulmonary artery systolic pressure of 45 mm Hg.

Which of the following is the most appropriate next step in management?

(A) Exercise echocardiography
(B) Medical therapy
(C) Percutaneous balloon mitral valvuloplasty
(D) Surgical mitral valve replacement

Item 56

A 56-year-old man is evaluated in the emergency department for progressive chest pain and dyspnea that began 3 hours ago. Medical history is significant for hypertension treated with lisinopril.

On physical examination, he is confused. Temperature is normal, blood pressure is 86/50 mm Hg, pulse rate is 118/min, and respiration rate is 24/min. Oxygen saturation breathing ambient air is 90%. Cardiac examination reveals an S_3 gallop. Crackles are noted on pulmonary examination. The extremities are cool to the touch.

An electrocardiogram is shown. A chest radiograph reveals pulmonary edema.

Aspirin is initiated in the emergency department.

Which of the following is the most appropriate immediate management?

(A) Admission to the ICU for medical stabilization
(B) Intravenous metoprolol
(C) Percutaneous coronary intervention
(D) Sublingual nitroglycerin
(E) Thrombolytic therapy

Item 57

A 54-year-old man is evaluated during a routine examination. He is asymptomatic, and he exercises regularly without any limitations. Medical history is significant for hypertension and a bicuspid aortic valve with an enlarged aortic root (measuring 5.1 cm 6 months ago). Family history is unremarkable. His only medication is losartan.

On physical examination, blood pressure is 122/74 mm Hg. Cardiac examination reveals a midsystolic ejection click and a grade 2/6 crescendo-decrescendo systolic murmur at the second right intercostal space. The remainder of the examination is unremarkable.

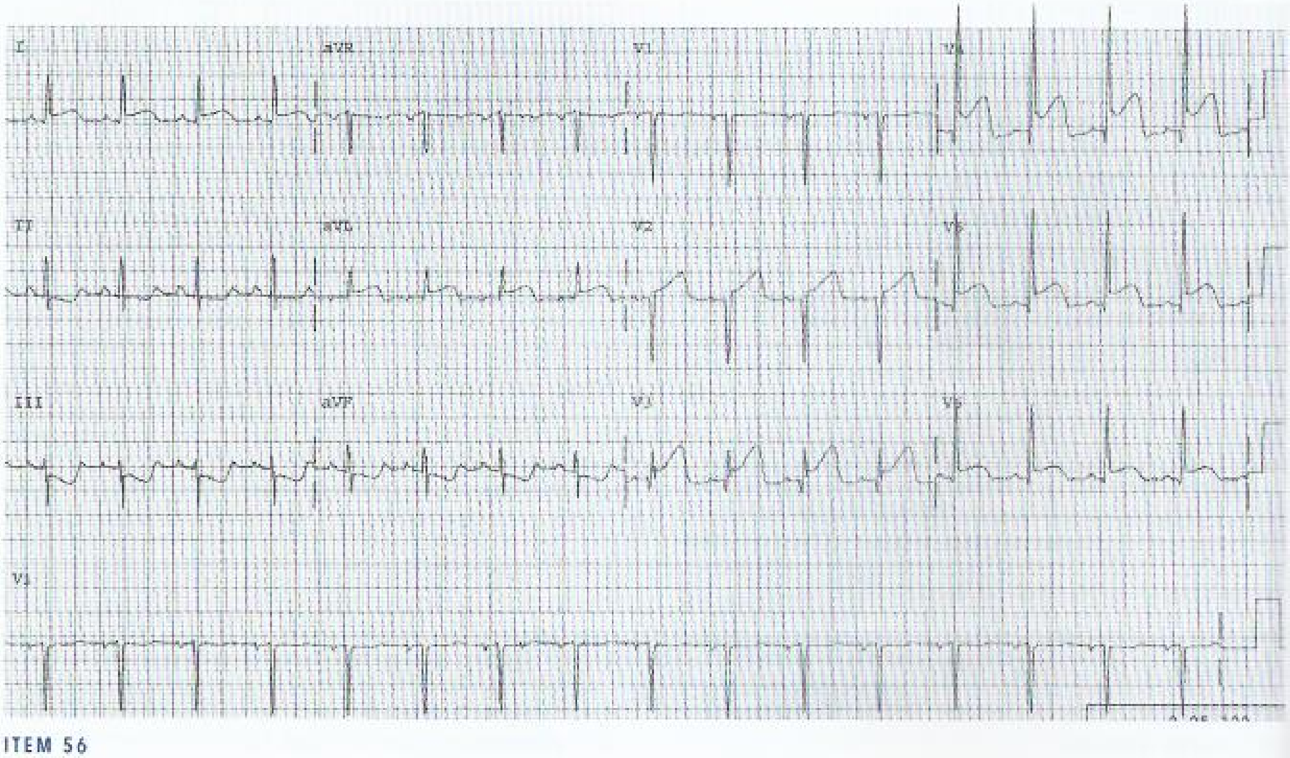
Transthoracic echocardiogram shows normal left ventricular function and a bicuspid aortic valve. The mean gradient across the aortic valve is 20 mm Hg, and the aortic valve area is 1.6 cm². The ascending aorta is 5.1 cm; the descending thoracic aorta is incompletely visualized.

Which of the following is the most appropriate management?

(A) Aortic valve replacement and ascending aortic repair
(B) Ascending aortic repair
(C) Dobutamine stress echocardiography
(D) Repeat echocardiography in 6 months

Item 58

A 36-year-old woman is evaluated in the emergency department for progressive dyspnea. She gave birth 3 weeks ago. The pregnancy and delivery were uncomplicated. She has no history of cardiovascular disease.



ITEM 56

On physical examination, temperature is normal, blood pressure is 100/72 mm Hg in both arms, pulse rate is 102/min and regular, and respiration rate is 26/min. The estimated central venous pressure is elevated. Cardiac palpation reveals a diffuse apical impulse. The S_1 and S_2 are soft. An S_3 and S_4 are present. A grade 2/6 holosystolic murmur is heard at the apex. Crackles are auscultated bilaterally.

An electrocardiogram demonstrates sinus tachycardia without ST-T-wave changes. Transthoracic echocardiogram reveals ventricular dilatation with global reduction in contractility; the left ventricular ejection fraction is 30%.

Which of the following is the most likely diagnosis?

(A) Acute aortic dissection
(B) Acute pulmonary embolism
(C) Peripartum cardiomyopathy
(D) Takotsubo cardiomyopathy

Item 59

A 48-year-old man is evaluated for a 6-month history of intermittent palpitations with accompanying lightheadedness and near syncope. The episodes last approximately 5 minutes and occur once or twice per week. He cannot identify any precipitating triggers for his symptoms. Medical history is notable for hypertension. His only medication is chlorthalidone.

On physical examination, vital signs and the remainder of the examination are normal.

An electrocardiogram shows normal sinus rhythm with no evidence of preexcitation.

Which of the following is the most appropriate diagnostic testing option?

(A) Electrophysiology study
(B) External event recorder
(C) 24-Hour ambulatory electrocardiographic monitor
(D) Implantable loop recorder

Item 60

A 70-year-old woman is evaluated in the emergency department for dyspnea. For the past 5 days, she has had progressive shortness of breath associated with a nonproductive cough. Symptoms are greatest with exertion and possibly when lying down. She has had no fever, chest pain, or increase in her chronic lower extremity edema. Her other medical problems are chronic venous insufficiency, COPD, and hypertension. Medications are chlorthalidone, amlodipine, lisinopril, and a tiotropium inhaler.

On physical examination, she is afebrile, blood pressure is 144/88 mm Hg, pulse rate is 90/min, and respiration rate is 22/min. Oxygen saturation is 94% breathing ambient air. BMI is 36. Because her neck is large, it is not possible to estimate central venous pressure. Breath sounds are distant, with occasional end-expiratory wheezing. Heart sounds are distant, and extra sounds or murmurs are not detected. There is 2+ ankle edema with hyperpigmentation localized to the medial aspect of the ankles.

B-type natriuretic peptide level is 128 pg/mL (128 ng/L).

A chest radiograph shows increased radiolucency of the lung, flat diaphragms, and a narrow heart shadow consistent with COPD.

An electrocardiogram shows evidence of left ventricular hypertrophy.

This patient's B-type natriuretic peptide level is most consistent with which of the following causes of dyspnea?

(A) Acute heart failure
(B) Chronic heart failure
(C) Noncardiac disease
(D) Cannot be determined

Item 61

H

A 77-year-old man is evaluated for a 4-week history of progressive left foot pain that occurs at rest. He also has calf muscle pain that worsens when he ambulates. Medical history is significant for type 2 diabetes mellitus, hypertension, and hyperlipidemia. Medications are low-dose aspirin, metformin, amlodipine, lisinopril, and rosuvastatin.

On physical examination, temperature is 36.8 °C (98.2 °F), blood pressure is 134/74 mm Hg, and pulse rate is 92/min. The left foot is cool. There is a shallow 3.0 cm × 2.5-cm ulceration on the medial aspect of the left first metatarsal. Pedal pulses are diminished on the right and absent on the left. Left foot sensation and muscle strength are intact.

The ankle-brachial index is 0.62 on the right and unobtainable on the left.

Which of the following is the most appropriate next step in management?

(A) Add vorapaxar
(B) Invasive angiography of the left leg
(C) Magnetic resonance angiography
(D) Primary below-knee amputation

Item 62

H

A 68-year-old woman is evaluated in the emergency department for a 1-hour history of chest pain. Medical history is significant for hypertension and a 20-year history of type 2 diabetes mellitus. Medications are metformin, quinapril, and aspirin.

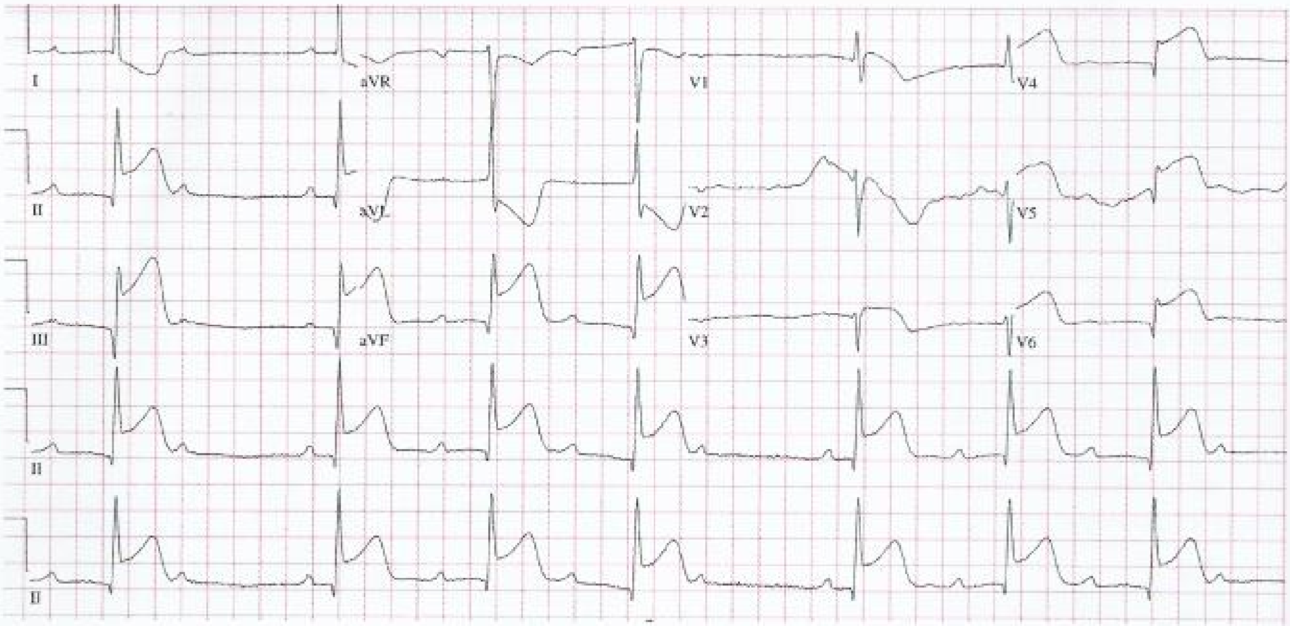
On physical examination, blood pressure is 95/60 mm Hg, pulse rate is 50/min, and respiration rate is 16/min. The patient is alert and conversant. The precordial cadence is not regular. There is no evidence of pulmonary or peripheral congestion, and the extremities are warm.

Laboratory studies reveal a serum troponin T level of 1.1 ng/mL (1.1 µg/L).

An electrocardiogram is shown (see top of next page).

Which of the following is the most appropriate next step in management of this patient's arrhythmia?

(A) Cardiac catheterization
(B) Echocardiography
(C) Permanent pacemaker implantation
(D) Temporary pacing



ITEM 62

Item 63

A 73-year-old man is evaluated during a routine examination. He is physically active and participates regularly in charitable running events. He has no cardiac symptoms, and his medical history is unremarkable.

On physical examination, vital signs are normal. The lungs are clear. Jugular venous pulse is normal. Carotid upstrokes are normal. The apical impulse is palpable and not displaced or sustained. There is a grade 3/6 diastolic decrescendo murmur best heard at the left lower sternal border. The remainder of the examination is normal.

A transthoracic echocardiogram shows severe aortic regurgitation. The left ventricular ejection fraction is 65%. The left ventricle is minimally dilated with an end-systolic dimension of 40 mm.

Which of the following is the most appropriate next step in management?

(A) Carvedilol
(B) Lisinopril
(C) Surgical aortic valve replacement
(D) Clinical and echocardiographic follow-up in 6 to 12 months

H Item 64

A 65-year-old woman is evaluated in the hospital following primary percutaneous coronary intervention with stent placement in the mid left anterior descending artery. She presented 4 hours ago with findings of an anterior myocardial infarction complicated by heart failure. Medical history is significant for hyperlipidemia, hypertension, type 2 diabetes mellitus, and previous ACE inhibitor–induced cough. Medications are atorvastatin, aspirin, clopidogrel, metformin, and furosemide.

On physical examination, vital signs are normal. Oxygen saturation is 98% on 3 L oxygen by nasal cannula. The estimated central venous pressure is elevated. An S_3 is present. Pulmonary examination reveals bibasilar crackles.

Laboratory studies are notable for normal serum creatinine and serum potassium levels.

A chest radiograph shows pulmonary edema. An echocardiogram demonstrates a left ventricular ejection fraction of 40%.

Which of the following is the most appropriate treatment?

(A) Carvedilol
(B) Diltiazem
(C) Hydralazine–isosorbide dinitrate
(D) Valsartan

Item 65

A 36-year-old man is evaluated for a 3-day history of progressive exertional dyspnea and palpitations. Medical history is notable for hypertrophic cardiomyopathy and mild mitral regurgitation. His only medication is metoprolol succinate.

On physical examination, pulse rate is 116/min and irregularly irregular. Oxygen saturation is 98% breathing ambient air. There is jugular venous distention. A grade 3/6 systolic crescendo-decrescendo murmur is heard along the left sternal border. The remainder of the examination is normal.

An electrocardiogram demonstrates atrial fibrillation with rapid ventricular response. Transesophageal echocardiogram shows asymmetric septal hypertrophy and dynamic left ventricular outflow tract obstruction, with

a gradient of 36 mm Hg. There is no evidence of left atrial appendage thrombus.

His CHA_2DS_2-VASc score is 0 points.

In addition to acute anticoagulation with heparin, which of the following is most appropriate for thromboembolic risk reduction in this patient?

(A) Dabigatran
(B) Dose-adjusted warfarin
(C) High-dose aspirin
(D) No further therapy

Item 66

A 78-year-old man is evaluated for exertional dyspnea. He was previously asymptomatic, but 4 months ago he began having shortness of breath during moderate levels of activity. The dyspnea dissipates with rest. He is otherwise healthy and takes no medications.

On physical examination, temperature is normal, supine blood pressure is 132/80 mm Hg, pulse rate is 80/min, and respiration rate is 22/min. The lungs are clear to auscultation. The carotid upstroke is delayed. There is a grade 3/6 late-peaking systolic murmur best heard at the base of the heart with radiation to both carotid arteries. S_1 is normal; the aortic component of S_2 is diminished. The remainder of the examination is unremarkable.

An echocardiogram demonstrates a left ventricular ejection fraction of 65%. There is moderate aortic stenosis, with a mean gradient of 28 mm Hg and an aortic valve area of 1.5 cm^2.

Which of the following is the most appropriate next step in management?

(A) Cardiac catheterization
(B) Surgical aortic valve replacement
(C) Transcatheter aortic valve replacement
(D) Continued clinical observation

Item 67

A 24-year-old woman undergoes routine evaluation. She has not seen a physician recently but reports no symptoms. She was diagnosed with a ventricular septal defect at age 7 months. Regular evaluation was performed during childhood. Medical history is otherwise noncontributory, and she takes no medications.

On physical examination, vital signs are normal. The jugular venous pressure and apical impulse are normal. No parasternal impulse is noted. The S_1 and S_2 are masked by a loud holosystolic murmur noted at the left lower sternal border. The remainder of the examination is unremarkable.

An electrocardiogram and chest radiograph are normal. A transthoracic echocardiogram demonstrates a membranous ventricular septal defect with a small left-to-right shunt. The left ventricular size and function are normal, with an ejection fraction of 60%. The right heart chambers and valve function are normal. The estimated pulmonary artery pressure is normal.

Which of the following is the most appropriate management?

(A) Cardiac catheterization
(B) Cardiac magnetic resonance imaging
(C) Endocarditis prophylaxis
(D) Follow-up in 3 to 5 years

Item 68

H

A 35-year-old woman is evaluated in the emergency department for a 3-week history of progressive dyspnea, fatigue, chest "fullness," and bilateral peripheral edema. Her medical history is notable for systemic lupus erythematosus manifested by malar rash, polyarticular arthritis, and previous pleural effusion. Her medications are hydroxychloroquine, ibuprofen, and prednisone.

On physical examination, temperature is 38.1 °C (100.6 °F), blood pressure is 108/68 mm Hg with pulsus paradoxus of 18 mm Hg, pulse rate is 160/min, and respiration rate is 18/min. Oxygen saturation is 97% breathing ambient air. Jugular venous distention to the angle of the mandible is present. Heart sounds are soft. No rubs, murmurs, or diastolic sounds are present. Pitting edema is noted bilaterally to above the ankle.

A chest radiograph and electrocardiogram are shown (see top of next page).

Which of the following is the most likely diagnosis?

(A) Cardiac tamponade
(B) Constrictive pericarditis
(C) Pulmonary embolism
(D) Pulmonary hypertension

Item 69

A 56-year-old man is evaluated for cardiovascular risk assessment. At a recent employee health screening, he was informed that he has elevated cholesterol levels. He feels well and exercises three to four times per week without any symptoms. He does not use tobacco. Medical history is unremarkable. Family history is notable for a myocardial infarction in his father at age 54 years. He takes no medications.

On physical examination, the patient is afebrile, blood pressure is 124/82 mm Hg, and pulse rate is 76/min. BMI is 28. Cardiovascular examination is normal.

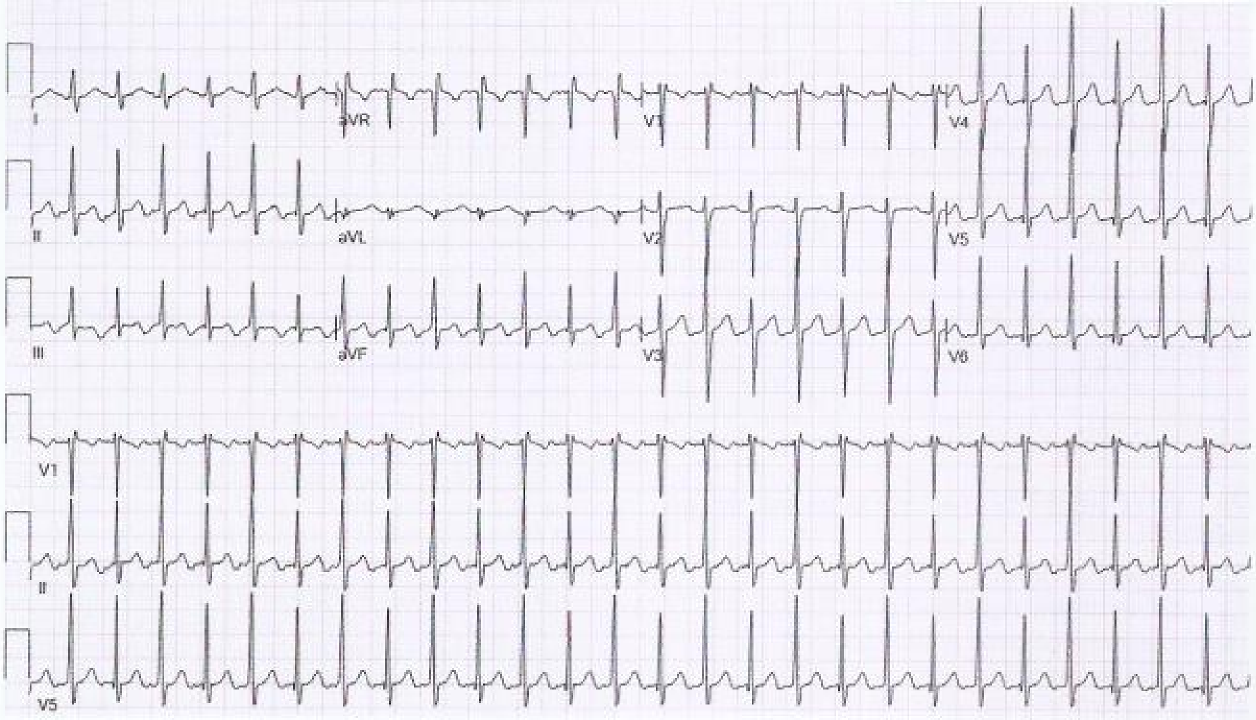
Laboratory studies:

Total cholesterol	194 mg/dL (5.02 mmol/L)
HDL cholesterol	38 mg/dL (0.98 mmol/L)
LDL cholesterol	122 mg/dL (3.16 mmol/L)
Triglycerides	170 mg/dL (1.92 mmol/L)

His 10-year risk for atherosclerotic cardiovascular disease using the Pooled Cohort Equations is 7%.

Which of the following is the most reasonable next step in management?

(A) Adenosine cardiac magnetic resonance imaging
(B) Coronary artery calcium scoring
(C) Exercise stress echocardiography
(D) Lipoprotein(a) measurement
(E) Pharmacologic nuclear stress testing



ITEM 68

Item 70

A 69-year-old man is evaluated after a recent hospitalization for heart failure. On hospital admission, he was appropriately treated, and an echocardiogram showed a left ventricular ejection fraction of 30% and left ventricular hypertrophy. He is currently asymptomatic. Medical history is otherwise significant for hypertension and hyperlipidemia. Medications are enalapril, furosemide, low-dose aspirin, and atorvastatin.

On physical examination, vital signs are normal. There is no jugular venous distention. Cardiac examination is normal. No edema is noted.

Which of the following is the most appropriate treatment?

(A) Add bisoprolol

(B) Add diltiazem

(C) Add spironolactone

(D) Discontinue enalapril and add losartan

(E) No additional therapy

Item 71

A 64-year-old man is evaluated following coronary angiography. He initially presented several weeks ago for progressive exertional chest pain and shortness of breath. Nuclear stress testing demonstrated a large anterior stress defect and an ejection fraction of 33%. Coronary angiography was significant for 90% stenosis of the proximal left anterior descending artery, a chronically occluded right coronary artery, and 80% stenosis of the left circumflex artery. He currently has stable dyspnea and chest pressure with moderate activity. Medical history is significant for hyperlipidemia, hypertension, and type 2 diabetes mellitus. He is taking optimal doses of aspirin, lisinopril, carvedilol, amlodipine, atorvastatin, and metformin.

On physical examination, temperature is normal, blood pressure is 125/70 mm Hg, pulse rate is 60/min, and respiration rate is 18/min. The remainder of the physical examination is unremarkable.

Which of the following is the most appropriate next step in management?

(A) Add ticagrelor
(B) Coronary artery bypass graft surgery
(C) Multivessel percutaneous coronary intervention
(D) Percutaneous coronary intervention of the left anterior descending artery
(E) Continue current medical therapy

Item 72

A 42-year-old woman is evaluated for a 3-year history of palpitations and fatigue. She reports no chest pain, dizziness, near-syncope, or syncope. An exercise stress test and echocardiogram were normal when she was evaluated for palpitations 1 year ago. There is no family history of sudden cardiac death or heart failure. Her only medication is metoprolol.

On physical examination, vital signs and the remainder of the examination are unremarkable.

An electrocardiogram is shown. Ambulatory 24-hour electrocardiographic monitoring shows frequent monomorphic premature ventricular contractions (22% of all beats) and frequent ventricular bigeminy. An echocardiogram obtained 1 week ago showed mild to moderate global decreased left ventricular function with a left ventricular ejection fraction of 45%.

Which of the following is the most appropriate management?

(A) Amiodarone
(B) Cardiac catheterization
(C) Cardiopulmonary exercise testing
(D) Catheter ablation of premature ventricular contractions

Item 73

H

An 86-year-old woman is hospitalized for acute decompensated heart failure. Her medical history is significant for a stroke 4 years ago, hypertension, severe COPD, and stage 3 chronic kidney disease. She underwent diuresis with furosemide overnight and is now resting comfortably. Her outpatient medications are lisinopril, atorvastatin, low-dose aspirin, tiotropium, and as-needed albuterol.

On physical examination, temperature is normal, blood pressure is 95/65 mm Hg, pulse rate is 80/min, and respiration rate is normal. Oxygen saturation is 90% on 2 L of oxygen by nasal cannula. Bilateral crackles are noted in the bottom quarter of the lung fields. The estimated central venous pressure is elevated. S_1 is diminished. A grade 3/6 holosystolic murmur and soft diastolic rumble are present at the apex.

An echocardiogram shows a flail segment involving the posterior leaflet of the mitral valve and severe regurgitation. The left ventricular ejection fraction is 60%.

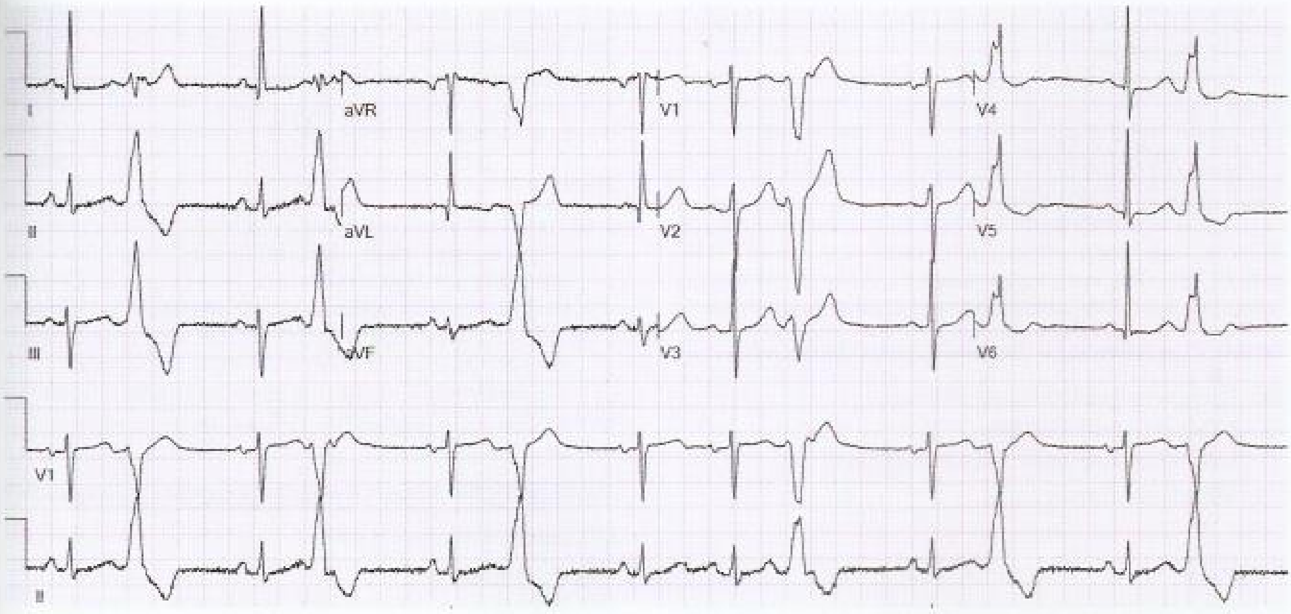
Cardiac and pulmonary surgical risks are estimated to be high (estimated operative mortality, 10%).

Which of the following is the most appropriate next step in management?

(A) Mitral valve replacement
(B) Surgical mitral valve repair
(C) Transcatheter mitral valve repair
(D) Continue current medical therapy

Item 74

A 62-year-old woman is evaluated for a 2-month history of exertional right leg pain. She has no associated chest pain,



ITEM 72

Self-Assessment Test

shortness of breath, or other symptoms. Medical history is significant for hypertension. Medications are lisinopril and chlorthalidone.

On physical examination, vital signs are normal. The right dorsalis pedis and posterior tibialis pulses are faint, and the left dorsalis pedis and posterior tibialis pulses are slightly diminished.

Laboratory studies:

Total cholesterol	180 mg/dL (4.66 mmol/L)
HDL cholesterol	54 mg/dL (1.40 mmol/L)
LDL cholesterol	101 mg/dL (2.62 mmol/L)
Triglycerides	125 mg/dL (1.41 mmol/L)

The right ankle-brachial index is 0.75, and the left is 0.92.

The patient's 10-year risk for atherosclerotic cardiovascular disease is 5.4% based on the American College of Cardiology/American Heart Association Pooled Cohort Equations.

In addition to aspirin and dietary and exercise counseling, which of the following is the most appropriate treatment?

(A) Evolocumab
(B) Ezetimibe
(C) High-intensity atorvastatin
(D) Moderate-intensity pravastatin
(E) No additional therapy

Item 75

A 72-year-old man is evaluated for a 4-month history of progressive exertional dyspnea. He has a 3-year history of ischemic cardiomyopathy, and in the past 6 months, he has had two hospitalizations for heart failure exacerbations. He currently has shortness of breath at rest. Medical history is otherwise significant for renal cell carcinoma treated with surgical resection 4 years ago. Medications are enalapril, bisoprolol, furosemide, atorvastatin, and aspirin.

On physical examination, temperature is normal, blood pressure is 104/80 mm Hg, pulse rate is 98/min, and respiration rate is 18/min. His neck veins are flat. Cardiac examination reveals an S_3. There is no peripheral edema. Extremities are cool.

Laboratory studies show a blood urea nitrogen level of 40 mg/dL (14.3 mmol/L) and a serum sodium level of 134 mEq/L (134 mmol/L). The serum creatinine level is 1.7 mg/dL (150.3 µmol/L), which is increased from 1.4 mg/dL (123.8 µmol/L) 3 months ago.

An electrocardiogram shows a QRS duration of 90 ms. An echocardiogram shows a left ventricular ejection fraction of 15%, left ventricular diastolic diameter of 8.2 cm (normal 3.9-5.3 cm), and moderate mitral regurgitation.

Which of the following is the most appropriate management?

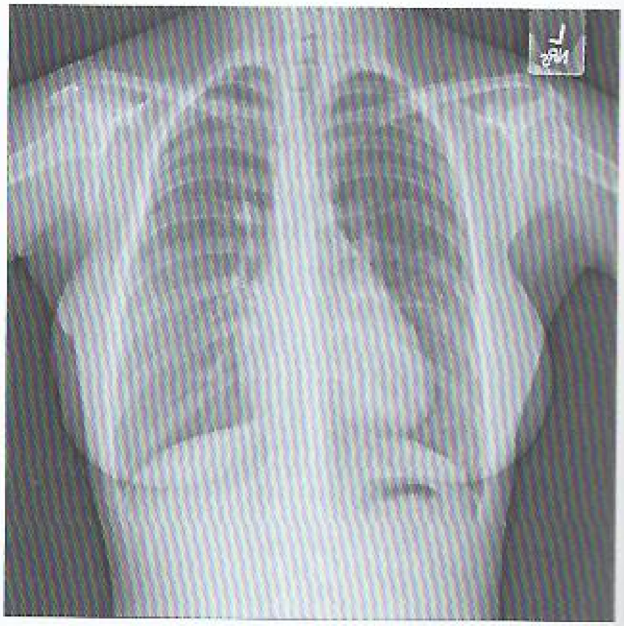
(A) Cardiac resynchronization therapy
(B) Cardiac transplantation
(C) Left ventricular assist device placement
(D) Mitral valve repair

Item 76

A 31-year-old woman undergoes preconception cardiac evaluation. Medical history is significant for tetralogy of Fallot with a palliative right subclavian artery-to-pulmonary artery (Blalock-Taussig) shunt in infancy and subsequent closure of the shunt and enlargement of the right ventricular outflow tract at 3 years of age. She is asymptomatic.

On physical examination, vital signs are normal. The estimated jugular venous pressure is elevated with a visible *a* wave. The apical impulse is normal; a parasternal impulse is noted at the left sternal border. S_1 is normal, and S_2 is single, with a soft early systolic murmur at the second left intercostal space. A grade 2/6 diastolic decrescendo murmur is noted at the left sternal border that increases with inspiration. The remainder of the examination is normal.

A chest radiograph is shown.



Which of the following is the most likely diagnosis?

(A) Aortic regurgitation
(B) Mitral stenosis
(C) Pulmonary valve regurgitation
(D) Recurrent ventricular septal defect

Item 77

A 68-year-old man is evaluated during a routine examination. He is asymptomatic. Medical history is significant for hypertension and hyperlipidemia. He has a 50-pack-year smoking history but quit smoking at age 45 years. Medications are low-dose aspirin, atorvastatin, and amlodipine.

On physical examination, vital signs are normal.

An abdominal aortic duplex ultrasound shows an abdominal aortic aneurysm with a maximum diameter of 3.5 cm.

Which of the following is the most appropriate management?

(A) Aortic aneurysm repair
(B) CT angiography
(C) Repeat aortic ultrasonography in 24 to 36 months
(D) No further testing

H

Item 78

A 46-year-old man is evaluated in the hospital for a 6-week history of fatigue and worsening dyspnea. Medical history is significant for a bicuspid aortic valve. He takes no medications.

On physical examination, temperature is 38.1 °C (100.6 °F), blood pressure is 118/58 mm Hg, pulse rate is 92/min, and respiration rate is 18/min. Oxygen saturation is 98% breathing 2 L of oxygen by nasal cannula. Cardiac examination reveals a grade 2/6 diastolic murmur heard best at the left lower sternal border. There are crackles at the lung bases bilaterally. Conjunctival hemorrhage is present in the left eye.

Laboratory studies are notable for a leukocyte count of 15,000/µL (15×10^9/L). Three sets of blood cultures are positive for gram-positive cocci.

An electrocardiogram shows sinus rhythm, a PR interval of 220 ms, and QRS duration of 100 ms.

Which of the following is the most appropriate diagnostic test to perform next?

(A) Cardiac magnetic resonance imaging
(B) Coronary CT angiography
(C) Transesophageal echocardiography
(D) Transthoracic echocardiography

Item 79

A 69-year-old man is evaluated during a follow-up visit. He initially presented with a 3-month history of chest pressure and dyspnea that occurred primarily with exertion. Despite maximal medical therapy, his symptoms have not abated and adversely affect his quality of life. Medical history is significant for type 2 diabetes mellitus, hypertension, and hyperlipidemia. Medications are low-dose aspirin; metformin; long-acting nitroglycerin; and optimal doses of metoprolol, lisinopril, ranolazine, and simvastatin.

On physical examination, blood pressure is 128/73 mm Hg, and pulse rate is 60/min. Cardiac examination reveals a normal S_1 and S_2 without an S_3 or S_4. There is no lower extremity edema.

Coronary angiogram is significant for a normal left main coronary artery and a 90% stenosis in the proximal left anterior descending artery resulting from ulcerated plaque.

Which of the following is the most appropriate management?

(A) β-Carotene
(B) Cardiac rehabilitation
(C) Percutaneous coronary intervention
(D) Ticagrelor

Item 80

A 26-year-old woman seeks preconception counseling. She has a history of mitral stenosis and underwent mitral valve replacement with a tilting disc mechanical prosthesis 5 years ago. She is asymptomatic. Medications are warfarin, 4 mg/d, and low-dose aspirin.

On physical examination, a normal mechanical S_1 and normal S_2 are appreciated. The remainder of the examination is unremarkable.

Laboratory studies reveal an INR of 3.0 (therapeutic target, 3.0).

An electrocardiogram demonstrates normal sinus rhythm.

In addition to continuing low-dose aspirin, which of the following is the most appropriate anticoagulation regimen for this patient during the first trimester?

(A) Continue INR-adjusted warfarin
(B) Stop warfarin and start apixaban
(C) Stop warfarin and start unfractionated heparin, 5000 units subcutaneously twice daily
(D) Stop warfarin and start weight-based low-molecular-weight heparin

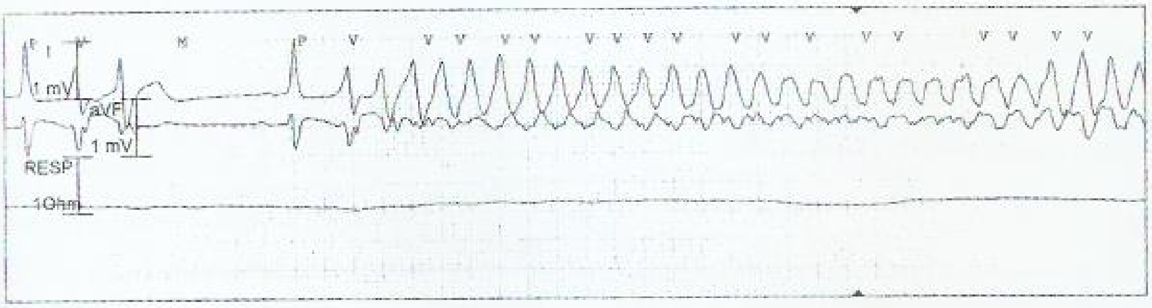
Item 81

H

A 51-year-old woman is evaluated in the ICU after being admitted 2 days ago for severe community-acquired pneumonia. A chest radiograph demonstrated right lower lobe consolidation, and she was started on moxifloxacin. Today, she developed an arrhythmia that terminated after 20 seconds. An electrocardiogram (ECG) obtained at the time of admission was normal. Medical history is significant for hypertension, hyperlipidemia, and depression. Other medications are venlafaxine, carvedilol, and simvastatin.

On physical examination, temperature is 38.4 °C (101.1 °F), blood pressure is 140/90 mm Hg, pulse rate is 61/min, and respiration rate is 18/min. Diminished breath sounds are located in the right lower posterior thorax. The remainder of the examination is unremarkable.

An ECG at the time of the arrhythmic event is shown. An ECG after the episode reveals a corrected QT interval of 550 ms.



ITEM 81

H CONT.

Which of the following medications should be discontinued on the basis of this patient's ECG findings?

(A) Carvedilol
(B) Moxifloxacin
(C) Simvastatin
(D) Venlafaxine

Item 82

A 40-year-old man is evaluated during a routine examination. He has a history of cardiac murmur. He is asymptomatic and active, cycling 12 miles three or four times per week.

On physical examination, vital signs are normal. There is no jugular venous distention. Cardiovascular examination reveals a point of maximal impulse that is displaced laterally and is diffuse. A grade 3/6 early diastolic decrescendo murmur is heard at the left parasternal third intercostal space. Lungs are clear. There are brisk, prominent distal extremity pulses.

A transthoracic echocardiogram demonstrates a bicuspid aortic valve and severe aortic regurgitation. Left ventricular end-systolic dimension is enlarged at 58 mm. Left ventricular ejection fraction is 50%. The proximal ascending aortic diameter is 50 mm (normal, <35 mm).

Which of the following is the most appropriate management?

(A) Aortic valve and root replacement
(B) Clinical and echocardiographic surveillance
(C) Initiation of nifedipine therapy
(D) Treadmill stress echocardiography

H Item 83

A 52-year-old man is evaluated before discharge. Medical history is significant for atrial fibrillation and a 7-year history of heart failure with reduced ejection fraction. He was initially hospitalized for a 2-week history of increasing exertional dyspnea, peripheral edema, and a weight gain of 4.1 kg (9 lb). He had not been taking his medications for the past month. He underwent diuresis with a loss of 6.8 kg (15 lb), and he currently feels well. Medications are furosemide, digoxin, warfarin, and low doses of carvedilol and lisinopril.

On physical examination, vital signs are normal. Other than an irregularly irregular rhythm, cardiopulmonary examination is normal. There is no peripheral edema.

Which of the following is the most appropriate management?

(A) Add ivabradine
(B) Add spironolactone
(C) Perform cardioversion
(D) Schedule follow-up within 1 week

Item 84

A 50-year-old man was diagnosed with hypertrophic cardiomyopathy following an episode of syncope. An implantable cardioverter-defibrillator was placed, and metoprolol was initiated. Genetic testing revealed a mutation of the β-myosin heavy chain gene associated with hypertrophic cardiomyopathy. Medical history is otherwise unremarkable. The patient has a 16-year-old daughter who is asymptomatic.

Which of the following is the most appropriate management of this patient's daughter?

(A) Electrocardiography and echocardiography screening at age 21 years
(B) Electrocardiography and echocardiography screening at age 40 years
(C) Electrocardiography and echocardiography screening if symptoms develop
(D) Genetic counseling and testing

Item 85

A 29-year-old woman is evaluated during a routine office visit. She was recently diagnosed with rheumatoid arthritis, for which she is taking naproxen and methotrexate. She is otherwise well. She does not smoke, drinks one alcoholic beverage daily, and engages in strenuous physical activity 5 days per week for 30 minutes each session. Her mother and father are first-generation Japanese immigrants, both in excellent health.

On physical examination, vital signs are normal. Cardiovascular examination is normal. There is evidence of synovitis involving the second, third, and fourth metacarpophalangeal joints bilaterally.

Her most recent lipid profile showed a total cholesterol level of 128 mg/dL (3.32 mmol/L) and a calculated LDL cholesterol level of 72 mg/dL (1.86 mmol/L).

Which of the following is the most significant risk factor for future cardiovascular disease?

(A) Activity level
(B) Alcohol consumption
(C) Ethnicity
(D) Rheumatoid arthritis

Item 86

A 26-year-old woman is evaluated for palpitations and fatigue of several months' duration. Her symptoms are present at rest and aggravated during light activity, including climbing stairs and walking quickly. She reports no dyspnea, chest pain, orthopnea, lower extremity edema, or syncope. Medical history is otherwise unremarkable, and she takes no medications.

On physical examination, temperature is normal, blood pressure is 110/65 mm Hg, and pulse rate is 115/min. Orthostatic vital signs do not demonstrate any significant changes with posture. Precordial examination reveals mild tachycardia but regular rhythm with no gallops. No thyroid fullness or tremors are noted. The remainder of the examination is normal.

Laboratory studies are significant for a normal complete blood count, serum thyroid-stimulating hormone level, and 24-hour excretion of urine catecholamines.

A 12-lead electrocardiogram is notable for sinus tachycardia with a normal P-wave axis. A 24-hour ambulatory electrocardiographic monitor shows sinus tachycardia throughout the waking hours, with a decline in heart rate to less than 90/min during the night. The average heart rate is 110/min. An echocardiogram reveals a structurally normal heart with normal ventricular function.

Which of the following is the most likely diagnosis?

(A) Generalized anxiety disorder
(B) Inappropriate sinus tachycardia
(C) Somatic symptom disorder
(D) Subclinical hyperthyroidism

Item 87

A 68-year-old man is evaluated for a 2-month history of exertional dyspnea. Medical history is significant for diabetes mellitus, hypertension, and hyperlipidemia. Medications are lisinopril, hydrochlorothiazide, metformin, and atorvastatin.

On physical examination, vital signs are normal. Oxygen saturation is 99% breathing ambient air. Cardiopulmonary examination shows a regular rhythm and a paradoxically split S_2. There is no peripheral edema.

An electrocardiogram is shown.

Which of the following is the most appropriate diagnostic test to perform next?

(A) Adenosine single-photon emission CT
(B) Coronary artery calcium scoring
(C) Exercise single photon emission CT
(D) Exercise electrocardiography

Item 88

H

A 27 year old woman is hospitalized with a 2-month history of progressive exertional dyspnea and edema. She has no history of recent flu-like symptoms, weight change, arthritis, or chest pain.

On physical examination, the patient is afebrile, blood pressure is 118/66 mm Hg, pulse rate is 112/min, and respiration rate is 18/min. Oxygen saturation is 98% breathing ambient air. There is jugular venous distention to the angle of the jaw. Crackles are present at the lung bases. Cardiac examination reveals an S_3. Peripheral edema is noted.

Complete blood count, serum electrolytes, kidney function tests, liver chemistry tests, glucose level, and lipid levels are normal.

An electrocardiogram shows sinus tachycardia with normal intervals and no conduction delay. An echocardiogram demonstrates a left ventricular ejection fraction of 25% and normal left ventricular diastolic diameter.

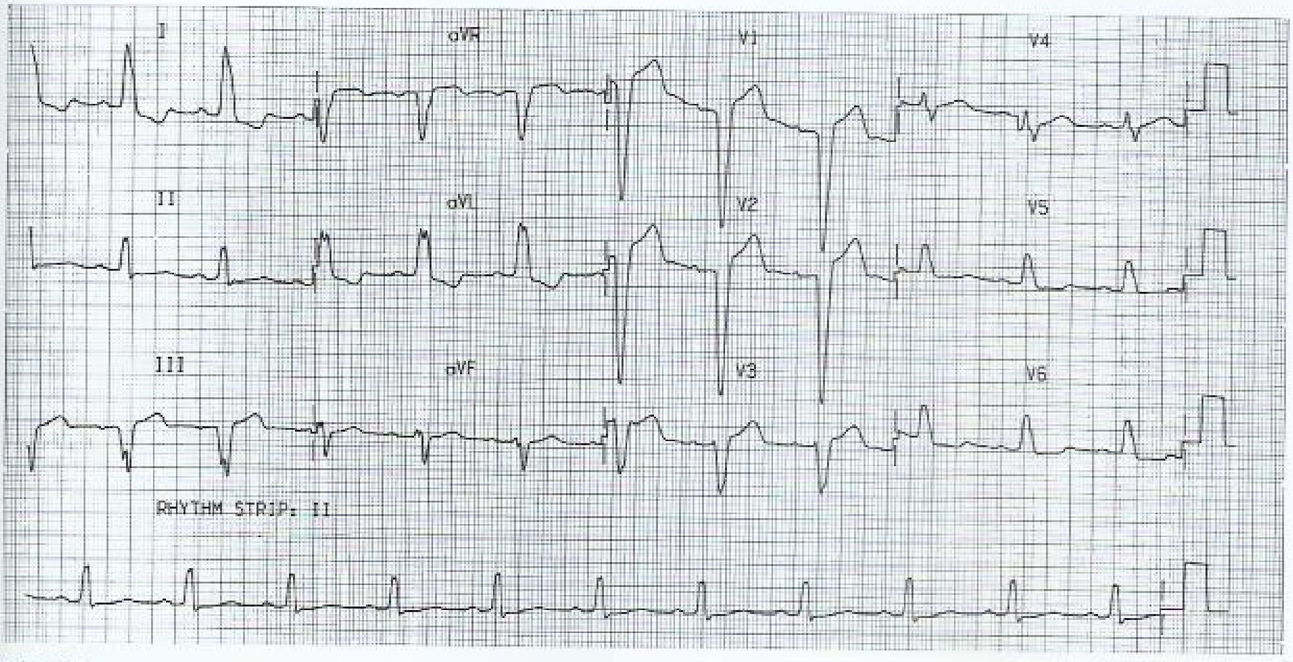
Which of the following is the most appropriate diagnostic test to perform next?

(A) Acute and convalescent viral titers
(B) Cardiac catheterization
(C) Serum iron and ferritin studies
(D) Thyroid function studies

Item 89

H

A 66-year-old man is evaluated in the emergency department for chest pain and dyspnea. Three days ago, he experienced the sudden onset of substernal chest pain. His symptoms waxed and waned over a period of 3 hours and then spontaneously subsided. Today, he began experiencing progressive shortness of breath with symptoms occurring at



ITEM 87

H CONT.

rest. His medical history is significant for hypertension and hyperlipidemia. His medications are hydrochlorothiazide, atenolol, and atorvastatin.

On physical examination, he appears distressed. Temperature is normal, blood pressure is 95/50 mm Hg, pulse rate is 115/min, and respiration rate is 24/min. Oxygen saturation is 90% breathing 4 L of oxygen by nasal cannula. Jugular venous pulse is elevated and visible, with exaggerated *x* and *y* descents, and the estimated central venous pressure is 12 cm H_2O. Bilateral crackles are noted. A soft, early systolic murmur with an S_3 is audible in the apical area. An early diastolic rumble is present.

An electrocardiogram demonstrates significant Q waves in the inferolateral leads and elevated ST segments. A chest radiograph confirms the presence of heart failure with cardiomegaly and bilateral pulmonary edema.

Which of the following is the most likely diagnosis?

(A) Aortic stenosis
(B) Cardiac tamponade
(C) Mitral regurgitation
(D) Tricuspid regurgitation

H

Item 90

A 76-year-old woman is evaluated before discharge. She was diagnosed with a non-ST-elevation myocardial infarction 3 days ago. She declined angiography, and nuclear stress testing revealed a small lateral perfusion defect and normal left ventricular ejection fraction. She has had no further discomfort since admission. Medical history is significant for hyperlipidemia, hypertension, and transient ischemic attack. Medications are low-dose aspirin, ramipril, metoprolol, and atorvastatin.

On physical examination, vital signs and the remainder of the examination are unremarkable.

In addition to low-dose aspirin, which of the following is the optimal antithrombotic regimen for this patient?

(A) Prasugrel
(B) Ticagrelor
(C) Warfarin
(D) No additional antithrombotic therapy

Item 91

A 72-year-old man is evaluated for a 1-year history of bilateral lower extremity edema and abdominal distention. Eight years ago he had esophageal carcinoma treated with radiotherapy. Medical history is otherwise significant for hypertension, type 2 diabetes mellitus, and hypercholesterolemia. Medications are bumetanide, atorvastatin, metformin, and lisinopril.

On physical examination, the patient is afebrile, blood pressure is 170/90 mm Hg, pulse rate is 90/min, and respiration rate is normal. Jugular venous distention is present to the angle of the mandible while seated, with prominent pulsations. Cardiac examination reveals an early diastolic sound at the apex. The liver is palpable 5 cm below the costal margin. The abdomen is distended with ascites. There is bilateral pitting edema to the level of the thighs. Pulmonary examination reveals no crackles.

Laboratory studies are significant for a B-type natriuretic peptide level of 96 pg/mL (96 ng/L).

Chest radiographs are shown. A 12-lead electrocardiogram demonstrates normal sinus rhythm with normal QRS voltage. Echocardiogram demonstrates normal right and left ventricular size and function. Left ventricular wall thickness is normal. Mild tricuspid regurgitation is present. There are respiratory variation in the filling of the right and left ventricles, ventricular septal shift during respiration, and dilation of the inferior vena cava. The estimated right ventricular systolic pressure is 46 mm Hg. There is no pericardial effusion.

Which of the following is the most likely diagnosis?

(A) Cardiac amyloidosis
(B) Constrictive pericarditis
(C) Heart failure with preserved ejection fraction
(D) Restrictive cardiomyopathy

Item 92

A 35-year-old woman is evaluated for exertional dyspnea of 6 months' duration. She reports no other symptoms. Medical history is unremarkable, and she takes no medications.

On physical examination, vital signs are normal. Oxygen saturation is 96% breathing ambient air. The estimated central venous pressure is elevated. Apical impulse is normal; a parasternal impulse is noted at the left sternal border. A soft systolic murmur is heard at the second left intercostal space, and a diastolic flow rumble is heard at the left sternal border. Fixed splitting of the S_2 is noted throughout the cardiac cycle. The remainder of the physical examination is normal.

An electrocardiogram demonstrates right axis deviation and incomplete right bundle branch block.

Which of the following is the most likely diagnosis?

(A) Atrial septal defect
(B) Bicuspid aortic valve with aortic stenosis
(C) Congenital pulmonary stenosis
(D) Mitral stenosis

Item 93

A 55-year-old woman is evaluated after a recent hospital admission for ischemic stroke. She presented with mild right-sided hemiparesis, but it completely resolved after the second hospital day. An electrocardiogram, transthoracic echocardiogram, and carotid artery ultrasound were normal. A subsequent transesophageal echocardiogram was also normal. She has a 10-year history of hypertension treated with hydrochlorothiazide.

On physical examination, vital signs are normal. Cardiac examination reveals a regular rate and rhythm. Neurologic examination is nonfocal. Hand grip strength, arm flexion, and arm extension are 5/5 on the right and left sides. There is no edema.

A 12-lead electrocardiogram demonstrates normal sinus rhythm.

Which of the following is the most appropriate diagnostic testing option?

(A) Antiphospholipid antibody testing
(B) Cardiac catheterization
(C) 30-Day event-triggered loop recording
(D) 48-Hour ambulatory electrocardiographic monitoring

H

Item 94

A 72-year-old woman is evaluated in the hospital for a 2-week history of increasing exertional dyspnea and weight gain of 3.3 kg (7.3 lb). Medical history is significant for idiopathic cardiomyopathy with a left ventricular ejection fraction of 25% and hypertension. Medications are lisinopril, metoprolol succinate, furosemide, spironolactone, and digoxin.

On physical examination, the patient is afebrile, blood pressure is 158/68 mm Hg, pulse rate is 96/min, and respiration rate is 18/min. Oxygen saturation is 98% breathing ambient air. Jugular venous distention is present. Cardiac examination reveals an S_3 and a grade 2/6 apical holosystolic murmur. The lungs have occasional bibasilar crackles. The extremities are warm. Peripheral edema is noted.

Laboratory studies are significant for a serum creatinine level of 1.9 mg/dL (168 µmol/L), a serum potassium level of 4.5 mEq/L (4.5 mmol/L), and a serum sodium level of 139 mEq/L (139 mmol/L).

Which of the following is the most appropriate intravenous treatment?

(A) Dopamine
(B) Furosemide
(C) Milrinone
(D) Nesiritide

Item 95

A 26-year-old man is hospitalized for suspected bacterial endocarditis. He has a long history of injection drug use and has used heroin within the past month. Two weeks ago, he began feeling feverish, and over the past 3 days, he has been increasingly short of breath. He takes no medications.

On physical examination, temperature is 38.7 °C (101.6 °F), blood pressure is 90/50 mm Hg, pulse rate is 95/min, and respiration rate is 16/min. Bilateral lung crackles are present. Jugular venous distention is noted. A grade 2/6 holosystolic murmur is heard at the apex with an S_3. Skin findings are shown.

The electrocardiogram is normal. A chest radiograph shows bilateral pulmonary edema and cardiomegaly.

Blood cultures are obtained.

Which of the following is the most appropriate next step in management?

(A) Cardiac CT
(B) Chest MRI
(C) Transesophageal echocardiography
(D) Transthoracic echocardiography

Item 96

A 55-year-old woman is evaluated in the hospital for a single 10-minute episode of chest pain at rest, which occurred 1 hour before presentation. Medical history is significant for hypertension and hyperlipidemia. Medications are hydrochlorothiazide, ramipril, and pravastatin.

On physical examination, vital signs are normal. The remainder of the examination is unremarkable.

Laboratory studies are notable for normal serum troponin levels.

An electrocardiogram demonstrates 1 mm ST-segment depressions in leads V_1 through V_6.

Aspirin and metoprolol are initiated.

Which of the following is the most appropriate management?

(A) Amlodipine
(B) Enoxaparin and eptifibatide
(C) Exercise stress testing
(D) Urgent angiography

Item 97

A 68-year-old man is evaluated for a 4-month history of intermittent left calf pain. He has a history of cigarette smoking but quit 6 months ago. Medical history is otherwise significant for hyperlipidemia. Medications are low-dose aspirin and high-intensity atorvastatin.

On physical examination, vital signs are normal. BMI is 29. Femoral pulses are diminished bilaterally. Popliteal, right dorsalis pedis, and right posterior tibialis pulses are faint. The left dorsalis pedis and posterior tibialis pulses are not palpable. Cardiac examination is normal.

The ankle-brachial index is 0.67 on the left and 0.91 on the right.

He is enrolled in a supervised exercise program. Three months later, the patient calls to report that despite adherence to the exercise program, his symptoms have progressed.

Which of the following is the most appropriate next step to reduce this patient's leg pain?

(A) Add clopidogrel
(B) Discontinue atorvastatin and initiate rosuvastatin
(C) Initiate cilostazol
(D) Refer for invasive angiography

Item 98

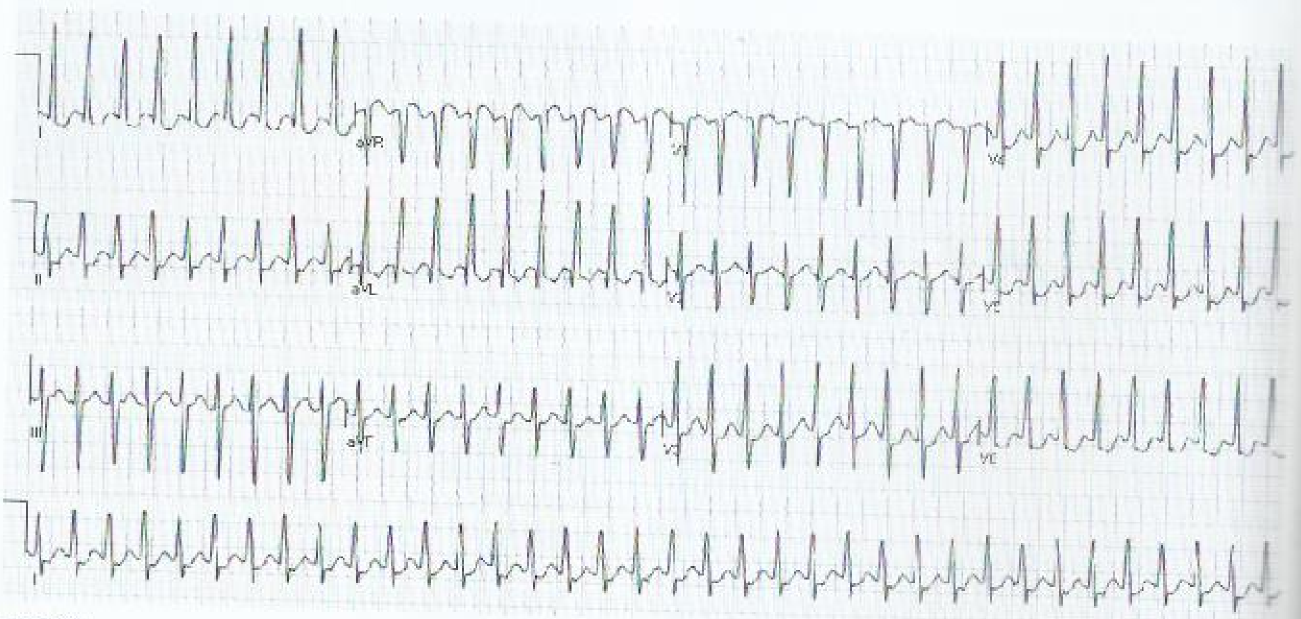
A 39-year-old man is evaluated in the emergency department for palpitations and shortness of breath that developed abruptly 45 minutes ago. He has no significant medical history and takes no medications.

On physical examination, blood pressure is 110/48 mm Hg, and pulse rate is 216/min; other vital signs are normal. Cardiac examination reveals a rapid and regular heart rate. The S_1 does not exhibit variable intensity. The rhythm does not change with a Valsalva maneuver.

A 12-lead electrocardiogram obtained in the emergency department is shown.

Which of the following is the most appropriate next step in treatment?

(A) Adenosine
(B) Amiodarone
(C) Ibutilide
(D) Synchronized cardioversion



ITEM 98

Item 99

A 62-year-old man is evaluated for a 1-year history of progressive fatigue, dyspnea on exertion, and lower extremity edema. He has been hospitalized twice in the past year for heart failure. Medical history is otherwise unremarkable. His current medications are furosemide, amlodipine, and spironolactone. He is black.

On physical examination, temperature is normal, blood pressure is 106/68 mm Hg, pulse rate is 68/min, and respiration rate is 14/min. Oxygen saturation breathing ambient air is normal. Jugular venous distention is noted. No crackles are present. A grade 2/6 holosystolic murmur is heard at the left lower sternal border and increases with inspiration. There is no S_3 or S_4. The liver is enlarged. Pitting edema is present to the mid shin bilaterally.

An electrocardiogram reveals sinus rhythm, biatrial enlargement, and low voltage of the QRS complexes. Q waves are present in leads V_1 through V_3. Echocardiogram reveals severe concentric left ventricular hypertrophy with wall thickness of 16 mm, moderate biatrial dilatation, normal left ventricular cavity size, a left ventricular ejection fraction of 55%, and no regional wall motion abnormalities. Diastolic dysfunction is noted. Right ventricular size and systolic function are normal, and the right ventricular wall thickness is slightly increased. The estimated right ventricular systolic pressure is 68 mm Hg. Tricuspid regurgitation is present. There is no pericardial effusion.

Which of the following is the most likely diagnosis?

(A) Cardiac amyloidosis
(B) Constrictive pericarditis
(C) Hypertensive heart disease
(D) Hypertrophic cardiomyopathy

Item 100

A 45-year-old man undergoes a pre-employment physical examination. Medical history is notable for aortic coarctation with an end-to-end anastomosis performed at 4 years of age. He reports no symptoms, works full time, and performs regular exercise without limitation. He takes no medications.

On physical examination, vital signs are normal. An ejection click is noted at the left lower sternal border. A grade 2/6 mid-peaking systolic murmur is noted at the second right intercostal space. The femoral pulses are normal, and no radial artery-to-femoral artery pulse delay is present. The remainder of the physical examination is normal.

Which of the following is the most likely cause of this patient's systolic murmur?

(A) Aortic stenosis
(B) Hypertrophic cardiomyopathy
(C) Mitral regurgitation
(D) Recurrent coarctation

Item 101

A 45-year-old man is evaluated during a second follow-up visit after hospitalization for new-onset heart failure with reduced ejection fraction. His ejection fraction at the time of diagnosis 2 months ago was 42%. He reports feeling better, with improving exercise tolerance and no exertional dyspnea. Medications are lisinopril, low-dose carvedilol, and furosemide. He is black.

On physical examination, the patient is afebrile, blood pressure is 120/76 mm Hg, pulse rate is 84/min, and respiration rate is 16/min. The estimated central venous pressure is normal. There is no S_3. Lungs are clear, and there is no peripheral edema.

Which of the following is the most appropriate treatment?

(A) Add digoxin
(B) Add hydralazine and isosorbide dinitrate
(C) Increase carvedilol
(D) Increase furosemide

Item 102

H

A 65-year-old man was hospitalized 24 hours ago with findings of a large anterior myocardial infarction. He underwent primary percutaneous coronary intervention with stent placement in the proximal left anterior descending artery. He is currently asymptomatic. Medical history is significant for hyperlipidemia and hypertension. Medications are atorvastatin, aspirin, prasugrel, captopril, and metoprolol.

On physical examination, temperature is normal, blood pressure is 110/65 mm Hg, pulse rate is 65/min, and respiration rate is 18/min. Oxygen saturation is 98% breathing ambient air. The remainder of the examination is unremarkable.

An electrocardiogram obtained in the coronary care unit is shown (see top of next page).

Which of the following is the most appropriate treatment?

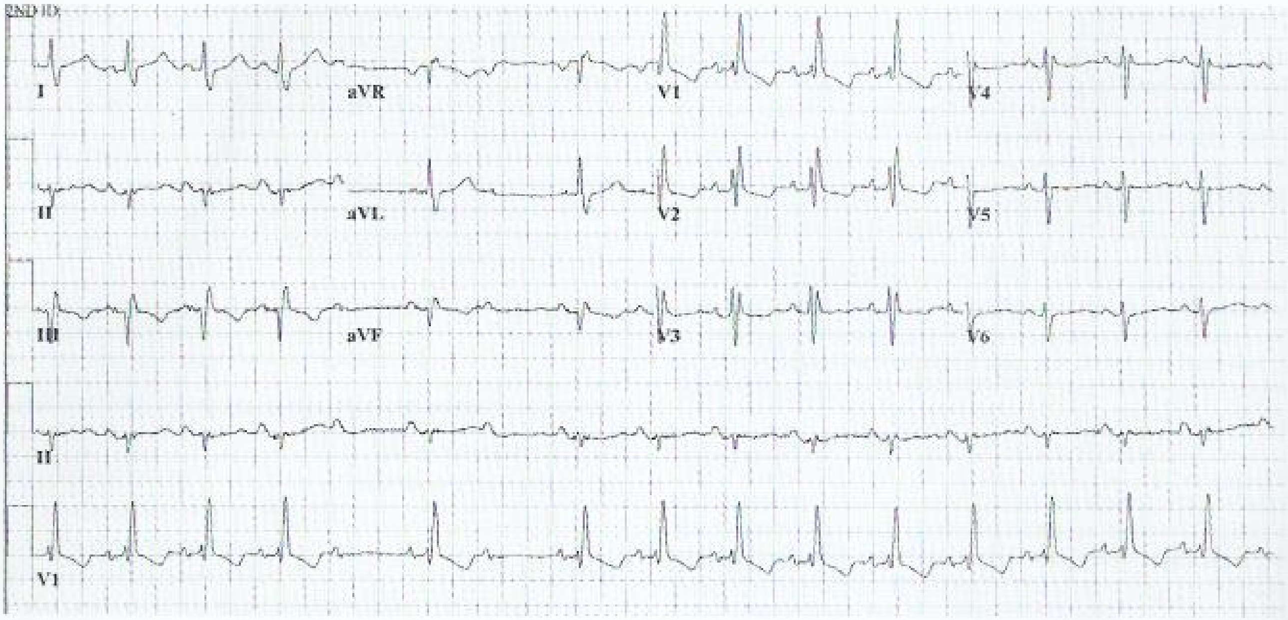
(A) Atropine
(B) Discontinue metoprolol and observe
(C) Emergent coronary angiography
(D) Emergent pacing

Item 103

A 45-year-old man is evaluated for hypertension. He is otherwise healthy and has not had any symptoms. His father died of an acute myocardial infarction at age 49 years. He takes no medications.

On physical examination, temperature is normal, blood pressure is 172/80 mm Hg, pulse rate is 80/min, and respiration rate is normal. The lungs are clear. Jugular venous pulse is normal. S_1 and S_2 are normal. There is a soft ejection click that precedes a grade 2/6 diastolic decrescendo murmur, which is best heard at the right lower sternal border.

A transthoracic echocardiogram shows a bicuspid aortic valve with mild aortic regurgitation. The left ventricular ejection fraction is 50%. The ascending aorta is enlarged, with a dimension of 42 mm in the mid-portion.



ITEM 102

Which of the following is the most appropriate next step in management?

(A) Annual transthoracic echocardiography
(B) CT angiography of the aorta
(C) Infective endocarditis prophylaxis
(D) Surgical aortic valve replacement

Item 104

A 62-year-old woman is evaluated during a routine examination. She feels well and has no exercise limitations. Medical history is significant for hypertension treated with enalapril. She does not smoke. At her last examination 4 years ago, her blood pressure was 122/76 mm Hg. Laboratory studies at that time revealed a serum total cholesterol level of 184 mg/dL (4.77 mmol/L), serum HDL cholesterol level of 42 mg/dL (1.09 mmol/L), and hemoglobin A_{1c} value of 5.4%. At that time, according to the Pooled Cohort Equations, her 10-year risk for atherosclerotic cardiovascular disease was calculated to be 3.8%. She has gained 5 kg (11 lb) since then.

On physical examination today, blood pressure is 140/90 mm Hg. BMI is 29. The remainder of the physical examination is unremarkable.

Laboratory studies are significant for a serum total cholesterol level of 250 mg/dL (6.47 mmol/L), a serum HDL cholesterol level of 30 mg/dL (0.78 mmol/L), and a hemoglobin A_{1c} value of 6.6%. A subsequent fasting plasma glucose level is 130 mg/dL (7.2 mmol/L).

Which of the following confers the highest risk for atherosclerotic cardiovascular disease in this patient?

(A) Diabetes mellitus
(B) Diastolic blood pressure of 90 mm Hg
(C) HDL cholesterol level of 30 mg/dL (0.78 mmol/L)
(D) Systolic blood pressure of 140 mm Hg
(E) Total cholesterol level of 250 mg/dL (6.47 mmol/L)

Item 105

A 71-year-old man is evaluated for a 10-day history of malaise and fatigue. Two years ago, he underwent dual-chamber pacemaker implantation for third-degree atrioventricular block. He reports discomfort at the site of his pacemaker. He has had no fever, chills, or weight loss. Medical history is otherwise significant for well-controlled hypertension and hyperlipidemia treated with chlorthalidone and atorvastatin.

On physical examination, vital signs are normal. The skin overlying the patient's pacemaker pocket is slightly erythematous and is warm and tender to palpation. The remainder of the physical examination is noncontributory.

A complete blood count and erythrocyte sedimentation rate are ordered.

Which of the following is the most appropriate management?

(A) Blood cultures
(B) Empiric therapy with cephalexin
(C) Pacemaker pocket aspiration
(D) PET/CT scanning

Item 106

A 69-year-old man is evaluated in the emergency department for a 1-week history of progressive exertional dyspnea followed by the development of rest dyspnea. He reports an unchanged nonproductive cough without chest pain. Symptoms were not preceded by a respiratory tract infection. He has been sleeping in a reclining chair at night. Medical history is significant for COPD and ischemic cardiomyopathy with a left ventricular ejection fraction of

20%. He has a 30-year history of cigarette smoking but quit 7 years ago. Current medications are a tiotropium inhaler, lisinopril, carvedilol, furosemide, and low-dose aspirin.

On physical examination, the patient is afebrile, blood pressure is 152/88 mm Hg, pulse rate is 98/min, and respiration rate is 22/min. Oxygen saturation is 95% breathing ambient air. The neck veins cannot be assessed because of large neck size. The heart sounds are distant. Pulmonary examination reveals distant breath sounds and a prolonged expiratory phase but no wheezes. Peripheral edema is noted.

A chest radiograph shows an enlarged cardiac silhouette and no infiltrates. An echocardiogram reveals a left ventricular ejection fraction of 20% and a right ventricular systolic pressure of 40 mm Hg.

Which of the following is the most likely cause of this patient's symptoms?

(A) COPD exacerbation
(B) Heart failure exacerbation
(C) Pneumonia
(D) Pulmonary embolism

H Item 107

A 64-year-old man is evaluated in the emergency department for a 1-week history of exertional chest pain and onset of rest pain 3 hours ago. During the evaluation, he develops ventricular fibrillation. The patient undergoes rapid defibrillation. He is currently awake with ongoing chest pain. Medical history is significant for hyperlipidemia, hypertension, type 2 diabetes mellitus, tobacco use, and previous stroke. Medications are aspirin, lisinopril, metoprolol, metformin, and simvastatin.

On physical examination, the patient is alert and oriented. Temperature is normal, blood pressure is 100/60 mm Hg, pulse rate is 110/min, and respiration rate is 24/min. Oxygen saturation is 98% breathing 4 L of oxygen by nasal cannula. Pulmonary examination reveals bibasilar crackles.

An electrocardiogram demonstrates left bundle branch block, a new finding since electrocardiography 8 months ago.

Which of the following is the most appropriate next step in management?

(A) Intravenous amiodarone
(B) Primary percutaneous coronary intervention
(C) Therapeutic hypothermia
(D) Urgent coronary artery bypass graft surgery

Item 108

A 68-year-old man is evaluated for a 4-month history of right arm fatigue and dizziness. Last week, he became dizzy while standing on a 10-foot ladder and cleaning his gutters with his right hand. His symptoms improved after 3 minutes of rest. He reports that right arm activity reproduces his arm fatigue and discomfort, mainly in the forearm. Medical history is significant for hypertension and hyperlipidemia. He has a 60-pack-year smoking history. Medications are lisinopril, amlodipine, and atorvastatin.

On physical examination, temperature is normal, blood pressure is 110/65 mm Hg in the right arm and 145/85 mm Hg in the left arm, and pulse rate is 72/min. A bruit is heard over the right supraclavicular fossa. Left carotid upstroke is normal. The right radial pulse and right carotid pulse are faint, and the left radial pulse is slightly diminished. Cardiac examination is normal.

Which of the following is the most appropriate diagnostic test to perform next?

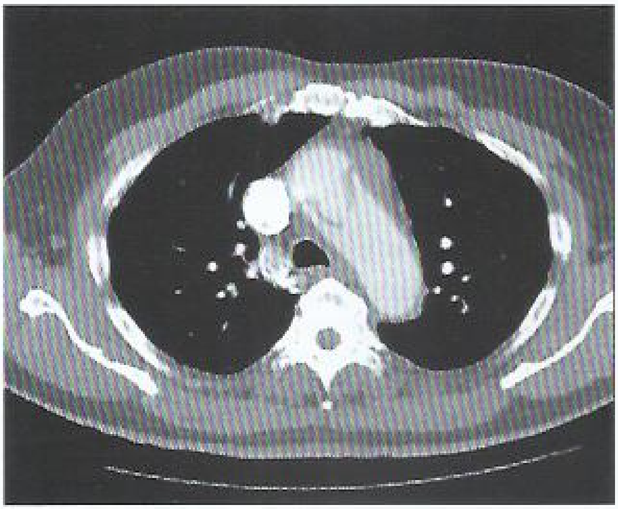
(A) Adson maneuver (thoracic outlet maneuver)
(B) Ankle-brachial index
(C) Carotid duplex ultrasonography
(D) CT angiography of the chest and neck

Item 109 H

A 42-year-old man is evaluated in the emergency department for a 3-hour history of severe chest pain that radiates to the back. The pain is sharp and tearing in character. Medical history is significant for hypertension. Medications are amlodipine and lisinopril.

On physical examination, blood pressure is 128/78 mm Hg in the right arm and 162/99 mm Hg in the left arm, and pulse rate is 110/min. Lungs are clear to auscultation. Other than tachycardia, examination of the heart is normal. Right radial and brachial pulses are diminished.

A chest CT scan is shown.



Which of the following is the most appropriate management?

(A) Coronary angiography
(B) Medical therapy alone
(C) Open surgical aortic repair
(D) Thoracic endovascular aortic repair

Item 110

A 48-year-old woman is evaluated during a new-patient visit. She reports no symptoms. She runs 5 miles a day 5 days per week. Medical history is otherwise unremarkable. She takes no medications.

On physical examination, vital signs are normal. The estimated central venous pressure is 6 cm H_2O. Cardiac examination reveals a grade 2/6 holosystolic murmur that is best heard at the apex and radiates toward the axilla. An ejection click is not audible. The lungs are clear to auscultation. No edema is present.

Which of the following is the most appropriate management?

(A) Cardiac magnetic resonance imaging
(B) Transesophageal echocardiography
(C) Transthoracic echocardiography
(D) Routine clinical follow-up without imaging

Item 111

A 62-year-old man is evaluated for a 6 month history of bilateral lower extremity edema. He was started on furosemide 2 months ago, with minimal change in the edema. He has no history of lung disease or recent surgery. His medical history is notable for permanent pacemaker implantation 2 years ago for symptomatic sinus node dysfunction. He takes no medications other than furosemide.

On physical examination, vital signs are normal. The lungs are clear. The estimated central venous pressure is elevated at 10 cm H_2O with a prominent *v* wave. A mild right ventricular heave is palpable. A grade 3/6 holosystolic murmur is noted at the left lower sternal border. The murmur varies slightly with respiration and is associated with an early diastolic filling sound. S_1 and S_2 are normal. There is no hepatosplenomegaly. Bilateral lower extremity pitting edema is present up to the level of the knees. The remainder of the physical examination is normal.

Which of the following is the most appropriate next step in management?

(A) Cardiac magnetic resonance imaging
(B) Coronary angiography
(C) Right heart catheterization
(D) Transthoracic echocardiography

Item 112

A 64-year-old man is evaluated during a follow-up visit for stable angina. He is currently taking metoprolol and wishes to discontinue this medication owing to side effects. He has normal left ventricular function and no symptoms of heart failure. Medical history is significant for hyperlipidemia, hypertension, and coronary artery disease treated with coronary artery bypass graft surgery. Medications are low-dose aspirin and maximum doses of lisinopril, metoprolol, isosorbide mononitrate, ranolazine, and atorvastatin.

On physical examination, temperature is normal, blood pressure is 120/60 mm Hg, pulse rate is 70/min, and respiration rate is 18/min. Oxygen saturation is 98% breathing ambient air. The remainder of the examination is unremarkable.

The patient is switched to diltiazem.

Which of the following is the most appropriate management of this patient's medication regimen?

(A) Decrease ranolazine
(B) Increase atorvastatin
(C) Switch lisinopril to ramipril
(D) No medication adjustment

Item 113

An 81-year-old man is evaluated before elective hip arthroplasty. Medical history is significant for hypertension and osteoarthritis. He reports no chest pain, palpitations, exertional dyspnea, or other symptoms of cardiovascular disease. His medications are lisinopril and celecoxib.

On physical examination, vital signs are normal. The cardiopulmonary examination is normal. Range of motion of the right hip is limited by pain without overlying erythema or warmth.

Laboratory studies reveal normal kidney function and electrolyte levels.

A 12-lead electrocardiogram is shown. Findings are unchanged from 7 years ago.

ITEM 113

Which of the following is the most appropriate management?

(A) Dobutamine echocardiography
(B) Echocardiography
(C) Prophylactic pacemaker insertion
(D) No further testing or intervention

Item 114

A 72-year-old woman is evaluated during a follow-up visit. She has a 3-year history of heart failure with a left ventricular ejection fraction of 25% and New York Heart Association functional class III symptoms. She has an implantable cardioverter-defibrillator. She reports manageable lightheadedness with standing. Medications are lisinopril, carvedilol, and spironolactone at maximally tolerated doses.

On physical examination, the patient is afebrile, blood pressure is 98/64 mm Hg, and pulse rate is 68/min. The estimated central venous pressure is 6 cm H_2O. An S_3 is present. The lungs are clear to auscultation. There is no lower extremity edema.

Which of the following is the most appropriate management?

(A) Add ivabradine
(B) Add valsartan-sacubitril
(C) Discontinue carvedilol and start ivabradine
(D) Discontinue lisinopril and start valsartan-sacubitril
(E) Continue current medications

Item 115

A 38-year-old woman is evaluated for intermittent palpitations. She reports no other symptoms. Medical history is unremarkable, and she takes no medications.

On physical examination, vital signs are normal. The estimated central venous pressure is elevated. Apical impulse is normal, a parasternal impulse is present at the left sternal border, and a soft systolic murmur is heard at the second left intercostal space. Fixed splitting of the S_2 is noted throughout the cardiac cycle. The remainder of the physical examination is normal.

An electrocardiogram demonstrates right-axis deviation and incomplete right bundle branch block. A chest radiograph shows right heart enlargement. A transthoracic echocardiogram demonstrates a 1.5-cm ostium secundum atrial septal defect. The right heart chambers are enlarged and the estimated pulmonary artery systolic pressure is normal.

Which of the following is the best management?

(A) Cardiac magnetic resonance imaging
(B) Device closure of the atrial septal defect
(C) Endocarditis prophylaxis
(D) Measurement of functional aerobic capacity

Item 116

An 88-year-old man is evaluated for chest tightness and dyspnea. His symptoms began 8 months ago and now occur with ambulation. Medical history is significant for type 2 diabetes mellitus, hypertension, chronic kidney disease, and a transient ischemic attack that occurred 4 years ago. Current medications are metformin, atorvastatin, lisinopril, and low-dose aspirin.

On physical examination, temperature is normal, blood pressure is 145/82 mm Hg, pulse rate is 64/min, and respiration rate is normal. The lungs are clear. A grade 3/6 late-peaking systolic murmur is auscultated at the cardiac base with radiation to the carotid arteries. There is no S_3.

Echocardiogram demonstrates severe aortic stenosis with a mean gradient of 62 mm Hg and an aortic valve area of 0.65 cm².

Cardiac surgery assessment estimates the surgical risk to be high (estimated risk for mortality, 10%; estimated risk for major morbidity plus mortality, 38%).

Which of the following is the most appropriate treatment?

(A) Balloon aortic valvuloplasty
(B) Medical therapy
(C) Surgical aortic valve replacement
(D) Transcatheter aortic valve replacement

Item 117

H

A 66-year-old man is evaluated in the hospital following ST-elevation myocardial infarction treated with primary percutaneous coronary intervention of the left anterior descending artery 4 days ago. His initial presentation was complicated by the presence of heart failure and pulmonary edema. He is asymptomatic and ambulating, and he is nearly ready for discharge. Medical history is significant for hyperlipidemia, type 2 diabetes mellitus, and hypertension. Medications are aspirin, prasugrel, lisinopril, carvedilol, atorvastatin, and basal and prandial insulin.

On physical examination, vital signs are normal. Oxygen saturation is 99% breathing ambient air. The remainder of the examination is unremarkable.

Laboratory studies are significant for a serum creatinine level of 1.0 mg/dL (88.4 µmol/L) and a serum potassium level of 3.7 mEq/L (3.7 mmol/L).

An echocardiogram shows a left ventricular ejection fraction of 35%.

Which of the following is the most appropriate treatment?

(A) Eplerenone
(B) Isosorbide mononitrate
(C) Valsartan
(D) Warfarin

Item 118

H

A 63-year-old man is evaluated in the emergency department for progressive dyspnea. The patient reports increasing difficulty breathing while lying flat. He has a history of atrial fibrillation and underwent catheter ablation 1 week ago. Medical history is otherwise significant for hypertension. He has no history of heart failure or left ventricular dysfunction. Medications are warfarin, dronedarone, and lisinopril.

H CONT.

On physical examination, temperature is normal, blood pressure is 88/72 mm Hg, pulse rate is 112/min, and respiration rate is 16/min. Pulsus paradoxus of 12 mm Hg is present. Oxygen saturation breathing ambient air is 96%. Cardiac examination reveals elevated estimated central venous pressure. Heart sounds are difficult to auscultate. Lung examination reveals no crackles.

An electrocardiogram demonstrates sinus tachycardia.

Which of the following is most likely responsible for the patient's symptoms?

(A) Atrioesophageal fistula
(B) Cardiac tamponade
(C) Pulmonary vein stenosis
(D) Retroperitoneal bleeding

Item 119

A 43-year-old woman is evaluated during a follow-up visit. Six months ago, she was diagnosed with heart failure and pulmonary sarcoidosis. Cardiac magnetic resonance imaging suggested possible cardiac sarcoidosis. She is feeling better after initiation of therapy, but she still has exertional dyspnea when walking up one flight of stairs. An echocardiogram obtained 1 week ago showed a left ventricular ejection fraction of 30%. Medications are candesartan, carvedilol, and spironolactone. She has also been taking prednisone for cardiac sarcoidosis for the past 6 months.

On physical examination, temperature is normal, blood pressure is 98/60 mm Hg, and pulse rate is 58/min. There is no jugular venous distention. Lungs are clear to auscultation. Cardiac examination is normal. No edema is noted.

An electrocardiogram shows a QRS duration of 158 ms, left bundle branch block, and first degree atrioventricular block.

Which of the following is the most appropriate management?

(A) Add furosemide
(B) Increase carvedilol
(C) Perform endomyocardial biopsy
(D) Refer for placement of an implantable cardioverter-defibrillator with cardiac resynchronization therapy

Item 120

A 42-year-old man is evaluated in the emergency department for an 8-hour history of acute-onset chest pain. The patient characterizes the pain as sharp and persistent. Medical history is significant for hypertension and hyperlipidemia. Medications are lisinopril and atorvastatin.

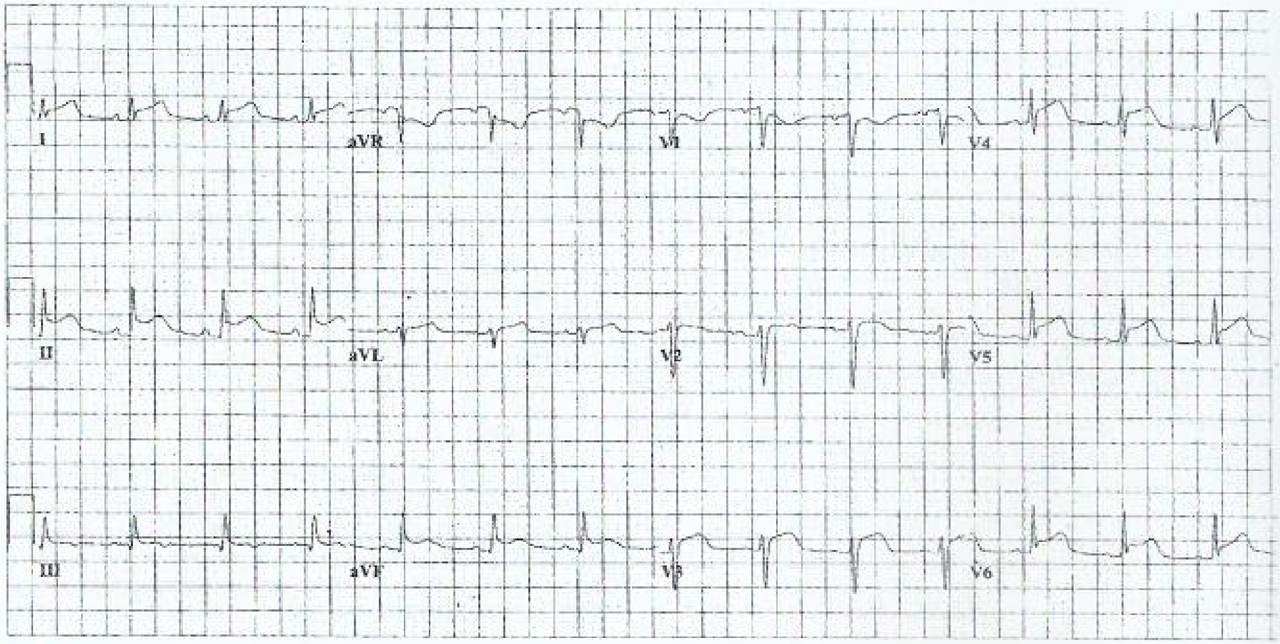
On physical examination, temperature is 37.2 °C (99.0 °F), blood pressure is 136/84 mm Hg, and respiration rate is normal. There is no jugular venous distention. The lungs are clear to auscultation. Cardiac examination reveals no rubs, murmurs, or gallops. Peripheral pulses are full and equal.

Laboratory studies reveal an elevated C-reactive protein level and leukocyte count of 9000/µL (9.0×10^9/L). Serum troponin T level is normal on arrival and 1 hour later.

An electrocardiogram is shown. Transthoracic echocardiogram demonstrates normal left ventricular size and function without segmental wall motion abnormalities. There is a small pericardial effusion measuring 4 mm.

Which of the following is the most appropriate management?

(A) Echocardiographic-guided pericardiocentesis
(B) Emergent cardiac catheterization
(C) Exercise treadmill stress testing
(D) High-dose aspirin and colchicine



ITEM 120

Answers and Critiques

H

Item 1 Answer: D

Educational Objective: Diagnose acute rejection in a cardiac transplant patient.

Endomyocardial biopsy will most likely establish the diagnosis. For cardiac transplant recipients, the risk for rejection is highest within the first 6 months after transplantation and then within the first year. After that time period, the incidence of rejection is quite low. This post-transplant patient is presenting with signs and symptoms of acute heart failure, including abdominal discomfort, exertional dyspnea, and an S_3. Additionally, the presence of cannon *a* waves suggests complete heart block, and the electrocardiogram is confirmatory, with P waves that march independent of the narrow QRS complex (*arrows*). All of these findings are consistent with acute rejection in a patient within the first year after cardiac transplantation, and the most appropriate test for diagnosis is endomyocardial biopsy. It is important to note that most patients with clinical rejection will not have any symptoms of heart failure; therefore, routine endomyocardial biopsies are performed within the first year after transplantation.

Abdominal CT would not establish the diagnosis. This patient's symptoms are most likely secondary to acute congestion; the patient's complete heart block and other cardiac findings should focus the clinician's attention on the heart. Abdominal CT should be performed only when the abdomen is thought to be the primary cause of the patient's symptoms.

Coronary artery disease is a common long-term complication of cardiac transplantation, and by 5 years after transplantation, vasculopathy is present in almost 50% of patients. Coronary artery disease would be more likely in a patient further removed from transplantation; therefore, coronary angiography would not establish the diagnosis.

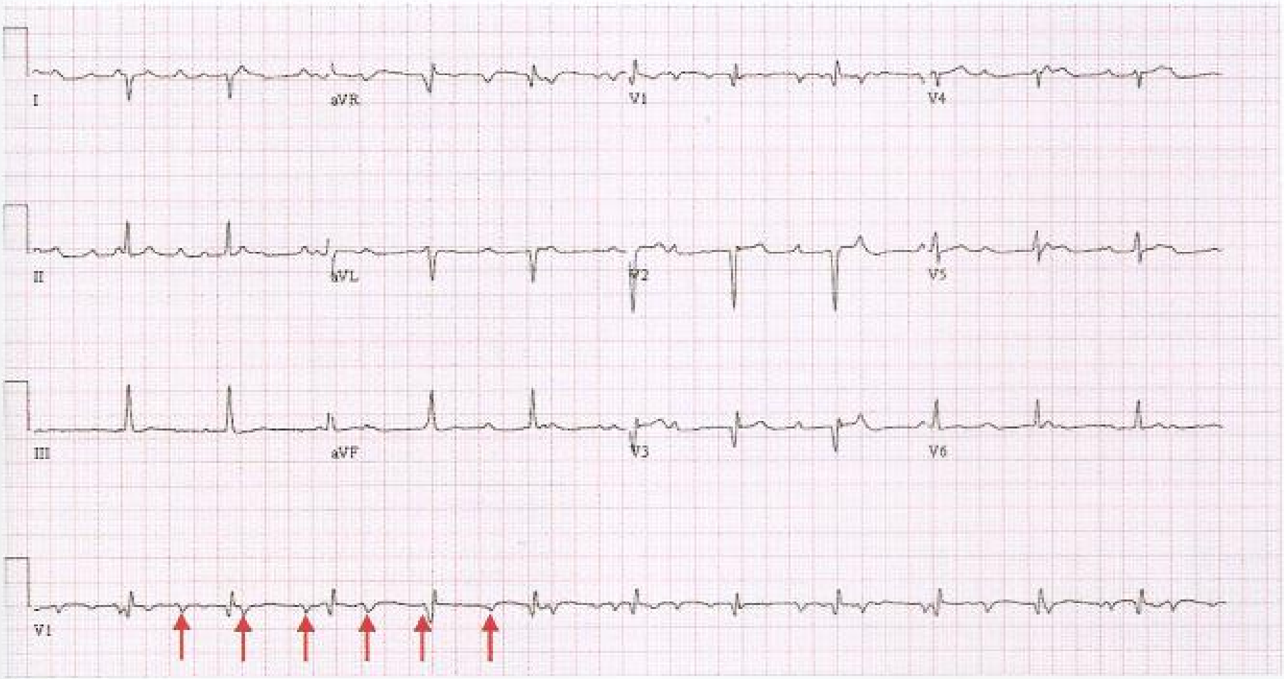
Echocardiography will confirm a decreased ejection fraction in this patient but cannot establish the diagnosis of rejection.

KEY POINT

- The risk for cardiac transplant rejection is highest within the first 6 months after transplantation and then within the first year; endomyocardial biopsy should be routinely performed within the first year after cardiac transplantation to diagnose rejection.

Bibliography

Birati EY, Rame JE. Post-heart transplant complications. Crit Care Clin. 2014;30:629-37. [PMID: 24996612] doi:10.1016/j.ccc.2014.03.005



ITEM 1

H

Item 2 Answer: D

Educational Objective: Treat a patient with a non-ST-elevation acute coronary syndrome with an early invasive strategy.

This patient should undergo urgent angiography. Patients with a non-ST-elevation acute coronary syndrome (NSTE-ACS) should undergo risk stratification before invasive treatment because the link between revascularization and clinical outcomes is less clear in these patients than in patients with ST-elevation myocardial infarction (STEMI). Risk stratification tools, such as the TIMI risk score, can be used to determine which patients with NSTE-ACS should be treated with an invasive strategy versus an ischemia-guided approach. An early invasive strategy benefits patients with high TIMI risk scores (5-7) and intermediate TIMI risk scores (3-4). This patient has a TIMI risk score of 5, as indicated by the presence of three traditional risk factors for coronary artery disease, aspirin use within the last week, age older than 65 years, two or more angina episodes in the past 24 hours, and significant ST-segment deviation on electrocardiogram. His score places him at high risk for death and cardiac ischemic events, and despite the absence of elevated cardiac biomarker levels, urgent coronary angiography is warranted.

Stress testing with adenosine nuclear stress testing or exercise stress electrocardiography could be considered for purposes of risk stratification if this patient declines an early invasive strategy. However, an invasive strategy has been shown to improve the composite clinical endpoint of death, recurrent myocardial infarction, and repeat hospitalization compared with an ischemia-guided approach in patients with NSTE-ACS.

In patients with suspected NSTE-ACS with a normal initial troponin level and inconclusive electrocardiographic findings, further diagnostic studies may be indicated. Coronary CT angiography is appropriate, and rest single-photon emission CT may be appropriate. However, in this patient with a high pretest probability of CAD, coronary CT angiography would only delay critical therapy.

KEY POINT

- Patients with a non-ST-elevation acute coronary syndrome who have a high or intermediate TIMI risk score should be treated with an early invasive strategy.

Bibliography

Amsterdam EA, Wenger NK, Brindis RG, Casey DE Jr, Ganiats TG, Holmes DR Jr, et al; ACC/AHA Task Force Members. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014;130:2354-94. [PMID: 25249586] doi:10.1161/CIR.0000000000000133

Item 3 Answer: B

Educational Objective: Treat degenerative mitral regurgitation with surgical mitral valve repair.

The most appropriate next step in management is surgical mitral valve repair. Myxomatous degeneration of the mitral valve is common, affecting 1% to 2% of the general population. In 10% of patients, the valvular lesion can progress, become life threatening, and require surgery. The only definitive therapy for severe mitral regurgitation is mitral valve surgery. Options are mitral valve repair, mitral valve replacement with preservation of part or all of the mitral apparatus, and mitral valve replacement with removal of the mitral apparatus. Mitral valve repair is generally preferred to valve replacement because it is associated with improved survival in retrospective studies. Mitral valve repair is strongly recommended for chronic severe primary mitral regurgitation in (1) symptomatic patients with left ventricular ejection fraction greater than 30%, (2) asymptomatic patients with left ventricular dysfunction (left ventricular ejection fraction of 30%-60% and/or left ventricular end-systolic diameter ≥40 mm), and (3) patients undergoing another cardiac surgical procedure. Additionally, mitral valve repair is reasonable in asymptomatic patients with chronic severe primary mitral regurgitation who have new-onset atrial fibrillation or pulmonary hypertension (pulmonary artery systolic pressure >50 mm Hg). Notably, a left ventricular ejection fraction of 60% or less is used in defining left ventricular systolic dysfunction in mitral regurgitation because aortic emptying into the left atrium contributes to the relatively lower afterload conditions and higher ejection fraction despite impaired left ventricular performance.

Serial evaluations every 6 to 12 months are recommended for patients with severe mitral regurgitation who do not have indications for surgery. This patient meets the criteria for surgery; therefore, serial evaluations would not be appropriate at this time.

Many patients who could benefit from mitral valve repair are denied surgery because of high surgical risk, advanced age, or comorbid conditions. A catheter-based device can improve mitral valve function by delivering a clip percutaneously to approximate the valve leaflet edges and improve leaflet coaptation at the origin of the mitral regurgitation jet. The device is approved for patients with significant symptomatic degenerative mitral regurgitation for whom mitral valve surgery poses a prohibitive risk. This patient is healthy and does not have comorbid conditions that would significantly increase surgical risk; therefore, transcatheter repair is not indicated.

KEY POINT

- Mitral valve repair is strongly recommended for chronic severe primary mitral regurgitation in symptomatic patients with left ventricular ejection fraction greater than 30%, asymptomatic patients with left ventricular dysfunction, and patients undergoing another cardiac surgical procedure.

Bibliography

Foster E. Clinical practice. Mitral regurgitation due to degenerative mitral valve disease. N Engl J Med. 2010;363:156-65. [PMID: 20647211] doi:10.1056/NEJMcp0906782

Item 4 Answer: A

Educational Objective: Diagnose hypertension related to bevacizumab therapy.

Bevacizumab is the most likely cause of this patient's hypertension. Bevacizumab is a monoclonal antibody that blocks angiogenesis by inhibiting vascular endothelial growth factor (VEGF) A. It is effective in combination with standard chemotherapy for the treatment of metastatic colon and gynecologic cancers. Inhibition of VEGF appears to cause hypertension through several mechanisms, including altered nitric oxide production, increased endothelin-1 production, and alterations in the pressure-natriuresis relationship. As such, bevacizumab-related hypertension is a mechanism-dependent, on-target toxicity, which results directly from inhibition of the VEGF signaling pathway rather than as a nonspecific drug side effect. Bevacizumab-related hypertension affects a high proportion of treated patients, and incidence is dose dependent. Hypertension is most commonly detected at approximately 60 days after therapy initiation and is reversible upon discontinuation of the medication. Because large increases in both diastolic and systolic blood pressures can occur as early as the first week of therapy, all patients taking an angiogenesis inhibitor (such as bevacizumab) should have their blood pressure carefully monitored during therapy, particularly early on. There is no preferred antihypertensive agent for treatment. Interestingly, the development of hypertension may be a marker of a therapeutic response or improved cancer outcome for patients treated with this class of drugs.

Cisplatin has been associated with increased risk for venous thromboembolism, supraventricular tachycardia, myocardial ischemia, and cardiomyopathy, but it has not been associated with hypertension.

Glucocorticoids, such as dexamethasone, may contribute to hypertension through an unclear mechanism. However, the timing and degree of hypertension observed in this patient are typical of a bevacizumab-induced reaction.

The most common cardiotoxicities associated with paclitaxel are bradycardia and heart block. Most of these events are asymptomatic, and routine cardiac monitoring is not advocated. Paclitaxel can uncommonly cause hypertension (1% incidence) but is more likely to cause hypotension (up to 12% incidence). When used in combination with doxorubicin, paclitaxel is associated with cardiomyopathy, which occurs at a higher incidence than with doxorubicin alone.

KEY POINT

- The monoclonal antibody bevacizumab is associated with the development of significant but reversible hypertension.

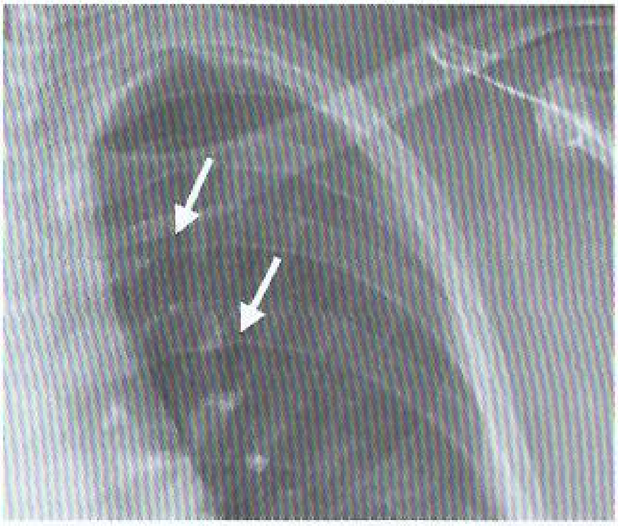
Bibliography

Robinson ES, Khankin EV, Karumanchi SA, Humphreys BD. Hypertension induced by vascular endothelial growth factor signaling pathway inhibition: mechanisms and potential use as a biomarker. Semin Nephrol. 2010;30:591-601. [PMID: 21146124] doi:10.1016/j.semnephrol.2010.09.007

Item 5 Answer: B

Educational Objective: Diagnose aortic coarctation.

The most likely diagnosis is aortic coarctation. This patient has dyspnea in the setting of aortic stenosis and hypertension, and she has clinical features of upper extremity hypertension and a radial artery-to-femoral artery pulse delay that suggest a mechanical obstruction between the radial and femoral arteries. A systolic murmur heard over the left chest is common in patients with severe aortic coarctation; these murmurs can arise from the obstruction or the collateral blood flow. The patient's chest radiograph demonstrates rib notching (*arrows*) affecting several of the posterior ribs; rib notching results from exaggerated collateral blood flow diverting blood around the area of obstruction. The patient additionally has aortic stenosis associated with a bicuspid aortic valve, which is present in more than 50% of patients with aortic coarctation. Cerebral artery aneurysm also occurs with increased frequency in patients with aortic coarctation.



The syndrome of aortic dissection usually presents with sharp or tearing chest and/or back pain. It may be accompanied by syncope, heart failure, or stroke and is rarely asymptomatic. Chest pain with concomitant acute ischemia in a distant arterial bed (stroke, limb ischemia) should prompt consideration of dissection. The chest radiograph does not demonstrate features of aortic dilatation or mediastinal widening characteristic of dissection.

Although the physical examination findings in a patient with severe essential hypertension often include an S_4, blood pressure and pulse differentials between the upper and lower extremities are not expected.

Renovascular hypertension is a common cause of hypertension, occurring primarily in patients with diffuse atherosclerosis. The physical examination in a patient with renovascular hypertension is usually normal, with the exception of hypertension and possible epigastric bruit; blood pressure and pulse differentials between upper and lower extremities are not expected.

KEY POINT

- Aortic coarctation is characterized by clinical features of upper extremity hypertension and a radial artery-to-femoral artery pulse delay as well as radiographic findings of "figure 3 sign" and rib notching.

Bibliography

Tanous D, Benson LN, Horlick EM. Coarctation of the aorta: evaluation and management. Curr Opin Cardiol. 2009;24:509-15. [PMID: 19667980] doi:10.1097/HCO.0b013e328330cc22

H **Item 6 Answer: E**

Educational Objective: Manage a patient with acute limb ischemia.

The most appropriate next step in the management of this patient with acute limb ischemia (ALI) is urgent invasive angiography to determine the extent of disease and to plan treatment. ALI is defined by a sudden or rapid decrease in limb perfusion, often manifested as a new pulse deficit, rest pain, pallor, and/or paralysis. The most common causes of ALI include in situ thrombosis of a lower extremity bypass graft or endovascular stent and thromboembolism. Patients with ALI and a viable extremity are most commonly treated with surgical embolectomy or catheter-directed thrombolysis. This patient is demonstrating several classic signs of ALI, including pulselessness, pallor, and pain, and he is at heightened risk for ALI owing to his history of femoral-popliteal bypass graft surgery. The most appropriate next step is to perform invasive angiography to define the level of occlusion and to determine whether surgical embolectomy or catheter-directed thrombolysis is an option. Delay in treatment may lead to worsening limb perfusion, limb necrosis, or the need for lower extremity amputation.

Noninvasive imaging studies, such as arterial duplex ultrasonography and CT angiography, may be useful to detect the level of stenosis and extent of disease, but these tests will substantially delay the treatment of ALI in this patient.

Emergent lower extremity amputation is necessary in patients with ALI who have a nonviable extremity (gangrene, paralysis); however, this patient exhibits signs of viability (intact sensation and muscle strength) and should not undergo immediate amputation.

In contrast to the treatment of acute ischemic stroke or acute ST-elevation myocardial infarction, systemic thrombolytic therapy (such as with recombinant tissue plasminogen activator) has not been proved beneficial in the treatment of ALI and should not be used in this patient.

KEY POINT

- In patients with acute limb ischemia, invasive angiography should be performed immediately to define the anatomic level of occlusion and plan for revascularization.

Bibliography

Creager MA, Kaufman JA, Conte MS. Clinical practice. Acute limb ischemia. N Engl J Med. 2012;366:2198-206. [PMID: 22670905] doi:10.1056/NEJMcp1006054

Item 7 Answer: D

Educational Objective: Manage antithrombotic therapy in a patient with atrial fibrillation and coronary artery disease.

This patient with coronary artery disease (CAD) and atrial fibrillation should be treated with oral anticoagulation alone. Thromboembolism (stroke or systemic embolism) is the most feared and devastating complication of atrial fibrillation. Patients with atrial fibrillation and a moderate to high risk for stroke (CHA_2DS_2-VASc score ≥2) should be treated with oral anticoagulation for stroke prevention. This patient has a CHA_2DS_2-VASc score of 5 (1 point each for female sex, hypertension, and vascular disease; 2 points for age ≥75 years) and should receive oral anticoagulation therapy. Dose-adjusted warfarin is an effective low-cost option for stroke prevention in patients with atrial fibrillation. The chief limitations of warfarin are the need for frequent INR monitoring and adjustment as well as the numerous food and drug interactions associated with its use. The FDA has approved several non–vitamin K antagonist oral anticoagulants for the prevention of stroke in patients with nonvalvular atrial fibrillation, including dabigatran, rivaroxaban, edoxaban, and apixaban. These agents are superior, or at least noninferior, to warfarin in the prevention of stroke in patients with nonvalvular atrial fibrillation and do not necessitate routine coagulation monitoring. Warfarin remains the agent of choice in patients with valvular atrial fibrillation.

Antiplatelet therapy with aspirin is typically indicated in patients with CAD; however, aspirin alone or dual antiplatelet therapy (aspirin plus clopidogrel) is insufficient for stroke prevention in patients at high risk, such as this one.

Combination therapy with oral anticoagulation and antiplatelet therapy, such as aspirin or clopidogrel, is associated with significantly increased risk for bleeding and no apparent incremental benefit. This patient already has several risk factors for bleeding, including a low BMI, hypertension, and female sex, and it is important to minimize the risk for bleeding when oral anticoagulation is prescribed. In patients with atrial fibrillation and CAD, it is recommended that antiplatelet therapy be discontinued unless the patient has recent active CAD, defined as acute coronary syndrome or revascularization in the past 12 months. Because this patient has a history of percutaneous coronary intervention performed 5 years ago, there is no indication for concomitant antiplatelet therapy with oral anticoagulation.

KEY POINT

- For most patients with high-risk atrial fibrillation and stable coronary artery disease, oral anticoagulation therapy without an antiplatelet agent is sufficient for prevention of both acute coronary syndromes and thromboembolism.

Bibliography

Steinberg BA, Kim S, Piccini JP, Fonarow GC, Lopes RD, Thomas L, et al; ORBIT-AF Investigators and Patients. Use and associated risks of concomitant aspirin therapy with oral anticoagulation in patients with atrial

fibrillation: insights from the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) Registry. Circulation. 2013;128:721-8. [PMID: 23861512] doi:10.1161/CIRCULATIONAHA.113.002927

Item 8 Answer: C

Educational Objective: Evaluate for coronary artery disease in a patient with left ventricular hypertrophy.

This patient should undergo exercise stress echocardiography to evaluate for coronary artery disease (CAD). This patient's symptoms, age, and sex place him at intermediate risk for CAD. His resting electrocardiogram (ECG) demonstrates left ventricular hypertrophy with significant repolarization abnormalities (ST segment depressions >0.5 mm), findings that limit the ability to interpret the ECG during exercise. Because this patient requires further testing to diagnose obstructive CAD and is able to exercise, he should undergo exercise stress testing with adjunctive imaging, either echocardiography or a nuclear perfusion study. Other uninterpretable ECG findings that should prompt stress testing with imaging include left bundle branch block, ventricular paced complexes, digitalis effect, and preexcitation.

Coronary angiography is an invasive test that carries significant risks. It should be considered in patients who have a high pretest probability for obstructive CAD, including symptomatic patients with abnormal findings on noninvasive testing for CAD or patients with an acute coronary syndrome.

Coronary artery calcium scoring is predominantly used in asymptomatic patients with intermediate risk for CAD to provide additional risk stratification for the purpose of guiding primary prevention.

Exercise stress ECG is inappropriate in this patient with abnormalities on a baseline ECG. Such findings preclude the use of ECG stress testing because they interfere with the ability to accurately interpret changes that may occur with stress.

Exercise stress testing is preferred to pharmacologic stress testing in most clinical scenarios because valuable prognostic information is gained from the patient's exercise capacity. Pharmacologic nuclear stress testing is generally reserved for patients who are unable to exercise.

KEY POINT

- Stress testing with adjunctive imaging should be performed in patients with suspected coronary artery disease who have baseline electrocardiographic (ECG) abnormalities that preclude the use of ECG stress testing, such as ST-segment depressions greater than 0.5 mm, left bundle branch block, ventricular paced complexes, digitalis effect, and preexcitation.

Bibliography

Fihn SD, Gardin JM, Abrams J, et al; American College of Cardiology Foundation.; American Heart Association Task Force on Practice Guidelines.; American College of Physicians; American Association for Thoracic Surgery; Preventive Cardiovascular Nurses Association; Society for Cardiovascular Angiography and Interventions; Society of Thoracic Surgeons. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol. 2012 Dec 18;60(24):e44-e164. [PMID: 23182125]

Item 9 Answer: A

Educational Objective: Treat effusive constrictive pericarditis.

The most appropriate management is ibuprofen and colchicine. This patient has subacute signs of elevated right heart pressure. Pulsus paradoxus is present, and the echocardiogram demonstrates a moderately sized pericardial effusion with evidence of tamponade. The intrapericardial pressure is reduced to normal following drainage, whereas the intracardiac pressures remain elevated and equalized despite drainage, consistent with a diagnosis of effusive constrictive pericarditis. Effusive constrictive pericarditis may occur following idiopathic or infectious pericarditis or radiation therapy. CT or cardiac magnetic resonance imaging may demonstrate thickening of the pericardium, but calcification is usually absent. Fever, leukocytosis, elevated erythrocyte sedimentation rate, and a pericardial friction rub may be present but are not universally so. Similar to acute pericarditis, NSAIDs and colchicine are first-line therapy. Close follow-up is recommended. Pericardiectomy may be required in patients with pericarditis that does not respond to medical therapy.

Isoniazid, rifampin, pyrazinamide, and ethambutol are initial therapy for tuberculous pericarditis; however, this patient does not have risk factors for tuberculosis, and his interferon-γ release assay result is negative. An elevated concentration of adenosine deaminase (>50 U/L) in the pericardial fluid is 100% sensitive for tuberculosis; a negative result rules out tuberculous involvement.

Pericardiectomy is recommended for patients with effusive constrictive pericarditis that does not respond to first-line therapy with NSAIDs and colchicine.

A pericardial subxiphoid window is indicated for patients with recurrent hemodynamically significant pericardial effusion despite medical therapy, as may occur with malignant effusions. This intervention would not provide adequate hemodynamic relief from constriction.

KEY POINT

- Effusive constrictive pericarditis is characterized by findings compatible with constrictive pericarditis and a concomitant effusion; NSAIDs and colchicine are first-line therapy, and close follow-up is recommended.

Bibliography

Syed FF, Ntsekhe M, Mayosi BM, Oh JK. Effusive-constrictive pericarditis. Heart Fail Rev. 2013;18:277-87. [PMID: 22422296] doi:10.1007/s10741-012-9308-0

Item 10 Answer: C

Educational Objective: Differentiate between pseudostenosis and true aortic stenosis.

The most appropriate next step in management is dobutamine echocardiography. This patient has low-flow, low gradient aortic stenosis. The primary abnormality may be either severe ventricular dysfunction with pseudostenosis or critical aortic stenosis. Severe ventricular dysfunction with diminished cardiac output leads to decreased opening forces on the aortic valve, and the valve area may be calculated to be low even though the valve is not anatomically severe (pseudostenosis). Dobutamine, an inotropic agent, can be used to increase cardiac output and differentiate between these two entities. Dobutamine will cause an increase in the aortic valve area in pseudostenosis, whereas in anatomically severe aortic stenosis, the aortic valve area will not significantly increase.

Aortic valve replacement should be considered for patients with anatomically severe aortic stenosis. This procedure is currently inappropriate for a patient in whom the diagnosis of severe aortic stenosis has not been established.

Coronary angiography is recommended before valve surgery in patients with severe valvular heart disease and a history of coronary artery disease, suspected myocardial ischemia, or left ventricular systolic dysfunction. These patients may require concomitant revascularization at the time of surgery. However, coronary angiography is indicated only in patients for whom valve surgery has been determined to be appropriate.

The 2016 American College of Cardiology/American Heart Association/Heart Failure Society of America heart failure focused update recommends that valsartan-sacubitril be substituted for an ACE inhibitor or an angiotensin receptor blocker in patients with chronic symptomatic heart failure with reduced ejection fraction (New York Heart Association functional class II or III) who have tolerated ACE inhibitor or angiotensin receptor blocker therapy well. In this patient, differentiation of pseudostenosis from true aortic stenosis is most appropriate before initiating an increase in medical therapy.

KEY POINT

- In patients with findings of low-flow, low-gradient aortic stenosis, the primary abnormality may be either severe ventricular dysfunction with pseudostenosis or critical aortic stenosis; dobutamine echocardiography is needed to distinguish between the two entities.

Bibliography

O'Sullivan CJ, Praz F, Stortecky S, Windecker S, Wenaweser P. Assessment of low-flow, low-gradient, severe aortic stenosis: an invasive evaluation is required for decision making. EuroIntervention. 2014:10 Suppl U:U61-8. [PMID: 25256333] doi:10.4244/EIJV10SUA9

H Item 11 Answer: D

Educational Objective: Treat cardiogenic shock.

The most appropriate initial treatment of this patient with cardiogenic shock is to start dobutamine. Cardiogenic shock is defined by persistent symptomatic hypotension and end-organ dysfunction. Patients present with acute kidney failure, evidence of liver dysfunction with elevated aminotransferase levels, poor peripheral perfusion with cool extremities, and impaired mental status. Cardiogenic shock secondary to progressive heart failure is generally treated with an inotropic agent, such as dobutamine or milrinone. Patients with peripheral vasoconstriction (increased systemic vascular resistance) often benefit from the addition of a pure vasodilator, such as sodium nitroprusside. In this case, dobutamine would be a better option than milrinone, even in the setting of relative tachycardia, because milrinone is excreted through the kidneys and could build to a toxic level given her current kidney function.

β-Blockers such as carvedilol should be continued during a heart failure hospitalization whenever possible. In a patient with volume overload without signs of low cardiac output, β-blockers can often be continued at the maintenance dose while the patient is undergoing diuresis. However, in a patient with low cardiac output such as this one, β-blockers should be discontinued, owing to their negative inotropic effects, even in the setting of tachycardia.

Digoxin is a weak inotrope that reduces hospitalizations in patients with heart failure. Although this patient's digoxin level is low, the dose should not be increased in the setting of acute kidney failure. Additionally, increasing digoxin would not be expected to adequately improve cardiac output in this patient.

Although afterload reduction is reasonable to decrease myocardial oxygen demand and improve forward flow in patients with acute decompensation, a short-acting intravenous agent, such as nitroprusside or nitroglycerin, would be administered instead of increasing the dosage of an oral ACE inhibitor, such as lisinopril.

KEY POINT

- In patients with cardiogenic shock, inotropes such as dobutamine or milrinone may be considered to improve cardiac function.

Bibliography

Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Drazner MH, et al; American College of Cardiology Foundation. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2013;62:e147-239. [PMID: 23747642] doi:10.1016/j.jacc.2013.05.019

Item 12 Answer: D

Educational Objective: Treat atrial flutter refractory to medical therapy.

Catheter ablation is the most appropriate treatment for this patient with electrocardiographic evidence of atrial flutter. Atrial flutter is an organized macro-reentrant tachycardia with discrete regular atrial activity on electrocardiogram, usually with a rate of 250/min to 300/min. Typical atrial flutter is characterized electrocardiographically by a sawtooth

pattern with inverted flutter waves in leads II, III, and aVF and positive flutter waves in lead V_1. Management of atrial flutter is similar to that for atrial fibrillation and includes catheter ablation, antiarrhythmic drug therapy, and cardioversion. Catheter ablation is the definitive treatment for typical atrial flutter, owing to a very high success rate (>95%) and low complication rate. This patient with typical atrial flutter has symptoms (palpitations, fatigue, and exercise intolerance) despite adequate rate control with metoprolol, and treatment with catheter ablation offers the best balance of benefits and risks.

Antiarrhythmic drug therapy carries a high risk for recurrent atrial flutter and is therefore not the best option for this patient. Additionally, amiodarone is associated with substantial risk for end-organ toxicity, including thyroid dysfunction, neurologic side effects (such as tremor), liver dysfunction, and pulmonary toxicity.

Cardiac catheterization would be appropriate if there were a high pretest probability of obstructive coronary artery disease; however, this patient has normal findings on echocardiogram without evidence of stress-induced wall motion abnormalities.

Cardioversion to restore sinus rhythm could be considered, but this patient is hemodynamically stable and already has experienced a recurrence of atrial flutter after previous cardioversion. Cardioversion may therefore be ineffective for long-term control of the patient's symptoms.

KEY POINT

- Patients with symptomatic atrial flutter despite adequate medical therapy and rate control should undergo catheter ablation.

Bibliography

Page RL, Joglar JA, Caldwell MA, Calkins H, Conti JB, Deal BJ, et al. 2015 ACC/AHA/HRS guideline for the management of adult patients with supraventricular tachycardia: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol. 2016;67:e27-e115. [PMID: 26409259] doi:10.1016/j.jacc.2015.08.856

Item 13 Answer: B

Educational Objective: Diagnose patent ductus arteriosus.

This patient has a patent ductus arteriosus (PDA). A continuous murmur heard beneath the left clavicle that envelops the S_2 is typical of a PDA; it is often described as a "machinery" murmur. A tiny PDA is generally asymptomatic with an inaudible murmur. Patients with a small PDA may have an audible murmur but no other cardiovascular features. Patients with a moderate-sized PDA may have bounding pulses, a wide pulse pressure, left heart enlargement and dysfunction, and clinical heart failure. A large PDA may present with pulmonary hypertension and shunt reversal (Eisenmenger syndrome) in adults.

Aortic regurgitation due to a bicuspid aortic valve causes a diastolic murmur, most commonly heard along the left sternal border. A brief systolic murmur is also commonly heard at the second right intercostal space, from increased flow across the bicuspid aortic valve. A systolic ejection click is often heard in patients with bicuspid aortic valve, but a continuous murmur that envelops the S_2 is not expected.

Pulmonary regurgitation occurs most commonly after balloon or surgical intervention for congenital pulmonary stenosis. It is characterized by a diastolic murmur heard along the left sternal border that increases with inspiration; a systolic ejection murmur is also commonly heard from increased flow across the pulmonary valve. Although the pulmonary component of S_2 may be reduced or absent in patients with pulmonary regurgitation, separation between systole and diastole is distinct, and the aortic component should be audible.

A small ventricular septal defect (VSD) presents with a loud holosystolic murmur located at the left sternal border that may obliterate the S_2; a palpable thrill is often present. The pressure gradient between the ventricles determines the murmur quality and duration. A diastolic component of the murmur is not expected. Small VSDs do not cause left heart enlargement or pulmonary hypertension. Progressive pulmonary hypertension results in shortening of the murmur.

KEY POINT

- Patients with a small patent ductus arteriosus may present with a continuous murmur beneath the left clavicle that envelops the S_2 but no other cardiovascular features.

Bibliography

Baumgartner H, Bonhoeffer P, De Groot NM, de Haan F, Deanfield JE, Galie N, et al; Task Force on the Management of Grown-up Congenital Heart Disease of the European Society of Cardiology (ESC). ESC guidelines for the management of grown up congenital heart disease (new version 2010). Eur Heart J. 2010;31:2915-57. [PMID: 20801927] doi:10.1093/eurheartj/ehq249

Item 14 Answer: B

Educational Objective: Diagnose cardiac syndrome X.

The most likely diagnosis is cardiac syndrome X. This relatively young patient with no traditional risk factors for coronary artery disease has typical angina, abnormal stress testing results, and angiographically normal coronary arteries. Cardiac syndrome X is a frequent cause of chest pain syndromes in women, and patients often present without traditional risk factors for coronary artery disease. The chest pain is often indistinguishable from classic exertional angina, and stress testing results are frequently abnormal. Many hypotheses have been proposed to explain the pathogenesis of cardiac syndrome X, with one of the most accepted centering on microvascular dysfunction as the cause. Although vasodilators should be tried, symptoms can be difficult to treat.

An acute coronary syndrome is unlikely given the lack of risk factors, duration of symptoms, and normal coronary angiogram.

Diagnostic criteria for somatic symptom disorder are as follows: at least one somatic symptom causing distress or

interference with daily life; excessive thoughts, behaviors, and feelings related to the somatic symptoms; and persistent somatic symptoms for at least 6 months (does not have to be the same symptom for 6 months). This patient does not fulfill the diagnostic criteria for somatic symptom disorder.

Takotsubo cardiomyopathy, also known as stress cardiomyopathy or apical ballooning syndrome, is a cause of nonexertional chest pain associated with electrocardiographic changes (often ST-segment elevations) and elevated cardiac enzymes. There is often, but not always, an antecedent psychological or physical stressor. The timing and exertional nature of this patient's symptoms are not consistent with the diagnosis of takotsubo cardiomyopathy.

KEY POINT

- Cardiac syndrome X is characterized by angina and stress testing abnormalities in the absence of angiographically significant coronary artery disease.

Bibliography

Löffler AI, Bourque JM. Coronary microvascular dysfunction, microvascular angina, and management. Curr Cardiol Rep. 2016;18:1. [PMID: 26694723] doi:10.1007/s11886-015-0682-9

Item 15 Answer: B

Educational Objective: Treat a patient with intermittent claudication with supervised exercise training.

The most appropriate next step in the management of this patient with established peripheral artery disease (PAD) and symptoms of intermittent claudication is to initiate a supervised exercise program. In addition to medical therapy with cilostazol, supervised exercise training is recommended to improve symptoms and walking distance in patients with intermittent claudication. The recommended program consists of supervised exercise therapy for at least 30 to 45 minutes occurring at least 3 times per week for at least 12 weeks. A meta-analysis of 27 studies demonstrated that supervised exercise training was more effective than home-based exercise training for improvement in walking distance and claudication distance. However, there was no difference in general quality of life or community-based walking at 3 months. Unsupervised exercise programs are defined as walking advice or a structured home-based exercise program.

Antiplatelet therapy with aspirin or clopidogrel is recommended in patients with symptomatic PAD and can be considered in patients with asymptomatic PAD to reduce the risk for myocardial infarction, stroke, or vascular death. Dual antiplatelet therapy is not recommend in patients with PAD in the absence of other indications (drug-eluting stent placement or prosthetic distal lower extremity bypass) because of the increased risk for bleeding and the absence of evidence demonstrating improved clinical outcomes.

Approximately 2% to 4% of patients with stable claudication progress to critical limb ischemia or require surgical revascularization and/or amputation annually. In this patient with stable but progressive intermittent claudication, medical therapy and exercise training are indicated at this time; however, if conservative therapy fails or symptoms become life limiting, anatomic imaging with magnetic resonance angiography or CT angiography and subsequent revascularization (endovascular or surgical) would be appropriate.

KEY POINT

- In patients with intermittent claudication, supervised exercise training is recommended to improve symptoms and walking distance.

Bibliography

Vemulapalli S, Dolor RJ, Hasselblad V, Schmit K, Banks A, Heidenfelder B, et al. Supervised vs unsupervised exercise for intermittent claudication: a systematic review and meta-analysis. Am Heart J. 2015;169:924-937.e3. [PMID: 26027632] doi:10.1016/j.ahj.2015.03.009

Item 16 Answer: A

Educational Objective: Evaluate an abdominal aortic aneurysm with CT angiography before endovascular aneurysm repair.

The most appropriate next step in management of this patient with an abdominal aortic aneurysm (AAA) is CT angiography of the abdominal aorta and iliac vessels to plan for aortic repair. The strongest risk factor for rupture of an AAA is maximal aortic diameter; this measurement is the dominant indication for repair. Aortic repair should be performed in suitable patients with an AAA diameter of 5.5 cm or larger, in patients with rapid expansion in AAA size (>0.5 cm/year), and in patients presenting with symptoms resulting from AAA (abdominal or back pain/tenderness). In patients with an indication for aortic repair, the choice is between open surgical repair and endovascular aneurysm repair (EVAR). Open surgical repair involves abdominal flank incision and opening the aneurysm sac with interposition of a synthetic graft. EVAR is a less invasive method involving intraluminal introduction of a covered stent through the aneurysm sac, with the stent acting as a sleeve. The choice of procedure is driven by several considerations, including the patient's operative risk, expected lifespan, and ability to adhere to the monitoring requirements of EVAR; the location of the AAA; and involvement of the renal and mesenteric arteries. Suprarenal and juxtarenal aneurysms most often necessitate open surgical repair, whereas infrarenal aneurysms may be treated with open surgery or EVAR. In this patient, CT angiography or magnetic resonance angiography should be performed to determine the location and extent of the AAA. Abdominal duplex ultrasonography is insufficient to determine AAA location. In addition, CT measurements exceed ultrasound measurements in 95% of cases.

Although controlling risk factors for cardiovascular disease is essential in patients with AAA, there is little compelling evidence for treating hypertension in these patients with a specific agent, including β-blockers, to prevent aneurysm expansion. Because this patient's blood pressure is well controlled, no change in antihypertensive therapy is

indicated. Importantly, an AAA with a diameter of 6.2 cm has a 10% to 20% annual risk for rupture, and definitive surgical therapy is indicated.

KEY POINT

- In patients with an indication for abdominal aortic aneurysm repair, the choice between open surgical repair and endovascular aneurysm repair is driven in part by the location of the aneurysm and involvement of the renal and mesenteric arteries.

Bibliography

Hong H, Yang Y, Liu B, Cai W. Imaging of abdominal aortic aneurysm: the present and the future. Curr Vasc Pharmacol. 2010;8:808-19. [PMID: 20180767]

Item 17 Answer: D

Educational Objective: Recognize hyperlipidemia as a risk factor for cardiovascular disease.

This patient's hyperlipidemia most increases his risk for cardiovascular disease (CVD). Most cardiovascular risk can be attributed to modifiable risk factors, and among them, elevated cholesterol levels impart the highest risk for CVD. Reductions in lipid levels can decrease overall risk, and current cholesterol treatment guidelines focus on risk for future cardiovascular events rather than absolute lipid levels. For primary prevention of cardiovascular events, the treatment goal is a reduction in the LDL cholesterol level of at least 50% in high-risk patients and a reduction of 30% to 50% in moderate risk patients. This patient's 10-year cardiovascular risk based on the American College of Cardiology/American Heart Association Pooled Cohort Equations risk calculator is 7.9%, and statin therapy should be initiated.

Moderate alcohol intake (one to two drinks daily for men, one drink daily for women) has been linked with decreased incidence of CVD; however, heavy alcohol consumption has been shown to increase cardiovascular risk. The deleterious effects of alcohol consumption must be weighed against the potential benefits when patients are counseled about risk modification.

The risk for CVD varies considerably among different ethnic groups. The prevalence of heart disease is lower among persons of Hispanic ethnicity than in most other ethnic groups, and Hispanics tend to have lower rates of traditional modifiable risk factors.

Family history of premature CVD is an independent cardiovascular risk factor but typically adds little precision when included in multivariate risk models. In most studies, premature CVD is defined as CVD in a first-degree male relative younger than 55 years or a first-degree female relative younger than 65 years. A family history of premature CVD doubles the risk for myocardial infarction in men and increases the risk by 70% in women. This patient's father died at age 61 years; therefore, family history is not the most important risk factor for this patient.

Although active smoking remains a strong risk factor for CVD, smoking cessation substantially reduces cardiovascular risk within 2 years, with risk returning to the level of a nonsmoker at approximately 10 years. Smoking status should be addressed at every visit, and cessation counseling should be offered to patients who are actively smoking.

KEY POINT

- Most cardiovascular risk can be attributed to modifiable risk factors; among them, elevated lipid levels impart the highest risk for cardiovascular disease.

Bibliography

Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F, et al; INTERHEART Study Investigators. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. Lancet. 2004;364:937-52. [PMID: 15364185]

Item 18 Answer: D

Educational Objective: Evaluate a patient with stable chronic heart failure.

Serum electrolyte measurement and kidney function studies should be performed at this visit. In patients with heart failure, each follow-up visit should include evaluation of current symptoms and functional capacity; assessment of volume status, electrolytes, and kidney function; and review of the patient's medication regimen for adequacy. It is also important to reinforce heart failure education and the need for diet and medication adherence. This patient with stable chronic heart failure is taking appropriate medications, has had no changes in his symptoms or exercise tolerance, and has no evidence of volume overload. Because he is taking a diuretic, an angiotensin receptor blocker, and spironolactone, assessing his electrolyte levels and kidney function is appropriate.

Routine repeat echocardiography is not recommended in a stable patient with heart failure. According to current guidelines, repeat echocardiography should be performed if the patient has had a change in clinical status, received a new medication that might significantly improve ejection fraction (such as a β-blocker), or is being considered for device therapy after medical optimization.

Twenty-four hour ambulatory electrocardiographic monitoring is not indicated to routinely screen for arrhythmias in patients with heart failure in the absence of symptoms or signs worrisome for an arrhythmia.

The B-type natriuretic peptide (BNP) level has prognostic value in patients with heart failure and can be used to determine whether heart failure is progressing. However, determining a prognosis according to an absolute value is difficult, and models that have used BNP levels have different BNP cutpoints and lengths of follow-up. At this time, a BNP level is not routinely obtained in an otherwise stable patient. Other biomarkers of myocardial fibrosis, such as soluble ST2 receptor and galectin-3, have been shown to be predictive of death and hospitalization in small trials, but their role in the management of patients with heart failure is not yet established.

KEY POINT

- In patients with heart failure, each follow-up visit should include evaluation of current symptoms and functional capacity; assessment of volume status, electrolytes, and kidney function; and review of the patient's medication regimen for adequacy.

Bibliography

Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Drazner MH, et al; American College of Cardiology Foundation; American Heart Association Task Force on Practice Guidelines. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2013 Oct 15;62(16):e147-239. [PMID: 23747642]

Item 19 Answer: B

Educational Objective: Manage Wolff-Parkinson-White syndrome.

The most appropriate next step in management is an electrophysiology study. This young woman with a history of palpitations and paroxysms of dyspnea and lightheadedness likely has atrioventricular reciprocating tachycardia associated with an accessory pathway between the atria and ventricles. Accessory pathway conduction is often observed as preexcitation on electrocardiogram (ECG). Because of early ventricular activation over the accessory pathway, the PR interval is shortened, and the initial part of the QRS complex is slurred (delta wave) because of ventricular depolarization adjacent to the pathway. Wolff-Parkinson-White syndrome is characterized by preexcitation on ECG accompanied by symptoms consistent with tachycardia. Symptoms concerning for arrhythmia in a patient with Wolff-Parkinson-White syndrome should prompt referral to a cardiologist or an electrophysiologist. In these patients, it is also important to obtain an echocardiogram to exclude structural heart disease associated with accessory pathways, including Ebstein anomaly.

In this case, the patient's symptomatic episodes could be caused by supraventricular tachycardia (orthodromic or antidromic reciprocating tachycardia) or preexcited atrial fibrillation. A diagnostic electrophysiology study is indicated to uncover the cause of her palpitations and to determine her risk for sudden cardiac death. The electrophysiology procedure also affords the opportunity to ablate the accessory pathway and potentially cure the arrhythmia. The cure rate of catheter ablation is as high as 95% to 99% in patients with an uncomplicated accessory pathway.

Atenolol and verapamil are atrioventricular nodal blockers and may be unsafe if the patient has anterograde conduction down the accessory pathway during atrial fibrillation. These drugs promote rapid 1:1 conduction from the atria to the ventricles over the accessory pathway during atrial fibrillation, which can lead to very rapid ventricular rates and ventricular fibrillation.

Flecainide is an antiarrhythmic drug that is frequently used to treat paroxysmal atrial fibrillation and other arrhythmias. Flecainide is not indicated in this patient because the type and mechanism of the arrhythmia are unknown. This patient requires risk stratification, which can be accomplished with an electrophysiology study. Furthermore, the age of the patient should be considered before antiarrhythmic therapy is initiated. Catheter ablation is preferred in young persons to avoid lifelong use of potentially toxic medications. This young woman may also wish to avoid these types of medications if she will be considering pregnancy in the future.

KEY POINT

- Patients suspected of having Wolff-Parkinson-White syndrome should undergo electrophysiology testing for risk stratification for sudden cardiac death.

Bibliography

Delacrétaz E. Clinical practice. Supraventricular tachycardia. N Engl J Med. 2006;354:1039-51. [PMID: 16525141]

Item 20 Answer: A

Educational Objective: Manage a patient with Marfan syndrome who is considering pregnancy.

The most appropriate management is to advise against pregnancy in this patient with Marfan syndrome and a dilated aorta. All women with Marfan syndrome have an increased risk for pregnancy-related aortic dissection and rupture. In women with Marfan syndrome and an ascending aortic diameter of 4.5 cm or greater, aortic repair surgery is recommended before pregnancy to reduce this risk. Some women with Marfan syndrome and an aortic diameter less than 4.5 cm, including those with rapid dilatation of the ascending aorta or a family history of aortic dissection, are at high risk for dissection during pregnancy and are counseled to have surgery before pregnancy. Generally, pregnancy is considered safe if the aortic diameter is smaller than 4.0 cm.

This patient is asymptomatic with normal left ventricular size and function and mild mitral regurgitation; therefore, she does not meet the criteria for mitral valve intervention. Although the mitral valve may warrant intervention at some point, this patient's dilated aorta is the major determinant of pregnancy risk.

Patients with Marfan syndrome who are considering pregnancy should have an aortic dimension smaller than 4.0 to 4.5 cm, with demonstrated stability for 6 months or longer. This patient does not meet these criteria, and repeat imaging demonstrating aortic stability will not provide reassurance about future pregnancy. Owing to the size of the aorta, this patient should be advised to avoid pregnancy and consider elective surgical repair. If she elects not to proceed with pregnancy or surgical repair at this time, repeat aortic root imaging should be performed in 6 months to confirm stability of the aortic dimensions.

Angiotensin receptor blockers, such as losartan, are considered second-line agents to β-blocker therapy for the control of hypertension and slowing aortic root expansion in patients with Marfan syndrome. Furthermore, ACE

inhibitors and angiotensin receptor blockers are contraindicated during pregnancy because of fetal toxicity. Fetal exposure to these agents during the first trimester can cause central nervous system and cardiovascular malformations, and exposure during the second trimester can cause developmental malformations of the kidneys and genitourinary system.

KEY POINT

- Women with Marfan syndrome have an increased risk for pregnancy-related aortic dissection and rupture.

Bibliography

Regitz-Zagrosek V, Blomstrom Lundqvist C, Borghi C, Cifkova R, Ferreira R, Foidart JM, et al; European Society of Gynecology (ESG). ESC guidelines on the management of cardiovascular diseases during pregnancy: the Task Force on the Management of Cardiovascular Diseases during Pregnancy of the European Society of Cardiology (ESC). Eur Heart J. 2011;32:3147-97. [PMID: 21873418] doi:10.1093/eurheartj/ehr218

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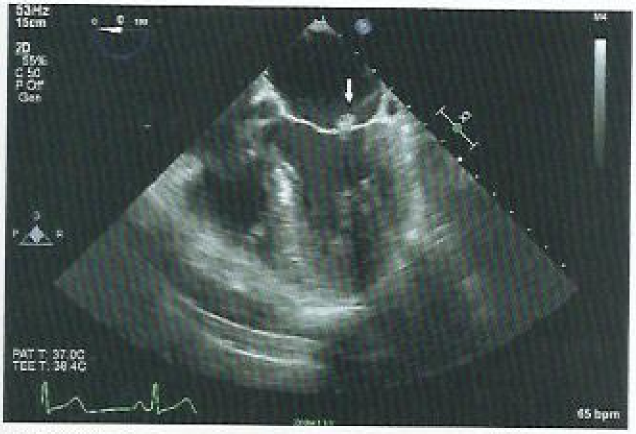
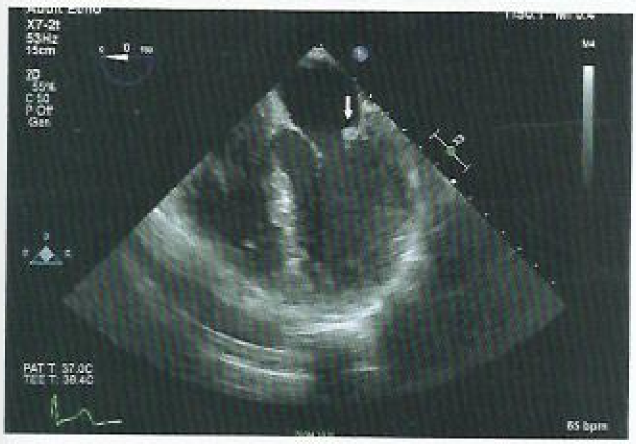
Item 21 Answer: D

Educational Objective: Diagnose a papillary fibroelastoma.

This patient's clinical history, physical examination findings, and echocardiographic features are most consistent with a papillary fibroelastoma (PFE). The echocardiographic images (shown) reveal a PFE (*arrows*) arising from the mitral valve. Most PFEs are small (averaging 12 mm × 9 mm), independently mobile, and attached to the endocardium by a stalk. They are more commonly associated with left-sided valves than right-sided valves or other endocardial surfaces. Patients may present with symptoms of embolism (including stroke or transient ischemic attack), angina, myocardial infarction, and peripheral embolization. PFE may also be discovered incidentally on echocardiogram. Surgery is indicated for symptomatic patients with PFE with acceptable operative risk. The treatment of asymptomatic patients with left heart PFE is controversial, although in one large case series, the risks for stroke and death were higher in patients who did not have surgery.





Bacterial endocarditis is less likely in this patient given the absence of constitutional symptoms, evidence of systemic inflammation, a predisposing valvular lesion, and risk factors for bacteremia (such as dental cleaning or injectable drug use).

Left atrial myxomas may cause cerebral embolic phenomena; however, most myxomas are substantially larger than fibroelastomas and are associated with obstructive symptoms and, in 10% to 15% of patients, an auscultatory "tumor plop." In 75% of cases, myxomas arise within the left atrium attached to the fossa ovalis, not valvular surfaces. Constitutional symptoms, such as fever, anorexia, and weight loss, related to tumor interleukin production may also be present.

Nonbacterial thrombotic endocarditis (NBTE), also known as verrucous, marantic, or Libman-Sacks endocarditis, is likely caused by endothelial injury in the presence of a hypercoagulable state. NBTE occurs on the atrial surface of the mitral valve, the ventricular side of the aortic valve, or both locations. Vegetations are typically small (<1 cm), broad based, and irregularly shaped (wart-like) and are most commonly associated with advanced malignancy or connective tissue disorders. This patient does not have evidence of a predisposing condition for NBTE, and the lesion does not have a wart-like or broad-based appearance.

KEY POINT

- Papillary fibroelastomas are small, independently mobile cardiac tumors that are typically attached to the left-sided valvular endocardium by a stalk; they may be associated with stroke, transient ischemic attack, angina, myocardial infarction, and peripheral embolization.

Bibliography

Val-Bernal JF, Mayorga M, Garijo MF, Val D, Nistal JF. Cardiac papillary fibroelastoma: retrospective clinicopathologic study of 17 tumors with resection at a single institution and literature review. Pathol Res Pract. 2013;209:208-14. [PMID: 23455367] doi:10.1016/j.prp.2013.02.001

Item 22 Answer: D

Educational Objective: Treat iron deficiency anemia in a patient with cyanotic congenital heart disease.

The most appropriate management is initiation of a short course of iron therapy for this patient with Eisenmenger

syndrome and symptomatic postoperative anemia. Most patients with cyanosis have compensated erythrocytosis with stable hemoglobin levels. Iron deficiency and resultant microcytosis in these patients is often caused by inappropriate phlebotomy or blood loss. Correction of iron deficiency is associated with increased exercise capacity and improved quality of life. This patient's baseline hemoglobin level was greater than 18 g/dL (180 g/L). She developed preoperative anemia and subsequent perioperative anemia that has persisted and caused dyspnea and fatigue. Oral iron therapy often causes a rapid increase in erythrocyte mass and requires careful monitoring. Administration of ferrous sulfate or ferrous gluconate is recommended with repeat hemoglobin assessment in 7 to 10 days. Once the serum ferritin level or transferrin saturation is within the normal range, iron supplementation may be discontinued. It is important not to exceed the acceptable serum ferritin level. In the absence of dehydration, a hemoglobin level greater than 20 g/dL (200 g/L) and a hematocrit level greater than 65% are associated with hyperviscosity symptoms, such as headache, difficulty concentrating, weakness, and fatigue.

Erythropoietin is used primarily in patients with anemia related to kidney disease. Iron therapy, not erythropoietin, is recommended for patients with cyanotic cardiac disease with iron deficiency anemia. This patient with cyanotic congenital heart disease and relative anemia is likely to have an elevated erythropoietin level; erythropoietin therapy for this patient will be expensive, likely ineffective, and potentially dangerous.

Heart-lung transplantation is an option for end-stage cardiopulmonary disease in patients with Eisenmenger syndrome; however, it is not indicated without a trial of standard medical therapy with iron.

Limited data are available regarding the efficacy of epoprostenol in patients with Eisenmenger syndrome and pulmonary hypertension. Intravenous epoprostenol is typically avoided because of the risk for paradoxical embolism with continuous intravenous therapy in patients with an intracardiac right-to-left shunt. Oral, subcutaneous, and inhaled therapies are preferred. However, this patient's symptoms are likely the result of iron deficiency, and a trial of iron replacement is first-line therapy.

KEY POINT

- In patients with cyanotic conditions, such as Eisenmenger syndrome, iron deficiency is common, and short-term iron therapy will improve exercise capacity and quality of life.

Bibliography

Tay EL, Peset A, Papaphylactou M, Inuzuka R, Alonso-Gonzalez R, Giannakoulas G, et al. Replacement therapy for iron deficiency improves exercise capacity and quality of life in patients with cyanotic congenital heart disease and/or the Eisenmenger syndrome. Int J Cardiol. 2011;151:307-12. [PMID: 20580108] doi:10.1016/j.ijcard.2010.05.066

Item 23 Answer: B

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Educational Objective: Treat ST-elevation myocardial infarction with thrombolytic therapy.

The most appropriate management of this patient with an acute inferior ST-elevation myocardial infarction (STEMI) is to administer full-dose reteplase. All patients who present with STEMI within 12 hours of symptom onset require prompt restoration of flow with primary percutaneous coronary intervention (PCI) or thrombolytic therapy. When a hospital is capable of performing primary PCI or the patient can be transferred from an index hospital to a PCI-capable center quickly (to achieve an expected first medical contact-to device time of 120 minutes or less), primary PCI is the preferred treatment option. Primary PCI is associated with higher rates of vessel patency and improved overall survival compared with thrombolytic therapy. In this case, transfer time is prohibitively long, and the patient is best treated with immediate thrombolysis with reteplase. After administration of thrombolytic therapy, the patient should be transferred to a PCI-capable center for rescue PCI in case of thrombolytic failure or for nonemergent angiography before discharge.

Evidence supports the efficacy of fondaparinux and ticagrelor as antithrombotic therapies in the setting of STEMI; however, neither agent will likely result in lysis of a clot. These drugs remain adjuvant treatment to a primary thrombolytic strategy.

Half-dose thrombolytic therapy in combination with glycoprotein IIb/IIIa blockade does not offer any additional benefit compared with full-dose thrombolysis in patients with STEMI.

Nitroprusside is a powerful vasodilator and has no role in the management of STEMI. Venodilators, such as nitrates and nitroprusside, must be used with caution in the setting of inferior myocardial infarction because they may result in significant drops in systolic blood pressure, particularly when associated with right ventricular infarction.

KEY POINT

- Thrombolytic therapy is recommended for patients with ST-elevation myocardial infarction when symptom onset is within 12 hours and primary percutaneous coronary intervention is not available within 120 minutes of first medical contact.

Bibliography

O'Gara PT, Kushner FG, Ascheim DD, Casey DE Jr, Chung MK, de Lemos JA, et al; American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2013;127:e362-425. [PMID: 23247304] doi:10.1161/CIR.0b013e3182742cf6

Item 24 Answer: C

Educational Objective: Diagnose peripheral artery disease in a patient with noncompressible arteries.

The most appropriate diagnostic test to perform next in this patient is a toe-brachial index. The diagnostic tool that is most

frequently used to identify peripheral artery disease (PAD) is the ankle-brachial index (ABI). To calculate the ABI, the higher ankle pressure in each leg is divided by the higher brachial pressure. An ABI of 0.90 or lower establishes a diagnosis of PAD, whereas an ABI greater than 1.40 indicates the presence of calcified, noncompressible arteries in the lower extremities and is considered uninterpretable. In patients with an ABI greater than 1.40, an appropriate next step is to measure toe pressure or calculate a toe-brachial index (systolic great toe pressure divided by systolic brachial pressure). A great toe systolic pressure below 40 mm Hg or a toe-brachial index below 0.70 is consistent with PAD. Because this patient has a left ABI of 1.65, a toe-brachial index is indicated.

Exercise ABI testing is useful when patients have a borderline ABI (0.91-1.00) or normal ABI (1.00-1.40) and a high likelihood of PAD. The American Heart Association has proposed a postexercise ankle pressure decrease of more than 30 mm Hg or a postexercise ABI decrease of more than 20% as a diagnostic criterion for PAD. Other organizations have proposed a postexercise ABI of less than 0.90 and/or a 30-mm Hg drop in ankle pressure after exercise. This patient's resting ABI value is greater than 1.40; therefore, exercise ABI is not indicated to diagnose PAD.

CT angiography and magnetic resonance angiography are often reserved for planning endovascular or surgical revascularization rather than for diagnosis of PAD.

In patients with venous leg ulcers, venous duplex ultrasonography is indicated to evaluate for chronic venous insufficiency and deep vein thrombosis (acute or chronic). The location of the ulceration and the lack of other findings consistent with venous disease make that diagnosis unlikely, and venous duplex ultrasonography is therefore unnecessary.

KEY POINT

- In patients with an ankle-brachial index greater than 1.40, a toe-brachial index may be used to diagnose peripheral artery disease.

Bibliography

Aboyans V, Criqui MH, Abraham P, Allison MA, Creager MA, Diehm C, et al; American Heart Association Council on Peripheral Vascular Disease. Measurement and interpretation of the ankle-brachial index: a scientific statement from the American Heart Association. Circulation. 2012;126:2890-909. [PMID: 23159553] doi:10.1161/CIR.0b013e318276fbcb

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Item 25 Answer: B

Educational Objective: Treat a patient with infective endocarditis and refractory bacteremia with cardiac valve surgery.

The most appropriate next step in management is cardiac valve surgery. This patient has infective endocarditis with refractory bacteremia. For patients such as this one, cardiac surgery is the most appropriate next step when there is evidence of persistent infection lasting longer than 5 to 7 days while the patient is receiving appropriate antimicrobial therapy. Cardiac surgery also is recommended for patients with infective endocarditis who have the following: symptomatic heart failure; left-sided involvement with *Staphylococcus aureus*, fungal infections, or highly resistant organisms; associated complications, such as heart block, annular or aortic abscess, or destructive penetrating lesions; or prosthetic valve infective endocarditis and relapsing infection.

Cardiac catheterization is not indicated in this patient and may increase the risk for embolization of vegetation or worsen hemodynamic status. Cardiac catheterization before planned cardiac surgery is indicated in patients with risk factors for coronary artery disease, which are not present in this patient.

The most common indications for intervention with an intra-aortic balloon pump are cardiogenic shock unresponsive to other interventions and acute mitral regurgitation. This patient does not have any indication for an intra-aortic balloon pump. Additionally, an intra-aortic balloon pump is contraindicated in the presence of significant aortic regurgitation, as seen in this patient, because it will increase the volume of regurgitant blood flow.

Surgical intervention should not be delayed for observation of the patient's response to another antibiotic once surgical indications have been met. In this patient, switching to another antibiotic without immediate surgical intervention may result in further decompensation of the patient's clinical status and an increased operative risk for intervention at a later time.

KEY POINT

- For patients with infective endocarditis, cardiac surgery is indicated for persistent infection lasting longer than 5 to 7 days while on appropriate antimicrobial therapy; symptomatic heart failure; left-sided involvement with *Staphylococcus aureus*, fungal infections, or highly resistant organisms; complications such as heart block, annular or aortic abscess, or destructive penetrating lesions; and prosthetic valve infective endocarditis and relapsing infection.

Bibliography

Baddour LM, Wilson WR, Bayer AS, Fowler VG Jr, Tleyjeh IM, Rybak MJ, et al; American Heart Association Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease of the Council on Cardiovascular Disease in the Young, Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and Stroke Council. Infective endocarditis in adults: diagnosis, antimicrobial therapy, and management of complications: a scientific statement for healthcare professionals from the American Heart Association. Circulation. 2015;132:1435-86. [PMID: 26373316] doi:10.1161/CIR.0000000000000296

Item 26 Answer: E

Educational Objective: Recognize the potential for underestimation of cardiovascular risk in patients with HIV infection.

This patient's HIV status will contribute most to the underestimation of his risk for atherosclerotic cardiovascular disease (ASCVD). This young patient has both traditional risk factors (hypertension and smoking) and a nontraditional risk

factor (HIV) for ASCVD, which is defined as coronary death or nonfatal myocardial infarction, or fatal or nonfatal stroke. The Pooled Cohort Equations are a risk assessment instrument developed from multiple community-based cohorts; their use as a primary risk assessment tool was recommended in the 2013 American College of Cardiology/American Heart Association (ACC/AHA) Guideline on Assessment of Cardiovascular Risk. The ACC/AHA ASCVD risk calculator based on the Pooled Cohort Equations includes age, sex, race, total and HDL cholesterol levels, systolic blood pressure, blood pressure-lowering medication use, presence of diabetes mellitus, and smoking status. With use of this method of calculating risk, a 10-year risk for ASCVD below 5% is considered low risk, 5% to below 7.5% is classified as intermediate risk, and 7.5% or higher is designated as high risk. This patient's calculated 10-year ASCVD risk is 6.2%.

Large observational studies have demonstrated a 1.5- to 2-fold increase in the risk for ASCVD among patients with HIV infection. The increased risk for ASCVD in HIV-infected patients is likely the result of interactions among the viral infection, host factors, traditional risk factors, and therapies for HIV. Traditional risk models, including the ACC/AHA ASCVD risk calculator based on the Pooled Cohort Equations, underestimate the risk for ASCVD in patients with HIV. Alternative risk models, including one based on the D:A:D (Data Collection on Adverse events of Anti-HIV Drugs) study, have been developed, but they lack validation and have not been widely adopted.

This patient's age, blood pressure, use of antihypertensive medications, and HDL cholesterol level are accounted for in the ACC/AHA ASCVD risk calculator and are not factors responsible for underestimating his ASCVD risk.

KEY POINT

- In patients with HIV infection, there is a 1.5- to 2-fold increased risk for coronary artery disease.

Bibliography

Vachiat A, McCutcheon K, Tsabedze N, Zachariah D, Manga P. HIV and ischemic heart disease. J Am Coll Cardiol. 2017 Jan 3;69(1):73-82. [PMID: 28057253.]

Item 27 Answer: C

Educational Objective: Evaluate for coronary artery disease with exercise electrocardiography.

The most appropriate test to establish a diagnosis of coronary artery disease (CAD) is exercise electrocardiographic (ECG) stress testing. This patient with cardiovascular risk factors (hypertension, hyperlipidemia) is exhibiting typical angina, which has the following characteristics: (1) substernal chest pain or discomfort that (2) is provoked by exertion or emotional stress and (3) is relieved by rest and/or nitroglycerin. Given her age, sex, and symptoms, she has an intermediate pretest probability of CAD (73%) and should undergo stress testing. In patients with a normal baseline ECG and the ability to exercise, exercise ECG is recommended as the initial test of choice. Exercise ECG can identify flow-limiting lesions indicative of CAD and also further risk stratify this patient. The additional prognostic information available with exercise, including functional capacity and heart rate and blood pressure response, can be used in prediction models, such as the Duke Treadmill Score, which uses several factors (development of symptoms, degree of ST-segment depression, and exercise duration) to provide incremental prognostic information for 5-year mortality risk. Heart rate recovery is another powerful predictor; patients with a heart rate drop of less than 12/min in the first minute after cessation of exercise have a higher mortality rate.

There is no indication for stress testing with additional imaging, such as adenosine single-photon emission CT or stress echocardiography, given this patient's normal baseline ECG findings. If the baseline ECG findings were uninterpretable or the exercise ECG stress test was indeterminate, additional testing with imaging would be warranted.

Coronary artery calcium scoring would identify the presence of CAD, but it would not detect a flow-limiting lesion as the cause of this patient's symptoms. Additionally, the absence of calcification during coronary artery calcium scoring does not exclude the presence of noncalcified plaque.

KEY POINT

- In patients with an intermediate probability of obstructive coronary artery disease, a normal baseline electrocardiogram, and the ability to exercise, exercise electrocardiography is recommended as the initial test of choice.

Bibliography

Mieres JH, Gulati M, Bairey Merz N, Berman DS, Gerber TC, Hayes SN, et al; American Heart Association Cardiac Imaging Committee of the Council on Clinical Cardiology. Role of noninvasive testing in the clinical evaluation of women with suspected ischemic heart disease: a consensus statement from the American Heart Association. Circulation. 2014;130:350-79. [PMID: 25047587] doi:10.1161/CIR.0000000000000061

Item 28 Answer: A

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Educational Objective: Treat a patient with heart failure and evidence of conduction delay.

The most appropriate treatment is the addition of carvedilol. This patient with heart failure with reduced ejection fraction has New York Heart Association functional class III symptoms. Guideline-directed medical therapy for heart failure includes treatment with an ACE inhibitor, β-blocker (specifically, metoprolol succinate, carvedilol, or bisoprolol), and an aldosterone antagonist. β-Blockers improve remodeling, increase ejection fraction, and reduce hospitalization and mortality when added to an ACE inhibitor and diuretic therapy. This patient is not taking a β-blocker; therefore, the most important intervention would be initiation of carvedilol to optimize the patient's medical therapy.

In patients with chronic symptomatic heart failure and left ventricular ejection fraction less than or equal to 35% who are in sinus rhythm and taking maximally tolerated

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doses of a β-blocker, ivabradine reduces heart failure–associated hospitalizations and the combined endpoint of mortality and heart failure hospitalization. Because this patient is not taking a β-blocker, ivabradine is not indicated.

Cardiac resynchronization therapy (CRT) is indicated for primary prevention of sudden cardiac death and to reduce the risk for hospitalization and death in patients with heart failure who have dyssynchrony. Criteria for CRT include an ejection fraction of less than or equal to 35%, New York Heart Association functional class II to IV heart failure symptoms despite guideline-directed medical therapy, sinus rhythm, and left bundle branch block with a QRS complex of 150 ms or greater. This patient fulfills the echocardiographic and electrocardiographic criteria for CRT, and if he continues to have refractory heart failure despite guideline-directed medical therapy for 90 days, he would be a candidate for CRT.

An ICD would protect this patient against sudden cardiac death; however, medical therapy is necessary first to alleviate his heart failure symptoms and improve his functional status. Many patients with new-onset heart failure experience significant improvements in ejection fraction with medical therapy and may not require or benefit from ICD placement.

KEY POINT

- Patients with left ventricular dysfunction due to ischemic cardiomyopathy, left bundle branch block, and heart failure symptoms should receive guideline-directed medical therapy before initiation of device therapy.

Bibliography

Epstein AE, DiMarco JP, Ellenbogen KA, Estes NA 3rd, Freedman RA, Gettes LS, et al; American College of Cardiology Foundation. 2012 ACCF/AHA/HRS focused update incorporated into the ACCF/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol. 2013;61:e6-75. [PMID: 23265327] doi:10.1016/j.jacc.2012.11.007

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Item 29 Answer: D

Educational Objective: Diagnose primary restrictive cardiomyopathy.

The most likely diagnosis is primary restrictive cardiomyopathy. Patients with constrictive pericarditis and restrictive cardiomyopathy present with similar symptoms and findings on echocardiography, and differentiation is an essential first step in diagnosis. In this patient, several features favor restrictive physiology: the elevated B-type natriuretic peptide level (often <100 pg/mL [100 ng/L] in constrictive pericarditis), the presence of severe pulmonary hypertension, the absence of pericardial thickening on cardiac magnetic resonance imaging, and the presence of delayed enhancement of myocardium consistent with myocardial fibrosis on cardiac magnetic resonance imaging. This patient's simultaneous right and left ventricular hemodynamic recordings demonstrate concordant rise and fall of systolic pressures with respiration. In constriction, an inverse relationship or discordance is present because of ventricular interdependence: right ventricular systolic pressure rises during inspiration coupled with a simultaneous decrease in left ventricular systolic pressure.

Fabry disease is a lysosomal storage disorder. Clinical manifestations begin in childhood and progress in an orderly fashion, with up to 70% of the following manifestations appearing by age 40 years: neuropathic pain, telangiectasias and angiokeratomas, and proteinuria and chronic kidney disease. The most common cardiac complications are concentric left ventricular hypertrophy, heart failure, coronary artery disease, left-sided valvular dysfunction, and conduction abnormalities. This patient's late onset of cardiac symptoms and lack of other findings make Fabry disease unlikely.

Although wall thickness may be normal in patients with hemochromatosis, the left ventricle is usually dilated, and the serum ferritin level would be greatly elevated in a patient with visceral involvement.

KEY POINT

- Restrictive cardiomyopathy is distinguished from constrictive pericarditis by an elevated B-type natriuretic peptide level and concordant rise and fall of left and right systolic pressures with respiration.

Bibliography

Garcia MJ. Constrictive pericarditis versus restrictive cardiomyopathy? J Am Coll Cardiol. 2016;67:2061-76. [PMID: 27126534] doi:10.1016/j.jacc.2016.01.076

Item 30 Answer: C

H

Educational Objective: Treat acute descending aortic dissection.

The most appropriate initial step in the management of this patient is initiation of medical therapy. Patients with type B acute aortic dissection without evidence of cardiogenic shock should be initially treated with medical therapy to control heart rate and reduce blood pressure. Intravenous β-blockers are first-line treatment, and sodium nitroprusside can be added if hypertension does not completely respond to β-blocker therapy. Current guidelines recommend reducing systolic blood pressure to 120 mm Hg or less in the first hour in patients with aortic dissection. Pain control is best accomplished with intravenous opioids. In patients with ascending aortic dissection (type A aortic dissection), intramural aortic hematoma, or descending aortic dissection (type B aortic dissection) with complications, immediate repair is warranted. Complications are defined as refractory pain, rapid aneurysmal expansion, rupture, or malperfusion syndrome. This patient has a type B aortic dissection arising just distal to the origin of the left subclavian artery with no evidence of complications. Therefore, medical therapy is the most appropriate treatment.

Endovascular stenting can be used to treat patients with descending aortic aneurysms; however, there is scant evidence to support this as an initial treatment option for

H CONT.

aneurysm with dissection. After medical stabilization, thoracic endovascular aortic repair (TEVAR) with stent grafting can be used; typical indications include descending aortic aneurysm diameter greater than 6.0 cm, rapid growth (>0.5 cm/year), or end-organ damage. TEVAR has the advantage over surgical operation of lower morbidity and shorter hospital stay, although there may be complications, including stroke, spinal ischemia, and aortic graft endoleaks. This patient should be treated with stent implantation only after medical stabilization.

Open surgical repair of the descending aorta is not recommended in patients with uncomplicated type B aortic dissection because of high rates of morbidity (such as paraplegia) and mortality. This patient has no signs or symptoms of complications that would prompt immediate surgical repair.

Repeat CT angiography at 12 hours is not indicated unless the patient does not stabilize with medical therapy. Serial imaging (usually magnetic resonance angiography) is typically performed in asymptomatic patients at the time of discharge and then periodically in patients who do not have an indication for aneurysmal repair to screen for extension or recurrence of the dissection, aneurysm formation, and leakage.

KEY POINT

- Patients with uncomplicated type B aortic dissection may be initially treated with medical therapy, including β-blockers, sodium nitroprusside, and opioids.

Bibliography

Mussa FF, Horton JD, Moridzadeh R, Nicholson J, Trimarchi S, Eagle KA. Acute aortic dissection and intramural hematoma: a systematic review. JAMA. 2016;316:754-63. [PMID: 27533160] doi:10.1001/jama.2016.10026

H

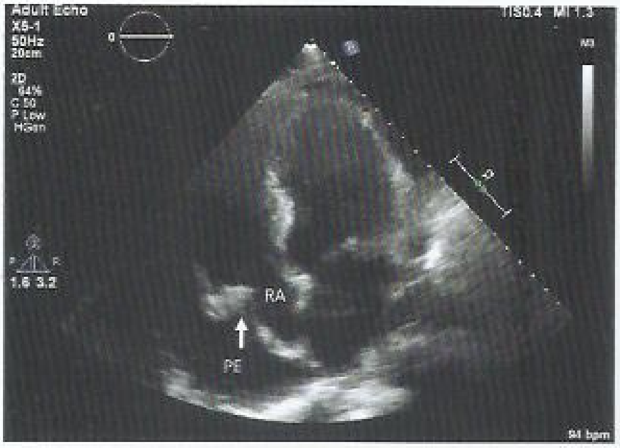
Item 31 Answer: C

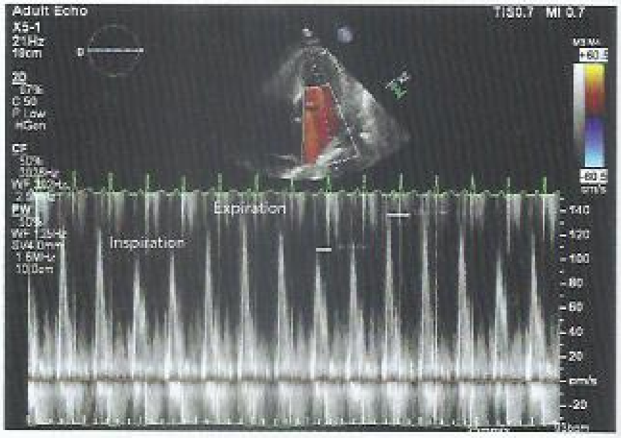
Educational Objective: Treat cardiac tamponade.

The most appropriate management is pericardiocentesis. This patient is taking minoxidil and hydralazine, both of which may be associated with the development of a pericardial effusion (PE). Tamponade occurs when intrapericardial pressure exceeds diastolic intracardiac pressures, which leads to compression of cardiac chambers and limits diastolic filling, stroke volume, and cardiac output, with a simultaneous increase in pulmonary capillary wedge pressure that leads to pulmonary edema. Definitive treatment of cardiac tamponade is pericardiocentesis or surgical pericardial drainage. In hemodynamically unstable patients, intravenous normal saline is used to stabilize the patient as a temporizing measure or bridge to definitive therapy. Despite the evidence of fluid overload, intravenous volume loading can help maintain or increase cardiac output. Low systolic blood pressure (<100 mm Hg) is the most readily accessible clinical finding that is predictive of a favorable response to volume loading.

Hemodialysis will decrease right heart filling pressure but not intrapericardial pressure, resulting in further compression of the intracardiac chamber and reduction in cardiac output. Similarly, intravenous loop diuretics or agents that actively dilate capacitance vessels, such as nitroglycerin, should be avoided because they will result in a relative increase in intrapericardial pressure to intracardiac pressure and further impair cardiac output.

Right heart catheterization is not typically performed in the diagnosis of cardiac tamponade. Echocardiography readily detects pericardial effusions and is the primary modality for diagnosing cardiac tamponade. Echocardiographic signs of cardiac tamponade include diastolic collapse of the right atrium and right ventricle, ventricular septal shifting with respiration, and enlargement of the inferior vena cava. An apical four-chamber echocardiographic view demonstrating PE with diastolic inversion (*arrow*) of the right atrium (RA) free wall is shown. With Doppler echocardiography, respiratory variation in mitral inflow can be detected early in the evolution of tamponade. In the pulsed-wave Doppler image, there is a significant and reproducible decrease (>25%) in passive diastolic flow during inspiration, which reflects enhanced ventricular interdependence. Changes in mitral inflow are highly sensitive and may precede changes in cardiac output, blood pressure, and other echocardiographic evidence of tamponade.





KEY POINT

- Definitive treatment of cardiac tamponade is pericardiocentesis or surgical pericardial drainage.

Bibliography

Adler Y, Charron P, Imazio M, Badano L, Barón-Esquivias G, Bogaert J, et al; European Society of Cardiology (ESC). 2015 ESC guidelines for the diagnosis and management of pericardial diseases: the Task Force for the Diagnosis and Management of Pericardial Diseases of the European Society of Cardiology (ESC) endorsed by: The European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J. 2015;36:2921-64. [PMID: 26320112] doi:10.1093/eurheartj/ehv318

Item 32 Answer: D

Educational Objective: Diagnose ticagrelor-related dyspnea.

Ticagrelor is the most likely cause of dyspnea in this patient with a normal physical examination, no electrocardiographic changes, and normal findings on imaging studies. Ticagrelor is a $P2Y_{12}$ inhibitor that may be used as a component of dual antiplatelet therapy in select patients with coronary artery disease, including those treated with percutaneous coronary intervention. Dyspnea is a well-recognized side effect of ticagrelor therapy. In clinical trials, 15% to 20% of patients taking ticagrelor experienced dyspnea, although only 5% to 7% required cessation of the drug. In most cases, ticagrelor-mediated dyspnea is self-limited, but it often results in additional testing.

Heart failure can complicate myocardial infarction. In this case, however, the normal findings on physical examination, chest radiograph, and echocardiogram make heart failure an unlikely cause of the patient's symptoms.

In patients with shortness of breath after myocardial infarction, it is important to rule out complications of recent percutaneous coronary intervention, such as in-stent stenosis and stent thrombosis. Patients with in-stent restenosis will exhibit recurrent signs and symptoms of ischemia, including chest pain and dyspnea; however, in-stent restenosis develops months to years after stent implantation, not weeks. In contrast to in-stent restenosis, stent thrombosis is usually a fulminant event, commonly manifesting as acute myocardial infarction or death. The timing and persistent nature of this patient's symptoms, coupled with the unchanged electrocardiographic findings, rule out stent thrombosis as a cause of this patient's symptoms.

Ventricular septal defect (VSD) resulting from rupture of the intraventricular septum is a rare complication of transmural infarction involving the right coronary artery (in which the VSD tends to affect the basal inferior septum) or the left anterior descending artery (in which the VSD is usually located within the apical septum). VSDs typically occur within 3 to 5 days of STEMI presentation. Patients present with worsening heart failure and shock, and a harsh holosystolic murmur may be heard at the left lower sternal border. A small NSTEMI would not result in a VSD, and the laboratory and physical examination findings rule out this diagnosis.

KEY POINT

- Dyspnea is a well-recognized and often self-limited side effect of ticagrelor therapy.

Bibliography

Bonaca MP, Bhatt DL, Cohen M, Steg PG, Storey RF, Jensen EC, et al; PEGASUS-TIMI 54 Steering Committee and Investigators. Long-term use of ticagrelor in patients with prior myocardial infarction. N Engl J Med. 2015;372:1791-800. [PMID: 25773268] doi:10.1056/NEJMoa1500857

Item 33 Answer: D

H

Educational Objective: Diagnose takotsubo cardiomyopathy.

Takotsubo cardiomyopathy is the most likely diagnosis. This previously healthy patient has symptoms and findings suggestive of an acute coronary syndrome. Cardiac catheterization demonstrates normal coronary arteries and wall motion abnormalities that do not follow one vascular territory, findings that are consistent with takotsubo cardiomyopathy. Takotsubo cardiomyopathy, or stress-induced cardiomyopathy, is a heart failure syndrome that typically occurs in older women and is usually precipitated by a stressful physical or emotional event, such as the death of a loved one, sudden surprise, or other acute stressors. It is associated with electrocardiographic changes suggestive of an acute myocardial infarction or a moderate increase in troponin levels, wall motion changes that extend beyond the territory of a single coronary artery, and normal or near-normal coronary arteries (<50% stenosis). Patients with a drop in ejection fraction should be treated with standard heart failure medications and typically have rapid recovery of left ventricular function.

Acute myocarditis usually presents with heart failure symptoms that develop over a few days to weeks. Occasionally, patients have symptoms for several months before heart failure is discovered. The classic presentation of viral myocarditis includes a viral prodrome with fever, myalgia, and upper respiratory tract symptoms. Patients present with dyspnea, chest pain, and arrhythmias. Electrocardiographic abnormalities are often present, along with evidence of myocardial damage with persistently elevated troponin levels. Acute-onset symptoms following an emotional event and apical ballooning on left ventriculography are not seen in acute myocarditis.

Giant cell myocarditis is an acute, rapidly progressive form of myocarditis associated with ventricular arrhythmias and progressive cardiac dysfunction despite medical therapy. This process usually occurs in persons younger than 40 years. The underlying mechanism is unknown but is thought to be autoimmune in origin. This patient's age and presentation are not compatible with giant cell myocarditis.

Tachycardia-induced cardiomyopathy is related to prolonged tachycardia or frequent premature ventricular contractions. Patients usually have findings related to the tachyarrhythmia (for example, palpitations) and heart failure. This patient's acute presentation is inconsistent with tachycardia-induced cardiomyopathy.

KEY POINT

- Takotsubo cardiomyopathy is a syndrome of reversible ventricular systolic dysfunction that is usually precipitated by an acute emotional or physiologic stressor; the hallmark is wall motion abnormalities that extend beyond a single coronary territory, identified by echocardiography or other imaging studies.

Bibliography

Sharkey SW. A clinical perspective of the takotsubo syndrome. Heart Fail Clin. 2016;12:507-20. [PMID: 27638021] doi:10.1016/j.hfc.2016.06.003

Item 34 Answer: C

Educational Objective: Treat symptomatic severe pulmonary valve stenosis.

Balloon valvuloplasty is the most appropriate management of this patient. The palpable, late peaking systolic murmur located at the second left intercostal space; absence of an ejection click; and features of right ventricular pressure overload suggest severe pulmonary valve stenosis. The echocardiogram confirms the presence of severe pulmonary valve stenosis with a peak systolic gradient of 65 mm Hg and mean systolic gradient of 50 mm Hg. Balloon valvuloplasty is recommended for symptomatic patients with appropriate valve morphology who have a peak Doppler gradient of greater than 50 mm Hg or a mean gradient greater than 30 mm Hg and favorable valve characteristics for percutaneous intervention.

Patients with pulmonary valve stenosis without a history of endocarditis or pulmonary valve replacement do not require endocarditis prophylaxis.

Exercise stress testing could help determine whether the patient has exercise limitations related to her pulmonary valve stenosis; however, the results would not change the recommendation for intervention.

Surgical pulmonary valve replacement should be considered when the valve is dysplastic or when more than moderate coexisting pulmonary valve regurgitation, a small annulus, severe subvalvar or supravalvar pulmonary valve stenosis, or another cardiac lesion that requires operative intervention is present. It is not the preferred treatment for this patient who has appropriate valve morphology for balloon valvuloplasty.

KEY POINT

- Balloon valvuloplasty is recommended for patients with symptomatic pulmonary valve stenosis who have appropriate valve morphology, a peak Doppler gradient of greater than 50 mm Hg or a mean gradient greater than 30 mm Hg, and valve characteristics favorable for percutaneous intervention.

Bibliography

Warnes CA, Williams RG, Bashore TM, Child JS, Connolly HM, Dearani JA, et al; American College of Cardiology. ACC/AHA 2008 guidelines for the management of adults with congenital heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Develop Guidelines on the Management of Adults With Congenital Heart Disease). Developed in Collaboration With the American Society of Echocardiography, Heart Rhythm Society, International Society for Adult Congenital Heart Disease, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol. 2008;52:e143-263. [PMID: 19038677] doi:10.1016/j.jacc.2008.10.001

Item 35 Answer: C

Educational Objective: Evaluate for coronary artery disease with coronary CT angiography in a patient with COPD.

Coronary CT angiography (CTA) is the most appropriate diagnostic test to perform next. This patient with an intermediate pretest probability of coronary artery disease (CAD) has chest pain without evidence of acute coronary syndrome, and he should undergo risk stratification. Because his baseline electrocardiogram (ECG) has evidence of left ventricular hypertrophy with repolarization abnormalities, which limits the ability to interpret exercise ECG findings, stress testing with adjunctive imaging or anatomic assessment for CAD is indicated. Coronary CTA is a noninvasive anatomic imaging study to evaluate for obstructive CAD. In the PROMISE trial, which compared coronary CTA with functional stress testing among patients with an intermediate pretest probability for CAD, the 2 year composite outcome (death, myocardial infarction, hospitalization for unstable angina, or major procedural complication) was similarly low with both types of diagnostic testing.

Vasodilators, such as regadenoson or adenosine, produce hyperemia and a flow disparity between myocardium supplied by unobstructed vessels and myocardium supplied by the stenotic vessel (in which the distal vasculature is already maximally dilated). In addition to identifying the presence of disease, perfusion imaging can define the location and extent of reduced perfusion and provide additional prognostic information. Single-photon emission CT with the vasodilator adenosine can be performed in patients with underlying reactive airways disease but should be avoided in patients who are actively wheezing, such as this one. The newer selective adenosine A_{2A} receptor agonists are associated with less bronchospasm; however, bronchospasm may still occur as a result of some activation of the A_{2B} and A_3 receptors.

Coronary angiography is an invasive test that carries significant risks. It should be considered in patients who have a high pretest probability for obstructive CAD, including symptomatic patients with abnormal findings on noninvasive testing for CAD or patients with an acute coronary syndrome.

KEY POINT

- Baseline electrocardiogram (ECG) abnormalities that limit the ability to interpret exercise ECG findings are an indication for stress testing with adjunctive imaging or anatomic assessment of coronary arteries.

Bibliography

Douglas PS, Hoffmann U, Patel MR, Mark DB, Al-Khalidi HR, Cavanaugh B, et al; PROMISE Investigators. Outcomes of anatomical versus functional testing for coronary artery disease. N Engl J Med. 2015 Apr 2;372(14):1291-300. [PMID: 25773919]

Item 36 Answer: C

Educational Objective: Evaluate sinus bradycardia.

Exercise treadmill stress testing is the most appropriate next step in management. Sinus bradycardia (sinus rhythm with a heart rate <60/min) may be appropriate in several situations, including in trained athletes or during sleep, when the heart rate may fall as low as 30/min. The most common intrinsic cause of inappropriate or pathologic sinus bradycardia (sinus node dysfunction) is age-related myocardial fibrosis in the vicinity of the sinus node. The most common extrinsic cause of sinus bradycardia is medication use. This young patient has asymptomatic bradycardia and chest pain atypical for cardiac ischemia. However, because of her history of occasional lightheadedness with exercise, this patient should undergo treadmill stress testing to evaluate her heart rate response to exercise (chronotropy) and further exclude symptomatic bradycardia.

Despite the pleuritic component to this patient's chest pain, she has no respiratory distress, has normal oxygen saturation, and can exercise without difficulty. Therefore, CT of the chest to exclude pulmonary embolism is not appropriate.

The utility of any diagnostic test should be interpreted in the context of the pretest likelihood of disease. Patients with a low probability of coronary artery disease, such as younger patients with atypical or nonanginal chest pain, have a higher incidence of false-positive test results and may undergo unnecessary testing without changing patient outcomes. Given this patient's extremely low pretest probability for coronary artery disease, coronary angiography is not indicated. Additionally, if this patient had an intermediate probability of coronary artery disease, noninvasive testing would be performed before angiography.

Pacemakers are indicated in patients with symptomatic bradycardia in the absence of a reversible cause. The decision to implant a pacemaker in this patient should be delayed until after the exercise stress test to ascertain whether she is truly asymptomatic.

KEY POINT

- In patients with sinus bradycardia and equivocal symptoms, exercise stress testing may be used to assess for chronotropic incompetence and determine suitability for pacemaker placement.

Bibliography

Epstein AE, DiMarco JP, Ellenbogen KA, Estes NA 3rd, Freedman RA, Gettes LS, et al; American College of Cardiology Foundation. 2012 ACCF/AHA/HRS focused update incorporated into the ACCF/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol. 2013;61:e6-75. [PMID: 23265327] doi:10.1016/j.jacc.2012.11.007

Item 37 Answer: B

Educational Objective: Treat hypertension during pregnancy.

In this pregnant patient, labetalol is the most appropriate treatment to achieve blood pressure control. Hypertension diagnosed before the 20th week of gestation is most consistent with a new diagnosis of chronic hypertension rather than preeclampsia. Pharmacologic treatment of chronic hypertension in pregnancy is recommended to achieve the goal of limiting maternal end-organ damage; there is no evidence that blood pressure control during pregnancy will prevent preeclampsia. The definitive threshold for treatment of chronic hypertension in pregnancy remains controversial. A 2013 guideline published by the American College of Obstetricians and Gynecologists made a strong recommendation for initiation of pharmacologic therapy for pregnant women with persistent chronic hypertension at a systolic blood pressure of 160 mm Hg or higher or a diastolic blood pressure of 105 mm Hg or higher. However, other guidelines, including one from the European Society of Cardiology, continue to recommend initiation of pharmacologic therapy at a systolic blood pressure of 150 mm Hg or higher or a diastolic blood pressure of 95 mm Hg or higher in women without symptoms or evidence of end-organ damage due to hypertension. Although all antihypertensive agents cross the placenta, methyldopa and labetalol appear to be the safest antihypertensive agents in pregnant women.

Diet and weight loss should be used in conjunction with pharmacologic therapy in this patient; however, nonpharmacologic strategies alone are insufficient in a patient with hypertension of this magnitude. Foregoing pharmacologic treatment of chronic hypertension may result in maternal end-organ damage.

ACE inhibitors (such as lisinopril), angiotensin receptor blockers (such as losartan), spironolactone, and direct renin inhibitors (aliskiren) are teratogenic and are therefore contraindicated during pregnancy. During the first trimester, these agents can cause central nervous system and cardiovascular malformations in the fetus. Second-trimester exposure can cause developmental malformations of the kidneys and genitourinary system.

KEY POINT

- Labetalol and methyldopa are the agents of choice in treating pregnant patients with hypertension.

Bibliography

Regitz-Zagrosek V, Blomstrom Lundqvist C, Borghi C, Cifkova R, Ferreira R, Foidart JM, et al; European Society of Gynecology (ESG). ESC guidelines on the management of cardiovascular diseases during pregnancy: the Task Force on the Management of Cardiovascular Diseases during Pregnancy of the European Society of Cardiology (ESC). Eur Heart J. 2011;32:3147-97. [PMID: 21873418] doi:10.1093/eurheartj/ehr218

Item 38 Answer: B

Educational Objective: Manage a patient with severe mitral regurgitation with appropriate surveillance.

In the absence of symptoms, the most appropriate timing for this patient's next clinical evaluation is in 6 to 12 months. Abnormalities in any of the structures of the mitral valve apparatus, including anterior and posterior mitral leaflets, the annulus, the papillary muscles, and the chordae tendineae, can result in mitral regurgitation. Organic, or primary, mitral regurgitation refers to processes involving the leaflets, such as mitral valve prolapse, myxomatous degeneration (the abnormal accumulation of proteoglycans), collagen vascular disease, and infective endocarditis. Processes that affect the support structures, such as coronary artery disease and left ventricular remodeling in the setting of left ventricular dysfunction, result in functional, or secondary, mitral regurgitation. This patient has asymptomatic severe mitral regurgitation resulting from myxomatous degeneration of the mitral valve with preserved left ventricular function. Surgical treatment with repair of the mitral valve is indicated for chronic severe primary mitral regurgitation in (1) symptomatic patients with left ventricular ejection fraction greater than 30%, (2) asymptomatic patients with left ventricular dysfunction (left ventricular ejection fraction of 30%-60% and/or left ventricular end-systolic diameter ≥40 mm), and (3) patients undergoing another cardiac surgical procedure. Mitral valve repair should also be considered in asymptomatic patients with chronic severe primary mitral regurgitation who have new-onset atrial fibrillation or pulmonary hypertension (pulmonary artery systolic pressure >50 mm Hg). Notably, recent studies have suggested a potential mortality benefit of early surgery for patients with asymptomatic severe mitral regurgitation with preserved left ventricular function when the operative risk is low. Therefore, consideration of early surgery, even in the absence of symptoms or an abnormal left ventricle, is appropriate in select candidates and should involve shared decision making with the patient. In this patient who has chosen to defer early surgery, clinical and echocardiographic surveillance is recommended, with follow-up every 6 to 12 months.

KEY POINT

- In patients with asymptomatic severe mitral regurgitation with preserved left ventricular function who do not have an indication for surgery, clinical and echocardiographic surveillance every 6 to 12 months is recommended.

Bibliography

Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP 3rd, Fleisher LA, et al. 2017 AHA/ACC focused update of the 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2017;135:e1159-e1195. [PMID: 28298458] doi:10.1161/CIR.0000000000000503

Item 39 Answer: B

Educational Objective: Treat asymptomatic lower extremity peripheral artery disease.

In this patient with asymptomatic peripheral artery disease (PAD) and acute coronary syndrome treated with percutaneous coronary intervention, the most appropriate next step in management is cardiac rehabilitation. Cardiac rehabilitation is indicated in all patients after hospitalization for acute coronary syndrome and percutaneous coronary intervention. In some patients, exercise can provoke symptoms of intermittent claudication; however, the presence of PAD is not a contraindication to cardiac rehabilitation.

Cilostazol, a phosphodiesterase inhibitor with antiplatelet and vasodilatory properties, is not indicated in patients without claudication, such as this one. There is no evidence that cilostazol prevents progression of disease or improves outcomes in asymptomatic patients with PAD.

This patient's iliac artery stenosis could be treated safely and effectively with an endovascular approach; however, endovascular treatment of PAD is not recommended in asymptomatic patients. There is no empiric evidence that endovascular intervention prevents disease progression to intermittent claudication or critical limb ischemia.

Vorapaxar inhibits thrombin-induced and thrombin receptor agonist peptide-induced platelet aggregation. Vorapaxar reversibly inhibits protease-activated receptor-1, although its long half-life makes it effectively irreversible. It does not appear to affect coagulation parameters, nor does it inhibit platelet aggregation due to adenosine diphosphate, collagen, or thromboxane mimetic activities. Vorapaxar has been shown to reduce hospitalizations for acute limb ischemia in patients with symptomatic PAD, an effect that was mostly driven by patients who experienced lower extremity bypass graft thrombosis. When added to standard antiplatelet therapy, vorapaxar was also associated with a significant increase in major bleeding. In this patient with asymptomatic PAD, the benefits of adding vorapaxar to standard therapy are uncertain.

KEY POINT

- Asymptomatic lower extremity peripheral artery disease is managed with aggressive risk factor modification; cilostazol and surgical intervention do not affect progression of disease or prevent acute limb ischemia.

Bibliography

Foley TR, Waldo SW, Armstrong EJ. Medical therapy in peripheral artery disease and critical limb ischemia. Curr Treat Options Cardiovasc Med. 2016;18:42. [PMID: 27181397] doi:10.1007/s11936-016-0464-8

Item 40 Answer: A

Educational Objective: Evaluate the eligibility of a patient with hypertrophic cardiomyopathy for participation in sports.

The most appropriate management is to advise this patient not to play basketball. This asymptomatic patient has findings

consistent with hypertrophic cardiomyopathy (HCM). HCM is the single most common cause of sudden death in young athletes, presumably due to ventricular arrhythmia triggered by high-intensity physical activity. The risk for ventricular arrhythmias in competitive athletes with HCM exists in the absence of conventional risk factors for sudden cardiac death. Therefore, the degree and distribution of hypertrophy, the presence and magnitude of left ventricular outflow tract obstruction, and the presence or absence of obstructive symptoms should not influence recommendations regarding athletic participation in patients with phenotypic expression of HCM. According to current recommendations from the American College of Cardiology/American Heart Association, athletes with a probable or unequivocal diagnosis of HCM may participate in competitive sports that are considered static and low intensity (categorized as class Ia sports). Examples of these sports include golf, curling, bowling, and cricket.

In patients with symptoms from HCM (such as dyspnea or syncope/near-syncope), medical therapy and lifestyle modification form the basis of therapy. Nonvasodilating β-blockers titrated to maximum tolerance are first-line treatment for symptomatic patients. However, β-blocker therapy should not be used for the sole purpose of allowing participation in athletics because the ability to effectively prevent sudden cardiac death with this strategy is unknown.

Catheter-based alcohol septal ablation or open surgical septal myectomy should be considered only in patients with HCM who have moderate to severe symptoms of obstruction despite maximal medical therapy or patients with recurrent syncope not related to arrhythmia. These invasive procedures should not be performed for the sole purpose of allowing participation in athletics.

Patients with HCM should be considered for implantable cardioverter-defibrillator therapy if they have any of the following risk factors for sudden cardiac death: (1) massive myocardial hypertrophy (wall thickness ≥30 mm), (2) previous cardiac arrest due to ventricular arrhythmia, (3) blunted blood pressure response or hypotension during exercise, (4) unexplained syncope, (5) nonsustained ventricular tachycardia on ambulatory electrocardiography, and (6) family history of sudden death due to HCM. An implantable cardioverter-defibrillator should not be placed solely for the purpose of allowing a patient to participate in high-intensity sports.

KEY POINT

- Athletes with a probable or unequivocal diagnosis of hypertrophic cardiomyopathy may participate in competitive sports that are considered static and low intensity.

Bibliography

Maron BJ, Udelson JE, Bonow RO, Nishimura RA, Ackerman MJ, Estes NA 3rd, et al. Eligibility and disqualification recommendations for competitive athletes with cardiovascular abnormalities: Task Force 3: hypertrophic cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy and other cardiomyopathies, and myocarditis: a scientific statement from the American Heart Association and American College of Cardiology. J Am Coll Cardiol. 2015;66:2362-71. [PMID: 26542657] doi:10.1016/j.jacc.2015.09.035

Item 41 Answer: C

H

Educational Objective: Diagnose ventricular free wall rupture as a complication of ST-elevation myocardial infarction.

The most likely diagnosis in this patient with recent ST-elevation myocardial infarction (STEMI) is ventricular free wall rupture. Although the devastating mechanical complications of myocardial infarction have become increasingly rare with the use of reperfusion therapies, clinicians must be able to recognize these complications. The classic presentation of ventricular free wall rupture is sudden-onset chest pain or syncope with rapid progression to pulseless electrical activity, as seen in this patient. Unlike a ventricular septal defect, which results in intracardiac shunting of blood, free wall rupture causes rapid accumulation of blood within the pericardium and consequent tamponade. As a result, mortality rates are extremely high. Free wall rupture is more common in older adults, women, patients with anterior myocardial infarction, those receiving anti-inflammatory agents, and patients with a significant delay in receiving reperfusion therapy (>12 hours).

Although aortic dissection can manifest as sudden death as a result of rupture, aortic dissection is less likely than ventricular free wall rupture to cause pulseless electrical activity 3 days after an anterior myocardial infarction. In patients with a first myocardial infarction without heart failure, pulseless electrical activity is highly predictive of left ventricular free wall rupture.

Patients with in-stent restenosis will exhibit recurrent signs and symptoms of ischemia, including chest pain. Stent restenosis is unlikely in this patient with recent stent placement, as this process occurs over months to years. Additionally, stent restenosis does not present with pulseless electrical activity.

Acquired ventricular septal defect from septal wall rupture may complicate inferior or anterior STEMI. Patients typically present with sudden-onset right-sided heart failure, shock, and a new loud systolic murmur associated with a palpable thrill. The defect develops in the days following the infarction as myocardial necrosis develops, resulting in an often serpiginous defect connecting the left ventricle to the right ventricle. This patient's clinical presentation is inconsistent with postinfarction ventricular septal defect.

KEY POINT

- Ventricular free wall rupture is a rare complication of myocardial infarction that produces sudden-onset chest pain or syncope with rapid progression to pulseless electrical activity.

Bibliography

López-Sendón J, Gurfinkel EP, Lopez de Sa E, Agnelli G, Gore JM, Steg PG, et al; Global Registry of Acute Coronary Events (GRACE) Investigators. Factors related to heart rupture in acute coronary syndromes in the Global Registry of Acute Coronary Events. Eur Heart J. 2010;31:1449-56. [PMID: 20231153] doi:10.1093/eurheartj/ehq061

H

Item 42 Answer: D

Educational Objective: Diagnose transient constrictive pericarditis.

The most likely diagnosis is transient constrictive pericarditis. This patient has signs of right-sided heart failure accompanied by fever, leukocytosis, an elevated erythrocyte sedimentation rate, and a pericardial friction rub. The echocardiogram demonstrates enhanced ventricular interdependence and equalization of diastolic pressures in all heart chambers. Cardiac magnetic resonance imaging demonstrates pericardial thickening with evidence of active inflammation. These features are consistent with the diagnosis of transient constrictive pericarditis. Transient constrictive pericarditis most often is idiopathic but may follow cardiac surgery. Initial therapy consists of an NSAID plus colchicine.

Patients with chronic constrictive pericarditis are sometimes misdiagnosed as having heart failure with preserved ejection fraction. Although this patient has evidence of right-sided heart failure and has a preserved ejection fraction, Doppler echocardiographic findings of ventricular interdependence and the relative low B-type natriuretic peptide level argue against heart failure with preserved ejection fraction.

Patients with perioperative graft failure with infarction would be more likely to demonstrate pathologic findings of infarction on electrocardiogram, and serum troponin levels may remain elevated.

Although it may be challenging to differentiate restrictive cardiomyopathy from pericardial constriction, the lack of features of heart failure until after coronary artery bypass graft surgery makes the diagnosis of restrictive cardiomyopathy unlikely. Additionally, patients with restrictive cardiomyopathy would not demonstrate evidence of enhanced ventricular interdependence, and the B-type natriuretic peptide level is typically greater than 400 pg/mL (400 ng/L).

KEY POINT

- Some patients with constrictive pericarditis can have reversible or transient pericardial inflammation that responds to anti-inflammatory agents; most cases are idiopathic, whereas others may be associated with recent cardiac surgery.

Bibliography

Gentry J, Klein AL, Jellis CL. Transient constrictive pericarditis: current diagnostic and therapeutic strategies. Curr Cardiol Rep. 2016;18:41. [PMID: 26995404] doi:10.1007/s11886-016-0720-2

Item 43 Answer: C

Educational Objective: Treat heart failure with preserved ejection fraction.

The most appropriate management is to discontinue hydrochlorothiazide and diltiazem and start furosemide. This elderly woman with heart failure with preserved ejection fraction (HFpEF) has signs and symptoms of volume overload in the setting of bradycardia. The cornerstone of treatment for patients with HFpEF is diuretic therapy to maintain euvolemia. Antihypertensive agents should also be used to maintain normal blood pressure in the setting of hypertension. Despite treatment with hydrochlorothiazide, this patient has evidence of volume overload, and she should be switched to furosemide for more efficacious diuresis. This patient is also taking diltiazem, which may be causing her bradycardia, and this agent should be discontinued. If the patient's heart rate fails to improve, she should be referred for pacemaker placement.

Ivabradine is a sinus node modulator that reduces heart failure–associated hospitalizations in select heart failure patients; however, it is indicated as therapy only in patients with a reduced left ventricular ejection fraction and heart rate higher than 70/min while receiving β-blocker therapy.

Although ACE inhibitors, angiotensin receptor blockers (such as valsartan), β-blockers, and aldosterone antagonists have been studied for the treatment of HFpEF, no drugs have been shown to reduce morbidity or mortality in these patients. Most recently, in the TOPCAT trial, there was no difference in the primary combined endpoint of death, aborted cardiac arrest, or heart failure hospitalization with spironolactone compared with placebo; however, spironolactone was associated with a reduction in heart failure hospitalizations. Notably, a retrospective analysis showed that spironolactone reduced the incidence of cardiovascular death and heart failure hospitalization in patients in the Americas compared with those in Eastern Europe, likely because of different patient demographic characteristics across regions.

Pacemaker placement would be indicated only for symptomatic bradycardia in the absence of a reversible cause; the response to diltiazem discontinuation should be assessed before pacemaker placement is considered in this patient.

KEY POINT

- The cornerstone of treatment for patients with heart failure with preserved ejection fraction is diuretic therapy to maintain euvolemia.

Bibliography

Redfield MM. Heart failure with preserved ejection fraction. N Engl J Med. 2016;375:1868-1877. [PMID: 27959663]

Item 44 Answer: B

Educational Objective: Diagnose ostium primum atrial septal defect.

This patient's examination findings and electrocardiogram (ECG) are consistent with a diagnosis of ostium primum atrial septal defect (ASD). The patient has clinical features of ASD, presenting with dyspnea, paroxysmal atrial fibrillation, and features of right heart volume overload with elevation of the central venous pressure and a right ventricular lift. A pulmonary midsystolic flow murmur is caused by increased flow from a large left-to-right shunt. Fixed splitting of the S_2 throughout the cardiac cycle is a characteristic clinical feature

of ASD. The apical systolic murmur of mitral regurgitation is related to the mitral valve cleft. This combination of fixed splitting of the S_2, mitral regurgitation murmur, and left-axis deviation on ECG are most consistent with an ostium primum ASD.

Patients with a coronary sinus ASD have features of right heart volume overload but do not have a mitral regurgitation murmur because no mitral valve disease is present. The ECG may be normal or demonstrate first-degree atrioventricular block and incomplete right bundle branch block.

Patients with ostium secundum ASD have right heart volume overload but do not generally have mitral regurgitation. The ECG may demonstrate first-degree atrioventricular block and incomplete right bundle branch block, or it may be normal. This patient's ECG finding of left axis deviation is not seen in patients with ostium secundum ASD.

Patients with sinus venosus ASD have features of right heart volume overload but do not have a mitral regurgitation murmur because no mitral valve disease is present. The ECG may be normal or demonstrate first-degree atrioventricular block, left P-wave axis or abnormal P-wave axis, and incomplete right bundle branch block, but left-axis deviation is not expected.

KEY POINT

- Fixed splitting of the S_2, a mitral regurgitation murmur, and left-axis deviation on electrocardiogram are consistent with an ostium primum atrial septal defect.

Bibliography

Warnes CA, Williams RG, Bashore TM, Child JS, Connolly HM, Dearani JA, et al; American College of Cardiology. ACC/AHA 2008 guidelines for the management of adults with congenital heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Develop Guidelines on the Management of Adults With Congenital Heart Disease). Developed in Collaboration With the American Society of Echocardiography, Heart Rhythm Society, International Society for Adult Congenital Heart Disease, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol. 2008;52:e143-263. [PMID: 19038677] doi:10.1016/j.jacc.2008.10.001

Item 45 Answer: D

Educational Objective: Assess the 10-year risk for atherosclerotic cardiovascular disease with the Pooled Cohort Equations.

The most appropriate next management step is to calculate this patient's 10-year atherosclerotic cardiovascular disease (ASCVD) risk. Results of lipid measurements and patient-specific data (age, race, blood pressure, hypertension treatment, diabetes mellitus, and smoking) allow for the calculation of 10-year ASCVD risk using the Pooled Cohort Equations. In adults aged 40 to 75 years who have at least one ASCVD risk factor (dyslipidemia, diabetes, hypertension, or smoking) and a calculated 10-year ASCVD risk of 10% or greater, the U.S. Preventive Services Task Force (USPSTF) recommends statin therapy for the primary prevention of ASCVD. The USPSTF also recommends that clinicians selectively prescribe statins to adults aged 40 to 75 years without a history of ASCVD who have one or more ASCVD risk factors and a calculated 10-year ASCVD event risk of 7.5% to 10% (grade C recommendation). Because this patient has one ASCVD risk factor (hypertension), it is appropriate that his risk be assessed, and through use of the Pooled Cohort Equations, his 10-year risk for ASCVD is 9.3%. According to the USPSTF recommendation, he should be considered as a potential candidate for statin therapy. The most recent American College of Cardiology/American Heart Association cholesterol treatment guideline recommends that patients without ASCVD or diabetes and a 10-year ASCVD risk of 7.5% or higher receive moderate- or high-intensity statin therapy.

The initiation of statin therapy might be reasonable for this patient but not until his 10-year ASCVD risk is calculated. Such information can be used to determine the need for and intensity of stain therapy.

The optimal interval for assessment of ASCVD risk is undetermined; however, it is reasonable to measure lipid levels every 5 years in adults aged 40 to 75 years. This patient should not wait 5 years to have his ASCVD risk assessed and delay potentially beneficial therapy.

KEY POINT

- Routine screening for lipid disorders and calculation of 10-year atherosclerotic cardiovascular disease risk by using the Pooled Cohort Equations should be performed in adults aged 40 to 75 years.

Bibliography

Bibbins-Domingo K, Grossman DC, Curry SJ, Davidson KW, Epling JW Jr, García FA, et al; US Preventive Services Task Force. Statin use for the primary prevention of cardiovascular disease in adults: US Preventive Services Task Force recommendation statement. JAMA. 2016;316:1997-2007. [PMID: 27838723] doi:10.1001/jama.2016.15450

Item 46 Answer: D

Educational Objective: Manage antithrombotic therapy in a patient with a prosthetic heart valve.

The most appropriate antithrombotic therapy is the combination of warfarin and aspirin. Lifelong oral anticoagulation with warfarin is recommended for all patients with a mechanical prosthesis and those with bioprostheses with other indications for anticoagulation. The target INR is based on prosthesis location, with a target of 2.5 for patients with a mechanical aortic prosthetic valve and 3.0 for patients with a mechanical mitral prosthetic valve and those with a mechanical aortic prosthetic valve and additional risk factors for thromboembolism (atrial fibrillation, left ventricular dysfunction, previous thromboembolism, hypercoagulable condition, or older-generation mechanical aortic valve replacement). The addition of aspirin (75-100 mg/d) is also recommended to reduce the risk for ischemic events. Adding aspirin to warfarin therapy reduces mortality, particularly mortality from vascular causes, and major systemic embolism (1.9% per year versus 8.5% per year). Although there is some increase in bleeding, the risk of the combined treatment was more than offset by the considerable benefit. The need for anticoagulation among patients with bioprosthetic valves is less clear. Oral

anticoagulation with warfarin should be considered for at least 3 months and as long as 6 months after implantation of a mitral or aortic bioprosthesis. An INR of 2.5 should be targeted in these patients. Long-term aspirin use is reasonable for all patients with bioprosthetic valves.

Apixaban, a direct factor Xa inhibitor, has not been studied for the prevention of valve thrombosis and thromboembolic events in patients with a mechanical valve prosthesis; therefore, it would be inappropriate to initiate apixaban in this patient.

Direct thrombin inhibitors, such as dabigatran, are contraindicated in patients with mechanical valves, owing to the excessive thrombotic complications observed in clinical trials with these agents.

Foregoing anticoagulation would be inappropriate for this patient because lifelong warfarin is indicated in all patients with a mechanical valve prosthesis to decrease the incidence of thromboembolism and the associated morbidity, such as ischemic stroke, cerebrovascular accident, and peripheral systemic embolism.

KEY POINT

- In patients with a mechanical prosthetic valve, low-dose aspirin is recommended in addition to warfarin therapy to reduce the risk for ischemic events.

Bibliography

Turpie AG, Gent M, Laupacis A, Latour Y, Gunstensen J, Basile F, et al. A comparison of aspirin with placebo in patients treated with warfarin after heart-valve replacement. N Engl J Med. 1993;329:524-9. [PMID: 8336751]

Item 47 Answer: A

Educational Objective: Treat wide-complex tachycardia due to atrial fibrillation with aberrant conduction.

The most appropriate next step in management is initiation of β-blocker therapy and anticoagulation. This older patient has paroxysmal atrial fibrillation with aberrant conduction, resulting in wide-complex tachycardia. The electrocardiogram (ECG) demonstrates a normal sinus beat followed by an irregularly irregular rhythm, and the QRS morphology (rSR pattern in lead V_1, deep terminal S waves in leads I and V_6) on ECG is consistent with typical right bundle branch block. The physical examination is also notable for a widely split S_2, which is typically heard during right bundle branch block. Atrioventricular nodal blocking agents, such as β-blockers, should be used to control this patient's heart rate and improve her symptoms. This patient is also at moderate to high risk for stroke given her CHA_2DS_2-VASc score of 4 (1 point each for hypertension and female sex; 2 points for age >75 years). Therefore, initiation of oral anticoagulation is also appropriate.

Adenosine is used in the acute treatment of arrhythmias to interrupt atrioventricular conduction and terminate supraventricular tachycardia; however, this patient's arrhythmia is not dependent on the atrioventricular node. Therefore, adenosine would not be of benefit.

Intravenous procainamide would be an appropriate option if the patient had preexcited atrial fibrillation due to an accessory pathway. The presence of an accessory pathway may be indicated on a resting ECG by the presence of two characteristics: a short PR interval when in sinus rhythm (see first beat on the ECG) and a delta wave (a sloping upstroke initiating the QRS complex, which may be wide due to sequential rather than parallel depolarization of the ventricles). This pattern on ECG is referred to as preexcitation, and when present with symptomatic tachycardia, it is called the Wolff-Parkinson-White syndrome. This patient's ECG is most consistent with aberrant conduction in the setting of atrial fibrillation, not preexcited atrial fibrillation.

Urgent cardioversion is unnecessary because the patient is hemodynamically stable and appears to have nonsustained atrial fibrillation on the basis of the intermittent nature of her symptoms. If the patient had a sustained arrhythmia accompanied by hemodynamic instability, emergent cardioversion would be indicated, regardless of the specific cause of the arrhythmia (that is, supraventricular versus ventricular).

KEY POINT

- Atrial fibrillation with aberrant conduction results in an irregularly irregular rhythm and a wide-complex tachycardia with a QRS morphology (rSR pattern in lead V_1, deep terminal S waves in leads I and V_6) on electrocardiogram typical of right bundle branch block.

Bibliography

Link MS. Clinical practice. Evaluation and initial treatment of supraventricular tachycardia. N Engl J Med. 2012;367:1438-48. [PMID: 23050527] doi:10.1056/NEJMcp1111259

Item 48 Answer: D

Educational Objective: Manage a patient with a thoracic aortic aneurysm and concomitant coronary artery disease.

The most appropriate management of this patient is simultaneous coronary artery bypass graft (CABG) surgery and aortic repair. On the basis of his angiographic findings (80% stenosis of the left main coronary artery bifurcation), he should undergo revascularization with CABG surgery. In patients with an ascending aorta or aortic root greater than 4.5 cm in diameter who require CABG surgery or surgery to repair valve pathology, aortic repair should be performed at the time of cardiac surgery. Anatomic imaging, such as CT angiography or magnetic resonance angiography, is recommended to plan for open aortic repair before the surgical procedure.

Patients with left main coronary artery disease have traditionally been treated with CABG surgery; however, because this patient has concomitant thoracic aortic aneurysmal disease, CABG surgery without aortic repair is not the best management option.

Patients with established coronary artery disease benefit from optimal medical therapy, including β-blockers and long-acting nitrates. However, given this patient's thoracic aortic aneurysm and severe coronary artery disease, optimal medical therapy in the absence of revascularization and aortic repair is inappropriate.

Percutaneous coronary intervention is not encouraged for patients with complex disease of the left main coronary artery, especially in the presence of a thoracic aortic aneurysm.

KEY POINT

- In patients with a thoracic aortic aneurysm greater than 4.5 cm in diameter who require coronary artery bypass graft surgery or surgery to repair valve pathology, aortic repair should be performed at the time of cardiac surgery.

Bibliography

Hiratzka LF, Bakris GL, Beckman JA, Bersin RM, Carr VF, Casey DE Jr, et al; American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. 2010 ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM guidelines for the diagnosis and management of patients with thoracic aortic disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, American Association for Thoracic Surgery, American College of Radiology, American Stroke Association, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of Thoracic Surgeons, and Society for Vascular Medicine. Circulation. 2010;121:e266-369. [PMID: 20233780] doi:10.1161/CIR.0b013e3181d4739e

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Item 49 Answer: D

Educational Objective: Diagnose left ventricular assist device–related thrombosis as the cause of stroke.

The most likely cause of stroke in this patient with a left ventricular assist device (LVAD) is LVAD-related thrombosis. Stroke is one of the most common complications after placement of an LVAD. Studies have shown that the incidence of hemorrhagic and embolic strokes approaches 20% at 1 year after LVAD insertion. Other complications of LVAD placement include gastrointestinal bleeding, usually secondary to arteriovenous malformations; pump malfunction; and thrombus formation in the pump that can lead to emboli, hemolysis, or pump stoppage.

Stroke due to large artery atherosclerosis, such as carotid artery stenosis, commonly occurs after local thrombus formation in the area of plaque rupture with subsequent distal embolization. Of the common causes of stroke, extracranial internal carotid artery atherosclerosis has the highest risk for recurrent stroke in the first 2 weeks. Advanced atherosclerotic disease is a much less likely cause of stroke in this 37-year-old man with cardiomyopathy than is thromboembolism related to LVAD placement.

A sizeable proportion of patients will have a cerebral infarction with no definitive cause identified on cardiac or vascular diagnostic testing, termed cryptogenic stroke. However, this diagnosis is not appropriate until a complete evaluation reveals no cause of the stroke, which is not the case for this patient.

Small subcortical infarcts (lacunes) commonly have a diameter of less than 1.5 cm and arise from occlusion of small perforating arteries emanating from the large intracranial vessels. This stroke subtype typically presents with only motor or sensory findings on examination; cortical hemispheric symptoms, such as visual field cuts, aphasia, or hemispatial neglect, are lacking. Lacunar infarction is not compatible with the patient's clinical presentation.

KEY POINT

- The incidence of hemorrhagic and embolic strokes approaches 20% at 1 year after insertion of a left ventricular assist device.

Bibliography

Robertson J, Long B, Koyfman A. The emergency management of ventricular assist devices. Am J Emerg Med. 2016;34:1294-301. [PMID: 27162114] doi:10.1016/j.ajem.2016.04.033

Item 50 Answer: D

Educational Objective: Diagnose a benign heart murmur.

The most appropriate management is routine clinical follow-up without imaging. Cardiac murmurs result from increased blood flow across a normal orifice (such as with anemia, thyrotoxicosis, pregnancy, or atrial septal defect), turbulent flow through a narrowed orifice (such as with aortic stenosis or mitral stenosis), or regurgitant flow through an incompetent valve (such as with aortic regurgitation or mitral regurgitation). Timing in the cardiac cycle, chest wall location, radiation, intensity, configuration, duration, and pitch all assist in the differential diagnosis.

Not all systolic murmurs are pathologic. Asymptomatic patients with short, soft systolic murmurs (grade <3) well localized to the left sternal border and associated with normal heart sounds do not usually require further investigation. Benign murmurs typically decrease in intensity with standing. The presence of any diastolic or continuous murmur, cardiac symptoms (chest pain, dyspnea, syncope), or abnormalities on examination (clicks, abnormal S_2, abnormal pulses) requires evaluation by echocardiography.

Various interventions may alter the intensity of murmurs. The murmur of hypertrophic cardiomyopathy may increase with standing or Valsalva maneuver; both maneuvers decrease venous return, which decreases left ventricular chamber size and increases the degree of obstruction. The click and murmur of mitral valve prolapse may move earlier in systole and increase in intensity as left ventricular volume decreases (standing or Valsalva maneuver). Aortic outflow murmurs increase in intensity in the beat following a premature ventricular contraction due to increased left ventricular volume. Murmurs of mitral regurgitation, ventricular septal defect, and aortic regurgitation increase with handgrip because of increased cardiac output and peripheral

resistance. Right-sided heart murmurs may increase during inspiration due to increased venous return.

Characteristics of the S_2 may assist in determining the diagnosis or the severity of a valvular lesion. A fixed split of S_2 (present during inspiration and expiration instead of only inspiration) results from a delay in right ventricular emptying and is strongly associated with atrial septal defect. A paradoxical split of S_2 (present during expiration) indicates a delay in left ventricular emptying, such as with severe aortic stenosis. Presence of a physiologic split (present during inspiration) is helpful for excluding severe aortic stenosis.

Because this patient likely has a benign systolic heart murmur and is asymptomatic, imaging with echocardiography or cardiac magnetic resonance imaging is not necessary.

KEY POINT

- Short, soft systolic murmurs (grade <3) that are well localized to the left sternal border and are not associated with symptoms often do not require further investigation.

Bibliography

Etchells E, Bell C, Robb K. Does this patient have an abnormal systolic murmur? JAMA. 1997;277:564-71. [PMID: 9032164]

Item 51 Answer: B

Educational Objective: Manage dual antiplatelet therapy in a patient with stable angina treated with drug-eluting stent placement.

This patient should receive dual antiplatelet therapy (DAPT) for 5 additional months, after which clopidogrel can be discontinued. In patients who undergo percutaneous coronary intervention (PCI), DAPT with aspirin plus a $P2Y_{12}$ inhibitor is indicated to prevent stent thrombosis and future cardiovascular events. However, recently, there has been considerable movement regarding the optimal duration of DAPT following drug-eluting stent placement. It is important to find the correct balance between blocking platelet activity during the process of reendothelialization of the stent and exposure to the attendant bleeding risk. Current guidelines suggest that the minimum duration for DAPT following drug-eluting stent placement for patients without an acute coronary syndrome is at least 6 months, with the option to continue therapy for a longer duration in those with a high risk for thrombosis-related complications and a favorable bleeding profile. Ultimately, the decision may be individualized at the patient level, such as with this patient, who is at relatively high bleeding risk given her age and comorbid conditions.

In patients who undergo PCI with bare metal stent placement, DAPT may be discontinued after 1 month; however, this patient with a drug-eluting stent requires longer therapy.

Patients with acute coronary syndrome treated with PCI (bare metal or drug-eluting stent placement) should be optimally treated with DAPT for at least 12 months.

Aspirin should be continued indefinitely in patients with coronary artery disease, unless contraindicated. No data support discontinuing both antiplatelet agents following PCI.

A study of DAPT comparing 12 months of therapy with 30 months of therapy suggested a benefit to the longer duration in some patients. Extending DAPT for a longer duration should be individualized on the basis of predicted risk for additional cardiovascular events and risk for bleeding.

KEY POINT

- Dual antiplatelet therapy is recommended for at least 6 months after drug-eluting stent placement for treatment of stable angina.

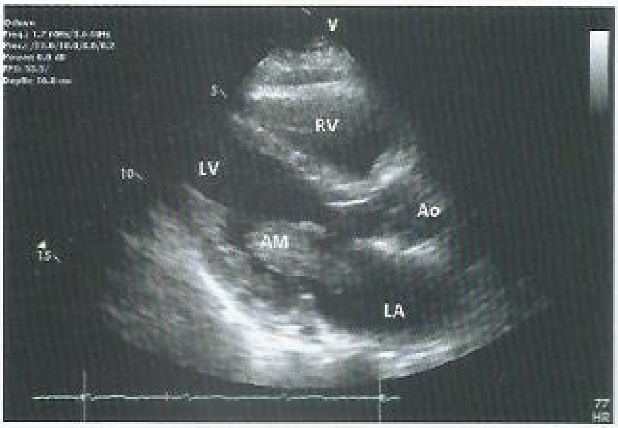
Bibliography

Levine GN, Bates ER, Bittl JA, Brindis RG, Fihn SD, Fleisher LA, et al. 2016 ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Thorac Cardiovasc Surg. 2016;152:1243-1275. [PMID: 27751237] doi:10.1016/j.jtcvs.2016.07.044

Item 52 Answer: E

Educational Objective: Treat an atrial myxoma.

The most appropriate treatment is surgical excision. This patient's history, physical examination findings, and echocardiographic features are all most consistent with a left atrial myxoma. The parasternal long-axis echocardiographic view (shown) demonstrates a large atrial myxoma (AM) prolapsing across the mitral valve from the left atrium (LA) to the left ventricle (LV) during diastole. Myxomas are connective tissue tumors with cells encompassed within mucopolysaccharide stroma. Most are attached to the left atrial wall in proximity to the fossa ovalis. Patients with an atrial myxoma most often present with symptoms related to obstruction or embolization, or constitutional symptoms related to production of tumor-based interleukin 6, such as fatigue, low-grade fever, and arthralgia. Dyspnea may be related to mitral valvular obstruction, which causes a diastolic rumble resembling mitral stenosis and an early diastolic sound ("tumor plop")



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heard in 10% to 15% of patients. Treatment for an atrial myxoma is urgent surgical excision.

Systemic anticoagulation would be appropriate in patients with a thrombus. Right atrial masses in patients with indwelling cardiac catheters are more likely to represent thrombus. PET and contrast-enhanced MRI/CT may be useful in evaluating metabolic activity and vascularity to differentiate a tumor from a thrombus. This patient has no risk factors for intracardiac thrombus, such as cardiac catheter, atrial fibrillation, or poor left ventricular function, making it an unlikely diagnosis.

Chemotherapy and radiotherapy are used to treat primary cardiac lymphoma. Suspicion for cardiac lymphoma would be higher if this patient were immunocompromised and had presented with a right atrial mass rather than an intra-atrial mass.

Empiric antibiotic therapy would be appropriate for suspected infective endocarditis. Although this patient has a low-grade fever, embolic phenomena, and constitutional symptoms, she has no risk factors for infective endocarditis and no leukocytosis. Additionally, attachment of the tumor to the fossa ovalis, not a valvular surface, makes infective endocarditis unlikely.

Percutaneous biopsy with echocardiographic guidance is sometimes useful in establishing the diagnosis of right-sided masses. However, percutaneous biopsy would not eliminate the need for surgical excision in this patient with embolic events.

KEY POINT

- Patients with an atrial myxoma may present with constitutional symptoms, embolic phenomena from tumor fragmentation, or symptoms referable to intracardiac obstruction (dyspnea, syncope); treatment is surgical excision.

Bibliography

Basso C, Rizzo S, Valente M, Thiene G. Cardiac masses and tumours. Heart. 2016 Aug 1;102(15):1230-45. [PMID: 27277840]

Item 53 Answer: C

Educational Objective: Diagnose Noonan syndrome associated with cardiovascular disease.

This patient has features of Noonan syndrome, which is an autosomal dominant disorder commonly associated with congenital cardiac lesions, including pulmonary stenosis; the valve is usually dysplastic. Noonan syndrome should be considered in all patients with pulmonary stenosis, particularly those with short stature, variable intellectual impairment, unique facial features, neck webbing, hypertelorism, and other cardiac abnormalities, including hypertrophic cardiomyopathy, atrial septal defect, and ventricular septal defect. This patient has severe pulmonary stenosis demonstrated by the physical examination findings of a palpable, late-peaking systolic murmur located at the second left intercostal space; absence of an ejection click; and features of right ventricular pressure overload. An ejection click may be audible in patients with pulmonary stenosis, but as severity progresses, the click disappears owing to loss of valve pliability. The echocardiogram in this patient confirms severe pulmonary stenosis with a peak systolic gradient of 65 mm Hg.

Down syndrome is a genetic disorder caused by the presence of a full or partial extra copy of chromosome 21. Characteristic features include small stature, unique facial features, and intellectual delays. Congenital cardiovascular disease occurs in more than 40% of affected persons, most commonly as a form of atrioventricular septal defect, including ostium primum atrial septal defect, inlet ventricular septal defect, or complete atrioventricular septal defect. Pulmonary stenosis is not typically seen unless associated with tetralogy of Fallot, which is also common in persons with Down syndrome.

Marfan syndrome is a genetic disorder caused by a mutation on chromosome 15. Findings typically include ocular, cardiovascular, skeletal, and systemic features that include tall stature with overgrowth of the long bones. The most common cardiovascular feature is aortic sinus dilatation with a propensity to dissection.

Turner syndrome is a genetic disorder that affects girls and women and is characterized by complete or partial absence of one of the X chromosomes. Affected persons often demonstrate short stature, webbed neck, low-set ears, low hairline, and primary infertility. Cardiac defects occur in about 45% of affected patients; the most common lesions include bicuspid aortic valve, aortic coarctation, and aortic aneurysm. Although pulmonary stenosis can occur in Turner syndrome, this man could not have Turner syndrome.

KEY POINT

- Noonan syndrome is commonly associated with congenital cardiac lesions, including pulmonary stenosis.

Bibliography

Bhambhani V, Muenke M. Noonan syndrome. Am Fam Physician. 2014;89:37-43. [PMID: 24444506]

Item 54 Answer: C

H

Educational Objective: Prevent sudden cardiac death in a patient with nonischemic cardiomyopathy.

Implantable cardioverter-defibrillator (ICD) placement is the most appropriate management of this patient with nonischemic cardiomyopathy and syncope that is concerning for an arrhythmic cause. He has several high-risk features for ventricular arrhythmia (New York Heart Association functional class II symptoms, ventricular ectopy, and syncope). ICD therapy is indicated to prevent sudden cardiac death.

Electroencephalography is indicated if seizure is suspected as the cause of syncope. However, this patient's presentation was not consistent with a diagnosis of seizure.

Exercise treadmill stress testing is a valuable test when exercise-induced arrhythmias are suspected. This patient's

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symptoms are not associated with exertion; therefore, exercise treadmill stress testing is unnecessary.

PET can be useful in the evaluation of nonischemic cardiomyopathy when cardiac sarcoidosis is suspected. However, this information would not be helpful in guiding the decision to insert an ICD in this patient at high risk for sudden cardiac death.

Tilt-table testing should be reserved for patients with recurrent syncope without known heart disease or those with heart disease in whom a cardiac cause of the syncope has been excluded. Because cardiac arrhythmias are the most likely cause of this patient's syncope, tilt-table testing is not appropriate.

KEY POINT

- Implantable cardioverter-defibrillator (ICD) therapy is indicated in patients with nonischemic cardiomyopathy who have a left ventricular ejection fraction less than or equal to 35% and who have New York Heart Association functional class II or III symptoms; ICD implantation is also reasonable for patients with nonischemic cardiomyopathy and unexplained syncope and significant left ventricular dysfunction.

Bibliography

Epstein AE, DiMarco JP, Ellenbogen KA, Estes NA 3rd, Freedman RA, Gettes LS, et al; American College of Cardiology Foundation; American Heart Association Task Force on Practice Guidelines; Heart Rhythm Society. 2012 ACCF/AHA/HRS focused update incorporated into the ACCF/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. Circulation. 2013 Jan 22;127(3):e283-352. [PMID: 23255456]

Item 55 Answer: A

Educational Objective: Evaluate symptomatic mitral stenosis with exercise echocardiography.

The most appropriate next step in management is exercise echocardiography. This patient has symptoms typical of severe mitral stenosis (progressive exertional dyspnea) but echocardiographic findings consistent with only moderate mitral stenosis. Symptoms of mitral stenosis can be indolent, with patients remaining asymptomatic for years and then presenting with a gradual decrease in activity. Other symptoms include dyspnea, orthopnea, fatigue, and, less commonly, hemoptysis or systemic embolization. Symptoms typically are not present until the mitral valve area is less than 1.5 cm^2, although tachycardia may precipitate symptoms at larger valve areas. In patients with a discrepancy between the clinical findings (debilitating symptoms) and the echocardiographic findings (moderate stenosis), additional testing is necessary to ensure that the patient's symptoms can be attributed to mitral stenosis. In this case, exercise echocardiography, using either pharmacologic or physical stressors, should be pursued to assess the response of the mitral gradient and pulmonary pressures. For patients with mitral stenosis, the valve gradient is heavily flow dependent and may become severely elevated only with exercise. Exercise and the accompanying increases in heart rate augment cardiac output and transvalvular flow and shorten the diastolic filling time in the left ventricle. These conditions can unmask mitral stenosis that does not appear to be functionally severe at rest. With an increase in left atrial pressures during exercise, significant pulmonary hypertension also may become evident.

Medical therapy for mitral stenosis consists of diuretics or long-acting nitrates, which may help alleviate symptoms such as dyspnea. In addition, β-blockers or nondihydropyridine calcium channel blockers can lower heart rate and improve left ventricular diastolic filling time. Medical therapy would be appropriate if the mitral stenosis were not hemodynamically significant or if she were not a surgical candidate.

After hemodynamically significant mitral stenosis is confirmed, percutaneous or surgical therapy can be considered. However, these interventions are not appropriate before confirmation with exercise echocardiography.

KEY POINT

- In patients with mitral stenosis who have a discrepancy between the clinical findings and the echocardiographic findings, exercise echocardiography should be pursued to assess the response of the mitral gradient and pulmonary pressures.

Bibliography

Aviles RJ, Nishimura RA, Pellikka PA, Andreen KM, Holmes DR Jr. Utility of stress Doppler echocardiography in patients undergoing percutaneous mitral balloon valvotomy. J Am Soc Echocardiogr. 2001;14:676-81. [PMID: 11447412]

Item 56 Answer: C

H

Educational Objective: Treat ST-elevation myocardial infarction complicated by cardiogenic shock.

Immediate percutaneous coronary intervention (PCI) is indicated in this patient with ST-elevation myocardial infarction (STEMI) complicated by cardiogenic shock. Cardiogenic shock is defined by persistent symptomatic hypotension and end-organ dysfunction. Patients have acute kidney failure, evidence of liver dysfunction with elevated aminotransferase levels, poor peripheral perfusion with cool extremities, and decreased mental status. Cardiogenic shock typically occurs as a consequence of a large anterior myocardial infarction, resulting in severely reduced left ventricular systolic function; it carries a mortality rate between 50% and 80%. Despite their instability, patients with cardiogenic shock (particularly those younger than 75 years of age) have a higher rate of survival if they undergo emergent revascularization with primary PCI in the catheterization laboratory.

Medical stabilization with intravenous vasoactive medications and, in severe cases, device-based hemodynamic support without prompt revascularization has been shown to be inferior to revascularization in the setting of shock and is not appropriate.

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In the treatment of STEMI, β-blockers are recommended at the time of initial presentation, except in patients with evidence of hypotension, cardiogenic shock, pulmonary congestion, advanced atrioventricular block, or other contraindications to β-blocker therapy. Intravenous metoprolol is the most widely used β-blocker for STEMI treatment. In this case, β-blockade should be withheld and introduced following reperfusion therapy.

Intravenous nitroglycerin can be used to treat patients with STEMI and hypertension or heart failure but should be avoided in the setting of systolic blood pressure less than 90 mm Hg, significant bradycardia or tachycardia, right ventricular infarction, or use of a phosphodiesterase inhibitor (such as sildenafil) in the past 24 to 48 hours.

Because the rates of achieving vessel patency are higher and more reliable with primary PCI than with thrombolysis, primary PCI is the preferred method of treating STEMI. Thrombolytic therapy would be indicated in this patient with STEMI if transfer to a PCI-capable center would result in a first medical contact-to-device time of more than 120 minutes.

KEY POINT

- Patients with ST-elevation myocardial infarction complicated by cardiogenic shock should undergo emergent revascularization with primary percutaneous coronary intervention.

Bibliography

O'Gara PT, Kushner FG, Ascheim DD, Casey DE Jr, Chung MK, de Lemos JA, et al; American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2013;127:e362-425. [PMID: 23247304] doi:10.1161/CIR.0b013e3182742cf6

Item 57 Answer: D

Educational Objective: Manage a patient with a bicuspid aortic valve and enlarged aortic root with surveillance echocardiography.

The most appropriate management of this patient with an ascending thoracic aortic aneurysm and a bicuspid aortic valve is repeat echocardiography in 6 months. Patients with a bicuspid aortic valve are prone to enlargement of the ascending aorta, and patients with both a bicuspid aortic valve and enlarged aortic dimensions are at higher risk for aortic dissection. Surveillance echocardiography should be performed in these patients to monitor aortic growth. Patients with a bicuspid aortic valve and a thoracic aortic aneurysm should undergo annual imaging if the aortic diameter has been stable and smaller than 4.5 cm. If the aortic diameter is 4.5 cm or larger or the rate of enlargement exceeds 0.5 cm/year, imaging should be performed every 6 months.

Operative aortic valve repair or replacement is indicated in asymptomatic patients with a bicuspid aortic valve and a thoracic aortic aneurysm diameter of 5.5 cm or larger, according to American College of Cardiology/American Heart Association guidelines. However, surgical intervention can be beneficial in those patients with a bicuspid aortic valve, thoracic aortic aneurysm diameter of 5.0 cm or larger, and an additional risk factor for dissection/rupture (such as family history of aortic dissection or aortic growth rate ≥0.5 cm/year). In this asymptomatic patient with an ascending aortic diameter of 5.1 cm without additional risk factors, it is premature to repair or replace the aorta.

Some patients with reduced left ventricular (LV) function and calcific aortic stenosis have severe aortic stenosis based on valve area but a gradient that is less than 30 mm Hg. Whether symptoms in this "low-flow/low-gradient" aortic stenosis are caused primarily by aortic valve disease with resultant LV dysfunction or the effective valve area is reduced owing to poor leaflet excursion can be best determined with dobutamine stress echocardiography. In this patient, there is no indication to perform dobutamine stress echocardiography, as he has normal LV function.

KEY POINT

- Patients with a bicuspid aortic valve and a thoracic aortic aneurysm should undergo echocardiography every 6 months if the aortic diameter is larger than 4.5 cm or the rate of enlargement exceeds 0.5 cm/year.

Bibliography

Hiratzka LF, Creager MA, Isselbacher EM, Svensson LG, Nishimura RA, Bonow RO, et al. Surgery for aortic dilatation in patients with bicuspid aortic valves: a statement of clarification from the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2016;67:724-31. [PMID: 26658475] doi:10.1016/j.jacc.2015.11.006

Item 58 Answer: C

Educational Objective: Diagnose peripartum cardiomyopathy.

The most likely diagnosis in this woman who is 3 weeks postpartum is peripartum cardiomyopathy. Peripartum cardiomyopathy is left ventricular systolic dysfunction with onset toward the end of pregnancy or in the months following delivery in the absence of another identifiable cause. Although patients may be asymptomatic, they often present with features of heart failure. Women with peripartum cardiomyopathy should be promptly treated with medical therapy, which may include β-blockers, digoxin, hydralazine, nitrates, or diuretics. ACE inhibitors, angiotensin receptor blockers, and aldosterone antagonists are teratogenic and should be avoided until after delivery.

Acute aortic dissection classically presents with sudden onset of chest or back pain that has a tearing or ripping quality. Dyspnea is less common. Physical examination findings include a blood pressure or pulse differential between the upper extremities. A diastolic murmur of aortic regurgitation may be heard at the cardiac base if the aortic valve is involved. Echocardiography demonstrates an enlarged

ascending aorta; the dissection flap may also be visible. Ventricular function is usually normal unless the aortic dissection has involved the coronary arteries, although regional abnormalities may be detected. This patient's clinical findings do not support a diagnosis of acute aortic dissection.

Pulmonary embolism can occur postpartum, particularly when prolonged bed rest is required during or following pregnancy. Patients with pulmonary embolism frequently present with dyspnea; however, this patient's presentation suggests heart failure, given the elevated venous pressure, pulmonary congestion, and global reduction in ejection fraction.

Takotsubo cardiomyopathy, also known as stress cardiomyopathy, is characterized by transient regional cardiac dysfunction, usually involving the apical and mid-portion of the left ventricle. It is usually precipitated by a stressful physical or emotional event. Postpartum cases of takotsubo cardiomyopathy have been reported, especially after cesarean delivery. Patients with takotsubo cardiomyopathy present with features that mimic an acute coronary syndrome: chest pain, ischemic electrocardiographic changes, and elevated cardiac biomarker levels. This patient's clinical picture is inconsistent with takotsubo cardiomyopathy.

KEY POINT

- Peripartum cardiomyopathy is left ventricular systolic dysfunction with onset toward the end of pregnancy or in the months following delivery in the absence of another identifiable cause; patients often present with features of heart failure.

Bibliography

Arany Z, Elkayam U. Peripartum cardiomyopathy. Circulation. 2016;133:1397-409. [PMID: 27045128] doi:10.1161/CIRCULATIONAHA.115.020491

Item 59 Answer: B

Educational Objective: Evaluate a patient for an arrhythmia.

An event recorder is the most appropriate diagnostic testing option for this patient. Because he has symptomatic palpitations associated with lightheadedness and near syncope, evaluation to identify the type and source of any present arrhythmias is important to his care. The intermittent and fleeting nature of arrhythmias can make diagnosis difficult. Diagnostic studies are selected on the basis of the presence and frequency of the patient's symptoms and the duration and timing of the recording. The diagnostic study best suited to capture this patient's symptomatic episodes is an external event recorder. The basic event monitor involves the patient activating or "triggering" the event monitor at the time of symptoms, capturing the rhythm. Some models capture the rhythm only at the time the event recorder is activated or held to the chest, or when electrodes are applied. Other models can capture the rhythm before and after the patient activates the recorder. The newest models are real-time continuous monitoring systems that automatically record and transmit heart rhythm data from the ambulatory patient to a monitoring station; data can also be sent at the time of patient activation. Patients are encouraged to keep a diary of when symptoms occur so that they may be correlated with arrhythmias shown on the electrocardiographic (ECG) tracing.

An electrophysiology study may be appropriate if this patient's arrhythmia cannot be diagnosed on the basis of less invasive techniques. It may also be helpful therapeutically if the rhythm is amenable to ablation.

Ambulatory ECG monitors are helpful in identifying arrhythmias in patients with daily symptoms. They can also be used to monitor for arrhythmias that may be asymptomatic, such as atrial fibrillation. This patient's symptoms occur once or twice per week; therefore, a 24-hour ambulatory ECG monitor may not capture the arrhythmia.

In patients with very infrequent or rare episodes (>30 days between episodes), an implantable loop recorder may be appropriate; however, these devices should not be used for initial evaluation, given the cost and risks, although minimal, associated with implantation. Implantable loop recorders can remain in place for years to evaluate for infrequent arrhythmias.

KEY POINT

- In patients with infrequent episodes of palpitations, presyncope, or syncope, an event recorder may be used to correlate symptoms with an arrhythmia.

Bibliography

Ruwald MH, Zareba W. ECG monitoring in syncope. Prog Cardiovasc Dis. 2013;56:203-10. [PMID: 24215752] doi:10.1016/j.pcad.2013.08.007

Item 60 Answer: D

Educational Objective: Interpret B-type natriuretic peptide level in an obese patient with dyspnea.

The cause of this patient's dyspnea is indeterminate on the basis of the B-type natriuretic peptide (BNP) level of 128 pg/mL (128 ng/L). In the Breathing Not Properly study of patients who presented to the emergency department with dyspnea, patients with heart failure had a mean BNP level greater than 600 pg/mL (600 ng/L), whereas those with noncardiac causes of dyspnea had levels of approximately 50 pg/mL (50 ng/L). Patients with a history of left ventricular dysfunction but not an acute exacerbation had a BNP level of approximately 200 pg/mL (200 ng/L). In a pooled analysis of 10 studies, BNP values less than 100 pg/mL (100 ng/L) excluded heart failure (90% sensitivity) and greater than 400 pg/mL (400 ng/L) supported the diagnosis of heart failure (74% specificity). BNP levels increase with age and worsening kidney function and are reduced in patients with an elevated BMI. BNP values less than 55 pg/mL (55 ng/L) are likely to rule out heart failure in patients with BMI greater than 35 (sensitivity 90%). In these patients, BNP levels greater than or equal to 170 pg/mL (170 ng/L) are 70% specific for the diagnosis of acute heart failure. This patient's BNP level is not helpful in ruling in or

ruling out cardiac disease as the cause of her dyspnea, and further evaluation is required.

KEY POINT

- Common factors other than ventricular wall stress that influence B-type natriuretic peptide (BNP) levels include kidney failure, older age, and female sex, all of which increase BNP levels; obesity reduces BNP levels.

Bibliography

Daniels LB, Clopton P, Bhalla V, Krishnaswamy P, Nowak RM, McCord J, et al. How obesity affects the cut points for B-type natriuretic peptide in the diagnosis of acute heart failure. Results from the Breathing Not Properly Multinational Study. Am Heart J. 2006;151:999-1005. [PMID: 16644321]

H

Item 61 Answer: B

Educational Objective: Treat critical limb ischemia.

The most appropriate next step in the management of this patient with critical limb ischemia is to perform invasive angiography of the affected limb with the intent to revascularize. Critical limb ischemia is a severe form of peripheral artery disease (PAD) characterized by ischemic rest pain and ulceration. Clinical findings in a patient with critical limb ischemia include an ankle-brachial index less than 0.40, a flat waveform on pulse volume recording, and low or absent pedal flow on duplex ultrasonography. In patients who undergo successful limb revascularization, the 1-year risk for major amputation is significantly lower than that in patients who do not undergo revascularization.

Vorapaxar inhibits thrombin-induced and thrombin receptor agonist peptide-induced platelet aggregation. In the TRA 2P-TIMI 50 trial, vorapaxar reduced hospitalizations for acute limb ischemia, mainly among patients who had previously undergone revascularization. The role of vorapaxar in patients with PAD is yet to be established.

Owing to the high morbidity and mortality associated with critical limb ischemia, immediate invasive angiography with endovascular revascularization, without additional noninvasive imaging, is often the most effective strategy to preserve tissue viability. Imaging studies such as magnetic resonance angiography would result in treatment time delays in this patient with critical limb ischemia and a viable limb. He should be referred directly for angiography and revascularization.

In patients with critical limb ischemia and a viable limb, angiography and revascularization is always preferred to primary major amputation of the lower extremity. Patients older than 65 years who undergo major amputation have a 1-year mortality rate of nearly 50% and a 3-year mortality rate higher than 70%.

KEY POINT

- In patients with critical limb ischemia, immediate invasive angiography with endovascular revascularization is often the most effective strategy to preserve tissue viability.

Bibliography

Gerhard-Herman MD, Gornik HL, Barrett C, Barshes NR, Corriere MA, Drachman DE, et al. 2016 AHA/ACC guideline on the management of patients with lower extremity peripheral artery disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2017;69:1465-1508. [PMID: 27851991] doi:10.1016/j.jacc.2016.11.008

H

Item 62 Answer: A

Educational Objective: Manage atrioventricular block in the setting of an acute coronary syndrome.

This patient has Mobitz type 1 second-degree atrioventricular (AV) block and evidence of an acute coronary syndrome, and she should undergo cardiac catheterization for emergent revascularization. This patient's chest pain, ST-segment elevation, and elevated troponin T level all indicate acute myocardial infarction. Additionally, the electrocardiogram demonstrates second-degree AV block, which is characterized by nonconducted P waves. The progressive prolongation of the PR interval before loss of AV conduction is consistent with Mobitz type 1 (Wenckebach block). There are many causes of AV block, including fibrosis and sclerosis of the conduction system, ischemic heart disease, and medication use (β-blockers, calcium channel blockers, digoxin). Reversible causes of AV block should always be identified and treated first. In this patient, cardiac catheterization and revascularization are indicated not only to treat the acute coronary obstruction but also to potentially correct the conduction deficit.

Transthoracic echocardiography should be performed in patients with myocardial infarction to evaluate left ventricular function and assess for potential structural complications; however, obtaining an echocardiogram is not the priority in this patient and does not help manage the arrhythmia. The most appropriate next step is cardiac catheterization.

Permanent or temporary pacemaker placement is not required in this case because the patient does not have symptomatic or hemodynamically unstable bradycardia or advanced AV block (Mobitz type 2 second-degree or third-degree AV block). If symptomatic or advanced conduction block persists after revascularization, permanent pacemaker implantation would be recommended.

KEY POINT

- Patients with atrioventricular block and evidence of acute coronary syndrome should undergo cardiac catheterization for diagnosis and possible revascularization.

Bibliography

Epstein AE, DiMarco JP, Ellenbogen KA, Estes NA 3rd, Freedman RA, Gettes LS, et al; American College of Cardiology Foundation. 2012 ACCF/AHA/HRS focused update incorporated into the ACCF/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol. 2013;61:e6-75. [PMID: 23265327] doi:10.1016/j.jacc.2012.11.007

Answers and Critiques

Item 63 Answer: D

Educational Objective: Manage aortic regurgitation that does not meet criteria for surgical valve replacement.

The most appropriate next step in management is clinical and echocardiographic follow-up in 6 to 12 months. This asymptomatic patient with severe aortic regurgitation does not currently meet the criteria for surgical aortic valve replacement. For patients with severe aortic regurgitation, surgical aortic valve replacement is recommended in the presence of symptoms attributable to regurgitation, left ventricular ejection fraction less than 50%, or another indication for cardiac surgery. In addition, surgical aortic valve replacement can be beneficial in asymptomatic patients with significant left ventricular dilatation (end-systolic dimension >50 mm or indexed end-systolic dimension >25 mm/m^2). In the absence of these findings, clinical evaluation and surveillance echocardiography every 6 to 12 months is recommended.

The clinical impact of β-blockers, such as carvedilol, in patients with chronic aortic regurgitation is uncertain. Carvedilol is useful in patients with severe aortic regurgitation and heart failure when combined with other standard therapies, such as diuretics, ACE inhibitors, and aldosterone antagonists; however, this patient has no indication for β-blocker therapy.

ACE inhibitors or angiotensin receptor blockers may be used in patients with chronic severe aortic regurgitation and concomitant hypertension, although these agents, as well as dihydropyridine calcium channel blockers, have not been shown to delay the need for surgery in asymptomatic patients without hypertension. Consequently, they are not indicated in this patient in the absence of hypertension.

KEY POINT

- For patients with severe aortic regurgitation, indications for surgery are the presence of attributable symptoms, left ventricular ejection fraction less than 50%, or significant left ventricular dilatation; in the absence of these findings, surveillance echocardiography every 6 to 12 months is recommended.

Bibliography

Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP 3rd, Guyton RA, et al; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2014;63:e57-185. [PMID: 24603191] doi:10.1016/j.jacc.2014.02.536

H

Item 64 Answer: D

Educational Objective: Treat a patient with ST-elevation myocardial infarction and heart failure with renin-angiotensin system inhibition.

The most appropriate treatment of this patient with anterior ST-elevation myocardial infarction (STEMI) complicated by heart failure is valsartan. This patient is at significant risk for short-term and long-term morbidity, and early institution of guideline-directed medical therapy (within 24 hours of presentation) is crucial to improve survival and keep the patient free of symptoms. Although ACE inhibitors are indicated in most patients with STEMI and particularly in patients with impaired left ventricular function and heart failure, angiotensin receptor blockers (such as valsartan) are a suitable alternative and offer similar morbidity and mortality benefits. Additionally, angiotensin receptor blockers are associated with a significantly lower incidence of cough and angioedema than ACE inhibitors. Because this patient has a history of ACE inhibitor-induced cough, valsartan is the most appropriate choice.

In patients with STEMI, β-blockers (such as carvedilol) decrease myocardial oxygen demand, reduce the incidence of ventricular arrhythmias, and improve long-term survival. Whenever possible, β-blockers should be introduced within the first 24 hours of STEMI presentation. The COMMIT/CCS-2 trial demonstrated that early β-blocker initiation was associated with lower risk for reinfarction and lethal ventricular arrhythmias, but it also increased risk for cardiogenic shock. In this case, the patient has evidence of pulmonary edema, and early institution of β-blockade may worsen heart failure and increase the risk for cardiogenic shock. A β-blocker should be initiated once the patient is stabilized.

Like β-blockers, calcium channel blockers (such as diltiazem) are negative inotropic and chronotropic agents. However, unlike β-blockers, calcium channel blockers are generally avoided in the context of STEMI and are contraindicated with left ventricular dysfunction.

Hydralazine-isosorbide dinitrate can be used as a vasodilator, particularly as an add-on therapy in the setting of chronic heart failure, although it has been shown to be inferior to ACE inhibitors in a head-to-head study. Hydralazine–isosorbide dinitrate would not be the preferred agent in this setting, unless the patient had a significantly elevated serum creatinine level or a history of ACE inhibitor–induced angioedema.

KEY POINT

- In patients with ST-elevation myocardial infarction, an ACE inhibitor should be initiated within 24 hours of presentation; an angiotensin receptor blocker may be used if the patient is intolerant of ACE inhibitors.

Bibliography

O'Gara PT, Kushner FG, Ascheim DD, Casey DE Jr, Chung MK, de Lemos JA, et al; American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2013;127:e362-425. [PMID: 23247304] doi:10.1161/CIR.0b013e3182742cf6

Item 65 Answer: B

Educational Objective: Treat atrial fibrillation in a patient with hypertrophic cardiomyopathy.

The most appropriate treatment to reduce the risk for thromboembolic events in this patient is dose-adjusted warfarin.

In patients with hypertrophic cardiomyopathy (HCM), atrial fibrillation occurs in 20% to 25% of cases, and dyspnea often develops related to reduced left ventricular diastolic filling and increased left ventricular outflow tract obstruction. Restoration and maintenance of sinus rhythm are important in reducing symptoms. There is also a high incidence of stroke in patients with HCM who have atrial fibrillation, regardless of the type of atrial fibrillation (paroxysmal, persistent, or permanent), and anticoagulation to reduce thromboembolic risk must be considered. In this patient, acute anticoagulation with heparin or low-molecular-weight heparin would be appropriate before cardioversion, followed by administration of dose-adjusted warfarin to achieve an INR of 2 to 3. Two observational studies of patients with atrial fibrillation in the setting of HCM have shown reduced incidence of stroke with this strategy compared with antiplatelet therapy or no treatment.

The use of non–vitamin K antagonist oral anticoagulants, such as dabigatran, for thromboembolic risk reduction in patients with HCM has not been adequately studied, and the efficacy of these drugs in this situation is unknown. In patients with HCM who cannot take warfarin, non–vitamin K antagonist oral anticoagulants are reasonable as second-line therapy; however, use of warfarin in this patient is not contraindicated.

Although this patient's calculated CHA_2DS_2-VASc score is low (0 points), initiating aspirin therapy or foregoing therapy would be inappropriate according to current guidelines. The CHA_2DS_2-VASc scoring system is frequently used for decision making with regard to stroke risk-reduction therapy in patients with atrial fibrillation; however, the predictive use of this tool for patients with HCM has not been validated. A low CHA_2DS_2-VASc score may not adequately predict true thromboembolic risk in patients with HCM and should not be used to guide therapy.

KEY POINT

- Patients with atrial fibrillation in the setting of hypertrophic cardiomyopathy should receive warfarin anticoagulation therapy to reduce thromboembolic risk.

Bibliography

Elliott PM, Anastasakis A, Borger MA, Borggrefe M, Cecchi F, Charron P, et al; Authors/Task Force members. 2014 ESC guidelines on diagnosis and management of hypertrophic cardiomyopathy: the Task Force for the Diagnosis and Management of Hypertrophic Cardiomyopathy of the European Society of Cardiology (ESC). Eur Heart J. 2014;35:2733-79. [PMID: 25173338] doi:10.1093/eurheartj/ehu284

Item 66 Answer: A

Educational Objective: Evaluate the severity of aortic stenosis with cardiac catheterization.

The most appropriate next step in management is cardiac catheterization. In patients with symptomatic severe aortic stenosis, surgery with aortic valve replacement is indicated as a life-saving therapy. However, accurate measures of the severity of stenosis are needed to ensure that symptoms are caused by valve obstruction, rather than concurrent coronary, pulmonary, or other systemic disease. The severity of aortic stenosis is determined by Doppler echocardiography and sometimes cardiac catheterization. In some patients, the Doppler echocardiogram may underestimate severity because of the angle-dependent nature of the study. An invasive hemodynamic study is indicated in symptomatic patients being considered for surgery when there are discrepancies between the findings on physical examination and the echocardiographic results. This patient's exertional dyspnea and physical examination findings (carotid tardus, diminished aortic component of S_2, late-peaking systolic murmur) are consistent with severe aortic stenosis; however, the echocardiogram reveals findings of only moderate aortic stenosis. Therefore, further evaluation with cardiac catheterization is needed.

Surgical or transcatheter aortic valve replacement is not indicated in this patient until there is certainty that the aortic valve lesion is severe and can account for the patient's symptoms.

Identification of symptomatic aortic stenosis is crucial; in the absence of symptoms, patients with aortic stenosis—even severe aortic stenosis—have a low risk for mortality, with an estimated risk for sudden death of less than 1%. Although variable, symptoms of heart failure, angina, or syncope generally begin once the valve area is below 1.0 cm^2. Once symptoms develop, prognosis is poor without valve replacement, with an average survival of less than 10% over the next 2 to 3 years. Therefore, continued clinical observation is not the best option for this patient.

KEY POINT

- In patients with symptoms of aortic stenosis and discrepancies between the physical examination and echocardiographic findings, the severity of stenosis should be established with cardiac catheterization before aortic valve replacement is performed.

Bibliography

Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP 3rd, Fleisher LA, et al. 2017 AHA/ACC focused update of the 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2017;70:252-289. [PMID: 28315732] doi:10.1016/j.jacc.2017.03.011

Item 67 Answer: D

Educational Objective: Manage a patient with a ventricular septal defect.

The most appropriate management for this patient with a small uncomplicated ventricular septal defect (VSD) is follow-up in 3 to 5 years. VSDs are defined by their location on the ventricular septum. The most common type of VSD is perimembranous, making up 80% of cases; these are usually isolated abnormalities. She has no associated symptoms, volume overload of the left heart, pulmonary hypertension, or valve regurgitation; therefore, periodic clinical evaluation and imaging are recommended. If pulmonary vascular disease

is present (pulmonary artery systolic pressure >50 mm Hg), patients should be advised against isometric or competitive exercise. In the absence of pulmonary hypertension, pregnancy in women with VSDs is generally well tolerated. It is unnecessary to suggest activity restriction in this patient with a small VSD and normal pulmonary artery pressure, and pregnancy should not be complicated by the VSD.

Cardiac catheterization is not indicated for this patient because her clinical presentation and echocardiogram do not demonstrate features of left heart enlargement or pulmonary hypertension. Cardiac catheterization is primarily performed to delineate the shunt ratio and to determine pulmonary pressures if clinical uncertainty exists regarding the degree or impact of a shunt, or if the VSD is incompletely assessed by echocardiographic measures.

Cardiac magnetic resonance imaging will usually demonstrate a membranous VSD and can quantitate the impact of the shunt on the left heart; however, it is not indicated in this patient because the clinical and echocardiographic assessment are sufficient to suggest that observation is appropriate.

Endocarditis prophylaxis is recommended for patients with unrepaired cyanotic congenital heart disease, including palliative shunts and conduits; a congenital heart defect that has been completely repaired with prosthetic material or device during the first 6 months after the procedure; and repaired congenital heart disease with residual defects. Patients with uncomplicated VSDs without a history of endocarditis do not require endocarditis prophylaxis.

KEY POINT

- Periodic follow-up with clinical evaluation and imaging are appropriate in patients with a small uncomplicated ventricular septal defect.

Bibliography

Penny DJ, Vick GW 3rd. Ventricular septal defect. Lancet. 2011;377:1103-12. [PMID: 21349577] doi:10.1016/S0140-6736(10)61339-6

Item 68 Answer: A

Educational Objective: Diagnose cardiac tamponade.

The most likely diagnosis is cardiac tamponade. Pericarditis is a common cardiac manifestation of systemic lupus erythematosus (SLE), occurring in up to 40% of patients with SLE. Pericarditis may be associated with a neutrophilic pericardial effusion that can rarely lead to tamponade. In this patient, progressive dyspnea, fatigue, chest fullness, and peripheral edema are symptoms consistent with significant cardiac tamponade, and the physical examination findings of jugular venous distention and pulsus paradoxus (fall in systolic pressure of >10 mm Hg with inspiration) are supportive. The chest radiograph demonstrates an enlarged cardiac silhouette ("water-bottle heart"), and the electrocardiogram demonstrates electrical alternans, which may represent swinging of the heart within a large pericardial effusion. This patient also has supraventricular tachycardia.

The pericardium in constrictive pericarditis is rigid and noncompliant, resulting in a total cardiac volume that is largely fixed. Ventricular filling occurs rapidly in early diastole and terminates abruptly near mid-diastole owing to the pericardial restraint. The jugular venous pressure is elevated in nearly all patients, with prominent *x* and *y* descents. Physical findings that also may be present include a pericardial knock, pulsus paradoxus, pleural effusion, congestive hepatomegaly, and peripheral edema or ascites. In patients with long-standing constrictive pericarditis, hepatic failure and cirrhosis may be present. Pericardial constriction would not lead to a large cardiac silhouette or electrical alternans, as seen in this patient.

Patients with SLE have increased risk for venous thromboembolic disease. The electrocardiogram in acute pulmonary embolism most commonly demonstrates sinus tachycardia but may also show a new complete or incomplete right bundle branch block or an S1Q3T3 pattern (prominent S wave in lead I, Q wave in lead III, and inverted T wave in lead III). An enlarged globular heart on chest radiograph and electrical alternans on electrocardiogram are not features.

Patients with SLE may have pulmonary thromboembolic disease, pulmonary veno-occlusive disease, or advanced interstitial lung disease with hypoxemia leading to pulmonary hypertension; however, severe symptomatic pulmonary hypertension is more commonly associated with scleroderma or mixed connective tissue disease. An enlarged globular heart on chest radiograph would be unlikely, and the electrocardiogram is likely to demonstrate a right axis deviation and right ventricular hypertrophy but not electrical alternans.

KEY POINT

- Findings of congestion, hypotension, pulsus paradoxus, enlarged cardiac silhouette on chest radiograph, and electrical alternans on electrocardiogram support the diagnosis of cardiac tamponade.

Bibliography

Imazio M. Pericardial involvement in systemic inflammatory diseases. Heart. 2011;97:1882-92. [PMID: 22016400] doi:10.1136/heartjnl-2011-300054

Item 69 Answer: B

Educational Objective: Evaluate a patient with intermediate cardiovascular risk with coronary artery calcium scoring.

This asymptomatic patient at intermediate risk for coronary artery disease can undergo coronary artery calcium (CAC) scoring for further risk stratification. He has an intermediate risk for myocardial infarction and coronary death (5% to less than 7.5% as defined by the Pooled Cohort Equations). Among these patients, further risk stratification can be helpful to identify patients who will benefit from primary prevention, including statin therapy. The evaluation of subclinical disease with CAC scoring is not a component of routine risk

assessment, and consideration is reserved for when the result is expected to lead to a change in management based on patient reclassification to a lower- or higher-risk group. A CAC score of 300 Agatston units or higher or a score in the 75th percentile or higher for age, sex, and ethnicity would reclassify this patient as high risk and prompt initiation of primary prevention therapy. Other factors that can help guide risk reclassification are an LDL cholesterol level of 160 mg/dL (4.14 mmol/L) or higher, evidence of other genetic hyperlipidemias, family history of premature coronary artery disease (age <55 years in a first-degree male relative, age <65 years in a first-degree female relative), high-sensitivity C-reactive protein level of 2 mg/L or more, ankle-brachial index less than 0.9, or elevated lifetime risk for cardiovascular disease.

Physiologic tests of coronary perfusion are not indicated because this patient is asymptomatic. Furthermore, adenosine cardiac magnetic resonance imaging, exercise stress echocardiography, and pharmacologic nuclear stress testing are not used to reclassify risk among asymptomatic patients.

Elevated levels of lipoprotein(a), a subtype of LDL cholesterol, have been associated with increased risk for cardiovascular disease, especially coronary artery disease. However, this marker has not been evaluated for purposes of reclassification of asymptomatic, intermediate-risk patients. Additionally, the 2013 American College of Cardiology/American Heart Association cholesterol treatment guideline does not address whether lipoprotein(a) is useful for guiding treatment because evidence is currently insufficient.

KEY POINT

- In patients with an intermediate 10-year risk for atherosclerotic cardiovascular disease, coronary artery calcium scoring may be used to further risk-stratify patients to guide primary prevention therapy.

Bibliography

Nezarat N, Kim M, Budoff M. Role of coronary calcium for risk stratification and prognostication. Curr Treat Options Cardiovasc Med. 2017 Feb;19(2):8. [PMID: 28275938]

Item 70 Answer: A

Educational Objective: Treat heart failure with reduced ejection fraction with β-blocker therapy.

This patient with heart failure with reduced ejection fraction (HFrEF) should be started on a β-blocker, such as bisoprolol. In patients with heart failure, each follow-up visit should include evaluation for progression of heart failure symptoms, assessment of volume status, and a review of the patient's medications to ensure guideline-directed treatment. Optimal medical therapy includes an ACE inhibitor, β-blocker (specifically, metoprolol succinate, carvedilol, or bisoprolol), and an aldosterone antagonist (in symptomatic patients). β-Blockers improve remodeling, increase ejection fraction, and reduce hospitalization and mortality when added to ACE inhibitor and diuretic therapy. β-Blocker and ACE inhibitor therapies are indicated for all classes of heart failure, including New York Heart Association functional class I. This patient was discharged from the hospital before initiation of β-blocker therapy, and he should be started on bisoprolol now.

Diltiazem and verapamil are associated with worse outcomes in patients with HFrEF, and these agents should not be used in this population. If calcium channel blockers are necessary for hypertension treatment, amlodipine or felodipine have been shown to be safe in patients with heart failure.

Aldosterone antagonists (spironolactone, eplerenone) have been studied in patients with heart failure and New York Heart Association functional class II to IV symptoms and have been shown to reduce mortality and morbidity. Because of the risk for kidney dysfunction and hyperkalemia, these drugs should be used only in patients with a serum creatinine level below 2.5 mg/dL (221 μmol/L) in men or below 2.0 mg/dL (176.8 μmol/L) in women, and with a serum potassium level below 5.0 mEq/L (5.0 mmol/L). These drugs are not as effective as diuretics at the doses used in heart failure therapy (12.5-25 mg/d for spironolactone, 25-50 mg/d for eplerenone). The patient is asymptomatic now, and spironolactone is not indicated. If it were indicated, it would not be added until after uptitration of the β-blocker and ACE inhibitor doses.

Angiotensin receptor blockers (ARBs), such as losartan, are a suitable alternative to ACE inhibitors for the treatment of HFrEF and offer similar morbidity and mortality benefits. In patients taking an ACE inhibitor, the primary reason to switch to an ARB is ACE inhibitor-induced cough or angioedema. Caution should be exercised when switching patients to an ARB as a result of angioedema because this side effect has been reported with ARB therapy as well. This patient does not have side effects that would prompt switching an ACE inhibitor to an ARB.

KEY POINT

- In patients with heart failure with reduced ejection fraction, β-blockers improve remodeling, increase ejection fraction, and reduce hospitalization and mortality when added to ACE inhibitor and diuretic therapy.

Bibliography

Goldberg LR. In the clinic. Heart failure. Ann Intern Med. 2010;152:ITC61-15; quiz ITC616. [PMID: 20513825] doi:10.7326/0003-4819-152-6-201006010-01006

Item 71 Answer: B

Educational Objective: Treat a patient with multivessel coronary artery disease and left ventricular dysfunction with coronary artery bypass graft surgery.

The most appropriate treatment is coronary artery bypass graft (CABG) surgery. This patient with three-vessel coronary artery disease (CAD), left ventricular dysfunction, and type 2 diabetes mellitus has symptoms of heart failure and angina despite optimal medical therapy. In patients with multivessel coronary artery disease, revascularization with CABG results

in decreased recurrence of angina, lower rates of myocardial infarction, and fewer repeat revascularization procedures compared with percutaneous coronary intervention (PCI). Unlike PCI, CABG surgery improves survival in patients with left main or three-vessel CAD and is recommended to reduce mortality in these high-risk patients. CABG surgery has also been shown to improve symptoms and survival in patients with ischemic cardiomyopathy. Long-term follow-up of the STICH trial demonstrated a survival advantage with CABG surgery compared with medical therapy alone among patients with multivessel CAD and severe left ventricular dysfunction. Additionally, CABG surgery has consistently been shown to be the superior revascularization strategy in patients with diabetes and multivessel disease who require revascularization.

Ticagrelor is indicated as a component of dual antiplatelet therapy following acute coronary syndrome, regardless of whether percutaneous coronary intervention is performed. However, there is no clear role for the addition of ticagrelor in this patient.

This patient has two separate indications for CABG surgery: (1) multivessel disease and reduced ejection fraction and (2) diabetes with concomitant multivessel disease. Patients with these indications who undergo CABG have improved survival compared with patients who receive only optimal medical therapy. Therefore, continuing this patient's medical therapy without further intervention would be inappropriate.

KEY POINT

- Coronary artery bypass graft surgery is recommended to improve survival in patients with multivessel coronary artery disease and left ventricular dysfunction and patients with diabetes mellitus and multivessel disease.

Bibliography

Velazquez EJ, Lee KL, Jones RH, Al-Khalidi HR, Hill JA, Panza JA, et al; STICHES Investigators. Coronary-artery bypass surgery in patients with ischemic cardiomyopathy. N Engl J Med. 2016;374:1511-20. [PMID: 27040723] doi:10.1056/NEJMoa1602001

Item 72 Answer: D

Educational Objective: Treat symptomatic premature ventricular contractions.

Catheter ablation is the most appropriate management of this patient with frequent symptomatic premature ventricular contractions (PVCs). PVCs are common and occur in up to 75% of healthy persons. In the absence of high-risk features (syncope, a family history of premature sudden cardiac death, structural heart disease), reassurance is often appropriate management. For patients with bothersome palpitations, the initial diagnostic test is electrocardiography (ECG). If the diagnosis is not established, 24- to 48-hour ambulatory ECG monitoring is used to diagnose and quantify the frequency of PVCs and determine whether they are monomorphic or polymorphic. Symptomatic or frequent monomorphic PVCs (>10,000 PVCs in 24 hours or >10% of all beats) require further evaluation and treatment. Exercise stress testing can be used to evaluate the patient for ischemia and assess the response of PVCs to exercise. In addition, patients with frequent PVCs or polymorphic PVCs should undergo echocardiography or other cardiovascular imaging (such as cardiac magnetic resonance imaging) to evaluate for the presence of structural heart disease. Up to one third of patients with frequent PVCs can develop PVC-induced cardiomyopathy and progressive left ventricular dysfunction, as documented in this patient. First-line therapy for symptomatic or frequent PVCs includes β blockers or calcium channel blockers. Patients with continued frequent PVCs despite medical therapy or those who develop left ventricular dysfunction should undergo catheter ablation, which resolves most cases of PVC-induced left ventricular dysfunction.

Amiodarone is usually effective in suppressing PVCs; however, it carries a high risk for adverse effects and end-organ toxicities. Therefore, amiodarone is best avoided in younger patients, such as this one.

This patient had a structurally normal heart and no evidence of ischemia on studies performed 1 year ago, and she has developed no new symptoms. Therefore, cardiac catheterization is not indicated.

Cardiopulmonary exercise testing includes assessment of respiratory gas exchange during treadmill or bicycle exercise for a more detailed assessment of functional capacity and differentiation between potential causes of exercise limitation (cardiac, pulmonary, or deconditioning causes versus volitional causes). It would not be the most appropriate next choice in a patient with a known decrease in left ventricular ejection fraction and frequent PVCs.

KEY POINT

- Patients with premature ventricular contraction–induced cardiomyopathy should be treated with catheter ablation.

Bibliography

Yokokawa M, Good E, Crawford T, Chugh A, Pelosi F Jr, Latchamsetty R, et al. Recovery from left ventricular dysfunction after ablation of frequent premature ventricular complexes. Heart Rhythm. 2013;10:172-5. [PMID: 23099051] doi:10.1016/j.hrthm.2012.10.011

Item 73 Answer: C

H

Educational Objective: Treat mitral regurgitation with transcatheter mitral valve repair.

The most appropriate next step in management is transcatheter mitral valve repair. Acute severe mitral regurgitation is associated with papillary muscle rupture following acute myocardial infarction, flail mitral valve (dissociation of the valve leaflet from the chordae), and infective endocarditis with leaflet perforation. The sudden large volume in the left atrium and ventricle results in rapid increases in left ventricular end-diastolic pressure and left atrial pressure, which lead to elevated pulmonary artery pressure and pulmonary edema. The diminished left ventricular stroke volume leads

H CONT

to hypotension and shock. Definitive therapy for severe mitral regurgitation is mitral valve surgery. Patients with acute severe mitral regurgitation typically require urgent surgery after hemodynamic stabilization. Positive inotropes, vasodilators, and diuretics are often used for symptom control and as a bridge to cardiac surgery. Mechanical support (for example, with an intra-aortic balloon pump) may be required before or during valve replacement.

Two surgical options are available: mitral valve repair and mitral valve replacement. Mitral valve repair is typically preferred to valve replacement because it is associated with better clinical outcomes. A nonoperative procedure, transcatheter mitral valve repair, is indicated for symptomatic patients with degenerative mitral regurgitation who are at prohibitive surgical risk, such as this patient. With this technique, the mitral valve is plicated using an approach from the femoral vein. In experienced centers, success rates are approximately 90%, with procedural mortality of approximately 2%.

Continuing the patient's current medical therapy is inappropriate. Acute severe mitral regurgitation is an emergency, and prompt mitral valve repair or replacement should be considered for all patients.

KEY POINT

- Transcatheter mitral valve repair is indicated for symptomatic patients with degenerative mitral regurgitation who are not surgical candidates.

Bibliography

Sorajja P, Mack M, Vemulapalli S, Holmes DR Jr, Stebbins A, Kar S, et al. Initial experience with commercial transcatheter mitral valve repair in the United States. J Am Coll Cardiol. 2016;67:1129-40. [PMID: 26965532] doi:10.1016/j.jacc.2015.12.054

Item 74 Answer: C

Educational Objective: Treat a patient with peripheral artery disease with statin therapy.

The most appropriate treatment is high-intensity atorvastatin. This patient with claudication has an ankle-brachial index of less than or equal to 0.90 on the right side, which is diagnostic for peripheral artery disease (PAD). PAD is considered a form of clinical atherosclerotic cardiovascular disease (ASCVD), and as such, this patient should be started on secondary prevention therapy. Additional forms of ASCVD include acute coronary syndrome, history of myocardial infarction, stable or unstable angina, coronary or other arterial revascularization, stroke, or transient ischemic attack. Patients aged 75 years or younger with ASCVD should be started on high-intensity statin therapy, unless a contraindication exists. Options for high-intensity statin therapy include atorvastatin, 40 mg/d or 80 mg/d, and rosuvastatin, 20 mg/d or 40 mg/d.

Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, such as evolocumab, are a new class of medications that dramatically decrease LDL cholesterol levels. PCSK9 inhibitors are currently approved as adjunctive therapy to diet and maximally tolerated statin therapy in patients with familial hypercholesterolemia or established ASCVD. Treatment with evolocumab has been associated with a reduction in the composite outcome of cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, and coronary revascularization but not cardiovascular mortality or all-cause mortality.

Ezetimibe impairs intestinal cholesterol absorption, resulting in a significant reduction in LDL cholesterol levels. Several trials have shown clinical benefit when ezetimibe is added to statin therapy. However, this patient is not yet taking a statin, and ezetimibe is not appropriate as monotherapy.

Moderate-intensity statin therapy with pravastatin is not the first choice for patients with clinical ASCVD because high-intensity statin therapy offers superior benefits in patients aged 75 years or younger. Patients older than 75 years can be considered for moderate-intensity statin therapy.

Although this patient's 10-year risk for ASCVD, as calculated using the American College of Cardiology/American Heart Association Pooled Cohort Equations, is lower than the threshold of 7.5% for initiation of primary prevention statin therapy, she should be started on high-intensity statin therapy because of her PAD.

KEY POINT

- Patients with peripheral artery disease should be treated statin therapy.

Bibliography

Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, et al; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2014;63:2889-934. [PMID: 24239923] doi:10.1016/j.jacc.2013.11.002

Item 75 Answer: C

Educational Objective: Manage end-stage heart failure with a left ventricular assist device.

The most appropriate management is left ventricular assist device (LVAD) placement. This patient has several signs and symptoms of advanced refractory heart failure, including New York Heart Association (NYHA) functional class IV symptoms despite optimal medical therapy, a low sodium level, worsening kidney function, low pulse pressure, cool extremities, and repeat hospitalizations in the past 6 months. In patients with end-stage heart failure, advanced treatments, including cardiac transplantation or mechanical circulatory support with an LVAD, should be considered. This patient is a good candidate for an LVAD as destination therapy. Placement of a continuous-flow LVAD reduces symptoms and improves survival compared with medical therapy in patients with end-stage heart failure. Although LVADs increase survival rates, they are associated with serious complications, including infection, gastrointes-

tinal bleeding, stroke, and pump thrombus. All patients with progressive heart failure symptoms should be engaged in a discussion about their prognosis, treatment options (including hospice), and the risks and benefits of each therapy.

Cardiac resynchronization therapy is indicated in patients with an ejection fraction less than or equal to 35%, NYHA functional class II to IV heart failure symptoms despite guideline-directed medical therapy, sinus rhythm, and left bundle branch block with a QRS complex of 150 ms or greater. This patient does not meet the electrocardiographic criteria.

Cardiac transplantation remains the gold standard therapy for patients with end-stage heart failure. Indications for cardiac transplantation in these patients include age younger than 65 to 70 years, no medical contraindications (diabetes with end-organ complications, malignancies within 5 years, kidney dysfunction, other chronic illnesses that will decrease survival), and good social support and adherence. Heart transplant is contraindicated in this patient.

This patient has significant mitral regurgitation, most likely secondary to his dilated left ventricle; however, mitral valve repair is unlikely to substantially improve his heart failure symptoms.

KEY POINT

- Patients with end-stage heart failure should be considered for cardiac transplantation or mechanical circulatory support with left ventricular assist device placement.

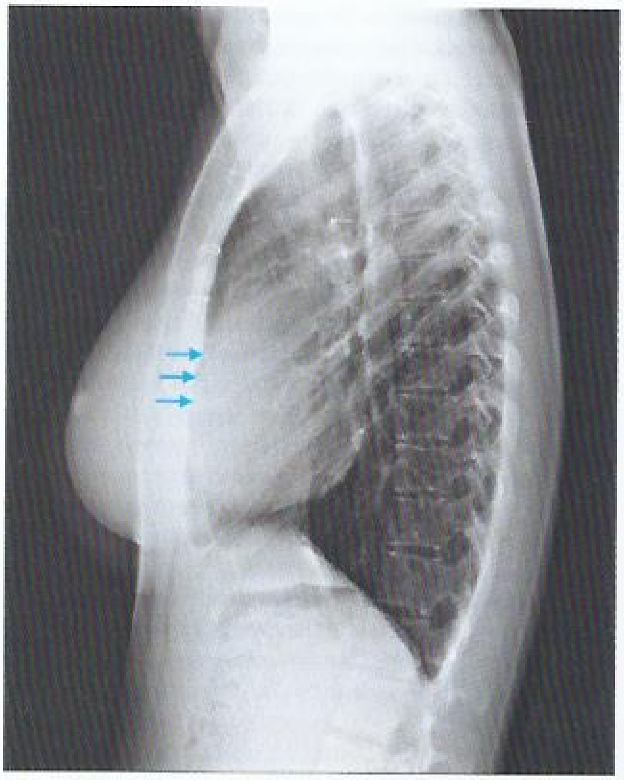
Bibliography

Stokes MB, Bergin P, McGiffin D. Role of long-term mechanical circulatory support in patients with advanced heart failure. Intern Med J. 2016;46:530-40. [PMID: 26010730] doi:10.1111/imj.12817

Item 76 Answer: C

Educational Objective: Diagnose pulmonary valve regurgitation as a late consequence of tetralogy of Fallot repair.

The most likely diagnosis is pulmonary valve regurgitation, which is the most common structural disorder resulting from tetralogy of Fallot (TOF) repair. Clinical findings include features of right heart volume overload with a parasternal lift and a soft systolic pulmonary outflow murmur. A single S_2 is heard because pulmonary valve function is sacrificed during TOF repair. TOF repair includes closure of the ventricular septal defect and relief of right ventricular outflow tract obstruction, which in turn results in pulmonary regurgitation, causing the diastolic murmur heard at the left sternal border that increases in intensity with inspiration. This patient's chest radiograph demonstrates evidence of previous sternotomy, a clip in the mediastinum from closure of the Blalock-Taussig shunt, a right-sided aortic arch (present in 25% of patients with TOF), and right heart enlargement (indicated by a rounded cardiac border and uplifted cardiac apex as seen on the frontal view and fullness in the retrosternal air space [*blue arrows*] on lateral view) (see top of next column).



These chest radiograph findings are consistent with repaired TOF with pulmonary regurgitation resulting in right heart enlargement.

Aortic regurgitation infrequently occurs late after TOF repair owing to progressive aortic enlargement. The diastolic murmur of aortic regurgitation is generally heard at the left sternal border and decreases in intensity with inspiration. A right ventricular prominence would not be expected in a patient with aortic regurgitation.

Mitral stenosis is not expected to occur late after TOF repair. Physical examination findings include increased intensity of S_1 and an apical diastolic murmur that increases during expiration.

Recurrent ventricular septal defect can occur in patients following TOF repair. However, the physical examination findings would include a systolic murmur heard at the left sternal border, which often obliterates the S_1 and S_2. Right ventricular prominence would not be expected in a patient with a recurrent ventricular septal defect.

KEY POINT

- Pulmonary regurgitation, presenting with a single S_2, a parasternal lift, and a soft systolic pulmonary outflow murmur, is the most common structural disorder resulting from tetralogy of Fallot repair.

Bibliography

Downing TE, Kim YY. Tetralogy of Fallot: general principles of management. Cardiol Clin. 2015;33:531-41, vii-viii. [PMID: 26471818] doi:10.1016/j.ccl.2015.07.002

Item 77 Answer: C

Educational Objective: Manage an abdominal aortic aneurysm with surveillance.

The most appropriate next step in the management of this patient with an abdominal aortic aneurysm (AAA) is repeat abdominal aortic ultrasonography. The optimal surveillance frequency for abdominal aortic aneurysm is controversial. As aneurysm size increases, risk for rupture also increases. For AAAs with a diameter smaller than 4.0 cm, the 5-year risk for rupture is 2%, and some guidelines recommend a surveillance interval of 24 to 36 months. AAAs with a diameter between 4.0 cm and 5.0 cm have a 5-year risk for rupture of 3% to 12%, and surveillance imaging is recommended more frequently (for example, every 6 to 12 months). AAAs with a diameter between 5.0 and 6.0 cm have a 5-year risk for rupture of 25%. Once an AAA reaches 5.5 cm in maximum diameter, surgical or endovascular repair is warranted, owing to the elevated risk for death due to aortic rupture. Repair is also indicated in patients with symptoms from AAA (abdominal tenderness or pain) and those with rapid expansion in AAA size (>0.5 cm/year). This patient with an AAA with a maximum diameter of 3.5 cm can be managed with surveillance abdominal ultrasonography. Because he is asymptomatic, he does not require surgical repair at this time.

Anatomic imaging tests, such as CT angiography or magnetic resonance angiography, are indicated to determine the exact location of the AAA (suprarenal, juxtarenal, or infrarenal) in planning for aortic repair. When an AAA does not meet the maximum diameter threshold for repair, such as in this patient, anatomic imaging with CT angiography is not indicated. Abdominal ultrasonography is preferred for serial monitoring of an AAA.

Pursuing no further testing or intervention would be inappropriate in this patient. An AAA predisposes the patient to an elevated risk for aortic rupture and death, and surveillance of the aneurysm is recommended.

KEY POINT

- Patients with an abdominal aortic aneurysm smaller than 5.5 cm should undergo surveillance ultrasonography, with frequency determined by aneurysm size.

Bibliography

Chaikof EL, Brewster DC, Dalman RL, Makaroun MS, Illig KA, Sicard GA, et al. SVS practice guidelines for the care of patients with an abdominal aortic aneurysm: executive summary. J Vasc Surg. 2009;50:880-96. [PMID: 19786241] doi:10.1016/j.jvs.2009.07.001

H

Item 78 Answer: C

Educational Objective: Evaluate for perivalvular abscess in a patient with infective endocarditis.

Transesophageal echocardiography (TEE) is the most appropriate diagnostic test to perform next. According to the modified Duke criteria, this patient has definite endocarditis, with one major criterion (persistently positive blood cultures) and three minor criteria (predisposing valvular abnormality [bicuspid valve], fever with temperature >38 °C [100.4 °F], and a vascular phenomenon [conjunctival hemorrhage]). On physical examination, he has a wide pulse pressure and evidence of a murmur of aortic regurgitation, findings that further support the diagnosis. Additionally, the electrocardiogram shows PR interval prolongation, which should raise suspicion for the presence of a periaortic abscess that is interfering with the conduction system and causing first-degree atrioventricular block. Perivalvular abscesses may be present in 30% to 40% of patients with infective endocarditis, and the risk may be further increased in those with a bicuspid aortic valve. The preferred imaging modality for evaluating patients with a high pretest probability of infective endocarditis or with potential complications of endocarditis is TEE, as it better visualizes vegetations and abscesses. TEE is also important for surgical planning.

Cardiac magnetic resonance (CMR) imaging is not the most appropriate initial imaging choice for patients with infective endocarditis. CMR imaging is effective in identifying intramyocardial infection, although it is a more complex technology with limited availability in some areas. CMR imaging is often used in situations in which a perivalvular abscess is suspected but transesophageal echocardiographic findings are equivocal.

Coronary CT angiography could be used for evaluation in patients suspected of having perivalvular infections if echocardiography cannot adequately identify the anatomy.

Transthoracic echocardiography can help identify the presence of a vegetation; however, there is an increased likelihood of detecting perivalvular abscess with TEE because of the closer proximity of the ultrasound probe to the valve structures. TEE is preferred to transthoracic echocardiography if this diagnosis is a consideration.

KEY POINT

- The preferred imaging modality for evaluating patients with a high pretest probability of infective endocarditis or with potential complications of endocarditis, such as abscess, is transesophageal echocardiography.

Bibliography

Iung B, Rouzet F, Brochet E, Duval X. Cardiac imaging of infective endocarditis, echo and beyond. Curr Infect Dis Rep. 2017;19:8. [PMID: 28233189] doi:10.1007/s11908-017-0560-2

Item 79 Answer: C

Educational Objective: Treat stable angina with percutaneous coronary intervention.

This patient with diabetes mellitus and single-vessel coronary artery disease should undergo revascularization with percutaneous coronary intervention (PCI) or coronary artery bypass grafting. PCI has not been shown to be superior to optimal medical therapy in patients with stable angina for reduction of cardiovascular endpoints, such as mortality and myocardial infarction. However, PCI has been associated with improvement

in quality of life by reducing the severity and frequency of angina. Current guidelines recommend that diagnostic angiography and PCI be reserved for patients with refractory symptoms while receiving optimal medical therapy, those who are unable to tolerate optimal medical therapy owing to side effects, or those with high-risk features on noninvasive exercise and imaging tests. This patient has 90% stenosis of the proximal left anterior descending artery and refractory symptoms; therefore, PCI is a reasonable therapeutic option.

The use of β-carotene, selenium, chromium, vitamin C, vitamin E, and estrogen has not been associated with improved cardiovascular outcomes or relief of symptoms and is not recommended in patients with ischemic heart disease.

Cardiac rehabilitation may be appropriate after revascularization occurs; however, this patient should first undergo revascularization to treat his crescendo angina symptoms.

Aspirin is associated with a decreased risk for myocardial infarction, stroke, and cardiovascular death in patients with coronary artery disease. Aspirin doses of 81 mg to 162 mg daily are recommended in all patients with established coronary artery disease unless contraindicated. In patients allergic to aspirin, clopidogrel is recommended as an alternative. The use of newer antiplatelet agents (prasugrel, ticagrelor) as monotherapy has not been tested in patients with stable angina. Dual antiplatelet therapy for chronic angina in the absence of stent placement is not recommended.

KEY POINT

- In patients with stable angina, diagnostic angiography and percutaneous coronary intervention are reserved for patients with refractory angina symptoms while receiving optimal medical therapy, those who are unable to tolerate optimal medical therapy owing to side effects, or those with high-risk features on noninvasive exercise and imaging tests.

Bibliography

Fihn SD, Gardin JM, Abrams J, Berra K, Blankenship JC, Dallas AP, et al; American College of Cardiology Foundation; American Heart Association Task Force on Practice Guidelines; American College of Physicians; American Association for Thoracic Surgery; Preventive Cardiovascular Nurses Association; Society for Cardiovascular Angiography and Interventions; Society of Thoracic Surgeons. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol. 2012 Dec 18;60(24):e44-e164. [PMID: 23182125]

Item 80 Answer: A

Educational Objective: Manage anticoagulation therapy in a patient with a mechanical valve prosthesis who is contemplating pregnancy.

The most appropriate anticoagulation regimen to prevent prosthesis thrombosis in this patient is INR-adjusted warfarin. Pregnant women with a mechanical valve prosthesis represent a high-risk subset of patients; concerns include valve thrombosis with its associated maternal risk, bleeding, and fetal morbidity and mortality. Warfarin anticoagulation appears to be the safest agent to prevent maternal prosthetic valve thrombosis; however, warfarin poses an increased fetal risk, with possible teratogenicity, miscarriage, and fetal loss due to intracranial hemorrhage. Risk to the fetus is dose related, and warfarin is the preferred anticoagulation regimen during the first trimester when the dose is 5 mg daily or less. During the second and early third trimesters, warfarin therapy is the preferred anticoagulation therapy.

Anticoagulation with apixaban is not recommended in patients with a mechanical valve prosthesis because of the potentially increased risk for valve thrombosis. In addition, its use has not been demonstrated to be safe during pregnancy.

In patients who prefer not to take warfarin during the first trimester of pregnancy, dose-adjusted intravenous unfractionated heparin can be used; however, 5000 units of unfractionated heparin will not provide adequate anticoagulation coverage for a patient with a mechanical prosthetic valve. Dose-adjusted, intravenous unfractionated heparin is an appropriate therapeutic option during the first trimester of pregnancy if the warfarin dose is more than 5 mg daily. Intravenous unfractionated heparin is the drug of choice for patients with a mechanical valve prosthesis around the time of delivery.

Weight-based low-molecular-weight heparin does not provide adequate anticoagulation coverage for a pregnant patient with a mechanical valve prosthesis and should not be used in this patient. Dose-adjusted low-molecular-weight heparin administered subcutaneously is appropriate during the first trimester if the warfarin dose is more than 5 mg daily.

KEY POINT

- In pregnant patients with a mechanical valve prosthesis, warfarin is the preferred anticoagulation therapy during the first trimester if the dose is 5 mg daily or less; warfarin is preferred to all other anticoagulants during the second and early third trimesters.

Bibliography

Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP 3rd, Guyton RA, et al; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2014;63:2438-88. [PMID: 24603192] doi:10.1016/j.jacc.2014.02.537

Item 81 Answer: B

Educational Objective: Manage acquired QT-interval prolongation.

Moxifloxacin should be discontinued in this patient who had an episode of nonsustained polymorphic ventricular tachycardia

H CONT.

(VT). VT is subdivided into sustained VT and nonsustained VT. VT is sustained when it persists for longer than 30 seconds or requires termination because of hemodynamic collapse. Nonsustained VT has three or more beats but lasts for less than 30 seconds. VT is also categorized by the morphology of the QRS complexes. VT is monomorphic if QRS complexes in the same leads do not vary in contour or polymorphic if the QRS complexes in the same leads vary in contour. In this patient, the electrocardiogram obtained after the episode of VT also demonstrates QT-interval prolongation, which is consistent with the diagnosis of torsades de pointes. Torsades de pointes is a special subset of polymorphic VT; the ventricular rate ranges from 200/min to 300/min and is associated with long QT syndrome, which may be congenital or acquired. The patient's electrocardiogram was normal upon admission, and her corrected QT interval is greater than 550 ms following the arrhythmic event, suggesting an acquired long QT interval. Causes of acquired QT-interval prolongation include medications such as antiarrhythmic agents, antibiotics (macrolides and fluoroquinolones), antipsychotic drugs, and antidepressants; structural heart disease; and electrolyte abnormalities.

Although carvedilol slows the heart rate and can increase the risk for bradycardia-dependent arrhythmias in patients with acquired QT-interval prolongation, discontinuing the offending QT-prolonging agents is the most important intervention in this patient.

Simvastatin is a statin used in the treatment of dyslipidemia. It has no effect on the QT interval and does not need to be discontinued.

Venlafaxine is a serotonin-norepinephrine reuptake inhibitor that is used to treat depression and anxiety disorders. There is a possible risk for QT-interval prolongation with venlafaxine, but there is no evidence that this occurs when the medication is taken as recommended. Therefore, discontinuation of venlafaxine is unnecessary.

KEY POINT

- QT-interval prolongation has many causes, including medications such as antiarrhythmic agents, antibiotics (macrolides and fluoroquinolones), antipsychotic drugs, and antidepressants; structural heart disease; and electrolyte abnormalities.

Bibliography

Isbister GK, Page CB. Drug induced QT prolongation: the measurement and assessment of the QT interval in clinical practice. Br J Clin Pharmacol. 2013;76:48-57. [PMID: 23167578] doi:10.1111/bcp.12040

Item 82 Answer: A

Educational Objective: Treat chronic aortic regurgitation with aortic valve and root replacement.

The most appropriate management is aortic valve and root replacement. This young, asymptomatic patient with a bicuspid aortic valve has significant aortic regurgitation. The transthoracic echocardiogram demonstrates a dilated left ventricle, mildly decreased systolic function, and a moderately dilated ascending aorta. Asymptomatic patients with severe aortic regurgitation who develop left ventricular dilatation or systolic dysfunction are at increased risk for sudden cardiac death, death, and heart failure. Therefore, these patients should be referred for aortic valve replacement. The prognosis of asymptomatic patients with severe aortic regurgitation but with normal left ventricular size and function is excellent. The American College of Cardiology/American Heart Association valvular heart disease guidelines recommend surgery in asymptomatic patients with severe aortic regurgitation when the left ventricular end-systolic dimension reaches 50 mm or the ejection fraction is less than 50%. In patients undergoing cardiac surgery, repair of the ascending aorta is indicated when the diameter exceeds 45 mm; thus, concomitant aortic root replacement, in addition to aortic valve replacement, is indicated in this patient.

In asymptomatic patients who do not meet surgical criteria, serial echocardiography is warranted to assess for disease progression. Patients with mild regurgitation should receive an annual clinical evaluation and echocardiography every 3 to 5 years, whereas patients with severe regurgitation should undergo clinical evaluation and echocardiography every 6 to 12 months.

For asymptomatic patients with normal systolic function and mild regurgitation, vasodilator therapy with nifedipine or ACE inhibitors is not recommended. For asymptomatic patients with normal systolic function and severe regurgitation, vasodilator therapy may be considered, but medical therapy does not supplant surgical intervention in these patients.

In patients with significant aortic regurgitation and equivocal symptoms, exercise-induced increases in pulmonary systolic pressure to more than 60 mm Hg (or a 25-mm Hg increase above baseline) identified during treadmill stress echocardiography suggest hemodynamic significance and may lead to earlier referral for surgical intervention. In this patient, however, ventricular dilatation and decreased ejection fraction are adequate criteria for recommending surgery.

KEY POINT

- Valve replacement surgery is recommended for asymptomatic patients with a bicuspid aortic valve and severe aortic regurgitation when the left ventricular end-systolic diameter reaches 50 mm or the left ventricular ejection fraction is less than 50%.

Bibliography

Enriquez-Sarano M, Tajik AJ. Clinical practice. Aortic regurgitation. N Engl J Med. 2004;351:1539-46. [PMID: 15470217]

Item 83 Answer: D

H

Educational Objective: Prevent heart failure readmission with early physician follow-up.

The most appropriate management is to schedule follow-up within 1 week of discharge. This patient was hospitalized for

H CONT.

a heart failure exacerbation. Before discharge, it is important to initiate several strategies to prevent readmission. First, the reason for the heart failure exacerbation should be identified. Often, it is impossible to determine a cause; however, in a situation such as this one, addressing the reasons for the patient's nonadherence might prevent readmission. Second, patients should be receiving optimal doses of evidence-based medications before discharge. When medications, especially β-blockers, are restarted, it is important to begin at a low dose and slowly uptitrate over time. Third, patients should not be discharged until they have achieved euvolemia with diuresis, and their electrolyte levels and kidney function are optimized. Finally, appropriate follow-up should be scheduled. Studies have shown that patients seen within 1 week of a heart failure discharge have reduced admissions compared with those with later outpatient contact. The purpose of an early visit is to reinforce heart failure education, ensure proper medication use, evaluate volume status, and uptitrate or initiate medications as needed. This patient is euvolemic and is taking appropriate medications, and he should be scheduled for a follow-up visit within 1 week to prevent readmission.

Ivabradine reduces heart failure–associated hospitalizations in patients with chronic symptomatic heart failure with left ventricular ejection fraction less than or equal to 35% who are in sinus rhythm and taking guideline-directed medical therapy. This patient has atrial fibrillation, and ivabradine is not indicated.

ACE inhibitor and β-blocker therapies should be uptitrated to maximally tolerated doses before initiation of spironolactone. It is important to add an aldosterone antagonist later, but the dosage of the other agents should be maximized first.

There is no evidence of a survival advantage or reduction in stroke with cardioversion and maintenance of sinus rhythm in patients with atrial fibrillation, including those with heart failure. Therefore, the decision to institute a rate or rhythm control strategy largely depends on symptoms and patient preference. Patients who are asymptomatic can be managed with rate control only, with a resting heart rate goal of less than 110/min. Patients with tachycardia-induced cardiomyopathy, heart failure, or left ventricular ejection fraction of less than 40% may require more stringent rate control (heart rate of 60/min to 80/min at rest).

KEY POINT

- Following heart failure hospitalization, early follow-up (within 1 week) should be scheduled to reinforce heart failure education, ensure proper medication use, evaluate volume status, and uptitrate or initiate medications as needed.

Bibliography

Lee KK, Yang J, Hernandez AF, Steimle AE, Go AS. Post-discharge follow-up characteristics associated with 30-day readmission after heart failure hospitalization. Med Care. 2016;54:365-72. [PMID: 26978568] doi:10.1097/MLR.0000000000000492

Item 84 Answer: D

Educational Objective: **Evaluate a patient for hypertrophic cardiomyopathy with genetic counseling and testing.**

The most appropriate management of the patient's 16-year-old daughter is genetic counseling and testing. Hypertrophic cardiomyopathy (HCM) is an autosomal dominant heritable disorder characterized by the presence of increased left ventricular wall thickness in the absence of loading conditions or other underlying causes. In patients with HCM and a known pathogenic mutation, genetic counseling and testing is recommended for all first-degree family members, regardless of the presence or absence of symptoms. In this case, genetic testing of the index patient has revealed a mutation known to be associated with HCM. Mutation-negative family members do not require further evaluation and have no increased risk for future development of HCM. Family members who test positive for an HCM-related genetic mutation should be further evaluated with physical examination, 12-lead electrocardiography, and echocardiography (or cardiac magnetic resonance imaging). Genetic counseling is an important facet of care for patients with HCM, regardless of whether genetic testing is performed. Counseling enables informed decision making about the risks and benefits of testing and facilitates interpretation of the results.

The development of HCM is a dynamic process, and phenotypic expression may change as a patient ages. Because of this, if the daughter tests positive for the mutated gene but the electrocardiogram and echocardiogram are normal, she may still require repeated screening because of the possibility of phenotypic disease expression at any age. In that case, screening with physical examination, echocardiography, and 12-lead electrocardiography is recommended annually starting at age 12 years until adulthood. For adults who are genotype-positive and phenotype-negative, screening should be performed every 5 years or with a change in clinical status.

Mutation carriers with phenotypic expression of HCM should undergo further risk stratification for sudden cardiac death.

KEY POINT

- Genetic counseling and testing are recommended for patients with hypertrophic cardiomyopathy (HCM) and for all first-degree family members of patients with HCM who have an identified genetic mutation, regardless of the presence or absence of symptoms.

Bibliography

Gersh BJ, Maron BJ, Bonow RO, Dearani JA, Fifer MA, Link MS, et al; American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. 2011 ACCF/AHA guideline for the diagnosis and treatment of hypertrophic cardiomyopathy: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Developed in collaboration with the American Association for Thoracic Surgery, American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Failure Society of America, Heart Rhythm Society, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol. 2011;58:e212-60. [PMID: 22075469] doi:10.1016/j.jacc.2011.06.011

Item 85 Answer: D

Educational Objective: Identify inflammatory disease as a risk factor for coronary artery disease.

This patient's most significant risk factor for cardiovascular disease (CVD) is the presence of rheumatoid arthritis. Patients with systemic inflammatory conditions, such as systemic lupus erythematosus and rheumatoid arthritis, have an increased risk for CVD. Patients with rheumatoid arthritis have a 1.5- to 2-fold elevated risk for coronary artery disease compared with the general population. Most deaths in patients with SLE and nearly 40% of deaths in patients with rheumatoid arthritis are cardiovascular and, in particular, heart failure related. The risk for CVD increases with the duration of the underlying inflammatory condition. In patients with rheumatoid arthritis, the risk for CVD increases from two times to three times that of the general population after 10 years' duration of rheumatoid arthritis. The increased atherosclerotic burden is likely a result of both the inflammatory process of the systemic disease, including a prothrombotic state, and the presence of traditional cardiovascular risk factors. The risk for future atherosclerotic CVD is typically calculated by using the American College of Cardiology/American Heart Association CVD risk calculator based on the Pooled Cohort Equations; however, this calculator underestimates risk in patients with nontraditional risk factors, as in this patient with rheumatoid arthritis.

Sedentary lifestyle, poor diet, and obesity contribute to increased cardiovascular risk and increased risk for diabetes mellitus. Moderate-intensity exercise for 30 minutes or longer on 5 to 7 days per week is recommended for nearly all persons and is being achieved by this patient.

Regular moderate alcohol consumption (one to two drinks daily for men, one drink daily for women) has been associated with a decreased incidence of CVD. Because of the known deleterious effects of drinking, the American Heart Association does not recommend that nondrinking patients consume moderate amounts of alcohol as a measure to decrease the risk for CVD. This patient has one drink per day, which is likely beneficial in reducing her CVD risk.

The prevalence of CVD and CVD risk factors in the United States varies by ethnicity. Hawaiians and Pacific Islanders have the highest rate of heart disease (19.1%), followed by American Indians and Alaska Natives (13.7%), non-Hispanic whites (11.1%), blacks (10.3%), Hispanics and Latinos (7.8%), and Asians (6.0%). This patient's ethnicity places her in the lowest risk category for CVD.

KEY POINT

- Patients with rheumatoid arthritis have a 1.5- to 2-fold elevated risk for coronary artery disease compared with the general population.

Bibliography

Crowson CS, Liao KP, Davis JM 3rd, Solomon DH, Matteson EL, Knutson KL, et al. Rheumatoid arthritis and cardiovascular disease. Am Heart J. 2013;166:622-628.e1. [PMID: 24093840] doi:10.1016/j.ahj.2013.07.010

Item 86 Answer: B

Educational Objective: Diagnose inappropriate sinus tachycardia.

This patient with sinus tachycardia and a structurally normal heart has symptoms, electrocardiographic features, and ambulatory electrocardiographic findings consistent with the diagnosis of inappropriate sinus tachycardia (IST). IST is characterized by elevated resting heart rate, with exaggerated increases in heart rate with light activity. The sinus rates typically decrease during sleep, as identified on this patient's ambulatory electrocardiographic monitor. IST frequently presents in women in their second to fourth decades and appears to be more common in health care professionals. Symptoms vary and can include palpitations, lightheadedness, syncope or near-syncope, dyspnea, and fatigue. Emotional manifestations, such as anxiety or depression, may also be present. Diagnosis of IST is based on the exclusion of other causes of tachycardia, such as hyperthyroidism, anemia, pheochromocytoma, and structural heart disease. First-line therapy is removal of aggravating factors and exercise therapy. In patients with bothersome and persistent symptoms, pharmacologic therapy with β-blockers or calcium channel blockers can be considered. Ivabradine is a relatively new drug that impairs the I_f or "I-funny" current and may play a role in the treatment of IST refractory to standard therapy.

The diagnostic criteria for generalized anxiety disorder are as follows: (1) excessive anxiety or worry about a number of events or activities occurring for 6 months or longer; (2) the patient recognizes it is difficult to control the worry; (3) the anxiety or worry is associated with three or more of the following symptoms: restlessness, easy fatigability, difficulty concentrating, irritability, muscle tension, and sleep disturbance; (4) the anxiety, worry, or symptoms cause impairment at school, work, or other settings and cannot be attributable to medical or other psychiatric conditions, medications, or substance use. Diagnostic criteria for somatic symptom disorder include at least one somatic symptom causing distress or interference with daily life; excessive thoughts, behaviors, and feelings related to the somatic symptom(s); and persistent somatic symptoms for at least 6 months. This patient does not fulfill the diagnostic criteria for generalized anxiety disorder or somatic symptom disorder.

Subclinical hyperthyroidism is a laboratory-based diagnosis, defined as the presence of a suppressed thyroid-stimulating hormone level with normal triiodothyronine and thyroxine levels. Symptoms of thyrotoxicosis are typically mild; most patients are asymptomatic. This patient's normal thyroid-stimulating hormone level argues against this diagnosis.

KEY POINT

- Diagnosis of inappropriate sinus tachycardia is based on symptoms and findings on ambulatory electrocardiographic monitoring after the exclusion of other causes of tachycardia, such as hyperthyroidism, anemia, pheochromocytoma, and structural heart disease.

Bibliography

Olshansky B, Sullivan RM. Inappropriate sinus tachycardia. J Am Coll Cardiol. 2013;61:793-801. [PMID: 23265330] doi:10.1016/j.jacc.2012.07.074

Item 87 Answer: A

Educational Objective: Evaluate for coronary artery disease in a patient with left bundle branch block on a baseline electrocardiogram.

Adenosine single-photon emission CT is the most appropriate next diagnostic test. This patient with several cardiovascular risk factors has exertional dyspnea, which may be an angina equivalent, and he should undergo stress testing to evaluate for coronary artery disease (CAD). Because his electrocardiogram (ECG) shows left bundle branch block, ST-segment changes with exercise cannot be used to evaluate for the presence of obstructive CAD. He must undergo stress testing with additional imaging, such as nuclear perfusion imaging or stress echocardiography. Exercise is typically the preferred mode of stress because of the additional functional information it provides. However, in the case of left bundle branch block, myocardial perfusion imaging with exercise or dobutamine stress may result in a false-positive perfusion defect in the basilar septum, and these stressors should be avoided. Instead, vasodilator stress testing should be used. Vasodilators, such as dipyridamole, regadenoson, and adenosine, produce hyperemia and a flow disparity between myocardium supplied by unobstructed vessels and myocardium supplied by the stenotic vessel (due to the inability of the distal vasculature to dilate).

Coronary artery calcium scoring, which quantifies the amount of calcium in the walls of the coronary arteries, would document the presence of atherosclerotic disease in this symptomatic patient with risk factors, but it would not determine whether there is obstructive CAD. Although the absence of any coronary artery calcification has been shown to have a high specificity for the absence of obstructive CAD, trials evaluating coronary artery calcium scoring have typically focused on primary prevention in asymptomatic patients.

KEY POINT

- In patients with left bundle branch block, the preferred diagnostic test for coronary artery disease is a vasodilator stress test because myocardial perfusion imaging with exercise or dobutamine stress may result in a false-positive perfusion defect in the basilar septum.

Bibliography

Hendel RC, Berman DS, Di Carli MF, Heidenreich PA, Henkin RE, Pellikka PA, et al; American College of Cardiology Foundation Appropriate Use Criteria Task Force. ACCF/ASNC/ACR/AHA/ASE/SCCT/SCMR/SNM 2009 appropriate use criteria for cardiac radionuclide imaging: a report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, the American Society of Nuclear Cardiology, the American College of Radiology, the American Heart Association, the American Society of Echocardiography, the Society of Cardiovascular Computed Tomography, the Society for Cardiovascular Magnetic Resonance, and the Society of Nuclear Medicine. J Am Coll Cardiol. 2009;53:2201-29. [PMID: 19497454] doi:10.1016/j.jacc.2009.02.013

Item 88 Answer: D

H

Educational Objective: Evaluate a patient with new-onset heart failure.

Thyroid studies should be performed next in this patient with new-onset heart failure. Once a diagnosis of heart failure is suspected, echocardiography should be performed to ascertain the left ventricular ejection fraction and to potentially determine the cause and chronicity of the patient's heart failure. A large, dilated left ventricle suggests a chronic process with less chance of recovery. The initial laboratory evaluation of patients with new-onset heart failure should include a B-type natriuretic peptide or N-terminal pro-B-type natriuretic peptide assay, complete blood count, serum electrolyte measurement, kidney function tests, liver chemistry tests, glucose and lipid levels, and serum thyroid-stimulating hormone measurement. Specifically, thyroid-stimulating hormone measurement is indicated to evaluate for occult hypo- or hyperthyroidism as a reversible cause of heart failure. In hyperthyroidism in particular, the predominant manifestation of thyroid dysfunction may be cardiac symptoms, which will abate when the hyperthyroidism is treated.

The classic presentation of viral myocarditis includes a viral prodrome with fever, myalgia, and upper respiratory tract symptoms, but a prodrome does not always occur. Patients present with dyspnea, chest pain, and arrhythmias. Electrocardiographic abnormalities are often observed. This patient's presentation is not typical for viral myocarditis, and viral studies are not indicated at this time.

Although coronary artery disease is the most common cause of heart failure, the investigation for coronary artery disease by stress testing or cardiac catheterization is not considered part of the routine evaluation of all patients with newly diagnosed heart failure, owing to expense and radiation exposure. Cardiac catheterization should be performed in patients presenting with angina or significant ischemia.

Hereditary hemochromatosis results from an autosomal recessive defect in the *HFE* gene, which leads to increased absorption of dietary iron. Patients may present with heart failure or arrhythmias. However, women do not develop overt iron overload until after menopause, and serum iron and ferritin studies are not indicated in this young woman.

KEY POINT

- The initial laboratory evaluation of patients with new-onset heart failure should include a B-type natriuretic peptide or N-terminal pro-B-type natriuretic peptide assay, complete blood count, serum electrolyte measurement, kidney function tests, liver chemistry tests, and serum thyroid-stimulating hormone measurement.

Bibliography

Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Drazner MH, et al; American College of Cardiology Foundation. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2013;62:e147-239. [PMID: 23747642] doi:10.1016/j.jacc.2013.05.019

H

Item 89 Answer: C

Educational Objective: Diagnose acute mitral regurgitation due to papillary muscle rupture.

The most likely diagnosis is acute mitral regurgitation. This patient has evidence of a recent inferolateral myocardial infarction and decompensated heart failure. The mitral regurgitation is likely secondary to papillary muscle dysfunction (or rupture) and/or ventricular dysfunction. In acute mitral regurgitation, heart failure symptoms may occur abruptly because there has not been time for adaptive chamber dilatation. The murmur of acute mitral regurgitation may be present only in early diastole, owing to rapid diastolic equalization of ventricular and atrial pressures caused by the high volume overload. In cases of severe mitral regurgitation, a diastolic rumble occurs because of the large regurgitant volume during diastole. If present, the systolic murmur of acute mitral regurgitation is typically soft and ends before A_2. It is best heard along the left sternal border and base of the heart, generally without a thrill.

In patients with aortic stenosis, the murmur characteristically gets louder and then softer (crescendo-decrescendo) during systole; it is loudest at the second right intercostal space, with radiation to the carotid arteries. These findings are not present in this patient.

Left ventricular free wall rupture is an often fatal complication of myocardial infarction that occurs 3 to 7 days after the initial event. Patients most commonly present with cardiac tamponade (due to hemopericardium), pulseless electrical activity, and death. Patients with cardiac tamponade typically do not have a heart murmur or a preserved or exaggerated *x* descent in the jugular venous pulse, as seen in this patient.

Most patients with mild to moderate tricuspid regurgitation are asymptomatic. Examination reveals a systolic murmur that is loudest at the left lower sternal border and increases with inspiration. Symptoms and signs of right-sided heart failure, such as fatigue, elevated jugular venous pulse, and lower extremity edema, may be found; however, tricuspid regurgitation does not cause volume overload in the lungs, as was observed in this patient.

KEY POINT

- Acute severe mitral regurgitation is associated with papillary muscle rupture following acute myocardial infarction.

Bibliography

Kutty RS, Jones N, Moorjani N. Mechanical complications of acute myocardial infarction. Cardiol Clin. 2013;31:519-31, vii-viii. [PMID: 24188218] doi:10.1016/j.ccl.2013.07.004

H

Item 90 Answer: B

Educational Objective: Manage dual antiplatelet therapy in a patient with non–ST-elevation myocardial infarction.

This patient with a non–ST-elevation myocardial infarction (NSTEMI) should receive low-dose aspirin indefinitely and ticagrelor for 1 year. Dual antiplatelet therapy, composed of aspirin and a $P2Y_{12}$ inhibitor, is indicated in all patients following acute coronary syndrome (ACS) for the prevention of vascular ischemic events. Aspirin should be continued indefinitely, and in patients with ACS treated with medical therapy alone, the optimal duration for $P2Y_{12}$ inhibitor therapy (clopidogrel or ticagrelor) is at least 12 months. Although clopidogrel is an option in this patient, in the PLATO trial, the combination of low-dose aspirin and ticagrelor was superior to aspirin and clopidogrel in reducing the incidence of cardiovascular death, myocardial infarction, and stroke following ACS; the effect size was identical in medically treated patients and those who underwent early invasive treatment. The American College of Cardiology and American Heart Association prefer ticagrelor to clopidogrel (class IIa, level B recommendation) but caution that additional studies with focused objectives are needed.

Prasugrel, another $P2Y_{12}$ inhibitor, is recommended for use only in patients with ACS who undergo percutaneous coronary intervention. Prasugrel is no more effective than clopidogrel in comparison studies of medically treated patients with ACS, and it carries a higher risk for bleeding than does clopidogrel.

Anticoagulation with warfarin is not routinely recommended following ACS unless there is another indication for its use, such as venous thromboembolic disease or atrial fibrillation.

Aspirin therapy alone would not offer adequate protection against cardiovascular events in this patient with NSTEMI.

KEY POINT

- Dual antiplatelet therapy, composed of aspirin and a $P2Y_{12}$ inhibitor, is indicated in all patients following acute coronary syndrome for the prevention of vascular ischemic events.

Bibliography

Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, et al; PLATO Investigators. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med. 2009;361:1045-57. [PMID: 19717846] doi:10.1056/NEJMoa0904327

Item 91 Answer: B

Educational Objective: Diagnose constrictive pericarditis.

The most likely diagnosis in this patient with a history of chest radiotherapy is constrictive pericarditis. Constrictive pericarditis is characterized by pericardial thickening, fibrosis, and sometimes calcification that impair diastolic filling and limit total cardiac volume. Most cases are viral or idiopathic in origin; however, cardiac surgery, chest irradiation, autoimmune disease, and tuberculosis or other bacterial infections may be causes. Patients with constrictive pericarditis most commonly present with indolent progression of right-sided heart failure symptoms, including peripheral edema, ascites, and fatigue.

Answers and Critiques

In this patient, signs of venous congestion predominate, pericardial calcification is present on the chest radiograph, and the serum B-natriuretic peptide level is low and does not suggest greatly increased wall tension. The echocardiographic findings of respiratory variation in filling of right and left ventricles, ventricular septal shift during respiration, and dilation of the inferior vena cava are characteristic of constrictive pericarditis.

Cardiac amyloidosis and restrictive cardiomyopathy are not associated with pericardial calcification, and patients with these conditions more commonly present with moderate to severe pulmonary hypertension rather than the mild pulmonary hypertension seen in this patient. Respiratory variation in filling of the right and left ventricles and ventricular septal shift during respiration are characteristic of pericardial constraint rather than myocardial disease.

Patients with heart failure with preserved ejection fraction will present with edema, exertional dyspnea, and fatigue. Normal systolic contraction and abnormal diastolic relaxation are present on echocardiogram and result in restricted filling and high filling pressures. Patients with heart failure typically have an elevated B type natriuretic peptide level, often greater than of 600 pg/mL (600 ng/L), which is not found in this patient.

KEY POINT

- Constrictive pericarditis is commonly characterized by symptoms of right-sided heart failure, low or normal B-type natriuretic peptide level, and the finding of pericardial thickening or calcification on imaging studies.

Bibliography

Jaworski C, Mariani JA, Wheeler G, Kaye DM. Cardiac complications of thoracic irradiation. J Am Coll Cardiol. 2013;61:2319-28. [PMID: 23583253] doi:10.1016/j.jacc.2013.01.090

Item 92 Answer: A

Educational Objective: Diagnose ostium secundum atrial septal defect.

An ostium secundum atrial septal defect (ASD) is the most likely diagnosis in this patient. Adults with an ASD most often present with dyspnea or atrial arrhythmias; elevated central venous pressure, fixed splitting of the S_2, and a right ventricular heave are characteristic findings. The fixed splitting of the S_2 in patients with an ostium secundum ASD results from prolongation of right ventricular systole and lack of respiratory change in the right ventricular stroke volume. With expiration, the decrease in venous return is counteracted by an increase in left-to-right shunting, resulting in a fixed right ventricular preload. A large left-to-right shunt causes a pulmonary midsystolic flow murmur and a tricuspid diastolic flow rumble owing to increased flow. In ostium secundum ASD, the electrocardiogram (ECG) demonstrates right-axis deviation and incomplete right bundle branch block.

Aortic stenosis due to a bicuspid aortic valve causes a systolic murmur at the second right intercostal space. The central venous pressure is normal in aortic stenosis, and a right ventricular impulse would not be expected. A systolic ejection click is often heard in patients with bicuspid aortic valve, but fixed splitting of the S_2 is not heard. The ECG typically demonstrates a normal axis and features of left ventricular hypertrophy.

Pulmonary stenosis is usually congenital, and severe obstruction can cause exertional dyspnea. Physical examination features depend on the severity of obstruction and associated elevation of right heart pressure; these include central venous pressure elevation with a prominent *a* wave and a parasternal impulse. The systolic murmur of pulmonary stenosis is generally heard at the second left intercostal space, and the timing of the murmur is related to stenosis severity. An ejection click is often heard; the proximity of the click to the S_2 varies depending on the severity of stenosis. S_2 becomes fixed in severe pulmonary stenosis. The ECG demonstrates right axis deviation and features of right ventricular hypertrophy.

Patients with mitral stenosis might present with symptoms of dyspnea. A right ventricular impulse can occur, and the central venous pressure might be elevated with associated pulmonary hypertension or tricuspid regurgitation. The murmur of mitral stenosis is generally best heard at the apex. An opening snap might be heard, followed by a diastolic murmur. Fixed splitting of the S_2 is not heard. The ECG typically demonstrates left atrial enlargement.

KEY POINT

- Elevated central venous pressure, fixed splitting of the S_2, a right ventricular heave, and right-axis deviation and incomplete right bundle branch block on electrocardiogram are characteristic findings in patients with ostium secundum atrial septal defect.

Bibliography

Baumgartner H, Bonhoeffer P, De Groot NM, de Haan F, Deanfield JE, Galie N, et al; Task Force on the Management of Grown-up Congenital Heart Disease of the European Society of Cardiology (ESC). ESC guidelines for the management of grown up congenital heart disease (new version 2010). Eur Heart J. 2010;31:2915-57. [PMID: 20801927] doi:10.1093/eurheartj/ehq249

Item 93 Answer: C

Educational Objective: Diagnose the cause of cryptogenic stroke.

The most appropriate diagnostic testing option is 30-day event-triggered loop recording. This patient had a cryptogenic stroke given the absence of an apparent vascular, structural, or thromboembolic cause for her ischemic event. Among patients aged 55 years and older who have a cryptogenic ischemic neurologic event, such as a stroke or transient ischemic attack, occult intermittent atrial fibrillation is thought to be present in up to 25% of cases. These patients have a high risk for recurrent stroke, and efforts should be made to

detect and treat atrial fibrillation for stroke prevention. Noninvasive ambulatory electrocardiographic (ECG) monitoring for 30 days improves the detection of atrial fibrillation by fivefold compared with short-term ECG monitoring. Patients who have premature atrial contractions and other findings of ectopy on short-term telemetry may be more likely to have paroxysmal atrial fibrillation. Patients who undergo longer-term ECG monitoring and are subsequently diagnosed with atrial fibrillation are also more likely to receive appropriate secondary prevention stroke therapy with oral anticoagulants.

Antiphospholipid antibodies are acquired autoantibodies against phospholipids and phospholipid-binding proteins, such as cardiolipin and β_2 glycoprotein I. In vitro, they can prolong clotting tests, but in vivo, they increase the risk for venous and arterial thrombosis and are associated with increased fetal loss. Testing for autoimmune and hypercoagulable disorders, such as antiphospholipid antibody syndrome, can be considered in young patients with otherwise unexplained stroke. Aside from stroke, this patient does not have any features concerning for a prothrombotic state or autoimmune disease. Therefore, testing for antiphospholipid antibodies is not appropriate.

Cardiac catheterization is not indicated in this patient. Because she had a normal transesophageal echocardiogram, there is no concern for a structural abnormality, such as an intracardiac shunt.

Short-term ECG monitoring (24-48 hours) with an ambulatory ECG monitor is inferior to extended ECG monitoring in the detection of paroxysmal atrial fibrillation.

KEY POINT

- In the evaluation of cryptogenic stroke, noninvasive ambulatory electrocardiographic (ECG) monitoring for 30 days improves the detection of atrial fibrillation by fivefold compared with short-term ECG monitoring.

Bibliography

Gladstone DJ, Spring M, Dorian P, Panzov V, Thorpe KE, Hall J, et al; EMBRACE Investigators and Coordinators. Atrial fibrillation in patients with cryptogenic stroke. N Engl J Med. 2014;370:2467-77. [PMID: 24963566] doi:10.1056/NEJMoa1311376

H

Item 94 Answer: B

Educational Objective: Treat acute decompensated heart failure with intravenous furosemide.

The most appropriate treatment is administration of intravenous furosemide. This patient with a history of heart failure has signs and symptoms of an acute exacerbation, with volume overload and possibly reduced kidney function. The mainstay of therapy for acute heart failure is intravenous diuretics. The intravenous diuretic dose should equal or exceed the patient's oral dose for chronic heart failure. If the patient does not respond appropriately to that dose, rapid uptitration should be performed to assist in fluid removal. A recent study assessing different diuretic strategies (normal versus high dose, bolus versus continuous infusion) in patients with acute decompensated heart failure showed no difference in the outcomes of length of stay, readmission, or kidney function between groups. The patient's usual outpatient medications should be cautiously continued unless the patient is hypotensive or demonstrates signs of poor perfusion (worsening kidney or liver function, cool extremities), in which case dose reduction or discontinuation of both the ACE inhibitor and β-blocker should be considered.

Low-dose dopamine plus diuretic therapy was studied in the ROSE trial to determine whether dopamine improves diuresis and preserves kidney function in patients with acute heart failure. Compared with placebo, there was no difference in patient symptoms, urine output at 72 hours, or kidney function. Intravenous dopamine would not benefit this patient.

Intravenous inotropes, such as milrinone or dobutamine, should be considered in patients with signs of poor perfusion to improve cardiac function; however, this patient has no signs of hypoperfusion to suggest that this exacerbation is related to low cardiac output. Additionally, the PROMISE study showed no benefit of routine inotropic therapy in patients admitted with a heart failure exacerbation.

The vasodilator nesiritide has not been shown to improve diuresis, reduce length of stay, or prevent readmissions when used routinely for patients hospitalized for a heart failure exacerbation. Nitroglycerin or nitroprusside is occasionally used in patients who are hypertensive or who have high systemic vascular resistance, but usually only in a closely monitored setting, such as the coronary care unit.

KEY POINT

- The mainstay of therapy for acute decompensated heart failure is intravenous diuretics.

Bibliography

Chen HH, Anstrom KJ, Givertz MM, Stevenson LW, Semigran MJ, Goldsmith SR, et al; NHLBI Heart Failure Clinical Research Network. Low-dose dopamine or low-dose nesiritide in acute heart failure with renal dysfunction: the ROSE acute heart failure randomized trial. JAMA. 2013;310:2533-43. [PMID: 24247300] doi:10.1001/jama.2013.282190

Item 95 Answer: D

Educational Objective: Evaluate suspected infective endocarditis with transthoracic echocardiography.

The most appropriate next step in management is transthoracic echocardiography (TTE). This patient has symptoms and signs that are suspicious for infective endocarditis. According to the modified Duke criteria for infective endocarditis, he meets three minor criteria (injection drug use, fever with temperature >38 °C [100.4 °F], and vascular phenomena [in this case, erythematous nonpainful macular lesions known as Janeway lesions]), which indicates a possible diagnosis of infective endocarditis. A definitive diagnosis may be made with positive blood cultures and characteristic echocardiographic findings. TTE, as a first-line imaging modality, is

indicated to identify vegetations or abscesses (diagnostic for infective endocarditis), determine the severity of valvular lesions, assess ventricular function, and detect complications. The sensitivity of TTE is approximately 75%; therefore, a negative imaging test result does not rule out the presence of infective endocarditis, and other imaging modalities should be used.

When the TTE findings are normal or inadequate in patients with a high pretest probability of infective endocarditis, or suspicion remains for undetected complications, further examination with TEE, cardiac CT, or MRI should be considered. The diagnostic sensitivity of TEE for infective endocarditis is approximately 90%. TEE is also superior to TTE in the detection of perivalvular abscesses, leaflet perforation, and other complications. Cardiac CT and chest MRI can be helpful in assessing for the presence of aortic root abscess when TEE is inconclusive, and CT is helpful to identify areas of peripheral embolization, such as in the kidney, spine, spleen, and brain. However, because of cost, accessibility, and invasiveness, TEE, chest MRI, and cardiac CT are not the best initial imaging choices.

KEY POINT

- Transthoracic echocardiography is the first-line imaging modality in patients suspected of having infective endocarditis to identify vegetations, determine the severity of valvular lesions, assess ventricular function, and detect complications.

Bibliography

Baddour LM, Wilson WR, Bayer AS, Fowler VG Jr, Tleyjeh IM, Rybak MJ, et al; American Heart Association Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease of the Council on Cardiovascular Disease in the Young, Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and Stroke Council. Infective endocarditis in adults: diagnosis, antimicrobial therapy, and management of complications: a scientific statement for healthcare professionals from the American Heart Association. Circulation. 2015;132:1435-86. [PMID: 26373316] doi:10.1161/CIR.0000000000000296

H

Item 96 Answer: C

Educational Objective: Manage non–ST-elevation acute coronary syndrome with an ischemia-guided approach.

Exercise stress testing is the most appropriate management of this patient with a non–ST-elevation acute coronary syndrome (NSTE-ACS). Many treatment options are available for patients with a NSTE-ACS, and risk stratification tools, such as the TIMI or GRACE risk scores, can be used to aid in diagnostic and therapeutic decision making. An ischemia-guided approach is appropriate in low-risk patients (TIMI score <2 or GRACE score <109), whereas intermediate- and high-risk patients should be treated with an early invasive strategy. With an ischemia-guided approach, cardiac catheterization is reserved for patients at very high clinical risk based on risk score and patients with active or intermittent ischemia, including those with angina despite medical therapy or evidence of ischemia on stress testing. Given this patient's ST-segment depression on electrocardiogram, her TIMI risk score is 1, or low risk. Stress testing is indicated to guide further management.

Amlodipine may be used to treat patients suspected of having coronary vasospasm. Although this patient's symptoms could be caused by coronary vasospasm, it would be prudent to exclude ischemic heart disease before initiating this treatment.

The benefit of glycoprotein IIb/IIIa inhibitors, such as eptifibatide, appears to be isolated to certain high-risk patients and those undergoing percutaneous coronary intervention, although use of these drugs has been declining in those settings. There is no role for glycoprotein IIb/IIIa blockade in this patient with a low TIMI risk score and normal cardiac enzyme levels.

In patients with NSTE-ACS who have an elevated clinical risk score, significant ST-segment deviation, or elevated cardiac biomarkers, cardiac catheterization is usually performed within 24 hours of presentation. However, an early invasive strategy is not indicated in this patient given her low TIMI risk score.

KEY POINT

- In patients with non–ST-elevation acute coronary syndrome, an ischemia-guided approach is appropriate for patients at low risk based on clinical risk score.

Bibliography

Amsterdam EA, Wenger NK, Brindis RG, Casey DE Jr, Ganiats TG, Holmes DR Jr, et al; ACC/AHA Task Force Members. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014;130:2354-94. [PMID: 25249586] doi:10.1161/CIR.0000000000000133

Item 97 Answer: C

Educational Objective: Treat a patient with intermittent claudication with cilostazol.

The most appropriate next step in management is to initiate cilostazol. In patients with intermittent claudication and confirmed lower extremity peripheral artery disease (PAD) with an abnormal ankle-brachial index (≤0.9), American College of Cardiology/American Heart Association guidelines recommend exercise training and medical therapy (cilostazol) to improve limb symptoms. In a meta-analysis of 15 studies, cilostazol, a phosphodiesterase inhibitor with antiplatelet and vasodilator activity, was shown to improve symptoms and walking distance in patients with claudication when compared with placebo. As with other oral phosphodiesterase inhibitors (such as milrinone), the FDA has placed a black box warning on the use of cilostazol in patients with heart failure. This patient with established PAD (left ankle-brachial index of 0.67) has been enrolled in a supervised exercise program but has progressive symptoms, and the next most appropriate step in his management is to add cilostazol to his medication regimen.

PAD is considered a coronary artery disease risk equivalent, and patients with PAD should be treated with

a high-intensity statin to prevent cardiovascular events. However, no evidence supports switching atorvastatin to rosuvastatin to reduce limb symptoms in these patients.

Guidelines recommend antiplatelet therapy for patients with PAD to reduce risk for myocardial infarction, stroke, or vascular death. However, in the absence of a specific indication, dual antiplatelet therapy has not been shown to have greater benefit than antiplatelet monotherapy in patients with PAD. Adding clopidogrel to aspirin would not relieve this patient's limb symptoms.

If this patient does not have improvement in his symptoms with cilostazol or cannot tolerate cilostazol therapy, he should be referred for invasive management (endovascular or surgical revascularization).

KEY POINT

- Smoking cessation, exercise training, and medical therapy (cilostazol) are recommended to improve limb symptoms in patients with peripheral artery disease and intermittent claudication.

Bibliography

Gerhard-Herman MD, Gornik HL, Barrett C, Barshes NR, Corriere MA, Drachman DE, et al. 2016 AHA/ACC guideline on the management of patients with lower extremity peripheral artery disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2017;69:1465-1508. [PMID: 27851991] doi:10.1016/j.jacc.2016.11.008

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Item 98 Answer: A

Educational Objective: Treat supraventricular tachycardia.

The most appropriate next step in treatment is administration of adenosine. This patient, who is symptomatic but hemodynamically stable, has supraventricular tachycardia (SVT). Because supraventricular impulses below the atrioventricular (AV) node are conducted normally, the electrocardiogram in SVT usually reveals narrow-complex tachycardia; however, the QRS complexes can be wide (>120 ms) in the presence of bundle branch block, aberrancy, pacing, or anterograde accessory pathway conduction (antidromic tachycardia). This patient's rhythm is consistent with the presence of an accessory pathway (orthodromic atrioventricular reciprocating tachycardia [AVRT]). Orthodromic AVRT is the most common type of AVRT, accounting for more than 90% to 95% of cases. This type of AVRT has a narrow QRS complex owing to conduction over the AV node and the His-Purkinje system. Vagal maneuvers, such as the Valsalva maneuver (bearing down), are first-line therapy for termination of SVT. Adenosine can be used to interrupt AV conduction if vagal maneuvers are ineffective, such as in this patient. Adenosine may also help ascertain the nature of an arrhythmia. For example, when adenosine is administered to patients with atrial tachycardia and rapid 1:1 conduction, it demonstrates persistent rapid P waves despite AV block, which indicates the presence of an atrial tachycardia. Adenosine is metabolized by adenosine deaminase in the blood and has a very short half-life (6 seconds). It is contraindicated in preexcited atrial fibrillation with antidromic tachycardia, which presents with a QRS duration greater than 120 ms due to conduction down the accessory pathway.

Amiodarone is frequently used to treat patients with recurrent ventricular tachycardia or maintain sinus rhythm after conversion from atrial fibrillation. It is not a guideline-recommended agent for the treatment of SVT.

Ibutilide is an intravenous antiarrhythmic drug approved for pharmacologic cardioversion of atrial fibrillation and atrial flutter of recent onset (within 7 days). Ibutilide is associated with an increased risk for polymorphic and monomorphic ventricular tachycardia, and several hours of electrocardiographic monitoring is required following administration.

Synchronized cardioversion should be reserved for patients who are hemodynamically unstable or those with continued SVT despite vagal maneuvers and adenosine.

KEY POINT

- Hemodynamically stable patients with supraventricular tachycardia refractory to vagal maneuvers should be given adenosine.

Bibliography

Page RL, Joglar JA, Caldwell MA, Calkins H, Conti JB, Deal BJ, et al; Evidence Review Committee Chair. 2015 ACC/AHA/HRS guideline for the management of adult patients with supraventricular tachycardia: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. Circulation. 2016;133:e506-74. [PMID: 26399663] doi:10.1161/CIR.0000000000000311

Item 99 Answer: A

Educational Objective: Diagnose amyloid cardiomyopathy.

The most likely diagnosis is cardiac amyloidosis. This patient has heart failure, elevated right heart pressure, and severe concentric wall thickening with preserved systolic function and severe pulmonary hypertension. The electrocardiogram paradoxically demonstrates low QRS voltage and a "pseudoinfarct" pattern: Q waves in the anteroseptal leads without regional wall motion abnormalities on echocardiogram. The most likely diagnosis is cardiac amyloidosis, likely related to a Val122Ile mutation in transthyretin (*TTR*), which is present in 3% to 4% of the black population. Cardiac amyloidosis should be suspected in black patients older than 50 years who have left ventricular wall thickening that is not explained by loading conditions (for example, hypertension or aortic stenosis) and present with heart failure or features of diastolic dysfunction. Although a monoclonal gammopathy is present in immunoglobulin light-chain (AL) amyloidosis, this is not a feature of TTR amyloidosis. Diagnosis is established by histopathology; endomyocardial biopsy is more sensitive than abdominal fat pad biopsy.

Patients with constrictive pericarditis usually have normal or only mildly increased left ventricular wall thickness. Severe pulmonary hypertension is usually not present.

Amyloidosis may be mistaken for hypertensive heart disease; however, the left ventricular wall thickness in this patient is greater than expected for a patient without hypertensive heart disease. Additionally, electrocardiographic features of left ventricular hypertrophy (increased voltage) would be expected.

Hypertrophic cardiomyopathy may be symmetric and nonobstructive and may demonstrate a restrictive filling pattern on echocardiogram. However, in most cases, the QRS voltage on electrocardiogram is congruent with the degree of hypertrophy.

KEY POINT

- Cardiac amyloidosis should be suspected in black patients older than 50 years who have left ventricular wall thickening that is not explained by loading conditions (for example, hypertension or aortic stenosis) and present with heart failure or features of diastolic dysfunction.

Bibliography

Shah KB, Mankad AK, Castano A, Akinboboye OO, Duncan PB, Fergus IV, et al. Transthyretin cardiac amyloidosis in black Americans. Circ Heart Fail. 2016;9:e002558. [PMID: 27188913] doi:10.1161/CIRCHEARTFAILURE.115.002558

Item 100 Answer: A

Educational Objective: Diagnose aortic stenosis associated with repaired aortic coarctation.

This patient most likely has a bicuspid aortic valve with associated aortic stenosis. A bicuspid aortic valve is present in more than 50% of patients with aortic coarctation. The systolic ejection click at the left sternal border suggests a bicuspid aortic valve. The murmur is mid peaking instead of late peaking, and the S_2 is still audible, suggesting mild to moderate aortic stenosis. A bicuspid aortic valve may occur with other cardiovascular and systemic abnormalities, such as aneurysm of the sinuses of Valsalva and patent ductus arteriosus. Patients with a bicuspid aortic valve are predisposed to aortic aneurysm and dissection owing to aortic connective tissue abnormalities. In patients with bicuspid aortic valve, the ascending aortic diameter should be assessed by echocardiography, with the evaluation interval determined by degree and rate of aortic dilation.

Hypertrophic cardiomyopathy is not an expected sequela of aortic coarctation or previous repair. The murmurs in hypertrophic cardiomyopathy characteristically include an ejection quality systolic murmur at the left sternal border related to outflow obstruction and a late systolic murmur at the apex related to mitral regurgitation from systolic anterior motion of the mitral valve. An ejection click is not heard in patients with hypertrophic cardiomyopathy.

Mitral regurgitation is not an expected finding in a patient with aortic coarctation, with or without previous repair. Clinical features in patients with mitral regurgitation include a holosystolic murmur, heard best at the apex and generally radiating to the axilla.

Recurrent coarctation occurs in approximately 20% of patients with previous coarctation repair. Clinical features include hypertension that is difficult to control with medical therapy and occasional claudication. Other features of recurrent coarctation not demonstrated in this patient include a radial artery–to–femoral artery pulse delay and a systolic murmur over the left anterior or posterior chest.

KEY POINT

- A bicuspid aortic valve is present in more than 50% of patients with aortic coarctation.

Bibliography

Phillips SD, Bonnichsen CR, McLeod CJ, Ammash NM, Burkhart HM, Connolly HM. Adults with congenital heart disease and previous intervention. Curr Probl Cardiol. 2013;38:293-357. [PMID: 23906039] doi:10.1016/j.cpcardiol.2013.05.002

Item 101 Answer: C

Educational Objective: Treat new-onset heart failure with maximal β-blocker therapy.

The dosage of carvedilol should be increased in this patient with new-onset heart failure who is symptomatically improving with standard heart failure therapy. All patients with heart failure with reduced ejection fraction should be treated with an ACE inhibitor and a β-blocker, such as carvedilol, to control heart failure symptoms, improve left ventricular ejection fraction, and decrease mortality. Data suggest improved outcomes with higher dosages of β-blockers. Therefore, in patients with new-onset heart failure, it is generally reasonable to increase the β-blocker dosage every 2 to 4 weeks until the patient achieves a heart rate of approximately 60/min or has symptomatic hypotension. Volume status should always be assessed before initiation and uptitration of a β-blocker because patients with volume overload will experience dyspnea if the dosage is increased. Because this patient has a systolic blood pressure of 120 mm Hg, a heart rate of 84/min, and no evidence of volume overload, he should be able to tolerate an increase in the β-blocker dosage. Repeat echocardiography should be performed to assess for improvement or recovery of ejection fraction once the ACE inhibitor and β-blocker have been uptitrated to maximally tolerated dosages.

Digoxin reduces the incidence of hospitalizations in patients with symptomatic heart failure. This patient is asymptomatic; therefore, there is no reason to start digoxin at this time.

Hydralazine and isosorbide dinitrate improve survival in patients who are black and are already receiving maximal therapy for New York Heart Association functional class III or IV heart failure symptoms. This patient has New York Heart Association functional class I symptoms and is not yet taking optimal dosages of medical therapy; both the ACE inhibitor and β-blocker dosages should be uptitrated before other therapies are added to this patient's medication regimen.

Diuretics are the primary treatment for symptoms of heart failure associated with volume overload. In general,

the lowest diuretic dosage that achieves euvolemia should be used. In this patient without evidence of fluid overload, there is no reason to increase the furosemide dosage.

KEY POINT

- All patients with heart failure with reduced ejection fraction should be treated with an ACE inhibitor and a β blocker; β blocker dosage should be uptitrated every 2 to 4 weeks until the patient achieves a heart rate of approximately 60/min or has symptomatic hypotension.

Bibliography

Okwuosa IS, Princewill O, Nwabueze C, Mathews L, Hsu S, Gilotra NA, et al. The ABCs of managing systolic heart failure: past, present, and future. Cleve Clin J Med. 2016;83:753-765. [PMID: 27726827] doi:10.3949/ccjm.83a.16006

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Item 102 Answer: D

Educational Objective: Treat Mobitz type 2 second degree atrioventricular block following ST elevation myocardial infarction.

This patient with Mobitz type 2 second degree atrioventricular (AV) block following a large anterior myocardial infarction requires temporary pacing. In the peri-infarct setting, arrhythmias are common, and benign forms of vagally mediated heart block must be differentiated from more serious conduction abnormalities. Second-degree AV block is frequently seen with acute myocardial infarction. When progressive PR prolongation is observed before a blocked beat, second degree Mobitz type 1 (Wenckebach) block is present. When the PR interval is constant before nonconducted P waves, the second degree block is termed Mobitz type 2 block. When 2:1 block is present, Mobitz type 1 versus type 2 block may not be distinguishable with surface electrocardiography. Mobitz type 2 second-degree AV block is an uncommon but potentially life threatening electrical complication of an anterior myocardial infarction. It usually represents a block lower in the conduction system and suggests significant conduction disease, likely resulting from ischemia and necrosis of the septum (along which the His Purkinje system is located). Because of the high risk for progression to complete heart block, prompt implantation of a temporary or permanent pacemaker is indicated.

Atropine improves AV nodal conduction and quickens the sinus rate. In patients with Mobitz type 2 block, atropine may not alter conduction, and the degree of heart block may paradoxically worsen. Furthermore, this agent has a relatively short lived effect and will not address the underlying pathology.

Cessation of β blocker therapy alone will not improve conduction in this patient, as the pathology of Mobitz type 2 block is beyond the AV node. In contrast, Mobitz type 1 second-degree AV block is frequently seen with acute inferior myocardial infarction and may be associated with periods of complete heart block. Observation and withholding of AV nodal blocking agents is appropriate in that context, as the need for permanent pacing is extremely low with inferior myocardial infarction.

In the absence of chest pain or ST segment elevations on electrocardiogram, urgent angiography is not indicated.

KEY POINT

- Mobitz type 2 second-degree atrioventricular block is an uncommon but potentially life-threatening electrical complication of anterior myocardial infarction; temporary or permanent pacing is indicated in this setting.

Bibliography

Epstein AE, DiMarco JP, Ellenbogen KA, Estes NA 3rd, Freedman RA, Gettes LS, et al; American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the ACC/AHA/NASPE 2002 Guideline Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices). ACC/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the ACC/AHA/NASPE 2002 Guideline Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices) developed in collaboration with the American Association for Thoracic Surgery and Society of Thoracic Surgeons. J Am Coll Cardiol. 2008;51:e1-62. [PMID: 18498951] doi:10.1016/j.jacc.2008.02.032

Item 103 Answer: B

Educational Objective: Diagnose aortopathy in a patient with a bicuspid aortic valve.

The most appropriate next step in management is CT angiography of the aorta. Bicuspid aortic valve is a common congenital heart abnormality, occurring in 1% to 2% of the general population. It is also heritable, and screening of first-degree relatives is recommended. Aortopathy commonly accompanies bicuspid aortic valve disease and may be associated with aortic aneurysm, dissection, and coarctation. Owing to the life threatening nature of these abnormalities, all patients with a bicuspid aortic valve should be evaluated for possible aortopathy. This patient's severe hypertension suggests the possibility of aortic coarctation. Without a diagnosis and therapeutic intervention, the mean life expectancy of unoperated patients with coarctation of the aorta is only 35 years; major complications consist of early coronary atherosclerosis, stroke, aortic dissection, systemic hypertension, and heart failure. The presence of a radial artery–to–femoral artery pulse delay may be helpful in diagnosis at the bedside, but the definitive study is an imaging evaluation (CT or cardiac magnetic resonance imaging).

Patients with a bicuspid aortic valve and severe aortic stenosis or regurgitation require echocardiography every 6 to 12 months; those with mild stenosis or regurgitation should have echocardiography every 3 to 5 years. This patient does not require annual echocardiography; rather, he should be promptly evaluated for abnormalities of the aorta because of the presence of a bicuspid aortic valve.

Bicuspid aortic valve carries an increased risk for infective endocarditis, and good dental care is important in these

patients. However, guidelines no longer recommend antibiotic prophylaxis for this patient population.

Surgical aortic valve replacement is not indicated for mild aortic regurgitation. In general, indications for aortic valve intervention include the presence of symptoms, left ventricular ejection fraction of 50% or less, moderate or severe aortic regurgitation at the time of other cardiac surgery, and significant left ventricular dilatation (end-systolic dimension >50 mm or indexed end-systolic dimension >25 mm/m²).

KEY POINT

- Bicuspid valve disease is commonly associated with abnormalities of the aorta, including aneurysm, dissection, and coarctation; therefore, all patients with a bicuspid aortic valve should be evaluated for possible aortopathy with CT or cardiac magnetic resonance imaging.

Bibliography

Warnes CA, Williams RG, Bashore TM, Child JS, Connolly HM, Dearani JA, et al. ACC/AHA 2008 guidelines for the management of adults with congenital heart disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (writing committee to develop guidelines for the management of adults with congenital heart disease). Circulation. 2008;118:2395-451. [PMID: 18997168] doi:10.1161/CIRCULATIONAHA.108.190811

Item 104 Answer: A

Educational Objective: Identify the impact of diabetes mellitus on risk for atherosclerotic cardiovascular disease.

The factor associated with the highest risk for atherosclerotic cardiovascular disease (ASCVD) is the diagnosis of diabetes mellitus. The presence of diabetes is associated with increased cardiovascular risk, particularly among women. Patients with diabetes have a two to four times increased risk for cardiovascular disease, with more than two thirds of patients with diabetes eventually dying of heart disease. The risk for stroke is increased 1.8- to 6-fold in patients with diabetes. Additionally, patients with diabetes are more likely to have undiagnosed coronary artery disease and have worse outcomes when hospitalized for other cardiovascular diseases, such as heart failure. In this patient, the development of diabetes alone (with all other risk factors held constant) nearly doubled her 10-year risk for ASCVD. Her current 10-year risk, including diabetes, changes in her age, and blood pressure and lipid levels, is 19.4%. Appropriate treatment of cardiovascular risk factors in patients with diabetes is associated with reduced cardiovascular risk. The most recent American College of Cardiology/American Heart Association cholesterol treatment guideline recommends that patients aged 40 to 75 years with diabetes and a 10-year ASCVD risk greater than or equal to 7.5% should receive high-intensity statin therapy. In patients in this age group with diabetes and a 10-year risk less than 7.5%, moderate-intensity statin therapy is recommended.

A diastolic blood pressure of 90 mm Hg, HDL cholesterol level of 30 mg/dL (0.78 mmol/L), systolic blood pressure of 140 mm Hg, and total cholesterol level of 250 mg/dL (6.47 mmol/L) have a relatively small effect on 10-year ASCVD risk compared with the presence of diabetes.

KEY POINT

- Patients with diabetes mellitus have a two to four times increased risk for cardiovascular disease, with more than two thirds of patients with diabetes eventually dying of heart disease.

Bibliography

Lloyd-Jones DM, Huffman MD, Karmali KN, Sanghavi DM, Wright JS, Pelser C, et al. Estimating longitudinal risks and benefits from cardiovascular preventive therapies among Medicare patients: the Million Hearts Longitudinal ASCVD Risk Assessment Tool: a special report from the American Heart Association and American College of Cardiology. J Am Coll Cardiol. 2017;69:1617-1636. [PMID: 27825770] doi:10.1016/j.jacc.2016.10.018

Item 105 Answer: A

Educational Objective: Diagnose infection of a cardiac implanted electronic device.

The most appropriate management of this patient is to obtain a complete blood count, erythrocyte sedimentation rate, and two sets of blood cultures. Patients with a cardiac implanted electronic device can develop a localized tissue infection at the implant site (pocket infection) or a systemic infection with bacteremia (such as endocarditis). These infections can occur after initial implantation, late after implantation, or after a battery replacement or revision. The most common pathogens are skin colonizers, such as the coagulase-negative *Staphylococcus* spp. and *S. aureus*. Symptoms of cardiac device infection include fever, chills, malaise, lassitude, or failure to thrive, especially in the elderly. There may also be local findings suggestive of infection, such as redness or warmth at the pacemaker pocket. These patients should undergo laboratory evaluation for signs of infection. An elevated erythrocyte sedimentation rate, leukocytosis with a left shift, and anemia all suggest infection of a cardiac implanted electronic device. All patients suspected of having infection (with or without fever) should have a minimum of two blood cultures drawn from separate sites. Once there is suspicion for infection of a cardiac implanted electronic device, referral to an electrophysiologist or an infectious disease specialist is mandatory.

Empiric antibiotic therapy without first identifying the presence and cause of the infection is not best medical practice. In addition, antibiotic therapy for a confirmed infection without removal of the device is not curative and is associated with a high fatality rate.

Pacemaker pocket aspiration should never be performed because it can seed a sterile pocket and lead to infection, especially if there is superficial cellulitis without deeper tissue involvement.

In patients with high suspicion of infection despite equivocal laboratory findings, PET/CT can help determine

whether there is evidence of local tissue inflammation consistent with a device infection. However, the basic evaluation for infection should be completed and analyzed first.

KEY POINT

- In all patients suspected of having infection of a cardiac implanted electronic device, a minimum of two blood cultures should be drawn from separate sites.

Bibliography

Harrison JL, Prendergast BD, Sandoe JA. Guidelines for the diagnosis, management and prevention of implantable cardiac electronic device infection [Editorial]. Heart. 2015;101:250-2. [PMID: 25550318] doi:10.1136/heartjnl-2014-306873

Item 106 Answer: B

Educational Objective: Diagnose an acute exacerbation of heart failure in a patient with COPD.

The most likely cause of this patient's symptoms is an exacerbation of heart failure. He demonstrates the classic heart failure symptoms of dyspnea, orthopnea, and peripheral edema. In particular, the patient's orthopnea, as evidenced by his sleeping in a recliner, correlates with a pulmonary capillary wedge pressure greater than 20 mm Hg, which is suggestive of left-sided heart failure. Other features that increase the likelihood of heart failure include the presence of paroxysmal nocturnal dyspnea (greater than twofold increased likelihood) and the presence of an S_3 (11 times greater likelihood). Factors that would decrease the likelihood of heart failure are the absence of dyspnea on exertion (50% decreased likelihood) and the absence of crackles on pulmonary auscultation. A recently enlarged cardiac silhouette also supports a cardiac process.

An exacerbation of COPD is less likely to be the cause of this patient's dyspnea because the patient has no productive cough. Additionally, exacerbations are commonly precipitated by a respiratory infection, which is absent in this patient.

If clinical findings suggest pneumonia, chest radiography should be performed. The chest radiograph must show an infiltrate for pneumonia to be diagnosed. When clinical symptoms and examination findings otherwise support the diagnosis of pneumonia, a false-negative chest radiograph is a possibility; volume depletion can cause an initial negative finding on chest radiograph that, upon rehydration and repeat imaging, may become positive. The absence of an infiltrate, fever, and lung findings make pneumonia an unlikely cause of the patient's dyspnea.

Deep venous thrombosis with a resultant pulmonary embolism is always a concern in patients with new-onset dyspnea. However, he reports no chest pain, and his dyspnea was slow in onset (over the course of 1 week) rather than an acute process. A pulmonary embolism should be considered in the differential diagnosis, but heart failure is the more likely cause.

KEY POINT

- Patients with heart failure classically present with symptoms of dyspnea, paroxysmal nocturnal dyspnea, orthopnea, and peripheral edema.

Bibliography

Wang CS, FitzGerald JM, Schulzer M, Mak E, Ayas NT. Does this dyspneic patient in the emergency department have congestive heart failure? JAMA. 2005;294:1944-56. [PMID: 16234501]

Item 107 Answer: B

Educational Objective: Treat ST-elevation myocardial infarction complicated by ventricular fibrillation.

Primary percutaneous coronary intervention (PCI) is the most appropriate next step in management. ST-elevation myocardial infarction (STEMI) is caused by a complete occlusion of an epicardial coronary artery by a thrombus at the site of plaque disruption. It is defined by the presence of ischemic chest pain (or an equivalent) and the presence of greater than 1-mm ST-segment elevation in two or more consecutive leads or new left bundle branch block on electrocardiogram. This patient presumably has an anterior myocardial infarction, which is complicated by ventricular fibrillation arrest. The electrocardiogram demonstrates left bundle branch block and is assumed to be new in onset. In some cases, ventricular arrhythmias may signify spontaneous reperfusion events, but the new left bundle branch block is worrisome for persistent left anterior descending artery occlusion, which remains the obvious culprit for the patient's presentation. Prompt reperfusion is required. Primary PCI is the preferred method of reperfusion in patients with STEMI.

Amiodarone may be necessary if this patient has recurrent ventricular fibrillation or ventricular tachycardia; however, amiodarone alone is unlikely to control his ischemic-related arrhythmias, and reperfusion is the foremost priority. Furthermore, intravenous amiodarone may precipitate hypotension and shock owing to its acute β-blocking activity, and it must be used carefully in patients with STEMI.

Therapeutic hypothermia is an important adjunct therapy to improve outcomes of patients experiencing out-of-hospital cardiac arrest, although hypothermia protocols are not indicated in noncomatose patients. This patient's arrest was a witnessed arrest, and the patient is awake and conversant.

Coronary artery bypass graft (CABG) surgery is not commonly performed for STEMI. Urgent CABG surgery is typically reserved for patients in whom thrombolytic therapy or PCI has failed, or for those who develop life-threatening mechanical complications, such as ventricular free wall rupture. Compared with PCI and thrombolytic therapy, urgent CABG surgery is associated with an increased death rate in the first 3 to 7 days after STEMI, and this potential harm must be carefully weighed against the potential benefits.

KEY POINT

- Primary percutaneous coronary intervention is the preferred method of reperfusion in patients with ST-elevation myocardial infarction.

Bibliography

Callaway CW, Donnino MW, Fink EL, Geocadin RG, Golan E, Kern KB, et al. Part 8: Post-cardiac arrest care: 2015 American Heart Association guidelines update for cardiopulmonary resuscitation and emergency cardiovascular care. Circulation. 2015;132:S465-82. [PMID: 26472996] doi:10.1161/CIR.0000000000000262

Item 108 Answer: D

Educational Objective: Diagnose upper extremity peripheral artery disease.

CT angiography is indicated in this patient suspected of having upper extremity peripheral artery disease (PAD). Upper extremity PAD is characterized by atherosclerotic narrowing of the arteries in the upper extremities. Most patients with upper extremity PAD have no symptoms, although patients may present with arm claudication, arm ischemia, or dizziness with arm activity (subclavian steal syndrome). In patients at risk for atherosclerotic cardiovascular disease, measurement of bilateral arm pressures is indicated in asymptomatic and symptomatic patients to assess for upper extremity PAD. A characteristic finding on physical examination is a difference in systolic blood pressures between the arms, typically more than 15 mm Hg. In this patient with exercise-induced arm pain and a systolic blood pressure differential of 35 mm Hg between arms, imaging of the innominate and subclavian arteries with CT angiography is appropriate to confirm the diagnosis of upper extremity PAD and plan for intervention, such as revascularization.

The Adson maneuver (or thoracic outlet maneuver) is used to evaluate for neurovascular impingement at the point where the subclavian vessels and brachial plexus pass the first rib and exit the thoracic cavity. Although thoracic outlet syndrome could account for this patient's arm fatigue, he does not have other symptoms or signs suggestive of this condition (for example, arm edema, numbness/tingling), and thoracic outlet syndrome does not explain his dizziness.

The ankle-brachial index is most useful in diagnosing lower extremity PAD. In this patient with upper extremity symptoms, an ankle-brachial index would not be helpful in confirming a diagnosis of innominate or subclavian stenosis.

Although bilateral carotid artery stenosis has been associated with dizziness or syncope in some patients, the systolic blood pressure differential in the upper limbs and diminished ipsilateral carotid pulsation make this diagnosis unlikely. Therefore, carotid duplex ultrasonography is not the most appropriate next step.

KEY POINT

- Symptoms of upper extremity peripheral artery disease may include arm claudication, arm ischemia, or dizziness with arm activity; CT angiography is useful to confirm the diagnosis and plan for intervention.

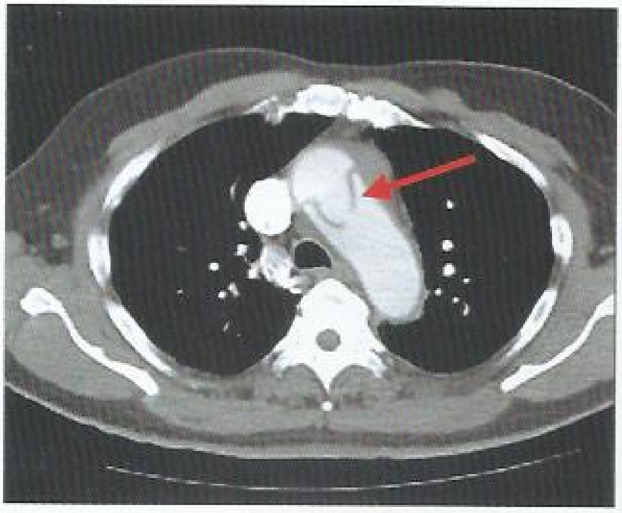
Bibliography

Ochoa VM, Yeghiazarians Y. Subclavian artery stenosis: a review for the vascular medicine practitioner. Vasc Med. 2011;16:29-34. [PMID: 21078767] doi:10.1177/1358863X10384174

Item 109 Answer: C

Educational Objective: Treat type A aortic dissection.

The most appropriate next step in the management of this patient with an acute type A aortic dissection is emergent open surgical aortic repair. This patient's CT scan (shown) reveals a dissection plane extending through the aortic arch (*arrow*). Acute aortic dissection classically manifests as sudden onset chest or back pain that has a tearing or ripping quality, such as in this patient; however, patients may present with hypertension, syncope, a murmur of aortic regurgitation, or heart failure in the setting of sudden aortic insufficiency. Unequal blood pressures in the upper extremities and asymmetric pulses further raise the suspicion for acute aortic dissection. Stanford type A aortic dissections, which originate within the ascending aorta or arch, confer a high risk for death and complications. The early mortality rate is approximately 1% per hour after symptom onset; therefore, patients with acute type A aortic dissection should be evaluated emergently for open surgical repair.



In patients with acute aortic dissection, performing coronary angiography before aortic repair has not been shown to alter in-hospital survival or the need for coronary artery bypass surgery at the time of aortic repair. Furthermore, coronary angiography often delays surgical repair.

Medical therapy for acute aortic dissection includes β-blockers, intravenous nitroprusside, and opioid analgesia. Surgery provides a survival benefit over medical therapy alone and is the definitive treatment.

Emergency surgery is recommended for all patients with type A aortic dissection. Concomitant aortic arch

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reconstruction, coronary artery reimplantation, aortic valve repair or replacement, or branch vessel repair may be required depending on the anatomy and pathology of the lesion. This patient has evidence of compromise of his right innominate artery with diminished right arm blood pressure and pulses and requires branch vessel repair, not endovascular stenting.

KEY POINT

- Patients with acute type A aortic dissection should be treated emergently with open surgical repair.

Bibliography

Erbel R, Aboyans V, Boileau C, Bossone E, Bartolomeo RD, Eggebrecht H, et al; ESC Committee for Practice Guidelines. 2014 ESC Guidelines on the diagnosis and treatment of aortic diseases: document covering acute and chronic aortic diseases of the thoracic and abdominal aorta of the adult. The Task Force for the Diagnosis and Treatment of Aortic Diseases of the European Society of Cardiology (ESC). Eur Heart J. 2014;35:2873-926. [PMID: 25173340] doi:10.1093/eurheartj/ehu281

Item 110 Answer: C

Educational Objective: Evaluate an asymptomatic murmur with transthoracic echocardiography.

The most appropriate management of this asymptomatic patient with a heart murmur is transthoracic echocardiography (TTE). Diastolic murmurs are always considered abnormal and require further structural evaluation. Systolic murmurs may be either innocent or indicative of significant valve disease. Some murmurs are associated with normal valves but abnormal systemic processes (for example, anemia and other high-output states, such as hyperthyroidism or pregnancy) or increased flow (for example, a systolic murmur in the setting of aortic regurgitation). Innocent murmurs are characteristically brief, are often midsystolic, do not radiate, and are associated with normal heart sounds and no hemodynamic abnormalities. Patients with grade 1 or 2 midsystolic murmurs (grade 1, faintest murmur that can be heard; grade 2, faint murmur but can be identified immediately) who are asymptomatic with no associated findings and those with continuous murmurs suggestive of a venous hum or mammary souffle (a continuous murmur heard over the breast in lactating women) do not warrant echocardiographic evaluation. TTE is indicated for patients with the following findings: (1) a systolic murmur grade 3/6 or higher (grade 3, moderately loud murmur; grade 4, loud murmur associated with a palpable thrill; grade 5, very loud murmur but cannot be heard without the stethoscope; and grade 6, can be heard without a stethoscope); (2) late or holosystolic murmurs; (3) diastolic or continuous murmurs; or (4) murmurs with accompanying symptoms. This patient with a holosystolic murmur that radiates to the axilla needs further evaluation with TTE.

Transesophageal echocardiography (TEE) provides improved image quality over TTE because the probe has only the thin tissue of the esophagus through which to image. TEE is indicated for patients with severe disease who need further quantification, for better identification of leaflet involvement (particularly for patients with mitral regurgitation), or when poor image quality on TTE limits image interpretation. The disadvantage compared with TTE is that it is invasive, requiring sedation and technical expertise distinct from TTE. TEE is not indicated until an initial assessment with TTE is made and findings suggest a need for additional information.

Cardiac magnetic resonance imaging or multidetector CT may provide information on left ventricular function, aortic dimensions, chamber sizes and volumes, and coronary anatomy. As with TEE, CMR imaging should not be performed until after an initial evaluation with TTE.

KEY POINT

- Transthoracic echocardiography is indicated for patients with systolic murmurs grade 3/6 or higher, late or holosystolic murmurs, diastolic or continuous murmurs, and murmurs with accompanying symptoms.

Bibliography

Premkumar P. Utility of echocardiogram in the evaluation of heart murmurs. Med Clin North Am. 2016;100:991-1001. [PMID: 27542419] doi:10.1016/j.mcna.2016.04.005

Item 111 Answer: D

Educational Objective: Evaluate tricuspid regurgitation with transthoracic echocardiography.

The most appropriate next step in management is transthoracic echocardiography. This patient has symptoms and signs consistent with tricuspid regurgitation. Severe tricuspid regurgitation may be well tolerated for a long period. Clinical signs of right-sided heart failure, such as elevated jugular venous pulse and peripheral edema, are an indication of severity. The murmur of tricuspid regurgitation is typically a holosystolic murmur heard along the left sternal border that increases during inspiration due to increased venous return. Causes of tricuspid regurgitation include rheumatic disease, radiation, endocarditis, myxomatous degeneration (prolapse), congenital abnormalities (Ebstein anomaly), carcinoid disease, and trauma (for example, chest wall impact or right ventricular biopsy). Placement of internal device leads for pacemakers and cardioverter-defibrillators is also a common cause of tricuspid regurgitation. In patients with suspected tricuspid regurgitation, transthoracic echocardiography is indicated to evaluate lesion severity, determine the cause, assess the size and function of the right-sided chambers, and estimate pulmonary artery pressures. Transesophageal echocardiography can also help demonstrate the relation of the device leads to tricuspid leaflets as a cause of tricuspid regurgitation.

Cardiovascular magnetic resonance (CMR) imaging may be helpful in the evaluation of tricuspid regurgitation if echocardiographic evaluation is suboptimal or inconclusive. In this patient, the pacemaker presents a contraindication to CMR imaging.

Coronary angiography and right ventriculography are not useful in the diagnosis of tricuspid regurgitation. Unlike mitral regurgitation, ischemic coronary artery disease is not a common cause of tricuspid regurgitation. Evaluation of right heart pressures may be indicated following echocardiography, particularly if there is discordant information obtained by clinical and echocardiographic evaluation, but right heart catheterization is not necessary at this time.

KEY POINT

- In patients suspected of having tricuspid regurgitation, transthoracic echocardiography is indicated to evaluate lesion severity, determine the cause, assess the size and function of the right-sided chambers, and estimate pulmonary artery pressures.

Bibliography

Lin G, Nishimura RA, Connolly HM, Dearani JA, Sundt TM 3rd, Hayes DL. Severe symptomatic tricuspid valve regurgitation due to permanent pacemaker or implantable cardioverter defibrillator leads. J Am Coll Cardiol. 2005;45:1672-5. [PMID: 15893186]

Item 112 Answer: A

Educational Objective: Manage drug-drug interactions in a patient with stable angina.

The most appropriate management is to decrease the dosage of ranolazine. This patient with stable angina is being transitioned from metoprolol, a β-blocker, to diltiazem, a calcium channel blocker. He is also currently taking several other antianginal therapies, notably ranolazine. Ranolazine decreases angina and modestly increases exercise times in patients with stable angina. Ranolazine inhibits the late sodium current, which in turn reduces sodium-dependent calcium currents, resulting in reduced wall tension and myocardial oxygen consumption. Ranolazine is primarily metabolized by cytochrome P450 3A4 (CYP3A4); therefore, caution should be exercised when prescribing ranolazine with CYP3A4 inhibitors, which will result in significantly increased plasma levels of ranolazine. Ranolazine should not be used with strong CYP3A4 inhibitors, such as ketoconazole, clarithromycin, and ritonavir. With moderate CYP3A4 inhibitors, including verapamil and diltiazem, the dosage should be decreased by 50% and should not exceed 500 mg twice daily. Ranolazine also has a modest QT-prolonging effect, but no proarrhythmic effect has been directly attributed to ranolazine.

The addition of diltiazem to this patient's medication regimen will not require increasing the dosage of atorvastatin. Diltiazem may in fact result in increased levels of atorvastatin, which is a CYP3A4 substrate.

There are no significant drug-drug interactions between lisinopril and diltiazem that would warrant switching to another ACE inhibitor.

Not adjusting this patient's medication regimen would result in excessive plasma levels of ranolazine and is not an acceptable option.

KEY POINT

- Ranolazine decreases symptoms of angina and modestly increases exercise times in patients with stable angina; it should not be used with strong CYP3A inhibitors, and dosage should be reduced when used in conjunction with moderate CYP3A inhibitors, such as diltiazem and verapamil.

Bibliography

Fihn SD, Gardin JM, Abrams J, Berra K, Blankenship JC, Dallas AP, et al; American College of Cardiology Foundation/American Heart Association Task Force. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology Foundation/American Heart Association task force on practice guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. Circulation. 2012;126:e354-471. [PMID: 23166211] doi:10.1161/CIR.0b013e318277d6a0

Item 113 Answer: D

Educational Objective: Manage first-degree atrioventricular block accompanied by bifascicular block.

No further testing or intervention is required at this time. This asymptomatic patient has first-degree atrioventricular (AV) block (PR interval >200 ms), right bundle branch block, and left posterior fascicular block. Right bundle branch block is diagnosed by the findings of a widened QRS complex (>120 ms); an RSR′ pattern in lead V_1; and a wide negative S wave in leads I, V_5, and V_6. Blocks may also occur in the anterior or posterior divisions (fascicles) of the left bundle; these are termed fascicular blocks (or hemiblocks). Left anterior fascicular block is recognized by a positive QRS complex in lead I and a negative QRS complex in lead aVF. Left posterior fascicular block is recognized by a negative QRS complex in lead I and a positive QRS complex in lead aVF. Conduction disturbances involving the right bundle branch and one of the two fascicles (anterior or posterior) of the left bundle branch are commonly referred to as bifascicular block. The presence of first-degree AV block with bifascicular block is often called "trifascicular block"; however, the term is misleading because true trifascicular block would indicate complete AV block.

There is no need for extensive cardiac evaluation of patients with asymptomatic bifascicular block other than a careful history and physical examination to exclude the diagnosis of occult cardiac disease. Therefore, echocardiography and dobutamine echocardiography are not indicated because occult ischemic or structural heart disease is not suspected in this patient.

Pacemakers are indicated in patients with symptomatic bradycardia in the absence of a reversible cause, hence the importance of establishing symptoms when evaluating patients with bradycardia. Pacing is not indicated in asymptomatic patients with first-degree AV block accompanied by bifascicular block because the risk for progression to complete heart block is less than 2% to 3% per year. As such, pacemaker insertion is not needed in this patient.

KEY POINT

- Asymptomatic first-degree atrioventricular block with bifascicular block does not require pacemaker implantation.

Bibliography

Da Costa D, Brady WJ, Edhouse J. Bradycardias and atrioventricular conduction block. BMJ. 2002;324:535-8. [PMID: 11872557]

Item 114 Answer: E

Educational Objective: Treat heart failure with reduced ejection fraction.

The most appropriate management of this patient with heart failure with reduced ejection fraction (HFrEF) is to continue the current medication regimen. Guideline directed medical therapy for symptomatic heart failure includes treatment with an ACE inhibitor, β-blocker (specifically, metoprolol succinate, carvedilol, or bisoprolol), and an aldosterone antagonist. All of these agents reduce mortality in patients with HFrEF. This patient is already taking guideline-directed medical therapy at maximally tolerated doses, as evidenced by her symptomatic orthostatic hypotension; therefore, no changes need to be made to her medication regimen.

Ivabradine inhibits the I_f or "I-funny" channel of the sinoatrial node, resulting in a reduction in heart rate. In patients with HFrEF (left ventricular ejection fraction ≤35%) and New York Heart Association functional class II to IV symptoms who are in sinus rhythm with a heart rate of 70/min or higher and taking guideline-directed medical therapy, treatment with ivabradine has been associated with a reduction in heart failure hospitalizations. Before the resting heart rate is assessed for potential initiation of ivabradine, β-blockers should be titrated to maximally tolerated doses. Because this patient has a heart rate of 68/min and is already taking a maximally tolerated dose of carvedilol, she is not a candidate for ivabradine. It is important to note that ivabradine should be given in addition to β-blocker therapy, not in its place.

Valsartan-sacubitril is an angiotensin receptor–neprilysin inhibitor, a new drug class that combines an angiotensin receptor blocker with a neprilysin inhibitor. The neprilysin inhibitor prevents the breakdown of B-type natriuretic peptide, leading to enhanced diuresis, natriuresis, and myocardial relaxation. Compared with ACE inhibitor therapy, this drug combination has been shown to reduce the composite endpoint of cardiovascular death or heart failure hospitalization by 20% in symptomatic patients with HFrEF. However, in a clinical trial assessing response to valsartan-sacubitril, the major cause of withdrawal was hypotension. In this patient who is taking an ACE inhibitor and β-blocker and is experiencing symptomatic orthostatic hypotension, the addition of valsartan-sacubitril is not indicated. Adding valsartan-sacubitril to her current medication regimen, which includes lisinopril, would greatly increase her risk for angioedema and hypotension. ACE inhibitors should be discontinued at least 36 hours before initiating valsartan-sacubitril. If she did not have symptomatic hypotension, switching lisinopril to valsartan-sacubitril would be an appropriate option.

KEY POINT

- Guideline-directed medical therapy for symptomatic heart failure with reduced ejection fraction includes an ACE inhibitor, β-blocker (specifically, metoprolol succinate, carvedilol, or bisoprolol), and aldosterone antagonist.

Bibliography

Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Colvin MM, et al. 2016 ACC/AHA/HFSA focused update on new pharmacological therapy for heart failure: an update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. J Am Coll Cardiol. 2016;68:1476-88. [PMID: 27216111] doi:10.1016/j.jacc.2016.05.011

Item 115 Answer: B

Educational Objective: Treat atrial septal defect.

Percutaneous atrial septal defect (ASD) device closure is the best management choice for this patient depending on favorability of anatomic features. Device closure is performed in the catheterization laboratory and is an option for patients with an isolated ostium secundum ASD. Indications for ASD device closure include right heart enlargement and symptoms. ASD closure is also reasonable for orthodeoxia-platypnea syndrome and before pacemaker placement because of the increased risk for systemic thromboembolism. An asymptomatic small ASD with no right heart enlargement can be monitored without closure. Surgical closure is indicated for nonsecundum ASDs, large secundum ASDs, anatomy unfavorable for device closure, and a secundum ASD in patients with coexistent cardiovascular disease requiring operative intervention, such as coronary artery disease or tricuspid regurgitation.

Cardiac magnetic resonance imaging can be used to detect a secundum ASD and can quantitate the effect of the defect by determining right ventricular volume; however, it is not indicated in this patient because the clinical assessment and echocardiogram are sufficient to guide the decision to close the ASD.

Endocarditis prophylaxis is recommended for patients with congenital heart disease characterized by unrepaired cyanotic disease, including palliative shunts and conduits; a congenital defect during the first 6 months after complete repair of the defect with prosthetic material or device; and repaired disease with residual defects. Patients with an uncomplicated ASD without a history of endocarditis do not require endocarditis prophylaxis.

Functional aerobic capacity measured by stress testing is not generally used to determine management in patients with ASDs.

KEY POINT

- Right heart enlargement and symptomatic disease are indications for device closure of an ostium secundum atrial septal defect.

Bibliography

Warnes CA, Williams RG, Bashore TM, Child JS, Connolly HM, Dearani JA, et al; American College of Cardiology. ACC/AHA 2008 guidelines for the management of adults with congenital heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Develop Guidelines on the Management of Adults With Congenital Heart Disease). Developed in Collaboration With the American Society of Echocardiography, Heart Rhythm Society, International Society for Adult Congenital Heart Disease, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol. 2008;52:e143-263. [PMID: 19038677] doi:10.1016/j.jacc.2008.10.001

Item 116 Answer: D

Educational Objective: Treat severe aortic stenosis with transcatheter aortic valve replacement in a patient with high surgical risk.

The most appropriate next step in management is transcatheter aortic valve replacement (TAVR). TAVR has emerged as a life-saving therapy for patients with severe aortic stenosis. In studies of patients with intermediate or high surgical risk, the outcomes of TAVR have been comparable or favorable to that of surgery, with similar rates of mortality and stroke. In the United States, TAVR is currently indicated for symptomatic patients with aortic stenosis and intermediate or high surgical risk, as assessed by a multidisciplinary heart team. Online tools, which are derived and regularly updated from national surgical databases, are available to assist with estimating surgical risk (for example, the Society of Thoracic Surgeons Adult Cardiac Surgery Risk Calculator [riskcalc.sts.org]). Although these calculators contain many data input fields, it is important to note that frailty as well as some other important patient and procedural characteristics are not part of the online assessment tools. Therefore, a comprehensive, holistic approach is required for determining patient surgical risk and candidacy for the various procedures to treat aortic stenosis. Frailty can be assessed with an examination of the patient's activities of daily living, independence in ambulation (for example, 6-minute walk distance), and various other geriatric tools.

Balloon aortic valvuloplasty may be considered as a bridge to transcatheter or surgical aortic valve replacement, but it has not been shown to improve the long-term prognosis of patients with aortic stenosis.

Medical therapy has not been found to be effective in slowing the disease progression in patients with aortic stenosis. Medical therapy would be pursued only if this patient declined aortic valve replacement or if he had morbidities that would preclude benefit from such surgery, such as a reduced life expectancy unrelated to valvular disease.

Surgical aortic valve replacement is not appropriate for this patient because his surgical risk was estimated to be high or prohibitive.

KEY POINT

- Transcatheter aortic valve replacement has been found to be comparable to surgical intervention and is indicated for symptomatic patients with aortic stenosis and intermediate or high surgical risk, as assessed by a multidisciplinary heart team.

Bibliography

Smith CR, Leon MB, Mack MJ, Miller DC, Moses JW, Svensson LG, et al; PARTNER Trial Investigators. Transcatheter versus surgical aortic-valve replacement in high-risk patients. N Engl J Med. 2011;364:2187-98. [PMID: 21639811] doi:10.1056/NEJMoa1103510

Item 117 Answer: A

H

Educational Objective: Treat ST-elevation myocardial infarction complicated by heart failure.

The most appropriate treatment is eplerenone. This patient had an anterior ST-elevation myocardial infarction (STEMI) complicated by moderate left ventricular (LV) dysfunction and heart failure. Optimizing this patient's medical therapy is fundamental to preventing further impairment of LV function and promoting favorable LV remodeling. Although β-blockers and ACE inhibitors (or angiotensin receptor blockers [ARBs]) form the backbone of postinfarction medical therapy aimed at preserving LV function, it is important to recognize when additional agents may be indicated. The EPHESUS trial established the benefits of aldosterone antagonism with eplerenone in patients with acute myocardial infarction and concomitant LV dysfunction, and current guidelines recommend adding an aldosterone antagonist to ACE inhibitor and β-blocker therapy in STEMI patients with left ventricular ejection fraction of 40% or less and either heart failure symptoms or diabetes mellitus. Because of the potassium-sparing effect of eplerenone, serum potassium levels should be carefully monitored. Eplerenone should be used with caution in those with underlying kidney disease.

Long-acting nitrates, such as isosorbide mononitrate, have no role in the management of patients immediately after ST-elevation myocardial infarction. Nitrates may be used for future angina or may be coupled with hydralazine in those with persistent LV dysfunction despite maximally tolerated doses of a β-blocker and ACE inhibitor; however, administering isosorbide mononitrate is not the most appropriate next step in this patient's management.

Although an ARB such as valsartan may be useful as an alternative to ACE inhibitor therapy, adding an ARB to a medication regimen that already includes an ACE inhibitor and β-blocker has been associated with an excess of adverse events and is therefore not recommended.

Warfarin therapy is recommended to reduce the risk for systemic embolization in patients with LV apical clots following large anterior myocardial infarction, although this recommendation is not based on a large randomized dataset. In this patient, no clots were noted on the echocardiogram, and empiric anticoagulation is not indicated according to current guidelines.

KEY POINT

- In patients with ST-elevation myocardial infarction, left ventricular ejection fraction of 40% or less, and either heart failure symptoms or diabetes mellitus, an aldosterone antagonist is recommended in addition to ACE inhibitor and β-blocker therapy.

Bibliography

Pitt B, Remme W, Zannad F, Neaton J, Martinez F, Roniker B, et al; Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study Investigators. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. N Engl J Med. 2003;348:1309-21. [PMID: 12668699]

H

Item 118 Answer: B

Educational Objective: Diagnose cardiac tamponade following catheter ablation of atrial fibrillation.

The catheter ablation–related complication that is most likely responsible for the patient's symptoms is cardiac tamponade. Although cardiac tamponade occurs in approximately 1% of patients who undergo catheter ablation procedures for atrial fibrillation, it is the most common serious complication and is likely to result in death if not recognized and treated urgently. Cardiac tamponade occurs within a mean of 10 days after the procedure, although it may occur within hours of the procedure or be delayed by weeks. Cardiac tamponade should be suspected when the patient has a compatible history, hypotension, elevated jugular venous pressure, narrow pulse pressure, and pulsus paradoxus. An enlarged cardiac silhouette may be seen on chest radiograph ("water-bottle heart"). The electrocardiogram typically demonstrates sinus tachycardia and electrical alternans. Echocardiography readily detects pericardial effusions and is the primary modality for diagnosing cardiac tamponade.

Patients who develop an atrioesophageal fistula most commonly present 1 to 4 weeks after the ablation procedure. Patients may exhibit a sudden onset of neurologic symptoms from esophageal air embolization. Patients may also present with fever, chest pain, seizures, transient ischemic attack after food intake, hematemesis, and endocarditis. MRI and CT are preferred as diagnostic studies.

Patients who develop dyspnea months to years after atrial fibrillation ablation may have pulmonary vein stenosis. Other symptoms may include cough, chest pain, and hemoptysis. Pulmonary vein stenosis occurs in approximately 1% to 3% of patients, but intervention to relieve symptoms is required in only 10% of these patients. Guidelines recommend CT or MRI as the preferred diagnostic test in symptomatic patients.

Vascular events, including hematomas, pseudoaneurysms at the arterial puncture site, and retroperitoneal hemorrhage from bleeding at the groin access site, are among the most common complications of catheter ablation. Symptoms include hypotension and ipsilateral flank pain. Symptom onset is typically within hours of the procedure. Diagnosis can be established with CT or ultrasonography. Retroperitoneal hemorrhage cannot explain this patient's distant heart sounds, elevated central venous pressure, or pulsus paradoxus.

KEY POINT

- Cardiac tamponade occurs in approximately 1% of patients who undergo catheter ablation procedures for atrial fibrillation; it is the most common serious complication and is likely to result in death if not recognized and treated urgently.

Bibliography

Maan A, Shaikh AY, Mansour M, Ruskin JN, Heist EK. Complications from catheter ablation of atrial fibrillation: a systematic review. Crit Pathw Cardiol. 2011;10:76-83. [PMID: 21988947] doi:10.1097/HPC.0b013e318224b7bd

Item 119 Answer: D

Educational Objective: Treat heart failure with an implantable cardioverter-defibrillator and cardiac resynchronization therapy.

The most appropriate management is placement of an implantable cardioverter-defibrillator (ICD) with cardiac resynchronization therapy (CRT). This patient has symptomatic heart failure with reduced ejection fraction that is most likely secondary to cardiac sarcoidosis. Although sarcoidosis predominantly affects the lungs, cardiac sarcoidosis is found in up to 10% of patients with sarcoidosis at the time of autopsy, and the diagnosis should always be considered in patients with heart failure and concomitant pulmonary sarcoidosis. In patients with heart failure who have an ejection fraction less than 35%, continued symptoms despite maximally tolerated medical therapy, and expected survival of at least 1 year, ICD placement is indicated. When these criteria are accompanied by left bundle branch block with a QRS duration greater than or equal to 150 ms on electrocardiogram, as in this patient, CRT is also recommended. CRT improves left ventricular ejection fraction, functional capacity, and, most importantly, survival in symptomatic patients with an ejection fraction less than 35% and a wide QRS complex or left bundle branch block.

Diuretics, such as furosemide, are the principal therapy for volume overload in patients with heart failure. Patients should be treated with diuretics until they achieve a state of euvolemia. This patient does not have any evidence of volume overload and therefore does not require a diuretic.

β-Blockers, such as carvedilol, have a mortality benefit in patients with heart failure with reduced ejection fraction. It is generally reasonable to increase the β-blocker dosage every 2 to 4 weeks until the patient achieves a heart rate of approximately 60/min or has symptomatic hypotension. In this patient with a current heart rate below 60/min, increasing the β-blocker dosage is inappropriate.

Although cardiac sarcoidosis can be difficult to diagnose, endomyocardial biopsy is not indicated in suggestive cases. Cardiac sarcoidosis results in patchy myocardial

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involvement, and a negative biopsy result would not be reassuring that cardiac sarcoidosis is not present. The two imaging modalities that are most sensitive for diagnosing cardiac sarcoidosis are cardiac magnetic resonance imaging and PET.

When sarcoidosis is first diagnosed, treatment with glucocorticoids can improve ejection fraction and reduce arrhythmias. This patient has already been treated with prednisone for 6 months, and further therapy is unlikely to result in additional improvement. Therefore, she should receive an ICD with CRT.

KEY POINT

- Cardiac resynchronization therapy is indicated in patients with an ejection fraction less than or equal to 35%, New York Heart Association functional class II to IV heart failure symptoms despite guideline-directed medical therapy, sinus rhythm, and left bundle branch block with a QRS duration of 150 ms or greater.

Bibliography

Russo AM, Stainback RF, Bailey SR, Epstein AE, Heidenreich PA, Jessup M, et al. ACCF/HRS/AHA/ASE/HFSA/SCAI/SCCT/SCMR 2013 appropriate use criteria for implantable cardioverter-defibrillators and cardiac resynchronization therapy: a report of the American College of Cardiology Foundation appropriate use criteria task force, Heart Rhythm Society, American Heart Association, American Society of Echocardiography, Heart Failure Society of America, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, and Society for Cardiovascular Magnetic Resonance. J Am Coll Cardiol. 2013;61:1318-68. [PMID: 23453819] doi:10.1016/j.jacc.2012.12.017

Item 120 Answer: D

Educational Objective: Treat acute pericarditis.

High-dose aspirin and colchicine are indicated in this patient with acute pericarditis without high-risk features. Acute pericarditis is diagnosed in this patient by the presence of sharp chest pain of acute onset without evidence of myocardial necrosis, an electrocardiogram demonstrating widespread ST-segment elevation and PR-segment depression, and a small pericardial effusion. The elevated C-reactive protein level also supports acute pericarditis. Admission to the hospital is appropriate for patients with acute pericarditis who have at least one high-risk feature, including high fever (temperature >38 °C [100.4 °F]), subacute onset (gradual onset over several days), large pericardial effusion (>20 mm), oral anticoagulation therapy, or immunosuppression. First-line therapy includes aspirin (750-1000 mg) or ibuprofen (600 mg) every 8 hours for 1 to 2 weeks plus colchicine (0.5 mg/d) for 3 months. In this patient, initiation of anti-inflammatory therapy with early outpatient follow-up is appropriate.

Pericardiocentesis is reserved for treatment of patients with tamponade or for diagnosis in patients with pericardial effusion when there is a high clinical suspicion of a malignant, bacterial, or fungal cause.

Cardiac catheterization would be appropriate in the setting of an ST-elevation myocardial infarction to facilitate percutaneous coronary intervention. However, the widespread ST-segment elevation on this patient's electrocardiogram is atypical for ST-elevation myocardial infarction, which more commonly causes ST-segment elevation within a specific vascular distribution. Furthermore, the lack of biomarker evidence of myocardial necrosis after prolonged chest pain does not support a diagnosis of acute coronary syndrome.

Although this patient has risk factors for coronary artery disease, exercise treadmill stress testing has no role. Additionally, in the setting of acute pericarditis, exercise-associated ST-T wave changes are not interpretable for ischemic coronary artery disease.

KEY POINT

- In patients with acute pericarditis, first-line treatment is high-dose aspirin or NSAIDs and adjuvant colchicine therapy.

Bibliography

Adler Y, Charron P, Imazio M, Badano L, Barón-Esquivias G, Bogaert J, et al; European Society of Cardiology (ESC). 2015 ESC guidelines for the diagnosis and management of pericardial diseases: the Task Force for the Diagnosis and Management of Pericardial Diseases of the European Society of Cardiology (ESC). Endorsed by the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J. 2015;36:2921-64. [PMID: 26320112] doi:10.1093/eurheartj/ehv318

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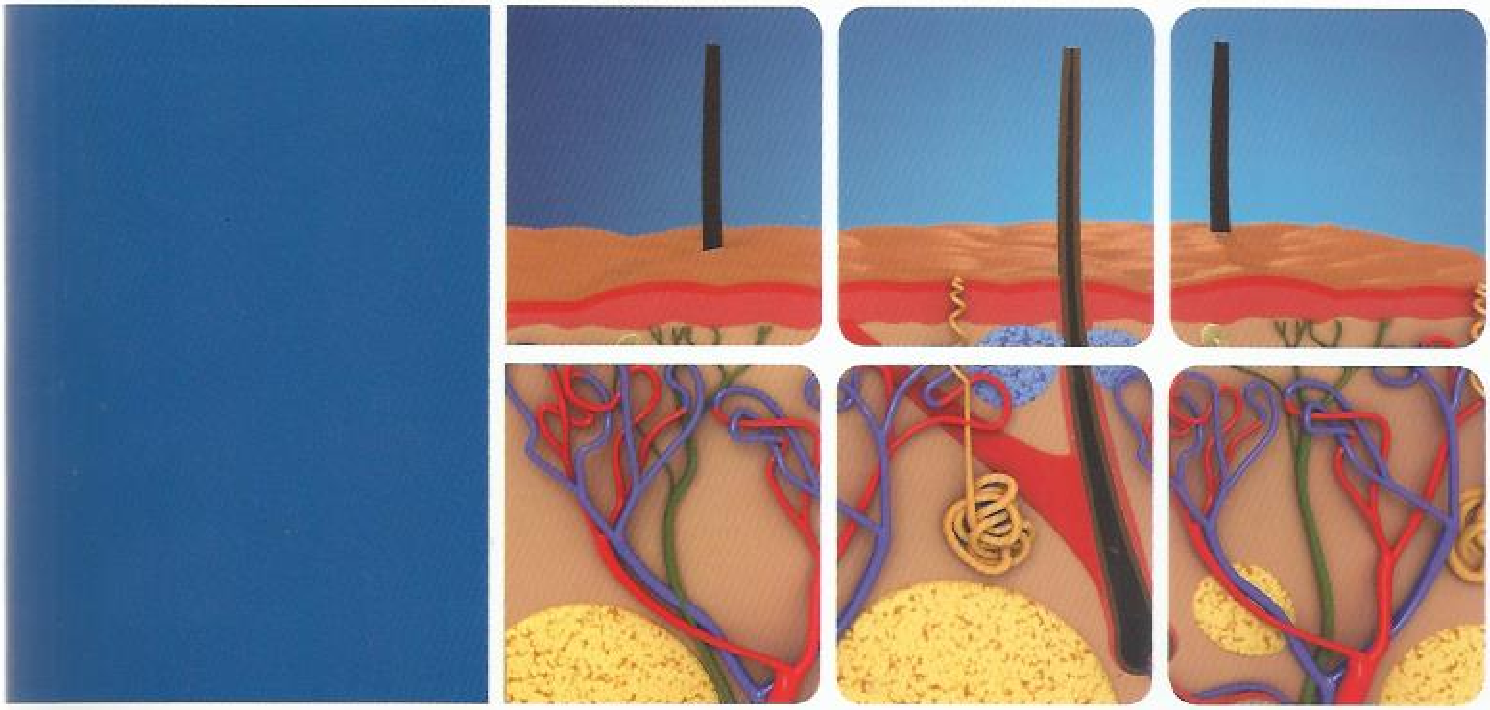

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- Diagnose disease states that are less common and sometimes overlooked and confusing
- Improve management of comorbid conditions that can complicate patient care
- Determine when to refer patients for surgery or care by subspecialists
- Pass the ABIM Certification Examination
- Pass the ABIM Maintenance of Certification Examination

Target Audience

- General internists and primary care physicians
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Key Points in the text that relate to High Value Care concepts (that is, concepts that discuss balancing clinical benefit with costs and harms) are designated by the HVC icon [HVC].

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Dermatology High Value Care Recommendations

The American College of Physicians, in collaboration with multiple other organizations, is engaged in a worldwide initiative to promote the practice of High Value Care (HVC). The goals of the HVC initiative are to improve health care outcomes by providing care of proven benefit and reducing costs by avoiding unnecessary and even harmful interventions. The initiative comprises several programs that integrate the important concept of health care value (balancing clinical benefit with costs and harms) for a given intervention into a broad range of educational materials to address the needs of trainees, practicing physicians, and patients.

HVC content has been integrated into MKSAP 18 in several important ways. MKSAP 18 includes HVC-identified key points in the text, HVC-focused multiple choice questions, and, for subscribers to MKSAP Digital, an HVC custom quiz. From the text and questions, we have generated the following list of HVC recommendations that meet the definition below of high value care and bring us closer to our goal of improving patient outcomes while conserving finite resources.

High Value Care Recommendation: A recommendation to choose diagnostic and management strategies for patients in specific clinical situations that balance clinical benefit with cost and harms with the goal of improving patient outcomes.

Below are the High Value Care Recommendations for the Dermatology section of MKSAP 18.

- There is a generic equivalent in each class of topical glucocorticoids.
- Cost-effective treatment of hand dermatitis includes topical emollients such as petrolatum and minimizing hand washing (see Item 54).
- Combined topical glucocorticoids and antifungal agents should be avoided.
- Use plain petrolatum in place of topical antibiotics on clean wounds.
- Over-the-counter treatment of seborrheic dermatitis includes selenium sulfide or zinc pyrithione shampoos.
- Discontinuation of the causative drug is the first step in treating drug reactions.
- Topical antibiotics should not be used as monotherapy for acne.
- The diagnosis of folliculitis can be made from the clinical presentation.
- Pruritus may persist for weeks after eradication of scabies and does not require retreatment.
- Most "spider bites" are actually misdiagnosed folliculitis or furuncles.
- Excision of dysplastic nevi is reserved for lesions that are changing in size and color, are symptomatic, or stand out from other nevi.
- Evaluation for urticaria is not recommended unless history suggests a specific cause.
- A gluten-free diet is first-line treatment for dermatitis herpetiformis.
- All forms of lupus benefit from sun avoidance and a broad-spectrum sunscreen.
- Heliotrope rash and Gottron papules are pathognomonic for dermatomyositis.
- Löfgren syndrome is pathognomonic for sarcoidosis.
- Do not screen for susceptibility to Stevens-Johnson syndrome and toxic epidermal necrolysis with HLA-B*1502 and HLA-B*5801.
- To avoid unnecessary treatment, obtain culture or microscopic confirmation of onychomycosis.
- Treatment of eczema, venous insufficiency, and interdigital tinea infection can decrease the risk of recurrent cellulitis (see Item 20).
- Routine systemic antibiotics are not indicated for venous stasis ulcers.
- Actinic purpura is a normal sign of aging and requires no additional testing.

Dermatology

Approach to the Patient with Dermatologic Disease

General internists, in their day-to-day clinical interactions, will often be called upon to evaluate dermatologic problems. A thorough understanding of the skin and its associated structures is required (**Figure 1**).

Morphology

Morphology of skin lesions can be categorized as primary or secondary. Primary skin lesion morphology is the appearance of a rash or growth in its initial or unaltered state. Dermatologic conditions can be categorized as growths or rashes. Growths are localized areas of abnormal skin, whereas rashes are more widespread in appearance. Over time, with itching or rubbing, secondary skin changes may occur.

Table 1 lists primary and secondary skin lesions. Other important characteristics of skin lesions include color, distribution, grouping, and configuration. Rather than focusing initially on identification of specific rashes and their characteristics, a differential diagnosis should be developed based on morphologic features of the primary skin disease. For example, a linear pattern is often seen in contact dermatitis, a grouped pattern is seen in herpes viral infections, and tinea infections are often annular.

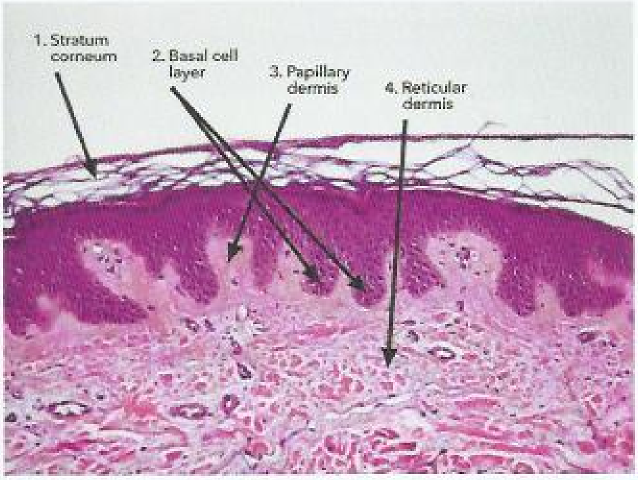

FIGURE 1. Structure of the skin showing: (1) Stratum corneum; (2) Basal cell layer; (3) Papillary dermis; and (4) Reticular dermis.

TABLE 1. Types of Skin Lesions

Primary Skin Lesions	**Characteristics**
Macule	Small flat discoloration of the skin typically <1 cm in diameter
Patch	Flat discoloration of the skin >1 cm in diameter often with surface change, such as scale
Papule	Small <1 cm elevation of the skin, solid in nature
Plaque	Flat-topped "plateau-like" elevation of the skin >1 cm in diameter
Nodule	Space-occupying lesion within the dermis; larger than a papule and located deeper
Cyst	Fluid-filled nodule containing fluid that is expressible
Vesicle	Small clear fluid-filled blister <1 cm
Bulla	Larger clear fluid-filled blister >1 cm
Pustule	Vesicle filled with purulent material
Atrophy	Loss of one or more portions of the skin
Burrow	Serpiginous epidermal streaking/ disruption caused by scabies mite
Comedo	Noninflammatory lesion caused by keratin debris within the sebaceous gland/hair follicle orifice; can be open or closed
Telangiectasia	Visibly dilated, but not palpable, blood vessel in the epidermis
Wheal/Hive	Transient, edematous, erythematous papule or plaque
Secondary Skin Lesions	**Characteristics**
Crust	Dried serous fluid commonly derived from blisters or pustules; often moist and yellow or brown
Excoriation	Defect in the epidermis often caused by scratching
Fissure	Linear break in the epidermis, usually along skin lines on the palms or soles
Lichenification	Visible thickening of the stratum corneum resulting in accentuation of the normal skin lines
Scale	Thickened stratum corneum; often dry and white or gray
Ulcer	Full-thickness destruction of the epidermis into the underlying dermis

Physical Examination

No standardized method has been developed for how to best perform a full-body skin examination, but experts agree that patients should be fully undressed and covered with an examination gown. Attempting to perform a full-body skin examination by having patients lift their shirt or roll up their sleeves is insufficient. Proper lighting is essential, as side lighting can often detect subtle elevations of the skin. A systematic approach is recommended. One method is to start with the head and neck, working down to the torso, upper extremities, and lower extremities. Care should be taken to ensure that the digits, umbilicus, and scalp are thoroughly examined. A full-body skin examination should take 2 minutes. The routine skin examination may be incorporated into the complete physical examination by assessing the torso when auscultating the heart and lungs, the arms while checking blood pressure and pulse, and the back while listening to the lungs. The skin examination is a good time to reinforce ultraviolet light protection techniques and review the signs and symptoms of skin cancer (see Common Neoplasms). The most recent U.S. Preventive Services Task Force (USPSTF) statement found insufficient evidence to screen adults for skin cancer, including persons with increased risk of skin cancer.

Rashes in persons with skin of color may be harder to detect since the pink-red color that is a sign of inflammation can be more subtle on darker skin. Persons with skin of color often have normal variations in skin color with areas of hyperpigmentation along the gingiva and lines of demarcation on the trunk and extremities. Scrapes, bug bites, or acne often heal with hyperpigmentation. Areas of active inflammation from seborrhea, eczema, or psoriasis may develop hyper- or hypopigmentation.

Diagnostic Tests for Skin Disorders

Diagnostic tools and tests that may augment the physical examination include preparation of specimens using potassium hydroxide (KOH), wet mounting, or Tzanck preparations; and use of a Wood lamp or a dermatoscope to visualize lesions. These techniques and tools are easy to use and have minimal equipment requirements; however, skill and experience are necessary for accurate and reliable interpretation.

If tinea or candida is suspected, a scraping of the skin at the leading edge of the rash is done. The scale is placed on a microscope slide, and KOH is applied to the specimen. The presence of branching hyphae indicates tinea, whereas the presence of pseudohyphae indicates candida. Similarly, a wet mount is done when evaluating for scabies. In this case, mineral oil is used in place of KOH. Mineral oil will allow the scabies mite to stay alive and will aid in detection.

A Wood lamp is an inexpensive ultraviolet light that can be used to evaluate hypo- and depigmentation as seen in vitiligo. It can also detect skin fluorescence associated with erythrasma and the urine fluorescence in patients with porphyria cutanea tarda. The Tzanck preparation can detect multinucleated giant cells within a blister cavity, thus determining a herpes viral infection. The Tzanck preparation does not distinguish between members of the herpes virus family. A hand-held microscope, called a dermatoscope, is a tool used predominately to help with the evaluation of pigmented skin lesions.

In addition, no office is complete without a camera and the capability to store photographs. Serial photographs can be used to follow the progress or improvement of a rash, to follow changes in a pigmented nevus, or to document the location of biopsy sites for proper location.

The clinician must determine whether a patient has a dermatologic emergency or urgency that requires immediate intervention or referral. **Table 2** describes situations that mandate immediate intervention or referral to a specialist.

KEY POINTS

- Rather than focusing initially on identification of specific rashes and their characteristics, a differential diagnosis should be developed based on morphologic features of the primary skin disease.
- The best method to evaluate dermatologic conditions is the full-body examination.

TABLE 2. Dermatologic Emergencies
Widespread erythema or erythroderma (drug eruption, bacterial toxin-mediated disease, severe psoriasis)
High fever and widespread rash (severe drug eruptions, rickettsial diseases)
Diffuse peeling or sloughing of skin (toxic epidermal necrolysis, infection)
Dark, dusky, purple areas of painful skin (impending skin loss from infection or severe drug eruption)
Mucosal inflammation, erosions, or ulceration (severe drug eruption, autoimmune blistering disease with high risk of morbid scarring)
Widespread blistering (autoimmune blistering disease, infection, severe drug eruption)
Purpura, particularly "retiform" or lacey, patterned purpura (vasculitis, vasculopathy, infection, autoimmune disease)
Broad areas of exquisitely painful skin out of proportion to clinical examination findings (necrotizing fasciitis)
Angulated purpura of the distal extremities (sepsis, autoimmune phenomena)
Palpable purpura (small vessel vasculitis from infection, medications, or autoimmune reactions)
Immunosuppressed, particularly patients with neutropenia, with skin lesions of unknown cause in the setting of fever, particularly red or purple nodules (skin signs of infection in immunosuppressed hosts)
Purple or necrotic skin lesions in immunosuppressed hosts (angioinvasive fungal infection)
Rapidly growing lesions in immunosuppressed hosts (infection, malignancy)
Worrisome pigmented lesions warrant urgent (not emergent) referral and evaluation (melanoma)

Therapeutic Principles in Dermatology

General Considerations

The effectiveness of a topical medication depends largely on its ability to be absorbed through the skin. Absorption is dependent on the chemical structure of the medication, its concentration, skin hydration, skin thickness, and the delivery vehicle.

In general, ointments have a higher potency than creams, which in turn have a higher potency than solutions or suspensions. The various vehicles that are available are listed in Table 3. Creams rub in and dissipate without leaving a residue, and patients tend to favor their use. The alcohol content and drying nature of gels can cause burning and stinging on non-intact skin. An occlusive vehicle such as an ointment increases penetration, but adherence may be low because of its greasy feel.

Table 4 outlines the various categories of topical medications, including those most frequently used and the indications for which they are used.

TABLE 3. Vehicles for Topical Medications

Vehicle	Characteristics
Cream	Equal mixture of oil and water with a smooth texture and whitish in color
	Easily rubs in and leaves minimal residue
	High patient preference because of aesthetic feel and appearance
Foam	Preparation that merges a gas (propane or butane) with the medication
	Allows the medication to be dispersed within a field of minute bubbles
	Used predominantly in terminal-hair-bearing skin
Gel	Semisolid vehicle with alcohol base
	Drying in nature
	Irritating to broken skin due to alcohol content
Lotion	Thicker in nature than a solution due to its increased emollient properties
	Base is typically water
	Easy to apply on large areas
Ointment	Oil in water mixture with a transparent clear appearance and greasy/oily texture
	Most occlusive of the vehicles
	Highest viscosity
	Difficult to use under clothing, on hands/fingers of an active person
Patch	Unique vehicle that is applied to skin
	Standardized method of releasing medication over time
Powder	Solid particulate preparation
	Typically used in skin folds to aid in moisture control and to reduce skin-on-skin friction
Solution	The active medication is suspended in a water or alcohol base
	Viscosity of water, easy to apply to scalp/hair-bearing areas
Suspension	Oil and water mixture that separates when allowed to sit
	Must be shaken thoroughly before use

Topical Glucocorticoids

Topical glucocorticoids are used for their anti-inflammatory effects. Because they are applied directly to the area of involvement, systemic adverse effects are minimized. Topical glucocorticoids are classified by their potency level. One should become comfortable with one in each class from weak to ultra potent. There is a generic equivalent in each class, allowing for a cost-effective approach (**Table 5**).

In general, twice-daily dosing is the most common dosing schedule, and the medication should be applied in a thin film. A rule of thumb is that 30 grams of a topical glucocorticoid will be enough to cover the entire surface of a 70 kg adult, once. Proportionately less is needed for smaller areas.

Topical glucocorticoids may cause striae, easy bruising, atrophy, and telangiectasia. Side effects are most frequently seen when using higher potencies for longer periods of time; in areas of thin skin (such as the face); skin folds; or when used under occlusion. Use of glucocorticoids around the eyes can exacerbate glaucoma and cause cataracts.

TABLE 4. Frequently Used Topical Medications

Medication	Indications
Topical glucocorticoids	Inflammatory dermatoses
Topical antifungals	Cutaneous fungal infections
Terbinafine, nystatin, econazole, miconazole, ciclopirox, clotrimazole	
Topical retinoids	
Tretinoin, adapalene	Acne
Tazarotene	Psoriasis
Topical antibiotics	
Mupirocin, neomycin, bacitracin	Antibacterial agents
Erythromycin, clindamycin	Acne
Metronidazole	Rosacea
Topical chemotherapy	
5-fluorouracil	Actinic keratosis
Antiparasitic	
Permethrin	Scabies
Vitamin D analogues	
Calcipotriene	Psoriasis

TABLE 5. Potency and Examples of Topical Glucocorticoids

Potency	Glucocorticoid
Weak	Hydrocortisone 1.0% or 2.5%
Low	Desonide 0.05%
	Triamcinolone acetonide 0.025%
	Fluocinolone acetonide 0.01%
Medium	Triamcinolone acetonide 0.1%
	Fluocinolone acetonide 0.025%
	Betamethasone valerate 0.1%
	Fluticasone propionate 0.05%
	Hydrocortisone butyrate 0.1%
	Hydrocortisone valerate 0.02%
High	Betamethasone dipropionate 0.05%
	Fluocinonide 0.05%
	Halcinonide 0.1%
	Amcinonide 0.1%
	Desoximetasone 0.25%
	Triamcinolone acetonide 0.5%
Ultra	Augmented betamethasone dipropionate 0.05%
	Clobetasol propionate 0.05%
	Halobetasol propionate 0.05%
	Diflorasone diacetate 0.05%
	Flurandrenolide tape

Topical Antifungal Agents

Topical antifungal agents are used to treat tinea or candida infections. Topical azole antifungal agents are suitable for treatment of localized infection, whereas oral agents are used to treat recurrent, recalcitrant, or widespread disease.

Topical glucocorticoids are frequently commercially combined with topical antifungal agents (clotrimazole-betamethasone). These combinations should be avoided. The use of a combination drug can worsen some tinea infections and when used in the groin area has a high risk of causing striae.

Topical Immunomodulators

Topical immunomodulators (tacrolimus ointment and pimecrolimus cream) can be used in place of topical glucocorticoids on the face, in skin folds, or in occlusive areas of the body (axilla/groin) for an extended period of time without the development of atrophy, striae, and telangiectasia. These medications have a black box warning for the rare development of skin cancer and cutaneous lymphoma.

Topical Retinoids

Topical retinoids are used frequently in the treatment of acne and psoriasis. They are vitamin A analogues with effects on keratinocyte proliferation and differentiation. Use should be avoided in pregnancy due to the risk of teratogenicity.

Topical Antibiotics

Clindamycin and erythromycin are two topical antibiotics used in the treatment of acne. They are well tolerated and have few to no side effects. Bacterial resistance has been shown to occur when using the agents as solo therapy. The combination of benzoyl peroxide and a topical antibiotic has shown to limit bacterial resistance. Over-the-counter combination antibiotics are used frequently. They typically have minimal side effects. The most frequent side effect is allergic contact dermatitis. This is seen with neomycin and bacitracin.

Phototherapy

When taken 2 hours before ultraviolet A (UVA) light exposure, oral psoralen increases the absorption of UVA. Historically, the combination of psoralen plus UVA (PUVA) phototherapy for the treatment of psoriasis has been shown to be effective but significantly increased the risk for developing skin cancer. Newer phototherapy units using a narrow band of ultraviolet B (UVB) has been shown to be safe and effective with a much smaller risk of skin cancer.

KEY POINTS

- Topical glucocorticoids can avoid the adverse effects of systemic glucocorticoid therapy but can cause striae, easy bruising, atrophy, and telangiectasia.
- There is a generic equivalent in each class of topical glucocorticoids, allowing for a cost-effective approach. **HVC**
- Combined topical glucocorticoids and antifungal agents should be avoided. **HVC**

Common Rashes

Eczematous Dermatoses

Eczematous dermatoses are common inflammatory conditions that present as pruritic, erythematous patches or plaques that may show weeping or dry scaling at various stages. These dermatoses lead to impaired skin barrier function, often allowing for secondary bacterial infections.

Treatment includes avoidance of known triggers, use of mild cleansers followed by immediate application of fragrance-free emollients and topical anti-inflammatory medications.

Atopic Dermatitis

Atopic dermatitis commonly presents on the face and flexural surfaces, such as the popliteal and antecubital fossae (**Figure 2**). Excoriations and thickening (lichenification) of the skin from scratching often accompany other signs of the atopic triad (allergic rhinitis, asthma, and eczema). The pathogenesis is

FIGURE 2. Atopic dermatitis showing skin thickening (lichenification) due to scratching and dry scaling in the popliteal flexure.

thought to be caused by a mutation in filaggrin, a protein in the epidermis important in the barrier function of the skin. Affected skin is often secondarily infected by *Staphylococcus aureus* due to a decrease in antimicrobial peptides. The use of fragrance-free, non–soap-based cleansers and moisturizers along with topical glucocorticoids is the primary treatment.

Topical calcineurin inhibitors, such as tacrolimus and pimecrolimus, are steroid-sparing agents useful for areas such as the face and skin folds where permanent atrophy from long-term or potent topical glucocorticoid use is a concern.

Contact Dermatitis

Pathophysiology and Evaluation

There are two types of contact dermatitis: allergic and irritant. Allergic contact dermatitis is a type IV, T-cell–mediated, delayed hypersensitivity reaction. On re-exposure to a specific allergen, sensitized T-cells trigger an inflammatory cascade, leading to an eczematous eruption at the site of contact; rarely, a widespread eruption (id reaction) may occur. Irritant contact dermatitis is more common than allergic contact dermatitis and is not immune mediated. Irritant contact dermatitis occurs from direct damage to the skin from harsh chemicals, soaps, or detergents.

Discovering the cause of contact dermatitis is essential to its treatment and prevention. A detailed history can help identify the cause, but often epicutaneous patch testing is needed to identify the source (**Figure 3 A** and **Figure 3 B**). For patch testing, a number of standardized chemicals are applied to the skin and removed 48 hours later. Evaluation is performed at the time of patch removal and again 5 to 7 days later to assess for redness and eczematous reaction at any of the sites. Because allergies can develop over time, a long history of using a product without a problem does not exclude that product as a potential trigger.

Common Causes of Allergic Dermatitis

Urushiol, the allergen that is a common cause of allergic contact dermatitis, is found in plants such as poison ivy, oak, and sumac, which are members of the genus *Toxicodendron* (formerly *Rhus*). Clinically, it presents with intensely pruritic, often linear, vesicular papules, plaques, and vesicles (**Figure 4**). Lesions can present at different locations at different times up to 14 days after exposure in sensitized patients. Fluid from vesicles and blisters is not antigenic. After exposure, patients should remove any contaminated clothing and gently wash the skin with soap and water. It is critical for those sensitive to these antigens to avoid inhaling any smoke resulting from the unintentional or inadvertent burning of these plants as the smoke contains allergenic plant particles.

Nickel, another common allergen, is commonly found in everyday items such as jewelry, zippers, cell phones, and even medical devices. Eczematous dermatitis of the lower abdomen is a common presentation of a nickel allergy from a snap or

FIGURE 3. (*A*) Epicutaneous patch testing is commonly applied to the back to evaluate for allergic contact dermatitis. (*B*) The erythematous patch identified 48 hours after epicutaneous patch testing indicates a positive reaction to a specific allergen (methylisothiazolinone).

FIGURE 4. Linear erythematous plaques and vesicles are commonly seen in allergic contact dermatitis from poison ivy.

belt buckle. Patients may use a commercially available nickel test kit to identify items that contain nickel.

Fragrances are also common allergens found in many cosmetic products, moisturizers, and detergents. They may also be present as flavoring agents of toothpastes, mouthwashes, and food beverages.

Neomycin and bacitracin are commonly used for wound care. They can cause an allergic contact dermatitis that mimics a wound infection. Given the prevalence of sensitivity to these products, patients should use plain petrolatum in place of topical antibiotics to aid healing of clean wounds.

Almost all household cleansers and personal hygiene products contain preservatives that can produce allergic contact dermatitis. Certain occupations also are at increased risk of allergic contact dermatitis (**Table 6**).

KEY POINT

HVC
- Use plain petrolatum in place of topical antibiotics to aid healing of clean wounds and avoid developing allergic contact dermatitis.

Treatment of Contact Dermatitis

Avoidance of the causative agent is preventive and curative. Topical glucocorticoids are used while the patient and clinician work together to identify and eliminate the source. Severe allergic contact eruptions may necessitate a 2- to 3-week taper of systemic glucocorticoids. Because of the risk of rebound dermatitis, shorter courses of systemic glucocorticoids are not recommended.

Lichen Simplex Chronicus

Lichen simplex chronicus is a condition caused by repetitive scratching or rubbing. Predisposing conditions include atopic dermatitis, xerosis, and psychiatric conditions such as obsessive-compulsive disorder. Lichen simplex chronicus manifests as thickened plaques with erythema and hyperpigmentation (**Figure 5**). Exaggerated skin markings are seen on the surface of the skin as well. Common sites include the genitals, back of the neck, wrists, ankles, and lower legs. Lichen simplex chronicus is treated with moisturizers, high and ultrapotent topical glucocorticoids, and intralesional glucocorticoid injections.

Intertrigo

Intertrigo is dermatitis involving adjacent skin folds (axillary, inframammary, abdominal, and inguinal) (**Figure 6**). Predisposing conditions include obesity, friction, occlusion, and factors that interfere with immune response, such as

TABLE 6. Common Contact Allergens

Contact Allergens	Occupations/Exposures
Benzophenones	Sunscreens (contact and photocontact dermatitis)
Balsam of Peru	Common fragrance in personal care products and foods
Methacrylate	Dental fillings, cement for joint replacement (orthopedic surgeons and dentists)
Methylisothiazolinone	Baby wipes, personal care products
Paraphenylenediamine	Permanent hair dye
Formaldehyde and formaldehyde-releasing preservatives (Quaternium-15)	Cosmetics and personal care products
Rubber accelerators (carba mix, thiurams, benzothiazoles)	Shoe and glove dermatitis; common in health care workers
Cocamidopropyl betaine	Personal care products (shampoos)

FIGURE 5. As atopic dermatitis becomes chronic, the skin becomes lichenified with accentuated skin lines (lichen simplex chronicus) and, particularly in dark skin, hyperpigmented.

FIGURE 6. Intertrigo, a chronic recurrent skin condition seen in obese patients, is caused by moist conditions in skin fold areas and is worsened by heat and exercise. The rash is confined to the intertriginous areas and does not extend beyond these boundaries. Secondary infection with *Candida* may occur, as with this patient. Clues to *Candida* infection include small red papules on the periphery of the rash.

diabetes mellitus. Intertrigo presents with erythematous, macerated plaques. Secondary infection with *Candida* is common and may be suspected by the presence of multiple small red papules and pustules that surround the main rash (satellite pustules).

Treatment of intertrigo consists of drying the area and use of agents such as antifungal powder, to reduce moisture and maceration and to prevent secondary yeast infection. Short courses of low-potency topical glucocorticoids may be added to treat the associated inflammation. If secondary *Candida* infection is suspected, concomitant treatment with topical antifungal agents can be added.

Hand Dermatitis

Hand dermatitis often results from a combination of causes such as excessive hand washing, contact dermatitis, atopic dermatitis, or dyshidrotic eczema (pompholyx). It is most commonly seen in patients who hold jobs involving frequent or prolonged exposure to water, chemicals, and occlusive gloves (health care, house cleaning, food preparation, hairstyling). It is characterized by pruritic, erythematous plaques on the palmar and dorsal hands, which can lead to fissuring and lichenification over time (**Figure 7**). Dyshidrotic eczema presents with vesicles on the palms and sides of the fingers.

The differential diagnosis of hand eczema includes tinea, psoriasis, and scabies. The entire body should be examined for other rashes that may help differentiate hand dermatitis from these other rashes. If tinea is suspected, the feet should be examined for tinea pedis and onychomycosis (two feet-one hand syndrome).

Treatment includes topical emollients such as petrolatum. A potent topical glucocorticoid may be necessary during flares. Triggers should be identified and avoided, and hand washing minimized. White cotton glove liners are recommended inside of rubber gloves when working with chemicals and water.

Xerotic Eczema

Also called eczema craquelé or asteatotic eczema, xerotic dermatitis is often seen on the lower extremities of older persons. Dry weather and excessive bathing are known inciting factors. The lesions are erythematous with plate-like cracked scale, often resembling a dried up creek bed (**Figure 8**). Although aging is the most common cause, hypothyroidism or medications such as diuretics may be implicated.

FIGURE 7. Hand dermatitis with findings of palmar edema, erythema, desquamation, and fissuring.

FIGURE 8. Severe xerotic eczema is characterized by redness and a "tile-like" pattern on dry skin (xerosis) with evidence of trauma from scratching. This typically occurs during midwinter in northern climates.

Treatment consists of thick emollients and potent topical glucocorticoids for a 2- to 3 week course.

Nummular Eczema

Nummular eczema, also called discoid eczema, is characterized by coin-shaped, pruritic, scaly plaques (**Figure 9**). This form of eczema is common on the extremities. The round shape may lead to confusion between this form of eczema and other conditions, such as tinea corporis, nummular psoriasis, or contact dermatitis. Tinea corporis often has a partially cleared center and scaling at the periphery. Psoriasis is often located on the elbows, knees, scalp, or intergluteal cleft and has larger, thicker white scale. Contact dermatitis may be suggested by location on the body that matches contact with a potential allergen.

Potent topical glucocorticoids and emollients are the preferred treatment.

Stasis Dermatitis

Stasis dermatitis, which can be very pruritic and erythematous, is common in patients with chronic lower extremity edema, most commonly secondary to venous stasis (**Figure 10**). Symptoms are often bilateral with medial distal leg predominance, although it may be unilaterally symptomatic. Dependent edema, hyperpigmentation, and dilated veins are common associated findings. Symptoms can be managed topically with glucocorticoids and emollients, but the condition will not significantly improve until the edema is addressed with leg elevation and compression stockings. Because of a similar clinical presentation, stasis dermatitis can be misdiagnosed as cellulitis; however, cellulitis is usually unilateral, more acute in onset, and often associated with pain, leukocytosis, and occasionally fever.

FIGURE 9. The coin-shaped erythematous plaques are characteristic of nummular dermatitis.

FIGURE 10. Stasis dermatitis characterized by edema, bilateral erythematous patches, weeping vesicles, ankle varicosities, and hyperpigmentation.

KEY POINTS

- Allergic contact dermatitis is a type IV T cell–mediated delayed hypersensitivity reaction and is best diagnosed with epicutaneous patch testing.
- Hand dermatitis is characterized by pruritic, erythematous plaques on the hands and results from a combination of causes, such as excessive hand washing, contact dermatitis, atopic dermatitis, or dyshidrotic eczema (pompholyx).
- Stasis dermatitis is sometimes misdiagnosed as cellulitis; however, cellulitis is usually unilateral, more acute in onset, and often associated with pain, leukocytosis, and occasionally fever. HVC

Papulosquamous Dermatoses

Papulosquamous dermatoses are characterized by scaly papules and plaques caused by inflammation of the epidermis.

Psoriasis

Psoriasis is a chronic, inflammatory dermatosis, typically presenting with thick, well-demarcated erythematous plaques with overlying silvery scale (**Figure 11**). It affects approximately 2% to 4% of the population. The incidence peaks at age 30 to 39 years and again around 60 years. Disease severity can range drastically with some patients having only one plaque to an erythrodermic presentation involving more than 90% of the body surface area. Psoriasis has many clinical presentations,

FIGURE 11. Psoriasis presents as well-demarcated, erythematous, polymorphous plaques with silvery scale.

the most common being plaque psoriasis, or psoriasis vulgaris. Nail psoriasis can involve both fingernails and toenails. It presents clinically with nail pitting, onycholysis (separation of nail plate from nail bed), and "oil spots" (**Figure 12**). Other less common subtypes include guttate psoriasis (commonly seen in pediatric patients), palmoplantar psoriasis (frequently with pustules as the primary lesion), and inverse psoriasis (often seen without scale in the intertriginous areas). Inverse psoriasis is frequently misdiagnosed because of lack of scale, location (flexural), and resemblance to other common dermatologic conditions such as tinea, intertrigo, and allergic contact dermatitis.

Psoriasis is a systemic disease, not just a skin problem. Approximately 30% of patients have concurrent psoriatic arthritis. Patients with severe psoriasis also have a greater risk of cardiovascular disease, which is the leading cause of death among these patients, and chronic kidney disease. Psoriasis is associated with multiple cardiovascular risk factors including obesity, hypertension, diabetes, dyslipidemia, and the metabolic syndrome. The proposed link between psoriasis and cardiovascular disease is thought to be inflammation with similar cytokines involved in both psoriatic and atherosclerotic plaques.

FIGURE 12. Nail pitting, onycholysis, and yellow-red discoloration (oil spots) are often present when the nails are involved in psoriasis.

Smoking tobacco may worsen psoriasis, and all patients should be counseled against smoking especially because of the elevated risk of cardiovascular disease. The pharmacologic treatment of psoriasis depends on the severity of the disease. Topical glucocorticoids are the mainstay of treatment for localized disease. Topical vitamin D analogues are also used as monotherapy or in combination with topical glucocorticoids. In patients with skin involvement of greater than 10% body surface area (severe psoriasis), psoriatic arthritis, psoriasis recalcitrant to topical treatments, or psoriasis in locations such as scalp or groin, systemic therapies, including phototherapy and traditional treatments such as methotrexate, acitretin, and cyclosporine, should be considered. Newer systemic therapies are the phosphodiesterase-4 inhibitor (apremilast) and biologic agents (tumor necrosis factor α inhibitors, interleukin-12/interleukin-23 inhibitors, and interleukin-17 inhibitors). These treatments target the cytokines involved in the pathogenesis of psoriasis.

KEY POINTS

- Psoriasis typically presents as thick, well-demarcated erythematous plaques with overlying silvery scale.
- Cardiovascular disease is the leading cause of death among patients with severe psoriasis.
- Topical glucocorticoids are the mainstay of treatment for localized disease; however, in patients with extensive involvement, psoriatic arthritis, psoriasis recalcitrant to topical treatments, or psoriasis in locations such as scalp or groin, phototherapy, methotrexate, acitretin, and cyclosporine should be considered.

Lichen Planus

Lichen planus is a T cell–mediated disease classically presenting as pruritic, flat-topped, violaceous papules, often on the flexural surfaces of the extremities (wrists and ankles) and mucous membranes (**Figure 13**). This disease is fairly common with an incidence of 0.2% to 1% in adults. Other variants include mucosal, genital, bullous, atrophic, and hypertrophic lichen planus. Mucosal lesions have lacy white streaks (Wickham striae) or erosions and ulcerations. There can also be nail thickening and onycholysis, which can lead to scarring around the cuticle (dorsal pterygium).

Lichen planus tends to resolve over 1 to 2 years, although oral and nail lichen planus are more persistent. Some but not all studies have shown an increased prevalence of hepatitis C infection in patients with lichen planus. Squamous cell carcinoma transformation has been reported most

FIGURE 13. Lichen planus presents as purple, flat-topped papules most commonly on the ankles and wrists.

commonly in erosive oral lichen planus and hypertrophic lichen planus.

Potent topical glucocorticoids are effective in most patients. Systemic glucocorticoids, oral retinoids, sulfasalazine, and phototherapy are reserved for severe cutaneous or persistent oral disease.

KEY POINTS

- Lichen planus appears as pruritic, flat-topped, violaceous papules, often on the flexural surfaces of the extremities and mucous membranes.
- Lichen planus is treated with potent topical glucocorticoids; however, systemic glucocorticoids, oral retinoids, sulfasalazine, and phototherapy are used for severe or persistent oral disease.

Pityriasis Rosea

Pityriasis rosea is a common rash that may be related to reactivation of human herpesvirus 6 or 7. Pityriasis rosea begins as a single annular patch or plaque with fine scaling (the herald patch), typically on the trunk, followed by numerous smaller skin-colored to pink papules and plaques erupting along skin cleavage lines (**Figure 14**). This distribution on the posterior thorax can resemble a "fir tree" pattern. The herald patch is absent in up to 50% of cases, but when present it usually precedes the smaller plaques by several days up to 2 weeks.

Most patients do not need treatment, as these lesions are often asymptomatic and resolve over a few weeks to months. For patients with pruritus, a topical glucocorticoid and/or oral antihistamine can be used for symptomatic relief. Macrolide antibiotics, acyclovir, and phototherapy have all been reported to speed up resolution, but these treatments are generally not recommended. It is important to rule out secondary syphilis, which can look similar, but typically also involves the palms and soles and is usually associated with generalized lymphadenopathy.

KEY POINT

- Secondary syphilis can be mistaken for pityriasis rosea but it typically involves the palms and soles and is usually associated with generalized lymphadenopathy. **HVC**

Seborrheic Dermatitis

Seborrheic dermatitis is a common condition characterized by greasy yellow, scaly, erythematous patches in seborrheic areas (the scalp, face, ears, upper chest, axillae, and inguinal folds) (**Figure 15**). Specific areas of involvement on the face are the eyebrows, medial aspects of the cheeks, inter-eyebrow region, and the nasal ala. Men are more frequently affected than women. This disease is believed to be caused by a heightened sensitivity to lipophilic yeasts such as *Malassezia*. It is more prevalent in patients who are immunocompromised, such as those with HIV/AIDS or organ transplant patients. In HIV/AIDS patients, the severity of seborrheic dermatitis is inversely

FIGURE 14. The oval-shaped patches of pityriasis rosea often follow along skin cleavage lines.

FIGURE 15. Seborrheic dermatitis, with fine, oily scale around the medial eyebrows.

correlated with the CD4 counts, may extend beyond typical locations, and may be difficult to control. Patients with Parkinson disease or Down syndrome also have a higher prevalence of seborrheic dermatitis. Diagnosis is made clinically based on the distribution and appearance. Factors contributing to flares include sleep deprivation and stress.

Treatment includes over-the-counter medications such as selenium sulfide or zinc pyrithione shampoos. Ketoconazole shampoo and cream are effective as well. Patients should be counseled to apply the shampoo on the skin and allow it to sit for 5 minutes before washing off. Weak or low-potency topical glucocorticoids can be used in combination with antifungal treatments when severely inflamed. Oral ketoconazole is not recommended owing to the risk of liver and adrenal gland toxicity, although other oral antifungal agents may be used for severe or refractory disease. If conventional therapies are not effective, other diagnoses must be considered including rosacea, lupus erythematosus, atopic dermatitis, and contact dermatitis.

KEY POINT

HVC
- Inexpensive treatment of seborrheic dermatitis includes over-the-counter medications such as selenium sulfide or zinc pyrithione shampoos.

Miliaria

Miliaria (prickly heat, heat rash) is caused by the occlusion and subsequent rupture of the eccrine sweat ducts at various levels. An overgrowth of *Staphylococcus epidermis* may contribute to the pathogenesis in miliaria. Clinically, it presents as numerous nonfollicular 1- to 3-mm papules or pustules that can arise with any condition causing sweating and skin occlusion. Miliaria can be subtyped by the level at which the eccrine sweat glands are occluded. Miliaria crystallina is caused by an occlusion at the stratum corneum and is characterized by asymptomatic clear subcorneal vesicles that can be easily ruptured (**Figure 16**). This tends to be more common in neonates.

FIGURE 16. Miliaria crystallina with clear, fragile vesicles without inflammation.

Miliaria pustulosa describes the condition when vesicles have turbid fluid within them (**Figure 17**). Miliaria rubra is characterized by multiple small pink papules. It is the most common form and usually found on the trunk, particularly the back. It is the result of a deeper occlusion of the eccrine duct causing an intraepidermal-dermal vesicle.

Supportive therapy involves eliminating predisposing factors such as sweating and removal of occluding agents or conditions. Low-potency topical glucocorticoids can be used sparingly if symptomatic.

Transient Acantholytic Dermatosis

Transient acantholytic dermatosis, also known as Grover disease, is a relatively common benign eruption that is most often seen in middle-aged to elderly white men. The eruption presents as discrete papules, some of which may be scaly, and papulovesicles on the trunk (**Figure 18**). Symptomatically there are varying degrees of pruritus that may be associated with seasonal flares during the winter and spring. The cause is unknown, but there are specific conditions that are commonly

FIGURE 17. Miliaria pustulosa showing numerous 1-mm non-inflammatory pustules on the back of a hospitalized patient, seen in this image as small white dots.

FIGURE 18. A patient with transient acantholytic dermatosis (Grover disease) showing recurrent outbreaks of pruritic, red papules, some of which are scaly, on the back. The image also shows numerous tan-colored seborrheic keratoses.

associated including chronic sun damage, eczema, and psoriasis. Transient acantholytic dermatosis can be triggered by dry skin, sweating, increased body temperature, acute sun exposure, certain medications, and internal neoplasms. The diagnosis can be confirmed by a skin biopsy that characteristically shows acantholysis of the epidermis with variable amounts of dyskeratosis.

Treatment includes moisturizers, emollients, and medium to high-potency topical glucocorticoids. For severe and recalcitrant cases, oral retinoids, in particular isotretinoin, and psoralen with ultraviolet A (PUVA) can be used; neither is FDA approved for transient acantholytic dermatosis.

Disorders of Pigmentation

Vitiligo

Vitiligo is a common acquired autoimmune condition resulting in patchy depigmentation of the skin and is characterized by the loss of function or absence of melanocytes. Its prevalence is between 0.5% and 1.0%. Affecting both sexes equally, vitiligo can occur at any age, and it can be psychologically distressing. Clinically, it appears as completely depigmented, well-demarcated symmetric macules or patches with no scale. Its onset is insidious and asymptomatic, starting as smaller macules that gradually enlarge (**Figure 19**). It tends to be more visible in darker skin types (**Figure 20**) or in sun-exposed areas as the surrounding skin will become darker with sun exposure. The hair in the patches of vitiligo can become depigmented as well. The most commonly affected areas involve the extensor surfaces such as the dorsal hands and feet, elbows, and knees, and the periorificial areas such as around the mouth, eyes, rectum, and genitals. It can be associated with other autoimmune conditions such as diabetes and thyroid disease.

FIGURE 19. Well-demarcated symmetric patches of depigmented skin with no scale and accentuation of normal, sun-exposed skin typical of vitiligo.

FIGURE 20. Classic vitiligo with well-demarcated symmetric patches of depigmented skin with no scale in a darkly pigmented person.

Occasionally, it can be challenging to distinguish vitiligo from other conditions that cause depigmentation such as postinflammatory hyperpigmentation, tinea versicolor, pityriasis alba, and leprosy.

Postinflammatory hypopigmentation is a loss of skin pigmentation following resolution of inflammatory or infectious dermatoses. Topical or intralesional glucocorticoids can also cause hypopigmentation, which can be difficult to distinguish from postinflammatory hypopigmentation. Upon cessation of the glucocorticoid, the pigmentation will typically return. Other causes of postinflammatory hypopigmentation may include chemical irritants and destructive therapeutic procedures such as cryosurgery or laser therapy. The diagnosis of postinflammatory hypopigmentation is based upon recognition of hypomelanotic or amelanotic macules or patches that correspond to previous inflammatory lesions. If the diagnosis is in doubt, a skin biopsy may assist in identifying the responsible inflammatory lesion. Postinflammatory hypopigmentation typically resolves without specific therapy over weeks to months.

The diagnosis of tinea versicolor can be verified with a potassium hydroxide preparation showing hyphae and yeast cells. In addition, Wood lamp examination may disclose yellow to yellow-green fluorescence.

Pityriasis alba occurs in children and adolescents. Defining characteristics include patches of hypopigmentation on face, neck, upper trunk, and proximal extremities. Lesions typically manifest some border irregularity and are associated with a fine scale.

Tuberculoid leprosy presents with a small number of hypopigmented anesthetic lesions with raised margins.

Partial or complete depigmentation is also seen in idiopathic guttate hypomelanosis, a very common hypopigmentation disorder. Guttate hypomelanosis manifests as 2- to 6-mm hypopigmented round or oval macules on the trunk and

extremities of middle-aged and older persons (**Figure 21**). Idiopathic guttate hypomelanosis may be the results of chronic ultraviolet (UV) exposure, trauma, and normal aging.

Other causes of depigmentation include drug-induced leukoderma and melanoma-associated leukoderma. Leukoderma has been reported in patients with advanced melanoma treated with immunotherapy such as high-dose interleukin-2, interferon alfa, ipilimumab (anti-CTLA-4), and granulocyte-macrophage colony stimulating factor. Some genodermatoses such as tuberous sclerosis, piebaldism, and Waardenburg syndrome also cause depigmentation.

History and physical examination including a Wood lamp examination to help accentuate the depigmentation and the distribution of the lesions will help confirm the diagnosis. Lesions due to complete absence of melanin, such as vitiligo, will appear bright white and sharply delineated when examined with a Wood light. This is most helpful to identify hypopigmented or depigmented lesions in fair-skinned persons that otherwise may not be visible. Vitiligo can be associated with other autoimmune conditions such as diabetes mellitus and thyroid disease. Those conditions should be screened for,

FIGURE 21. Partial or complete depigmentation is also seen in idiopathic guttate hypomelanosis, which manifests as 2- to 6-mm hypopigmented macules on the trunk and extremities.

but otherwise treatment involves methods to normalize the pigmentary discrepancies.

Treatment for depigmented skin can be challenging, prolonged, and suboptimal. Topical therapies involve high-potency topical glucocorticoids or immunomodulators (tacrolimus, pimecrolimus). Phototherapy with UV light is also an option and can be the treatment of choice for widespread involvement. Repigmentation occurs first around hair follicles as they are thought to be the reservoirs for melanocytes. As a result, repigmented skin will initially have a speckled appearance. Depigmentation therapy can also be considered if the vitiligo is so widespread that there are only a few remaining islands of normal pigmented skin. Monobenzyl ether of hydroquinone can be applied to the remaining normal islands of skin to permanently destroy the melanocytes.

KEY POINTS

- Vitiligo is an acquired autoimmune condition that causes the loss of melanocytes and subsequent depigmentation of the skin and can be associated with other autoimmune conditions such as diabetes and thyroid disease.
- Postinflammatory hypopigmentation is a loss of skin pigmentation following resolution of inflammatory or infectious dermatoses.
- Partial or complete depigmentation is seen in idiopathic guttate hypomelanosis manifesting as hypopigmented round or oval macules on the trunk and extremities of middle-aged and older persons.

Melasma

Melasma, also known as chloasma or the mask of pregnancy, is a common acquired condition resulting in patchy hyperpigmentation of the skin on the face. It can also be seen on the upper extremities. In this condition, the melanocytes overproduce melanin due to a multitude of factors including ultraviolet radiation, genetic predisposition, and hormonal influence (pregnancy, oral contraceptives). Women and those with darker skin types are more commonly predisposed. Clinically, it presents as ill-defined, tan to dark brown, reticulated patches mostly on the sun-exposed areas of the face (malar, mandibular, and centrofacial regions) (**Figure 22**). It worsens with sun exposure. The main differential diagnoses include postinflammatory hyperpigmentation, freckles, and lentigines. Melasma will fade during the postpartum period with sun protection and discontinuation of oral contraceptives. It will take months to years for pigmentation to normalize.

Treatment can be challenging and prolonged. The mainstay of treatment is strict sun protection, avoidance or discontinuation of the causative factors, and bleaching agents. Hydroquinone is typically used with concentrations ranging from 2% (over the counter) to 4% (prescription). The use of

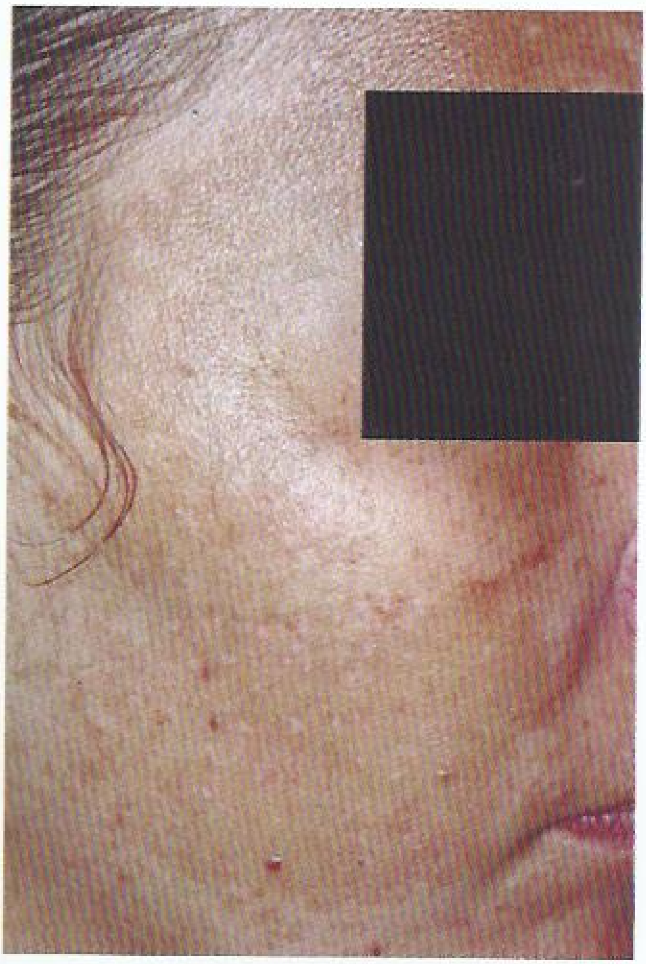

FIGURE 22. Ill-defined, reticulated hyperpigmented patches on malar cheeks typical for melasma.

hydroquinone should be monitored as it can cause drug-induced ochronosis, a bluish gray discoloration. There are combinations of hydroquinone, tretinoin, and glucocorticoid topical creams that can be used nightly. Chemical peels can also help improve appearance. Laser and light based therapies are another option for patients with refractory melasma, although they are used with caution as they can flare melasma as well. Caution must be used for darker skin types as irritating topical agents can result in inflammation and worsen pigmentation with postinflammatory hyperpigmentation.

Postinflammatory hyper- or hypopigmentation can occur after any cause of natural or iatrogenic related inflammation (acne, dermatitis, folliculitis). Postinflammatory hyperpigmentation is most common in those with skin of color. It presents as hyperpigmented macules or patches at sites of previous inflammation. Postinflammatory hyperpigmentation can cause significant psychological stress and can take months to years to resolve. The first step in treatment is to treat the underlying skin condition causing the inflammation. Hydroquinone can be used and when used in combination with tretinoin, it can augment its effect. Lasers and chemical peels can also be used with caution as any therapy that is irritating can be counterproductive.

KEY POINTS

- Melasma, which results in patchy hyperpigmentation on the face during pregnancy or with oral contraceptive use, is treated with strict sun protection, avoidance or discontinuation of causative factors, and bleaching agents such as hydroquinone.
- Postinflammatory hyperpigmentation presents as hyperpigmented macules or patches at sites of previous inflammation and is most common in those with skin of color.

Drug Reactions

Drug reactions are an important consideration when weighing a differential diagnosis for any rash, as medications can produce almost any pattern of skin disease. The most common types of cutaneous adverse reactions are exanthematous/morbilliform, urticarial, fixed drug, photosensitivity, hypersensitivity vasculitis, and the severe cutaneous adverse reactions (see Dermatologic Emergencies). Medications can also induce an array of specific diseases including psoriasis, bullous pemphigoid, and cutaneous lupus erythematosus (**Table 7**). Discontinuing the causative drug is the first step in treating drug reactions.

A morbilliform (measles-like) or exanthematous drug eruption consists of symmetrically arranged erythematous macules and papules, some discrete and others confluent. Morbilliform reactions are the most common drug reactions and are most likely a type IV delayed hypersensitivity reaction. As such, the rash appears in the first or second week after drug exposure, although subsequent exposures can produce a reaction much more quickly. Patients develop pink papules and macules that coalesce symmetrically to form plaques. The papules are often dense and monomorphic and are accompanied by varying degrees of pruritus beginning on the trunk and progressing distally across the limbs (**Figure 23**). Palms and soles are usually spared. This type of reaction is classically induced with amoxicillin use in acute Epstein Barr virus infection. Treatment involves cessation of the causative agent, systemic and/or topical glucocorticoids, and oral H_1 antihistamines. Patients should be counseled to contact their clinician if they develop fevers, skin pain, blisters, pustules, or mucous membrane involvement indicating a more serious and potentially life-threating condition.

Urticarial reactions are the second most common type of cutaneous drug reaction and represent a type I hypersensitivity with IgE-mediated release of histamine. Wheals, pink-to-red effervescent edematous plaques with a surrounding flare, appear within minutes to a few hours after exposure to the

TABLE 7. Drug Reaction Patterns

Reaction Type	Classic Agents	Time to Onset	Additional Features
Exanthematous/Morbilliform	Antibiotics (penicillins, sulfonamides, cephalosporins), NSAIDs, allopurinol, antiepileptic agents	4-14 days	No effective test for causation, gold standard to determine causation is rechallenge (not recommended)
Urticarial			
Immunologic	Penicillin, anesthetic agents, ACE inhibitors	Minutes to a few hours	Most chronic urticaria are not drug related, but aspirin may cause or exacerbate chronic cases of urticaria
Non-immunologic	Vancomycin, rifampicin, acetylcysteine, opiates, radiocontrast agents	Minutes to a few hours	Red person syndrome is related to infusion rate of vancomycin
Photosensitivity			
Phototoxic	Voriconazole, demeclocycline, doxycycline, NSAIDs, fluoroquinolones, amiodarone, celery, limes	Hours	Voriconazole phototoxicity can cause skin cancer within a few years of treatment May result in fingernail shedding
Photoallergic	Hydrochlorothiazide, sulfonamide antibiotics, sulfonylureas, tricyclic antidepressants, sunscreens, fragrances containing 6-methylcoumarin, musk ambrette, or sandalwood oil	7-10 days for first exposure, hours for subsequent	May persist after ultraviolet light exposure (fall or winter months)
Neutrophilic			
Acneiform eruptions	EGFR inhibitors, glucocorticoids, androgens, lithium, iodinated cold medications	Variable	Acneiform eruptions with EGFR inhibitors portend a favorable treatment prognosis of the cancer
Sweet syndrome	GM-CSF, All-trans-retinoic acid, SMX-TMP	Variable	
Neutrophilic eccrine hidradenitis	Cytarabine	Variable	
Pigmentation	Minocycline, amiodarone, hydroxychloroquine, antiretroviral therapy, bleomycin, gold salts	Variable	Most appear on sun-exposed areas Bleomycin may cause flagellate pigmented macules on the back Zidovudine may cause pigmentation or pigmented streaking of the fingernails Minocycline may cause hyperpigmentation on sun-exposed areas and on acne scars
Fixed drug	Sulfonamides, NSAIDs, antiepileptic agents, tetracyclines	1-2 weeks after initial exposure, 24 hours for subsequent	Pseudoephedrine-related reactions may not pigment
Vasculitis	NSAIDs, antibiotics, hydrochlorothiazide, furosemide, minocycline, TNF inhibitors, propylthiouracil, GM-CSF, levamisole	1-3 weeks, within 3 days of rechallenge	Levamisole is used to add bulk and weight to cocaine. Drug-induced vasculitis is often ANCA positive, with both p- and c-ANCA patterns

EGFR = epidermal growth factor receptor; GM-CSF = granulocyte-macrophage colony-stimulating factor; SMX-TMP = sulfamethoxazole and trimethoprim; TNF = tumor necrosis factor.

FIGURE 23. A morbilliform drug eruption consists of symmetrically arranged erythematous macules and papules, some discrete and others confluent.

CONT.

causative agent (**Figure 24**). Patients may experience a spectrum of severity, from a few isolated wheals, to angioedema if the cutaneous edema becomes deep and confluent. In the most severe cases, anaphylaxis can occur, causing airway compromise and cardiovascular collapse. Nonimmunologic histamine release secondary to medications results in redness or flushing of the skin and variable pruritus without urticaria. Treatment of urticarial reactions is dependent on severity, with minor cases treated as described for exanthematous reactions, whereas anaphylaxis may require epinephrine, fluid resuscitation, and airway protection (for more information, see Urticaria).

Fixed drug reactions recur in the same site (or sites) on the skin with each exposure. Pink-to-purple circinate plaques with central dusky discoloration or vesiculation appear most commonly on the lips, face, fingers, and genitals (**Figure 25**). The first exposure typically generates one plaque that recurs in the same location with each repeat encounter. Additional plaques may develop with subsequent exposures. Lesions typically resolve with muddy brown postinflammatory hyperpigmentation.

Photosensitivity disorders are a collection of conditions that have in common an abnormal skin response following exposure to ultraviolet radiation. Conceptually, it is useful to consider photosensitivity disorders that are idiopathic and those that are associated with application or ingestion of a drug or agent that causes cellular damage when exposed to ultraviolet radiation. Photosensitivity reactions related to exogenous agents are either phototoxic or photoallergic.

Polymorphous light eruption is the most common idiopathic photosensitivity disorder. It typically manifests before the age of 30 and is most common in fair-skinned women, first appearing in the spring and early summer. The rash will persist for weeks and resolve without scarring even with continued exposure to the sun. Lesions appear within hours of sun exposure and are found on the sun-exposed body parts. While many different types of eruptions may occur, the most

FIGURE 24. Urticarial drug reaction to amoxicillin with puffy pink plaques and an annular configuration.

FIGURE 25. A fixed drug reaction causing an intense, dark red, oval patch. The patch will gradually fade, leaving postinflammatory hyperpigmentation.

common are pruritic skin-colored or pink papules. Other variants include vesicles, bullae, and plaques. The type of lesion will remain consistent in an individual with each occurrence.

Phototoxicity can occur in anyone with a threshold concentration of the responsible chemical or drug and is more common than photoallergy. Photoallergy is a cell-mediated immune response found in previously sensitized individuals that can be elicited by small amounts of offending agent. Phototoxic reactions present as an exaggerated sunburn within minutes to hours of sun exposure. Photoallergic reactions occur more commonly after topical exposure of a sensitizing agent and present as pruritic, eczematous eruptions within 24 to 48 hours after sun exposure on sun-exposed body parts (**Figure 26**). Treatment of photosensitivity disorders includes avoidance of allergens and photosensitizing drugs and broad-spectrum sunscreens if testing has ruled out sunscreen sensitivity.

H Drugs are the most common cause of hypersensitivity vasculitis, a small vessel vasculitis. The American College of Rheumatology proposed criteria for the diagnosis of hypersensitivity vasculitis in a patient with vasculitis that are moderately sensitive and specific. Suggestive findings include palpable purpura and/or petechiae, which may be associated with fever, urticaria, arthralgia, and lymphadenopathy. These findings are typically associated with a low complement level and elevated erythrocyte sedimentation rate. The mainstay of treatment is drug discontinuation and avoidance. Severe or persistent symptoms may require systemic glucocorticoids. Medications can also cause a small/medium vessel ANCA-associated vasculitis (see Cutaneous Manifestations of Systemic Disease). H

FIGURE 26. A photoallergic drug reaction from hydrochlorothiazide. The patient is experiencing pink, scaly, eczematous plaques on the arms. Note sparing of the area that was photo-protected by wristwatch. Phototoxic reactions (not pictured) result in pink edematous macules or blistering, much like a sunburn.

KEY POINTS

- Morbilliform and urticarial reactions are the first and second most common drug reactions, respectively.
- Fixed drug reactions recur in the same site (or sites) with each exposure and consist of pink-to-purple circinate plaques with central dusky discoloration or vesiculation most commonly on the lips, face, fingers, and genitals.
- Photosensitivity disorders are a collection of conditions that have in common an abnormal skin response following exposure to ultraviolet radiation.
- Hypersensitivity vasculitis presents as palpable purpura and/or petechiae and may be associated with fever, urticaria, arthralgia, and lymphadenopathy.
- Discontinuation of the causative drug is the first step in treating drug reactions. HVC

Acneiform Eruptions

Acne

Acne is a chronic inflammatory condition affecting the pilosebaceous unit (hair follicle and sebaceous gland). Although it is most common during adolescence, acne can affect people at any age. The clinical features of acne are open comedones (blackheads), closed comedones (whiteheads), inflammatory papules and pustules, and nodulocystic lesions on the face, neck, chest, shoulders, and back (**Figure 27** and **Figure 28**).

FIGURE 27. Note conspicuous papules and pustules (<5 mm), large open comedones on the nose, and one nodule (5 mm) at the lateral eyebrow area.

FIGURE 28. Extensive acne involvement of upper and mid-back with papules, pustules, nodules, granulation tissue, postinflammatory erythema, hyperpigmentation, and scarring.

TABLE 8. Types of Acneiform Eruptions	
Acneiform Eruption	**Distinguishing Characteristics**
Perioral/ periorificial dermatitis	Papules and pustules around mouth, eyelids, or nose; more common in women; possibly induced by topical glucocorticoids
Rosacea	Flushing, telangiectasias; lack of comedones; pustules common on nose, cheeks, forehead, and chin
Folliculitis	Follicular-based papules and pustules; often on scalp or trunk; most commonly caused by *Staphylococcus aureus*
Drug induced	Monomorphic pustules and papules; common inciting medications are glucocorticoids, lithium, anticonvulsants, and epidermal growth factor receptor inhibitors
Chloracne	Appears in scrotal region, postauricular scalp; history of exposure to halogenated aromatic compounds (dioxin)
Pseudofolliculitis barbae	Common in beard area; skin-colored or erythematous papules at hair-bearing sites; more common in black men

Acneiform lesions are common, and the differential diagnosis is broad. Variations in distribution and primary lesions may provide clues to help differentiate acne from other diagnoses (**Table 8**). Finally, rapid onset of acne combined with other signs of hyperandrogenism such as hirsutism and oligomenorrhea warrants consideration of polycystic ovary syndrome, congenital adrenal hyperplasia, or an underlying adrenal or ovarian tumor.

The pathogenesis is attributed to abnormal keratinization within the hair follicle, excess sebum production (stimulated by androgens), colonization of the follicle by *Propionibacterium acnes*, and the release of inflammatory cytokines. Treatments are directed at all four mechanisms (**Figure 29**).

There are numerous classification and grading scales used for the assessment of acne. These systems are typically based on factors such as the number and severity of the acne lesions. There is no universally agreed upon system. A common grading system is to classify acne as mild, moderate, and severe. Mild acne consists of primarily comedones with few inflammatory papules and no nodules or cysts. Moderate acne involves

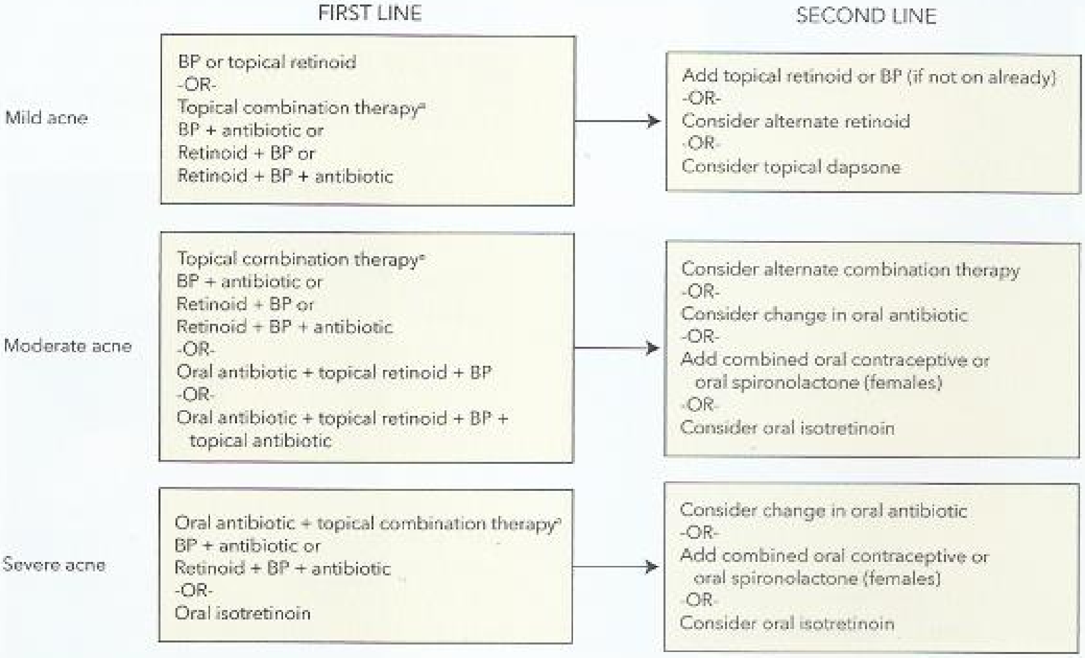

FIGURE 29. Treatment algorithm for the management of acne vulgaris in adolescents and young adults. BP = benzoyl peroxide.

[a]The drug may be prescribed as a fixed combination product or as a separate component.

Reprinted with permission from Zaenglein AL, Pathy AL, Schlosser BJ, et al. Guidelines of care for the management of acne vulgaris. J Am Acad Dermatol. 2016 May;74(5):945-73.e33. [PMID: 26897386] doi: 10.1016/j.jaad.2015.12.037. Epub 2016 Feb 17.

several comedones and inflammatory papules. A few nodules may be present as well. Severe acne is characterized by large lesion counts involving comedones and inflammatory pustules along with several cysts.

Topical retinoids (tretinoin, adapalene, tazarotene) are first-line treatments for all types of acne as they are effective for both comedonal and inflammatory acne. Retinoids help normalize the keratinization of the hair follicle and are comedolytic, thus reducing follicular plugging. They also decrease inflammatory cytokines that are activated by *P. acnes* and reduce postinflammatory hyperpigmentation. Topical retinoids may cause erythema, burning, and dryness. All topical retinoids are contraindicated in pregnancy. Adapalene and tretinoin are classified by the FDA as pregnancy category C whereas tazarotene is pregnancy category X.

Topical antibiotics are helpful in inflammatory acne as they target *P. acnes* and exhibit anti-inflammatory effects. Because of increased antibiotic resistance, topical antibiotics should not be used as monotherapy. It is recommended that topical antibiotics be combined with topical benzoyl peroxide in treatment for mild, moderate, or severe acne. Topical benzoyl peroxide has bactericidal properties and is not known to promote the development of resistant bacteria. Benzoyl peroxide may cause irritation and allergic contact dermatitis in some patients. The common topical antibiotics clindamycin and erythromycin are pregnancy category B while topical benzoyl peroxide is pregnancy category C.

Oral antibiotics are frequently used for moderate to severe inflammatory acne and acne resistant to topical treatment alone. Oral antibiotics inhibit *P. acnes* and can also decrease inflammation. Tetracycline-based antibiotics are often used as they exhibit both of these desirable properties. Oral antibiotics should be limited to 3 months, when possible, to decrease the risk of antibiotic resistance. Tetracycline-based antibiotics are pregnancy category D.

In severe nodulocystic or recalcitrant acne, oral isotretinoin should be considered. The iPLEDGE program is an FDA-approved regulatory program to prevent birth defects from isotretinoin. Isotretinoin is pregnancy category X.

Adult acne is more common in women and is related to androgenic hormones. It typically presents along the jawline and often flares with the menstrual cycle. Combined estrogen and progesterone oral contraceptives are effective acne treatments for inflammatory acne in women and girls older than age 14 years without evidence of hyperandrogenism. The use of spironolactone, an aldosterone receptor antagonist with antiandrogen activity, can also be effective in the treatment of acne. Oral contraceptives or spironolactone should be considered as second-line therapy that can to be added to other treatments in women with moderate to severe acne. Oral contraceptives are pregnancy category X whereas spironolactone is pregnancy category D.

When counseling patients with acne, it is important to stress the importance of adherence to treatment and the time course for improvement, often several weeks to months. In addition to prescribed medications, only products labeled as non-comedogenic should be used for cosmetics and moisturizers.

KEY POINTS

- The clinical features of acne are open comedones (blackheads), closed comedones (whiteheads), inflammatory papules and pustules, and nodulocystic lesions on the face, neck, chest, shoulders, and back.
- Treatment of comedonal and inflammatory acne includes topical retinoids, benzoyl peroxide, and topical antibiotics; because of increased antibiotic resistance, topical antibiotics should not be used as monotherapy. **HVC**
- Oral antibiotics are frequently used for moderate to severe inflammatory acne and acne resistant to topical treatment alone.
- Isotretinoin is indicated for severe nodulocystic and recalcitrant acne; it is associated with severe birth defects and must be administered through the federal regulatory program iPLEDGE.

Rosacea

Rosacea is an inflammatory condition that produces small pink papules and pustules on the central face in the third to sixth decades of life. Rosacea is most common among patients with light complexions from Irish and English decent. There are a variety of clinical presentations of rosacea including erythrotelangiectatic, papulopustular, phymatous, and ocular rosacea. This condition is defined by chronic inflammation of the pilosebaceous units with increased vascular reactivity. The pathogenesis of rosacea is still undetermined.

The papulopustular variant of rosacea can be confused with acne, but rosacea does not present with comedonal lesions (**Figure 30**). Telangiectasias are seen in the erythrotelangiectatic subtype (**Figure 31**). Most patients also have

FIGURE 30. Papulopustular rosacea causes erythema and pink papules of the convexities of the face, namely, the forehead, nose, cheeks, and chin.

FIGURE 31. Erythrotelangiectatic rosacea presents predominantly with patches of erythema and telangiectasia.

frequent flushing in response to triggers such as stress, alcohol consumption, heat, and excessive sunlight. The erythema of the cheeks can mimic the malar rash of systemic lupus erythematosus. Unlike lupus, however, the erythema of rosacea includes the nasolabial folds. Ocular rosacea may present in isolation or with associated skin findings. In ocular rosacea, the conjunctiva appears injected, and patients often describe a "gritty sensation." In phymatous rosacea, severe sebaceous hyperplasia and chronic inflammation lead to fibrous overgrowth of the skin creating a nodular, tumor like deformation of the facial structures. Rhinophyma is the form most frequently encountered, and it is almost exclusively found in men (**Figure 32**).

FIGURE 32. Rhinophyma, characterized by hyperplastic sebaceous glands and enlargement of the nose, in a patient with long-standing, uncontrolled rosacea.

Treatment for rosacea is targeted toward the most prominent signs and symptoms in each patient (**Table 9**). Treatment of erythrotelangiectatic rosacea focuses primarily on behavioral modifications such as: avoidance of identified triggers of flushing, proper use of sun protection, and use of gentle skin cleansers. Treatment for papulopustular rosacea includes topical metronidazole, azelaic acid, and topical ivermectin. Topical glucocorticoids should be avoided. Oral antibiotics, such as low-dose doxycycline, have been shown to help control inflammation in ocular and papulopustular rosacea. This low dose decreases side effects and reduces the prevalence of bacterial resistance. Topical brimonidine and oxymetazoline are alpha-2 agonists, which can be used for temporarily reducing erythema in rosacea. Laser therapy (pulsed dye laser) is also effective for erythema and telangiectasias. In severe cases, isotretinoin may be used. In the case of severe rhinophyma, surgery is the treatment of choice.

TABLE 9. Management of Rosacea

	Interventions	FDA Pregnancy Category[a,b]
Avoidance	Sun-protection (sunscreen or sun-protective clothing)	N/A
	Triggers: Foods (spicy, warm), alcohol, warm environments	N/A
Topical	Metronidazole, 0.75% or 1%	B
	Sodium sulfacetamide/sulfur	C
	Azelaic acid, 15%-20%	B
	Topical calcineurin inhibitors (pimecrolimus, tacrolimus)	C
	Permethrin	B
Systemic	Tetracycline antibiotics (doxycycline, 40 mg)	D
	Macrolide antibiotics	B
	Erythromycin, azithromycin, clarithromycin	C
Laser, light, and surgical	Lasers (PDL, Nd:YAG, CO_2, and others)	Avoid
	Intense pulsed light	
	Electrosurgery	

Nd:YAG = neodymium-doped yttrium aluminium garnet; PDL = pulsed dye laser.

[a]FDA categories: (A) Studies on pregnant humans show no risk (safe); (B) No clinical data of human risk but uncertain; (C) Risk cannot be ruled out; (D) Evidence of risk; (X) Contraindicated during pregnancy. See MKSAP 18 General Internal Medicine.

[b]The FDA has published changes in pregnancy and lactation labeling for prescription drugs, effective June 30, 2015 (see www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm). The pregnancy letter categories will be removed with the new labeling requirements; however, for prescription drugs that were previously approved, these changes will be phased in gradually. Labeling will include information relevant to the use of the drug in pregnant women (such as dosing and potential risks to the developing fetus), information about using the drug while breastfeeding (such as the amount of drug in breast milk and potential effects on the breastfed infant), and information regarding potential risks to females and males of reproductive potential who take the drug. Prescribing information for individual preparations should be consulted for more specific information.

KEY POINTS

- Rosacea is an inflammatory condition that produces small pink papules and pustules on the central face in the third to sixth decades of life.
- Most patients with rosacea have frequent flushing in response to triggers such as stress, alcohol consumption, heat, and excessive sunlight.
- Treatment for papulopustular rosacea includes topical metronidazole, azelaic acid, and topical ivermectin; oral antibiotics, such as low-dose doxycycline, have been shown to help control inflammation in ocular and papulopustular rosacea.

Hidradenitis Suppurativa

Hidradenitis suppurativa is an inflammatory skin disorder of the apocrine glands. This disease tends to occur more commonly in women and typically begins after puberty. Areas frequently affected are intertriginous areas such as the axilla, groin, and under the breasts. The condition is characterized by comedones, painful nodules, abscesses, draining sinuses, and scarring (**Figure 33**). Risk factors include obesity, family history, and cigarette smoking. For this reason, weight loss and smoking cessation are encouraged.

Hidradenitis suppurativa is extremely difficult to treat. No single treatment has been effective for all patients; however, there are several options available, depending on the patient's presentation and circumstances (**Table 10**). Decolonization with dilute bleach baths and chlorhexidine washes may be used in addition to topical clindamycin. Common systemic treatments are oral antibiotics, such as tetracyclines or the combination of clindamycin and rifampin. Systemic retinoids and oral zinc gluconate have been used as well with limited evidence of effectiveness. Recently, the tumor necrosis factor α inhibitor adalimumab became the first FDA-approved treatment for moderate to severe hidradenitis suppurativa.

FIGURE 33. Hidradenitis suppurativa often presents with tender subcutaneous nodules. The nodules may spontaneously rupture or coalesce, forming painful, deep dermal abscesses.

TABLE 10. Treatment Options for Hidradenitis Suppurativa

Disease Severity	Treatment Options/ Considerations
Mild	
Predominantly comedones, small papules or pustules, solitary nodules	Antibacterial washes, topical antibiotics, analgesics, warm compresses Smoking cessation and weight loss recommended for all disease severity categories
Moderate	
Multiple nodules, abscesses or cysts; scarring	Oral antibiotics with antibacterial washes and/or topical antibiotics, analgesics, wide local excision Women: Oral contraceptives, spironolactone
Severe	
Multiple nodules, sinus tracts, scarring	Referral to dermatologist or surgeon for consideration of wide local excision, tumor necrosis factor α inhibitors, or clinical trial

Surgery may be required for chronic hidradenitis suppurativa. This may involve incision and drainage or deroofing of painful abscesses and sinus tracts. Radical wide excision may also be used for refractory cases after other therapeutic options have been exhausted. Even after successful surgical treatment, recurrence is common.

Common Skin Infections

Bacterial Skin Infections

Folliculitis

Folliculitis results from inflammation of the hair follicles. It typically presents as perifollicular erythematous papules and pustules on the face, scalp, trunk, and thigh; however, it can appear on any hair-bearing area of skin (**Figure 34**). Pruritus is a common symptom. Risk factors for folliculitis are occlusive dressings or clothing, increased sweating, obesity, and long-term topical glucocorticoid use.

Folliculitis can be noninfectious (HIV-associated eosinophilic folliculitis) or infectious. The most frequent cause of infectious folliculitis is *Staphylococcus aureus*. Other common infectious causes are gram-negative bacteria (*Klebsiella* species, *Enterobacter* species) from prolonged antibiotic treatment for acne and from *Pseudomonas aeruginosa*, which is associated with hot tubs (**Figure 35**). Other causes of infectious folliculitis are the yeast *Malassezia*; viral folliculitis from

FIGURE 34. Pink papules and pustules centered on hair follicles, characteristic of folliculitis.

FIGURE 35. Erythematous papules with flare seen in hot tub folliculitis. The skin under the bathing suit is characteristically involved.

herpes simplex or varicella zoster; and *Demodex* folliculitis, which is caused by a mite found in the pilosebaceous unit of normal skin, causing a rosacea-like rash. The diagnosis of folliculitis can be made from history and clinical presentation. Bacterial cultures can be performed from pustules but are usually not necessary. Skin biopsies can be performed when causes other than bacterial infection, such as fungal or herpetic infections, are suspected.

Treatment for bacterial folliculitis is antibacterial soaps or antibacterial washes such as chlorhexidine, but topical antibiotics also can be used. Systemic antibiotics, with coverage against *S. aureus*, may be required for refractory or recurrent folliculitis. *Pseudomonas* folliculitis is usually self-limited, although oral ciprofloxacin may be effective. Gram-negative folliculitis is usually treated with ampicillin or ciprofloxacin. Refractory cases require oral isotretinoin therapy. *Malassezia* folliculitis often responds to topical antifungal agents, although oral fluconazole might be more effective. Systemic antiviral agents should be used for herpetic folliculitis, whereas topical permethrin or oral ivermectin is effective treatment for *Demodex* folliculitis.

KEY POINT

- The diagnosis of folliculitis can be made from history and clinical presentation; however, skin biopsies can be performed when causes other than bacterial infection, such as fungal or herpetic infections, are suspected. HVC

Abscesses/Furuncles/Carbuncles

H

Abscesses are soft tissue infections comprising collections of pus and bacteria within the dermis and subcutaneous tissue. They present as painful, fluctuant, erythematous nodules (**Figure 36**). Furuncles (or boils) are deeper infections of the hair follicle involving the dermis and subcutaneous tissue. Furuncles present as erythematous nodules with an overlying pustule. Multiple furuncles can coalesce into carbuncles, characterized by larger erythematous nodules with pus draining from multiple follicles. Carbuncles are typically located on the posterior neck, back, and the thighs. Fever and malaise can accompany carbuncles. *S. aureus* is the most common cause of abscesses, furuncles, and carbuncles, and there is an increasing prevalence of soft tissue infections caused by community-acquired methicillin-resistant *S. aureus* (MRSA).

Primary treatment for abscesses, furuncles, and carbuncles is incision and drainage. Gram stain and culture should be obtained from the purulent drainage when antibiotics are going to be administered (moderate and severe infections). Adjunctive oral antibiotic therapy is indicated for patients with moderate infections who have systemic signs of infection. Empiric treatment with an oral antibiotic active against MRSA such as trimethoprim-sulfamethoxazole or doxycycline is recommended. Empiric treatment with agents such as vancomycin, daptomycin, or linezolid is recommended in immunocompromised patients, patients who fail incision and drainage plus oral antibiotics, or patients with hypotension and systemic inflammatory response syndrome (severe infection). Treatment is then adjusted based on sensitivities from the culture of the purulent drainage.

FIGURE 36. A staphylococcal abscess on the posterior thigh presenting as a tender, erythematous, fluctuant nodule topped by a central pustule.

H CONT.

In the case of recurrent abscesses, other diagnoses should be considered, such as hidradenitis suppurativa, pilonidal cysts, or underlying conditions such as diabetes or HIV infection. Although MRSA decolonization in the community is controversial, the use of dilute bleach baths or chlorhexidine and topical mupirocin to the nares also may be considered for recurrent infections. H

KEY POINT

- Primary treatment for abscesses, furuncles, and carbuncles is incision and drainage; moderate infections should also be treated with trimethoprim-sulfamethoxazole or doxycycline.

H

Methicillin-Resistant *Staphylococcus aureus* in Hospitalized Patients

There has been a significant increase in hospital admissions for skin and soft tissue infections. MRSA infections have contributed to this increase and are associated with higher costs, longer hospitalizations, and higher morbidity and mortality rates.

Hospitalized patients are a common source of MRSA, but there is no consensus on effective screening measures. Active surveillance by performing screening cultures for MRSA is performed in many hospitals. Screening is usually performed by swabbing the nares, the most frequent site of colonization, although detection rates increase when screening of the nares is combined with cultures from the oropharynx and perineum. Screening policies also vary among hospitals. Some hospitals screen all admissions, whereas others screen only admissions to the ICU.

In patients who screen positive for MRSA, contact precautions using gown and gloves are effective in reducing transmission. Hand hygiene with soap and water or alcohol cleansers significantly reduces transmission and can decrease health care-associated infections. Decolonization of MRSA with daily chlorhexidine baths and the application of mupirocin to the nares twice a day for 5 days has shown to be effective in decreasing infections in the ICU.

In hospitalized patients with complicated skin and soft tissue infections, including purulent cellulitis, traumatic wound infections, and those who fail initial antibiotic therapy, therapy for MRSA should be considered pending culture data. Options include intravenous administration of vancomycin, daptomycin, telavancin, clindamycin, and linezolid. Oral linezolid is also an option. H

Impetigo

Impetigo is a superficial infection of the epidermis most commonly caused by *S. aureus* or group A streptococci. Impetigo is classified as bullous or nonbullous impetigo. It is most commonly seen in children but can present in adults as well.

Bullous impetigo is usually caused by *S. aureus*, which produces exfoliative toxins targeting the adhesion molecule desmoglein-1 between keratinocytes. This results in a localized blister formation (**Figure 37**). This same toxin is responsible for the more extensive exfoliation seen in staphylococcal scalded skin syndrome. Bullous impetigo presents as small vesicles that evolve into flaccid blisters. These blisters often rupture, leaving a collarette of scale and honey-colored crusted erosions. Nonbullous impetigo is more common and can be caused by either *S. aureus*, group A streptococci, or both. Nonbullous impetigo is characterized by erythematous papules or plaques with honey-colored crust (**Figure 38**). Satellite lesions are common. Nonbullous impetigo occurs on normal skin but can appear at areas of inflammatory conditions such as atopic dermatitis. Ecthyma is a variant of impetigo characterized by an ulcerative lesion with an overlying eschar that extends into the dermis and may be associated with lymphadenitis (**Figure 39**).

FIGURE 37. Clear, fluid-filled blisters with surrounding erythema on the legs of a patient with bullous impetigo.

FIGURE 38. Nonbullous impetigo is a superficial infection characterized by a yellowish, crusted surface that may be caused by staphylococci or streptococci.

FIGURE 39. Superficial, saucer-shaped ulcers with overlying crusts are the classic findings of ecthyma. They almost always occur on the legs or feet and are usually caused by streptococci.

Diagnosis is typically made based on clinical appearance, but bacterial culture can be obtained from the blister fluid or exudative crust to identify the pathogen. Treatment consists of washing with soap and water and removal of the crust. Topical antibiotic treatment with mupirocin or retapamulin is effective in most cases of impetigo. Oral antibiotics are recommended for patients with widespread infection if outbreaks occur involving multiple people as well as in cases of ecthyma. Recommended antibiotics are cephalexin or dicloxacillin, unless MRSA is suspected or confirmed.

H Cellulitis/Erysipelas

Cellulitis and erysipelas are both nonpurulent, superficial, spreading skin infections. Cellulitis typically refers to an infection involving the deeper dermis and subcutaneous tissue. Although erysipelas can be considered synonymous with cellulitis, it is often used to describe an infection limited to the upper dermis and superficial lymphatics. Erysipelas is also a term used when cellulitis only involves the face. Both cellulitis and erysipelas result from compromise in the skin barrier (trauma, ulcers, lymphedema, peripheral vascular disease, or previous cellulitis) allowing bacterial entry. The clinical presentation of cellulitis includes spreading patches of erythema with associated tenderness, warmth, and edema. It is usually found unilaterally on a lower extremity (**Figure 40**). Erysipelas classically has a more demarcated erythematous border than cellulitis. Systemic symptoms such as fever, tachycardia, and leukocytosis can be present in both. There are several conditions that can mimic cellulitis (**Table 11**). The

FIGURE 40. Cellulitis, a rapidly spreading, deep, subcutaneous-based infection, is characterized by well-demarcated area of warmth, swelling, tenderness, and erythema that may be accompanied by lymphatic streaking.

TABLE 11. Differential Diagnosis of Cellulitis

Disease	Clinical Characteristics
Cellulitis	Well-demarcated erythematous plaque with erythema, pain, warmth, and swelling; associated lymphadenopathy can occur. Systemic symptoms include fever, chills, and malaise. Bilateral lower extremity cellulitis suggests an alternative diagnosis.
Stasis dermatitis	Erythematous, scaly, and eczematous patches most common on the lower extremities and usually affecting both legs with associated hyperpigmentation. Findings can persist for months to years. The medial ankle can be more severely involved, and ulcerations are common in this area. The erythema also can be striking, involving the ankle and extending to below the knee. Sharp demarcation often is less common in stasis dermatitis. Overlying cellulitis can develop in the setting of stasis dermatitis.
Contact dermatitis	Pruritic, geometric, and erythematous patches with superficial scale; differentiated from cellulitis by pruritus as opposed to pain.
Panniculitis (erythema nodosum)	Painful, erythematous, subcutaneous, ill-defined nodules present bilaterally. Many panniculitides will resolve with hyperpigmentation. The acute onset of pain and erythema may be concerning for cellulitis, although distinct subcutaneous nodules would be unusual.
Deep venous thrombosis	Pain, swelling, and associated erythema and warmth in one leg, with changes often more prominent in the calf. A brightly erythematous, well-demarcated plaque is not often seen, although red, blue, or violaceous surface changes can be seen.
Herpes zoster	Grouped vesiculopustules on an erythematous patch or plaque localized to one area (dermatome). The erythema can be well defined. The presence of grouped, crusted vesiculopustules or punched out erosions is uncommon in cellulitis. Bacterial superinfection can occur.

For a complete list of potential entities in the differential diagnosis of cellulitis, please see the bibliography.

H CONT. most common cause of cellulitis is group A streptococci followed by *S. aureus*. Blood cultures and skin biopsies are not usually needed.

For immunocompetent patients with mild cellulitis/erysipelas (no systemic signs of infection), empiric oral therapy directed against streptococci is recommended with penicillin, amoxicillin, cephalexin, dicloxacillin, or clindamycin. In patients with systemic signs of infection, intravenous treatment with penicillin, ceftriaxone, cefazolin, or clindamycin is recommended. In patients who have failed oral antibiotic therapy, who are immunocompromised, who have systemic inflammatory response syndrome and hypotension, or who have evidence of deeper necrotizing infection with findings such as bullae and desquamation, surgical evaluation for debridement and empiric broad spectrum antibiotic therapy with vancomycin plus either imipenem, meropenem, or piperacillin-tazobactam are recommended. Treatment is then adjusted based on culture and sensitivity results from lesion-associated specimens.

Patients with cellulitis have annual recurrence rates of 8% to 20%. Treating predisposing factors such as edema, obesity, diabetes, and venous insufficiency might decrease recurrence. Examination and treatment of the interdigital toe spaces for tinea infection, maceration, and fissuring can also prevent recurrence. The prophylactic use of antibiotics is effective in preventing recurrence of cellulitis and should be considered in patients with more than three episodes of cellulitis per year. H

KEY POINTS

- For immunocompetent patients with mild cellulitis, begin empiric therapy with penicillin, amoxicillin, cephalexin, dicloxacillin, or clindamycin.
- HVC Treating predisposing factors such as edema, obesity, tinea pedis, and venous insufficiency may decrease recurrent episodes of cellulitis.

Pitted Keratolysis

Pitted keratolysis is a bacterial infection of the soles of the feet, or (less commonly) the palms of the hand, with characteristic appearance and odor. As the name suggests, the infection manifests as scale and pitting of the skin surface. These pits may coalesce into larger erosions (**Figure 41**). In the United States, the infection is most common among patients with hyperhidrosis and prolonged occlusion of the feet (athletes, military personnel, laborers). Other than appearance and odor, symptoms are usually minimal and limited to mild pruritus or slight discomfort. Treatment is with topical antibacterial therapy such as clindamycin, erythromycin, or over-the-counter benzoyl peroxide preparations. In addition, the use of topical antiperspirants (aluminum hydroxide) and frequent changing and washing of socks should be used to keep the feet (or hands) dry and clean. The most common causative organisms are *Kytococcus sedentarius*, *Dermatophilus congolensis*, *Corynebacterium* species, and *Actinomyces* species.

FIGURE 41. Pitted keratolysis presents with small indented pits on a background of hyperkeratosis and results from increased sweating of the feet. It is a superficial bacterial infection most commonly due to *Kytococcus sedentarius*, *Dermatophilus congolensis*, *Corynebacterium* or *Actinomyces* species.

Erythrasma

Erythrasma is a benign superficial bacterial infection of the skin. Afflicted patients report red-brown plaques in the groin, crural folds, gluteal folds, axillae, or less commonly in the interdigital or inframammary regions (**Figure 42**). The skin often has a thin, wrinkled appearance similar to cigarette paper, and patients are often misdiagnosed with a dermatophyte infection. Symptoms, limited to mild pruritus, are minimal in most patients. In the immunocompromised patient, severe invasive disease has been described. The causative organism is most commonly *Corynebacterium minutissimum*. This organism produces porphyrins that fluoresce a soft, coral red under a Wood lamp. Clinical appearance and fluorescence are the best means of diagnosis, as histopathology may be unremarkable and skin scrapings are not helpful. Treatment is best accomplished with oral erythromycin, clarithromycin, or tetracyclines, but cure with topical antibiotics is reported.

Superficial Fungal Infections

Tinea

Tinea (dermatophytosis) is classified based on body site that is involved: tinea pedis ("athlete's foot") (**Figure 43**), tinea manuum

FIGURE 42. Erythrasma presents with sharply demarcated fine, pink-to-brown scaling patches that are typically found in skin-fold areas. The rash will fluoresce a coral red with Wood lamp illumination.

FIGURE 43. Erythematous patches with peripheral scale and associated onychomycosis (onychodystrophy with subungual debris of nails) in tinea pedis.

(hand), tinea cruris ("jock itch") (**Figure 44**), tinea capitis (scalp) (**Figure 45**), tinea faciei (face), and tinea corporis (body excluding the genital area or inguinal folds) (**Figure 46**). There are three species from the genera *Epidermophyton*, *Microsporum*, and *Trichophyton* that cause superficial fungal infections in humans, *Trichophyton rubrum* being the most common.

Dermatophytosis can also be classified as anthropophilic, zoophilic, and geophilic, based on host and mode of transmission. Anthropophilic dermatophytes are found in humans, cause little inflammation, and are transmitted from human to human or through fomites. Zoophilic dermatophytes are

FIGURE 44. Tinea cruris, a dermatophyte infection of the groin, pubic region, and thighs, presents as erythematous annular to serpiginous lesions with peripheral scale and central clearing.

FIGURE 45. Kerion can be a result of tinea capitis infection and presents as painful boggy erythematous plaques with folliculitis and abscess formation.

FIGURE 46. Tinea corporis presents with a characteristic erythematous annular centrifugally growing patches with a raised rim of peripheral scale.

transmitted from animals to humans from direct or indirect contact and cause inflammation and occasionally cause suppurative dermatophytosis. Geophilic dermatophytes only occasionally infect humans through direct contact but also cause inflammatory dermatophytosis. Infection is more prevalent in hot and humid climates and in patients who are immunocompromised, particularly those taking chronic glucocorticoid therapy.

The characteristic clinical presentation of tinea corporis, cruris, and faciei is annular scaly patches with central clearing and varying degrees of inflammation. Tinea cruris spares the scrotum in contrast to candida intertrigo, which is in the differential diagnoses. Concomitant tinea pedis and cruris are not uncommon. In tinea capitis, the invasion of the hair follicle leads to small broken hairs with the surrounding scalp showing erythematous scaly patches with varying degrees of crust and numbers of pustules. Occipital adenopathy is frequently seen. The chronic form of tinea pedis and tinea manuum presents as mildly pruritic scaly patches involving most of the palms and soles in a "moccasin" or "glove" distribution (**Figure 47**). One hand and two feet tinea is a characteristic pattern of involvement. Tinea pedis can have a more acute form with 1- to 2-mm vesicles and can be extremely pruritic. The interdigital variant of tinea pedis shows fissures and maceration in the folds. Tinea incognito refers to tinea that has been erroneously treated with topical glucocorticoids, which initially decreases pruritus, but leads to a clinical presentation that is less inflammatory and can result in invasion of the follicular epithelium.

FIGURE 47. Mildly erythematous patches with fine scale that are well demarcated and are confined to the lateral foot, heel, and sole characteristic of "moccasin" type tinea pedis.

Tinea can be suspected based on clinical presentation and pruritus; however, diagnosis is based on visualization by microscopic examination of branching hyphae in the keratin (scale) using a potassium hydroxide preparation. To confirm the diagnosis, a fungal culture can be performed, which provides species identification, and is the preferred method for diagnosing tinea capitis. Hair shafts should be included in the specimen.

Dermatophytosis of non-hair-bearing skin with limited involvement can be treated topically with imidazole creams, such as miconazole, clotrimazole, and ketoconazole, applied once to twice daily for 2 to 4 weeks, ensuring that the application extends a few centimeters beyond the advancing border. Other topical agents including terbinafine 1% and ciclopirox olamine 0.77% can also be used. Unlike superficial fungal infections caused by *Candida*, dermatophytes do not respond to topical nystatin. Combined antifungal agents and topical glucocorticoids should be avoided as they can lead to increased recurrences and treatment failures. Dermatophytosis of hair-bearing skin, including tinea capitis, or those with recurrent or extensive skin involvement, should be treated with oral antifungal agents such as terbinafine or itraconazole. Tinea should be treated to prevent skin breakdown, which can be an entry port for bacterial infection.

KEY POINTS

- The characteristic clinical presentation of tinea infection is annular scaly patches with central clearing and varying degrees of inflammation.
- Diagnosis of tinea is made by microscopic examination of branching hyphae in the keratin (scale) using a potassium hydroxide preparation.
- Dermatophytosis of non-hair-bearing skin with limited involvement can be treated topically with imidazole creams (miconazole, clotrimazole, ketoconazole); however, treatment of infections on hair-bearing skin or extensive or recurrent involvement should be treated with oral terbinafine or itraconazole.

Pityriasis Versicolor

Pityriasis versicolor or tinea versicolor is caused by commensal lipophilic fungi that live in the hair follicles and stratum corneum. Pityriasis versicolor is one of the most common, chronic, superficial fungal infections and is typically found in young adults. Caused by *Malassezia furfur*, pityriasis versicolor is most common in warm, humid environments. It presents as asymptomatic, oval-to-round, minimally scaly,

hyperpigmented or hypopigmented macules that can coalesce into patches on the trunk and upper extremities (**Figure 48**).

The diagnosis of pityriasis versicolor can often be made by clinical presentation but may be confirmed by visualization of short rod-shaped hyphae and round yeast ("spaghetti and meatballs") on microscopic examination of skin scrapings using a potassium hydroxide preparation. Topical treatment using ketoconazole 2% shampoo or selenium sulfide suspension is effective. Either treatment should be applied from the upper neck to the thighs and used to wash the scalp. Oral itraconazole can be used for those with extensive disease or frequent recurrences. Because recurrences are high, weekly use of topical treatments can be preventive.

Candidiasis

Candida species, in particular *C. albicans*, can cause superficial infections in moist occluded skin such as the intertriginous areas, oropharynx mucosa, and genitals, as well as disseminated disease in immunocompromised, hospitalized patients (see MKSAP 18 Infectious Disease). Antibiotic therapy increases the number of colonizing organisms present in skin and mucous membranes leading to an increased risk of infection.

Intertrigo is an inflammatory skin disease that involves the axillae, inframammary, and inguinal folds (**Figure 49**). *Candida* is the most common secondary infection in intertrigo with obesity being an important risk factor. It presents as erythematous patches with satellite pustules that are often macerated. Diagnosis is frequently made on clinical grounds alone, but a potassium hydroxide preparation can show spores and pseudohyphae. For successful treatment, the area should be dry, and use of absorbent powers and zinc oxide paste can be helpful. Topical imidazoles and nystatin are generally effective, but recurrences are common. For widespread infection, oral fluconazole can be added.

FIGURE 49. Bright red patches and plaques with satellite papules and pustules in the intertriginous area beneath the breasts characteristic of candidiasis.

FIGURE 48. Hypopigmented scaly macules coalescing into patches on the back characteristic of pityriasis versicolor.

Chronic paronychia is associated with irritants or allergens and is caused by frequent exposure to water. Exacerbations can be caused by *Candida*, and successful treatment includes treating the underlying irritant or allergic contact dermatitis, as well as treatment with topical or oral antifungal agents, depending on the severity of the infection (see Nail Disorders).

Viral Skin Infections

Herpes Simplex Virus

For both herpes simplex virus types 1 (HSV1) and 2 (HSV2), transmission usually occurs by direct contact with infected secretions, skin lesions, or asymptomatic shedding. Both HSV1 and HSV2 can cause oral and genital lesions; however, infections with HSV1 are usually above the waist (oral, facial), whereas HSV2 infections are usually below the waist (genital). The seroprevalence of HSV increases with age, with HSV1 IgG antibodies being present in most adults. HSV2 seroprevalence increases with the number of sexual partners and high-risk sexual behaviors.

HSV causes a clinically unapparent primary infection through skin and mucous membranes where it replicates locally. This is followed by a short viremia, and the virus subsequently establishes latency through retrograde axonal transport in sensory nerve ganglions. Characteristically, HSV1 is found in the trigeminal ganglion and HSV2 in the sacral ganglion. Recurrent lesions are caused by reactivation of the virus. Symptomatic primary and recurrent infections typically remain localized and are named according to the site of infection, regardless of the HSV subtype responsible: herpetic gingivostomatitis, herpes labialis ("cold sore"), herpes facialis, and herpes genitalis.

The classic presentation is a group of painful, small vesicles on an erythematous base, transitioning to pustules and subsequent crusting of the lesions over time (**Figure 50**). Erosions or ulcers may also develop. HSV is the most common

FIGURE 50. Herpes simplex virus infection with characteristic grouped vesicles on an erythematous base that recur in the same location.

H CONT.

cause of painful genital ulcers, although chancroid also causes painful ulcers. Other infections (syphilis, granuloma inguinale, lymphogranuloma venereum) often cause nonpainful ulcerations (see MKSAP 18 Infectious Disease). However, a diagnosis based on the presence or absence of pain may be misleading.

With any sexually transmitted infection, HIV testing also is important. Symptomatic primary infections are usually more severe and of longer duration than recurrences. There is associated burning, tingling, and pain, which can be a prodrome in recurrences. Reactivation is higher in persons who are immunocompromised, and it can be triggered by trauma, ultraviolet light exposure, psychosocial stress, and fever. In herpes genitalis, recurrences are more frequent with HSV2 and in women, and asymptomatic shedding occurs in most patients with HSV2 but not HSV1.

The diagnosis is typically made on clinical grounds; however, for distinction between subtypes of HSV or from varicella zoster virus, other methods can be used (**Table 12**). Oral antiviral agents (acyclovir, valacyclovir, or famciclovir) can be used to treat primary infections, episodic or secondary recurrences, and as suppression or prophylaxis for patients with six or more recurrences per year. Oral antiviral agents are most effective when started during the prodrome of recurrences. Dosing varies for primary, secondary, and prophylaxis, as well as by site of infection and for immunocompromised patients. Topical therapies are less effective in improving symptoms and reducing disease duration. H

KEY POINTS

- The classic presentation of herpes simplex virus infection is a group of painful, small vesicles on an erythematous base, transitioning to pustules with subsequent crusting of the lesions over time.
- Oral antiviral agents (acyclovir, valacyclovir, or famciclovir) can be used to treat primary infections, episodic or secondary recurrences, and as suppression or prophylaxis for patients with six or more recurrences per year.

Varicella/Herpes Zoster

H

Varicella-zoster virus is a DNA virus that causes varicella (chickenpox), which is an acute illness with fever and an eruption of vesicles on an erythematous base that is transmitted by respiratory droplets (**Figure 51**). After primary infection, the virus remains latent in the dorsal root or cranial ganglia. Reactivation causes herpes zoster or shingles (**Figure 52**). Prodromal symptoms, such as burning, stinging, or tingling,

TABLE 12. Methods for Detecting Herpes Virus

Method	Sample	Utility
Hematoxylin and eosin staining	Skin biopsy	Characteristic histologic findings with immunohistochemistry to differentiate HSV from VZV
Direct fluorescence antibody	Unroofed vesicle	Discriminates between HSV1, HSV2, and VZV
Polymerase chain reaction	Unroofed vesicle	Discriminates between HSV1, HSV2, and VZV
Serologies	Peripheral blood	Diagnosis of primary infection with seroconversion of virus-specific IgG antibodies
Tzanck preparation	Unroofed vesicle	Multinucleated keratinocytes and cytopathic effect does not differentiate HSV from VZV. Technically difficult.
Viral culture	Unroofed vesicle	Delay of 48-72 hours but can discriminate HSV1, HSV2, and VZV; useful for antiviral sensitivities

HSV1 = herpes simplex virus 1; HSV2 = herpes simplex virus 2; VZV = varicella zoster virus.

FIGURE 51. This patient has chickenpox (primary varicella zoster virus infection), which is characterized by the simultaneous onset of fever and a cutaneous eruption. Chickenpox lesions develop in crops such that lesions in different stages of development (macules, papules, vesicles, pustules, crusted erosions) are present at the same time on any one part of the body. Also, lesions are most prominent on the trunk rather than the extremities.

FIGURE 52. Typical herpes zoster of the trunk, characterized by painful grouped vesicles on an erythematous base in a dermatomal distribution.

H CONT.

often occur in a localized region, followed by a dermatomal eruption of grouped vesicles or pustules on an erythematous base. The most common dermatomes affected are in the thoracic region. With involvement of the first division of the trigeminal nerve (forehead extending over upper eyelid, or nasal tip involvement), ophthalmologic evaluation is mandatory as herpes zoster ophthalmicus and possible blindness can result. If vesicles are noted in the external ear canal, evaluation by an otolaryngologist may be required as peripheral facial paralysis and auditory/vestibular symptoms can occur (Ramsay Hunt syndrome).

Herpes zoster can be complicated by postherpetic neuralgia and has been associated with an increased risk of cerebrovascular disease. Postherpetic neuralgia is defined as chronic neuropathic pain that persists for 3 months or more after the initial onset of herpes zoster. The risk, severity, and complications of herpes zoster, in particular postherpetic neuralgia, are increased in older patients, those with greater initial pain and more severe infection, and possibly in patients that are immunosuppressed or on immunosuppressive or immunomodulating medications.

Diagnosis of herpes zoster can usually be made by characteristic dermatomal presentation. For unusual cases or when the distinction between herpes simplex virus and herpes zoster is required, ancillary studies are available (see Table 12). Oral acyclovir, valacyclovir, or famciclovir is effective for treating herpes zoster if initiated within 72 hours of presentation and can shorten the disease course as well as help prevent postherpetic neuralgia. Current evidence is insufficient to support the addition of glucocorticoids with acyclovir to improve quality of life or the incidence of postherpetic neuralgia.

A recombinant zoster vaccine is now preferred to the live attenuated zoster vaccine in adults 60 years and older to prevent or attenuate illness caused by herpes zoster infection and to reduce the risk of postherpetic neuralgia. For individuals previously immunized with the live attenuated vaccine, revaccination with the recombinant vaccine is recommended. H

KEY POINTS

- After primary infection with the varicella zoster virus, the virus remains latent in the dorsal root or cranial ganglia, and reactivation causes herpes zoster or shingles, which presents as a painful dermatomal vesicular eruption.
- Oral acyclovir, valacyclovir, or famciclovir is effective for treating herpes zoster if initiated within 72 hours of presentation; it can shorten the disease course as well as help prevent postherpetic neuralgia.

Warts

Warts (verruca and condyloma) are caused by a human papillomavirus (HPV), which is ubiquitous. There are numerous HPV subtypes, but certain ones are associated with specific clinical lesions and are more common at certain sites (**Table 13**). Verruca vulgaris (common warts) are skin-colored digitate papules with thrombosed capillaries. Verruca plana (flat warts) are skin-colored, flat-topped papules (**Figure 53**). Condyloma acuminata (genital warts) are smooth to digitate papules that are skin-colored to tan (**Figure 54**). Verruca plantaris/palmaris (plantar/palmar warts) are exo-/endophytic papules with thrombosed capillaries manifesting as black dots when the top of the wart is pared down. HPV

TABLE 13. Human Papillomavirus Subtypes

Subtype	Clinical Lesion (Location)
1	Verruca plantaris/palmaris (soles/palms)
2, 4	Verruca vulgaris (fingers, knees, and elbows)
3,10	Verruca plana (face and legs; associated with shaving)
6,11	Condyloma acuminata
16,18,31,33	Condyloma acuminata (associated with high risk for cervical, anal, and penile cancer)

FIGURE 53. The common wart is a verrucous papule that is keratotic and exophytic.

FIGURE 54. Anogenital warts (condyloma acuminatum) present as verrucous papules over the penile shaft and foreskin with adjacent erosions after imiquimod therapy.

FIGURE 55. Molluscum contagiosum is a common cutaneous infection resulting from poxvirus infection. It occurs in young children and sexually active adults. It presents as firm, umbilicated yellow papules with varying degrees of surrounding erythema.

infection can occur at any age but is typically seen in children and young adults. Larger, more numerous lesions that are recalcitrant to treatment can be seen in immunocompromised persons.

Diagnosis is clinical. Warts are usually self-limited; however, in severe cases, including those with a protracted course or in immunocompromised persons, destructive treatments can be used. Location of the lesions has to be taken into account when selecting treatment, and can be associated with pigment change or scarring. Numerous treatments (salicylic acid, cryotherapy, tricarboxylic acid, cantharidin, and podophyllin) geared at destroying infected keratinocytes are available. All of these treatments should be repeated every 3 to 4 weeks until resolution. Larger lesions should be pared prior to treatment.

HPV vaccination is recommended for young persons to prevent cervical and anal carcinoma. Anogenital warts may also be prevented if the vaccine is effective against HPV 6 and 11 (see MKSAP 18 General Internal Medicine).

Molluscum Contagiosum

Molluscum contagiosum is caused by a poxvirus. Infection occurs in children, in adults as a sexually transmitted disease, and in patients with AIDS. The lesions are white-to-yellow smooth papules with an umbilicated center (**Figure 55**). Many patients develop a surrounding eczematous host response. They can be located anywhere on the skin, but in adults the genital area is typically involved, whereas in patients with AIDS the face is the most common area of infection and the lesions tend to be larger. Transmission is by direct contact or by fomites.

Diagnosis is based on clinical appearance, but skin biopsy on equivocal cases shows eosinophilic intracytoplasmic inclusions within keratinocytes. Molluscum contagiosum is usually self-limited, but in severe cases, those with a protracted course, or in immunocompromised persons, destructive modalities or topical medications can be used. Any of these treatments can be associated with scarring and pigment change. Destructive treatments include cryotherapy, curettage, tricarboxylic acid, cantharidin, and podophyllin. Medical treatments consist of topical tretinoin and topical imiquimod.

Infestations

Scabies

Scabies (*Sarcoptes scabiei*) infestation is characterized by intensely pruritic, crusted papules, nodules, and burrows that develop in the interdigital spaces, wrists, ankles, breasts, periumbilical area, and genitals (**Figure 56**). In older adults, the immunocompromised, or Down syndrome patients, highly contagious crusted (Norwegian) scabies occurs with extensive thick concrete-like scale. Scabies is transmitted by close personal contact, and diagnosis is performed by microscopic identification of the mites, eggs, or feces from skin scrapings prepared with mineral oil (**Figure 57**). See **Table 14** for treatment. Pruritus may persist for weeks after eradication of scabies and does not necessarily represent resistance or reinfection. "Postscabetic pruritus" can be treated with antihistamines, topical glucocorticoids, and, if severe, oral glucocorticoids can be used.

KEY POINT

- Pruritus may persist for weeks after eradication of scabies and does not necessarily represent resistance or reinfection. **HVC**

Lice

There are three types of lice that infest humans: head (*Pediculus humanus capitis*), body (*Pediculus humanus*

FIGURE 56. A burrow is present on the proximal hypothenar eminence. Scrapings of the black dot at the lower end of the burrow revealed the mite pictured in Figure 57.

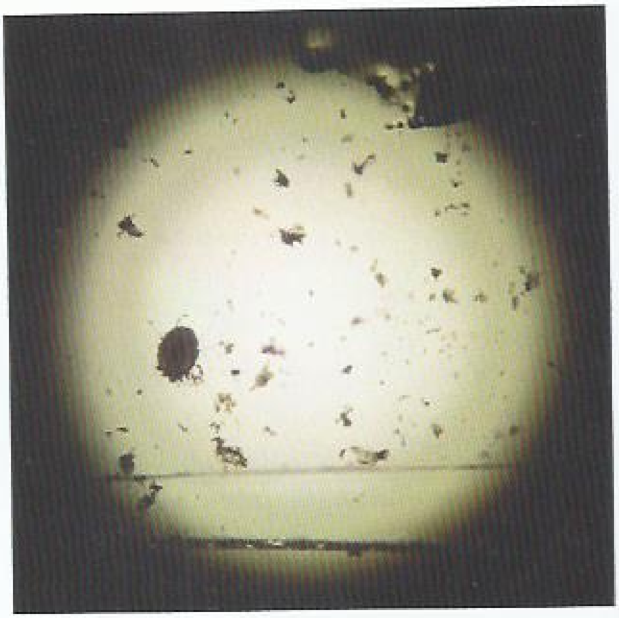

FIGURE 57. *Sarcoptes scabiei* mite seen on mineral oil preparation of skin scrapings.

TABLE 14. Treatment of Infestations

Infestation	Treatment
Scabies (including pregnant women)	1. Treat all members of the household 2. Wash and dry bedding, linens, clothing, towels in high heat; repeat in 1 week 3. Topical 5% permethrin cream applied from neck down, repeat in 7 days; emphasize use under fingernails
Crusted scabies	1. In addition to 1 and 2 above, topical 5% permethrin applied daily for 7 days, then twice weekly until cure AND oral ivermectin on days 1, 2, 8, 9, and 15. Do not use ivermectin in pregnant women.
Pediculosis capitis (head lice) AND *Pthirus pubis* (pubic lice)	1. 1% permethrin cream rinse; 0.5% malathion for resistance 2. Clear nits and eggs with fine tooth comb 3. Wash and dry clothes and bedding in high heat 4. Use petrolatum ointment for eyelash infestation
Pediculosis corporis (body lice)	1. Destroy or wash and dry clothing or bedding in high heat
Bed Bugs	1. Professional extermination 2. Wash and dry clothing and bedding in high heat; repeat in 1 week

corporis), and pubic lice (*Pthirus pubis*). Head lice live on the scalp and attach eggs (nits) to the proximal hair shaft (**Figure 58**). Transmission occurs by close personal contact or by fomites such as bedding, clothing, or hairbrushes.

Body lice live in the seams of clothing and not on the skin. Excoriations result in crusted papules or linear petechiae on the trunk, neck, and proximal arms. Maculae ceruleae are blue-brown macules from subcutaneous hemorrhage at sites of feeding.

Pubic lice (crab louse) are typically spread by sexual contact but may attach to other sites such as eyebrows or eyelashes (*Pediculosis ciliaris*). Symptoms include itching in affected area and maculae ceruleae. See Table 14 for treatment.

Bed Bugs

Relaxed international travel and pesticide regulations have led to the resurgence of the bed bug (*Cimex lectularius*). Bed bugs live in floorboards, walls, vents, or furniture and crawl to the host to feed overnight. They do not live on the human body. Bites are characteristically linearly arranged urticarial papules ("breakfast, lunch, and dinner" bites) on exposed skin (**Figure 59**). See Table 14 for treatment.

FIGURE 58. Multiple nits appearing as white adhesions to the black hair.

FIGURE 59. Bedbug bites usually occur in a series ("breakfast, lunch, and dinner"). The lesions are painless, pruritic, urticaria-like papules.

Bites and Stings

Spiders

There is often confusion in diagnosing spider bites. Most "spider bites" described by patients are actually folliculitis or furuncles; most spider bites are characterized by wheals, papules, or pustules. It is rare to see a punctum. Bites may itch or burn with most symptoms resolving in about 1 week. Bites may become secondarily infected from scratching.

Spider bites causing severe systemic symptoms are rare and are inflicted by a limited number of spiders. Each spider has a specific geographic distribution. For example, the brown recluse spider, *Loxosceles reclusa*, is found in the southern and central United States (**Figure 60**). Its bite can occasionally cause severe skin necrosis with significant pain and systemic symptoms.

KEY POINT

- Most "spider bites" described by patients are actually folliculitis or furuncles; most spider bites are characterized by wheals, papules, or pustules. HVC

Hymenoptera

H

Bees, wasps, and ants belong to the order Hymenoptera. Following a sting, the stinger should be removed to prevent continuing envenomation. Small local reactions are treated with cold compresses, whereas large symptomatic local reactions (~10 cm) may require systemic glucocorticoids to reduce swelling and pruritus. In sensitized persons, systemic reactions such as hives, flushing, or even anaphylaxis may occur. These patients should carry an injectable epinephrine pen and be referred to an allergist for possible venom immunotherapy.

Fire ants (*Solenopsis invicta*), which are mostly found in the southern United States, have sharp jaws and a posterior stinger. The ants latch with their jaws and repeatedly sting while rotating around the bite site, which results in a central papule ringed with pustules. H

KEY POINT

- Persons sensitized to hymenoptera stings should carry an injectable epinephrine pen.

FIGURE 60. Brown recluse spiders are quite shy, and their bites are often misidentified and overdiagnosed.

Worms

Cutaneous larva migrans results from hookworm penetration of bare skin. As the worm migrates through the skin, it leaves elevated serpiginous pruritic lesions (**Figure 61**). Wearing shoes outdoors (especially on the beach) prevents transmission from animal feces. Treatment is ivermectin, albendazole, or cryotherapy at the advancing edge of the eruption.

Fleas

Fleas are the one of the most common causes of papular urticaria characterized by itchy papules on the legs and arms (**Figure 62**). The cat flea (*Ctenocephalides felis*) is the most common.

FIGURE 61. Serpiginous, linear red track marks that are pathognomonic for cutaneous larva migrans. Cutaneous larva migrans (creeping eruption) is a parasitic skin disease caused by migration of the hookworm larva within the superficial layers of the skin.

FIGURE 62. Papular urticaria reaction with surrounding inflammation on the leg characteristic of a flea bite.

Cuts, Scrapes, and Burns

Minor wounds can be cleaned gently with soap and water to remove any foreign materials and then properly bandaged. A thin layer of plain petrolatum can be applied to the damaged skin surface before applying a nonadherent bandage. Topical antibiotics can be used for wounds that are in locations that have increased risk for secondary infection such as the perineum or major skin folds. Topical antibiotics such as neomycin and bacitracin have activity against gram-positive and selected gram-negative organisms but may lead to contact allergy. Mupirocin is effective only against gram-positive organisms, with little risk of contact sensitivity, although bacterial resistance is increasing.

Cuts and Scrapes

Minor cuts and scrapes should be cleaned gently with soap and water, irrigated if necessary to remove any foreign material, and dressed with a bandage. If a cut extends into the dermis and is more than a puncture, it should be sutured together. Small cuts can be glued together with topical skin adhesive. Areas with increased tension (across the knee) are best sutured.

Burns

Burns may be caused by a multitude of agents including chemical, thermal, electrical, and ultraviolet light (**Figure 63**). Thermal burns are assessed based on the amount of surface area of involvement, depth of burn, and specific area involved. Grading of burns is seen in **Table 15**. Estimating the body surface area involved is based on the rule of 9s. The head and neck represent 9% body surface area, each arm is 9%, each leg 18%, the anterior trunk is 18%, the posterior trunk is 18%, and the genital region is 1% of body surface area. Minor burns in areas of low risk for infection with a small body surface area of involvement can be treated with gentle cleansing and application of a sterile dressing with petrolatum. Wounds prone to

FIGURE 63. First-degree burn with small, red well-defined macule occurring after accidentally touching the skin with a hot curling iron.

TABLE 15. Burn Grading		
Degree	**Structures Involved**	**Signs and Symptoms**
First	Epidermis	Red and tender skin
Second		
Partial thickness	Epidermis destroyed; partial dermis	Blisters, sloughed skin, red, painful
Full thickness	Epidermis and dermis destroyed	Dry, white, yellow, or red and painful
Third	Epidermis, dermis, and fat destroyed	Dry, black, minimal pain
Fourth	Same as third degree, but also involving muscle and or bone	Dry, black, minimal pain

developing infection may be best treated with a topical antibiotic in addition to the sterile dressing.

Common Neoplasms

Benign Neoplasms

Seborrheic Keratosis

Seborrheic keratoses are benign pigmented neoplasms of keratinocyte origin that are common in adults. They are "stuck-on" papules and plaques that occur anywhere on the body but are most common on the trunk and spare the palms, soles, and mucous membranes. Seborrheic keratoses range in size from a few millimeters to several centimeters. Usually they are brown, but they can range in color from tan to black (**Figure 64**). They can mimic melanoma and squamous cell carcinoma, but skin biopsy confirms the diagnosis. They may become irritated or excoriated. When seborrheic keratoses are symptomatic, they may be treated with cryotherapy or shave removal.

FIGURE 64. Seborrheic keratoses are brown, scaly, waxy papules/plaques that commonly occur in older persons. They frequently have a "stuck-on" appearance and often have verrucous (warty) surface changes as well. Seborrheic keratoses typically demonstrate horn cysts (epidermal cysts filled with keratin) on the surface that can best be visualized on dermoscopy.

Melanocytic Nevi

Melanocytic nevi are benign neoplasms composed of melanocytes commonly referred to as "moles." They occur anywhere on the body including palms, soles, and mucous membranes. Melanocytic nevi can appear early in childhood and increase in number until middle age. They vary in clinical appearance depending on the location of melanocytes within the skin (**Table 16** and **Figure 65**). Clinically they can mimic melanoma, necessitating a biopsy for accurate diagnosis.

Dysplastic Nevi

H

Dysplastic nevi are melanocytic nevi that are often asymmetric, irregularly bordered, have more than one shade of brown, and may be quite large in diameter. Many have a "fried egg" appearance with an eccentric dark brown papular center and surrounding light brown ring. Dysplastic nevi can display one or more of the identifying characteristics of melanoma (see Malignant Melanoma), making an accurate clinical diagnosis impossible. In cases of uncertainty, a biopsy of the lesion can typically exclude melanoma; however, it is imperative to sample the entire lesion including a 1- to 2-mm border of normal surrounding skin.

TABLE 16. Types of Melanocytic Nevi		
Type	**Location of Melanocyte Nests in Skin**	**Clinical Appearance**
Junctional melanocytic nevus	Dermal-epidermal junction	Brown-to-black macules
Compound melanocytic nevus	Dermal-epidermal junction and dermis	Tan-to-brown papules or nodules
Intradermal melanocytic nevus	Dermis	Tan-to-skin-colored papules

FIGURE 65. Compound melanocytic nevi are tan-to-brown papules with regular borders and even color.

H CONT.

Although melanoma can arise within any melanocytic nevi, including dysplastic nevi, the risk of this occurring within any given lesion is quite small. Removal is reserved for those lesions that display particularly worrisome features, are changing in size and color, are symptomatic, or stand out from the patient's other nevi. Patients with multiple dysplastic nevi are at risk for developing melanoma and should be monitored closely (**Figure 66**). Some of these patients have dysplastic nevus syndrome. Criteria for this syndrome include a history of melanoma in one or more first- or second-degree relatives, the presence of a large number of nevi (>50), multiple nevi having atypical clinical features, and multiple nevi that have atypical histologic features. These patients are at increased risk of melanoma and should have yearly full-skin examinations. H

KEY POINTS

- Dysplastic nevi can display one or more of the identifying characteristics of melanoma; patients with multiple dysplastic nevi are at increased risk of melanoma and should have yearly full-skin examinations.
- HVC Excision of dysplastic nevi is reserved for lesions that display particularly worrisome features, are changing in size and color, are symptomatic, or stand out from the patient's other nevi.

Halo Nevi

Halo nevi are melanocytic nevi with an admixed chronic lymphocytic infiltrate that signifies regression of the nevus. Halo nevi are central brown-to-tan macules or papules with a surrounding "halo" of hypopigmented or depigmented skin (**Figure 67**). They most frequently present on the back of teenagers or young adults. Multiple halo nevi have been associated with melanoma; therefore, these patients should have a complete skin examination.

FIGURE 66. Dysplastic nevi are commonly larger than 6 mm and have irregular borders. This patient has numerous dysplastic nevi and is at increased risk for melanoma.

Sebaceous Hyperplasia

Sebaceous hyperplasia is a common benign condition consisting of flesh-colored or yellow umbilicated papules found on the face of older patients, particularly the forehead (**Figure 68**). The lesions are often multiple and are more common in patients with rosacea. Histologically, there is enlargement of the sebaceous glands surrounding a hair follicle. Sebaceous hyperplasia can mimic basal cell carcinoma and may necessitate a biopsy for accurate diagnosis.

Callus/Corns

A callus is a collection of thickened, hardened stratum corneum that presents as a flat papule or plaque at the site of repetitive trauma, frequently under bones. Sometimes the term "corn" is used interchangeably with callus; however, corns have more distinct edges, are more rounded, and have a central core that can be soft or hard. Corns are typically seen on the sides or tops of toes. Treatment is by mechanical or chemical paring with salicylic acid, but removing the pressure from the site is necessary to prevent reformation.

FIGURE 67. Halo nevus, with a depigmented halo surrounding a brown papule.

FIGURE 68. Sebaceous hyperplasia presenting as a yellow-to-pink papule with a central umbilication on the forehead.

Acrochordon (Skin Tags)

Acrochordons (skin tags) are skin colored, pedunculated papules (**Figure 69**). They are most commonly seen on the neck and skin folds in older adults. Skin tags appear with increased frequency during the second trimester of pregnancy and may regress postpartum. Skin tags are frequently seen in obese patients and in patients with diabetes mellitus. Perianal skin tags are common in patients with Crohn disease. If lesions become necrotic or crusted, they may require removal with cryotherapy or snip excision. They can be of cosmetic concern, especially when numerous. The presence of numerous lesions, particularly in the setting of obesity and acanthosis nigricans, is associated with insulin resistance.

Cherry Angiomas

Cherry angiomas are benign vascular lesions with a familial predisposition that present in adulthood and become more numerous with age. They are discrete red-to-violaceous papules that blanch with pressure, more common on the trunk but can be seen anywhere on the skin (**Figure 70**). Shave removal or electrocautery may be required for lesions that are traumatized or bleeding.

Dermatofibroma

Dermatofibromas are benign, fibrohistiocytic lesions that are common on the extremities, particularly the legs of young women, and are associated with trauma. Dermatofibromas are tan-to-brown discrete papules that often have a slightly darker brown ring encircling the main part of the lesion; they "dimple" when lateral pressure is applied to the lesion with the thumb and first finger (**Figure 71**). Treatment is not necessary, and recurrences are common after shave removal. Multiple dermatofibromas have been associated with HIV infection and systemic lupus erythematosus.

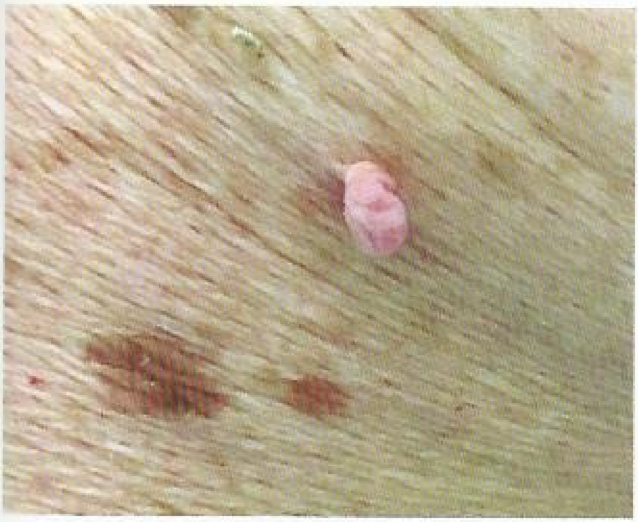

FIGURE 69. Acrochordons (skin tags) are skin-colored papules that arise on areas of friction, such as the neck, axillae, and groin.

FIGURE 70. Cherry angioma is characterized by a blanchable, pink-to-red, small dome-shaped papule.

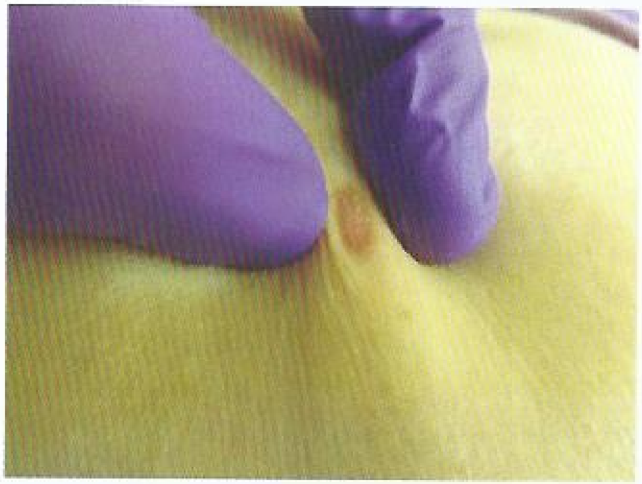

FIGURE 71. The "dimple sign" is a characteristic clinical feature of dermatofibromas which are firm tan papules.

Solar Lentigines and Ephelides

Solar lentigines are tan or light brown, 1- to 3-cm well-defined macules on sun-exposed areas of older adults, commonly referred to as "liver spots" (**Figure 72**). They are a marker of sun damage. Ephelides or "freckles" are 2- to 5-mm tan macules on sun-exposed areas that appear in childhood and darken with sun exposure. When solar lentigines or ephelides are larger than 1 cm or irregular in shape, melanoma is in the clinical differential diagnosis and a biopsy should be considered.

Hypertrophic Scars and Keloids

Hypertrophic scars are raised firm nodules or plaques at the site of an injury that can be tender or pruritic (**Figure 73**). They usually have a good response to intralesional glucocorticoids and may regress spontaneously.

Keloids are firm, rubbery papules, nodules, or plaques that extend beyond the site of injury, but can also form

FIGURE 72. Solar lentigines (solar lentigo) are brown macules and patches that occur in middle aged to elderly fair-skinned persons in sun-damaged areas. Although benign, they may occasionally be difficult to distinguish from melanoma. Useful discriminating characteristics include more homogeneous pigmentation and lighter color.

FIGURE 73. Hypertrophic scars are raised firm plaques at sites of injury. As opposed to keloids, they characteristically do not exceed the site of the original injury.

spontaneously, including from inflammatory lesions of acne. They are more common in people with pigmented skin and on the chest and ears. Treatment is difficult and is associated with high rates of recurrence. It requires excision with subsequent intralesional glucocorticoids.

Pyogenic Granulomas

Pyogenic granulomas or lobular capillary hemangiomas are friable red papules that grow quickly and bleed easily (**Figure 74**). The name is misleading as they are neither pyogenic nor granulomatous. They are more common in women during pregnancy and with certain medications (antiretroviral agents and oral retinoids). Treatment for symptomatic lesions is shave removal or electrocautery.

Epidermal Inclusion Cysts

Epidermal inclusion cysts (sebaceous cysts) are subepidermal nodules with an epithelial lining and a core of accumulated keratin debris (**Figure 75**). They often have a central punctum by which foul-smelling material can be expressed. When epidermal inclusion cysts rupture, they may become tender, inflamed, and occasionally infected. Pilar cysts are similar

FIGURE 74. Pyogenic granulomas are red and friable benign vascular tumors that arise spontaneously or secondary to trauma and grow rapidly.

FIGURE 75. Epidermal inclusion cysts are either found incidentally or present as a firm non-tender lump. If they rupture, a local inflammatory response to the necrotic debris released can mimic infection. It is very common for women on the major or minor labia.

lesions that occur on the scalp. Treatment is by excision, but the epithelial lining must be removed to avoid recurrences.

Lipomas

Lipomas are benign neoplasms of mature adipocytes that present as mobile, subcutaneous nodules or tumors. Patients can have a single lesion or multiple, and they are most common on the trunk. Angiolipomas are a variant with a vascular component that is often painful and more common on the upper extremities. When symptomatic or larger, lipomas and angiolipomas can be excised.

Digital Myxoid Cysts

Digital myxoid (mucous) cysts are slow-growing, translucent papules most commonly seen in the distal interphalangeal joint or the proximal nail fold of the fingers, although the toes can also be affected. Nail deformity, pain, and discharge can be complications. Symptomatic treatment can be done by incision and drainage, but recurrences are common and there is a risk of infection and scarring.

Xanthoma

Xanthomas are characteristic skin conditions associated with primary or secondary hyperlipidemias. Xanthomas are yellow, orange, reddish, or yellow-brown papules, plaques, or nodules. The type of xanthoma closely correlates with the type of lipoprotein that is elevated. The most common xanthoma types include eruptive, plane, xanthelasma, tuberous, and tendinous.

Eruptive xanthomas present as clusters of erythematous papules typically on the extensor surfaces. They are most often associated with extremely high serum triglyceride levels. Plane xanthomas are yellow-to-red plaques found in skin folds of the neck and trunk. They can be associated with familial dyslipidemias and a variety of hematologic malignancies. Xanthelasma is a type of plane xanthoma localized to the periorbital area, most commonly on the upper medial eyelid (**Figure 76**), and is characterized by soft, nontender, nonpruritic plaques. Xanthelasma can occur without hyperlipidemia, particularly in older persons, but is often associated with familial dyslipidemias when seen in a younger person. These lesions are a classic feature of primary biliary cirrhosis, a condition often associated with marked hypercholesterolemia. Tendon xanthomas are subcutaneous nodules occurring on the extensor tendons; they are associated with familial hypercholesterolemia.

FIGURE 76. Xanthelasma is a type of plane xanthoma that presents as asymptomatic, flat, yellow-to-orange papules or plaques around eyelids that can be associated with familial dyslipidemia in young adults.

Neurofibromas

Neurofibromas are benign nerve-sheath tumors that present as soft, skin-colored papules that show invagination of the papule with lateral pressure ("buttonhole" sign). Single lesions are common in adults, especially on the trunk. Multiple neurofibromas are seen in neurofibromatosis type 1 (von Recklinghausen disease) (**Figure 77**). Treatment of symptomatic lesions is by excisional biopsy.

Precancerous and Cancerous Neoplasms

Skin cancer is a major public health concern, and one in five people in the United States will develop it. Most cases are caused by excessive ultraviolet (UV) light exposure. People of all skin pigmentation can develop skin cancer, but fair skinned persons are more prone to the effects of UV light exposure.

Basal Cell Carcinoma

H

Basal cell carcinoma (BCC) is a malignant neoplasm arising from the basal layer of the epidermis. It is the most common type of skin cancer and cancer in general. Metastasis rarely occurs; however, without treatment, it can cause significant local tissue destruction. Vital structures, such as eyes, ears, and nose, may be damaged. The most common causative factor is UV light exposure. There are different histologic

FIGURE 77. Neurofibromas present as soft, compressible, flesh-colored papules and nodules. Multiple neurofibromas are seen in neurofibromatosis type 1 (von Recklinghausen disease).

H CONT.

subtypes that result in varying clinical appearance including superficial, pigmented, sclerotic, and nodular. Patients usually present with a new growth that is bleeding or not healing. They often have other signs of photodamage, such as freckles, lentigines, and actinic keratoses.

Nodular basal cell carcinoma is the most common type of BCC. It presents as a pearly or translucent nodule or papule with arborizing telangiectasias. It may have a central depression or ulceration with a rolled waxy border (**Figure 78**). The term "rodent ulcer" is used to describe the ulceration. Nodular BCC is most commonly found on the face, especially the nose. Histologically, nodular BCC is a low-risk subtype, but its counterpart, micronodular BCCs, poses a higher risk. They can only be distinguished by histologic assessment.

The superficial type of basal cell carcinoma appears as a pink-red patch with or without scale. It may have a slight threadlike pearly rolled border. It can be confused for an actinic keratosis, squamous cell carcinoma in situ, or a patch of dermatitis such as psoriasis or nummular dermatitis. Superficial BCC tends to be a persistent solitary patch that does not respond to topical glucocorticoids. Biopsy provides definitive diagnosis.

Pigmented BCC presents as shiny blue-black papules, nodules, or plaques that can appear translucent with blue-black speckles with a rolled border. It is more common in patients with darker skin.

Sclerotic BCC, which includes morpheaform and infiltrative subtypes, presents as atrophic plaques or papules that can resemble a scar. Although it is the least common, it is a high-risk, aggressive histologic subtype.

The diagnosis of BCC should be confirmed histologically with a shave or punch biopsy. Treatment of BCC should be based on patient's preference and health status, the location of the lesion, histologic subtype, size, and primary versus recurrent nature. Therapeutic options include surgery (standard excision, Mohs micrographic surgery); electrodessication and curettage; cryosurgery; topical chemotherapy; radiation therapy; and for metastatic or inoperable lesions, oral hedgehog pathway inhibitors (vismodegib, sonidegib). Surgical excision is the most commonly used intervention and results in the highest cure rate. H

Mohs micrographic surgery is a highly specialized surgical technique that combines pathology and surgery for complete margin control and tissue conservation. It is appropriately used for cancers in the head and neck region, those that are large or recurrent, or in areas where tissue-sparing is critical for function (vital structures) (**Figure 79**). Radiation therapy is generally reserved for inoperable tumors or patients who refuse surgical treatment. Topical chemotherapy with 5-fluorouracil or imiquimod can be used for superficial BCC; however, its cure rate is user dependent.

Treatment course lasts for weeks and results in marked inflammation and irritation. Topical therapies are inappropriate for deep, recurrent, or sclerotic tumors. Curettage and electrodessication can be used for superficial or nodular BCCs on the trunk. It should not be used for tumors 2 cm or larger, those with poorly defined borders, recurrent or high-risk histologic subtypes, and those appearing in certain anatomic locations (face, scalp, eyelids). Cryosurgery for BCCs is different than that for actinic keratosis. The margin, depth, and temperature have to be monitored to achieve cure.

Follow-up skin examination every 6 to 12 months is recommended as the risk of developing another BCC is increased. Prevention with sun protection is highly recommended including routine use of sunscreens with sun protection factor greater than 35, protective clothing (wide brim hats, long sleeves), and avoidance of midday sun (10 AM to 2 PM).

FIGURE 78. Pearly nodule with arborizing telangiectasias (bottom left) and ulceration characteristic of nodular basal cell carcinoma.

FIGURE 79. Untreated basal cell carcinomas (BCC) over time can become large and cause significant local tissue damage. BCC occurring in the mask area of the face and BCC with certain histology expand not only in the skin, but can invade deeper tissues including fascia, muscle, bone and nerves. These tumors are at high risk of recurrence after treatment along with structural damage. Biopsy of the tumor is needed to ascertain tumor histology, which directs appropriate management, which will likely include Mohs micrographic surgery.

KEY POINTS

- Nodular basal cell carcinoma is the most common type of basal cell carcinoma, typically presenting as a pearly or translucent nodule or papule with arborizing telangiectasias; it may often have a central depression or ulceration with a rolled waxy border.
- The diagnosis of basal cell carcinoma should be confirmed histologically with a shave or punch biopsy.
- Surgical excision is the most commonly used treatment for basal cell carcinoma and results in the highest cure rate; Mohs micrographic surgery is used for cancers in the head and neck region, those that are large or recurrent, or in areas where tissue-sparing is critical for function.

Actinic Keratosis

Actinic keratoses are precancerous lesions of the epidermis. Approximately 1% to 5% of actinic keratoses will develop into squamous cell skin cancers. They present as ill-defined pink scaly ("sandpaper") thin papules or plaques mostly in sun-exposed areas (**Figure 80**). Individual lesions can be treated with cryotherapy. In patients with diffuse actinic damage, field treatment with topical chemotherapy creams (such as 5-fluorouracil or imiquimod) or photodynamic therapy can be used. Lesions that do not resolve with cryotherapy or are more indurated will require a biopsy to rule out an invasive neoplasm.

Squamous Cell Carcinoma

Squamous cell carcinoma (SCC), the second most common skin cancer, is a malignant neoplasm of keratinocytes. It presents as pink, scaly indurated plaques, papules, or nodules that can ulcerate, bleed, or become crusty (**Figure 81** and **Figure 82**). It can be painful. Risk factors are UV light, ionizing radiation, chemical carcinogens (coal tar, soot, and arsenic), viruses (human papillomavirus), and immunosuppression (organ transplant, hematologic malignancies, HIV infection). SCC occurs in areas of sun exposure and areas of chronic injury (burn scars, irradiated sites, erosive discoid lupus erythematosus). In comparison to lightly pigmented patients, those patients with darker pigment more often develop SCC in regions with chronic inflammation or scarring and more frequently on the lower extremities. SCC can be locally invasive and has the potential to metastasize. Histologically, it can range from well-differentiated SCC to poorly differentiated SCC, which is the more aggressive subtype. High-risk factors for SCC are tumor diameter greater than 2 cm, tumor thickness greater than 2 mm, poorly differentiated subtypes, perineural invasion, and tumor location of the ear or nonglabrous lip (**Figure 83**).

With SCC in situ (Bowen disease), malignant keratinocytes are confined to the epidermis. It appears as larger scaly pink and tan plaques with well-defined borders (**Figure 84**). Skin biopsy can distinguish SCC in situ from actinic keratoses.

FIGURE 81. Pink scaly plaque consistent with squamous cell carcinoma.

FIGURE 82. Pink hyperkeratotic nodule on sun exposed skin consistent with squamous cell carcinoma.

FIGURE 80. Actinic keratoses are typically pink thin papules that occur on sun-exposed areas, particularly the face and dorsal arms. Actinic keratoses result from chronic sun exposure, and their presence identifies persons who are at increased risk of developing invasive squamous cell carcinomas. Actinic keratoses are a precancerous condition.

FIGURE 83. Squamous cell carcinoma lesions on the lower lip most commonly arise from sun damage, often in the setting of actinic cheilitis.

FIGURE 84. Bowen disease (squamous cell carcinoma in situ) typically presents as a gradually enlarging, well-demarcated erythematous plaque with an irregular border and surface crusting or scaling.

Surgical excision including Mohs micrographic surgery for high-risk SCC tends to be the first-line treatment given its potentially aggressive behavior and risk of metastasis. Radiation is an option if surgery is contraindicated. In cases of metastasis, chemotherapy can also be considered.

KEY POINTS

- Squamous cell carcinoma presents as pink, scaly indurated plaque, papules, or nodules that can ulcerate, bleed, or become crusty.
- Surgical excision, including Mohs micrographic surgery, is first-line treatment for squamous cell carcinoma on the head and neck, given its potentially aggressive behavior and risk of metastasis; in cases of metastasis, chemotherapy can also be considered.

Keratoacanthoma

H

Keratoacanthoma is considered to be a variant of SCC by some and a benign tumor by others. Histologically, it can resemble an SCC. It has a distinct appearance and clinical course. It appears rapidly (within 4 to 6 weeks) as a round pink nodule with a central, keratin-filled crater, giving it a "volcaniform" appearance (**Figure 85**). After its rapid growth, some keratoacanthomas tend to involute in 6 months. Because it is difficult to differentiate from SCC, they are often treated with surgical excision. H

Malignant Melanoma

H

Melanoma is a malignant neoplasm of the melanocytes. Although it is less common than BCC and SCC, it is histologically aggressive and has a much higher rate of metastasis. It is responsible for most skin cancer deaths. In the United States, the incidence of melanoma is increasing faster than any other cancer. The estimated lifetime risk of developing melanoma is 1 in 50. It tends to affect a younger population. There are four clinical subtypes: superficial spreading, lentigo maligna, acral lentiginous, and nodular melanoma. Risk factors include UV light (both chronic and intermittent blistering sunburns), genetics (family history, and *CDKN2A* and *CDK4* gene mutations), large number of nevi, dysplastic nevi, and fair skin.

In general, the ABCDEs of identifying characteristics can help diagnose melanoma where "A" stands for Asymmetry, "B" for irregular Border, "C" for multiple Colors, "D" for Diameter greater than 6 mm, and "E" for Evolution or change over time. Not all melanomas follow all of these characteristics, so if there is a lesion that is different from the patient's other nevi, a biopsy should be considered.

Superficial spreading melanoma is the most common type (**Figure 86**). It can occur anywhere on the body; however, in men, the most common location is the back, whereas in women, it is more often found on the legs.

FIGURE 85. Rapidly growing, pink "volcaniform" nodule with central crust that is characteristic of a keratoacanthoma.

FIGURE 86. A superficial spreading melanoma with prominent Asymmetry, irregular Borders, Color variation, and large size (Diameter)—ABCD.

Lentigo maligna is more often found on the head and neck region. It is associated with frequent chronic UV light exposure. It is usually found in older patients, peaking in the seventh and eighth decades of life. It presents as ill defined, asymmetric brown or black macules or patches, often reaching a diameter of 5 to 7 cm prior to invasion (**Figure 87**). The change and darkening of the lesion can be very insidious and can be mistaken for a solar lentigo or seborrheic keratoses.

Acral lentiginous melanoma occurs on the palms, soles, and distal fingers and toes. It is an ill-defined, black macule plaque, and it more frequently occurs in patients with darker skin (**Figure 88**). The average time to diagnosis is 2 years. The 5-year survival rate for melanoma in blacks and Hispanics, even after adjusting for age, stage, site, and socioeconomic status, is lower compared with white patients.

Nodular melanoma begins in the vertical growth phase and is more aggressive. It is rapid growing and presents as blue-black, smooth, or eroded nodules occurring anywhere on the body (**Figure 89**).

FIGURE 87. Ill-defined asymmetric brown patch consistent with a lentigo maligna which presents as a slowly enlarging, variegated, pigmented patch on sun-damaged skin.

FIGURE 88. Ill-defined, asymmetric black gray ulcerated plaque on the heel typical of acral lentiginous melanoma.

FIGURE 89. Nodular melanomas typically present as uniformly dark blue or black "berry-like" lesions that most commonly originate from normal skin. They can also arise from preexisting nevi, as did this melanoma. Nodular melanomas grow vertically rather than horizontally.

All suspicious pigmented lesions must be biopsied. The preferred method to biopsy a pigmented lesion is an excisional biopsy with 1- to 2-mm margin to obtain the entire lesion and to prevent sampling error. Shave biopsies should be avoided in most pigmented lesions as there is risk of transecting a melanoma and preventing true staging of the lesion. A modified technique that can be helpful is the "scoop" biopsy where the deep dermis or subcutaneous tissue is removed to get underneath the lesion. In wide, ill-defined lesions, it may be prohibitive to remove the entire lesion, so an incisional biopsy is acceptable. Definitive treatment cannot be determined until

H CONT. histologic confirmation and final staging of the tumor is completed. H

Poor prognostic factors include male gender, increasing age, increased tumor thickness (Breslow depth), ulceration, increased tumor mitotic rate, and head/neck/trunk locations. Melanomas are staged with the tumor, nodal, and metastasis (TNM) system (https://cancerstaging.org/references-tools/quickreferences/Documents/MelanomaLarge.pdf).

Survival is dependent on early diagnosis. Treatment is based on the stage of melanoma. In the first and second stage, surgical treatment is used to remove the lesion and a margin of clinically normal skin (wide local excision). The size of the margin is based on the depth of the lesion. Melanomas that are stage IB or higher are often considered for sentinel node biopsy for assessing prognosis. Stage III melanoma is treated with wide local excision, lymph node dissection, and possible adjuvant interferon. Immunotherapy has emerged as the primary systemic treatment for stage IV melanoma. Combination treatment with an anti-PD1 antibody (pembrolizumab, nivolumab) with ipilimumab, an anti-CTLA4 antibody, is most often selected for patients with metastatic melanoma (see MKSAP 18 Hematology and Oncology). Survival data suggest that up to 80% of patients receiving this combination will be alive at 2 years. Chemotherapy is typically reserved for patients who have progressed despite optimal systemic therapy. Radiation is usually reserved for palliative therapy for metastasis to the brain and bones. Thorough follow up including a full body skin examination at routine intervals is crucial for patients with a history of melanoma.

KEY POINTS

- Identifying characteristics of melanoma are Asymmetry, irregular Border, multiple Colors, Diameter greater than 6 mm, and Evolution or change over time (ABCDEs).
- All suspicious pigmented lesions must be biopsied; the preferred method to biopsy is an excisional biopsy with 1- to 2-mm margin.
- For stage I and stage II, treatment of melanoma is surgical excision with the size of the margin based on the depth of the lesion; stage III is treated with wide local excision, lymph node dissection, and possible adjuvant interferon; and stage IV is treated with immunotherapy; chemotherapy is reserved for patients who progress despite optimal immunotherapy.

Pruritus

Pruritus, or itching, is one of the most common symptoms in dermatology. Itch sensation is transmitted to the central nervous system by C-fibers (which are distinct from C-fibers that transmit pain signals) and can be very disruptive to a patient's quality of life. Pruritus is commonly associated with a variety of skin diseases, yet it may also be seen independent of skin pathology. When first evaluating pruritus, it is important to establish if the itch is secondary to an inflammatory skin condition or present without a primary rash.

Several inflammatory skin diseases are associated with pruritus, including atopic dermatitis, contact dermatitis, lichen planus, and urticaria. Significant pruritus is also associated with burns and healing skin, and in xerotic, or dry skin, especially in older patients.

H When pruritus occurs in the absence of skin findings, a variety of systemic diseases should be considered. Uremic pruritus is common in patients with chronic or end-stage kidney disease. It typically presents within 3 months of starting hemodialysis. Pruritus can also be associated with cholestatic hepatobiliary diseases (**Figure 90**). Pruritus associated with cirrhosis from alcoholic liver disease or hepatitis C infection can occur in the absence of cholestasis. Thyroid disease and polycythemia vera are other systemic diseases that might present with itching. Generalized pruritus may also be the presenting symptom in malignancies such as lymphocytic leukemia and Hodgkin lymphoma. Certain infections, such as HIV, may present with generalized itching as well. H

Various psychiatric or somatization conditions can also manifest as itching (psychogenic itch) (**Figure 91**). Pruritus typically worsens during stressful or traumatic events. Patients with chronic pruritus have increased depression and impaired quality of life. Neuropathic pruritus describes the itch that is caused by dysfunction of a peripheral or central nerve(s) due to surgery, trauma, arthritis, neuropathy, or infection (postherpetic neuralgia). Neuropathic itch is often localized to a small, well-circumscribed area; examples include the forearm (brachioradial pruritus), posterior shoulder, or mid to upper back (notalgia paresthetica) (**Figure 92**).

H A review of systems, complete blood count, thyroid function studies, kidney function tests, liver chemistry tests, HIV

FIGURE 90. Linear excoriations in a patient with cholestatic liver.

FIGURE 91. Patients with psychogenic itch often report nonhealing sores, such as those seen on this patient's arm. The lesions often have a linear or irregular shape from repeated manipulation. Scars from previous episodes are often seen among the active lesions.

FIGURE 92. A localized and persistent area of pruritus without associated primary skin lesions, usually on the back or forearms, suggests neuropathic itch. This patient's area of hyperpigmentation is secondary to chronic scratching.

H CONT. test, and chest radiograph are necessary to help guide further workup. In addition, a review of the patient's medications, including supplements and illicit drugs, should be performed. Common medications that can cause pruritus are opiates, calcium channel blockers, hydrochlorothiazide, and NSAIDs (Table 17). H

TABLE 17. Common Medications That May Cause Pruritus
Calcium channel blockers
Hydrochlorothiazide
Opioids
NSAIDs
ACE inhibitors
Anticoagulants
Antibiotics (trimethoprim/sulfamethoxazole)
Selective serotonin reuptake inhibitors

Patient education is critical to the management of any pruritic condition. The primary lesson for most patients is scratching causes skin damage that contributes to an "itch-scratch-itch" cycle. Treatment of pruritus is directed at addressing the underlying cause. The treatment of inflammatory skin conditions with topical glucocorticoids and emollients can help alleviate pruritus. Topical anti-itch medications containing menthol can also be helpful. First-generation oral antihistamines can be sedating and helpful for pruritus at night. For older patients with xerotic skin, comprehensive dry skin care should be reviewed. This includes bathing in warm water followed by immediate application of a thick emollient. Products that contain perfumes or dyes should be avoided as xerotic skin is at greater risk of irritation due to a compromised skin barrier.

Topical treatments may not be as effective for systemic causes of pruritus. Gabapentin can be effective in treating pruritus associated with burns, neuropathic itch, and uremic pruritus. Phototherapy can also be used for uremic pruritus. Ursodeoxycholic acid can be considered for cholestatic pruritus.

KEY POINTS

- When pruritus occurs in the absence of skin findings, a variety of systemic causes, including kidney or liver diseases, thyroid disease, or HIV, should be considered.
- Reactions to common medications, such as opiates, calcium channel blockers, hydrochlorothiazide, and NSAIDs, are frequent causes of pruritus.
- Topical glucocorticoids and emollients are appropriate treatment for pruritus associated with inflammatory skin conditions.

Urticaria

Urticaria (hives) are localized areas of edema caused by mast cell degranulation and the release of inflammatory proteins, including histamine, leukotrienes, complement, and prostaglandins. Urticaria is characterized by well-demarcated H

H CONT.

erythematous plaques ranging in size from 1 to 8 cm that appear quickly and resolve in a matter of hours (**Figure 93**). Individual lesions may be erythematous or white, often surrounded by a red halo, and have a variety of shapes including round, oval, annular, arciform, and serpiginous. The center of a lesion is typically blanchable pink or clear skin. These lesions are extremely pruritic and tend to appear on body sites with repetitive pressure or rubbing, such as the waistline and posterior neck. Although individual urticarial lesions should resolve in less than 24 hours, recurrent crops of hives may last for weeks. Most cases of urticaria resolve spontaneously, and the cause is never determined. If the episodes last for longer than 6 weeks, the condition is classified as chronic urticaria. If the individual urticarial lesions do not resolve after 24 hours, or if they are accompanied by systemic symptoms (joint pain, fever), urticarial vasculitis must be considered.

The diagnosis of urticaria is clinical. Physical maneuvers that can help with diagnosis include circling lesions and seeing if they have resolved within 24 hours, and gently scratching uninvolved skin with the wooden end of tongue depressor to see if urticaria (not just redness) can be induced (dermatographism). The cause of urticaria is investigated primarily by history and physical examination; skin biopsies are not generally needed. Skin biopsy, however, is helpful in the diagnosis of urticarial vasculitis and should be considered in patients with painful lesions, systemic symptoms, or persistent individual lesions.

Viral infection and medication reaction are the most common causes of acute urticaria in adults. Food-induced allergic reactions can be severe, and the most commonly implicated foods are shellfish, peanuts, and tree nuts. Infrequent but important causes include autoimmune thyroid disease and malignancies, particularly lymphoma. Physical urticaria is induced by a physical stimulus such as sunlight, sweating, physical pressure, vibration, water, or cold temperature.

FIGURE 93. Urticarial lesions on the waist characterized by small and large edematous and erythematous plaques of various shapes.

Angioedema is a transient, localized subcutaneous or submucosal form of urticaria caused by extravasation of fluid into interstitial tissues. Angioedema may occur with or without urticaria and can be a component of anaphylaxis. Angioedema involving the face and airway is an emergency, and its initial treatment involves systemic epinephrine and glucocorticoids.

Hereditary angioedema, distinct from the more typical mast cell associated angioedema, is caused by activation of the complement cascade due to lack of or dysfunction of C1 esterase inhibitor. Hereditary angioedema may cause sporadic localized edema involving the head and neck and is differentiated from mast cell-associated angioedema by the lack of typical urticarial lesions. Diagnosis is by testing for quantitative and functional levels of C1 esterase inhibitor and C4 complement levels.

Diagnostic workup for urticaria is not recommended unless history suggests a specific cause. If symptoms persist, laboratory tests, including a complete blood count with differential, urinalysis, erythrocyte sedimentation rate or C-reactive protein, thyroid-stimulating hormone, and liver chemistry tests, can be considered. If associated with systemic symptoms or suspicion of urticarial vasculitis, testing directed by the findings should be considered. H

KEY POINTS

- Urticaria is characterized by well-demarcated erythematous pruritic plaques that appear quickly and resolve in a matter of hours; diagnostic workup for urticaria is not recommended unless history suggests a specific cause. HVC
- Hereditary angioedema is caused by activation of the complement cascade due to lack of or dysfunction of C1 esterase inhibitor.
- Nonsedating, long-acting antihistamines are the treatment of choice for urticaria; topical antihistamines have not been found to be effective and may lead to allergic contact dermatitis. HVC

Autoimmune Bullous Diseases

Bullous or blistering dermatoses can be acquired from an autoimmune process or from a genetic defect and are characterized by blistering or erosion of the skin. Autoimmune bullous diseases (ABDs) are caused by antibodies interfering with cohesion between keratinocytes of the epidermis (desmosomes) or between the epidermis and dermis (basement membrane zone) (**Table 18**). ABDs can be subdivided into intraepidermal and subepidermal disorders. Intraepidermal ABDs present with flaccid vesicles that rupture easily, whereas

TABLE 18. Characteristics of Autoimmune Blistering Diseases

Disease	Clinical Characteristics	Pathology	Comments
Pemphigus vulgaris	Tender, fragile blisters and erosions seen in oral mucosa and skin; mucous membrane lesions much more common than in bullous pemphigoid; Nikolsky sign (rubbing of the skin resulting in blister formation) is positive	Suprabasilar clefting compared with subepidermal clefting seen in bullous pemphigoid DIF/IIF: intercellular pattern within the epidermis	Incidence varies by country and ethnicity and is estimated to be 0.5 to 3.2 cases per 100,000 persons per year
Pemphigus foliaceus	Scaling and crusted lesions on face and upper trunk, and erythroderma with no mucosal involvement; Nikolsky sign is positive	High granular or subcorneal clefting compared with suprabasal clefting seen in pemphigus vulgaris DIF/IIF: intercellular pattern within the epidermis	Incidence varies by country with estimated occurrence of 0.5 to 6.6 cases per million persons per year Endemic pemphigus foliaceus (fogo selvagem) occurs in central and southwestern Brazil and Colombia and has a higher incidence with up to 50 cases per million persons per year and up to 3.4% of the population affected
Paraneoplastic pemphigus	Painful oral, conjunctival, esophageal, and laryngeal erosions occur more commonly than in pemphigus vulgaris; it is a polymorphous skin eruption marked by confluent erythema, bullae, erosions, and intractable stomatitis; patients also have respiratory problems that may be fatal	Mixed pattern of both suprabasal acantholysis and interface dermatitis DIF/IIF: IgG binds in an intercellular pattern within the epidermis; reactants at the dermal-epidermal junction. The combination of intercellular and subepidermal deposition of immunoreactants is a clue to the diagnosis.	High mortality rate (up to 90%) and association with underlying neoplasms: non-Hodgkin lymphoma (42%), chronic lymphocytic leukemia (29%), Castleman disease (10%)
IgA pemphigus	A vesicopustular eruption with clear blisters that rapidly transform into pustules; trunk and proximal extremities are most commonly involved, with relative sparing of the mucous membranes	Subcorneal collection of neutrophils DIF shows deposition of intercellular IgA at the epidermal surfaces	Newly described disease with unknown frequency
Bullous pemphigoid	Tense blisters preceded by intense pruritus or urticarial lesions most commonly seen in the elderly on the trunk, limbs, and flexures; does not usually present with oral lesions	Subepidermal bullae without acantholysis and with prominent eosinophils DIF shows linear IgG deposition at the basement membrane zone	One of most common autoimmune blistering diseases with up to 4.3 cases per 100,000 persons per year
Epidermolysis bullosa acquisita	Mechanically induced bullae and erosions mostly on extensor areas that heal with scarring and milia	Subepidermal cleavage without acantholysis DIF shows IgG deposition at the basement membrane zone that localizes to the base on salt-split skin	Rare disease with unknown frequency Can be associated with inflammatory bowel disease
Cicatricial pemphigoid	Presents with bullae, erosions, milia, and scarring seen on mucous membranes and conjunctivae of middle-aged to elderly persons; oral mucosa is almost always involved; conjunctival lesions are also common	Histology is similar to bullous pemphigoid DIF may reveal patterns similar to bullous pemphigoid, linear IgA bullous dermatosis, or epidermolysis bullosa acquisita	Rare disease with estimated incidence of 0.9 to 1.1 cases per million persons per year Increased risk for malignancy in some patients Prompt treatment should be initiated to avoid permanent ocular and oral scarring

(Continued on the next page)

TABLE 18. Characteristics of Autoimmune Blistering Diseases *(Continued)*

Disease	Clinical Characteristics	Pathology	Comments
Dermatitis herpetiformis	Severely pruritic grouped vesicles or erosions on elbows, knees, back, scalp, and buttocks; lesions occur in crops and are symmetrically distributed; often the vesicles are not seen because the process is so itchy that they are almost immediately broken	Histology shows neutrophilic infiltrate at the tips of the dermal papillae causing subepidermal separation DIF shows granular IgA deposition	Common blistering disease with 10 to 11 cases per 100,000 persons per year Nearly all patients with dermatitis herpetiformis will have celiac disease
Linear IgA bullous dermatosis	Pruritic, discrete, or clustered bullae in a herpetiform pattern ("cluster of jewels"); annular or polycyclic lesions with vesicles and bullae at the periphery are common	Subepidermal bullae with neutrophils Can be indistinguishable from dermatitis herpetiformis, epidermolysis bullosa acquisita, or bullous lupus DIF shows linear IgA deposition	In adults, the estimated incidence is 0.6 cases per 100,000 persons per year Ocular involvement can occur A variant can occur in children called chronic bullous dermatosis of childhood
Porphyria cutanea tarda (and pseudoporphyria)	Erosions and bullae on hands and forearms, and occasionally face and feet, that heal with milia, hyperpigmentation, and hypopigmented scars. Porphyria cutanea tarda (but not pseudoporphyria) can also present with hypertrichosis on the face	Subepidermal bullae with little inflammation; dermal papillae protrude upward into the blister cavity and thickened upper dermal capillary walls DIF: deposition of immunoglobulins and complement around the dermal capillaries and linear at the basement membrane zone	Common disorder with estimated incidence of 1 case per 25,000 persons per year Not a true autoimmune blistering disorder but should be included in the differential diagnosis Can be associated with hepatitis C infection

DIF = direct immunofluorescence; IIF = indirect immunofluorescence.

subepidermal ABDs show intact, tense bullae. Although most of the ABDs are idiopathic, medications can also cause variants of almost all the disorders, and a thorough medication review is essential (**Table 19**).

The most sensitive method for the diagnosis of ABD is a skin biopsy. A skin (shave or punch) biopsy of an intact, early vesicle or bullae with adjacent normal skin should be submitted in formalin and processed for hematoxylin and eosin staining. Each of the ABDs has characteristic histologic findings that suggest a differential diagnosis. In addition, a biopsy for direct immunofluorescence (DIF) in Michel transport medium should be performed. For optimal sensitivity, biopsies for DIF should be from noninvolved perilesional skin. The histologic findings together with the pattern on DIF can usually render a diagnosis.

H Bullous pemphigoid is the most common subepidermal ABD and overall the most common ABD. Onset is usually in adults 60 years of age and older and presents with urticarial and eczematous lesions that progress to tense bullae on an erythematous base (**Figure 94**). Oral involvement is present in approximately 20% of patients. There are varying degrees of pruritus with bullous pemphigoid. Bullae heal with pigment change but otherwise do not scar. It typically has a protracted course with exacerbations and remission. In the past, morbidity was high, but steroid-sparing agents result in successful management.

Pemphigus vulgaris is the most common intraepidermal ABD, and its incidence increases with age. It presents with oral or vaginal erosions and flaccid vesicles that rupture easily and leave erosions (**Figure 95**). Pemphigus vulgaris has a positive Nikolsky sign whereby light lateral friction on perilesional skin induces a blister. Lesions heal with pigment change but otherwise do not scar. Prior to the use of oral glucocorticoids and steroid-sparing agents, mortality was high owing to secondary infection and sepsis. H

Pemphigus foliaceus is a superficial intraepidermal ABD that is most common in middle-aged adults. It presents with crusted erosions on the scalp, head/neck, and trunk without mucous membrane involvement (**Figure 96**). It can be associated with autoimmune diseases, in particular lupus erythematosus.

Epidermolysis bullosa acquisita is a subepidermal ABD with a varied clinical presentation with onset in adulthood. Unlike bullous pemphigus, classic epidermolysis bullosa acquisita presents at sites of friction or trauma (hands, elbows, buttocks, axillae) with tense bullae that are not on an erythematous base. It heals with scarring (milia). Because of the generally noninflammatory nature of epidermolysis bullosa acquisita, treatment is difficult and avoidance of trauma is an important aspect of the regimen.

Dermatitis herpetiformis is a subepidermal ABD that is extremely pruritic. It is a lifelong condition with onset in

TABLE 19. Drug-Induced Autoimmune Blistering Disorders

Condition	Medications
Pemphigus	Thiol group (D-penicillamine, captopril, gold, pyrithioxine) Amoxicillin Ampicillin Cephalosporins Rifampin
Pemphigoid	Furosemide Amoxicillin Ampicillin Phenacetin Penicillin Penicillamine Psoralen plus ultraviolet A (PUVA) β-Blockers Terbinafine
Cicatricial pemphigoid	Penicillamine Indomethacin Practolol Clonidine Topical pilocarpine
Linear IgA bullous dermatosis	Vancomycin Captopril Amoxicillin Ampicillin Diclofenac Lithium
Pseudoporphyria	Furosemide Naproxen Oxaprozin Tetracycline Voriconazole

FIGURE 94. Bullous pemphigoid is characterized by subepidermal bullae blisters that are tense and do not rupture easily. It predominantly involves nonmucosal surfaces. Sites of predilection are the lower abdomen, inner thighs, groin, axillae, and flexural aspects of the arms and legs.

FIGURE 95. The flaccid, intraepidermal vesicle of pemphigus vulgaris are readily broken, leaving behind weeping erosions.

FIGURE 96. The superficial blisters in pemphigus foliaceus result in multiple erosions and crusting (similar to "corn flakes"). Intact vesicles are not seen regularly.

adulthood. There are small tense vesicles and papules, which are rarely intact, presenting as excoriations on the elbows, knees, and buttocks (**Figure 97**). Most patients have celiac disease. A gluten-free diet is first-line treatment for dermatitis herpetiformis, but additional therapy with dapsone is often is required. Before initiating therapy with dapsone, patients should be checked for glucose-6-phosphate dehydrogenase deficiency.

Management of ABDs depends on the symptoms, extent of disease, and associated comorbidities. For localized disease, topical or intralesional glucocorticoids may be sufficient. Because the epidermal barrier is disrupted in these conditions, secondary bacterial infection can lead to exacerbations. In general, treatments for ABD are not FDA approved and recommendations are based on expert opinion, consensus, and published evidence. The goal is to decrease circulating antibodies with the subsequent elimination of antibodies binding to skin antigens and the restoration of function. Initial treatment is with prednisone until no new vesicles or blisters are present. This is followed by a slow taper and the addition of a steroid-sparing agent. Recently rituximab has been shown to have high efficacy in pemphigus vulgaris.

KEY POINTS

- Autoimmune blistering diseases are characterized by persistent pruritic or painful vesicles or bullae with erosions of the skin.
- HVC A gluten-free diet is first-line treatment for dermatitis herpetiformis, but additional therapy with dapsone is often is required.
- Management of autoimmune bullous diseases depends on the symptoms, the extent of disease, and the associated comorbidities; immunosuppressive medications are often required.

FIGURE 97. Dermatitis herpetiformis is an autoimmune bullous disease that causes intensely pruritic small papulovesicles classically grouped on the scalp, elbows, knees, back, and buttocks. Due to intense pruritus, erosions and excoriations are the most common clinical finding.

Cutaneous Manifestations of Internal Disease

Rheumatology

Lupus Erythematosus

Lupus erythematosus (LE) is a family of autoimmune conditions featuring autoantibodies directed against nuclear targets. Cutaneous lupus erythematosus (CLE) can exist with or without systemic disease; however, as many as 80% of systemic lupus erythematosus (SLE) patients have some degree of skin disease. CLE is divided into two broad categories: lupus-specific skin disease and lupus-nonspecific skin disease. Lupus-specific skin disease is further divided into three groups: acute cutaneous lupus erythematosus (ACLE), subacute cutaneous lupus erythematosus (SCLE), and chronic cutaneous lupus erythematosus (CCLE) (**Figure 98**). The lupus-specific skin diseases are defined by their clinicopathologic characteristics and are not found in other conditions. Nonspecific skin disease may appear in other unrelated disorders.

The classic malar "butterfly" rash (**Figure 99**) is characteristic of ACLE; however, ACLE can also manifest as a "maculopapular" variant that is photosensitive and distributed over the chest, upper back, and arms. Both rashes are pink-violet macules to scaly papules and plaques. In vibrant cases, severe inflammation can cause separation of the epidermis, which appears similar to Stevens-Johnson syndrome/toxic epidermal necrosis (SJS/TEN) and may involve oral ulcerations. This is sometimes referred to as apoptotic epidermolysis syndrome. Bullous lupus, a variant of ACLE, is a blistering disorder caused by antibodies to the anchoring fibrils of the epidermis. Essentially all patients with ACLE have SLE and as such tend to

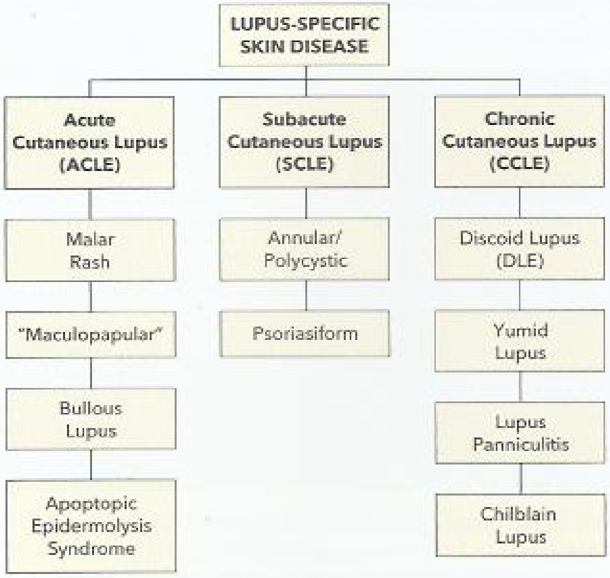

FIGURE 98. Classification of lupus-specific skin disease.

FIGURE 99. Malar butterfly rash in a patient with acute cutaneous lupus erythematosus showing pink-violet plaques with sparing of the nasolabial folds.

have systemic symptoms and positive serologies. The rash of ACLE does not scar.

SCLE appears as one of two variants: annular and polycyclic photosensitive plaques on the back, chest, and extremities, or psoriasiform scaly plaques in a similar distribution (**Figure 100**). SCLE does not scar, but may resolve with temporary pigmentary changes. Fewer than one in four SCLE patients have SLE, and as many as one in three are drug induced (**Table 20**). The latter may resolve with withdrawal of the causative agent. Up to 70% of patients with SCLE have an elevated antinuclear antibody titer, with anti-Ro and anti-La being overrepresented.

CCLE is another group of related skin diseases. Discoid lupus (DLE) is the most common. DLE lesions start as red-to-violet plaques that develop a hyperpigmented border and thick adherent scale in the center (**Figure 101**). Pulling back the scale will reveal projections from the underside that resemble carpet tacks. Eventually the centers of lesions become atrophic and depigmented, causing permanent alopecia if occurring in hair-bearing areas (**Figure 102**). Plaques favor the head and neck, particularly the scalp and conchal bowls (the hollow of the auricle of the external ear). CCLE in general has a low association with SLE, and DLE of the head and neck has approximately a 10% risk of underlying systemic disease.

FIGURE 100. Subacute cutaneous lupus erythematosus presenting as pink nonscarring annual and polycyclic macules and plaques on the chest and neck.

TABLE 20. Most Common Medications Causing Drug-Induced Cutaneous Lupus

ACE inhibitors
Griseofulvin
Hydralazine
Hydrochlorothiazide
NSAIDs
Proton pump inhibitors
Terbinafine
Tumor necrosis factor inhibitors

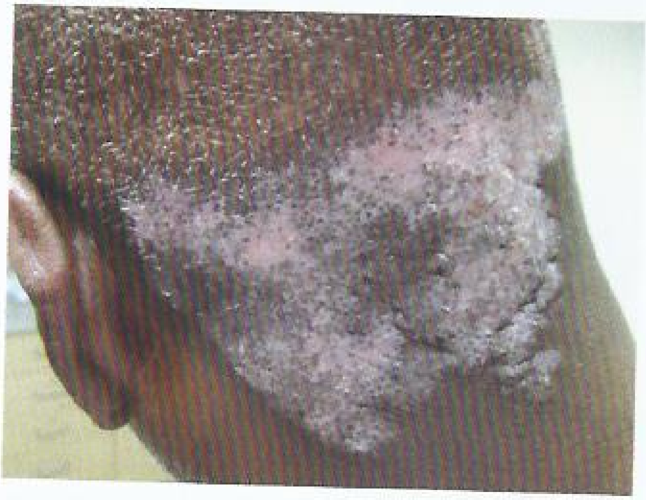

FIGURE 101. Chronic discoid lupus erythematosus on the occiput, with hyperpigmented borders, depigmented centers, dilated empty follicular ostia.

Lupus panniculitis appears as painful red indurated subcutaneous plaques that eventually cause atrophy and scarring depressions of the skin. DLE can often be seen overlying lupus panniculitis. The condition typically appears on the cheeks, lateral arms, breasts, and buttocks. Rarely lupus panniculitis transforms to a form of cutaneous T-cell lymphoma.

Chilblains or pernio are tender purple papulovesicles or plaques that appear on toes and fingers (**Figure 103**). They are triggered by exposure to cold or moisture and are unrelated to Raynaud phenomenon. They respond well to warming and calcium channel blockers.

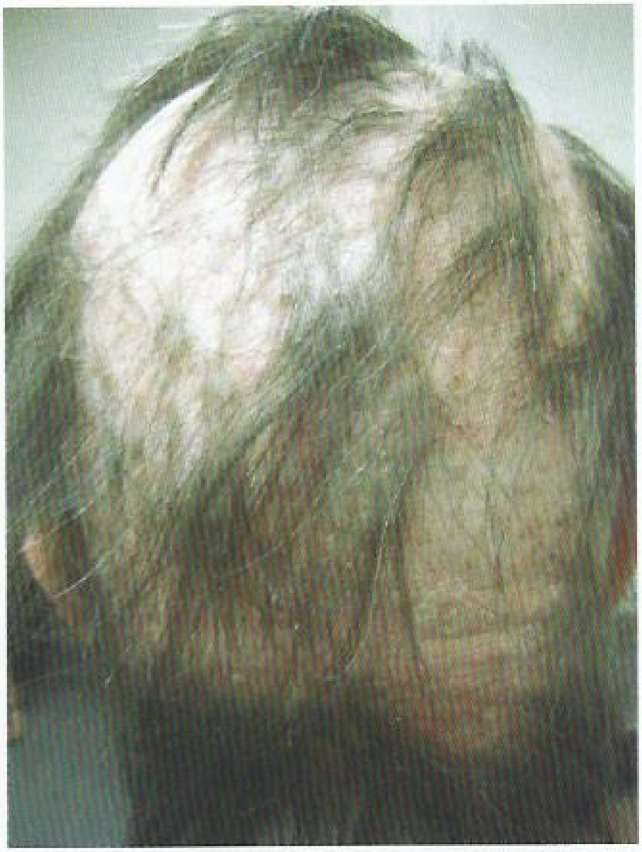

FIGURE 102. Active discoid lupus erythematosus of the scalp with scarring hair loss.

FIGURE 103. Chilblains/pernio in a patient with systemic lupus erythematosus appearing as tender purple plaques on the toes.

Tumid lupus presents with dermal macules or plaques on sun-exposed skin and is the most photosensitive of the lupus-specific skin diseases. It is uncommonly found in association with SLE (**Figure 104**).

Two lupus-nonspecific features are included in the Systemic Lupus International Collaborating Clinics criteria. First, oral or nasal ulcerations, a variant of minor aphthae, appear as white tender erosions of the oro- or nasopharynx. Second, "lupus hair," which is a variant of nonscarring alopecia, is a form of telogen effluvium. It may be localized, patchy, or diffuse. Most typical is a recession of the frontal hairline with sparse, short, wiry, and broken hairs left behind. Hair regrowth can be a sign of disease control.

FIGURE 104. Tumid lupus showing reticulate pink dermal plaques on the forehead in typical photodistribution.

Therapy for cutaneous lupus includes antimalarial agents such as hydroxychloroquine, methotrexate, mycophenolate mofetil, cyclosporine, dapsone, and combination therapy (**Table 21**). Thalidomide is effective for some patients with chronic cutaneous lupus.

The importance of photoprotection in the patient with lupus cannot be overstated. Patients should avoid peak sun hours and use barrier protection such as protective clothing and wide brim hats. Broad spectrum sunscreen (ultraviolet A and B filters) should be worn every day, with frequent reapplication. Sunlight and other sources of ultraviolet light drive disease activity, cause flares in stable patients, or even flare systemic disease.

KEY POINTS

- Lupus-specific skin disease is further divided into three groups: acute cutaneous lupus erythematosus (ACLE), subacute cutaneous lupus erythematosus (SCLE), and chronic cutaneous lupus erythematosus (CCLE)

(Continued)

TABLE 21. Treatment for Cutaneous Lupus Erythematosus
Antimalarial agents (hydroxychloroquine, may add quinacrine if not effective, or switch to chloroquine)
Cyclosporine, dapsone
Immunosuppressants (methotrexate, azathioprine, mycophenolate mofetil)
Rigorous solar protection and avoidance
Systemic retinoids (acitretin)
Thalidomide, leflunomide
Tobacco cessation
Topical anti-inflammatory agents (glucocorticoids or calcineurin inhibitors)

KEY POINTS ***(continued)***

- Essentially all patients with ACLE have systemic lupus erythematosus (SLE), and the most common manifestation of ACLE is a malar rash; SLE is much less commonly associated with SCLE and CCLE.
- Therapy for cutaneous lupus is antimalarial agents such as hydroxychloroquine, methotrexate, mycophenolate mofetil, cyclosporine, dapsone, and combination therapy.
- HVC Photoprotection, including avoiding peak sun hours, protective clothing, and the use of a broad-spectrum sunscreen, is an essential part of therapy for all forms of lupus.

Dermatomyositis

Dermatomyositis is an autoimmune disease that affects skin and proximal muscles in varying degrees of combination. Heliotrope rash (with pink-violet macules to edematous plaques on the eyelids) and Gottron papules (with lichenoid pink-violet papules on the knuckles, elbows, or knees) are pathognomonic signs of dermatomyositis. Patients commonly exhibit pink scaly plaques or macules on the scalp that extend onto the superior forehead, with varying degrees of nonscarring hair loss. The "shawl sign" refers to the pink-violet or poikilodermatous photodistributed macules with spotty hyper- and hypopigmentation ("salt and pepper") with telangiectasia and atrophy on the upper back, whereas the anterior V-sign references similar findings on the upper chest in a V shape (**Figure 105**). The Gottron sign manifests as pink macules over the knuckles, elbows, or knees without papules (**Figure 106**). The nailfold capillary beds of patients with dermatomyositis often demonstrate alternating areas of dilatation and dropout with periungual erythema. Cuticular overgrowth and hemorrhagic infarcts are also characteristic.

FIGURE 105. The shawl sign demonstrating a photodistributed erythematous patchy rash on the upper back in a patient with dermatomyositis.

FIGURE 106. Gottron papules are violaceous, slightly scaly plaques over the bony prominences on the hands.

Dermatomyositis and cutaneous lupus erythematosus can appear clinically similar. These conditions can be distinguished by sparing of the knuckles and upper eyelids in cutaneous lupus erythematosus, whereas dermatomyositis favors these areas. Dermatomyositis and CLE are essentially indistinguishable on skin biopsy.

Amyopathic dermatomyositis refers to characteristic skin findings without clinical or laboratory evidence of muscle disease for 6 months without treatment. This variant of dermatomyositis is about as common as classical disease. Amyopathic dermatomyositis is important to recognize because it carries similar risks for malignancy and interstitial lung disease (see MKSAP 18 Rheumatology).

The antisynthetase syndrome is a constellation of findings including dermatomyositis, hyperkeratotic, fissured skin on the palmar and lateral aspects of fingers (mechanic's hands), fevers, Raynaud phenomenon, elevated titers of anti-synthetase antibodies, and often interstitial lung disease. Anti-Jo1 is the prototypical antisynthetase antibody (**Figure 107**).

The cutaneous manifestations of dermatomyositis typically improve with the treatment of the associated myositis. It is a photosensitive disease, so aggressive photoprotection is foundational. Topical glucocorticoids are recommended as initial therapy but are often inadequate to control the skin lesions. Antimalarial agents can be helpful but can also flare the disease or cause drug-induced myopathy. Methotrexate, azathioprine, mycophenolate mofetil, and cyclosporine can be helpful. There are several reports supporting the use of JAK/STAT inhibitors in resistant cases. Intravenous immunoglobulin is a valuable tool in cases of severe recalcitrant skin disease.

FIGURE 107. Mechanic hands with hyperkeratotic, fissured skin on the palmar and lateral aspects of fingers seen in a patient with antisynthetase syndrome.

KEY POINTS

HVC • The heliotrope rash and Gottron papules are pathognomonic signs of dermatomyositis.

- Cutaneous lupus erythematosus can be distinguished from dermatomyositis by sparing of the knuckles and upper eyelids; dermatomyositis favors these areas.
- Photoprotection, topical glucocorticoids, antimalarials, and other systemic agents are typically needed to control the skin manifestations of dermatomyositis.

Sclerosing Disorders

The scleroderma family of disorders is discussed in the MKSAP 18 Rheumatology section. Patients with sclerosing disorders may exhibit skin findings that include "puffy hands" (early diffuse systemic sclerosis) and skin tightening (advanced diffuse systemic sclerosis) (**Table 22**). Raynaud phenomenon, especially with periungual capillary changes, is very common in systemic sclerosis and usually precedes skin disease (**Figure 108**).

Treatment with disease-modifying anti-inflammatory drugs such as methotrexate and mycophenolate are recommended to slow the progression of cutaneous sclerosis but result in only modest benefit. Patients with progressive sclerosis will progress to sclerodactyly or thick, hide-like skin of the fingers. This skin sclerosis will progress from distal to proximal (**Figure 109**). Both diffuse and limited sclerosis can affect the face resulting in restriction of the oral aperture, atrophied lips, and perioral creases radiating around the mouth (**Figure 110**). Sclerosis can result in acroosteolysis (resorption of the finger tips) and fixed contractures of the fingers, wrists, elbows, or feet.

Localized scleroderma (morphea) begins as red-violet plaques that progress to isolated sclerotic circumscribed plaques (**Figure 111**). The scarring sclerosis is permanent, and

TABLE 22. Cutaneous Features of Systemic Sclerosis
Digital infarction that may lead to autoamputation
Fingertip ulcers with rat bite appearance
Matte telangiectases (face and lips mostly, but also on body)
Periungual erythema, and tortuous dilated capillary loops
Rhagades (radial creases extending outward from lips)
Salt and pepper hyperpigmentation or depigmentation (typically in areas of sclerosis)
Sclerodactyly

FIGURE 108. The hand is the most likely site for attacks of vasospasm that characterize Raynaud phenomenon. A typical episode is precipitated by cold exposure, which is soon followed by distinctive color changes of white (ischemic phase) or blue (cyanotic phase). With rewarming there is the onset of redness, which heralds reperfusion.

FIGURE 109. Sclerodactyly (skin thickening over the fingers) extending proximal to the metacarpophalangeal joints in a patient with diffuse systemic sclerosis. Flexion contractions of the digits are present, most notable in the fifth digit.

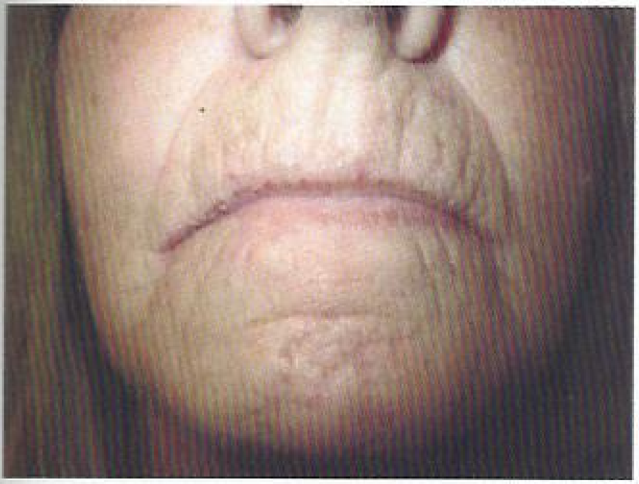

FIGURE 110. Rhagades (perioral fissures or a cluster of scars radiating around the mouth), lip atrophy and telangiectases in patient with limited systemic sclerosis.

FIGURE 111. Plaque morphea with red-violet inflammation at the border that indicates continued inflammatory activity.

active lesions will have a violet-pink border that fades as disease activity burns out. Most commonly, patients will have one to a few plaques, but the disease can generalize. Morphea is not associated with sclerodactyly or systemic disease (esophageal dysmotility, interstitial lung disease, or kidney involvement). Raynaud phenomenon is uncommon in these patients. Treatment is best accomplished with topical and systemic glucocorticoids or calcineurin inhibitors, methotrexate, or UVA therapy.

Eosinophilic fasciitis is sclerosis of the deep dermis and subcutis. Patients report tightening of the skin, mostly on the arms, and the appearance of the "dry river bed sign." This sign alludes to the collapsed appearance veins in the arms. The condition has been described to appear after periods of intense physical activity. Treatment includes systemic glucocorticoids or methotrexate.

KEY POINTS

- Raynaud phenomenon, especially with periungual capillary changes, is very common in systemic scleroderma and usually precedes skin disease.
- Patients with sclerosing disorders may exhibit skin findings that include "puffy hands" (early diffuse systemic sclerosis) and skin tightening (advanced diffuse systemic sclerosis).

Rheumatoid Arthritis

Rheumatoid arthritis may feature several cutaneous features, most notably rheumatoid nodules and rheumatoid vasculitis.

Rheumatoid nodules are the most common cutaneous manifestations of rheumatoid arthritis and are recognized as firm, nontender, dermal to subcutaneous nodules that can be moveable or bound to underlying fascia or bone. They vary in size from 2 mm to 5 cm and appear most commonly over pressure points and on the extensor surfaces of joints or tendons (**Figure 112**); however, they have been described almost everywhere on and in the body, including lungs, lymph nodes, and other organs. About one third of rheumatoid arthritis patients develop rheumatoid nodules. During treatment with methotrexate, the nodules may rapidly proliferate (accelerated nodulosis).

FIGURE 112. Rheumatoid nodules appear as slowly developing, firm, painless, subcutaneous nodules located at pressure points or over the extensor surfaces of joints and tendons.

Rheumatoid vasculitis is much less common and typically occurs in elderly male smokers with long-standing disease and high titers of rheumatoid factor. It can appear as a small or medium-sized vasculitis, with pigmented purpura, nodules, or stellate purpura and ulcers, and may affect nerves or organs.

Vasculitis

Vasculitis is discussed in detail in MKSAP 18 Rheumatology. This section focuses only on the cutaneous findings of vasculitis.

Small-vessel vasculitis affects the capillaries and venules. Patients develop palpable purpura, and/or petechiae, which are nonblanching hemorrhages, on dependent areas such as the shins, feet, hips, and buttocks, as well as pressure areas such as under the elastic band of clothing (**Figure 113**). Lesions may coalesce to form purpuric plaques or ulcerate.

Small-vessel vasculitis is a finding, not a diagnosis, and determining the cause is critical. Idiopathic small-vessel vasculitis involving only the skin is common, but the findings of small-vessel vasculitis can be seen in many systemic diseases such as granulomatosis with polyangiitis, eosinophilic granulomatosis with polyangiitis, microscopic polyangiitis, cryoglobulinemic vasculitis, immunoglobulin A (IgA) vasculitis, drug reactions, and infective endocarditis. Skin biopsy with direct immunofluorescence is important, as cases with IgA deposition (rather than IgG or IgM) are more likely to have systemic effects. An urticarial variant will deplete complement levels and is highly associated with systemic lupus erythematosus. Complement levels, rheumatoid factor, antinuclear antibody, cryoglobulin, and hepatitis testing can be helpful to narrow the differential diagnosis.

FIGURE 113. Small-vessel vasculitis manifesting as palpable purpura and petechiae in a patient with subacute lupus erythematosus.

Treatment of idiopathic cutaneous small-vessel vasculitis includes elevation, compression, NSAIDs, and antihistamines. Complicated or chronic cases may require glucocorticoids, dapsone, colchicine, or immunosuppressants.

Medium-vessel vasculitis affects the arterioles, including those that travel through the subcutis to supply segments of the skin. Inflammation and destruction of the vessels results in tender nodules on the legs and livedo reticularis and may be associated with reticulate purpura (**Figure 114**) or stellate ulceration (see Dermatologic Emergencies). Severe cases can cause ischemia or infarction of the digits, nose, ears, or genitals. Examples of conditions that can cause medium-vessel vasculitis skin findings include polyarteritis nodosa, granulomatous polyangiitis, eosinophilic granulomatous polyangiitis, drug-induced vasculitis (particularly from cocaine cut with levamisole), and cryoglobulinemic vasculitis. Consider testing for hepatitis B and C in patients with medium-vessel vasculitis. There is a cutaneous-only variant of polyarteritis nodosa, which is treated in a similar fashion to idiopathic cutaneous small-vessel vasculitis.

Large-vessel vasculitis does not typically involve skin findings, except for a palpable temporal cord in giant cell arteritis or in severe cases of Takayasu arteritis where ischemia or necrosis may occur.

Cryoglobulinemia is a condition characterized by soluble antibodies that precipitate from serum when cooled below body temperature. The disease may manifest as a combination of small- and medium-vessel vasculitis (cryoglobulinemic vasculitis) and may exhibit symptoms from both or either category. Palpable purpura, subcutaneous nodules, reticulate purpura, or stellate ulceration may occur starting on the lower legs. Cryoglobulinemic vasculitis is usually secondary to another condition. Treatment is best directed at the underlying disease, but systemic glucocorticoids or rituximab can be helpful, particularly in cases associated with viral hepatitis.

FIGURE 114. Livedo reticularis on the feet, recognized as a red-blue, reticulated vascular network in a patient with systemic lupus erythematosus.

KEY POINTS

- Small-vessel vasculitis, recognized by the presence of palpable purpura, and/or petechiae in dependent areas, may be idiopathic and limited to the skin, or secondary to systemic vasculitides, autoimmune diseases, cryoglobulinemia, drugs, and infective endocarditis.
- Medium-vessel vasculitis can present with tender nodules on the legs and livedo reticularis and may be associated with reticulate purpura or stellate ulceration.
- Cryoglobulinemia may manifest as a combination of small- and medium-vessel vasculitis with palpable purpura, subcutaneous nodules, reticulate purpura, or stellate ulceration starting on the lower legs.

Nephrology

Persons with end-stage kidney disease often have cutaneous findings. These findings have an insidious onset and can be quite subtle in the early stages. Xerosis and pruritus are most frequently seen. Pruritus may lead to chronic excoriations, lichenification, and prurigo-like changes. The exact mechanism of how end-stage kidney disease causes pruritus is still unknown. It is likely caused by diminished excretion of metabolites.

Dialysis is helpful in some patients, but not all. The itching can be treated with oatmeal baths, the liberal use of emollients, and over-the-counter antipruritics. Traditional soaps should be avoided and replaced with synthetic detergent cleansers (Dove, Cetaphil, and Olay). Topical glucocorticoids, antihistamines, and phototherapy have also been found to be helpful. There are three unique skin disease states seen predominately in persons with end-stage kidney disease: calciphylaxis, Kyrle disease, and nephrogenic systemic fibrosis.

Calciphylaxis

H Calciphylaxis is a rare disease seen most commonly in persons with chronic end-stage kidney disease, and those on dialysis with an elevated calcium-phosphorous product greater than 70 mg^2/dL^2. Parathyroid hormone levels are often dramatically elevated. Although the precise mechanism is not fully elucidated, those with end-stage kidney disease exhibit abnormalities in the endothelial cells, which allow for an abnormal deposition of calcium within the lumen of the dermal arterial and capillary vasculature. As the calcium deposition increases, small thromboses form that lead to ischemia and infarctions of the overlying tissue (**Figure 115**). The tissue becomes necrotic, painful, and a potential source for secondary infection that may lead to sepsis and death. Patients with calciphylaxis have a greater than 80% 1-year mortality rate. Body areas with high adipose tissue content are preferentially affected. The thighs and abdominal pannus are two of the most frequent areas involved.

The initial presentation may start as tender dusky red macules or a livedo reticularis pattern. It quickly progresses to develop tender subcutaneous plaques with an overlying dusky red discoloration. Surrounding purpura is often found. The area of involvement quickly expands in an angulated arrangement. As the skin infarcts, a black eschar forms. Because of poor underlying blood flow, the sores do not heal, which leads to chronic open ulcers and eschars that are highly susceptible to infections. H

FIGURE 115. Calciphylaxis showing eschar with angulated border on a patient's thigh. Note the central necrosis with surrounding erythema.

In those patients with hyperparathyroidism, parathyroidectomy may be helpful. Surgical debridement of dead tissue and prompt treatment of infection is important. Using a low-calcium dialysate during dialysis may help reduce the calcium-phosphorous product and slow down the deposition of calcium in the small vessels. The use of intravenous sodium thiosulfate has been reported to be beneficial because it works by increasing the solubility of the calcium deposits, thus clearing the blockages. Bisphosphonates may be beneficial in patients who have failed other forms of therapy.

KEY POINTS

- Calciphylaxis lesions are painful areas of necrotic tissues caused by dermal vascular calcification in patients with severe chronic end-stage kidney disease and a high calcium-phosphorus product.
- Sodium thiosulfate, along with meticulous wound care, may be beneficial in treating patients with calciphylaxis.

Kyrle Disease

Kyrle disease, a type of perforating dermatosis, is seen in patients with end-stage kidney disease and diabetes mellitus. Patients develop pruritic hyperkeratotic umbilicated papules or nodules with overlying hyperpigmentation. Within the umbilicated region is a firm central keratin plug or core (**Figure 116**). This plug contains collagen bundles that are

FIGURE 116. Kyrle disease showing hyperkeratotic hyperpigmented umbilicated papules with a central keratin plug. This is caused by extrusion of collagen from the dermis into and through the epidermis.

being extruded through the epidermis. Treatment is directed at the pruritus with the use of oatmeal baths, synthetic detergent cleansers, and liberal use of emollients and topical antipruritic agents. If only a few nodules are present, surgical removal is a treatment consideration.

KEY POINT

- Pruritic umbilicated papules or nodules with hyperkeratotic cores are characteristic of Kyrle disease.

Nephrogenic Systemic Fibrosis

Nephrogenic systemic fibrosis occurs in patients with end-stage kidney disease who have been exposed to gadolinium-containing contrast agents. Patients present with symmetrical, fibrotic indurated papules, plaques, or subcutaneous nodules most commonly located on the legs, the mid-thighs, and upper arms (**Figure 117**). The skin findings can occur weeks to years after exposure to gadolinium-containing contrast dyes. There are many anecdotal treatments including ultraviolet A phototherapy, extracorporeal photopheresis, kidney transplantation, and cyclophosphamide. Because of screening protocols that have been put in place before patients are given gadolinium-based contrasts, there has been a marked reduction in the number of new cases of nephrogenic systemic fibrosis.

FIGURE 117. Indurated papules and plaques are characteristic of early nephrogenic systemic fibrosis. These will eventually coalesce into large plaques.

KEY POINTS

- Nephrogenic systemic fibrosis presents with symmetrical, fibrotic indurated papules, plaques, or subcutaneous nodules most commonly located on the legs, the mid-thighs, and upper arms.
- Gadolinium-based contrast dyes should be avoided in patients with severe end-stage kidney disease.

Gastroenterology

Inflammatory bowel disease has been found to have an association with the development of erythema nodosum and pyoderma gangrenosum. Although these skin conditions can be idiopathic, their presence should alert the clinician to look for an underlying inflammatory bowel disease.

Dermatitis herpetiformis is associated with celiac disease. Porphyria cutanea tarda is seen most frequently in association with alcoholic liver disease, hepatitis C infection, or hemochromatosis.

Patients with cirrhosis will often develop nonspecific skin findings such as palmar erythema, spider telangiectasia, xerosis, and pruritus. Terry nails, manifested by whitening of the nail bed caused by edema, are seen in end-stage liver disease (see Nail Disorders).

Pyoderma Gangrenosum

H

Approximately half the cases of pyoderma gangrenosum are associated with an underlying disease, such as inflammatory bowel disease, leukemia, or lymphoma. Pyoderma gangrenosum presents with an exquisitely tender papule, pustule, or nodule. The area quickly enlarges and begins to ulcerate in a cribriform pattern, with intervening strands of epithelium. There is a characteristic violaceous border with an overhanging epithelium (**Figure 118**) around the central exudative ulcer, which is often described as a "wet ulcer." The most frequent location is the lower leg. Pyoderma gangrenosum is also seen frequently in association with a stoma site (peristomal) after ostomy placement in a patient with inflammatory bowel disease. Pyoderma gangrenosum often occurs in the site of trauma (pathergy), and there are numerous reports of pyoderma becoming much worse after surgical debridement. Once the inflammation has been treated and the ulcer heals, patients are often left with a prominent atrophic scar.

Pyoderma gangrenosum is a diagnosis of exclusion and is made after ruling out other causes of ulcerations. For this reason, diagnosis can be challenging and delayed. Skin biopsies are nonspecific but will often show a neutrophilic-rich ulceration with marked tissue edema. Tissue cultures should be negative, but are frequently complicated by surface colonization.

Management of pyoderma gangrenosum is multidimensional. The underlying disease state must be evaluated and treated. Initial therapy directed at the ulcer is with glucocorticoids, and small areas can be treated with intralesional glucocorticoids or potent topical glucocorticoids; however, most patients will require systemic glucocorticoid treatment.

FIGURE 118. Pyoderma gangrenosum is an uncommon, neutrophilic, ulcerative skin lesion that begins as tender papules, pustules, or vesicles that spontaneously ulcerate and progress to painful ulcers with a purulent base and undermined, ragged, violaceous borders.

H CONT.

Many treatment options are available and include cyclosporine, infliximab, dapsone, colchicine, mycophenolate mofetil, intravenous immunoglobulin, methotrexate, and thalidomide. Trauma and surgical debridement should be avoided to prevent pathergy. Local wound care is often best achieved with a wound care specialist to ensure proper care to avoid secondary infection and to minimize other complications. Recognition and treatment of secondary infection are difficult and require vigilance and frequent evaluations. H

KEY POINTS

- Pyoderma gangrenosum presents as a tender papule, pustule, or nodule that rapidly develops into an ulcer; there is often a characteristic violaceous rim with a rolled or overhanging border.
- Approximately half the cases of pyoderma gangrenosum are associated with an underlying disease, such as inflammatory bowel disease, leukemia, or lymphoma.
- Pyoderma gangrenosum usually responds well to systemic glucocorticoids; trauma and surgical debridement should be avoided to prevent pathergy.

H

Dermatitis Herpetiformis

Dermatitis herpetiformis is a neutrophilic dermatoses caused by IgA antibodies against tissue and epidermal transglutaminase. Dermatitis herpetiformis typically presents with intensely pruritic papules and fragile vesicles that rapidly break leaving tiny erosions (see Autoimmune Bullous Diseases and MKSAP 18 Gastroenterology and Hepatology). The elbows, knees, scalp, and lower back are the most common sites of involvement. A skin biopsy will show numerous neutrophils stuffing the dermal papillae, and a granular pattern of IgA deposition will be seen on direct immunofluorescence.

Most patients with dermatitis herpetiformis will have an underlying gluten-sensitive enteropathy; however, they are usually free of gastrointestinal symptoms. Interestingly, only 20% of patients with celiac disease will go on to develop dermatitis herpetiformis; however, all patients with dermatitis herpetiformis should be evaluated for underlying bowel involvement. Treatment is usually initiated with dapsone and a gluten-free diet. Dapsone is quickly effective in inducing a clinical remission, but a gluten-free diet is the preferred long-term management of both the skin and bowel disease. H

KEY POINT

- Patients with dermatitis herpetiformis should be evaluated for celiac disease, and long-term treatment is best achieved with a gluten-free diet. HVC

H

Porphyria Cutanea Tarda

Porphyria cutanea tarda presents with increased skin fragility noted on sun-exposed areas, most frequently on the dorsal hands. Small vesicles rupture leaving erosions (**Figure 119**). On close examination, milia are often seen in the healed areas that were once vesicles. Milia represent small epidermal inclusion cysts that develop after subepidermal blister formation. As the disease progresses, hyperpigmentation of skin and hypertrichosis of the forehead/temples is commonly seen. Jaundice may be present.

Porphyria cutanea tarda is most commonly caused by an acquired defect of hepatic uroporphyrinogen decarboxylase (UPDC) enzyme. Reduced UPDC activity results in the accumulation of porphyrinogens that are oxidized to porphyrin. Accumulated porphyrins are photosensitizing and when they are transported to the skin cause phototoxicity on light

FIGURE 119. Porphyria cutanea tarda manifests as a chronic blistering disease with epidermal erosions on sun-exposed skin, especially on the backs of the hands.

H CONT exposure. Chronic hepatitis C infection is the most likely cause, followed by alcohol-induced liver damage and hemochromatosis. A urine sample examined under Wood lamp illumination will fluoresce. The diagnosis can be confirmed by increased plasma or urine porphyrin level analysis.

The treatment is aimed at decreasing iron overload. In addition to treating the underlying condition, phlebotomy is the mainstay of therapy. Low-dose hydroxychloroquine is an effective second option for those who do not have significant iron overload. It is dosed at 200 mg once or twice weekly. H

Hematology/Oncology

Cutaneous manifestations of malignancy include both malignancy-related cutaneous paraneoplastic syndromes and skin disorders (**Table 23**) and hereditary syndromes with an

TABLE 23. Paraneoplastic Disorders: Conditions That Are Strongly Linked to Internal Malignancy

Condition	Clinical Findings	Associated Malignancy/Comments
Acanthosis nigricans	Velvety or verrucous hyperpigmentation of intertriginous areas, weight loss, glossitis	Adenocarcinoma, usually GI or GU, most commonly of the stomach; also occurs in patients with endocrinopathy
Amyloidosis	"Pinch purpura" in sites of thin skin such as the periorbital area, usually accompanied by macroglossia and smoothing of the tongue	Seen in multiple myeloma or systemic amyloidosis
Bazex syndrome (also known as acrokeratosis paraneoplastica)	Psoriasiform, violaceous scaling on the acral surfaces (fingers, toes, nose, and ears); keratoderma may also be present	Squamous cell carcinoma of the upper respiratory tract or upper GI tract; effective therapy of an associated cancer is followed by resolution of the dermatosis
Carcinoid syndrome	Episodic flushing, often accompanied by diarrhea and bronchospasm; can eventually result in telangiectasia or permanent ruddiness	Primarily due to GI carcinoid tumors metastatic to the liver; tumor removal is followed by resolution of the skin and systemic findings
Dermatomyositis	Heliotrope rash, Gottron papules, shawl sign, photodistributed violaceous erythema; scaly erythema of the scalp with diffuse alopecia; periungual telangiectasias and cuticular overgrowth	20% to 25% of patients with dermatomyositis had, have, or will have a malignancy; ovarian cancer is overrepresented; paraneoplastic course is possible but unusual
Ectopic ACTH syndrome	Generalized hyperpigmentation	Small cell lung cancer; tumor removal can result in improvement of the pigmentation
Extramammary Paget disease	Erythematous scaly patch or plaque on the perineal skin, scrotum, or perianal area	Cancer of the GI or GU tract is present in 25% of patients; it is not contiguous with the dermatosis; the dermatosis is a malignancy and needs appropriate excision or ablation
Leser-Trélat sign	Rapid appearance or inflammation of multiple seborrheic keratoses; often occurs in conjunction with acanthosis nigricans	Same cancer association as acanthosis nigricans; seborrheic keratoses are common lesions; Leser-Trélat sign is very rare
Necrobiotic xanthogranuloma	Purple-orange nodules and plaques, often on the upper eyelids, which frequently ulcerate	90% of patients have an associated paraproteinemia (generally IgG κ) and may develop multiple myeloma
Necrolytic migratory erythema	Intertriginous erythema, scales, and erosions; glossitis and angular cheilitis are common	Glucagon-secreting tumor of the pancreas
Neutrophilic dermatoses	Sweet syndrome; atypical pyoderma gangrenosum (bullous lesions with a blue-gray border, often on the hands, arms, or face)	Myeloid leukemia, myelofibrosis, and refractory anemias; these disorders also occur without malignancy in 80% to 90% of patients
Paget disease of the breast	Erythematous, irregularly bordered plaque on the nipple	Represents an extension of a ductal adenocarcinoma of the breast
Paraneoplastic pemphigus	Severe mucosal erosions, tense and flaccid bullae that may be widespread	Non-Hodgkin B-cell lymphoma, Castleman disease, chronic lymphocytic leukemia
Scleromyxedema	Waxy fine papules over the face, neck, and upper trunk	Most patients have an associated paraproteinemia (generally IgG λ) and may develop overt multiple myeloma
Tripe palms	Rugose folds on the palms and soles; may occur with or without acanthosis nigricans	If occurring with acanthosis nigricans, same cancer association; if occurring without acanthosis nigricans, squamous cell carcinoma of the head and neck or lungs

ACTH = adrenocorticotropin hormone; GI = gastrointestinal; GU = genitourinary.

associated risk of malignancy with cutaneous findings as part of the syndrome (**Table 24**).

Sweet Syndrome

Sweet syndrome, or acute febrile neutrophilic dermatosis, is characterized by fever, neutrophilia, a dense dermal infiltrate on histology, and characteristic skin lesions. Skin lesions are painful, edematous, red-to-violaceous "juicy" papules and plaques, most common on the face, neck, and extremities (**Figure 120**). Additional diagnostic criteria include responsiveness to oral glucocorticoids and absence of infection. Most cases of Sweet syndrome typically develop after an upper respiratory or gastrointestinal infection or in the setting of hematologic abnormalities, particularly myelodysplastic syndrome and myelodysplastic syndrome evolving into acute myeloid leukemia (**Table 25**). Sweet syndrome has also been associated with solid malignancies and medications (particularly neutrophil-stimulating medications such as granulocyte-colony stimulating factor and all-trans retinoic acid. In addition to the skin eruption, patients typically have high fevers, leukocytosis with a left shift, elevated inflammatory markers, and often muscle or joint pain.

Amyloidosis

The hallmark of systemic amyloidosis with cutaneous involvement and cutaneous amyloidosis is extracellular deposition of altered amyloid protein in the skin. In primary (systemic) immunoglobulin light-chain amyloidosis (AL), AL amyloid deposits in multiple organs including the skin. Skin manifestations are present in 30% to 40% of patients and include generalized waxy appearance, easy bruising with minor pressure (pinch purpura) (**Figure 121**), violaceous discoloration around the eyes ("raccoon eyes"), yellow waxy papules and plaques especially in a periorbital location (**Figure 122**), dystrophic nails, and macroglossia (**Figure 123**). When the

TABLE 24. Genetic Diseases with Cancer Associations and Skin Findings[a]

Condition	Clinical Findings	Associated Malignancy/Comments
Birt-Hogg-Dube syndrome	Fine white sclerotic facial papules (fibrofolliculomas or trichodiscomas); spontaneous pneumothoraces	Kidney cancer
Cowden syndrome	Tan facial papules (tricholemmomas) and oral papillomas or cobblestoning	Adenocarcinomas of the breast or thyroid and/or polyps of the gastrointestinal tract
Muir-Torre syndrome (Lynch syndrome)	Sebaceous neoplasms and keratoacanthomas (squamous cell carcinoma subtype)	Adenocarcinomas of the gastrointestinal tract or other tumors of the genitourinary tract. Lung, breast, and hematologic malignancies may occur.
Reed syndrome	Tender cutaneous papules (leiomyomas); uterine fibroids	Kidney cancer
Tuberous sclerosis complex	Multiple cutaneous lesions (facial angiofibromas, ash leaf spots, hypopigmented macules, subungual papules); cortical tubers and seizures; female patients may develop lymphangioleiomyomatosis	Kidney cancer

[a]This table is a brief review focused on genetic diseases that can present in adulthood; this is not a comprehensive list of genetic skin diseases with cancer associations.

FIGURE 120. The tender skin lesions of Sweet syndrome appear as "juicy" indurated edematous red-purple plaques and nodules, sharply demarcated from the adjacent skin.

TABLE 25. Associations with Sweet Syndrome

Acute myelogenous leukemia
Behçet disease
Chronic leukemias
Inflammatory bowel disease
Multiple myeloma
Myelodysplastic syndrome
Myeloproliferative disorders
Relapsing polychondritis
Rheumatoid arthritis
Solid tumors (rare)
Thyroid disease

FIGURE 121. Extensive purpura in a 66-year-old man with amyloidosis. Only minor pressure will cause dermal bruising ("pinch purpura"). The ecchymoses labeled V3-V6 are from suction cup ECG chest leads used the day before this photo was taken.

FIGURE 122. A 50-year-old man with prominent periorbital purpura. Easy bleeding leads to characteristic "pinch purpura" (arrow).

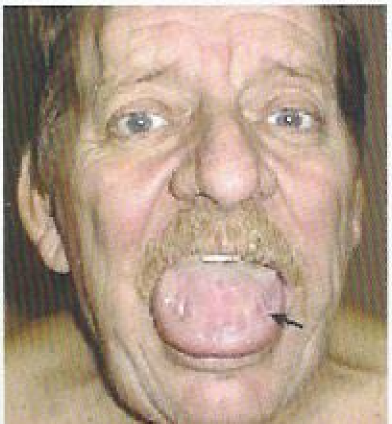

FIGURE 123. Massive infiltration by amyloid leading to macroglossia. Note the indentations from teeth pressing on the firm and enlarged tongue (arrow).

diagnosis is suspected, patients should be screened with immunofixation of serum and urine and serum free light chain assay. Skin biopsies for the diagnosis of AL are controversial, as even when amyloid protein is seen in the dermis, the biochemical composition must be established with immunofixation studies (see MKSAP 18 Hematology and Oncology).

Endocrinology

Many patients with endocrine disorders have associated dermatologic conditions. This section will focus on some conditions associated with thyroid disease and diabetes mellitus, since a high proportion of these patients have at least one dermatologic complication.

Eruptive Xanthomas

Eruptive xanthomas are characterized by a rapid onset of numerous yellow papules with surrounding erythema primarily on the extensor surfaces of the extremities and buttocks. Diagnosis is made by a skin biopsy that shows lipid-laden macrophages in the dermis. Eruptive xanthomas are pathognomonic of hypertriglyceridemia with a vast number of these patients also having a diagnosis of diabetes mellitus. Lesions typically resolve with control of carbohydrate and lipid metabolism.

Acanthosis Nigricans

H

Acanthosis nigricans presents as velvety-to-verrucous, gray-to-brown thickening with accentuation of skin marking and is seen in the intertriginous folds and neck (**Figure 124**).

FIGURE 124. Acanthosis nigricans, characterized by a velvety brown plaque in a patient with insulin resistance.

Histologically, the pigment change results from epidermal thickening. Acanthosis nigricans is more common in persons of color. It can be associated with diabetes or a malignant and paraneoplastic syndrome. Therefore, a diagnosis of acanthosis nigricans should prompt screening for diabetes and, if of acute onset, screening for malignancy. It is mainly of cosmetic concern and resolves when the underlying condition is treated. Topical salicylic acid, retinoids, and ammonium lactate have modest benefit.

Necrobiosis Lipoidica

Necrobiosis lipoidica is a chronic condition that is seen mainly in patients with diabetes mellitus, both type 1 (more commonly) and type 2. Necrobiosis lipoidica presents as well-demarcated, indurated, yellow brown oval plaques with central atrophy and telangiectasias. Lesions are typically seen on the bilateral pretibial areas but can occur anywhere on the body.

The diagnosis is usually made on clinical findings, but a punch biopsy of skin to include subcutaneous tissue can be performed to confirm the diagnosis. Histology shows a necrobiotic granulomatous dermatitis. Only a small portion of patients with diabetes (0.3% to 1.6%) develop necrobiosis lipoidica, and in most patients the diabetes precedes necrobiosis lipoidica. Patients with necrobiosis lipoidica without diabetes should be monitored closely for diabetes. Glycemic control does not usually lead to resolution of necrobiosis lipoidica. Treatment is challenging, and relapses are common.

Pretibial Myxedema

Autoimmune thyroid disease, particularly Graves disease, may uncommonly be associated with pretibial myxedema, an accumulation of glycosaminoglycans in the dermis, usually over the lower legs. Pretibial myxedema presents with firm nodules and plaques with a "peau d' orange" appearance on the pretibial area (**Figure 125**). Diagnosis is based on clinical findings, elevated thyroid-stimulating immunoglobins, and skin biopsy showing characteristic accumulation of mucin in the dermis. Control of the hyperthyroidism does not usually lead to resolution of pretibial myxedema.

FIGURE 125. Pretibial myxedema is generally seen in patients with Graves disease. It is also termed thyroid dermopathy. It results from the accumulation of glycosaminoglycans in the dermis that leads to characteristic thickening and the development of firm, compressible plaques with a "peau d'orange" appearance.

Infectious Disease

Dermatologic conditions are very common in patients with HIV and AIDS, and in some this may be the first clue of infection. Cutaneous manifestations can be divided into three categories: immunologic (decreasing CD4 count), related to antiretroviral therapy, and increased prevalence or severity of endemic infections. Many of these conditions are also found in the general population; however, in patients with HIV, they tend to have increased severity, prevalence, atypical presentations, and be recalcitrant to treatment. Because of atypical presentations and the increased risk of infections, if the diagnosis cannot be made on clinical grounds, two skin biopsies should be performed: one for histologic evaluation and the second for bacterial, mycobacterial, and fungal culture.

Acute seroconversion syndrome (primary HIV infection) is an acute mononucleosis like illness that occurs in many (90%) but not all patients 2 to 4 weeks after infection. Clinical presentation includes fever, sore throat, cervical adenopathy, and an exanthem. The exanthem is made up of asymptomatic erythematous macules and papules involving the face and trunk. The recommended algorithm for diagnosing HIV infection involves use of the fourth-generation HIV test. This test combines an immunoassay for HIV antibody with a test for HIV p24 antigen.

Many HIV-associated primary dermatologic disorders, including xerosis, atopic dermatitis, seborrheic dermatitis, and psoriasis, are related to the T-cell imbalances. Atopic dermatitis and xerosis are related and present with dry skin and eczematous patches. Both conditions are associated with pruritus, which is often severe and can be recalcitrant resulting in a high burden of morbidity for these patients. In seborrheic dermatitis, there are erythematous patches with greasy scale on the scalp, nasal labial folds, and chest. This condition is extremely common in patients with HIV, and most patients with AIDS have some compatible findings. The prevalence of psoriasis, which presents with plaques with overlying scale, and psoriatic arthritis, is increased in patients with AIDS but not those with HIV. New-onset pruritus, atopic dermatitis, seborrheic dermatitis, and psoriasis that is severe and recalcitrant to treatment should prompt testing for HIV/AIDS.

Eosinophilic folliculitis is a condition that is almost exclusively seen in AIDS, in particular in later stages. It presents as extremely pruritic, erythematous follicular-based papules and pustules on the upper trunk, neck, and face. Skin biopsy is diagnostic, showing numerous eosinophils within the follicular infundibulum with destruction of the sebaceous gland. Treatment is challenging with first-line therapy being medium- to high-potency topical glucocorticoids.

Pulmonary

Sarcoidosis is an inflammatory granulomatous disease commonly associated with skin manifestations, some of which predict specific internal organ involvement. Lupus pernio is sarcoidosis of the nose and central face, manifesting as violaceous subcutaneous plaques or nodules, often with some overlying scaling. Lupus pernio is more common in skin of color and is associated with an increased risk for extracutaneous disease, particularly intrathoracic sarcoidosis. Sarcoid lesions may also preferentially develop in sites of trauma, and these lesions are also associated with an increased risk of pulmonary disease. Other more common cutaneous manifestations of sarcoidosis include violaceous papules on the nose, periorbitally and around the oropharynx, and nasal openings.

Limited cutaneous sarcoidosis is treated with topical or intralesional glucocorticoids and more extensive disease is typically treated with hydroxychloroquine. Patients who fail to respond may be treated with thalidomide, methotrexate, or occasionally TNF-α inhibitors.

H Erythema nodosum is the most common form of panniculitis, or inflammation of the fat. Erythema nodosum manifests as ill-defined, tender, bilateral dermal red or violaceous nodules, most commonly on the bilateral shins (**Figure 126**). Most resolve spontaneously over 4 to 6 weeks. Erythema nodosum is a nonspecific reaction to some systemic process.

The most common associations are streptococcal infection, hormones (including oral contraceptives, hormone replacement therapy, or pregnancy), inflammatory bowel disease, sarcoidosis, and other medication reactions. The appearance of erythema nodosum in patients with sarcoidosis usually signifies an acute presentation with a good long-term prognosis. The combination of erythema nodosum, arthritis, hilar lymphadenopathy, and fevers constitute Löfgren syndrome. This set of findings is so specific for sarcoidosis that a biopsy is not needed to confirm the diagnosis. Most cases of erythema nodosum resolve spontaneously, and therapy is supportive in nature with NSAIDs and compression stockings. H

FIGURE 126. Erythema nodosum manifests as painful, red-brown nodules on the anterior shins.

KEY POINT

- Löfgren syndrome consists of erythema nodosum, arthritis, and hilar lymphadenopathy; this is so specific for sarcoidosis that a biopsy is not needed to confirm the diagnosis. HVC

Dermatologic Emergencies

Retiform Purpura

H Retiform is a descriptive term for a net-like, branching, or stellate configuration, reflecting the vascular structure of the skin. Purpura refers to the nonblanching dark red or purple color resulting from extravasation of erythrocytes into the skin (**Figure 127**). Retiform purpura signifies total occlusion of cutaneous arterioles with downstream necrosis and hemorrhage in the watershed area of the vessel. Occlusion of several adjacent vessels may result in purpura and necrosis of body segments (**Figure 128**), particularly in acral regions (digits, ears, genitals).

Retiform purpura is a description, not a diagnosis, and the cause must be determined to preserve life and limb. Because of their devastating consequences, thrombotic and embolic causes should be considered first. Thrombotic causes can be due to unregulated coagulation such as disseminated intravascular coagulation, thrombotic thrombocytopenic purpura, or warfarin- or heparin-induced thrombosis. The heart and large vessels may be sources of emboli as seen with bacterial or marantic endocarditis, atrial myxoma, or cholesterol emboli following an intravascular procedure.

Diagnosis is made by history and examination (**Table 26**). The evaluation should be directed by the most likely associated disorder. A wide net of testing may be necessary in the critically ill patient without a clearly identified underlying condition. In a stable patient, skin biopsy can further direct the evaluation. Treatment is directed toward the underlying cause.

FIGURE 127. Retiform purpura on the lower legs due to vasculitis characterized by dark red or purple net-like, branching, or stellate configuration.

FIGURE 128. Retiform purpura resulting in ulceration and necrosis secondary to total occlusion of cutaneous arterioles.

TABLE 26. Differential Diagnosis for Retiform Purpura

Category	Examples
Vasculitis	Rheumatoid vasculitis
	Polyarteritis nodosa
	Granulomatosis with polyangiitis
	Eosinophilic granulomatosis with polyangiitis
	Systemic lupus erythematosus
	Cryoglobulinemic vasculitis
	Scleroderma
Thrombotic	Disseminated intravascular coagulopathy
	Thrombotic thrombocytopenic purpura/ hemolytic uremic syndrome
	Antiphospholipid syndrome
	Inherited and acquired thrombophilias
	Myeloproliferative disorders
Embolic	Fat emboli
	Septic emboli
	Cholesterol emboli
	Infectious and marantic endocarditis
Arteriopathy	Calciphylaxis
Infectious	Meningococcemia
	Angioinvasive fungi
	Ecthyma gangrenosum
	Necrotizing fasciitis
Drug-related	Heparin
	Warfarin
	Levamisole-adulterated cocaine

Erythema Multiforme

H CONT

Erythema multiforme (EM) minor is an immune-mediated condition that can be recognized by its classic targetoid plaques with characteristic histopathologic features. The sharply defined circinate plaques feature two differently colored concentric rings (pale inner ring, red outer ring) surrounding a pale, dusky, vesiculated or crusted center (**Figure 129**). These plaques typically appear on the face and acral sites, such as the back of the hands, the arms, legs, or feet. The palms and soles may also be involved. Crops of lesions persist for approximately 7 days and resolve without scarring. Most cases of EM minor are caused by infections, herpes simplex virus 1 and 2 being the most common followed by *Mycoplasma pneumoniae*, particularly in children. Drug-induced cases of EM minor are less frequent and typically result from NSAIDs, antiepileptic agents, or sulfonamides. Mucosal involvement is rare, but if present, is trivial.

EM major has severe mucosal involvement and systemic symptoms in addition to typical skin findings found in EM minor. Lesions in the mouth blister and become painful erosions. They are often polycyclic and involve the buccal mucosa and lips, where the edges may suggest the concentric rings of EM. The eyes, nasopharynx, and genitals are less commonly affected. Fever and malaise may precede rash, and joint pain and swelling have been described. Internal organ involvement should prompt reconsideration of the diagnosis. Skin biopsy can be helpful when the diagnosis is unclear, and direct immunofluorescence can be used to exclude the possibility of autoimmune blistering disease. EM can recur, and in approximately 70% of patients this is associated with herpes simplex virus infection. These patients may benefit from suppressive antiviral therapy. Antimicrobial therapy is helpful if *M. pneumoniae* is the trigger of EM. If a drug is implicated, the immediate first step is stopping the drug. Systemic

FIGURE 129. Targetoid lesions of erythema multiforme characterized by two concentric rings (pale inner ring, red outer ring) surrounding a pale or dusky center.

H CONT. glucocorticoids are highly effective for decreasing inflammation and pain, even when patients have an infectious trigger, and short courses (3-4 weeks) should be considered early in the disease. H

KEY POINTS

- Erythema multiforme can be recognized by classic targetoid plaques that appear on the face and acral sites, such as the back of the hands, the arms, legs, or feet.
- Most cases of erythema multiforme are caused by herpes simplex virus or *Mycoplasma pneumoniae*; drug-induced cases of erythema multiforme minor are less frequent and typically result from NSAIDs, antiepileptic agents, or sulfonamides.
- HVC Erythema multiforme can recur, and in approximately 70% of patients this is associated with herpes simplex virus infection; these patients may benefit from suppressive antiviral therapy.

H Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) represent a spectrum of severe mucocutaneous reactions defined by the extent of affected body surface area (BSA) involved with blisters and erosions. They are the most severe and deadly of the cutaneous adverse drug reactions. SJS refers to patients with less than 10% BSA affected. Greater than 30% BSA affected is the criterion for TEN. Patients with BSA between 10% and 30% are referred to as SJS/TEN overlap syndrome. Key features include full-thickness epidermal necrosis with involvement of mucous membranes. Essentially all cases of TEN are temporally correlated with medications (**Table 27**), whereas about 25% of SJS cases are caused by infection or vaccination. HIV infection, kidney disease, uncontrolled autoimmune disease, and human leukocyte antigen type (HLA-B*1502 and HLA-B*5801) also contribute to increased risk. Patients of Asian and South Asian ancestry who are positive for HLA-B*1502 have up to a 10% risk for SJS/TEN when exposed to aromatic anticonvulsants (carbamazepine, phenytoin, and phenobarbital). HLA-B*5801 positivity predicts risk of SJS/TEN upon exposure to allopurinol. The role of genetic screening to prevent these reactions is unsettled.

Symptoms begin usually within 1 to 3 weeks of exposure to the inciting agent. Patients may notice fever, malaise, and symptoms of upper respiratory infections followed by skin pain, grittiness or sand-like irritation of the eyes, and odynophagia. Shortly thereafter, patients develop red or purple dusky macules on the trunk that progress to vesicles, erosion, and ulceration (**Figure 130**). Painful erosions develop in the mouth, eyes, or genitals in as many as 95% of patients. Unlike EM's predilection for the extremities, SJS and TEN favor the trunk and face. SJS/TEN patients may exhibit atypical targetoid macules demonstrating one or two colored rings, which can be distinguished from the three colored zones of EM. The presence of extensive epidermal sloughing and a positive Nikolsky sign further differentiate SJS/TEN from EM major (**Table 28**).

Systemic manifestations are common in SJS/TEN patients. All patients experience fever and malaise. Lymphadenopathy, elevated transaminase levels, and cytopenias are common. Pneumonitis, nephritis, hepatitis, and myocarditis are possible. Hypovolemia and electrolyte imbalances due to loss of the skin barrier are common.

The acute phase of the disease lasts 1 to 2 weeks, and skin reepithelization may take 2 to 4 weeks. Mortality is high with 5% to 10% of SJS cases being fatal and as many as one in three patients with TEN dying from complications related to the disease. Most deaths result from secondary infection, complications of transcutaneous fluid loss, or respiratory distress. Early identification and withdrawal of the causative medication improve outcomes. The SCORTEN scale is a validated, severity of illness tool for TEN and SJS that can be applied early in the course of the disease. The mortality rate is directly correlated with the number of SCORTEN variables that are fulfilled (**Table 29**).

Treatment of SJS/TEN is highly controversial. Intravenous glucocorticoids or intravenous immune globulins are probably the most commonly used treatments, but neither is supported by strong evidence. Supportive care in an ICU with experienced nursing staff is critical for wound care, and many

TABLE 27. Medications Most Commonly Leading to Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis
Allopurinol
Aminopenicillins (ampicillin, amoxicillin)
Carbamazepine
Lamotrigine
Nevirapine
Phenytoin
Sulfamethoxazole-trimethoprim
Sulfasalazine

FIGURE 130. Swelling of the lips with vesicles on the lower lip and erosions and mucosal sloughing on the upper lip secondary to Steven-Johnson syndrome.

TABLE 28. Comparison of Erythema Multiforme, Stevens-Johnson Syndrome, and Toxic Epidermal Necrolysis

	Erythema Multiforme (EM)	Stevens-Johnson Syndrome (SJS)	Toxic Epidermal Necrolysis (TEN)
Morphology	Typical 3-zoned target	Atypical targets and confluent erythema with sloughing	Extensive, confluent erythema with sloughing
Distribution	Favors extremities	Trunk and extremities; up to 10% body surface area involvement[a]	Trunk and extremities; at least 30% body surface area involvement[a]
Mucosal disease (oral, eye, genitourinary)	1 or 2 sites	2 or more sites	2 or more sites
Constitutional symptoms	+	++/+++	+++
Etiology:			
Infection (%)	50	26	6
Drugs implicated in (%)	50	74	94
Mortality rate (%)	0	5-13	25-39

[a]SJS/TEN overlap: 10% to 30% body surface area involvement, remaining features the same as SJS.

TABLE 29. SCORTEN Tool Values

SCORTEN Features	Values Associated with Poor Prognosis
Age	>40 years
Malignancy	Present
Heart rate	>120/min
Body surface area	>10%
Plasma glucose	>252 mg/dL (13.98 mmol/L)
Blood urea nitrogen	>28 mg/dL (9.99 mmol/L)
Bicarbonate	<20 mEq/L (20 mmol/L)

The likelihood of death increases with each feature. Five or more features is associated with a 90% mortality rate.

Data from: Bastuji-Garin S, Fouchard N, Bertocchi M, Roujeau JC, Revuz J, Wolkenstein P. SCORTEN: a severity-of-illness score for toxic epidermal necrolysis. J Invest Dermatol. 2000 Aug;115(2):149-53. PubMed PMID: 10951229.

H CONT

patients are transferred to a burn center. Infection is a significant cause of mortality. A low threshold is recommended for performing cultures and initiation of empiric antibiotics, but use of prophylactic antibiotics is not recommended. Ophthalmologic and urologic consultations are mandatory if ocular or genital involvement is present, as destructive scarring may occur in these areas. H

KEY POINTS

- Key features of Stevens-Johnson syndrome and toxic epidermal necrolysis include full-thickness epidermal necrosis with involvement of mucous membranes, which is potentially lethal due to secondary infection, complications of transcutaneous fluid loss, or respiratory distress.
- Stevens-Johnson syndrome and toxic epidermal necrolysis are distinguished by the amount of skin detachment that is involved.

(Continued)

KEY POINTS *(continued)*

- Intravenous glucocorticoids or intravenous immune globulins are the most commonly used treatments for Stevens-Johnson syndrome and toxic epidermal necrolysis; supportive care in an ICU or burn unit is critical for wound care.
- The role of genetic screening for HLA-B*1502 and HLA-B*5801 to prevent Stevens-Johnson syndrome and toxic epidermal necrolysis is unsettled. HVC

Drug Hypersensitivity Syndrome (or DRESS Syndrome) H

Drug hypersensitivity syndrome (DHS) and drug reaction with eosinophilia and systemic symptoms (DRESS) are synonymous and represent another severe life-threatening medication reaction. The most common culprit medications include sulfonamide antibiotics, allopurinol, and anticonvulsants, but many more medications have been implicated (**Table 30**). Unlike other medication reactions, the onset of symptoms is delayed, often by 2 to 6 weeks, from the time of exposure. Patients begin with fever and flulike symptoms, which are quickly followed by burning skin pain and rash. Patients typically develop a morbilliform exanthem that starts on the face and upper trunk and spreads distally (**Figure 131**). Eventually

TABLE 30. Medications Most Commonly Causing DRESS Syndrome

Abacavir
Allopurinol
Aromatic antiepileptic drugs (carbamazepine, phenytoin, and phenobarbital)
Minocycline
Proton pump inhibitors
Sulfasalazine

FIGURE 131. Generalized morbilliform eruption in a patient with drug reaction with eosinophilia and systemic symptoms (DRESS). Vesicles, blisters, and pustules may also be seen.

H CONT.

the patients develop striking facial edema and redness, a hallmark of this condition. Oral mucosal involvement is common but is less severe than SJS/TEN or EM major.

Systemic involvement is necessary for the diagnosis and most commonly features eosinophilia or an atypical lymphocytosis and elevated transaminase levels. Hypotension, shock, and multisystem organ damage are possible, and death occurs in about 10% of patients. Immediate discontinuation of the causative agent is mandatory, and systemic glucocorticoids tapered over weeks to months can be helpful. DRESS caused by an aromatic antiepileptic agent can also pose a serious threat due to cross reaction with other aromatic antiepileptics. For example, if phenytoin causes DHS but is appropriately stopped, neither phenobarbital nor carbamazepine should be substituted because of the risk of cross reaction.

Acute Generalized Exanthematous Pustulosis

Acute generalized exanthematous pustulosis (AGEP) refers to the rapid onset of a pustular rash following a medication exposure in a patient without a history of pustular psoriasis. Onset may be as soon as 1 day after exposure to the medication or a few days at most. Patients present with fever, erythema, and eventually develop myriad dense non-folliculocentric pustules, primarily in skin folds and on the trunk (**Figure 132**). A total of 80% of cases are caused by antibiotics. Most cases are self-limited and resolve within 2 weeks. Treatment consists of cessation of the causative agent and supportive care, but topical and systemic glucocorticoids may be helpful for symptomatic relief. The condition carries a mortality rate of less than 5%.

Erythroderma

Erythroderma is defined as diffuse erythema covering 80% to 90% body surface area and is commonly associated with pruritus, peripheral edema, erosions, scaling, and lymphadenopathy (**Figure 133**). The most common causes are idiopathic (up to 40%), exacerbation of a preexisting rash, or medication reaction (**Table 31**). Atopic dermatitis or psoriasis can flare to erythroderma following injudicious usage and abrupt cessation of systemic glucocorticoids. Alopecia, nail dystrophy, and thickening of the palms and soles are indicative of a long-standing cause such as cutaneous T-cell lymphoma, graft-versus-host disease,

FIGURE 132. Pinpoint pustules on a background of erythema in a patient with acute generalized exanthematous pustulosis.

FIGURE 133. Erythroderma with redness and scaling secondary to pityriasis rubra pilaris.

TABLE 31. Causes of Acute and Chronic Erythroderma

Causes of Acute Erythroderma	Causes of Chronic Erythroderma
Atopic dermatitis (flare)	Atopic dermatitis
Psoriasis (flare)	Psoriasis
Medication reaction	Cutaneous T-cell lymphoma
Autoimmune disease	Graft-versus-host disease
Staphylococcal scalded skin syndrome	Pityriasis rubra pilaris
Toxic shock syndrome	
Sézary syndrome (will transition to chronic)	

psoriasis, or pityriasis rubra pilaris. Drug reactions, staphylococcal scalded skin syndrome, and autoimmune bullous diseases often have a more acute onset without a long-standing history of preceding dermatosis. When erythroderma is acute, thick scaling of the palms and soles or nail changes do not occur. Complications may result from heat and fluid loss across the inflamed skin.

Management of erythroderma involves treatment of infection and managing fluid and electrolyte imbalance. Emollients will help to restore the skin barrier, and topical glucocorticoids and systemic antihistamines will improve pruritus.

KEY POINTS

- Erythroderma is defined as diffuse erythema covering 80% to 90% body surface area and is commonly associated with pruritus, peripheral edema, erosions, scaling, and lymphadenopathy.
- Most cases of erythroderma are idiopathic; however, it may also be caused by exacerbation of a preexisting rash or a medication reaction.
- Management of erythroderma involves treatment of the infection and managing fluid and electrolyte imbalance; emollients will help to restore the skin barrier, and topical glucocorticoids and systemic antihistamines will improve pruritus.

Hair Disorders

Hypertrichosis/Hirsutism

Hypertrichosis is the abnormal growth of hair on an area of the body. Although it's typically a cosmetic concern, hypertrichosis can also be a cutaneous sign of an underlying systemic condition (Table 32). Hirsutism is a subclass of hypertrichosis

TABLE 32. Diagnosing Excessive Hair Growth in Women

Differential Diagnosis of Excess Hair Growth	Associated Causes and Findings	Initial Testing/Assessment
Hirsutism (androgen-dependent sites)	Polycystic ovary syndrome: chronic anovulation, hyperandrogenemia, menstrual irregularities, infertility, obesity	Medical history (oligo- or anovulation); clinical or biochemical signs of hyperandrogenism; and echogenic evidence of polycystic ovaries and exclusion of other causes
	Ovarian tumors (many types): persistent bloating, early satiety, abdominal pain	Testosterone, DHEAS, pelvic ultrasound
	Cushing syndrome: acne, striae, moon facies, abdominal obesity, muscle wasting	Overnight low-dose dexamethasone suppression test, 24-hour urine free cortisol, or late-night salivary cortisol
	Congenital adrenal hyperplasia: salt-losing crisis, ambiguous genitals, precocious puberty, oligo- or amenorrhea	17-hydroxyprogesterone
	Prolactinoma: galactorrhea, visual changes, amenorrhea	Serum prolactin level
	Drug-induced: testosterone, DHEAS, danazol, corticotropin, high-dose glucocorticoids, androgenic progestins, acetazolamide, anabolic steroids	Medication history
Idiopathic/familial	Present since puberty Slow development/progression Normal menses Family history	Serum testosterone, 17-hydroxyprogesterone, DHEAS
Hypertrichosis (non-androgen-responsive hair)	Porphyria: blistering, skin fragility, scarring	24-hour urine porphyrins
	Hyperthyroidism: weight loss, anxiety, tachycardia, increased sweating	TSH, T_3, and free T_4
	Drug-induced: cyclosporine, phenytoin, diazoxide, minoxidil, hexachlorobenzene, penicillamine, methyldopa, metoclopramide, reserpine	Medication history
Acquired hypertrichosis lanuginosa (rare)	Excessive growth of fine lanugo hair (white or blonde, 1-2 cm long) on all hair-bearing surfaces, including the face. Associated with malignancy, especially colorectal cancer	Age-appropriate and symptom-directed cancer screening

DHEAS = dehydroepiandrosterone; TSH = thyroid stimulating hormone; T_3 = triiodothyronine; T_4 = thyroxine.

that specifically affects androgen-sensitive hair. It is characterized by excessive hair growth in a male pattern distribution in women or children, often associated with hyperandrogenism (**Figure 134**). Androgen-sensitive hair is located in the groin, lower abdomen, breasts, chin, lateral cheeks, and upper cutaneous lip. It is seen in about 8% to 10% of women. Other signs of hyperandrogenism such as acne, androgenic alopecia, and virilism should be sought. In suspicious cases, selected laboratory testing and imaging should be done (see MKSAP 18 Endocrinology and Metabolism).

Treatment involves addressing the underlying condition. For women with hirsutism, estrogen-progestin contraceptives are a common and effective initial therapy. Additional antiandrogens such as spironolactone or finasteride may be added in 6 months if there is suboptimal response to the oral contraceptive. Antiandrogen therapy should not be used as monotherapy because of potential teratogenic effects on the male fetus. Therapeutic options for the hair itself include hair removal (shaving, depilatories, waxing, or tweezing), camouflaging with bleach, and eflornithine cream. Eflornithine cream inhibits hair growth and must be used indefinitely to be effective. Other methods of destroying the hair bulb include electrolysis and laser hair removal, and although these results may last longer, both of these methods can be painful, costly, and require multiple treatments.

Alopecia

Alopecia is the loss of hair that is either localized or generalized. When evaluating alopecia, first determine if it is localized (patchy) or generalized (diffuse). Then determine if hair loss is scarring or nonscarring (**Table 33**). Scarring alopecia results in permanent hair loss, whereas nonscarring alopecia is usually reversible. Scarring alopecia can be distinguished by the absence of follicular openings (ostia). The diagnosis of most cases can be determined by history and physical examination and confirmed with a 4-mm punch

FIGURE 134. Terminal hair growth on the lateral cheeks in a patient with hirsutism secondary to polycystic ovary syndrome.

biopsy. The area of the scalp with active hair loss (not an area of scar) should be chosen for biopsy. Scalp and hair biopsies may require special processing techniques and referral to a dermatopathologist.

KEY POINTS

- When evaluating alopecia, first determine if it is localized (patchy) or generalized (diffuse); then determine if the hair loss is scarring or nonscarring.
- Scarring alopecia results in permanent hair loss, whereas nonscarring alopecia is usually reversible.

Nonscarring Localized and Generalized Alopecia

Alopecia areata is characterized by round or oval patches of nonscarring acute hair loss. It affects both women and men, and onset occurs before the age of 30. It presents as well-circumscribed round patches with no hair. The scalp is smooth and scaleless. The rim of the patches has characteristic "exclamation point" hairs that narrow close to the skin surface (**Figure 135**). The exact cause is unknown; however, an autoimmune mechanism is postulated due to the high association with other autoimmune conditions such as type 1 diabetes mellitus and autoimmune thyroiditis. In about 10% to 15% of patients, there is complete loss of scalp hair (alopecia totalis) and all of the body hair (alopecia universalis).

Traumatic alopecia includes traction alopecia, trichotillomania, and iatrogenic damage from chemicals and heat. Traumatic alopecia can begin as nonscarring; however, with continuing trauma, the alopecia can become permanent and scarring.

Androgenic alopecia, or patterned baldness, is due to the postpubertal terminal hair replacement, first with miniaturized follicles and eventually with atrophic follicles. It is seen in both men and women. Prevalence varies by populations studied. In comparison to white persons, pattern baldness is less common in Chinese, Japanese, and American Indians. The onset begins after puberty and can be gradual. In men, it presents as bitemporal hairline recession followed by vertex baldness (**Figure 136**). In women, it more often presents as generalized thinning rather than baldness and is often first recognized as widening of the part on the crown (**Figure 137**).

Telogen effluvium is caused by a traumatic event (emotionally or physiologically) that disrupts the natural hair cycle resulting in diffuse hair shedding. The hairs on the scalp are all in different stages of the hair cycle, mostly anagen (growing) and telogen (resting). After a traumatic event, the hairs in the anagen phase are prematurely converted into the telogen phase. Hair shedding occurs about 3 months after the inciting event. This is most commonly seen in women in the postpartum period. In most cases, telogen effluvium is self-limiting with resumption of normal hair growth with resolution of the inciting factor.

TABLE 33. Management of Selected Types of Alopecia

Type of Alopecia	Treatment Options	Possible Systemic Associations
Androgenetic alopecia	Men: Topical minoxidil 5%,[a] 5-α reductase inhibitors (finasteride,[a] dutasteride) Women: Topical minoxidil 5% foam,[a] spironolactone (spironolactone should not be administered during pregnancy and should be used with a highly effective contraceptive in premenopausal women) Both: Hair transplant, cosmetic camouflage	Men: Increased rate of prostate cancer (if onset in the 20s) Women: Polycystic ovary syndrome
Alopecia areata	<50% scalp involvement: watchful waiting, topical glucocorticoids ± topical minoxidil, anthralin, intralesional glucocorticoid >50% scalp involvement: topical immunotherapy (squaric acid or DPCP), topical glucocorticoids, ± topical minoxidil, phototherapy, wigs or other cosmetic camouflage, intralesional triamcinolone for brows, bimatoprost for eyelashes	Autoimmune disease (hyperthyroidism, hypothyroidism, vitiligo, pernicious anemia, diabetes mellitus) Atopic eczema
Telogen effluvium	Remove or correct potential trigger Watchful waiting	Anemia, thyroid disease, significant weight loss, eating disorders, parturition, high fever, major surgery, blood loss, mental stress Medications: Anabolic steroids or supplemental androgens Antithyroid medications Antiepileptics β-blockers Oral retinoids Warfarin
Tinea capitis	Oral therapy with terbinafine, fluconazole, or itraconazole for about 6 weeks Oral therapy with griseofulvin for ~12 weeks	Screen close contacts
Discoid lupus erythematosus	Sunscreen or other sun-protection Glucocorticoids: Topical are first line Intralesional for recalcitrant or thick lesions Oral reserved for patients with rapid progression Antimalarial agents Retinoids: topical or oral if severe	Systemic lupus erythematosus (5%-10%) ROS for symptoms Examination for signs Urinalysis, ANA
Traumatic alopecia	Traction/styling alopecia: decrease tension from styling practices Trichotillomania: Cognitive behavioral therapy If severe or recalcitrant, antidepressants or anxiolytics may be helpful	Concomitant psychiatric disorder is more common in adults than children Consider referral to psychiatrist or psychologist
Lichen planopilaris	Topical, intralesional, or oral glucocorticoids, antimalarial agents, immunosuppressants	Check for concomitant lichen planus on the skin, nails, and oral and genital mucosa
Frontal fibrosing alopecia	Antimalarial agents, 5-α reductase inhibitors	
Central centrifugal cicatricial alopecia	Topical and intralesional glucocorticoids, oral tetracyclines, antimalarial agents, immunosuppressants, minimal hair grooming	

ANA = antinuclear antibody; DPCP = diphenylcyclopropenone; ROS = review of systems.

[a]FDA-approved treatment for that condition/indication.

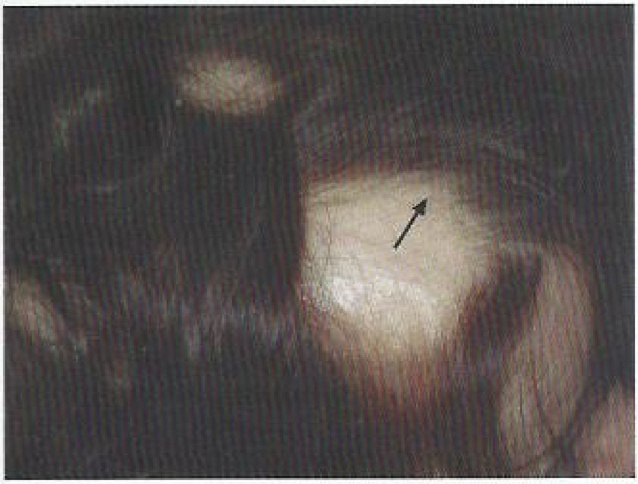

FIGURE 135. Well-demarcated, smooth, oval patches of hair loss. Note the smooth scalp and short hairs near the rim of the balding patch (arrow). Closer examination of these hairs will reveal "exclamation point" hairs (hairs that narrow close to the skin surface).

FIGURE 136. Typical distribution of androgenic alopecia in a male. Note the bitemporal hairline recession and vertex hair loss.

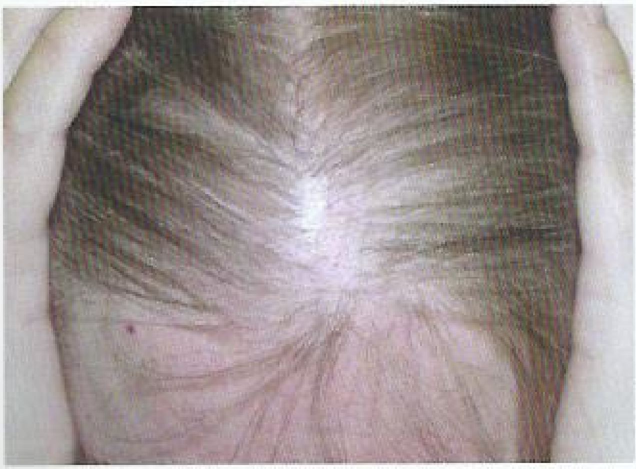

FIGURE 137. Androgenic alopecia in a female. Note the widening of the part width at the crown.

KEY POINT

- Alopecia areata, a nonscarring alopecia, presents as well-circumscribed round patches with no hair; the rim of the patches has characteristic "exclamation point" hairs that narrow close to the skin surface.

Scarring Localized and Generalized Alopecia

Discoid lupus erythematous on the scalp can result in scarring localized alopecia. It presents as multiple pink, scaling hypo- and hyperpigmented scarring plaques (**Figure 138**) (see Common Rashes).

Acne keloidalis nuchae is a chronic inflammatory disorder of the follicles causing an alopecic scar on the nape of the neck (**Figure 139**). It can be pruritic. Pseudofolliculitis barbae occurs on the face and anterior neck. It is likely due to the curvature of the hair shaft and repeated trauma such as from shaving. When the curved hairs grow out after shaving, they curve downward into the skin, inciting an inflammatory response. This causes small pustules that can become keloidal. These conditions most commonly affect black men.

Lichen planopilaris is a diffuse scarring alopecia that more commonly affects postmenopausal women. It presents as mild scaling and limited erythema and scale surrounding the follicle (**Figure 140**). Associated symptoms are pain, burning, and pruritus.

FIGURE 138. Multiple pink scarring plaques of hair loss in discoid lupus.

FIGURE 139. Multiple papules and pustules at the nape of the neck characteristic of early acne keloidalis nuchae.

FIGURE 140. Lichen planopilaris is a cause of scarring alopecia and often demonstrates redness around the follicles.

Nail Disorders

The nail complex is composed of the nail plate, hyponychium, proximal and lateral nail folds, cuticle, nail bed, and matrix. The hyponychium is the skin underneath the distal free edge of the nail plate. It seals the junction between the distal nail plate and the nail bed. The nail fold protects the nail matrix and produces the cuticle. The nail bed is adherent to the bottom of the nail plate. Nail disorders can be caused by various diseases, infections, trauma, and drugs (**Table 34**).

Infection

Onychomycosis is a fungal (dermatophyte) infection of the nail commonly seen in elderly persons, especially those with comorbidities such as diabetes mellitus, peripheral vascular disease, or immunosuppression. The most common sites of infection are the toenails. It can appear as distal subungual and proximal subungual onychomycosis. Distal subungual onychomycosis is the most common pattern. The distal nail plate becomes discolored (yellow, white, or brown) and thickened. Under the nail plate, there is an accumulation of subungual debris, resulting in separation of the plate from the bed (onycholysis) (**Figure 141**). Proximal subungual onychomycosis appears similar except that it starts at the proximal nail fold. This pattern is rare and can be associated with HIV and immunosuppression.

Onychomycosis is treated mostly for cosmetic reasons. Confirmation of infection with potassium hydroxide preparation, staining with periodic acid-Schiff, or fungal culture should be done before treatment. Topical antifungal agents are of limited efficacy. Oral therapy with terbinafine or itraconazole is more effective.

KEY POINTS

- Onychomycosis is a fungal (dermatophyte) infection of the nail commonly seen in elderly persons, especially those with comorbidities such as diabetes mellitus, peripheral vascular disease, or immunosuppression.
- Oral therapy with terbinafine or itraconazole is the preferred treatment for onychomycosis; confirmation of infection should be done before treatment. HVC

Paronychia

Paronychia is an infection of the nail fold. Infection is caused by trauma or chronic maceration leading to an incompetent cuticle. Acute paronychia is painful swelling of the nail fold, most commonly caused by *Staphylococcus aureus*. It typically affects only one nail. Chronic paronychia tends to be more insidious and involve multiple fingers. In adults, it is most often seen in those with frequent hand immersion in water. There is tender swelling in the nail folds with missing or dystrophic cuticles (**Figure 142**). Chronic paronychia can cause ridging of the nail plate. It is a multifactorial condition with several inciting factors including water, irritants, and possibly *Candida* species. Treatment of acute paronychia includes the use of warm compresses, incision and drainage, and in severe cases, oral antibiotics. For chronic paronychia, minimizing inciting factors is key. Treatment includes topical glucocorticoids and antifungal agents to reduce inflammation and minimizing inciting factors.

KEY POINT

- Acute paronychia is a painful swelling of the nail fold, most commonly caused by *Staphylococcus aureus*, typically affecting one nail; chronic paronychia tends to be more insidious and involve multiple fingers.

Inflammatory Dermatosis

Psoriasis affects fingernails more commonly than toenails. If the nail matrix is affected, tiny multiple pits will be seen on

TABLE 34. Nail Findings Associated with Possible Systemic Conditions

Nail Finding	Description	Associated Diseases
Nail Plate		
Koilonychia (spoon nails)	Thin curving up nail with everted edges (spoon)	Iron disorders (Plummer-Vinson syndrome, hemochromatosis, iron deficiency anemia); chronic injury
Trachyonychia	Rough sandpaper nails on all 20 nails	Lichen planus; psoriasis; eczema; idiopathic
Onychogryphosis	Curved, hypertrophic nails resembling claw	Trauma; peripheral vascular disease; neglect
Onychomadesis	Periodic shedding of the nail beginning at its proximal end due to temporary arrest of the matrix	Severe systemic illness (high fever, toxic epidermal necrosis, erythroderma, scarlet fever, surgery, medications)
Transverse indentations (Beau lines)	Transverse furrows beginning in the matrix	Systemic illness or major trauma (childbirth, measles, acute febrile illnesses, drug reaction)
Pitted nails	Tiny indentations on the nail plate due to abnormal keratinization of the proximal nail matrix	Psoriasis; alopecia areata; lichen planus
Nail Color		
Half and half (Lindsey) nails	Proximal nail is white and the distal nail is red, pink, brown with a sharp line of demarcation	Chronic kidney disease
Terry nails	Distal 1-2 mm of nails have normal pink color but proximal end has abnormal white appearance	Liver disease; chronic heart failure; diabetes mellitus; normal aging
Melanonychia	Diffuse/partial brown-black	Chemotherapy agents, antimalarial agents, minocycline, gold; common in dark skin types; trauma
	Longitudinal melanonychia – vertical brown band	Nevus; lentigo; drugs; melanoma; trauma
Green nail syndrome	Onycholytic toenails with green discoloration	Prolonged immersion in fresh water and infection with *Pseudomonas aeruginosa*
Blue nails	Blue lunulae	Argyria, antimalarials, hepatolenticular degeneration
		5-Fluorouracil and azidothymidine
Yellow	Yellow nail syndrome	Aging, dermatophyte infection
		Lymphedema; chronic pulmonary disease
Red lunulae		Carbon monoxide poisoning; subungual digital myxoid cyst; heart failure
Periungual/Cuticle		
Ragged cuticles (Samitz sign)	Dystrophic, ragged-appearing cuticles	Dermatomyositis
Periungual erythema	Alternating areas of capillary dilated, torturous vessels and capillary dropout; red cuticles	Dermatomyositis; scleroderma; lupus erythematosus (less common)

FIGURE 141. Yellow hypertrophic nail plate and subungual debris from onychomycosis.

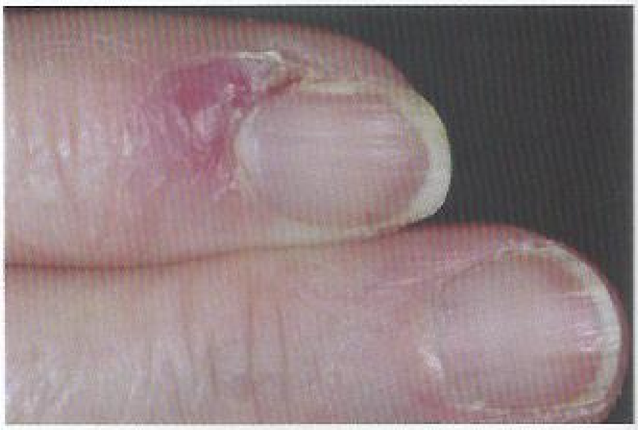

FIGURE 142. Tender, pink swelling of the proximal and lateral nail fold due to chronic paronychia. Note the dystrophic cuticle.

the nail plate (**Figure 143**). In cases of nail bed involvement, yellow-brown discoloration (oil stains) can occur. Other findings include nail plate thickening, separation of the nail plate from the nail bed, distal nail plate crumbling, and splinter hemorrhages (**Figure 144**). Patients with psoriatic nail involvement are often affected by psoriatic arthritis.

Lichen planus, in about 10% of cases, can affect the nails. It causes nail plate dystrophy including thinning, red streaking, and pterygium unguis formation, which is the scarring of the proximal nail fold and matrix (**Figure 145**).

Ingrown Toenail

An ingrown toenail is the result of the nail plate growing into the lateral nail fold causing an inflammatory response.

FIGURE 143. Nail pitting in a patient with psoriasis.

FIGURE 144. Other characteristic features of nail psoriasis include distal onycholysis (separation of the nail plate from the underlying nail bed) [arrow] and splinter hemorrhages, which represent the "Auspitz sign" (punctuate bleeding) in the nail bed. In addition, some patients may display the "oil-drop sign" (circle), which is characterized by a localized tan to brown discoloration of the nail. In more severe forms of psoriatic involvement, there can be thickening and crumbling of the nails.

FIGURE 145. Lichen planus can cause pitting, onycholysis, and nail dystrophy. Lichen planus is a common cause of 20-nail dystrophy (trachyonychia) characterized by roughness and longitudinal ridging of the nail plate on all 20 nails.

Ingrown toenails of the great toe are most common, presenting as painful swelling of the lateral nail fold (**Figure 146**). There may be some weeping granulation tissue.

Conservative treatment for mild to moderate ingrown nails involve wider shoes, trimming the nail plate straight across, antiseptic application, and inserting a cotton pledget under the nail edge. For severe cases, partial or complete nail avulsion with matricectomy may be necessary.

Melanonychia

Melanonychia is a brown banded pigmentation of the nail plate that can be caused by increased melanin production of the melanocytes in the nail matrix, benign hyperplasia, and melanoma (see Common Neoplasms). Longitudinal melanonychia is

FIGURE 146. Tender pink swelling of the lateral nail fold with some pink granulation tissue growing on the lateral distal end suggesting an ingrown toenail.

the transverse brown-black band on the nail plate (**Figure 147**), most commonly found on dark-skinned patients. Multiple nails are usually involved. Longitudinal, irregular melanonychia on a single nail can be a sign of melanoma.

Squamous Cell Carcinoma

Squamous cell carcinoma of the nail unit often presents with pain, swelling, and erythema. It commonly arises in the nail fold and appears as a hyperkeratotic papule and plaque similar to warts (**Figure 148**). If treatment of a wart does not progress as expected, a biopsy is warranted to rule out squamous cell carcinoma, which is strongly associated with human papillomavirus infection.

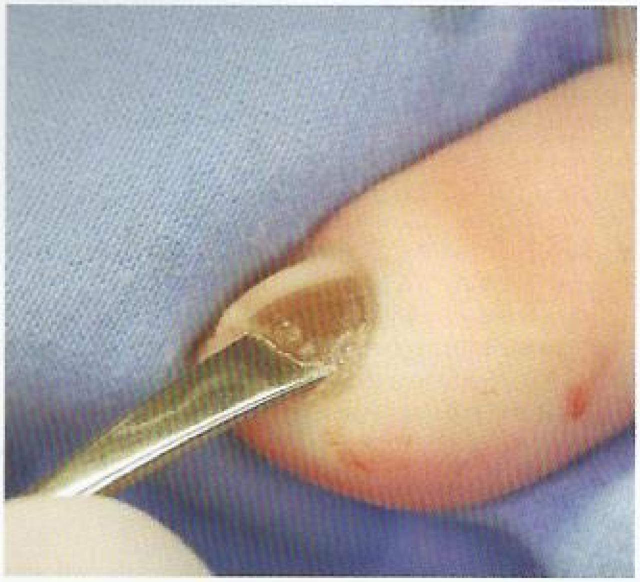

FIGURE 147. Longitudinal brown pigmentation with transverse streaks on the nail plate characteristic of melanonychia.

FIGURE 148. Verruca plaque on the lateral nail fold that looks like a wart but biopsy demonstrated squamous cell carcinoma.

Disorders of the Mucous Membranes

Melanotic Macule

A melanotic macule is a small, well-circumscribed, brown-to-black mucosal lesion. The most common location is the lower lip (**Figure 149**), but they may also be found on the gingival, buccal mucosa, or tongue, or within the genital mucosa. If large, papular, or not well-circumscribed, biopsy should be performed to rule out melanoma. Solitary lesions are the rule, and multiple lesions suggest the possibility of rare inherited disorders such as Peutz-Jeghers syndrome.

Amalgam Tattoo

Amalgam dental fillings contain metals that can be inadvertently implanted into the adjacent mucosa at the time of dental filling. They present as blue-gray macules and do not change over time. In cases of uncertainty, a mucosal biopsy should be performed.

Leukoplakia and Erythroplakia

Leukoplakia is a premalignant lesion that presents as white patches on the oral mucosa (**Figure 150**). It should be differentiated from oral candidiasis and oral hairy leukoplakia. Oral hairy leukoplakia (Epstein-Barr virus induced) occurs in patients with HIV infection and presents as adherent linear white plaques on the lateral surface of the tongue. Erythroplakia, appearing as red mucosal patches, has a high risk of malignant transformation. Both leukoplakia and erythroplakia require biopsy to rule out dysplasia. These conditions are seen most frequently in tobacco users.

FIGURE 149. Small, well-circumscribed darkly pigmented melanotic macule occurring on the vermilion border of the lower lip.

FIGURE 150. Oral hairy leukoplakia is a precancerous lesion that presents as linear white patches or plaques on the lateral surface of the tongue with changes in the surface texture.

Oral Candidiasis

Oropharyngeal candidiasis presents as white-to-red plaques that are painful (**Figure 151**). The white surface of the plaques can be scraped off. *Candida* is also responsible for angular cheilitis (perleche) presenting as fissuring and maceration of the angle of the mouth due to drooling and poorly fitting dentures. Risk factors for oral candidiasis include immunosuppression, diabetes mellitus, use of antibiotics, oral and inhaled glucocorticoids, and smoking. First-line treatment includes azole troches or nystatin swish and swallow mouthwash. Oral fluconazole may be required for severe, recalcitrant, or recurrent cases.

Aphthous Ulcers

Aphthous ulcers ("canker sores") are recurrent ulcers with a gray pseudomembrane base and an erythematous halo that affect lips, buccal mucosa, and tongue (**Figure 152**). Diagnosis

FIGURE 151. Oral candidiasis most commonly presents as painful white, fluffy, nonadherent film on the tongue, buccal mucosa, or palate.

FIGURE 152. Aphthous ulcer is characterized by painful, discrete shallow, round to oval ulcer with a gray base and red surrounding halo typically less than 1 cm in diameter.

is by clinical findings and history of self-healing. Severe, recurrent oral ulcers suggest the possibility of infection or a systemic disease such as Behçet syndrome, Crohn disease, HIV infection, or erythema multiforme.

KEY POINT

- Severe, recurrent oral aphthous ulcers may suggest a systemic disease such as Behçet syndrome, Crohn disease, HIV infection, or erythema multiforme.

Lichen Planus

Oral lichen planus can be isolated or associated with skin lesions or be part of a vulvovaginal syndrome. Oral lesions appear as erythematous patches with an overlying white lacelike pattern (Wickham striae), typically on the buccal mucosa (**Figure 153**). Treatment often requires systemic

FIGURE 153. Lichen planus is an autoimmune disease of unknown cause that can affect the skin, mucous membranes, scalp, or nails. Common clinical findings of mucosal lichen planus are a white reticulated network on the buccal mucosa (Wickham striae); desquamative gingivitis; and chronic, painful erosions on the oral or vulvar mucosa.

steroid-sparing agents in addition to medium- to high-potency topical glucocorticoids.

Actinic Cheilitis and Squamous Cell Carcinoma

Actinic cheilitis is a premalignant condition that presents as scaly patches with erosions on the lower lip and is the result of chronic sun damage. Management is with topical chemotherapy agents (5-fluorouracil), imiquimod, laser therapy, photodynamic therapy, or cryotherapy.

The development of a nodule or ulcer suggests squamous cell carcinoma, most often found on the lower lip of older men (see Common Neoplasms). Risk factors include tobacco, alcohol use, and ultraviolet radiation. Other predisposing conditions include lichen planus and lichen sclerosus. In all cases of suspected squamous cell carcinoma, biopsy is required to establish the diagnosis.

KEY POINT

- Actinic cheilitis is a premalignant condition that presents as scaly patches with erosions on the lower lip; the development of a nodule or ulcer suggests squamous cell carcinoma.

FIGURE 154. Lichen sclerosus is a chronic inflammatory mucocutaneous disease characterized by "parchment-like" or "cigarette paper" skin that circumferentially involves the vaginal introitus and perianal area with a "figure 8" morphology; some patients may have thickened or lichenified areas. It may predispose the patient to subsequent development of squamous cell carcinoma. Image reproduced from the CDC Public Health Image Library.

Lichen Sclerosus

Lichen sclerosus is a chronic inflammatory disease that most often affects women in the fifth or sixth decade of life. It presents as a white, atrophic patch that circumferentially involves the vaginal introitus and perianal area with a "figure 8" morphology (**Figure 154**). Extragenital lesions can occur. Biopsy is required for the diagnosis. Treatment is with potent topical glucocorticoids. If left untreated, permanent scarring can occur, and chronic lesions are at risk for squamous cell carcinoma.

Black Hairy Tongue

Black hairy tongue is characterized by elongation and defective desquamation of filiform papillae (**Figure 155**). It is more common in men and with advancing age. Management includes good oral hygiene and tongue brushing.

FIGURE 155. Black hairy tongue is a benign self-limited disorder. The clinical appearance of black discoloration and thickened papillae without other symptoms is characteristic.

Geographic Tongue

Geographic tongue is fairly common and may be sporadic, familial, or associated with psoriasis. These migratory patterned patches of smooth red surfaces and white patches on the dorsal tongue (**Figure 156**) are usually asymptomatic, but discomfort and burning may be reported, which are exacerbated by hot or spicy foods. About 40% of patients will develop tongue fissures.

FIGURE 156. Geographic tongue (benign migratory glossitis) showing irregularly shaped, map-like migratory patches on the dorsal tongue.

FIGURE 157. Venous stasis ulcers of the medial lower extremity with associated changes of edema, hyperpigmentation, and evidence of previous healed ulcers.

Foot and Lower Leg Ulcers

Venous stasis ulcers, arterial insufficiency ulcers, and neuropathic ulcers are the most common ulcerations of the feet and lower extremities. The proper diagnosis is important since treatments are directed at the underlying cause.

Venous Stasis Ulcers

Venous stasis ulcers account for up to 70% of all leg ulcers. They occur on the lower extremities in the area from the midcalf to the ankle, most commonly near the medial malleolus, and are associated with signs of chronic venous insufficiency. Venous stasis ulcers can be single or multiple and are typically irregularly shaped, shallow, and often weep serous fluid (**Figure 157**). The presence of fibrinous tissue is common, and ulcers are rarely necrotic. Pain may or may not be present.

Physical findings suggestive of venous stasis ulcers include edema, varicosities, eczematous changes, brown pigmentation from hemosiderin deposition, lipodermatosclerosis (fibrosis of subcutaneous tissue), atrophic blanche (pale plaques of scar tissue), and evidence of healed ulcers. Diagnosis is usually made clinically, although duplex ultrasonography can be helpful in evaluating venous reflux and obstruction, or if the diagnosis is unclear. Ankle-brachial indexes should be measvured to rule out concurrent arterial disease.

Treatment consists of compression therapy, which improves venous flow, reduces edema, and promotes fibrinolysis. Compression therapy is best administered through the use of high compression, multicomponent bandaging; other options include elastic or inelastic compression bandages (Unna boots, compression stockings) or intermittent pneumonic compression devices. Compression is avoided if the ankle-brachial index is less than 0.8, and referral to a vascular specialist should be considered.

Local wound care includes debridement of devitalized tissue. Simple nonadherent dressings appear to be as effective as other more expensive dressings, and the addition of topical cadexomer iodine may improve healing. When added to standard care, oral pentoxifylline, simvastatin, and aspirin have been shown to increase ulcer healing. Lower quality evidence suggests that flavonoids and hydroxyethyl rutoside may also improve healing. Routine use of systemic antibiotics is not recommended except for patients with suspected infection (increased pain, drainage, surrounding cellulitis). Superficial venous surgery reduces 1-year ulcer recurrence rate in patients with superficial venous reflux. Bilayer artificial skin replacement may improve healing of venous ulcers compared to compression and simple dressings. H

KEY POINTS

- Venous stasis ulcers occur on the lower extremities in the area from the midcalf to the ankle and are associated with signs of chronic venous insufficiency.
- The mainstay of venous ulcer treatment consists of compression therapy, which improves venous flow, reduces edema, and promotes fibrinolysis.
- Routine use of systemic antibiotics is not recommended for the treatment of venous stasis ulcers except for patients with suspected infection (increased pain, drainage, surrounding cellulitis). **HVC**

Arterial Insufficiency Ulcers

Arterial leg ulcers account for up to 25% of leg ulcers. Arterial insufficiency is typically due to atherosclerosis, which leads to

H CONT.

inadequate oxygenation of the tissue and ulcer formation. Common risk factors are smoking, obesity, diabetes, hyperlipidemia, hypertension, and increased age. Common locations are the distal toes, on the anterior portion of the lower leg where minimal collateral arterial circulation is present, and at sites of trauma. Arterial ulcers are usually painful and have sharply demarcated borders with a dry, pale gray or yellow wound base without evidence of granulation tissue (**Figure 158**). Claudication and rest pain are commonly present. If tissue necrosis is present, the wound may be covered by an eschar. Other findings include cool extremities with digital hair loss; shiny, taunt skin around the ulcer; and delayed capillary refill time. The key diagnostic test is an ankle-brachial index less than or equal to 0.9.

Treatment must involve aggressive risk factor management and measures to increase blood supply to the affected area. Surgical revascularization, percutaneous balloon angioplasty, or stent placement is usually necessary. Arterial ulcers are treated with local wound care similar to venous stasis ulcers. H

KEY POINTS

- Arterial insufficiency ulcers are usually located at the distal extremities, such as the distal toes and anterior portion of the lower leg, where minimal collateral arterial circulation is present.
- Arterial ulcers are painful and usually have sharply demarcated borders with a dry, pale gray or yellow wound bed.
- Treatment of arterial ulcers must involve risk factor management and measures to increase blood supply to the affected area.

H Neuropathic Ulcers

Neuropathic ulcers arise secondary to repetitive trauma to the skin, typically in patients with diabetic peripheral neuropathy and a reduced awareness of pressure or trauma to the skin. Diabetic ulcers are painless, are most common on the plantar surface of the feet, and have associated callus and foot deformity (Charcot foot) (**Figure 159**). The skin is warm and dry with signs of fissuring and breakdown. Polymicrobial infections are common, and patients are at increased risk of osteomyelitis (see MKSAP 18 Infectious Disease). Surgical debridement of necrotic tissue along with redistributing pressure is important to achieve healing. Offloading measures include foot inserts, therapeutic shoes, and removable cast walkers. H

KEY POINTS

- Neuropathic ulcers arise secondary to repetitive trauma to the skin, typically in patients with diabetes mellitus.
- Treatment of neuropathic ulcers includes surgical debridement and redistributing or offloading pressure.

Other Causes of Lower Extremity Ulcers

H

Pressure ulcers of the heels and lateral ankles are common in bedridden patients due to necrosis from persistent pressure. Rarer causes of ulcers (**Table 35**) should be suspected based on a suggestive history, physical findings, and lack of response to traditional therapies. In these cases, a punch or incisional biopsy should be considered. The sampled tissue should include both ulcer edge and bed, and the tissue should also be sent for bacterial, fungal, and mycobacterial cultures. Further workup and treatment are directed at the underlying cause. H

FIGURE 158. Arterial insufficiency ulcers appear sharply demarcated or "punched out" with a dry pale, gray or yellow base and the surrounding skin is red, taunt, and tender.

FIGURE 159. Neuropathic ulcer located over the first metatarsal head with associated callus in a patient with diabetes mellitus.

TABLE 35. Other Causes of Leg Ulcers

Diagnosis	Characteristics/Associations
Pyoderma gangrenosum	Often follows trauma Undermined or violaceous borders Associated with inflammatory bowel disease, rheumatoid arthritis, and monoclonal gammopathy
Vasculitis	Findings may include palpable purpura, livedo reticularis Associated with autoimmune disorders, infections, and other causes of vasculitis
Calciphylaxis	Advanced disease is characterized by painful angulated necrotic ulcers with eschars most commonly found on buttocks, abdomen, and thighs in patients with end-stage kidney disease
Vasculopathy (microthrombi)	Painful, necrotic, and usually multiple ulcers associated with hypercoagulable states
Malignant ulcer	Chronic, nonhealing ulcer at site of chronic inflammation or prior trauma Most commonly squamous cell carcinoma, basal cell carcinoma, or melanoma
Necrobiosis lipoidica diabeticorum	Typically starts as a yellow-brown plaque that ulcerates Higher incidence in patients with diabetes mellitus
Sickle cell disease	Painful ulcers on the medial and lateral malleoli May occur spontaneously or after trauma Can be associated with hydroxyurea therapy

Dermatologic Conditions of Pregnancy and Aging

Pregnancy and Lactation

Women who are pregnant or lactating can present with unique skin findings, some of which are physiologic (**Table 36**) and others that may require treatment (**Table 37**). Preexisting skin conditions may be exacerbated during pregnancy or uniquely arise during pregnancy. Pruritic urticarial papules and plaques of pregnancy (PUPPP) is the most common specific dermatosis of pregnancy (**Figure 160**). Clinically, PUPPP appears late in the third trimester as erythematous plaques in the distribution of striae typically with sparing of the periumbilical skin. While the lesions may be restricted to abdominal striae, they may also appear on the arms and legs. Persistent and bothersome pruritus is a symptomatic hallmark of the condition. The condition usually resolves shortly after delivery. For symptom control, low- to medium-potency topical glucocorticoids are often first-line therapy; nonsedating antihistamines are sometimes required to control pruritus.

H Pemphigoid gestationis (herpes gestationis) is a pruritic blistering disease typically appearing during the second or third trimester. Urticarial plaques, papules, and vesicles first appear surrounding the umbilicus, but can involve the palms and soles. It usually spares the mucous membranes (**Figure 161**). A skin biopsy demonstrating a subepidermal bulla with neutrophils can confirm the diagnosis. Treatment with topical glucocorticoids is usually initiated for pruritus, and the lesions spontaneously remit following delivery. Pemphigoid gestationis is associated with an increased risk of fetal growth restriction and prematurity. H

Treatment of dermatologic conditions during pregnancy can be challenging, as special consideration needs to be made for potential medication-induced teratogenicity. The FDA has published changes in pregnancy and lactation labeling for prescription drugs, effective June 30, 2015. The pregnancy letter categories will be removed with the new labeling requirements; however, for prescription drugs that were previously approved, these changes will be phased in gradually. This section will refer to previously approved drugs and their letter categories of risk (**Table 38**). It is important to consider these drugs when prescribing for women of childbearing age. For some drugs, there are regulatory programs to monitor medications such as iPledge for isotretinoin, STEPs for thalidomide, and mycophenolate REMS for mycophenolate mofetil.

Dermatologic surgery under local anesthesia (lidocaine) can be safely done during pregnancy if necessary; however, opiates and sedatives should be avoided in pregnant and lactating women.

Aging

Similar to other organs, the skin's functional capacity diminishes with age, thus increasing its susceptibility to cutaneous disorders such as dermatoses and skin cancer. Clinically and histologically, the skin structure changes (**Table 39**) from both intrinsic and extrinsic mechanisms (ultraviolet light, smoking). Nails can change as well. The nail growth rate begins to decline after the age of 25. Decreased lipophilic sterols and free fatty acids cause nails to develop some ridging and become

TABLE 36. Physiologic Changes Associated with Pregnancy

Category	Finding	Treatment After Pregnancy
Pigmentary	Melasma (mask of pregnancy) characterized by ill-defined brown macules on face	Sun protection
	Linea nigra appears as a vertical linear hyperpigmentation on abdomen	Spontaneous resolution over time
	Areolae, axillae, and genitals darken	Spontaneous resolution over time
	Moles may darken	Melanoma can occur during pregnancy; biopsy if there is significant change
Vascular	Angiomas develop commonly on the face, neck, and extremities	Spontaneous resolution over time for most lesions
	Palmar erythema may be diffuse or limited to thenar and hypothenar eminences	Spontaneous resolution over time
	Saphenous, vulvar, and hemorrhoidal varicosities	Medical or surgical therapy for unresolved extremity varicosities after pregnancy
	Pyogenic granulomas can develop on the gingiva and fingers. Gingival hyperemia is universally present.	Spontaneous resolution
Hair	Hypertrichosis can develop on the face, but arms, back, and suprapubic regions may also be affected. Terminal hair growth is likely to be permanent without treatment.	See Hair Disorders; lanugo hairs resolve spontaneously
	Postpartum telogen effluvium is common and recognized as hair shedding. Hair may become sparse.	Spontaneous resolution over time
Nail	Onycholysis appears as white discoloration at end with separation of the nail plate from the nail bed	Spontaneous resolution in most cases
Connective Tissue	Striae gravidarum (stretch marks) appears as linear atrophic scars that may start as pink/red then become paler on abdomen, breasts, and thighs	No effective treatment

TABLE 37. Pregnancy Dermatoses

	Description/Area	Timing/Course	Treatment	Fetal Involvement
Prurigo of pregnancy	Prurigo nodules (firm, pruritic nodules); extremities more often than abdomen	After first trimester; resolves after pregnancy	None indicated; can consider topical glucocorticoids	None
Pemphigoid gestationis (herpes gestationis)	Pruritic, vesiculobullous eruption Abdomen, umbilicus; can generalize	Late pregnancy, but can occur in any trimester, or immediately postpartum Spontaneously remits weeks to months after delivery	Self-limited; topical and systemic glucocorticoids, antihistamines Commonly recurs in subsequent pregnancies	Increase risk of prematurity; small for gestational age infants; neonatal pemphigoid gestationis
Pruritic urticarial papules and plaques of pregnancy	Pruritic erythematous and edematous papules and plaques that may become vesicular Within abdominal striae; can generalize Spares umbilicus, face, palms, soles	End of third trimester, immediately postpartum	Self-limited, resolving shortly after delivery; topical glucocorticoids; antihistamines	None
Intrahepatic cholestasis of pregnancy	Pruritus with excoriations; jaundice	Late second trimester, third trimester	Resolves within days of delivery; ursodeoxycholic acid for pruritus Recurs in subsequent pregnancies	Increased risk of premature labor; fetal distress; stillbirth
Generalized pustular psoriasis of pregnancy (impetigo herpetiformis)	Peripheral pustules on pink polycyclic patches	Third trimester	Systemic glucocorticoids; resolves postpartum Recurs in subsequent pregnancies	Low birth weight; intrauterine growth restriction; premature rupture of membranes; stillbirth

FIGURE 160. Characteristic appearance of pruritic urticarial papules and plaques of pregnancy (PUPPP) in a gravid woman with edematous, erythematous plaques on the abdomen involving the striae. Note the relative sparing of the umbilicus.

FIGURE 161. Classic appearance of pemphigoid gestationis with pruritic vesicles and pink plaques surrounding the umbilicus in a gravid woman.

more brittle. Generally, chest, axillary, and pubic hair all decrease with age. In men, there is increased hair in eyebrows, the nostrils, and external auditory meati. In women, the vellus hairs on the chin and upper lip convert into course terminal hairs possibly due to reduced estrogen levels. Hair graying can occur due to depletion of hair bulb melanocytes.

Dryness (xerosis cutis) is one of the most prevalent skin conditions in an aging population. While pilo-sebaceous glands become larger with age, there is a 50% reduction in sebum production. Excessive xerosis can cause xerotic dermatitis (eczema). It occurs more often in the winter (low humidity) and on the lower legs. It presents as dry fissured patches

TABLE 38. Selected Systemic Medications to Avoid During Pregnancy and Lactation Commonly Used in Dermatology

Medication	FDA Category	Risks
Tetracyclines	D	Dental staining and enamel hypoplasia in the second and third trimester
		Acute fatty liver of pregnancy
Trimethoprim-Sulfamethoxazole	C	Interference with folic acid metabolism
Isotretinoin	X	Increased fetal loss during first trimester
		Microtia; external ear canal stenosis; cleft palate; hydrocephalus; cardiac outflow trace defects
Acitretin	X	Craniofacial, cardiac, thymic, and central nervous system malformation
Tazarotene (topical)	X	Similar retinoid anomalies in animal studies
Spironolactone	C	Delayed sexual maturation in female rats and feminization of male rat fetuses
		No reported risk in humans in case reports
Methotrexate	X	Increased risk of miscarriage
		Micrognathia; developmental delays; craniosynostosis, small low-set ears; limb abnormalities; growth retardation
		Potential fathers should not be on medication
Glucocorticoids	C	In high doses, possible growth retardation and inhibition of endogenous corticosteroid production
Mycophenolate mofetil	D	Increased risk of miscarriage
		Anomalies of distal limbs, hearts, esophagus, kidney, external ear, and face

FDA categories: (A) Studies on pregnant women show no risk (safe); (B) No clinical data of human risk but uncertain; (C) Risk cannot be ruled out; (D) Evidence of risk; (X) Contraindicated during pregnancy.

The FDA has published changes in pregnancy and lactation labeling for prescription drugs, effective June 30, 2015 (see www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm). The pregnancy letter categories will be removed with the new labeling requirements; however, for prescription drugs that were previously approved, these changes will be phased in gradually. Labeling will include information relevant to the use of the drug in pregnant women (such as dosing and potential risks to the developing fetus), information about using the drug while breastfeeding (such as the amount of drug in breast milk and potential effects on the breastfed infant), and information regarding potential risks to females and males of reproductive potential who take the drug. Prescribing information for individual preparations should be consulted for more specific information.

TABLE 39. Skin Changes Due to Intrinsic and Extrinsic Aging

	Intrinsic	Extrinsic (Photoaging, Smoking)
Pigmentation	Skin pallor	Diffuse pigmentation
		Lentigines
Epidermis	Thinned	
	Xerosis	
Dermis	Fine wrinkles	Coarse furrows
	Decreased elasticity	Pebbly texture (elastosis)
	Decreased skin temperature	Solar purpura
		Telangiectasia
Other	Subcutaneous fat loss	
	Decreased skin temperature	
Nails	Brittle and ridging	
Hair	Graying	

with a scalelike appearance (**Figure 162**). Severe xerosis can cause pruritus. Subsequent itching can result in actinic purpura. Good skin care measures are recommended, including the frequent application of emollients, especially immediately after bathing, to reduce dryness. Topical glucocorticoids can be applied to areas of inflamed skin.

Actinic purpura appears as purpuric macules or patches, most commonly on the forearms, due to minor trauma such as scratching (**Figure 163**). There may be associated stellate pseudoscars that are atrophic scars occurring after the skin tears. Actinic purpura is due to blood vessel fragility and dermal atrophy from aging. No additional testing needs to be done. There is no therapy for the purpura but sun protection is recommended to prevent further damage.

KEY POINT

- Actinic purpura is due to blood vessel fragility and dermal atrophy from aging; no additional testing needs to be done. HVC

Infection

Group living arrangements such as skilled nursing facilities can predispose elderly persons to infestations with scabies, lice, or bedbugs (see Infestations). Herpes zoster and postherpetic neuralgia can occur more frequently in the elderly (see Common Skin Infections). Onychomycosis is more common in elderly populations (see Nail Disorders).

Chronic Wounds/Poor Wound Healing

Elderly persons with mobility impairments and comorbidities (cardiovascular disease, diabetes mellitus) are predisposed to chronic wounds such as venous, pressure, and diabetic foot ulcers (see Foot and Leg Ulcers).

FIGURE 162. Characteristic findings of xerotic eczema located on the anterior leg showing fine, porcelain-like cracks on eczematous skin.

FIGURE 163. Purpuric ill-defined patches (actinic purpura) and ill-defined tan macules (solar lentigines) on atrophic skin demonstrating signs of aging.

Bibliography

Approach to the Patient with Dermatologic Disease

Bibbins-Domingo K, Grossman DC, Curry SJ, Davidson KW, Ebell M, Epling JW Jr, et al; US Preventive Services Task Force. Screening for Skin Cancer: US Preventive Services Task Force Recommendation Statement. JAMA. 2016;316:429–35. [PMID: 27458948] doi:10.1001/jama.2016.8465

Fenske NA, Cohen LE. The dermatologic exam. Emerg Med Clin North Am. 1985;3:643–58. [PMID: 2414092]

Jackson R. The importance of being visually literate. Observations on the art and science of making a morphological diagnosis in dermatology. Arch Dermatol. 1975;111:632–6. [PMID: 1130808]

Therapeutic Principles in Dermatology

du Vivier A. Tachyphylaxis to topically applied steroids. Arch Dermatol. 1976;112:1245–8. [PMID: 999300]

Miller JA, Munro DD. Topical corticosteroids: clinical pharmacology and therapeutic use. Drugs. 1980;19:119–34. [PMID: 7363838]

Smith ES, Fleischer AB Jr, Feldman SR. Nondermatologists are more likely than dermatologists to prescribe antifungal/corticosteroid products: an analysis of office visits for cutaneous fungal infections, 1990–1994. J Am Acad Dermatol. 1998;39:43–7. [PMID: 9674396]

Walsh P, Aeling JL, Huff L, Weston WL. Hypothalamus-pituitary-adrenal axis suppression by superpotent topical steroids. J Am Acad Dermatol. 1993;29:501–3. [PMID: 8349876]

Wilson R, Camacho F, Clark AR, Young T, Inabinet R, Yentzer BA, et al. Adherence to topical hydrocortisone 17-butyrate 0.1% in different vehicles in adults with atopic dermatitis [Letter]. J Am Acad Dermatol. 2009;60:166–8. [PMID: 19103374] doi:10.1016/j.jaad.2008.09.031

Common Rashes

Antonov D, Schliemann S, Elsner P. Hand dermatitis: a review of clinical features, prevention and treatment. Am J Clin Dermatol. 2015;16:257–70. [PMID: 25920436] doi:10.1007/s40257-015-0130-z

Atzmony L, Reiter O, Hodak E, Gdalevich M, Mimouni D. Treatments for cutaneous lichen planus: a systematic review and meta-analysis. Am J Clin Dermatol. 2016;17:11–22. [PMID: 26507510] doi:10.1007/s40257-015-0160-6

Borda LJ, Wikramanayake TC. Seborrheic dermatitis and dandruff: a comprehensive review. J Clin Investig Dermatol. 2015;3. [PMID: 27148560] doi:10.13188/2373-1044.1000019

Cassler NM, Burris AM, Nguyen JC. Asteatotic eczema in hypoesthetic skin: a case series. JAMA Dermatol. 2014;150:1088–90. [PMID: 25029204] doi:10.1001/jamadermatol.2014.394

Eichenfield LF, Tom WL, Berger TG, Krol A, Paller AS, Schwarzenberger K, et al. Guidelines of care for the management of atopic dermatitis: section 2. Management and treatment of atopic dermatitis with topical therapies. J Am Acad Dermatol. 2014;71:116–32. [PMID: 24813302] doi:10.1016/j.jaad.2014.03.023

Grover RW. Transient acantholytic dermatosis. Arch Dermatol. 1970;101:426–34. [PMID: 5440816]

Kouris A, Christodoulou C, Efstathiou V, Platsidaki E, Tsatovidou R, Torlidi-Kordera E, et al. Comparative study of quality of life and obsessive-compulsive tendencies in patients with chronic hand eczema and lichen simplex chronicus. Dermatitis. 2016;27:127–30. [PMID: 27172307] doi:10.1097/DER.0000000000000180

Metin A, Dilek N, Demirseven DD. Fungal infections of the folds (intertriginous areas). Clin Dermatol. 2015;33:437–47. [PMID: 26051058] doi:10.1016/j.clindermatol.2015.04.005

Nast A, Jacobs A, Rosumeck S, Werner RN. Efficacy and safety of systemic long-term treatments for moderate-to-severe psoriasis: a systematic review and meta-analysis. J Invest Dermatol. 2015;135:2641–8. [PMID: 26046458] doi:10.1038/jid.2015.206

Warshaw EM, Maibach HI, Taylor JS, Sasseville D, DeKoven JG, Zirwas MJ, et al. North American contact dermatitis group patch test results: 2011–2012. Dermatitis. 2015;26:49–59. [PMID: 25581671] doi:10.1097/DER.0000000000000097

Yim KM, Armstrong AW. Updates on cardiovascular comorbidities associated with psoriatic diseases: epidemiology and mechanisms. Rheumatol Int. 2017;37:97–105. [PMID: 27221457] doi:10.1007/s00296-016-3487-2

Disorders of Pigmentation

Alikhan A, Felsten LM, Daly M, Petronic-Rosic V. Vitiligo: a comprehensive overview Part I. Introduction, epidemiology, quality of life, diagnosis, differential diagnosis, associations, histopathology, etiology, and work-up. J Am Acad Dermatol. 2011;65:473–91. [PMID: 21839315] doi:10.1016/j.jaad.2010.11.061

Felsten LM, Alikhan A, Petronic-Rosic V. Vitiligo: a comprehensive overview Part II: treatment options and approach to treatment. J Am Acad Dermatol. 2011;65:493–514. [PMID: 21839316] doi:10.1016/j.jaad.2010.10.043

Sheth VM, Pandya AG. Melasma: a comprehensive update: part I. J Am Acad Dermatol. 2011;65:689–97; quiz 698. [PMID: 21920241] doi:10.1016/j.jaad.2010.12.046

Sheth VM, Pandya AG. Melasma: a comprehensive update: part II. J Am Acad Dermatol. 2011;65:699–714; quiz 715. [PMID: 21920242] doi:10.1016/j.jaad.2011.06.001

Silverberg JI, Silverberg NB. Clinical features of vitiligo associated with comorbid autoimmune disease: a prospective survey [Letter]. J Am Acad Dermatol. 2013;69:824–6. [PMID: 24124820] doi:10.1016/j.jaad.2013.04.050

Stollery N. Pigmentation disorders. Practitioner. 2015;259:30–1. [PMID: 26738250]

Drug Reactions

Calabrese LH, Michel BA, Bloch DA, Arend WP, Edworthy SM, Fauci AS, et al. The American College of Rheumatology 1990 criteria for the classification of hypersensitivity vasculitis. Arthritis Rheum. 1990;33:1108–13. [PMID: 2202309]

Monteiro AF, Rato M, Martins C. Drug-induced photosensitivity: Photoallergic and phototoxic reactions. Clin Dermatol. 2016;34:571–81. [PMID: 27638435] doi:10.1016/j.clindermatol.2016.05.006

Svensson CK, Cowen EW, Gaspari AA. Cutaneous drug reactions. Pharmacol Rev. 2001;53:357–79. [PMID: 11546834]

Acneiform Eruptions

Das S, Reynolds RV. Recent advances in acne pathogenesis: implications for therapy. Am J Clin Dermatol. 2014;15:479–88. [PMID: 25388823] doi:10.1007/s40257-014-0099-z

Mehdizadeh A, Hazen PG, Bechara FG, Zwingerman N, Moazenzadeh M, Bashash M, et al. Recurrence of hidradenitis suppurativa after surgical management: A systematic review and meta-analysis. J Am Acad Dermatol. 2015;73:S70–7. [PMID: 26470621] doi:10.1016/j.jaad.2015.07.044

Micheletti RG. An update on the diagnosis and treatment of hidradenitis suppurativa. Cutis. 2015;96:7–12. [PMID: 27051885]

Oge LK, Muncie HL, Phillips-Savoy AR. Rosacea: diagnosis and treatment. Am Fam Physician. 2015;92:187–96. [PMID: 26280139]

van Zuuren EJ, Fedorowicz Z. Interventions for rosacea: abridged updated Cochrane systematic review including GRADE assessments. Br J Dermatol. 2015;173:651–62. [PMID: 26099423] doi:10.1111/bjd.13956

Woodruff CM, Charlie AM, Leslie KS. Hidradenitis Suppurativa: a guide for the practicing physician. Mayo Clin Proc. 2015;90:1679–93. [PMID: 26653298] doi:10.1016/j.mayocp.2015.08.020

Zaenglein AL, Pathy AL, Schlosser BJ, Alikhan A, Baldwin HE, Berson DS, et al. Guidelines of care for the management of acne vulgaris. J Am Acad Dermatol. 2016;74:945–73.e33. [PMID: 26897386] doi:10.1016/j.jaad.2015.12.037

Common Skin Infections

Amin AN, Cerceo EA, Deitelzweig SB, Pile JC, Rosenberg DJ, Sherman BM. Hospitalist perspective on the treatment of skin and soft tissue infections. Mayo Clin Proc. 2014;89:1436–51. [PMID: 24974260] doi:10.1016/j.mayocp.2014.04.018

Blaise G, Nikkels AF, Hermanns-Lê T, Nikkels-Tassoudji N, Piérard GE. Corynebacterium-associated skin infections. Int J Dermatol. 2008;47:884–90. [PMID: 18937649] doi:10.1111/j.1365-4632.2008.03773.x

Chen X, Anstey AV, Bugert JJ. Molluscum contagiosum virus infection. Lancet Infect Dis. 2013;13:877–88. [PMID: 23972567] doi:10.1016/S1473-3099(13)70109-9

Chipolombwe J, Török ME, Mbelle N, Nyasulu P. Methicillin-resistant Staphylococcus aureus multiple sites surveillance: a systemic review of the literature. Infect Drug Resist. 2016;9:35–42. [PMID: 26929653] doi:10.2147/IDR.S95372

Huang SS, Rifas-Shiman SL, Warren DK, Fraser VJ, Climo MW, Wong ES, et al; Centers for Disease Control and Prevention Epicenters Program. Improving methicillin-resistant Staphylococcus aureus surveillance and reporting in intensive care units. J Infect Dis. 2007;195:330–8. [PMID: 17205470]

Laureano AC, Schwartz RA, Cohen PJ. Facial bacterial infections: folliculitis. Clin Dermatol. 2014;32:711–4. [PMID: 25441463] doi:10.1016/j.clindermatol.2014.02.009

Kaushik N, Pujalte GG, Reese ST. Superficial fungal infections. Prim Care. 2015;42:501–16. [PMID: 26612371] doi:10.1016/j.pop.2015.08.004

Kullar R, Vassallo A, Turkel S, Chopra T, Kaye KS, Dhar S. Degowning the controversies of contact precautions for methicillin-resistant Staphylococcus aureus: a review. Am J Infect Control. 2016;44:97–103. [PMID: 26375351] doi:10.1016/j.ajic.2015.08.003

Oh CC, Ko HC, Lee HY, Safdar N, Maki DG, Chlebicki MP. Antibiotic prophylaxis for preventing recurrent cellulitis: a systematic review and meta-analysis. J Infect. 2014;69:26–34. [PMID: 24576824] doi:10.1016/j.jinf.2014.02.011

Stevens DL, Bisno AL, Chambers HF, Dellinger EP, Goldstein EJ, Gorbach SL, et al; Infectious Diseases Society of America. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the Infectious Diseases Society of America. Clin Infect Dis. 2014;59:e10–52. [PMID: 24973422] doi:10.1093/cid/ciu444

Pedrosa AF, Lisboa C, Gonçalves Rodrigues A. Malassezia infections: a medical conundrum. J Am Acad Dermatol. 2014;71:170–6. [PMID: 24569116] doi:10.1016/j.jaad.2013.12.022

Pereira LB. Impetigo – review. An Bras Dermatol. 2014;89:293–9. [PMID: 24770507]

Talan DA, Mower WR, Krishnadasan A, Abrahamian FM, Lovecchio F, Karras DJ, et al. Trimethoprim-Sulfamethoxazole versus placebo for uncomplicated skin abscess. N Engl J Med. 2016;374:823–32. [PMID: 26962903] doi:10.1056/NEJMoa1507476

He L, Zhang D, Zhou M, Zhu C. Corticosteroids for preventing postherpetic neuralgia. Cochrane Database Syst Rev. 2008:CD005582. [PMID: 18254083] doi:10.1002/14651858.CD005582.pub2

Infestations

Dadabhoy I, Butts JF. Parasitic skin infections for primary care physicians. Prim Care. 2015;42:661–75. [PMID: 26612378] doi:10.1016/j.pop.2015.07.004

Drugs for sexually transmitted infections. Treat Guidel Med Lett. 2013;11:87–94; quiz 96. [PMID: 23979529]

Johnstone P, Strong M. Scabies. BMJ Clin Evid. 2014;2014. [PMID: 25544114]

Vasievich MP, Villarreal JD, Tomecki KJ. Got the travel bug? A review of common infections, infestations, bites, and stings among returning travelers. Am J Clin Dermatol. 2016;17:451–462. [PMID: 27344566]

Bites and Stings

Foulke GT, Anderson BE. Bed bugs. Semin Cutan Med Surg. 2014;33:119–22. [PMID: 25577850]

Kang JK, Bhate C, Schwartz RA. Spiders in dermatology. Semin Cutan Med Surg. 2014;33:123–7. [PMID: 25577851]

Prickett KA, Ferringer TC. Helminths: a clinical review and update. Semin Cutan Med Surg. 2014;33:128–32. [PMID: 25577852]

Rosamilia LL. Scabies. Semin Cutan Med Surg. 2014;33:106–9. [PMID: 25577847]

Steen CJ, Carbonaro PA, Schwartz RA. Arthropods in dermatology. J Am Acad Dermatol. 2004;50:819–42, quiz 842–4. [PMID: 15153881]

Cuts, Scrapes, and Burns

Lloyd EC, Rodgers BC, Michener M, Williams MS. Outpatient burns: prevention and care. Am Fam Physician. 2012 Jan 1;85(1):25–32. Review. Erratum in: Am Fam Physician. 2012 Jun 15;85(12):1127. PubMed PMID: 22230304

Monseau AJ, Reed ZM, Langley KJ, Onks C. Sunburn, thermal, and chemical injuries to the skin. Prim Care. 2015;42:591–605. [PMID: 26612374] doi:10.1016/j.pop.2015.07.003

Singer AJ, Dagum AB. Current management of acute cutaneous wounds. N Engl J Med. 2008;359:1037–46. [PMID: 18768947] doi:10.1056/NEJMra0707253

Common Neoplasms

Davis J, Bordeaux J. Squamous cell carcinoma. JAMA Dermatol. 2013;149:1448. [PMID: 24352728] doi:10.1001/jamadermatol.2013.6947

Duffy K, Grossman D. The dysplastic nevus: from historical perspective to management in the modern era: part I. Historical, histologic, and clinical aspects. J Am Acad Dermatol. 2012;67:1.e1–16; quiz 17–8. [PMID: 22703915] doi:10.1016/j.jaad.2012.02.047

Higgins JC, Maher MH, Douglas MS. Diagnosing common benign skin tumors. Am Fam Physician. 2015;92:601–7. [PMID: 26447443]Wick MR. Cutaneous melanoma: A current overview. Semin Diagn Pathol. 2016;33:225–41. [PMID: 27229301] doi:10.1053/j.semdp.2016.04.007

Sobanko JF, Lynm C, Rosenbach M. Basal cell carcinoma. JAMA Dermatol. 2013;149:766. [PMID: 23783161] doi:10.1001/jamadermatol.2013.368

Wick MR, Gru AA. Metastatic melanoma: pathologic characterization, current treatment, and complications of therapy. Semin Diagn Pathol. 2016;33:204–18. [PMID: 27234321] doi:10.1053/j.semdp.2016.04.005

Wiznia LE, Federman DG. Treatment of Basal Cell Carcinoma in the Elderly: What nondermatologists need to know. Am J Med. 2016;129:655–60. [PMID: 27046242] doi:10.1016/j.amjmed.2016.03.003

Pruritus

Pereira MP, Kremer AE, Mettang T, Ständer S. Chronic pruritus in the absence of skin disease: pathophysiology, diagnosis and treatment. Am J Clin Dermatol. 2016;17:337–48. [PMID: 27216284] doi:10.1007/s40257-016-0198-0

Silverberg JI. Practice gaps in pruritus. Dermatol Clin. 2016;34:257–61. [PMID: 27363881] doi:10.1016/j.det.2016.02.008

Urticaria

Bernstein JA, Lang DM, Khan DA, Craig T, Dreyfus D, Hsieh F, et al. The diagnosis and management of acute and chronic urticaria: 2014 update. J Allergy Clin Immunol. 2014;133:1270–7. [PMID: 24766875] doi:10.1016/j.jaci.2014.02.036

Fine LM, Bernstein JA. Guideline of chronic urticaria beyond. Allergy Asthma Immunol Res. 2016;8:396–403. [PMID: 27334777] doi:10.4168/aair.2016.8.5.396

Maurer M, Church MK, Marsland AM, Sussman G, Siebenhaar F, Vestergaard C, et al. Questions and answers in chronic urticaria: where do we stand and where do we go? J Eur Acad Dermatol Venereol. 2016;30 Suppl 5:7–15. [PMID: 27286498] doi:10.1111/jdv.13695

Staubach P, Zuberbier T, Vestergaard C, Siebenhaar F, Toubi E, Sussman G. Controversies and challenges in the management of chronic urticaria. J Eur Acad Dermatol Venereol. 2016;30 Suppl 5:16–24. [PMID: 27286499] doi:10.1111/jdv.13696

Autoimmune Bullous Diseases

Huang A, Madan RK, Levitt J. Future therapies for pemphigus vulgaris: rituximab and beyond. J Am Acad Dermatol. 2016;74:746–53. [PMID: 26792592] doi:10.1016/j.jaad.2015.11.008

Jaleel T, Kwak Y, Sami N. Clinical approach to diffuse blisters. Med Clin North Am. 2015;99:1243–67, xii. [PMID: 26476251] doi:10.1016/j.mcna.2015.07.009

Krishnareddy S, Lewis SK, Green PH. Dermatitis herpetiformis: clinical presentations are independent of manifestations of celiac disease. Am J Clin Dermatol. 2014;15:51–6. [PMID: 24293087] doi:10.1007/s40257-013-0051-7

Stavropoulos PG, Soura E, Antoniou C. Drug-induced pemphigoid: a review of the literature. J Eur Acad Dermatol Venereol. 2014;28:1133–40. [PMID: 24404939] doi:10.1111/jdv.12366

Cutaneous Manifestations of Internal Disease

Balwani M, Desnick RJ. The porphyrias: advances in diagnosis and treatment. Blood. 2012;120:4496–504. [PMID: 22791288] doi:10.1182/blood-2012-05-423186

Braswell SF, Kostopoulos TC, Ortega-Loayza AG. Pathophysiology of pyoderma gangrenosum (PG): an updated review. J Am Acad Dermatol. 2015;73:691–8. [PMID: 26253362] doi:10.1016/j.jaad.2015.06.021

Cacoub P, Comarmond C, Domont F, Savey L, Saadoun D. Cryoglobulinemia vasculitis. Am J Med. 2015;128:950–5. [PMID: 25837517] doi:10.1016/j.amjmed.2015.02.017

Goeser MR, Laniosz V, Wetter DA. A practical approach to the diagnosis, evaluation, and management of cutaneous small-vessel vasculitis. Am J Clin Dermatol. 2014;15:299–306. [PMID: 24756249] doi:10.1007/s40257-014-0076-6

Grönhagen CM, Fored CM, Linder M, Granath F, Nyberg F. Subacute cutaneous lupus erythematosus and its association with drugs: a population-based matched case-control study of 234 patients in Sweden. Br J Dermatol. 2012;167:296–305. [PMID: 22458771] doi:10.1111/j.1365-2133.2012.10969.x

Iaccarino L, Ghirardello A, Bettio S, Zen M, Gatto M, Punzi L, et al. The clinical features, diagnosis and classification of dermatomyositis. J Autoimmun. 2014;48–49:122–7. [PMID: 24467910] doi:10.1016/j.jaut.2013.11.005

Kim SW, Kim MS, Lee JH, Son SJ, Park KY, Li K, et al. A clinicopathologic study of thirty cases of acquired perforating dermatosis in Korea. Ann Dermatol. 2014;26:162–71. [PMID: 24882969] doi:10.5021/ad.2014.26.2.162

Larson KN, Gagnon AL, Darling MD, Patterson JW, Cropley TG. Nephrogenic systemic fibrosis manifesting a decade after exposure to gadolinium. JAMA Dermatol. 2015;151:1117–20. [PMID: 26017458] doi:10.1001/jamadermatol.2015.0976

Molina-Ruiz AM, Cerroni L, Kutzner H, Requena L. Cutaneous deposits. Am J Dermatopathol. 2014;36:1–48. [PMID: 23249837] doi:10.1097/DAD.0b013e3182740122

Murphy-Chutorian B, Han G, Cohen SR. Dermatologic manifestations of diabetes mellitus: a review. Endocrinol Metab Clin North Am. 2013;42:869–98. [PMID: 24286954] doi:10.1016/j.ecl.2013.07.004

Nigwekar SU, Kroshinsky D, Nazarian RM, Goverman J, Malhotra R, Jackson VA, et al. Calciphylaxis: risk factors, diagnosis, and treatment. Am J Kidney Dis. 2015;66:133–46. [PMID: 25960299] doi:10.1053/j.ajkd.2015.01.034

Petri M, Orbai AM, Alarcón GS, Gordon C, Merrill JT, Fortin PR, et al. Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus. Arthritis Rheum. 2012;64:2677–86. [PMID: 22553077] doi:10.1002/art.34473

Reunala T, Salmi TT, Hervonen K, Laurila K, Kautiainen H, Collin P, et al. IgA antiepidermal transglutaminase antibodies in dermatitis herpetiformis: a significant but not complete response to a gluten-free diet treatment [Letter]. Br J Dermatol. 2015;172:1139–41. [PMID: 25196300] doi:10.1111/bjd.13387

Rochet NM, Chavan RN, Cappel MA, Wada DA, Gibson LE. Sweet syndrome: clinical presentation, associations, and response to treatment in 77 patients. J Am Acad Dermatol. 2013;69:557–64. [PMID: 23891394] doi:10.1016/j.jaad.2013.06.023

Rose TA Jr, Choi JW. Intravenous imaging contrast media complications: the basics that every clinician needs to know. Am J Med. 2015;128:943–9. [PMID: 25820169] doi:10.1016/j.amjmed.2015.02.018

Sharma A, Dhooria A, Aggarwal A, Rathi M, Chandran V. Connective tissue disorder-associated vasculitis. Curr Rheumatol Rep. 2016;18:31. [PMID: 27097818] doi:10.1007/s11926-016-0584-x

Thrash B, Patel M, Shah KR, Boland CR, Menter A. Cutaneous manifestations of gastrointestinal disease: part II. J Am Acad Dermatol. 2013;68:211.e1–33; quiz 244–6. [PMID: 23317981] doi:10.1016/j.jaad.2012.10.036

Tilstra JS, Lienesch DW. Rheumatoid nodules. Dermatol Clin. 2015;33:361–71. [PMID: 26143419] doi:10.1016/j.det.2015.03.004

Volkmann ER, Furst DE. Management of systemic sclerosis-related skin disease: a review of existing and experimental therapeutic approaches. Rheum Dis Clin North Am. 2015;41:399–417. [PMID: 26210126] doi:10.1016/j.rdc.2015.04.004

Werth VP. Clinical manifestations of cutaneous lupus erythematosus. Autoimmun Rev. 2005;4:296–302. [PMID: 15990077]

Dermatologic Emergencies

Darlenski R, Kazandjieva J, Tsankov N. Systemic drug reactions with skin involvement: Stevens-Johnson syndrome, toxic epidermal necrolysis, and DRESS. Clin Dermatol. 2015;33:538–41. [PMID: 26321400] doi:10.1016/j.clindermatol.2015.05.005

Law EH, Leung M. Corticosteroids in Stevens-Johnson syndrome/toxic epidermal necrolysis: current evidence and implications for future research. Ann Pharmacother. 2015;49:335–42. [PMID: 25406459] doi:10.1177/1060028014560012

Marzano AV, Borghi A, Cugno M. Adverse drug reactions and organ damage: the skin. Eur J Intern Med. 2016;28:17–24. [PMID: 26674736] doi:10.1016/j.ejim.2015.11.017

Mistry N, Gupta A, Alavi A, Sibbald RG. A review of the diagnosis and management of erythroderma (generalized red skin). Adv Skin Wound Care. 2015;28:228–36; quiz 237–8. [PMID: 25882661] doi:10.1097/01.ASW.0000463573.40637.73

Roujeau JC. Re-evaluation of 'drug-induced' erythema multiforme in the medical literature [Letter]. Br J Dermatol. 2016;175:650–1. [PMID: 27373787] doi:10.1111/bjd.14841

Wysong A, Venkatesan P. An approach to the patient with retiform purpura. Dermatol Ther. 2011;24:151–72. [PMID: 21410606] doi:10.1111/j.1529-8019.2011.01392.x

Hair Disorders

Housman E, Reynolds RV. Polycystic ovary syndrome: a review for dermatologists: part I. Diagnosis and manifestations. J Am Acad Dermatol. 2014;71:847.e1–847.e10; quiz 857–8. [PMID: 25437977] doi:10.1016/j.jaad.2014.05.007

Mubki T, Rudnicka L, Olszewska M, Shapiro J. Evaluation and diagnosis of the hair loss patient: part I. History and clinical examination. J Am Acad Dermatol. 2014;71:415.e1–415.e15. [PMID: 25128118] doi:10.1016/j.jaad.2014.04.070

Mubki T, Rudnicka L, Olszewska M, Shapiro J. Evaluation and diagnosis of the hair loss patient: part II. Trichoscopic and laboratory evaluations. J Am Acad Dermatol. 2014;71:431.e1–431.e11. [PMID: 25128119] doi:10.1016/j.jaad.2014.05.008

Schmidt TH, Shinkai K. Evidence-based approach to cutaneous hyperandrogenism in women. J Am Acad Dermatol. 2015;73:672–90. [PMID: 26138647] doi:10.1016/j.jaad.2015.05.026

Wendelin DS, Pope DN, Mallory SB. Hypertrichosis. J Am Acad Dermatol. 2003;48:161–79; quiz 180–1. [PMID: 12582385]

Nail Disorders

Cohen PR, Scher RK. Geriatric nail disorders: diagnosis and treatment. J Am Acad Dermatol. 1992;26:521–31. [PMID: 1597537]

Goydos JS, Shoen SL. Acral lentiginous melanoma. Cancer Treat Res. 2016;167:321–9. [PMID: 26601870] doi:10.1007/978-3-319-22539-5_14

Hay RJ, Baran R. Onychomycosis: a proposed revision of the clinical classification [Editorial]. J Am Acad Dermatol. 2011;65:1219–27. [PMID: 21501889] doi:10.1016/j.jaad.2010.09.730

Hinshaw MA, Rubin A. Inflammatory diseases of the nail unit. Semin Cutan Med Surg. 2015;34:109–16. [PMID: 26176289] doi:10.12788/j.sder.2015.0132

Holzberg M. Common nail disorders. Dermatol Clin. 2006;24:349–54. [PMID: 16798432]

Disorders of the Mucous Membranes

Dubach P, Caversaccio M. Images in clinical medicine. Amalgam tattoo. N Engl J Med. 2011;364:e29. [PMID: 21488760] doi:10.1056/NEJMicm1011669

Fernandes D, Ferrisse TM, Navarro CM, Massucato EM, Onofre MA, Bufalino A. Pigmented lesions on the mucosa: a wide range of diagnoses. Oral Surg Oral Med Oral Pathol Oral Radiol. 2015;119:374–8. [PMID: 25687194] doi:10.1016/j.oooo.2014.11.015

Stoopler ET, Sollecito TP. Oral mucosal diseases: evaluation and management. Med Clin North Am. 2014;98:1323–52. [PMID: 25443679] doi:10.1016/j.mcna.2014.08.006

Foot and Lower Leg Ulcers

Alavi A, Sibbald RG, Phillips TJ, Miller OF, Margolis DJ, Marston W, et al. What's new: Management of venous leg ulcers: approach to venous leg ulcers. J Am Acad Dermatol. 2016;74:627–40; quiz 641–2. [PMID: 26979354] doi:10.1016/j.jaad.2014.10.048

Alavi A, Sibbald RG, Phillips TJ, Miller OF, Margolis DJ, Marston W, et al. What's new: management of venous leg ulcers: treating venous leg ulcers. J Am Acad Dermatol. 2016;74:643–64; quiz 665–6. [PMID: 26979355] doi:10.1016/j.jaad.2015.03.059

Kirsner RS, Vivas AC. Lower-extremity ulcers: diagnosis and management. Br J Dermatol. 2015;173:379–90. [PMID: 26257052] doi:10.1111/bjd.13953

Morton LM, Phillips TJ. Wound healing and treating wounds: differential diagnosis and evaluation of chronic wounds. J Am Acad Dermatol. 2016;74:589–605; quiz 605–6. [PMID: 26979352] doi:10.1016/j.jaad.2015.08.068

O'Donnell TF Jr, Passman MA, Marston WA, Ennis WJ, Dalsing M, Kistner RL, et al; Society for Vascular Surgery. Management of venous leg ulcers: clinical practice guidelines of the Society for Vascular Surgery ® and the American Venous Forum. J Vasc Surg. 2014;60:3S–59S. [PMID: 24974070] doi:10.1016/j.jvs.2014.04.049

Powers JG, Higham C, Broussard K, Phillips TJ. Wound healing and treating wounds: chronic wound care and management. J Am Acad Dermatol. 2016;74:607–25; quiz 625–6. [PMID: 26979353] doi:10.1016/j.jaad.2015.08.070

Dermatologic Conditions of Pregnancy and Aging

Blume-Peytavi U, Kottner J, Sterry W, Hodin MW, Griffiths TW, Watson RE, et al. Age-associated skin conditions and diseases: current perspectives and future options. Gerontologist. 2016;56 Suppl 2:S230–42. [PMID: 26994263] doi:10.1093/geront/gnw003

Kroumpouzos G, Cohen LM. Dermatoses of pregnancy. J Am Acad Dermatol. 2001;45:1–19; quiz 19–22. [PMID: 11423829]

Murase JE, Heller MM, Butler DC. Safety of dermatologic medications in pregnancy and lactation: Part I. Pregnancy. J Am Acad Dermatol. 2014;70:401.e1–14; quiz 415. [PMID: 24528911] doi:10.1016/j.jaad.2013.09.010

Sheth VM, Pandya AG. Melasma: a comprehensive update: part I. J Am Acad Dermatol. 2011;65:689–97; quiz 698. [PMID: 21920241] doi:10.1016/j.jaad.2010.12.046

Tyler KH, Zirwas MJ. Pregnancy and dermatologic therapy. J Am Acad Dermatol. 2013;68:663–71. [PMID: 23182064] doi:10.1016/j.jaad.2012.09.034

Tobin DJ. Introduction to skin aging. J Tissue Viability. 2017;26:37–46. [PMID: 27020864] doi:10.1016/j.jtv.2016.03.002

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This self-assessment test contains one-best-answer multiple-choice questions. Please read these directions carefully before answering the questions. Answers, critiques, and bibliographies immediately follow these multiple-choice questions. The American College of Physicians (ACP) is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

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CME credits and MOC points are available from the publication date of July 31, 2018, until July 31, 2021. You may submit your answer sheet or enter your answers online at any time during this period.

Directions

*Each of the numbered items is followed by lettered answers. Select the **ONE** lettered answer that is **BEST** in each case.*

H

Item 1

A 63-year-old man is evaluated for a skin eruption that is itchy and worsening for the past several weeks. Medical history is unremarkable, and he takes no medications.

On physical examination, vital signs are normal. There are tense bullae on an erythematous base and scattered erosions on the trunk and extremities.

Which of the following is the most appropriate diagnostic test to perform next?

(A) Biopsy of lesional skin for direct immunofluorescence
(B) Biopsy of lesional skin for histology
(C) Biopsy of lesional skin for histology and perilesional skin for direct immunofluorescence
(D) Biopsy of perilesional skin for histology and direct immunofluorescence

Item 2

A 25-year-old man is evaluated for recurrent skin eruption with oval lesions on the chest and upper back, which are occasionally itchy. The lesions began in late spring and worsened over the summer. Medical history is unremarkable, and he takes no medications.

On physical examination, vital signs are normal. Skin findings on the chest are shown.

Extremities and feet are unaffected.

Which of the following is the most likely diagnosis?

(A) *Candida albicans* infection
(B) Erythrasma
(C) Pityriasis versicolor
(D) Tinea corporis

Item 3

A 32-year-old man is evaluated for an intermittent pruritic rash of 8 years' duration. Medical history is significant for mild persistent asthma. His only medications are an albuterol inhaler and an inhaled glucocorticoid.

On physical examination, vital signs are normal. There is mild xerosis with erythematous plaques on the bilateral antecubital fossae, volar wrists, and anterior lower legs. Lichenification is present on the dorsal hands. Linear excoriations are found within many of the erythematous plaques on the arms.

Which of the following is the most appropriate treatment?

(A) Oral cephalexin
(B) Oral prednisone
(C) Topical glucocorticoids
(D) Topical ketoconazole
(E) Topical mupirocin

Item 4

H

A 43-year-old woman is evaluated for painful wheals on the upper legs and back that have been present for 2 weeks. Individual lesions resolve with bruising in 3 to 4 days. The patient also reports some associated joint pain, particularly of the small joints in her hands. Medical history is unremarkable, and she takes no medications.

On physical examination, vital signs are normal. There are polycyclic edematous plaques on the back and upper legs. The remainder of the examination, including joint examination, is normal.

Which of the following is the most appropriate management?

(A) Epicutaneous patch testing
(B) Ice cube provocation test
(C) Oral prednisone
(D) Skin biopsies
(E) Topical triamcinolone

Item 5

A 25-year-old man is evaluated for asymptomatic skin changes on his thighs. He has a 1-year history of plaque psoriasis on his elbows and knees for which he uses triamcinolone cream and calcipotriene cream. The patient has been applying these medications to the entire leg and arm. Prior to treatment, the patient's thighs were normal. He is otherwise in good health.

On physical examination, vital signs are normal. A thigh lesion is shown (see top of next page).

Which of the following is the most appropriate treatment for the patient's thighs?

(A) Add clobetasol cream
(B) Add terbinafine cream
(C) Discontinue calcipotriene cream
(D) Discontinue triamcinolone cream

ITEM 5

H

Item 6

A 35-year-old woman is evaluated for severe pain on the left side of the chest for 1 week followed by increased redness and the development of small blisters. Medical history is significant for rheumatoid arthritis. Medications are naproxen as needed, methotrexate folic acid, and an oral contraceptive.

On physical examination, skin findings are shown.

The remainder of the examination is unremarkable.

Which of the following is the most likely diagnosis?

(A) Chicken pox (varicella)
(B) Eczema herpeticum
(C) Herpes simplex virus
(D) Herpes zoster

H

Item 7

A 58-year-old woman was evaluated for dark brown pigmentation on her thumb nail. She noticed it was getting darker and wider. She is otherwise healthy and takes no medications.

On physical examination, vital signs are normal. The other nails are uninvolved. Nail findings are shown.

The remainder of the examination is normal.

Which of the following is the most likely diagnosis?

(A) Lichen planus
(B) Melanonychia
(C) Normal aging
(D) Onychomycosis

Item 8

A 25-year-old woman is evaluated for finger pain that began approximately 6 weeks ago. She works as a hairdresser. She is otherwise healthy and takes no medications.

On physical examination, vital signs are normal. Skin findings reveal ragged cuticles on most of her digits. On the third digit of the left hand, the nail fold is tender. Skin and nail findings are shown (see top of next page).

Which of the following is the most likely cause of this patient's tender finger lesion?

(A) Acute paronychia
(B) Chronic paronychia
(C) Onychomycosis
(D) Psoriasis

Item 9

A 60-year-old woman is evaluated for follow-up treatment of long-standing psoriasis. Medical history is significant for hypertension and hypercholesterolemia. Family history includes multiple family members with psoriasis. She has no joint symptoms, and her medications are atenolol and simvastatin.

On physical examination, vital signs are normal. There is no joint swelling.

ITEM 8

She has a total of 30% body surface area involvement with psoriasis without nail involvement.

Which of the following is the most appropriate treatment?

(A) Methotrexate
(B) Oral prednisone
(C) Tacrolimus ointment
(D) Topical calcitriol

Item 10

A 27-year-old woman is evaluated for itchy bumps on her abdomen. The patient is pregnant and in her third trimester. She was diagnosed with pruritic urticarial papules and plaques of pregnancy (PUPPP).

On physical examination, vital signs are normal. Skin findings are shown.

Which of the following is the most appropriate treatment?

(A) Early delivery
(B) Topical glucocorticoids
(C) Topical imiquimod
(D) Ursodeoxycholic acid

Item 11

H

A 65-year-old man is evaluated in the ICU for a rash limited to his back that was first noticed this morning. He was admitted to the ICU for hospital-acquired pneumonia following hip replacement surgery 3 days ago. Because of deteriorating respiratory function, he was intubated and placed on mechanical ventilation. His current medications are fentanyl and piperacillin-tazobactam.

On physical examination, temperature is 38.3 °C (100.9 °F), blood pressure is 110/60 mm Hg, pulse rate is 115/min, and respiration rate is 18/min (ventilator set rate is 14/min). Pulmonary examination reveals diffuse crackles. Skin findings are shown.

Which of the following is the most likely diagnosis?

(A) Acute generalized exanthematous pustulosis
(B) *Candida albicans* infection
(C) Miliaria
(D) Povidone iodine contact dermatitis

Item 12

An 18-year-old man is evaluated for a 6-month history of acne on his face, chest, and upper back. He is otherwise in good health. He has been treated with doxycycline, tretinoin cream, and topical clindamycin lotion for 6 months with minimal improvement.

On physical examination, vital signs are normal. Skin findings are shown (see top of next page).

The remainder of the examination is unremarkable.

Which of the following is the most appropriate treatment?

(A) Add topical benzoyl peroxide gel
(B) Add topical dapsone
(C) Change doxycycline to trimethoprim-sulfamethoxazole
(D) Discontinue current treatment and start oral isotretinoin
(E) Start oral prednisone

ITEM 12

Item 13

A 62-year-old woman is evaluated for a "sun allergy," manifesting as a rash on her scalp, eyelids, upper back, and knuckles. This started 2 years ago, but is less pronounced over the winter months. Medical history is unremarkable. Her only medication is hydrocortisone cream.

On physical examination, vital signs are normal. Pink-violet edematous macules are present on the eyelids. The scalp has pink-violet diffuse scaly macules with some thinning of the hair. There is a poikilodermatous pink scaly plaque on the upper back and posterior neck. The metacarpophalangeal and proximal interphalangeal joints have pink-violet flat-topped papules on their dorsal surface. There are dilated periungual capillary loops on each finger, and all 10 cuticles are dystrophic. There are no swollen joints, no abnormalities on strength testing, and no oral ulcerations.

Laboratory studies show antinuclear antibody titer of 1:640. All other laboratory values, including creatine kinase, aldolase, aspartate aminotransferase, and gamma-glutamyl transferase, are normal.

Which of the following is the most likely diagnosis?

(A) Amyopathic dermatomyositis
(B) Mixed connective tissue disease
(C) Polymorphus light eruption
(D) Systemic lupus erythematosus

Item 14

A 42-year-old man reported to the emergency department yesterday with a painful blistering rash, mouth sores, and eye pain. He started taking allopurinol 10 days ago for gout. He developed flu-like symptoms and skin pain 2 days ago. He was admitted last night with a diagnosis of toxic epidermal necrolysis. His allopurinol was discontinued, fluid and electrolyte resuscitation was initiated, and he was started on intravenous glucocorticoids.

On physical examination, heart rate is 95/min; the remaining vital signs are normal. Oxygen saturation is 98% breathing ambient air. The patient appears to be in pain. Extensive oral ulcerations are present but do not extend across the vermillion border. Large sheets of his skin are denuding, affecting more than 35% of his body surface area. His conjunctivae are injected and red. He has generalized lymphadenopathy.

Laboratory studies:

Aspartate aminotransferase	92 IU/L
Alanine aminotransferase	87 IU/L
Bicarbonate	22 mEq/L (22 mmol/L)
Blood urea nitrogen	27 mg/dL (9.6 mmol/L)
Plasma glucose	210 mg/dL (11.6 mmol/L)

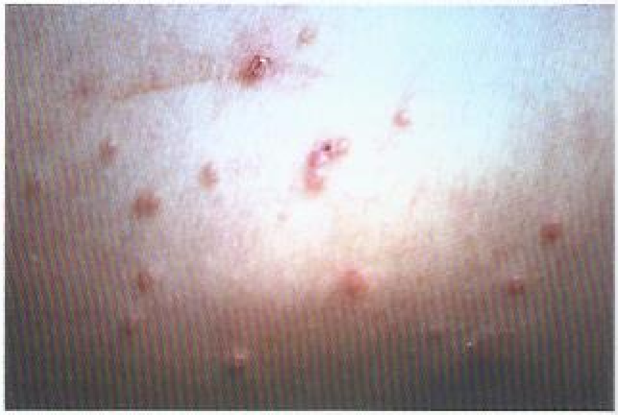
Which of the following factors has the greatest impact on this patient's prognosis?

(A) Age
(B) Heart rate
(C) Affected body surface area
(D) Plasma glucose level
(E) Serum bicarbonate level

Item 15

A 25-year-old woman is evaluated for pruritic lesions on the legs and in the groin area that first appeared several months ago. The patient is otherwise in good health and takes no medications.

On physical examination, vital signs are normal. Skin findings are shown.



Which of the following is the most likely diagnosis?

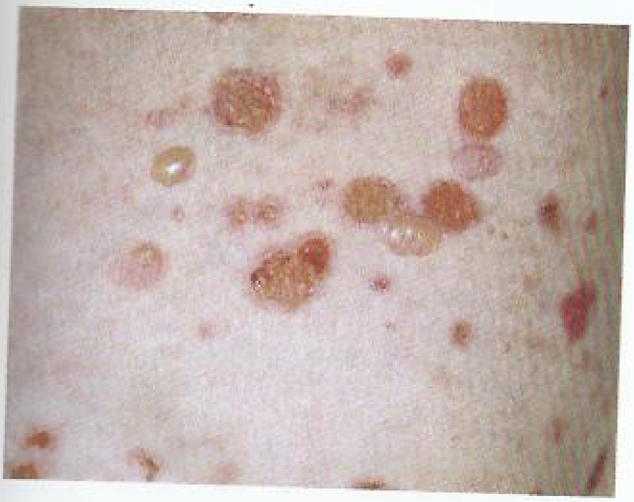
(A) Condylomata acuminata
(B) Herpes simplex virus infection
(C) Molluscum contagiosum infection
(D) Seborrheic keratoses

Item 16

A 65-year-old man is evaluated for pruritic hive-like lesions on the trunk and upper legs that are worsening and starting to blister. He has no oral or mucous membrane involvement. He has no significant medical history and takes no medications.

H CONT

On physical examination, vital signs are normal. Skin findings are shown.



Which of the following is the most likely diagnosis?

(A) Bullous pemphigoid
(B) Dermatitis herpetiformis
(C) Pemphigus foliaceus
(D) Pemphigus vulgaris

H

Item 17

A 24-year-old woman is evaluated for a 4-day history of a worsening pruritic rash on the chin. She is a kindergarten teacher. Medical history is unremarkable, and she takes no medications.

On physical examination, vital signs are normal. Skin findings are shown.

Which of the following is the most appropriate treatment?

(A) Oral doxycycline
(B) Topical hydrocortisone
(C) Topical mupirocin
(D) Topical neomycin/polymyxin B/bacitracin

H

Item 18

A 68-year-old man is evaluated for 3 weeks of painful "blood blisters" on his legs and feet. He has noticed burning and tingling of his right foot and three toes over the last 2 weeks. Medical history is significant for rheumatoid arthritis for 22 years. He is a 60 pack-year cigarette smoker. He occasionally uses cocaine. He denies fever, chills, and night sweats, anorexia, or weight loss. Medications are hydroxychloroquine and methotrexate.

On physical examination, temperature is 36.6 °C (97.8 °F), blood pressure is 134/79 mm Hg, and pulse rate is 82/min. Changes typical of destructive rheumatoid arthritis are apparent in the hands, wrists, elbows, and feet. Palpable purpura is present over the legs and ankles. Periungual purpura is present on three fingers. There is reduced sensitivity to pinprick and fine touch over the lateral right foot and dorsal lateral three toes. There is no murmur on his cardiac examination.

Laboratory studies show substantially elevated rheumatoid factor titer. Antinuclear antibody titer is less than 1:40. ANCA screen is negative. Complement levels are normal. Results of kidney and liver chemistry tests are normal.

Which of the following is the most likely cause of the patient's skin findings?

(A) Actinic purpura
(B) Illicit drug use
(C) Infective endocarditis
(D) Rheumatoid vasculitis

Item 19

A 38-year old woman is evaluated for a new rash on the chest, arms, and back. It appeared 3 weeks ago. It burns and itches and has not responded to over-the-counter hydrocortisone cream. The rash substantially worsened following a vacation at the beach. Medical history is significant for psoriasis vulgaris with involvement of the elbows and knees with psoriatic arthritis for 3 years' duration. Her only medication is adalimumab, which she started 2 months ago. It cleared her elbows and knees in about 3 weeks.

On physical examination, vital signs are normal. Representative skin findings are shown.

There is no facial rash, hair loss, rash in the ears, oral ulcerations, or swollen joints.

Laboratory studies show antinuclear antibody titer less than 1:40.

Which of the following is the most appropriate treatment for this patient?

(A) Add hydroxychloroquine
(B) Add methotrexate
(C) Add oral prednisone taper
(D) Discontinue adalimumab

H

Item 20

A 71-year-old man is evaluated for erythema and tenderness of the left lower leg for 1 week's duration. This is the second similar episode of the left lower leg. The last episode was 2 months ago. He was previously treated successfully with antibiotics.

On physical examination, temperature is 38.1 °C (100.6 °F), blood pressure is 125/75 mm Hg, respiration rate is 16/min, and pulse rate is 85/min. There is a well-demarcated, warm and tender erythematous patch on the anterior lower left leg extending from dorsal foot to mid shin. There is tissue maceration and fissuring between second and third toe spaces bilaterally. The remainder of the physical examination is normal.

In addition to initiating antibiotic therapy, which of the following is the most appropriate management?

(A) Following acute therapy, start prophylactic antibiotics
(B) Obtain blood cultures
(C) Obtain skin punch biopsy
(D) Staphylococcal decolonization with intranasal mupirocin
(E) Treat the interdigital intertrigo

H

Item 21

An 82-year-old woman is evaluated for a spot on her left cheek. Six months ago, she was diagnosed with an actinic keratosis. This lesion was treated with cryotherapy two times; however, the lesion is still persistent. On palpation, it is indurated. The lesion is shown.

Which of the following is the most appropriate next step in management?

(A) Cryotherapy
(B) Biopsy
(C) Topical imiquimod
(D) Wide local excision

H

Item 22

A 44-year-old man is evaluated for a new lesion on the side of his face. It has been present for several months and is asymptomatic. When he shaves he cuts it, and it starts bleeding. He is otherwise healthy and takes no medications.

On physical examination, vital signs are normal. Skin findings are shown.

The remainder of the examination is normal.

Which of the following is the mostly likely diagnosis?

(A) Basal cell carcinoma
(B) Dermal nevus
(C) Keratoacanthoma
(D) Nodular melanoma
(E) Squamous cell carcinoma

Item 23

A 54-year-old woman is evaluated for lumps that have appeared around the outside of her nostrils over the last 5 months. She has had arthralgias for the past 6 months. She takes no medications.

On physical examination, vital signs are normal. Skin findings are shown (see top of next page).

The remainder of the skin examination is normal.

Skin biopsy shows granulomas without necrosis or lymphocytic infiltration in the dermis.

Which of the following is the most likely diagnosis?

(A) Lepromatous leprosy
(B) Lupus pernio (cutaneous sarcoidosis)
(C) Lupus vulgaris (cutaneous tuberculosis)
(D) Systemic lupus erythematosus

ITEM 23

Item 24

A 63-year-old woman is evaluated for a lesion on her nose that is slowly enlarging and nonhealing. She is otherwise in good health and takes no medications.

On physical examination, vital signs are normal. The skin examination demonstrates a 0.8 × 0.6-cm pearly ulcerated papule with arborizing telangiectasias. The remainder of the examination is normal.

Biopsy of the lesion demonstrates basal cell carcinoma with high-risk micronodular and infiltrative histologic features.

Which of the following is the most appropriate treatment of this lesion?

(A) Cryotherapy
(B) Electrodesiccation and curettage
(C) Mohs micrographic surgery
(D) Topical 5-fluorouracil
(E) Vismodegib

Item 25

A 23-year-old woman is evaluated in the emergency department. Four days ago she developed a cold sore on her lower lip. This was followed by the development of painful sores throughout her mouth. The next day she developed a rash on her hands, arms, legs, and face, and eventually on her palms and soles. She takes no medications.

On physical examination, vital signs are normal. The patient has pain in her mouth, but is in no acute distress. Erosions are present in the oropharynx. There are five distinct monomorphic clustered 2- to 3-mm erosions on the left lower lip. Skin findings on the palm are shown.

The arms and face have lesions similar to those on the palm. There is no sloughing of the skin when shearing force is applied. The lesions affect about 7% body surface area. There is no corneal injection or tearing and no genital erosion or ulceration.

Which of the following is the most likely diagnosis?

(A) Disseminated gonococcemia
(B) Erythema multiforme major
(C) Stevens-Johnson syndrome
(D) Toxic epidermal necrolysis

Item 26

An 89-year-old woman is evaluated in the office for an annual examination. She has dementia. She was brought to the appointment by her caregiver who noted "bruises" on her arms. The patient says she does not remember what happened.

On physical examination, vital signs are normal. Skin findings are shown.

Which is the following is the most appropriate management?

(A) Biopsy the lesion
(B) Call adult protective services
(C) Obtain coagulation studies
(D) Prescribe triamcinolone ointment
(E) No intervention needed

H

Item 27

A 68-year-old woman is evaluated for a 12-month history of swelling of both of her lower legs. Over the past 4 months, there was worsening edema, erythema, scaling, and itching of the lower legs. She has not used any prescription or over-the-counter topical medications or emollients. Medical history is significant for hypertension and type 2 diabetes mellitus. Medications are lisinopril, amlodipine, hydrochlorothiazide, and metformin.

On physical examination, vital signs are normal. BMI is 32. Skin findings are shown.

There is no tenderness. Pedal pulses are strong bilaterally.

Laboratory studies, including leukocyte count, are within normal range.

Which of the following is the most likely diagnosis?

(A) Allergic contact dermatitis
(B) Cellulitis
(C) Leukocytoclastic vasculitis
(D) Psoriasis
(E) Stasis dermatitis

Item 28

A 40-year-old man is evaluated for a firm, flesh colored lesion that has been growing on the back for several months. Foul-smelling material can be expressed from the lesion. The patient is bothered by the periodic drainage. He is otherwise healthy and takes no medications.

On physical examination, vital signs are normal. There is a 3-cm subepidermal nodule with a central punctum on the upper back. There is no erythema or warmth of surrounding skin.

Which of the following is the most appropriate treatment for this patient?

(A) Excision
(B) Incision
(C) Incision and drainage
(D) Oral antibiotics

Item 29

A 27-year-old woman is evaluated in the office for generalized hair loss. She has not had any similar episodes previously. The patient is 3 months postpartum and does not take any medications.

On physical examination, vital signs are normal. The scalp skin itself appears normal with no erythema, scale, or scarring. The hair shafts are normal as well. As the hair was combed through, several hairs fell out at the root. The remainder of the examination is unremarkable.

Which of the following is the most appropriate management?

(A) Intralesional glucocorticoids
(B) Oral finasteride
(C) Topical minoxidil
(D) Reassurance

Item 30

A 24-year-old woman is evaluated for a rash on her face for several months' duration. It is asymptomatic but has gotten worse over the summer. She washes her face with soap and water twice daily and has recently changed soaps. Previously her skin was normal. She is otherwise healthy. Her only medication is an oral contraceptive pill, which she started 3 months ago.

On physical examination, vital signs are normal. Skin findings are shown.

Which of the following is the most likely diagnosis?

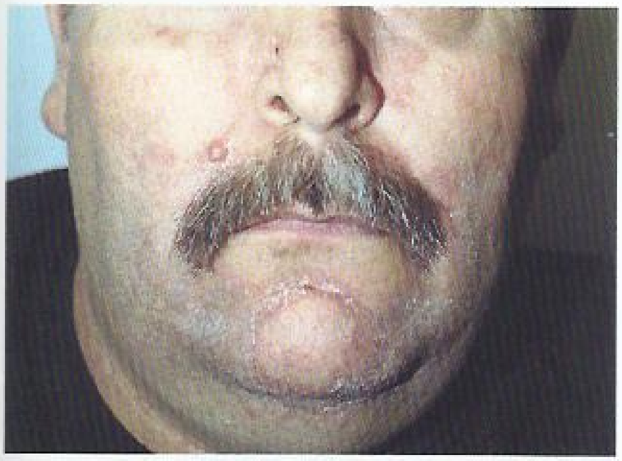
(A) Irritant contact dermatitis
(B) Melasma

(C) Morbilliform drug eruption
(D) Postinflammatory hyperpigmentation

Item 31

A 45-year-old man is evaluated for an explosive onset of a rash with greasy scale on the chin, nasolabial folds, scalp, and chest that is getting worse. He has never had this condition before. He has tried over-the-counter selenium sulfide shampoo and hydrocortisone cream without success. Medical history is otherwise unremarkable, and he takes no additional medications.

On physical examination, vital signs are normal. Skin findings are shown.



Which of the following is the most appropriate diagnostic test to perform next?

(A) Fasting blood glucose
(B) Fasting lipid panel
(C) Hepatitis C testing
(D) HIV testing

Item 32

A 60-year-old man is evaluated for dry skin and a pruritic rash of 6 months' duration. He is a farmer and has extensive exposure to the sun. The rash is transient, occurring most frequently during the winter and spring when his skin is dry, and is worsened by heat and sweating during the summer. The patient is otherwise well, has no other medical problems, and takes no medications.

On physical examination, vital signs are normal. Skin findings on the upper torso are shown (see top of next column).

The arms, legs, face, and mucous membranes are unaffected. The remainder of the examination is unremarkable.

Which of the following is the most likely diagnosis?

(A) Allergic contact dermatitis
(B) Atopic dermatitis
(C) Lichen planus
(D) Transient acantholytic dermatosis

ITEM 32

Item 33

A 30-year-old woman is evaluated for a dark spot on the lower lip for several months' duration. Medical history is unremarkable, and she takes no medications.

On physical examination, vital signs are normal. There is 2 × 3-mm perfectly round, well-circumscribed brown to black macule on the lower mucosal lip. Oral mucosa is otherwise normal.

Which of the following is the most likely diagnosis?

(A) Actinic cheilitis
(B) Amalgam tattoo
(C) Melanoma in-situ
(D) Melanotic macule

Item 34

A 47-year-old woman is evaluated for her skin "turning to leather." She notes that she had originally developed an itchy pink rash on the skin over her forearms, elbows, and upper arms. Eventually the rash turned to thick hard skin. She has similar skin findings in the area of her waistband. She denies symptoms of Raynaud phenomenon.

On physical examination, vital signs are normal. Skin findings are shown.

There are no changes over the face or lips.

Which of the following is the most likely diagnosis?

(A) Diffuse cutaneous systemic sclerosis
(B) Limited cutaneous systemic sclerosis (CREST)
(C) Localized scleroderma (morphea)
(D) Scleredema
(E) Scleromyxedema

Item 35

A 69-year-old man is evaluated for a new lesion behind his ear. It is asymptomatic. His wife noted that it first appeared last year and is growing. The patient is a farmer and has had many sunburns over his lifetime. He has no other medical problems and takes no medications.

On physical examination, vital signs are normal. Skin findings are shown.

Which of the following is the most likely diagnosis?

(A) Junctional melanocytic nevus
(B) Melanoma in situ, lentigo maligna
(C) Nodular melanoma
(D) Solar lentigo

Item 36

A 30-year-old woman is evaluated for an acne flare on her face. She is 12 weeks pregnant. When she was younger, she was on a course of isotretinoin, and it cleared her acne. She is otherwise in good health and has not been on any medications other than a prenatal vitamin since she became pregnant.

On physical examination, her vital signs are normal. Skin findings are shown (see top of next column).

The remainder of the examination is normal.

Which of the following is the most appropriate treatment for the patient?

(A) Oral doxycycline
(B) Oral isotretinoin
(C) Oral spironolactone
(D) Topical erythromycin
(E) Topical tazarotene

ITEM 36

Item 37

A 35-year-old man is evaluated after 3 weeks of worsening sinus pain and congestion. He was prescribed amoxicillin-clavulanate. Four days into his treatment, he developed a rash.

On physical examination, vital signs are normal. Skin findings are shown.

H CONT.

There is purulent postnasal drainage noted in the oropharynx. There are no oral, genital, or corneal erosions. There are no findings on the palms, soles, wrists, or ankles. The patient has no skin pain, mouth ulcers, or dysuria. His conjunctivae are injected, but there is no ocular pain.

Laboratory studies show peripheral eosinophilia. Other laboratory values, including creatinine, blood urea nitrogen, and liver chemistry tests, are unremarkable.

Which of the following is the most likely diagnosis?

(A) Drug reaction with eosinophilia and systemic symptoms (DRESS)
(B) Morbilliform drug reaction
(C) Stevens-Johnson syndrome
(D) Viral exanthem

Item 38

A 20-year-old woman is evaluated for white spots on her eyelids, hands, elbows, and knees for several months' duration. There was no previous rash. She is otherwise healthy and takes no medications.

On physical examination, vital signs are normal. Representative skin findings on the eyelids are shown.

The remainder of the examination is normal.

Which of the following is the most likely diagnosis?

(A) Pityriasis alba
(B) Tinea versicolor
(C) Tuberous sclerosis
(D) Vitiligo

Item 39

A 36-year-old woman is evaluated for a 6-year history of tender, foul-smelling, draining nodules in the inguinal folds. She has had occasional nodules in the axillae. She has taken multiple courses of oral clindamycin with only temporary improvement. She has a 14-pack-year smoking history. Medical history is otherwise unremarkable.

On physical examination, vital signs are normal. BMI is 34. There are tender nodules, draining sinus tracts, and comedones in the inguinal folds. Scarring is present in right and left axillae. Additional inguinal skin findings are shown.

Which of the following is the most likely diagnosis?

(A) Carbuncles
(B) Chancroid
(C) Epidermal inclusion cysts
(D) Hidradenitis suppurativa

Item 40

H

A 34-year-old woman is evaluated for a painful leg ulceration on her left anterior shin. The patient notes that the lesion began 2 weeks ago as a red papule after hitting her leg on her stairs at home. The initial papule expanded and ulcerated over the past 2 weeks. Medical history is significant for ulcerative colitis. Her only medication is mesalamine.

On physical examination, vital signs are normal. Skin findings are shown.

H CONT.

Which of the following is the most likely diagnosis?

(A) Acrodermatitis enteropathica
(B) Calciphylaxis
(C) Pyoderma gangrenosum
(D) Venous stasis ulcer

Item 41

A 64-year-old man is evaluated for treatment of extensive psoriasis on 20% body surface area, covering the knees, elbows, scalp, and trunk. Medical history is otherwise unremarkable, and he takes no medications.

On physical examination, vital signs are normal. He has no fingernail changes and no arthritis. Skin findings are shown.

Which of the following forms of phototherapy is the most appropriate initial treatment?

(A) Narrowband ultraviolet B (UVB) phototherapy
(B) Photodynamic therapy
(C) Psoralen plus ultraviolet A (PUVA) photochemotherapy
(D) Retinoid plus PUVA (RePUVA) photochemotherapy
(E) Ultraviolet A (UVA) phototherapy

H Item 42

A 44-year-old woman is evaluated for painful nodules, ulcers, and skin changes on the lower legs of 2 years' duration. She takes no medications.

On physical examination, vital signs are normal. Tender subcutaneous nodules, stellate ulcerations, and livido reticularis are evenly distributed bilaterally over her lower legs. The dorsalis pedis and posterior tibial pulses are normal. There are no varicosities present on the legs. The remainder of the examination is normal.

Laboratory studies show an erythrocyte sedimentation rate of 65 mm/h. Skin biopsy shows vasculitis of a mid-sized arteriole in the subcutis. ANCA screen is negative. Antinuclear antibodies titer is 1:40. C3 and C4 values are normal. Rheumatoid factor and hepatitis B and C tests are negative. Stool is negative for occult blood, and urinalysis is unremarkable.

Which of the following is the most likely diagnosis?

(A) Granulomatosis with polyangiitis
(B) Leukocytoclastic vasculitis
(C) Microscopic polyangiitis
(D) Polyarteritis nodosa
(E) Takayasu arteritis

Item 43

A 23-year-old woman is evaluated for 2 weeks of painful lumps on her legs. The lumps persist for several days and make it difficult for her to go to work as a waitress. She is a college student in Ohio where she has lived her whole life. She has not traveled outside of the state for the last 2 years. She has no swollen or painful joints. She denies abdominal pain, diarrhea, weight loss, night sweats, and fever. She is sexually active with one partner for the past 2 years. She is taking oral contraceptive pills.

On physical examination, vital signs are normal. There are tender faint pink-brown nodules on the shins bilaterally. The throat and tonsils appear normal. There is no joint swelling.

Pregnancy test is negative. Complete blood count, erythrocyte sedimentation rate, and antistreptolysin O titers are pending.

Barrier contraceptive methods are recommended in lieu of oral contraceptives.

Which of the following tests should be done next?

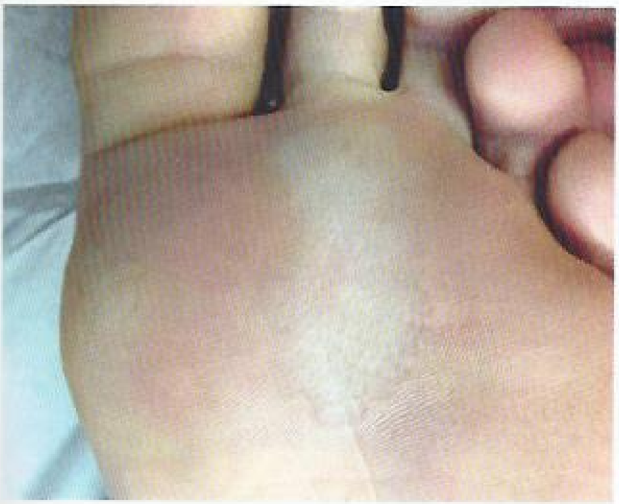
(A) Biopsy of a nodule
(B) Chest radiography
(C) Colonoscopy
(D) Nucleic acid amplification testing for gonorrhea

Item 44

A 19-year-old man is evaluated for 4 to 5 months of persistent itching, thickening of the skin, and odor of the feet. He also has hyperhidrosis of the palms and soles. Medical history is otherwise unremarkable, and he takes no medications.

On physical examination, vital signs are normal. Skin findings are shown (see top of next page).

There is substantial odor of the feet. There are no changes to the toenails. The axillae and groin are unremarkable.



Potassium hydroxide preparation of skin scrapings does not reveal fungal elements.

Which of the following is the most likely diagnosis?

(A) Aquagenic keratoderma
(B) Erythrasma
(C) Keratoderma blenorrhagicum
(D) Pitted keratolysis
(E) Tinea pedis

H

Item 45

A 65-year-old man is evaluated for a 2-month history of an ulcer on the left lower leg that will not heal. While the ulcer has been painful, there has been no significant change in this symptom. The ulcer is minimally exudative and has not been associated with increased warmth, swelling, or expanding erythema. Medical history is significant for hypertension, hyperlipidemia, and type 2 diabetes mellitus. Medications are rosuvastatin, enalapril, hydrochlorothiazide, and metformin.

On physical examination vital signs are normal. Skin findings are shown.

Ankle brachial index is 0.94 on both sides.

Which of the following is the most appropriate management for the ulcer?

(A) Compression therapy
(B) Oral cephalexin
(C) Oral cilostazol
(D) Topical povidone iodine

H

Item 46

A 52-year-old woman is evaluated in the emergency department for increasing redness, scaling, and itchiness of the skin. Over the last 2 days, it has expanded to cover most of her body. She complains of being cold and shivering. Her skin is flaking so badly she is embarrassed to go out in public. Medical history is significant for psoriasis since childhood and COPD for 5 years. She was treated for a COPD exacerbation last week with 5 days of 40 mg prednisone therapy. Medications are triamcinolone ointment, tiotropium, fluticasone/salmeterol, and albuterol as needed.

On physical examination, temperature is 37.8 °C (100 °F), blood pressure is 118/70 mm Hg, pulse rate is 100/min, and oxygen saturation is 97% breathing ambient air. BMI is 32. The patient is acutely uncomfortable, covered in many blankets and shivering. Her skin is leathery, indurated, and hot to the touch. Skin findings are shown.

There is active bleeding at a few sites where some scale has detached. Nail pitting is present on most of her fingernails. There are no conjunctival, oral, or genital lesions.

H CONT.

Which of the following is the most likely cause of the patient's new symptoms?

(A) Drug reaction with eosinophilia and systemic symptoms (DRESS)
(B) Prednisone
(C) Sézary syndrome
(D) Stevens-Johnson syndrome

Item 47

A 45-year-old man is evaluated for itching with dry scaling skin of 1 month's duration. His medical history is noncontributory, and he takes no medications.

On physical examination, vital signs are normal. Skin findings are shown.

The remainder of the examination is unremarkable.

Which of the following is the most appropriate diagnostic test to perform next?

(A) Potassium hydroxide examination
(B) Scabies preparation
(C) Tzanck preparation
(D) Wood lamp examination

Item 48

H

A 56-year-old woman is admitted to the hospital for painful, progressive skin ulceration and scabbing on the thighs of 2 weeks' duration. Medical history is significant for end-stage kidney disease requiring dialysis, type 2 diabetes mellitus, hypertension, and hypercholesterolemia. Medications are insulin, atenolol, erythropoietin, and a multivitamin.

On physical examination, she is afebrile. Blood pressure is 136/84 mm Hg, pulse rate is 108/min, respiration rate is 16/min, and oxygen saturation is 98% breathing ambient air. BMI is 32. Pedal pulses are normal. Skin findings are shown.

Laboratory studies show calcium level of 10.8 mg/dL (2.7 mmol/L), phosphorus level of 7.6 mg/dL (2.4 mmol/L), and parathyroid hormone level of 650 pg/mL (650 ng/L).

Blood cultures are negative.

Which of the following is the most likely diagnosis?

(A) Calciphylaxis
(B) Kyrle disease
(C) Nephrogenic systemic fibrosis
(D) Progressive systemic sclerosis

Item 49

H

A 28-year-old man is evaluated for a 4-day history of a tender nodule on the left dorsal hand. The patient thought the lesion started as a "spider bite," and it continued to increase in size and tenderness. He has no fever or chills. No other lesions are present.

Medical history is unremarkable, and he takes no medications.

On physical examination, vital signs are normal. Skin findings are shown (see top of next page).

The remainder of the examination is normal.

Laboratory values, including leukocyte count, are within normal range.

Which of the following is the most appropriate treatment?

(A) Antibiotic therapy based on culture result
(B) Incision and drainage
(C) Incision and drainage plus oral cephalexin
(D) Oral trimethoprim-sulfamethoxazole

ITEM 49

Item 50

An 18-year-old woman is evaluated for a mole on her back that has been changing in color for several weeks. There are no other associated symptoms. She has no significant medical history and takes no medications.

On physical examination, vital signs are normal. Skin findings are shown.

The remainder of the examination is unremarkable.

Which of the following is the most likely diagnosis?

(A) Compound melanocytic nevus
(B) Dysplastic nevus
(C) Halo nevus
(D) Malignant melanoma

Item 51

A 45-year-old man is evaluated for a 6 month history of pruritic rash in the inguinal and gluteal folds. He has used topical ketoconazole for 3 weeks with no improvement. Medical history is significant for type 2 diabetes mellitus. Medications are metformin and ketoconazole cream.

On physical examination, vital signs are normal. BMI is 32. Occipital scalp has erythematous plaque with scale. Skin findings are shown.

Similar findings are noted in the gluteal cleft. Elbows and knees are clear. Nail pitting is not present.

Which of the following is the most likely diagnosis?

(A) Allergic contact dermatitis
(B) Candidiasis
(C) Inverse psoriasis
(D) Seborrheic dermatitis
(E) Tinea cruris

Item 52

A 40-year-old man is evaluated during a follow-up visit for an extremely pruritic skin eruption for several months that was recently diagnosed as dermatitis herpetiformis. He denies gastrointestinal symptoms and is otherwise healthy and takes no medications.

On physical examination, vital signs are normal. There are numerous excoriations on elbows, knees, and buttocks with rare intact vesicles.

In addition to a gluten-free diet, which of the following is the most appropriate treatment for this patient?

(A) Betamethasone valerate
(B) Dapsone
(C) Diphenhydramine
(D) Prednisone
(E) Sulfasalazine

Item 53

H

A 68-year-old man is evaluated for a 3-year history of erythema of the bilateral lower extremities. The patient reports developing ulcerations 3 weeks ago and began applying neomycin/polymyxin B/bacitracin to the ulcerated area. Over the past week, he reports worsening erythema, weeping, and edema of the lower legs. His only medication is topical neomycin/polymyxin B/bacitracin ointment.

H CONT.

On physical examination, vital signs are normal. BMI is 34. There are strong pedal pulses. Skin findings are shown.

Laboratory studies show a leukocyte count of 8,200 µL (8.2×10^9/L).

Which of the following is the most appropriate initial management?

(A) Discontinue neomycin/polymyxin B/bacitracin ointment
(B) Start intravenous vancomycin
(C) Start oral clindamycin
(D) Start oral terbinafine
(E) Start topical triamcinolone ointment

Item 54

A 32-year-old woman is evaluated for a 10-month history of pruritus and scaling of both her hands. She is a child care worker and washes her hands frequently. Medical history is unremarkable, and she takes no medications.

On physical examination, vital signs are normal. Skin findings are shown (see top of next column).

There is no scale or erythema of the feet. The remainder of the examination is normal.

Results of potassium hydroxide microscopy from the scale on her hands are negative.

Which of the following is the most appropriate management?

(A) Epicutaneous patch testing
(B) Oral fluconazole
(C) Oral prednisone
(D) Thick emollients

ITEM 54

Item 55

A 16-year-old woman is evaluated for an acne breakout on her face for 6 months' duration. She has been using over-the-counter benzoyl peroxide products, but the acne is not improving. She is not sexually active. Medical history is unremarkable, and she takes no medications.

On physical examination, vital signs are normal. Skin findings show scattered open and closed comedones on the forehead, nose, and cheeks. There are no inflammatory pustules or nodules. The remainder of the examination is normal.

Which of the following is the most appropriate treatment?

(A) Isotretinoin
(B) Oral contraceptive pills
(C) Topical antibiotics
(D) Topical retinoids

Item 56

A 21-year-old man is evaluated 3 weeks following treatment of scabies. The patient lives alone, but his sexual partner had similar symptoms. Scabies was confirmed in both persons by microscopic examination of skin scrapings. Both were treated with two applications of 5% permethrin 2 weeks apart. Both patient and partner were adherent to the treatment protocol. The patient notes persistence of itching without the appearance of new lesions, whereas his partner is now asymptomatic.

Which of the following is the most appropriate next step?

(A) Begin an oral antihistamine and topical glucocorticoid
(B) Re-treat with 5% permethrin cream
(C) Treat with oral ivermectin
(D) Treat with combination oral ivermectin and 5% permethrin cream
(E) Treat with 1% lindane lotion

Item 57

A 45-year-old woman is evaluated for a 3-month history of ocular burning and a gritty sensation. Within the last day she has developed a red and swollen left upper eyelid. She has a 2-year history of facial flushing and intermittent pustules on the nose and cheeks. The flushing is worse during times of stress and with exercise. She is otherwise healthy and takes no medications.

On physical examination, vital signs are normal. There is erythema with telangiectasias on the bilateral cheeks, nasolabial folds, and nose. Several inflammatory pustules are on the nose and cheeks with no comedones. There is slight erythema of the left conjunctiva and prominent swelling of the left upper eyelid associated with a red to violet hue. The eyelash bases are coated with a fine crust.

The remainder of the examination is normal.

Which of the following is the most likely cause of her eye symptoms?

(A) Anterior scleritis
(B) Episcleritis
(C) Ocular rosacea
(D) Viral conjunctivitis

Item 58

A 28-year-old woman is evaluated for a rash on the bilateral shins for 1 month's duration. The lesions appeared suddenly and are slightly tender with palpation. She has no joint pain, fever, or cough. She has no diarrhea or abdominal problems. She is 4 months pregnant. Her only medication is prenatal vitamins.

On physical examination, vital signs are normal. Skin findings are shown.

Which of the following is the most likely diagnosis?

(A) Erythema nodosum
(B) Granuloma annulare
(C) Lipodermatosclerosis
(D) Necrobiosis lipoidica
(E) Pyoderma gangrenosum

Item 59

A 62-year-old man is evaluated for painful ulcerations on the right lower leg at the site of previous minor trauma. Medical history is significant for hypertension, type 2 diabetes mellitus, and hyperlipidemia. He is a 50-pack-year smoker. Medications are hydrochlorothiazide, lisinopril, metformin, and atorvastatin.

On physical examination, vital signs are normal. BMI is 28. The leg ulcers are shown.

He has increased pain with elevation of the right leg. Pedal pulses are weak on left leg and absent on right leg. The right lower leg is cool to touch. Resting ankle-brachial index is 0.3 on the right leg and 0.7 on the left leg.

Which of the following is the most appropriate management of the ulcer?

(A) Compression stockings
(B) Oral cilostazol
(C) Skin grafting
(D) Surgical revascularization

H Item 60

A 52-year-old man is evaluated for fragile skin and blisters on the dorsal hands of 2 years' duration. Medical history is significant for a 30-pack-year history of smoking and moderate alcohol consumption. He is a roofer and has had significant sun exposure. He is otherwise in good health and takes no medications.

On physical examination, vital signs are normal. He has hypertrichosis on the face. Skin findings are shown.

The remainder of the physical examination is normal.

Which of the following is the most likely diagnosis?

(A) Bullous pemphigoid
(B) Bullous tinea
(C) Dermatitis herpetiformis
(D) Pemphigus vulgaris
(E) Porphyria cutanea tarda

H Item 61

A 26-year-old woman is evaluated for a changing mole on her left lower leg. She says it is getting bigger and darker. The patient is 5 weeks pregnant. Her only medication is a prenatal vitamin.

On physical examination, vital signs are normal. There is an 8-mm black and gray asymmetric papule with irregular borders on her left medial calf.

Which of the following is the most appropriate next step in management?

(A) Biopsy the lesion now
(B) Biopsy after delivery
(C) Cryotherapy
(D) Provide reassurance

H Item 62

A 52-year-old man is evaluated for a rapidly enlarging, painful ulcer on the leg. It started as a small red "pimple" approximately 2 weeks ago and has been expanding over the past week. Medical history is significant for ulcerative colitis. His only medications are sulfasalazine and folic acid.

On physical examination, vital signs are normal. Skin findings are shown.

Tissue culture is negative.

Which of the following is the most appropriate initial treatment?

(A) Compression dressings
(B) Dapsone
(C) Prednisone
(D) Surgical debridement
(E) Topical hydrocortisone

Item 63

A 36-year-old woman is evaluated for a 3 day history of pruritic rash on the arms, legs, and face. She is very symptomatic and cannot concentrate on her tasks or sleep due to the intense itching. She is a summer camp counselor. Medical history is otherwise unremarkable, and she takes no medications.

On physical examination, vital signs are normal. Representative skin findings on the leg are shown.

The remainder of the examination is normal.

Which of the following is the most appropriate treatment?

(A) 7-day course of oral acyclovir
(B) 10-day course of oral doxycycline
(C) 6-day taper of oral methylprednisolone
(D) 21-day taper of oral prednisone
(E) Topical hydrocortisone 1%

Item 64

A 50-year-old man is evaluated for a several month history of itchy, scaly feet. It has persisted despite the application of a moisturizing lotion. He has no significant medical history and takes no medications.

On physical examination, vital signs are normal. There are erythematous scaly patches on the sides of the feet and maceration between toes. Toenails are normal. Microscopic examination using potassium hydroxide preparation shows branching hyphae in the keratin (scale).

Which of the following is the most appropriate treatment?

(A) Imidazole cream
(B) Nystatin cream
(C) Oral ketoconazole
(D) Topical betamethasone and clotrimazole

H

Item 65

A 62-year-old man was admitted to the hospital following a motor vehicle accident. He underwent a craniotomy for treatment of intracranial hemorrhage following which he was started on carbamazepine. On postoperative day 19, the patient was noted to have a rash on his chest, arms, proximal legs, and buttocks, as well as redness on his face. The next day he had diffuse papules and macules on his trunk and proximal extremities, tachycardia, and hypotension. Hypotension and tachycardia responded to fluid resuscitation.

On physical examination, vital signs are normal. The patient is lethargic and confused. Skin findings are shown.

He has prominent swelling in his face. There is minimal skin erosion and no sloughing when shearing pressure is applied with the examiner's finger. There are a few erosions in the oropharynx, but no eye or genital involvement. Generalized lymphadenopathy is present.

Which of the following is the most likely cause of this patient's clinical presentation?

(A) Drug reaction with eosinophilia and systemic symptoms (DRESS)
(B) Retiform purpura
(C) Stevens-Johnson syndrome
(D) Toxic epidermal necrolysis

Item 66

H

A 62-year-old man is evaluated for a 4-month history of itching all over his body. He has no fatigue, weight loss, or night sweats. His appetite is good. Medical history is significant for hypertension treated with hydrochlorothiazide. He has no risk factors for HIV infection.

On physical examination, vital signs are normal. There are a few scattered excoriations on the arms and lower legs. There are no other significant skin findings and no lymphadenopathy.

Laboratory studies, including complete blood count with differential, erythrocyte sedimentation rate, liver chemistry tests, serum creatinine, and thyroid-stimulating hormone level, are within normal range.

Which of the following is the most appropriate initial management?

(A) CT of the chest and abdomen
(B) Discontinue hydrochlorothiazide
(C) Start topical permethrin
(D) Start topical triamcinolone cream

Item 67

H

An 83-year-old man is seen in the office for routine follow-up. He has a history of hypertension and atrial fibrillation. Medications are hydrochlorothiazide and warfarin.

On physical examination, vital signs are normal. During lung auscultation, a 0.4 × 0.4-cm pink pearly papule with telangiectasias on his back is found.

Biopsy of the lesion reveals a basal cell carcinoma with low-risk histology.

Which of the follow is the most appropriate treatment?

(A) Electrodesiccation and curettage
(B) Mohs micrographic surgery
(C) Radiation
(D) Vismodegib

Item 68

An 18-year-old man is evaluated for an acute onset of hair loss on the scalp. The patient has a history of vitiligo. He is in good health and takes no medications.

On physical examination, vital signs are normal. His scalp findings are shown (see top of next page).

Which of the following is the most likely diagnosis?

(A) Alopecia areata
(B) Discoid lupus erythematosus
(C) Syphilis
(D) Tinea capitis
(E) Trichotillomania

Item 69

A 60-year-old woman is evaluated for easy bruising and bleeding after minor trauma, and a rash around her eyes. Medical history is unremarkable, and she takes no medications.

On physical examination, vital signs are normal. The patient has several ecchymoses located primarily on her arms and legs. Lesions around her eyes are shown.

Hepatomegaly is present. The remainder of the physical examination is unremarkable. Urinalysis demonstrates 4+ proteinuria but is otherwise unremarkable.

Which of the following is the most likely diagnosis?

(A) Amyloidosis
(B) Dermatomyositis
(C) Hyperlipidemia
(D) Sarcoidosis

Item 70

A 40-year-old man is evaluated for a new skin rash of 10 days' duration. The rash appeared abruptly and is not tender or pruritic. The patient has poorly controlled type 2 diabetes mellitus. His current medications include metformin and glyburide. Family history is unremarkable.

On physical examination, vital signs are normal. BMI is 25. There are several grouped 1- to 5-mm yellow papules on extensor surfaces of extremities and buttocks. Some of the papules have surrounding erythema. The remainder of the examination is normal.

Laboratory studies show a hemoglobin A_{1c} value of 12%.

Which of the following disorders is associated with the patient's skin findings?

(A) Familial dysbetalipoproteinemia
(B) Familial hypercholesterolemia
(C) Hypertriglyceridemia
(D) No underlying disorder

Item 71

A 45-year-old woman is evaluated for a new growth on the leg. It has been present for several months. Medical history is unremarkable, and she takes no medications.

On physical examination, vital signs are normal. Skin finding is shown.

Which of the following is the most likely diagnosis?

(A) Acrochordon
(B) Dermatofibroma
(C) Neurofibroma
(D) Pyogenic granuloma

Item 72

A 40-year-old man is evaluated for skin changes around the neck that are asymptomatic, but have been worsening over the past year. Medical history is unremarkable. He takes no medications.

On physical examination, vital signs are normal. BMI is 30. Skin findings are shown (see top of next page).

The remainder of the physical examination is unremarkable.

Which of the following is the most appropriate diagnostic test to perform next?

(A) Fasting blood glucose
(B) 24-Hour urine cortisol
(C) Thyroid-stimulating hormone and serum thyroxine
(D) Wood lamp evaluation

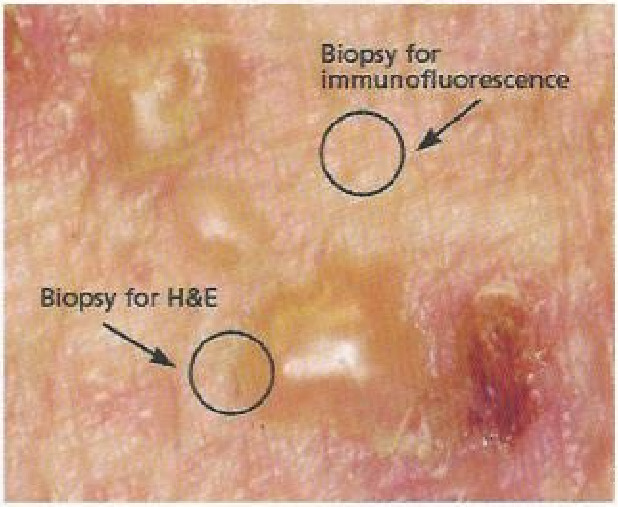
Answers and Critiques

H

Item 1 Answer: C

Educational Objective: Diagnose autoimmune bullous diseases.

This patient likely has an autoimmune bullous disease, and the most sensitive method for diagnosis is with two biopsies: one of lesional skin for histology, and one of perilesional skin for direct immunofluorescence, as shown.



Autoimmune blistering diseases result from autoantibodies to different antigens in the skin and have similar but distinct presentations. Clinically, they are characterized by persistent pruritic to painful blisters with erosions and variable mucosal and ocular involvement and scarring. These diseases often arise in older persons. Identification and diagnosis of these disorders are important because of the associated morbidity and mortality. Differentiation of the autoimmune blistering diseases can be made based on clinical features, but definitive diagnosis requires histopathologic examination and, in some patients, serologic testing for pathogenic antibodies.

Depending on the location of the targeted antigen, flaccid or tense bullae will be present clinically, and the corresponding separation can be appreciated using histopathology. In pemphigus, flaccid blisters correspond with suprabasilar separation, whereas tense bullae correspond with subepidermal blisters in bullous pemphigoid and epidermolysis bullosa acquisita.

A skin (shave or punch) biopsy of an intact, early vesicle or bullae with adjacent normal skin should be submitted in formalin and processed for hematoxylin and eosin to examine tissue histology. Each of the autoimmune bullous diseases has characteristic histologic findings that suggest a differential diagnosis. In addition, a perilesional skin biopsy should be submitted for direct immunofluorescence, either in saline or Michel transport medium.

The histologic findings together with the pattern on direct immunofluorescence can usually render a diagnosis. Serum from affected patients also can assist in diagnosis. The blood can be reacted with different substrates and will determine if circulating antibodies are present (indirect immunofluorescence). Tests such as serum enzyme-linked immunosorbent assays have been developed that detect the presence of specific antibodies in pemphigus vulgaris, pemphigus foliaceus, and bullous pemphigoid, and may correlate with disease activity. Other studies such as salt-split skin immunofluorescence may be useful in selected instances, but overall serum studies have lower sensitivities than biopsy.

KEY POINT

- To diagnose an autoimmune bullous disease, two biopsies often are performed: one of lesional skin for histology and one of perilesional normal skin for direct immunofluorescence.

Bibliography

Elston DM, Stratman EJ, Miller SJ. Skin biopsy: Biopsy issues in specific diseases. J Am Acad Dermatol. 2016;74:1-16; quiz 17-8. [PMID: 26702794] doi:10.1016/j.jaad.2015.06.033

Item 2 Answer: C

Educational Objective: Diagnose pityriasis (tinea) versicolor.

Pityriasis versicolor, often referred to as tinea versicolor, is one of the most common, chronic, superficial fungal infections. It is most common in warm, humid environments. It typically presents in young adults as asymptomatic, oval-to-round, minimally scaly, hyperpigmented or hypopigmented macules that can coalesce into patches on the trunk and upper extremities. Hypopigmentation is more common in darker-skinned persons. These areas often become more noticeable after exposure to the sun because the organism prevents the skin from tanning.

The diagnosis of pityriasis versicolor can often be made by clinical presentation but may be confirmed by visualization of short rod-shaped hyphae and round yeast ("spaghetti and meatballs") on microscopic examination of skin scraping using a potassium hydroxide preparation. Treatment of pityriasis versicolor with topical antiseborrheic shampoos or lotions such as selenium sulfide or ketoconazole leads to resolution of erythema and scaling, but the pigmentation changes may persist for longer periods of time.

Candida albicans infections occur in hot, moist occluded areas, such as the armpits, groin, and beneath the breasts. *Candida* appears as erythematous patches with

satellite pustules. Diagnosis is frequently made on clinical grounds alone, but a potassium hydroxide preparation can show spores and pseudohyphae.

Erythrasma is a superficial bacterial infection caused by *Corynebacterium minutissimum* that presents as mildly pruritic, thin erythematous-to-brown plaques with thin scale and an overlying wrinkled appearance and maceration in intertriginous areas such as the axillae, groin, and inframammary areas. The red-brown color and distribution in intertriginous areas distinguishes erythrasma from pityriasis versicolor. Diagnosis is typically made by clinical presentation but may be confirmed by coral-red fluorescence with a Wood lamp.

Tinea infections are superficial fungal infections caused by dermatophytes and classified by the site of infection. Tinea corporis appears in sites other than the feet, groin, face, or hand. It is characterized by annular patches with peripheral scale and central clearing that appear distinctly different from the hypo- or hyperpigmented patches of pityriasis versicolor. Diagnosis can often be made on clinical grounds, but a potassium hydroxide preparation of the scale shows fungal hyphae. A fungal culture can also be performed.

KEY POINT

- Pityriasis versicolor presents in young adults as asymptomatic, oval-to-round, minimally scaly, hyperpigmented or hypopigmented macules that can coalesce into patches on the trunk and upper extremities.

Bibliography

Kaushik N, Pujalte GG, Reese ST. Superficial fungal infections. Prim Care. 2015;42:501-16. [PMID: 26612371] doi:10.1016/j.pop.2015.08.004

Item 3 Answer: C

Educational Objective: Treat atopic dermatitis.

This patient has atopic dermatitis, and the most appropriate treatment is topical glucocorticoids. Eczematous dermatitis is a type of inflammation characterized by inflamed, dry, red, itchy skin. The terms *eczema* and *dermatitis* are often used interchangeably. There are multiple types of eczematous dermatoses. Atopic dermatitis is genetically driven and often affects areas such as the antecubital and popliteal fossae and typically presents in childhood. It is characterized by xerotic, pink, scaly skin and is most commonly seen on the periocular areas, posterior neck, antecubital and popliteal fossae, wrists, and ankles. The initial treatment for atopic dermatitis consists of good skin care with mild cleansers and thick emollients (petrolatum) along with topical glucocorticoids to decrease inflammation and pruritus.

Oral cephalexin is a first-generation cephalosporin antibiotic that can be used to treat selected skin infections. The use of oral antibiotics should be limited to conditions in which there is evidence of extensive bacterial infection. Clinical signs of bacterial infection typically include weeping of serous fluid, pustules, honey-colored crusting, unexplained worsening of dermatitis, or failure to respond to correct therapy. There is no indication for treatment with systemic antibiotics in this patient.

Oral prednisone should be considered only in severe, acute exacerbations of atopic dermatitis and not for regular management. Chronic oral glucocorticoid treatment can lead to side effects such as diabetes, osteoporosis, and compromised immune function, so this treatment would not be appropriate before treatment with topical glucocorticoids.

Topical ketoconazole is a treatment for superficial fungal infections. This patient has atopic dermatitis, so antifungal creams would not be used.

Topical mupirocin is the treatment for localized bacterial infections of the skin, such as impetigo. Although patients with atopic dermatitis are often secondarily colonized or infected with *Staphylococcus aureus*, routine use of topical antibiotics is not recommended. There is no indication in this patient that the skin is infected.

KEY POINT

- The initial treatment for atopic dermatitis consists of good skin care with mild cleansers and thick emollients along with topical glucocorticoids to decrease inflammation and pruritus.

Bibliography

Eichenfield LF, Tom WL, Berger TG, Krol A, et al. Guidelines of care for the management of atopic dermatitis: section 2. Management and treatment of atopic dermatitis with topical therapies. J Am Acad Dermatol. 2014 Jul;71(1):116-32. [PMID: 24813302]

Item 4 Answer: D

H

Educational Objective: Diagnose urticarial vasculitis.

This patient has urticarial vasculitis, and the most appropriate management is to obtain skin biopsies to confirm the diagnosis. A routine skin biopsy (for histology) and a biopsy for direct immunofluorescence (for immunoglobulin and complement deposits) should both be obtained. Typical urticarial wheals last for less than 24 hours (with individual lesions lasting only a few hours), resolve without cutaneous sequelae, and are pruritic and not painful. Urticarial vasculitis differs from urticaria in that individual lesions persist longer than 24 hours. Urticarial vasculitis more commonly presents with painful or burning lesions instead of pruritus and leave bruise-like changes when they resolve, which is atypical for usual urticaria. Patients with urticarial vasculitis often have an underlying autoimmune disease, most often lupus erythematosus, but even in the absence of an associated autoimmune disease, patients with urticarial vasculitis (particularly hypocomplementemic urticarial vasculitis) are at risk of multisystem disease, including nephritis. The patient's joint pain suggests the possibility of an additional underlying disorder. Skin biopsies are important in making the diagnosis and guiding further work-up and treatment.

Epicutaneous patch testing is performed to diagnose allergic contact dermatitis. Allergic contact dermatitis can

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occasionally present as typical urticarial, but this patient's history suggests urticarial vasculitis.

Physical urticaria is induced by a physical stimulus such as the sun, sweating, physical pressure, or cold temperature. An ice cube provocation test is performed to help diagnose cold urticaria. This test would not be helpful in diagnosing urticarial vasculitis. Neither allergic contact dermatitis nor physical urticaria can explain the patient's joint symptoms.

Treatment of urticaria is most effective with long-acting antihistamines, since they help treat active disease and prevent new flares of urticaria. Systemic glucocorticoids and immunosuppressive agents have been used for urticaria, but in most patients, maximizing the dose of the long-acting antihistamines is equally effective and safer. Glucocorticoids are often the mainstay of treatment for urticarial vasculitis, but it would be inappropriate to commit a patient to this therapy without first confirming the diagnosis.

Topical glucocorticoids, such as triamcinolone, have limited efficacy in typical and urticarial vasculitis and are not the best management for either condition.

KEY POINT

- Skin biopsies should be performed to evaluate for urticarial vasculitis when individual urticarial lesions are present for longer than 24 hours.

Bibliography

Bernstein JA, Lang DM, Khan DA, et al. The diagnosis and management of acute and chronic urticaria: 2014 update. J Allergy Clin Immunol. 2014 May;133(5):1270-7. [PMID: 24766875]

Item 5 Answer: D

Educational Objective: Treat striae and atrophy from topical glucocorticoids.

This patient should discontinue the triamcinolone cream. He has striae distensae, or stretch marks, recognized as erythematous, violaceous, or hypopigmented linear striations secondary to topical glucocorticoid use. Topical glucocorticoids decrease the production of collagen resulting in atrophy, stretch marks, and telangiectasia. The application of any topical glucocorticoid to normal skin for prolonged periods of time, especially under occlusion, may lead to these changes. Some persons are more prone to these side effects, which may occur after a brief period, whereas others take months of usage before side effects appear. Areas of the skin especially prone to atrophy are the thighs, groin, axillae, and face. Potent topical glucocorticoids should be avoided in these areas to reduce the risk of atrophy, and the patient should be counseled to apply the topical glucocorticoids only to lesional skin, not normal appearing skin. There is little data to support any therapy, including topical tretinoin, to reverse the side effects of topical glucocorticoids. Over time, patients will see an improvement in the atrophy as the effects of the glucocorticoids wear off and normal collagen production returns.

Triamcinolone is a medium-potency topical glucocorticoid. Adding a stronger topical glucocorticoid such as clobetasol would likely make the symptoms worse.

This patient's findings are most consistent with striae distensae. The scaly annular patch of a superficial fungal infection is not present, and therefore a topical antifungal agent such as terbinafine will not be of any benefit.

Calcipotriene is a vitamin D analogue used to treat psoriasis, and it has not been shown to cause atrophy, striae, or telangiectasia. Discontinuation of the calcipotriene would not result in improvement of the skin atrophy and striae in this patient.

KEY POINT

- Side effects from topical glucocorticoids include thinned skin, striae distensae (stretch marks), and easy bruising, and are likely to occur when they are used for extended periods of time, especially in skin folds or areas of occlusion.

Bibliography

Barnes L, Kaya G, Rollason V. Topical corticosteroid-induced skin atrophy: a comprehensive review. Drug Saf. 2015;38:493-509. [PMID: 25862024] doi:10.1007/s40264-015-0287-7

Item 6 Answer: D

H

Educational Objective: Diagnose herpes zoster.

Varicella zoster virus (VZV) is a DNA virus that causes two forms of cutaneous disease. This patient has symptoms of herpes zoster (shingles), recrudescent VZV, which typically presents as a painful, vesicular eruption confined to a single dermatome and is most commonly seen in immunocompromised or elderly patients. The clinical presentation of herpes zoster is characteristic. Prodromal symptoms, such as burning, stinging, or tingling, often occur in a localized region, followed by an eruption of grouped vesicles or pustules on an erythematous base. The outbreak is unilateral and does not cross the body's midline. The most common dermatomes affected are in the thoracic region. Diagnosis is based on clinical presentation but can be confirmed with a Tzanck preparation and/or viral direct fluorescent antibody or polymerase chain reaction testing. Oral antiviral agents (acyclovir, valacyclovir, or famciclovir) are typically used to treat herpes zoster infection and should be started within the first 72 hours of symptom onset for optimal response.

Primary infection with VZV causes chickenpox (varicella), a common disease in childhood. It is transmitted by aerosolized droplets; after a 2-week incubation period, it presents as pruritic papules and vesicles with an umbilicated center that appear in crops and heal with crusting. The virus becomes latent within dorsal root ganglia and can reactivate (10% to 20% risk), causing herpes zoster. A vaccine for primary VZV infection was approved for use in the United States in 1995.

Eczema herpeticum is a disseminated viral infection most often caused by primary infection of HSV and characteristically seen in patients with atopic dermatitis. It presents

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with disseminated punched-out erosions with crust, with a predilection for the face.

Cutaneous herpes simplex virus (HSV) infections have two common forms: herpes labialis (typically HSV1) or "cold sores/fever blisters" and genital herpes (typically HSV2). Herpes infection presents as vesicles on an erythematous base. Following primary infection, the virus lies dormant and can recur at the original site of infection. A prodrome of pain or burning often precedes recurrences.

KEY POINT

- Herpes zoster (shingles), recrudescent varicella zoster virus, typically presents as a painful, vesicular eruption confined to a single dermatome and is most commonly seen in immunocompromised or elderly patients.

Bibliography

Schmader K. Herpes Zoster. Clin Geriatr Med. 2016;32:539-53. [PMID: 27394022] doi:10.1016/j.cger.2016.02.011

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Item 7 Answer: B

Educational Objective: Diagnose melanonychia.

This patient has melanonychia, a brown longitudinal pigmentation of the nail plate. It can be a normal variant in persons with darker skin types, but it may also occur as a result of systemic disease, medication, infection, or an underlying melanocytic lesion such as malignant melanoma. It is extremely difficult to clinically differentiate benign melanonychia from acral melanoma involving the nail. Certain findings may suggest a stronger likelihood of melanoma and the need for biopsy. These include: melanonychia that first appears in adulthood; involvement of a single digit (especially thumb or great toe); rapid growth; width greater than 3 to 4 mm; proximal width greater than distal width; variation in pigmentation; secondary nail changes such as splitting or dystrophy; pigmentation that extends beyond the nail fold; or personal history of melanoma. This patient has longitudinal melanonychia limited to the thumb that is changing in width. Furthermore, in this photo, there is a pigmented macule on the lateral nailfold that is called a Hutchinson sign. This is an important clinical clue for subungual melanoma. A biopsy should be performed.

Lichen planus can develop in the nails. The nail plate will become thinner or be completely destroyed, and the cuticle may attach to the nail plate (pterygium). Other findings may include longitudinal ridging, nail plate thinning, and longitudinal fissuring. Red streaking of the nail may also occur. Patients may have other cutaneous or mucosal findings of lichen planus. This patient lacks the dystrophic changes commonly associated with lichen planus.

With aging, the thickness, curvature, surface, and color of the nail plate can change. The underlying mechanisms are unknown. The nail plate may become thicker or thinner. The normal texture of the nail can become rougher and more friable, resulting in striations and splitting. The color of the nail may become paler or yellow. These changes may predispose nails to onychomycosis, pain, and subungual hemorrhage. Normal aging is not associated with the occurrence of a growing, longitudinal stripe in one nail.

Onychomycosis is a fungal infection of the nail. The most common pattern is characterized by the distal corner of the nail becoming yellow and lifted, with the development of subungual debris. Eventually this process can spread proximally and laterally to involve the entire nail plate. Onychomycosis does not result in a well-defined dark brown longitudinal stripe as seen in this patient.

KEY POINT

- Melanonychia is a longitudinal brown pigmentation of the nail plate; it can be a normal variant in persons with darker skin types, but it may also occur as a result of systemic disease, medication, infection, or an underlying melanocytic lesion.

Bibliography

Goydos JS, Shoen SL. Acral lentiginous melanoma. Cancer Treat Res. 2016;167:321-9. [PMID: 26601870] doi:10.1007/978-3-319-22539-5_14

Item 8 Answer: B

Educational Objective: Diagnose chronic paronychia.

This patient has chronic paronychia. Chronic paronychia typically is present for 6 weeks or more and affects multiple fingers. Typical manifestations of chronic paronychia include red, swollen, and tender nail folds that lack a cuticle. It can also cause ridging and dystrophy of the nail plate. Chronic irritation from water or chemical contact is the primary cause. *Candida* species are often isolated. The cause of chronic paronychia is multifactorial, and an important component appears to be an eczematous process, which explains why patients with chronic paronychia respond better to topical glucocorticoid than topical antifungal therapy. The primary management includes minimizing wet work.

Acute paronychia is painful swelling of the nail fold, often following minor trauma, and most commonly is caused by *Staphylococcus aureus*. It typically only affects one nail. Management consists of warm compresses or soaks, incision and drainage, or topical or systemic antibiotics. This patient has chronic paronychia, which tends to be more insidious and involves multiple fingers.

Onychomycosis is a fungal infection of the nails. It affects 10% to 20% of adults and is the most common nail infection. Infection is more common in older men with comorbidities such as diabetes mellitus, peripheral vascular disease, and immunosuppression. Dermatophytes cause more than 90% of fungal nail infections. The most common pattern is distal subungual onychomycosis; the distal corner of the nail becomes yellow and lifted, and develops subungual debris. This can then spread proximally and laterally to involve the entire nail plate. Proximal subungual onychomycosis evolves similarly but begins at the proximal nail fold (the cuticle). This is a rare pattern and is associated with HIV infection or other severely immunocompromised patients. This patient's multiple nail involvement manifesting as red,

tender, and swollen nail folds and absent cuticles is not compatible with onychomycosis.

Nail changes occur in about 75% of persons with psoriasis. The most common nail abnormality observed on both fingernails and toenails is subungual hyperkeratosis. Toenails more often demonstrate thickening and discoloration (whitening or yellowing), whereas pitting and ridging are more common on fingernails. Some of the nail damage can result from concomitant onychomycosis. This patient's findings are not compatible with psoriasis.

KEY POINT

- Chronic paronychia appears as a loss of cuticle with tender, edematous nail folds involving multiple fingers; wet work can cause maceration and predispose to this condition.

Bibliography

Shafritz AB, Coppage JM. Acute and chronic paronychia of the hand. J Am Acad Orthop Surg. 2014;22:165-74. [PMID: 24603826] doi:10.5435/JAAOS-22-03-165

Item 9 Answer: A

Educational Objective: Treat moderate to severe psoriasis.

This patient has moderate to severe psoriasis (30% or more body surface area involvement) and should be treated with systemic agents. Patients with psoriasis covering more than 10% body surface area or those with psoriatic arthritis, recalcitrant palmoplantar psoriasis, pustular psoriasis, or psoriasis in challenging anatomic areas (groin, scalp) may be considered for systemic therapy. These include tumor necrosis factor inhibitors, acitretin, methotrexate, IL-23 and IL-17 inhibitors, and phototherapy. Tumor necrosis factor inhibitors, such as etanercept, adalimumab, and infliximab, are excellent options for treating patients with both severe psoriasis and psoriatic arthritis. The newer IL-12/IL-23 and IL-17 inhibitors have shown excellent efficacy in psoriasis treatment. Therapy with any of the systemic agents should be guided by a clinician experienced in their use, including appropriate evaluation for contraindications and careful monitoring.

Prednisone is not a good choice for the treatment of psoriasis, as the doses of prednisone required would lead to numerous side effects. Prednisone also has been shown to cause pustular and erythrodermic flares in a subset of patients with psoriasis. Oral glucocorticoids should also be avoided because they may worsen associated comorbidities such as hypertension and dyslipidemia.

Topical medications such as vitamin D analogues (for example, calcitriol), immunomodulators, and glucocorticoids can be used for the treatment of psoriasis; however, they are best used as solo agents in the treatment of mild disease with less than 10% body surface area involvement. These medications are often employed in conjunction with systemic therapy to treat small areas of psoriasis that remain after treatment with a systemic agent. Topical immunomodulators, pimecrolimus cream, or tacrolimus ointment are best used on the face or in intertriginous regions to avoid the atrophy seen with topical glucocorticoids.

KEY POINT

- Moderate to severe psoriasis is best treated with systemic agents; avoid prednisone as a therapy for psoriasis.

Bibliography

Mansouri Y, Goldenberg G. New systemic therapies for psoriasis. Cutis. 2015;95:155-60. [PMID: 25844781]

Item 10 Answer: B

Educational Objective: Treat pruritic urticarial papules and plaques of pregnancy (PUPPP).

The patient has pruritic urticarial papules and plaques of pregnancy (PUPPP), and the most appropriate treatment is topical glucocorticoids. PUPPP is a self-limiting condition that typically occurs in primiparous women at the end of the third trimester or immediately postpartum. Lesions are characterized as extremely pruritic, erythematous papules within striae, most often on the abdomen with sparing of the umbilicus. The lesions can be confined to the abdomen or spread to the extremities and torso. If the lesions coalesce, urticarial plaques within striae can be an additional finding. The symptoms typically last 4 to 6 weeks and usually abate by the second postpartum week.

Topical glucocorticoids can help relieve some of the symptoms. Glucocorticoids are pregnancy category C, but are generally thought to be safe, especially topical formulations.

Early delivery is rarely required to manage PUPPP. Most patients can be managed successfully with topical glucocorticoids and oral antihistamines. On rare occasions a burst of oral glucocorticoids with a quick taper can be used if the symptoms are particularly severe, and this approach is likely preferable to early delivery.

Topical imiquimod is an immunomodulator typically used for actinic keratoses, superficial basal cell carcinoma, and genital warts. It is not appropriate treatment for PUPPP.

Ursodeoxycholic acid is used in intrahepatic cholestasis of pregnancy (ICP). Symptoms include pruritus in most patients and jaundice in 10% to 25% of patients. Elevated serum bile acids are diagnostic of ICP. Ursodeoxycholic acid is effective for ICP. Fetal complications such as preterm labor, fetal distress, and intrauterine death are increased in ICP. Intrauterine deaths can occur late in gestation, and women with proven ICP typically are induced at 36 to 38 weeks of gestation. The patient's pruritic urticarial papules located on the abdomen are not compatible with the diagnosis of intrahepatic cholestasis of pregnancy, and ursodeoxycholic acid is not indicated.

KEY POINT

- Low- to medium-potency topical glucocorticoids are first-line therapy for pruritic urticarial papules and plaques of pregnancy (PUPPP).

Bibliography

Kroumpouzos G, Cohen LM. Dermatoses of pregnancy. J Am Acad Dermatol. 2001;45:1-19; quiz 19-22. [PMID: 11423829]

H

Item 11 Answer: C

Educational Objective: Diagnose miliaria.

The patient has miliaria. Miliaria or "heat rash" can appear as superficial clear vesicles or as multiple discrete red papules due to occlusion of eccrine sweat ducts. When the gland is clogged superficially, there are minute pustules that rupture easily and can be wiped off (miliaria crystallina). Miliaria rubra causes deeper red papules and some pustules when the clog is deeper and more inflammation is present. Miliaria is often seen in the setting of fever and occlusion. A typical clinical situation is a patient who is immobilized, either from pain or following surgery, and the sweat glands are occluded as a result. Therapy is guided toward cooling the affected area, allowing air circulation.

Acute generalized exanthematous pustulosis (AGEP) is not an uncommon febrile drug reaction. It tends to occur 1 to 2 days after the offending agent is given. β-Lactam antibiotics are the most common cause of AGEP. It presents as punctate nonfollicular sterile pustules on a background of erythema. It starts on the face and intertriginous areas and spreads to the trunk and extremities. The pustular nature of this condition and its typical location argue against the diagnosis of AGEP.

Candidiasis occurs most often in intertriginous areas. An occluded, warm, moist area is an ideal setting for *Candida albicans*. The skin findings tend to be bright red plaques with surrounding red satellite papules and pustules. The location and appearance of this patient's rash are not consistent with a *Candida albicans* infection.

Postsurgical contact dermatitis to povidone iodine is not uncommon. It tends to occur at the surgical site about 1 to 2 days after surgery. It appears as pruritic, weeping vesicles with underlying erythema often in a well-delineated shape where the povidone was applied. Its appearance is quite unlike miliaria, and it is unlikely that the patient had povidone applied to his back, making this an untenable diagnosis.

KEY POINT

- Miliaria or "heat rash" can appear as superficial clear vesicles or as multiple discrete red papules due to the occlusion of eccrine sweat ducts.

Bibliography

Haas N, Martens F, Henz BM. Miliaria crystallina in an intensive care setting. Clin Exp Dermatol. 2004;29:32-4. [PMID: 14723716]

Item 12 Answer: D

Educational Objective: Treat severe nodulocystic acne.

This patient has severe nodulocystic acne with evidence of scarring. The most appropriate treatment is oral isotretinoin. Isotretinoin is approved for treatment of severe cystic acne or acne not responsive to traditional combination therapy (topical antibiotics, oral antibiotics, and topical retinoids). This additional finding of scarring in this patient would also warrant treatment with isotretinoin. Isotretinoin is teratogenic and should be administered by a provider registered under the federal regulatory program iPLEDGE and who is familiar with the potential side effects of isotretinoin therapy.

Benzoyl peroxide is comedolytic and also has antibacterial properties. Benzoyl peroxide is available over the counter in a variety of formulations (lotion, gel, cream). Topical benzoyl peroxide is often used in combination therapy with topical antibiotics and topical retinoids to treat acne. Given the severity and duration of this patient's acne, topical benzoyl peroxide would not be the most effective treatment.

Topical dapsone is an approved treatment for mild to moderate acne but would likely provide minimal benefit to this patient with severe acne who is already on topical antibiotic therapy.

Changing doxycycline to trimethoprim-sulfamethoxazole is inappropriate treatment for this patient. Trimethoprim-sulfamethoxazole can be used for treatment of acne, but it is less effective than doxycycline or minocycline, and the potential risk of severe cutaneous drug reactions limits its long-term use. Guidelines recommend that the duration of oral antibiotic therapy be limited, specifically that oral antibiotics be used for 3 months and then discontinued for patients with good clinical improvement. The same antibiotic can be used again for patients with good clinical improvement who have a subsequent relapse. This patient has severe nodulocystic acne with scarring, so isotretinoin is the most appropriate treatment.

Oral prednisone should not be used for this patient. Systemic glucocorticoids are not an effective long-term treatment for acne. Steroid-induced acne is often a side effect of their use. Patients occasionally experience acute flares with the initiation of isotretinoin treatment, and a short course of oral prednisone can be added.

KEY POINT

- Isotretinoin is indicated for severe nodulocystic and recalcitrant acne; it is associated with severe birth defects and must be administered through the federal regulatory program iPLEDGE.

Bibliography

Zaenglein AL, Pathy AL, Schlosser BJ, Alikhan A, et al. Guidelines of care for the management of acne vulgaris. J Am Acad Dermatol. 2016 May;74(5):945-73. [PMID: 26897386]

Item 13 Answer: A

Educational Objective: Diagnose amyopathic dermatomyositis.

This patient has amyopathic dermatomyositis, an underrecognized presentation of dermatomyositis that does not include

muscle disease. These patients experience characteristic cutaneous features of dermatomyositis, such as the heliotrope sign, shawl sign, and Gottron papules, but muscle enzymes and strength testing are normal. Skin findings in dermatomyositis are photosensitive and tend to flare after sun exposure. Amyopathic dermatomyositis carries similar risk for underlying malignancy and pulmonary fibrosis. There is no strong consensus on how to screen for malignancy.

Mixed connective tissue disease is an overlap syndrome that includes features of systemic lupus erythematosus (SLE), systemic sclerosis, and/or polymyositis in the presence of anti-U1 ribonucleoprotein antibodies. Skin manifestations include sclerodactyly, scleroderma, calcinosis, telangiectasias, photosensitivity, malar rash, and Gottron rash. The absence of findings consistent with SLE and systemic sclerosis make this diagnosis unlikely.

Polymorphous light eruption (PMLE) is the most common idiopathic photosensitivity disorder. PMLE typically manifests before the age of 30 and is most common in fair-skinned women, first appearing in the spring and early summer. The rash will persist for weeks and resolve without scarring, even with continued exposure to the sun. Lesions appear within hours of sun exposure and are found on sun-exposed body parts. Although many different types of eruptions may occur, the most common are pruritic skin-colored or pink papules. PMLE does not explain the positive antinuclear antibody titer or periungual findings.

The most specific skin manifestations of systemic lupus erythematosus are variations on interface dermatitis, with pink-to-violet macules or plaques and varying scale or atrophy. Cutaneous lupus as a rule spares the upper eyelids and the knuckles. Inflammatory joint involvement occurs in 90% of patients with SLE. The absence of joint findings, rash over the knuckles, and periungual findings are not consistent with SLE.

KEY POINT

- Amyopathic dermatomyositis presents with skin findings characteristic of dermatomyositis, but without clinical or laboratory evidence of muscle disease; it carries risks for underlying malignancy.

Bibliography

Iaccarino L, Ghirardello A, Bettio S, Zen M, Gatto M, Punzi L, et al. The clinical features, diagnosis and classification of dermatomyositis. J Autoimmun. 2014;48-49:122-7. [PMID: 24467910] doi:10.1016/j.jaut.2013.11.005

H

Item 14 Answer: C

Educational Objective: Evaluate the prognosis in toxic epidermal necrosis (TEN).

Body surface area is the strongest prognostic indicator in Stevens-Johnson syndrome/toxic epidermal necrosis (SJS/TEN). Stevens-Johnson syndrome (SJS) and TEN are related clinical syndromes that are characterized by acute epidermal necrosis. The classification of SJS and TEN is determined by the percentage of body surface area with epidermal detachment: SJS involves less than 10%, SJS-TEN overlap involves 10% to 30%, and TEN involves greater than 30%. TEN is almost exclusively caused by medications, whereas SJS can also be triggered uncommonly by vaccines or infection. Patients may have flu-like symptoms for 1 to 3 days prior to the skin eruption. Initially, painful red-purple macules or patches develop on the trunk and extremities, which enlarge and coalesce. Two or more mucosal surfaces, such as the eyes, nasopharynx, mouth, and genitals, are involved in more than 80% of patients. Systemic inflammation can result in pneumonia, hepatitis, nephritis, arthralgia, and myocarditis. Loss of the skin barrier function can lead to infection, hypovolemia, electrolyte disturbances, and death. Prognosis for SJS/TEN can be estimated by application of the SCORTEN assessment tool at 24 hours after presentation. All of the listed answer choices are features of the SCORTEN, but the patient's body surface area has the greatest impact on the score.

SCORTEN is a severity-of-illness score validated for TEN. It incorporates blood Sugar (plasma glucose level >252 mg/dL [14.0 mmol/L]), presence of Cancer, Older age (>40 years), heart Rate (>120/min), Ten percent or more body surface area involvement on day 1, Electrolytes (serum bicarbonate <20 mEq/L [20 mmol/L]), and blood urea Nitrogen (>28 mg/dL [10 mmol/L]). Mortality is directly correlated with the number of SCORTEN variables that are fulfilled.

KEY POINT

- Body surface area involvement is the strongest prognostic indicator in Stevens-Johnson syndrome/toxic epidermal necrosis (SJS/TEN).

Bibliography

Bastuji-Garin S, Fouchard N, Bertocchi M, Roujeau JC, Revuz J, Wolkenstein P. SCORTEN: a severity-of-illness score for toxic epidermal necrolysis. J Invest Dermatol. 2000;115:149-53. [PMID: 10951229]

Item 15 Answer: C

Educational Objective: Diagnose molluscum contagiosum infection.

Molluscum contagiosum is a common cutaneous viral infection caused by the poxvirus molluscum contagiosum. It occurs in three settings: children, adults as a sexually transmitted disease, and AIDS patients. The lesions are flesh-colored to yellow smooth papules with a shiny surface and an umbilicated center. They can be located anywhere on the skin, but in adults they typically involve the genital area; in AIDS patients, they often involve the face. Diagnosis can be made by the clinical appearance. In immunocompromised patients, cryptococcosis, histoplasmosis, or *Penicillium marneffei* infections may resemble molluscum lesions and should be differentiated by skin biopsy. Although lesions can self-resolve, this may take months to years. Therapy includes destructive techniques including cryotherapy, salicylic acid, cantharidin, or physical removal with curettage.

Anogenital warts (condylomata acuminata) are the most common sexually transmitted infection and are most often

caused by human papillomavirus types 6 and 11. They present as single or multiple papules on the penis, vulva, or perianal area and may be variably sized flat-topped or cauliflower-like papules. They do not have a shiny surface nor are they umbilicated. Lesions are diagnosed based on clinical appearance. Although warts may resolve spontaneously, treatment often is required. Treatment of anogenital warts may include chemical or physical destruction, immunologic therapy, or excision.

Herpes simplex virus (HSV) infection presents as localized, grouped pink macules and papules that progress to vesicles on an erythematous base and then evolve into pustules with subsequent ulcers and erosions. HSV1 traditionally causes orofacial lesions, and HSV2 most often causes genital lesions; however, both viruses can lead to either oral or genital lesions. Diagnosis of HSV can be made clinically, but several rapid tests are widely available, such as direct-fluorescent antibody and polymerase chain reaction. Oral antiviral agents including acyclovir, valacyclovir, and famciclovir are considered first-line therapies.

Seborrheic keratosis is a benign neoplasm of the skin that has a "stuck-on" appearance. They have a wide range of shades from tan to black, have different morphologies, and vary in size from a few millimeters to several centimeters. It is more common with advancing age and can be seen anywhere on the body, but they characteristically spare the palms and soles. This young patient's shiny papules are not compatible with the diagnosis of seborrheic keratoses.

KEY POINT

- Molluscum contagiosum is a common cutaneous viral infection that initially appears as firm, umbilicated flesh-colored to yellow papules; in adults it is considered a sexually transmitted infection that frequently involves the genital area.

Bibliography

Ramdass P, Mullick S, Farber HF. Viral Skin Diseases. Prim Care. 2015;42:517-67. [PMID: 26612372] doi:10.1016/j.pop.2015.08.006

H

Item 16 Answer: A

Educational Objective: Diagnose bullous pemphigoid.

This patient most likely has bullous pemphigoid, a chronic autoimmune blistering disease (ABD). ABDs should be suspected in any patient with persistent or recurrent blisters involving the skin, eyes, or oral and genital mucosa. The clinical presentation can vary depending on the underlying disorder, ranging from large urticarial plaques to flaccid blisters that may almost instantly rupture and appear as erosions to intact tense bullae. ABDs can be subdivided into intraepidermal and subepidermal disorders. Intraepidermal ABDs clinically present with flaccid vesicles that are seldom clinically visualized. They rupture easily leaving painful erosions, whereas subepidermal ABDs show intact, tense bullae. The intact, tense blisters seen in this patient suggest a subepidermal ABD, such as bullous pemphigoid, as the clinical diagnosis.

Bullous pemphigoid presents with urticarial and eczematous lesions on the trunk and upper legs that progress to tense bullae on an erythematous base. Onset is usually in elderly adults. Oral involvement is present in approximately 20% of patients. A thorough examination of the eyes, oral mucosa, and genital/perianal mucosa should be performed because mucosal and ocular involvement can lead to scarring, resulting in blindness and vaginal or oral contractures. There are varying degrees of pruritus with bullous pemphigoid.

Dermatitis herpetiformis is a subepidermal ABD that is extremely pruritic. There are small tense vesicles and papules, which are rarely intact due to the extreme pruritus and resultant scratching; therefore the usual presentation is excoriations on the elbows, knees, and buttocks.

Pemphigus foliaceus and pemphigus vulgaris are intraepidermal ABD. Pemphigus foliaceus is most common in middle-aged adults. There are crusted erosions ("corn flakes") on the scalp, head/neck, and trunk without mucous membrane involvement. It can be associated with other autoimmune diseases. Drug-induced pemphigus often has this pattern.

Pemphigus vulgaris is the most common intraepidermal ABD, and its incidence increases with age. It presents with oral and/or vaginal erosions and flaccid vesicles. Pemphigus vulgaris is associated with a positive Nikolsky sign whereby light friction on perilesional skin induces a blister.

KEY POINT

- Bullous pemphigoid is a chronic autoimmune blistering disease that predominantly affects elderly patients; it presents with urticarial plaques with tense bullae on the trunk and upper legs.

Bibliography

Schmidt E, della Torre R, Borradori L. Clinical features and practical diagnosis of bullous pemphigoid. Immunol Allergy Clin North Am. 2012;32:217-32, v. [PMID: 22560135] doi:10.1016/j.iac.2012.04.002

Item 17 Answer: C

H

Educational Objective: Treat impetigo.

This patient has nonbullous impetigo, and the most appropriate treatment is topical mupirocin. Impetigo is most commonly caused by *Staphylococcus aureus* or beta-hemolytic streptococci. It is very contagious and most commonly seen in children. Impetigo can be either nonbullous or bullous impetigo. Bullous impetigo is a toxin-mediated process usually caused by production of an exfoliative toxin by *S. aureus*, which induces erythema and loss of the superficial layer of the epidermis. Nonbullous impetigo is the more common type and often affects the face or extremities. It appears as erythematous papules or pustules that rupture and then progress to erosions with overlying honey-colored crust. The diagnosis of impetigo often can be made based on clinical presentation; however, culture of the honey-colored crust can confirm the pathologic organism and obtain sensitivity testing, which is

important when treating extensive disease or staphylococcal scalded skin syndrome. This patient has only a few lesions, so the best treatment would be topical mupirocin. Mupirocin is a topical antibiotic that inhibits bacterial protein synthesis. It has good activity against both *S. aureus* and beta-hemolytic streptococci. There has been limited reported antibiotic resistance to mupirocin, and it is usually well tolerated. Washes with chlorhexidine and diluted bleach baths also can be used.

Oral doxycycline would be a treatment for patients with suspected or confirmed methicillin-resistant *Staphylococcus aureus* (MRSA) skin and soft tissue infection. Oral antibiotic therapy increases antibiotic resistance and has more potential side effects compared with topical therapy, so oral doxycycline would not be the most appropriate choice. Oral antibiotics should be reserved for patients with more extensive infection, involvement of deeper skin structures, or systemic symptoms such as fever. Cephalexin, dicloxacillin, erythromycin, amoxicillin-clavulanate, and clindamycin are the preferred initial systemic treatments for extensive impetigo.

Topical hydrocortisone is not appropriate to treat impetigo caused by *S. aureus* or beta-hemolytic streptococci. It may be used for eczematous dermatitis, but not for impetigo.

Topical neomycin/polymyxin B/bacitracin does have some activity again *S. aureus* and streptococci, but it is not as effective as mupirocin. Also, there is a higher risk of allergic contact dermatitis with topical antibiotics containing neomycin and bacitracin, so this would not be the most appropriate treatment in this patient.

KEY POINT

- A topical antibacterial agent, such as mupirocin, is the first-line therapy for localized impetigo.

Bibliography

Hartman-Adams H, Banvard C, Juckett G. Impetigo: diagnosis and treatment. Am Fam Physician. 2014 Aug 15;90(4):229-35. [PMID: 25250996]

Item 18 Answer: D

Educational Objective: Diagnose rheumatoid vasculitis.

Elderly smokers with long-standing rheumatoid arthritis and high rheumatoid factor titers are at risk for rheumatoid vasculitis. Rheumatoid vasculitis commonly affects small to medium sized vessels of the skin, digits, peripheral nerves, eyes, and heart. Small-vessel vasculitis (leukocytoclastic vasculitis) appears as palpable purpura. In medium-vessel disease, nodules, ulcerations, livedo reticularis, and digital infarcts can occur. Periungual purpura (Bywaters lesions) is the result of nailfold thrombosis and appears as purpuric papules on the digital pulp of a few digits and in the nail fold area.

Actinic purpura is caused by age- and sun damage-related capillary fragility and bleeding under atrophic skin. It is recognized as a flat, noninflamed ecchymosis typically in sun damaged skin on the forearms and dorsal hands.

Illicit drug use can result in leukocytoclastic vasculitis, most notably from cocaine adulterated with levamisole. These patients generally have palpable purpura, often with involvement of the ears. Laboratory studies typically show an elevated ANCA titer, with a mixed perinuclear and cytoplasmic pattern. These findings are absent in this patient.

Infective endocarditis can result in localized immune-mediated vasculitis secondary to vascular occlusion by infected microthrombi. Infective endocarditis is an unlikely diagnosis in this patient in the absence of heart murmur, fever (present in 90% of patients), or constitutional symptoms such as anorexia and weight loss.

KEY POINT

- Rheumatoid vasculitis typically occurs in elderly male smokers with long-standing rheumatoid arthritis and high titers of rheumatoid factor; it can appear as a small or medium-sized vasculitis and may affect nerves and other organs.

Bibliography

Sharma A, Dhooria A, Aggarwal A, Rathi M, Chandran V. Connective tissue disorder associated vasculitis. Curr Rheumatol Rep. 2016 Jun;18(6):31. [PMID: 27097818]

Item 19 Answer: D

Educational Objective: Treat drug-induced subacute cutaneous lupus erythematosus.

This patient has subacute cutaneous lupus erythematosus (SCLE), and she should discontinue adalimumab. Approximately one third of SCLE cases are drug induced. Tumor necrosis factor inhibitors such as adalimumab are a leading cause of drug-induced SCLE. Unlike psoriasis, SCLE is photodistributed, tends to burn more than itch, and has a lighter pink-to-violet tone when compared with the red tones of psoriasis. Psoriasis improves with sun exposure, whereas SCLE worsens with sun exposure. This patient's rash at presentation is different from the distribution and appearance of her psoriasis, and it is worsened in the sun rather than improved. These features argue against psoriasis treatment failure and point toward drug-induced SCLE. Medications should be evaluated as a cause of all cases of SCLE, particularly those affecting young white men who have a very low risk of developing lupus spectrum disease. Other common causative medications are hydrochlorothiazide, ACE inhibitors, NSAIDs, proton pump inhibitors, and terbinafine. Drug withdrawal typically leads to improvement in drug-induced SCLE.

Hydroxychloroquine is a first-line therapy for native cutaneous lupus, but cessation of adalimumab is a better choice for drug-induced SCLE.

Methotrexate is an excellent agent to add to tumor necrosis factor inhibitors to prevent or manage the development of human antichimeric antibodies, which may lead to treatment failure or resistance in psoriasis or psoriatic arthritis. Such treatment failure may manifest as a sudden loss of efficacy of therapy with recurrence of skin or joint

symptoms. This patient has no evidence of treatment failure, and the best management of the new rash is discontinuation of adalimumab.

A short prednisone taper might give the patient brief respite from her symptoms, but they would return shortly if adalimumab is not discontinued. Short prednisone tapers should be avoided in patients with psoriasis as significant rebound skin disease can occur, resulting in erythroderma in some patients.

KEY POINT

- Subacute cutaneous lupus erythematosus is frequently diagnosed as a drug-induced photosensitive rash characterized by erythematous annular scaly patches.

Bibliography

Grönhagen CM, Fored CM, Linder M, Granath F, Nyberg F. Subacute cutaneous lupus erythematosus and its association with drugs: a population-based matched case-control study of 234 patients in Sweden. Br J Dermatol. 2012;167:296-305. [PMID: 22458771] doi:10.1111/j.1365-2133.2012.10969.x

H

Item 20 Answer: E

Educational Objective: Manage recurrent cellulitis.

The most appropriate management of this patient is to treat the interdigital intertrigo. The diagnosis of cellulitis often is made based on the clinical presentation of a well-demarcated warm and tender erythematous plaque. Bacteria enter through superficial breaks in the skin or gain access by hematogenous spread. Treatment of the maceration and fissuring in the toe web spaces can decrease the risk of recurrent cellulitis. This fissuring, maceration, and scaling are often due to tinea pedis, which allows entry for *Streptococcus* and *Staphylococcus aureus* to infect the lower extremity. In addition, attempts should be made to identify and treat other predisposing conditions for cellulitis, such as edema, obesity, eczema, and venous insufficiency.

Because this is only the second episode of cellulitis for this patient, prophylactic antibiotics are inappropriate. There has been no attempt to address predisposing factors. Prophylactic antibiotics can be considered when a patient has three to four episodes of cellulitis per year. Treatment is usually with oral penicillin or erythromycin. Attempts to treat predisposing factors such as edema, obesity, venous insufficiency, and toe web abnormalities should be addressed first.

Blood culture is not recommended for cellulitis unless a patient has a malignancy and is on chemotherapy, or has neutropenia, severe immunodeficiency, an immersion injury, or an animal bite. This patient has none of these indications.

The patient has a classic presentation of cellulitis, and obtaining a skin biopsy is not necessary.

Staphylococcal decolonization with intranasal mupirocin can be considered for recurrent skin abscesses, but it is not effective for recurrent cellulitis.

KEY POINT

- Evaluation of the interdigital toe spaces and treatment of the maceration and fissuring in the web spaces and modification of other predisposing factors such as edema, obesity, eczema, and venous insufficiency can decrease the risk of recurrent cellulitis.

Bibliography

Stevens DL, Bisno AL, Chambers HF, Dellinger EP, et al. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the Infectious Diseases Society of America. Clin Infect Dis. 2014 Jul 15;59(2):e10-52. [PMID: 24973422]

Item 21 Answer: B

H

Educational Objective: Manage recalcitrant actinic keratosis.

The most appropriate management for this lesion is biopsy. Actinic keratoses are red scaly papules and plaques that occur in sun-exposed areas, most often in those over age 50. They have a "gritty" texture, and early lesions are often easier to palpate than to see. Diagnosis is usually made clinically rather than with biopsy. Individual lesions are often treated with cryotherapy. In patients with a large number of actinic keratoses, areas with multiple lesions are best treated with topical preparations (such as 5-fluorouracil or imiquimod); photodynamic therapy may also be performed.

If traditional therapies do not eradicate the lesions, there is a possibility that the clinical diagnosis is incorrect. In this case, the lesion is now indurated, which is not compatible with the diagnosis of actinic keratosis. Possible alternative diagnoses include basal cell and squamous cell carcinomas. Histologic diagnosis would give definitive diagnosis and guide treatment options.

Repeated cryotherapy may treat the superficial portion of the lesion, while the deeper portion of the tumor may continue to grow. Cryosurgery can be used to treat basal cell carcinomas; however, the targeted depth and the temperature of the lesion need to be carefully monitored. However, a definitive diagnosis is required before this therapy can be considered.

Topical imiquimod is an interferon inducer, and it can treat actinic keratosis by producing an immunologic reaction against the lesion. It is also used to treat some basal cell carcinomas; it is an effective treatment and approved only for the superficial pathologic subtype of basal cell carcinoma. However, a biopsy of the lesion is the first step in the proper management of this patient.

Standard treatment for most basal cell carcinomas is wide local excision; however, some histologic types and body locations require more aggressive management. Biopsy prior to excision is important because the histopathologic diagnosis should be used to guide treatment.

KEY POINT

- Actinic keratoses that do not resolve with cryotherapy or other appropriate therapy will require a biopsy to rule out an invasive neoplasm.

Bibliography

Siegel JA, Korgavkar K, Weinstock MA. Current perspective on actinic keratosis: a review. Br J Dermatol. 2016. [PMID: 27500794] doi:10.1111/bjd.14852

H

Item 22 Answer: A

Educational Objective: Diagnose basal cell carcinoma.

The patient has a basal cell carcinoma, the most common type of skin cancer. The lesion demonstrates typical findings with a translucent (pearly) papule and arborizing telangiectasias. It typically appears on sun-exposed areas in fair-skinned persons with a history of extensive sun exposure. It is usually asymptomatic and enlarges slowly over time. Although it rarely metastasizes, basal cell carcinoma can cause significant local tissue destruction if not removed.

Melanocytic nevi, often referred to as "moles," are found in persons of all ages. They are benign collections of melanocytes and histologically consist of nests of melanocytes occurring at the dermal-epidermal junction and dermis. They occur most commonly in sun-exposed areas. Junctional nevi are flat and often dark brown in color. Compound nevi are raised (papules) and may be irregularly pigmented. Dermal nevi are soft and flesh-colored and may resemble skin tags. This patient's translucent papule with telangiectasias is not consistent with the findings of a dermal nevus.

Keratoacanthomas tend to be rapidly growing pink nodules with a crusted hyperkeratotic core or central crater of crust and scale ("volcaniform"). Keratoacanthomas usually stabilize after a period of rapid growth and then slowly involute, eventually resolving completely. Since some lesions fail to resolve completely and may persist, they are usually treated with surgical excision. A rapidly growing nodule with a hyperkeratotic core is not consistent with this patient's findings.

Melanoma is a neoplasm of the pigment-making cells, melanocytes. The clinical features that suggest melanoma are represented by the mnemonic "ABCDE," where "A" stands for Asymmetry, "B" for irregular Border, "C" for multiple Colors, "D" for Diameter greater than 6 mm, and "E" for Evolution, meaning increasing size. Melanoma may be further classified into several different subtypes. Nodular melanomas are the most aggressive subtype and have an invasive component from the beginning. A nodular melanoma appears as a darkly pigmented, pedunculated, or polypoid nodule. Amelanotic variants do occur but are rare. The patient's translucent nodule is not consistent with the typical findings of a nodular melanoma.

Squamous cell carcinoma is the second most common type of skin cancer and the most common skin cancer in persons who are immunocompromised following solid organ transplant. Squamous cell carcinoma appears as a pink hyperkeratotic papule or nodule. Compared with basal cell carcinoma, it usually has scale and does not have that translucent, pearly appearance.

KEY POINT

- Basal cell carcinoma appears as asymptomatic translucent telangiectatic papules on sun-exposed areas in fair-skinned persons.

Bibliography

Rubin AI, Chen EH, Ratner D. Basal-cell carcinoma. N Engl J Med. 2005;353:2262-9. [PMID: 16306523]

Item 23 Answer: B

Educational Objective: Diagnose lupus pernio.

This patient has lupus pernio, a variant of sarcoidosis that involves granulomatous inflammation of the skin around the nares. Histopathology of sarcoidosis shows granulomatous inflammation of the affected tissue with noncaseating granulomas and minimal lymphocytic infiltration.

The term "lupus pernio" is a source of potential confusion. "Lupus" generally refers to systemic lupus erythematosus; "pernio" generally refers to a condition of purple papules on the distal digits exacerbated by cold and moisture; and lupus vulgaris is a form of tuberculosis of the skin. Lupus pernio has little to do with these, however. The typical appearance of lupus pernio includes violaceous subcutaneous plaques or nodules of the central face, often with some overlying scaling, most commonly seen in black persons. Patients with lupus pernio tend to have a chronic, refractory course, and extracutaneous disease. A careful evaluation for the presence of extracutaneous disease is necessary in any patient with cutaneous sarcoid, and treatment depends on other organ involvement and the severity of the clinical disease.

Lepromatous leprosy may consist of erythematous macules, papules, and nodules or occasionally simply diffuse infiltration and palpable thickening of the skin. The condition is often generalized in distribution at diagnosis. There is frequent involvement of the nasal mucosa resulting in nasal stuffiness and eventually a saddle-nose deformity. The patient's localized skin findings are most consistent with lupus pernio.

The classic findings of lupus vulgaris, a chronic, progressive form of cutaneous tuberculosis, include multiple discrete, red-brown papules that subsequently coalesce to form a slowly growing asymptomatic plaque most typically found on the head and neck. Histopathology will show granulomas with a variable degree of central caseating necrosis; this finding is absent in this patient, making lupus vulgaris an unlikely diagnosis.

The most specific skin manifestations of systemic lupus erythematosus are variations on interface dermatitis, with pink-to-violet macules or plaques and varying scale or atrophy. One example is acute cutaneous lupus erythematosus (ACLE), also known as malar or butterfly rash. ACLE consists of erythema and edema over the cheeks and bridge of the nose and sometimes the forehead and chin. Granuloma formation is not a feature of lupus-specific skin disease.

KEY POINT

- Lupus pernio is sarcoidosis of the nose and central face, manifesting as violaceous subcutaneous plaques or nodules, often with some overlying scale.

Bibliography

Wanat KA, Rosenbach M. Cutaneous Sarcoidosis. Clin Chest Med. 2015;36:685-702. [PMID: 26593142] doi:10.1016/j.ccm.2015.08.010

H

Item 24 Answer: C

Educational Objective: Treat high-risk basal cell carcinoma.

The most appropriate treatment for this lesion is Mohs micrographic surgery. Mohs micrographic surgery is a specialized surgical procedure that provides margin control while sparing as much normal skin as possible. Indications for Mohs micrographic surgery include tumors with aggressive histologic subtypes (micronodular, morpheaform, infiltrative, perineural involvement), high-risk and cosmetically sensitive locations (face, genitals), large tumors or tumors arising in scar tissue, and in patients who are immunosuppressed. Because this patient has a high-risk tumor that is located in a cosmetically sensitive location, Mohs surgery is the most appropriate treatment.

Small noninfiltrating basal cell carcinomas can be treated with cryotherapy; however, other surgical methods are more commonly used. To treat basal cell carcinomas appropriately with cryotherapy, the target temperature is −50 °C using liquid nitrogen as the cryogen and this requires local anesthesia. Hypopigmentation is often seen after cryotherapy. The histologic subtype and location of the basal cell carcinoma make cryotherapy inappropriate for this patient.

Electrodesiccation and curettage is a widely used treatment for noninfiltrating basal cell carcinomas on low-risk anatomic sites (trunk and extremities). High-risk infiltrative and micronodular basal cell carcinomas are not appropriate for electrodesiccation and curettage. Additionally, because it may result in a cosmetically unappealing scar on the nose, it should not be used for this patient.

Topical therapies including 5-fluorouracil and imiquimod are most effective for superficial basal cell carcinomas. Superficial basal cell carcinomas are well-demarcated, irregularly bordered red patches; they tend to enlarge radially rather than invading into deeper structures. Topical therapies are not effective for more aggressive histologic subtypes of basal cell carcinomas.

Vismodegib is an oral medication that inhibits the hedgehog signaling pathway. It is reserved for locally advanced or metastatic basal cell carcinomas. There are significant side effects including dysgeusia, alopecia, and muscle cramps.

KEY POINT

- Mohs surgery, a form of margin-controlled surgery that minimizes loss of normal tissue, is particularly useful for basal cell tumors in areas such as the head and neck, for large or recurrent tumors, for histologically high-risk tumors, or when cosmetic outcome is crucial.

Bibliography

Connolly SM, Baker DR, Coldiron BM, Fazio MJ, Storrs PA, Vidimos AT, et al; American Academy of Dermatology. AAD/ACMS/ASDSA/ASMS 2012 appropriate use criteria for Mohs micrographic surgery: a report of the American Academy of Dermatology, American College of Mohs Surgery, American Society for Dermatologic Surgery Association, and the American Society for Mohs Surgery. Dermatol Surg. 2012;38:1582-603. [PMID: 22958088] doi:10.1111/j.1524-4725.2012.02574.x

H

Item 25 Answer: B

Educational Objective: Diagnose erythema multiforme major.

Erythema multiforme (EM) features the development of characteristic tricolored targetoid plaques, as this patient demonstrates on the extremities and face. In EM major, these targetoid plaques are accompanied by mucous membrane involvement. The most common cause of EM is infection, and herpes simplex virus 1 and 2 are the most commonly recognized, followed by *Mycoplasma pneumoniae*. The treatment of EM major is supportive, and most cases resolve in a week. Suppressive therapy may be necessary for patients who have relapses of EM with herpes outbreaks.

Patients with disseminated gonococcal infection and bacteremia present with vesiculopustular or hemorrhagic macular skin lesions, fever, chills, and polyarthralgia. Knees, elbows, and distal joints are typical sites of involvement. Tenosynovitis of the dorsa of the hands and/or feet is a characteristic feature. Gonococcemia does not cause targetoid plaques or mucositis.

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are typically medication reactions. Mucous membrane involvement and targetoid lesions occur as well. Unlike EM, however, the targetoid lesions in SJS and TEN lack the true tricolor appearance and are thus labeled atypical targetoid plaques. Like EM, SJS can sometimes be triggered by infection, but unlike EM, SJS is characterized by necrosis and sloughing of the skin. SJS and TEN have systemic manifestations such as acute kidney injury and elevated liver chemistry tests, whereas EM does not.

KEY POINT

- Erythema multiforme major is recognized by targetoid lesions accompanied by mucous membrane involvement; a drug or infection (herpes simplex virus or *Mycoplasma pneumoniae*) can trigger erythema multiforme.

Bibliography

Stoopler ET, Houston AM, Chmieliauskaite M, Sollecito TP. Erythema Multiforme. J Emerg Med. 2015;49:e197-8. [PMID: 26281815] doi:10.1016/j.jemermed.2015.06.018

Item 26 Answer: E

Educational Objective: Diagnose actinic purpura.

Actinic purpura is a common incidental finding in elderly persons, and no intervention is needed at this time; however, reassurance should be provided to the patient and caregiver.

A myriad of changes occur in the skin over time; these can be due to chronologic aging alone or influenced by the cumulative effects of ultraviolet light exposure. Actinic purpura is caused by age-related capillary fragility and bleeding under atrophic skin. Minor trauma can cause impressive purpuric macules and patches, most commonly on the forearm. It is not a sign of vasculitis, a bleeding disorder, or nutritional deficiency, and it does not require additional evaluation with coagulation studies or therapy. Often associated with actinic purpura are stellate pseudoscars, jagged or linear atrophic scars that primarily occur on the forearms of patients with chronic actinic damage. Patients may or may not recall antecedent trauma. There is no treatment for actinic purpura. Good skin care measures such as emollient moisturizers can help reduce dryness and protect the skin from minor trauma such as scratching.

It is unnecessary to biopsy this lesion. There is no indication that it is a new growth or that this is an undiagnosed inflammatory skin condition or vasculitis.

Although it is good to be alert for abusive situations, in this case the findings are typical for actinic purpura.

Triamcinolone is a medium-potency glucocorticoid. Although initial application of the ointment will not harm the patient, chronic application of a medium-potency glucocorticoid on normal skin will result in thinning of the already thin skin, the development of striae and purpura, pigmentary changes, acneiform eruptions, and an increased risk for infection, resulting in more damage.

KEY POINT

- Actinic purpura is caused by age-related capillary fragility and bleeding under atrophic skin; minor trauma can cause impressive purpuric macules and patches, most commonly on the forearm.

Bibliography

Blume-Peytavi U, Kottner J, Sterry W, Hodin MW, Griffiths TW, Watson RE, et al. Age-associated skin conditions and diseases: current perspectives and future options. Gerontologist. 2016;56 Suppl 2:S230-42. [PMID: 26994263] doi:10.1093/geront/gnw003

H

Item 27 Answer: E

Educational Objective: Diagnose stasis dermatitis.

This patient has stasis dermatitis with the characteristic findings of bilateral edema, erythema, scaling, and pruritus of the bilateral lower legs. Crusting and erosions may also be seen. This is due to chronic venous insufficiency or other causes of chronic lower extremity edema. When secondary to chronic venous insufficiency, varicosities, telangiectasias, ulcers, and brown discoloration may also be noted. Symptomatic treatment with topical glucocorticoids and emollients should be used; however, the edema must be addressed with compression stockings and leg elevation for significant improvement to occur.

Allergic contact dermatitis is common in patients with stasis dermatitis. It commonly occurs due to the application of topical medications such as over-the-counter triple antibiotic ointment. This patient denies applying any topical medication or emollient to her legs, so her diagnosis would not be allergic contact dermatitis. In patients exposed to potential allergens, a clue to the diagnosis of contact dermatitis is the failure of the patient to respond to appropriate therapy for stasis dermatitis. In these patients, patch testing is often necessary to determine if a secondary allergic contact dermatitis is present.

Stasis dermatitis is often misdiagnosed as cellulitis. It would be unusual for cellulitis to present bilaterally. Unlike stasis dermatitis, cellulitis is typically tender and not pruritic. Cellulitis is usually hot to the touch and involves less scaling than stasis dermatitis.

Leukocytoclastic vasculitis is inflammation of the small vessels of the skin; it typically presents with nonblanching, violaceous papules (palpable purpura), and macules on the lower extremities. Leukocytoclastic vasculitis can be idiopathic, but it is usually associated with an infection or is often drug induced. Other causes of leukocytoclastic vasculitis include connective tissue disease, inflammatory bowel disease, and malignancies.

Psoriasis is characterized by well-demarcated, erythematous plaques with silvery scale. It commonly appears on the knees, elbows, and scalp. There can be associated nail changes (nail pits, onycholysis). This patient's clinical presentation is not consistent with psoriasis.

KEY POINT

- Stasis dermatitis is typically characterized by edema, erythema, scaling, and pruritus on the lower legs and occurs in patients with venous insufficiency or other causes of chronic lower extremity edema.

Bibliography

Eberhardt RT, Raffetto JD. Chronic venous insufficiency. Circulation. 2014 Jul 22;130(4):333-46. [PMID: 25047584]

Item 28 Answer: A

Educational Objective: Treat an epidermal inclusion cyst.

This patient has an epidermal inclusion cyst (sometimes called epidermoid cyst), and the most appropriate treatment is excision. The diagnosis of epidermal inclusion cysts is clinical. Epidermal inclusion cysts range from a few millimeters to several centimeters in size and are subepidermal, freely movable nodules with an epithelial lining and a core of accumulated keratin debris. They are most commonly found on the trunk. Epidermal inclusion cysts are often incorrectly referred to as "sebaceous cysts," a term that is erroneous because they possess keratin rather than sebum. Often they have a central punctum by which foul-smelling material can be expressed; the odor is derived from the presence of anaerobic bacteria. Epidermal inclusion cysts are benign but are frequently removed if they become bothersome to the patient. In this case, treatment is by excision with removal of the entire cyst wall.

When epidermal inclusion cysts rupture, they may become tender, inflamed, and occasionally infected. Ruptured cysts are often mistaken for furuncles or infectious abscesses. Ruptured cysts are treated with incision and drainage, and intralesional glucocorticoid injections may be used to reduce the inflammation.

Incision, as well as incision with drainage, can lead to temporary improvement of an inflamed epidermal cyst; however, recurrences are common as the epithelial lining must be removed for complete treatment. Therefore, these are not the preferred treatment.

Antibiotics are rarely required; they should only be used when there is concern for secondary infection.

KEY POINT

- Excision is the most appropriate treatment for bothersome epidermal inclusion cysts since the epithelial lining must be removed for complete treatment.

Bibliography

Higgins JC, Maher MH, Douglas MS. Diagnosing common benign skin tumors. Am Fam Physician. 2015;92:601-7. [PMID: 26447443]

Item 29 Answer: D

Educational Objective: Treat telogen effluvium.

This patient has telogen effluvium, and the most appropriate management is reassurance. Telogen effluvium is the most common cause of diffuse alopecia in adult women. Telogen effluvium is a generalized nonscarring alopecia that presents with excessive shedding of normal telogen club hairs. It is due to premature conversion of anagen hair follicles into the telogen, or final, phase of hair development after a physically or psychologically traumatic event such as surgery, parturition, or fever, commonly occurring 3 to 5 months after the event. It is particularly common after pregnancy. No specific therapy is required, and most cases will resolve spontaneously in about 6 to 12 months. Prognosis is especially good if the event causing the alopecia is identifiable.

Intralesional glucocorticoids are the treatment of choice for localized alopecia areata. This tends to present as rapid and complete loss of hair in well-demarcated round or oval patches. There may be some exclamation point hairs at the periphery.

In properly selected patients, finasteride is used to treat androgenic alopecia. Dihydrotestosterone (DHT) binds to androgen receptors in hair follicles, transforming terminal hair follicles to miniaturized hair follicles. Finasteride inhibits the conversion of testosterone to DHT and slows the process of androgenic alopecia. In androgenic alopecia the pattern of hair loss reflects the sensitivity of the hair follicle to DHT. Typically male-pattern hair loss starts with anterior hair line recession with eventual biparietal and vertex hair loss. In contrast, in women the top of the head is affected, and balding is not complete. A classic examination finding is a widening of the central part compared with the occipital part. Finasteride is contraindicated (FDA category X) in pregnant women because it is known to cause birth defects in the male fetus. Women who are or may potentially be pregnant should not take finasteride and should avoid contact with crushed or broken tablets because it can be absorbed through the skin.

Topical minoxidil can be used for male or female patterned hair loss. Minoxidil prolongs the duration of anagen, shortens telogen, and enlarges miniaturized follicles. Like finasteride, minoxidil is ineffective (and unnecessary) in hair loss caused by telogen effluvium.

KEY POINT

- Telogen effluvium is a generalized nonscarring alopecia triggered by a physically traumatic event such as surgery, parturition, or fever; it usually spontaneously resolves in about 6 to 12 months if the trigger is removed or treated.

Bibliography

Mubki T, Rudnicka L, Olszewska M, Shapiro J. Evaluation and diagnosis of the hair loss patient: part II. Trichoscopic and laboratory evaluations. J Am Acad Dermatol. 2014;71:431.e1-431.e11. [PMID: 25128119] doi: 10.1016/j.jaad.2014.05.008

Item 30 Answer: B

Educational Objective: Diagnose melasma.

This patient has melasma, an acquired hypermelanotic condition most commonly affecting women of childbearing age. It presents as tan-brown reticulated patches in the centrofacial, malar, and mandible areas. Pigmentation can develop rapidly, often over weeks. Melasma is more apparent or more frequent in patients with darker skin and who live in sunny areas. The pathogenesis is unknown. Common causes are hormonal factors such as pregnancy and oral contraceptives, ultraviolet light, and genetic predisposition. While melasma has no medical significance, it can be very distressing to patients. Treatment is challenging and involves strict sun avoidance and topical depigmenting agents and chemical peels.

Irritant contact dermatitis is caused by a direct toxic effect on the epidermis from exposure to a chemical such as a cleaning agent, other caustic substances, or repeated wetting and drying. For example, excessive washing with harsh soap will often lead to dry irritated skin, which is not immune mediated. This patient's skin findings include primarily hyperpigmentation without evidence of dry irritated skin, making irritant contact dermatitis unlikely.

Morbilliform (meaning measles-like) drug eruption is characterized by a sudden generalized symmetrical appearance of bright red macules and papules most prominently on the trunk and extremities. Systemic symptoms include pruritus and sometimes low-grade fever. Eruptions typically start within 1 week of starting a new medication. This patient's brown pigmentation on her face without systemic symptoms is not compatible with a morbilliform drug reaction.

Postinflammatory hyperpigmentation is a darkening of the skin resulting from cutaneous inflammation. Common causes include acne vulgaris and eczematous dermatoses.

The duration of postinflammatory pigmentary changes varies, depending on the location and degree of inflammation. Hyperpigmentation on the lower legs can take several years to fade. Some postinflammatory pigment changes are permanent. Treatment of postinflammatory pigment changes includes treatment of any underlying skin inflammation, sun avoidance or sun protection, and consideration of a bleaching cream. The patient had no history of a previous inflammatory skin condition making postinflammatory hyperpigmentation an unlikely diagnosis.

KEY POINT

- Melasma is an acquired hypermelanotic condition most commonly affecting women of childbearing age; it is characterized by tan-brown reticulated patches in the centrofacial, malar, and mandible areas.

Bibliography

Sheth VM, Pandya AG. Melasma: a comprehensive update: part I. J Am Acad Dermatol. 2011;65:689-97; quiz 698. [PMID: 21920241] doi:10.1016/j.jaad.2010.12.046

Item 31 Answer: D

Educational Objective: Diagnose HIV-associated seborrheic dermatitis.

This patient has new-onset seborrheic dermatitis that is unresponsive to typical therapy, and he should be tested for HIV. Seborrheic dermatitis presents as erythematous patches with greasy scale on the scalp, nasolabial folds, and chest. This condition is extremely common in HIV patients, and most patients with AIDS have some evidence of seborrheic dermatitis. The incidence and severity of seborrheic dermatitis is also increased in patients with neurologic conditions, in particular Parkinson disease. Patients with new or explosive onset of seborrheic dermatitis, or seborrheic dermatitis that is severe or extensive, found in unusual locations, or is resistant to treatment, should be evaluated for HIV infection.

Patients with diabetes mellitus can develop a wide range of skin findings such as hyperpigmentation of acanthosis nigricans, which tends to present in the intertriginous areas, particularly in the axillae, in obese persons with diabetes. Patients with type 1 diabetes are at increased risk for development of vitiligo. Patients with diabetes may develop orange, atrophic plaques on their anterior shins (necrobiosis lipoidica). Other cutaneous findings associated with diabetes are bullous diabeticorum (large, asymptomatic, noninflammatory bullae on the lower extremities) and scleredema (an uncommon skin finding characterized by edematous induration of the upper back). Diabetic dermopathy (multiple hyperpigmented macules on the anterior shins) is one of the most common cutaneous findings. Seborrheic dermatitis is not associated with diabetes.

Hyperlipidemia may be associated with xanthomas. Xanthomas are localized lipid deposits in organs and their cutaneous manifestations include several subtypes, most commonly eruptive xanthomas, tuberous xanthomas, tendinous xanthomas, and plane xanthomas. The subtype of xanthoma can often predict the most likely associated underlying disorder. Seborrheic dermatitis is not associated with hyperlipidemia.

Chronic hepatitis C infection is associated with porphyria cutanea tarda and lichen planus. Porphyria cutanea tarda presents with small, transient, easily ruptured vesicles in sun-exposed areas, mainly on the hands. Hypertrichosis may be seen on the tops of the hands or cheeks. Lichen planus is an acute eruption of purple, pruritic, polygonal papules that most commonly develops on the flexural surfaces, especially the wrists and ankles. Lichen planus can also occur in the mucous membranes appearing as white plaques. Seborrheic dermatitis is not associated with hepatitis C infection.

KEY POINT

- Patients with new or explosive onset of seborrheic dermatitis, or seborrheic dermatitis that is severe or extensive, found in unusual locations, or is resistant to treatment, should be evaluated for HIV infection.

Bibliography

Tschachler E. The dermatologist and the HIV/AIDS pandemic. Clin Dermatol. 2014;32:286-9. [PMID: 24559565] doi:10.1016/j.clindermatol.2013.08.012

Item 32 Answer: D

Educational Objective: Diagnose transient acantholytic dermatosis.

Transient acantholytic dermatosis, also known as Grover disease, is a benign common eruption that is most often seen in middle aged to elderly men. The eruption presents as small discrete papules, some of which may be scaly, and papulovesicles on the trunk. Symptomatically there are varying degrees of pruritus. Although the cause and pathogenesis are unknown, a very common association is xerosis. The eruption is frequently triggered by excessive sweating. Skin biopsy shows acantholytic dyskeratosis. Transient acantholytic dermatosis is typically self-limited, but therapy with topical glucocorticoids or moisturizers may be effective.

Allergic contact dermatitis is a pruritic eruption of patches and plaques with variable vesiculation. The eruption is found in areas of allergen exposure and typically worsens with subsequent exposures. In exuberant cases, the localized inflammation can lead to a secondary "id" reaction, a generalized acute cutaneous reaction in which pinpoint flesh-colored to red papules develop diffusely on the body. The absence of a known sensitizer and a pruritic rash that is worsened with heat and sweating is not consistent with allergic contact dermatitis. Histologic studies show spongiotic dermatitis with eosinophils.

Although atopic dermatitis is pruritic and associated with xerosis, it is clinically distinguished from transient acantholytic dermatosis by the presence of scaly eczematous patches with variable degrees of lichenification. Also, atopic

dermatitis in adults appears in the flexures of the extremities rather than the torso. Finally, the prevalence of atopic dermatitis decreases with age, whereas transient acantholytic dermatosis is more common in middle-aged to elderly men. On skin biopsy, there are variable degrees of spongiosis.

Lichen planus (LP) is characterized by pruritic, purple, polygonal papules that may coalesce into plaques characteristically involving the ankles and flexor surfaces of the wrist. Fine white lines may be visible on the surface of the papules or plaques. LP can also occur in the mucous membranes (mouth, vaginal vault, and penis) with white plaques that, if uncontrolled, may ulcerate. The eruption can also develop in the nails, leading to thickening and distortion of the nail plate. LP is most commonly idiopathic but may be induced by medications or possibly infection. The purple polygonal papules and plaques of LP are not consistent with this patient's rash. A skin biopsy shows lichenoid dermatitis.

KEY POINT

- Transient acantholytic dermatosis is characterized by red pruritic papules on the chest, flanks, and back associated with dry skin, heat, and sweating.

Bibliography

Berger TG, Shive M, Harper GM. Pruritus in the older patient: a clinical review. JAMA. 2013;310:2443-50. [PMID: 24327039] doi:10.1001/jama.2013.282023

Item 33 Answer: D

Educational Objective: Diagnose melanotic macule.

Melanotic macule or mucosal lentigo is a small, well-circumscribed, brown-to-black macule. The most common location is the lower mucosal lip, but they can occur on any mucosal surface. They are the mucosal counterpart of a lentigo on the skin. They are typically solitary, but multiple macules can occur. Numerous mucosal lentigines are associated with various syndromes such as Peutz-Jeghers and Laugier-Hunziker syndromes. Peutz-Jeghers syndrome is an autosomal dominant hamartomatous polyposis syndrome characterized by hamartomatous polyps in the gastrointestinal tract, mucocutaneous pigmentation, and an increased risk of cancer. Laugier-Hunziker syndrome is an acquired, benign disorder characterized by lentigines on the lips and buccal mucosa. It not associated with any systemic disorder.

Actinic cheilitis appears as chronic red-to-tan scaly patches with erosions and characteristically involves the lower lip. Actinic cheilitis is a premalignant condition and is considered the precursor to squamous cell carcinoma in situ. Treatment with topical chemotherapy agents (5-fluorouracil), imiquimod, laser therapy, photodynamic therapy, or cryotherapy is recommended. Actinic cheilitis differs from angular cheilitis, which is inflammation involving one or both corners of the mouth and often related to a bacterial or fungal infection.

Amalgam tattoos are the most common source of localized pigmentation on the buccal mucosa. Amalgam dental fillings contain metals that can become implanted into the adjacent mucosa at the time of application. They appear as blue-gray macules and do not change over time. The typical location for amalgam tattoos is the buccal mucosa, not the lip. Diagnosis can be made clinically, or confirmation can be made with biopsy and pathology. No treatment is necessary.

Although it can arise anywhere in the skin or mucous membranes, malignant melanoma most commonly occurs in sun-exposed areas. The back is the most common location in men, and the legs are the most common location in women. The clinical features that suggest melanoma are asymmetry, irregular border, multiple colors, diameter greater than 6 mm, and changing size. The more of these features a pigmented lesion possesses, the more worrisome it is for malignant melanoma or melanoma in-situ, and these entities must be excluded with an excisional biopsy. This patient's lesion is small, round, well-circumscribed and has no worrisome features of a melanoma.

KEY POINT

- Melanotic macules are well-circumscribed, brown-to-black macules that most commonly occur on the lower lip, although they may be seen on the gingiva, buccal mucosa, or tongue.

Bibliography

Müller S. Melanin-associated pigmented lesions of the oral mucosa: presentation, differential diagnosis, and treatment. Dermatol Ther. 2010;23:220-9. [PMID: 20597941] doi:10.1111/j.1529-8019.2010.01319.x

Item 34 Answer: C

Educational Objective: Diagnose localized scleroderma (morphea).

This patient has localized scleroderma, or morphea. Localized scleroderma is one of the scleroderma spectrum disorders, a group of diseases sharing the feature of skin hardening. The scleroderma spectrum disorders include systemic sclerosis (SSc), localized scleroderma, and scleroderma-like conditions. SSc is further characterized as two distinct subsets based on skin involvement: limited SSc and diffuse SSC. In limited SSc, scleroderma is restricted to the fingers and hands and, to a lesser extent, the face and neck. Scleroderma involving the fingers and hands, chest, abdomen, forearms, upper arms, and shoulders indicates diffuse SSc. Morphea is a localized form of scleroderma limited to one or more indurated plaques confined to the torso and proximal extremities. Although histologic findings of morphea are identical to those seen in patients with SSc, visceral manifestations and Raynaud phenomenon are absent. This patient has a generalized variant of morphea called pansclerotic morphea, which often appears in areas of friction and pressure, such as the waistband area or inframammary regions. Diffuse and limited SSc involve the fingers first, and sclerosis proceeds proximally, sometimes very rapidly.

Scleredema has a variable clinical presentation but is most easily recognizable as large, noninflammatory woody-indurated plaques over the shoulder girdle, neck, and upper extremities. In adults, scleredema occurs most commonly as a complication of diabetes mellitus but may be seen following a streptococcal infection in children or as a complication of monoclonal gammopathy.

Scleromyxedema is characterized by deposition of mucin with large numbers of stellate fibroblasts in the dermis, presenting as waxy yellow-red papules overlying thickened skin. It affects the face, upper torso, and upper extremities. The condition is rare but is most frequently associated with paraproteinemia and may therefore occur in the setting of multiple myeloma or AL amyloidosis. In a few patients, a mild inflammatory myopathy may accompany the disorder.

KEY POINT

- Localized scleroderma (morphea) is characterized as isolated sclerotic circumscribed plaques; it is not associated with Raynaud phenomenon or systemic disease and does not include sclerodactyly.

Bibliography

Sperber K, Ash J, Gutwein F, Wasserrman A, Rao V, Tratenberg M. Localized scleroderma: a clinical review. Curr Rheumatol Rev. 2016. [PMID: 27604889]

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Item 35 Answer: B

Educational Objective: Diagnose lentigo maligna.

This patient has a melanoma in situ, lentigo maligna subtype. The clinical features that suggest melanoma are represented by the mnemonic "ABCDE," where "A" stands for Asymmetry, "B" for irregular Border, "C" for multiple Colors, "D" for Diameter greater than 6 mm, and "E" for Evolution, meaning increasing size. The more of these features a pigmented lesion possesses, the more worrisome it is for melanoma. Unfortunately, melanomas do not always adhere to these criteria; they may be red or flesh colored, smaller than 6 mm, perfectly symmetric, or homogeneously colored. Thus, a low threshold for biopsy should be present for any atypical-appearing skin lesion, changing or symptomatic nevus, or any mole that stands out from the background nevi pattern of the particular patient.

Melanoma may be further classified into several different subtypes. Lentigo maligna is a subtype of melanoma in situ that tends to arise on the head and neck region of elderly persons, especially those with a long history of sun damage. They are more indolent and slow growing. As the name would imply, it clinically often resembles a benign solar lentigo. A biopsy would provide the definitive diagnosis.

Melanocytic nevi are benign growths of melanocytes commonly referred to as "moles." The junctional component of the term indicates where the melanocytic nests are located. In junctional melanocytic nevi, the melanocytic nests are located in the dermal-epidermal junction. They clinically appear as brown-to-black uniform macules during early childhood and can increase in number through middle age. It is very rare for a new melanocytic nevus to appear at the age of 69.

Nodular melanoma is the most aggressive form of malignant melanoma. It is rapid growing and begins with an invasive vertical growth phase. It appears as blue-black, smooth, or eroded nodules, occurring anywhere on the body. Nodular melanomas are responsible for most deaths from melanoma.

Solar lentigines are brown, well-demarcated macules and patches that occur on the sun-exposed skin of older persons, particularly the face and dorsal hands. Previously, they were often referred to as "liver spots" because their color resembles that of the liver. Although benign, they are a marker for someone who has relatively fair skin and has received a significant amount of sun exposure over the years. They frequently occur near more worrisome lesions such as actinic keratoses or skin cancers. Lentigines with atypical features or broad, growing lentigines (particularly on the face of older, light-skinned persons) should be biopsied to rule out lentigo maligna. This patient has had extensive sun exposure and now has a growing lesion making lentigo maligna a more likely diagnosis. A biopsy is required to establish the correct diagnosis.

KEY POINT

- Melanoma in situ, lentigo maligna subtype is typically found on the head and neck region of older persons; it is associated with frequent chronic ultraviolet light exposure.

Bibliography

Longo C, Pellacani G. Melanomas. Dermatol Clin. 2016;34:411-419. [PMID: 27692447] doi:10.1016/j.det.2016.05.004

Item 36 Answer: D

Educational Objective: Treat mild inflammatory acne in pregnancy.

The patient has some mild inflammatory and comedonal acne that would be best treated with topical erythromycin. There are two main types of acne lesions: inflammatory and noninflammatory. The prototypical lesion of noninflammatory acne is the comedone, which results from follicular plugging by keratin. Comedones can be open ("blackheads") or closed ("whiteheads"). Acne typically starts with closed comedones that are visible as subtle small 1- to 2-mm flesh-colored papules. Inflammatory acne consists of erythematous pustules, nodules, or cysts (deeper and often painful) that occur later and are the result of inflammation in and around the hair follicle. Lesion morphology should guide treatment. It is also important to consider the safety of medications used for acne treatment during pregnancy. Topical erythromycin is pregnancy category B and can be used safely during pregnancy. To reduce the incidence of bacterial resistance, topical erythromycin can be combined with topical benzoyl peroxide, also safe in pregnancy.

Doxycycline is pregnancy category D and can cause dental staining and enamel hypoplasia when used in the second and third trimesters; it is not to be used during pregnancy.

Isotretinoin is a teratogen (pregnancy category X) and can cause fetal loss, especially when used in the first trimester. It can also cause severe head and cardiac defects. Oral isotretinoin is reserved for the treatment of severe nodulocystic acne and gram-negative folliculitis in nonpregnant patients. Patients must be monitored carefully once therapy with isotretinoin is initiated and participation in the risk prevention program iPLEDGE is mandated for all patients, providers, and dispensing pharmacies. Mandatory office visits are required every 30 days with regular monitoring for pregnancy and medication side effects.

Acne in women, particularly those whose acne flares around menses, may respond to spironolactone. Spironolactone is pregnancy category C, and in rat studies has caused delayed sexual maturation in female rats and feminization of male rat fetuses.

Topical retinoids are appropriate for comedonal and mild inflammatory acne. Tazarotene is a topical retinoid, but is rated pregnancy category X and should not be used in this patient.

KEY POINT

- Management of dermatologic conditions during pregnancy with topical agents should be considered before prescribing systemic medications because they are lower risk, with the exception of tazarotene (category X).

Bibliography

Murase JE, Heller MM, Butler DC. Safety of dermatologic medications in pregnancy and lactation: Part I. Pregnancy. J Am Acad Dermatol. 2014;70:401.e1-14; quiz 415. [PMID: 24528911] doi:10.1016/j.jaad.2013.09.010

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Item 37 Answer: B

Educational Objective: Diagnose morbilliform drug reaction.

This patient is experiencing a classical morbilliform, or exanthematous, drug eruption, which is the most common form of cutaneous adverse drug reaction. Morbilliform eruptions begin 4 to 14 days after the initiation of a new medication. Characteristic skin findings begin as coalescing fine monomorphic papules on the trunk and spread distally and symmetrically. Peripheral eosinophilia or leukocytosis may be seen, but other signs of systemic involvement are not present. The therapy is to stop the medication and treat symptomatically with antihistamines and medium-potency topical glucocorticoids for a brief time while the reaction resolves.

Drug reaction with eosinophilia and systemic symptoms (DRESS) is another severe cutaneous adverse reaction. Its onset is notably remote from initiation of the offending agent, often by as much as 2 to 6 weeks. While eosinophilia is a feature of DRESS syndrome, DRESS is associated with other signs of systemic involvement such as liver chemistry abnormalities. DRESS may manifest a morbilliform appearance, but typical features also include skin pain and pronounced facial edema that are absent in morbilliform drug eruption.

Stevens-Johnson syndrome results in necrosis and sloughing of the epidermis. Skin pain and involvement of mucous membranes is a key feature. Rare cases of Stevens-Johnson syndrome are precipitated by an infection, but this patient's skin findings are more consistent with morbilliform eruption.

Viral exanthem may appear identical in morphology to a morbilliform drug eruption. However, the appearance of this rash should be closer to the onset of symptoms of the infection, as opposed to 3 weeks later. In this case, a common cause of morbilliform reaction and development of rash within 4 days of starting the medication makes morbilliform reaction more likely.

KEY POINT

- Characteristic findings of morbilliform drug reaction include erythematous papules coalescing into plaques, often with some pruritus, and no accompanying systemic symptoms.

Bibliography

Ferner RE. Adverse drug reactions in dermatology. Clin Exp Dermatol. 2015;40:105-9; quiz 109-10. [PMID: 25622648] doi:10.1111/ced.12572

Item 38 Answer: D

Educational Objective: Diagnose vitiligo.

The patient has vitiligo, an autoimmune disease that causes the loss of melanocytes and subsequent depigmentation of the skin. It usually presents in childhood or young adulthood with a peak onset between 10 and 30 years. The most commonly affected areas involve the extensor surfaces such as the dorsal hands, elbows, and knees, and the periorificial areas such as around the mouth, eyes, rectum, and genitals, and it is often bilaterally symmetrical. It appears as completely white, well-demarcated regular macules or patches with no scale. Its onset is insidious and asymptomatic, starting as smaller macules and gradually enlarging. Treatment is challenging and typically starts with topical glucocorticoids or immunomodulators. Vitiligo can be associated with other autoimmune conditions such as diabetes mellitus, alopecia areata, or Hashimoto thyroiditis.

Pityriasis alba is characterized by hypopigmented patches and is most often seen on the face and upper arms of dark-pigmented children. Lesions typically manifest some border irregularity and are associated with a fine scale. The cause is unknown and considered a mild eczematous process. The irregular borders and scale of pityriasis alba are not consistent with vitiligo.

Tinea versicolor is a superficial fungal infection caused by *Malassezia furfur* and is most common in warm, humid environments. It presents as hypopigmented, hyperpig-

mented, or pink patches that are dry and slightly scaly. Although the patches can occur anywhere, the neck, upper back, and chest, with extension to the abdomen or extremities, are commonly affected. These areas often become more noticeable after exposure to the sun because the organism prevents the skin from tanning. Scaly patches are not consistent with vitiligo.

Tuberous sclerosis is an inherited disorder with the classic triad of angiofibromas, mental deficiency, and epilepsy. Other associated features include ash-leaf hypomelanotic macules, periungual fibromas, collagenomas, and café-au-lait macules. Hypomelanotic macules range in number and are found in about 85% of tuberous sclerosis cases. They are present at birth or develop during childhood. The appearance of this patient's depigmented lesions at age 20 and absence of epilepsy and mental deficiency makes tuberous sclerosis an unlikely diagnosis.

KEY POINT

- Vitiligo is an autoimmune disease that causes the loss of melanocytes and subsequent depigmentation of the skin appearing as completely white, regular, well-demarcated macules or patches with no scale.

Bibliography

Alikhan A, Felsten LM, Daly M, Petronic-Rosic V. Vitiligo: a comprehensive overview Part I. Introduction, epidemiology, quality of life, diagnosis, differential diagnosis, associations, histopathology, etiology, and work-up. J Am Acad Dermatol. 2011;65:473-91. [PMID: 21839315] doi:10.1016/j.jaad.2010.11.061

Item 39 Answer: D

Educational Objective: Diagnose hidradenitis suppurativa.

This patient has hidradenitis suppurativa, a chronic inflammatory disease that predominantly affects the apocrine-gland-bearing areas of the skin. The common sites are the axillae, breasts and inframammary creases, inguinal folds, and gluteal cleft. It is recognized by its characteristic inflammatory abscesses, sinus tracts (with foul-smelling drainage), and scarring in intertriginous areas. The pathogenesis of hidradenitis begins with follicular occlusion but not infection or inflammation of the apocrine glands. Following occlusion, secretions build up in the follicular duct and result in rupture and a subsequent inflammatory reaction that resembles a bacterial abscess. Following this, an acute inflammatory reaction is triggered in the surrounding tissue. The role of bacteria is controversial and is likely a secondary colonization since lesions are initially sterile, and antibiotics are not entirely effective in preventing new lesions. Hidradenitis is associated with smoking, obesity, and metabolic syndrome. The chronic and recurrent nature of hidradenitis helps distinguish it from other infectious causes. Treatment is difficult. Clindamycin-rifampin combination antibiotics, infliximab, and surgical excision have the greatest evidence of effectiveness. It is important to recognize hidradenitis suppurativa early in order to initiate management to reduce scarring and progression of the disease.

Carbuncles can present as tender nodules with purulent drainage; however, these typically respond well to antibiotics and are not chronic in nature. Recurrent carbuncles or abscesses should raise suspicion for possible hidradenitis. Sinus tracts are not typically involved with carbuncles.

Chancroid is a sexually transmitted disease caused by *Haemophilus ducreyi*. It presents with one or more painful ulcerations, typically on the penis or labia. Inguinal lymphadenopathy may be present, but sinus tracts and inflammatory abscesses are not seen.

Epidermal inclusion cysts are benign nodules with a central punctum and a chamber containing keratinaceous material. When punctured, they often eject a copious amount of foul-smelling keratinaceous material. The cyst wall may occasionally rupture, leading to the formation of a tender red swollen nodule that resembles a furuncle. Epidermal inclusion cysts are typically solitary lesions with no sinus tract involvement and minimal scarring.

KEY POINT

- Hidradenitis suppurativa is characterized by inflammatory abscesses, sinus tracts, and scarring in intertriginous areas; it is associated with smoking, obesity, and the metabolic syndrome.

Bibliography

Micheletti RG. An update on the diagnosis and treatment of hidradenitis suppurativa. Cutis. 2015 Dec;96(6 Suppl):7-12. [PMID: 27051885]

Item 40 Answer: C

H

Educational Objective: Diagnose pyoderma gangrenosum.

This patient has pyoderma gangrenosum (PG). PG is an autoimmune neutrophilic dermatosis in which neutrophils invade and fill the dermis, leading to marked tissue edema and possible ulceration. PG may also present with bullous lesions, pustulonodules, and vegetative plaques. The typical history is a small pustule or red nodule that may develop after trauma and rapidly expands causing an edematous, infiltrated, actively inflamed border and a painful, exudative wet ulcer. Classically the border is described as violaceous or "gun-metal gray" and, because of the nature of the inflammation, the epidermis often overlies the ulcer, with a "hanging border" or residual thin anastomosing strands of epidermis remaining over the expanding ulcer. These lesions also display pathergy, a worsening/expansion of a lesion after trauma. Because of this characteristic, debridement should be avoided in these lesions.

Although pyoderma gangrenosum can be idiopathic, it is most commonly associated with inflammatory bowel disease (Crohn disease and ulcerative colitis). It is also associated with several other conditions including leukemia, myeloma, hepatitis C, and systemic lupus erythematosus. Management starts with investigating and treating the underlying

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cause. Depending on the severity of disease, treatment also includes application of potent topical glucocorticoids, systemic glucocorticoids, and immunosuppressive agents such as azathioprine, cyclosporine, and infliximab.

Acrodermatitis enteropathica (AE) is an inherited or acquired metabolic disorder characterized by perioral and acral (in the extremities) erythematous and vesiculobullous dermatitis and alopecia related to zinc deficiency. AE has been associated with Crohn disease, but not ulcerative colitis. This patient's ulcer is not consistent with AE.

Clinically, lesions of calciphylaxis are exquisitely painful subcutaneous nodules or plaques with overlying red-brown discoloration and often superimposed angulated purpuric patches, often with central necrosis. Patients with advanced calciphylaxis may have ulceration or large, thick, black eschar formation. Given this patient's lack of kidney disease, her history of inflammatory bowel disease, and the description of the ulceration, pyoderma gangrenosum is the most likely diagnosis.

Venous stasis ulcers tend to be associated with chronic venous insufficiency and arise on the medial aspects of the lower legs. They are typically shallow and lack the characteristic undermined borders of PG. This patient also did not have the background venous stasis changes such as edema, varicosities, and pigmentary changes seen in venous stasis ulcerations.

KEY POINT

- Pyoderma gangrenosum presents as a painful, exudative ulcer with a purulent base and ragged, edematous, violaceous, "overhanging" border; it may be idiopathic but it can be associated with an underlying disease.

Bibliography

Pompeo MQ. Pyoderma gangrenosum: recognition and management. Wounds. 2016 Jan;28(1):7-13. [PMID: 26779805]

Item 41 Answer: A

Educational Objective: Treat psoriasis with narrowband ultraviolet B (UVB) therapy.

Narrowband ultraviolet B (UVB) therapy has become the standard form of phototherapy used in the initial treatment of psoriasis. The light source emits a narrow band of UVB radiation, in this case 311 nm of ultraviolet light. This wavelength was chosen for its efficacy and the fact that this wavelength of light is not absorbed by DNA. The theory is that if the light is not absorbed by DNA, less skin damage will occur, and there will be far fewer skin cancers as a side effect of the therapy. Broadband UVB was the mainstay of therapy until the advent of narrowband UVB. Broadband is still used in some centers today. Broadband UVB emits light in the 280 to 320 nm range; 260 nm is the wavelength of light with the maximum absorption by DNA. DNA absorption of UVB drops off dramatically after 290 nm. Broadband UVB contains wavelengths of light capable of causing DNA damage, leading to ultraviolet skin damage and ultimately skin cancer.

Photodynamic therapy is not used for the treatment of psoriasis, but rather for the treatment of actinic keratoses. Aminolevulinic acid, a chemical precursor of the heme synthesis pathway, is applied to the skin before its exposure to visible blue light. Aminolevulinic acid is used as a photosensitizer and is absorbed by the actinically damaged skin cells; upon exposure to light it causes necrosis of the actinically damaged skin by producing reactive oxygen species. It can be extremely painful for patients to undergo photodynamic therapy.

Psoralen plus ultraviolet A (PUVA) therapy is now used almost exclusively for the treatment of cutaneous T-cell lymphoma. It is effective for treating psoriasis, but it has been shown to cause an increase in the risk of nonmelanoma and melanoma skin cancer. For these reasons, it is not used as first-line therapy for psoriasis.

Oral retinoid (acitretin) plus PUVA therapy, also called RePUVA, has been used in the past for treating psoriasis and cutaneous T-cell lymphoma. It is highly efficacious, but has the highest side effect profile of the various forms of phototherapy and is not used frequently today. Short-term complications of RePUVA include profound nausea in some and risk of treatment-related burns. Long-term complications include an 11-fold increase in cutaneous squamous cell carcinoma and slight increase in the risk for basal cell carcinoma, melanocytic atypia, and melanoma.

Ultraviolet A (UVA) alone is rarely used in the dermatology clinic. Morphea (localized scleroderma) has been shown to benefit from exposure to UVA phototherapy.

KEY POINT

- Narrowband ultraviolet B (UVB) is the standard form of phototherapy used in the treatment of extensive psoriasis.

Bibliography

Lim HW, Silpa-archa N, Amadi U, Menter A, Van Voorhees AS, Lebwohl M. Phototherapy in dermatology: A call for action [Editorial]. J Am Acad Dermatol. 2015;72:1078-80. [PMID: 25981004] doi:10.1016/j.jaad.2015.03.017

Item 42 Answer: D

H

Educational Objective: Diagnose cutaneous-only polyarteritis nodosa.

This patient has the cutaneous-only variant of polyarteritis nodosa (PAN). PAN is a medium-vessel vasculitis not associated with the development of ANCAs. The skin may be the only organ involved (cutaneous-only PAN) or it may be involved as part of a systemic disease. Biopsy of an affected organ will show medium-vessel vasculitis.

Patients with cutaneous-only PAN experience tender subcutaneous nodules from vascular inflammation, stellate erosions, or ulcerations from ischemia in the watershed of the affected vessels, and they may develop livedo reticularis or livedoid purpura. Cutaneous-only disease treatment is guided by symptoms and may include systemic antihistamines, colchicine, dapsone, or immunosuppressants such

H CONT.

as azathioprine. Symptoms of systemic PAN may include abdominal pain or gastrointestinal bleeding (if the mesenteric vessels are affected), hypertension (if the renal vessels are affected), neuropathy (typically mononeuritis multiplex), and constitutional symptoms. Biopsy of an affected organ will show a medium-vessel vasculitis. Although patients with systemic PAN are frequently found to have preceding chronic viral hepatitis, most patients with cutaneous-only PAN are not usually virally infected.

Granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA) are ANCA-associated small- and medium-vessel vasculitides. Skin findings can include palpable purpura; tender subcutaneous nodules; or necrosis of digits, nose, tongue, or genitals. Typical organ involvement includes the upper respiratory tract (including sinuses and ears), lungs, and kidney. GPA is associated with positive enzyme-linked immunosorbent assay (ELISA) for anti-proteinase 3 antibodies, and MPA is associated with anti-myeloperoxidase antibodies. Biopsy will usually show small-vessel involvement (not present in this case). Although a minority of patients with GPA and MPA may be ANCA-negative, the lack of any other characteristic systemic involvement in the ANCA-negative setting makes it extremely unlikely that this patient has an ANCA-associated vasculitis.

Leukocytoclastic vasculitis (LCV) is a finding, not a diagnosis. It manifests as palpable purpura (not present in this case) and is always secondary to another condition. Infections, autoimmune conditions such as systemic lupus erythematosus or rheumatoid arthritis, or medications may precipitate LCV. It lacks the tender nodules, stellate ulcerations, and livedoid skin changes of a medium-vessel vasculitis.

Takayasu arteritis is a large-vessel vasculitis that typically does not have skin findings; Takayasu arteritis should be suspected in patients under 40 years with unexplained systemic inflammation and/or signs and symptoms of large-vessel impairment.

KEY POINT

- Patients with cutaneous-only polyarteritis nodosa experience tender subcutaneous nodules from vascular inflammation, stellate erosions, or ulcerations from ischemia in the watershed of the affected vessels, and may develop livedo reticularis or livedoid purpura.

Bibliography

Alibaz-Oner F, Koster MJ, Crowson CS, Makol A, Ytterberg SR, Salvarani C, et al. The clinical spectrum of medium-sized vessel vasculitis. Arthritis Care Res (Hoboken). 2016. [PMID: 27564269] doi:10.1002/acr.23007

Item 43 Answer: B

Educational Objective: Evaluate erythema nodosum with chest radiography.

This patient needs a chest radiograph to complete the evaluation of her erythema nodosum (EN). EN is the most common form of panniculitis, or inflammation of the fat, with most inflammation concentrated on the intralobular septae. Because the inflammation is deep under the skin, the clinical manifestation seen on the surface is often tender, ill-defined erythema with some substance on palpation, which may fade from an active inflammatory red-pink to dull brown. Most commonly, EN occurs bilaterally and symmetrically on the anterior shins; however, it may also appear in any fatty area. Although lesions will often come and go, most resolve over 4 to 6 weeks. EN is a nonspecific reaction pattern occurring in response to some systemic process. EN can be idiopathic, but the most common associations are streptococcal infection, hormones (including oral contraceptives, hormone replacement therapy, or pregnancy), inflammatory bowel disease, sarcoidosis, lymphoma, and medication reactions. The diagnosis of EN can be clinically based on the acute onset of tender nodules on the bilateral shins typically in a young woman. Biopsy is not necessary in typical lesions.

Most authorities recommend a chest radiograph in the evaluation of EN to assess for the presence of lymphoma, sarcoidosis, tuberculosis, and fungal infection such as coccidioidomycosis.

In the absence of gastrointestinal symptoms, a colonoscopy for inflammatory bowel disease is unlikely to reveal a causative diagnosis. Patients with disseminated gonococcal infection and bacteremia manifest vesiculopustular or hemorrhagic macular skin lesions, not tender subcutaneous nodules as seen in this patient.

Patients with disseminated gonococcal infection present with dusky pustules or purpura, fever, chills, and polyarthralgia. Knees, elbows, and distal joints are typical sites of involvement. Subcutaneous nodules are not features of this infection

KEY POINT

- A chest radiograph is recommended in the evaluation of erythema nodosum to assess for the presence of lymphoma, sarcoidosis, tuberculosis, and fungal infection such as coccidioidomycosis.

Bibliography

Chowaniec M, Starba A, Wiland P. Erythema nodosum - review of the literature. Reumatologia. 2016;54:79-82. [PMID: 27407284] doi:10.5114/reum.2016.60217

Item 44 Answer: D

Educational Objective: Diagnose pitted keratolysis.

Pitted keratolysis is a bacterial infection most commonly caused by *Kytococcus sedentarius*. The key features are waxy or scaly plaques, thickening of the plantar skin (keratoderma), small punctate erosions in the plaques that may coalesce to form broader erosions, and odor. Risk factors for infection include excess sweating (hyperhidrosis) and prolonged occlusion of the feet in footwear. Usually symptoms are minimal, with most complaints directed toward odor, but minor itching can occur. Treatment is best accomplished with

topical antibiotics and keeping the feet dry, including the use of topical antiperspirants.

Aquagenic keratoderma presents with wrinkling, translucency, and scaling of the palmar hands and plantar feet shortly after exposure to water and is associated with carrier status of the cystic fibrosis gene. Aquagenic keratoderma does not feature pitting.

Erythrasma is also a bacterial infection that tends to involve intertriginous areas such as the axillae and the crural folds. Skin may develop a finely wrinkled, cigarette paper texture, but would not feature pitting. Erythrasma will fluoresce to a coral red color with a Wood lamp examination because of bacterial porphyrin production.

Keratoderma blenorrhagicum is a keratoderma of the palms or soles associated with reactive arthritis. With this rash, patients develop psoriasiform red plaques with lamellar scale. Patients may have other features of reactive arthritis such as asymmetric monoarthritis or oligoarthritis in the lower extremities, enthesopathy, dactylitis, and sacroiliitis.

Tinea pedis can cause scaling and itching of the feet. Patients typically develop pink or red scaly plaques with a serpiginous or arcuate discrete border. Scale is often emphasized at the edge of plaques. Pustules may be present at hair follicles, but pitting and strong odor are not typical. Potassium hydroxide preparation of skin scrapings should reveal fungal elements, except in partially treated cases.

KEY POINT

- Pitted keratolysis is a superficial bacterial infection characterized by small pits and punctate erosions primarily on the plantar aspects of the feet; risk factors include increased perspiration (hyperhidrosis) and prolonged occlusion of the feet.

Bibliography

Leung AK, Barankin B. Pitted Keratolysis. J Pediatr. 2015;167:1165. [PMID: 26316369] doi:10.1016/j.jpeds.2015.07.056

H

Item 45 Answer: A

Educational Objective: Treat venous stasis ulcers with compression therapy.

This patient has a venous stasis ulcer, and the most appropriate additional management is compression therapy. Venous stasis ulcers are the most common leg ulcers. Most patients have a history of stasis dermatitis and often have some level of scarring and dyspigmentation on the bilateral lower extremities. Venous stasis ulcers usually occur on the distal lower leg, particularly the medial aspect of the ankle, and may result from a minor trauma, a medical procedure, or an acute stasis dermatitis flare. The symptoms vary from negligible discomfort to significant pain. The ulcers tend to have an irregular border and surrounding hyperpigmentation, and the skin and subcutaneous tissues are thickened, resulting in lipodermatosclerosis (fibrosing panniculitis of the subcutaneous tissue). Patients often have varicose veins and peripheral edema. Treatment is directed toward three main areas: reducing the peripheral edema, creating a wound environment that is conducive to healing, and treating any secondary infection that may be present. Reduction of peripheral edema is achieved by the use of compression stockings, pneumatic compression boots, and compression dressings (Unna boots). Compression is the key to venous ulcer healing.

Oral cephalexin is a treatment for cellulitis and other skin infections. Clues to suggest active infection are rapidly expanding ulcer size, worsening pain, heat, swelling and increased surrounding erythema, and copious exudate; these findings are absent and indicate that oral antibiotics should not be used. Furthermore, the inappropriate use of antibiotics can result in the emergence of resistant organisms.

Oral cilostazol is used to increase peripheral blood flow for the treatment of intermittent claudication. It is sometimes used in the treatment of arterial insufficiency ulcers, but evidence supporting its effectiveness is sparse. Because this patient has a venous stasis ulcer, oral cilostazol would not be used.

The use of topically applied antiseptics, such as hydrogen peroxide, povidone iodine, acetic acid, and sodium hypochlorite, is not supported by evidence. Some animal studies have demonstrated that the cellular toxicities of these agents exceed their bactericidal activities. Therefore, topical antiseptics should not be used in the management of venous ulcers.

KEY POINT

- The mainstay of venous ulcer treatment consists of compression therapy.

Bibliography

Kirsner RS, Vivas AC. Lower extremity ulcers: diagnosis and management. Br J Dermatol. 2015 Aug;173(2):379-90. [PMID: 26257052]

H

Item 46 Answer: B

Educational Objective: Diagnose erythroderma following systemic glucocorticoid therapy.

Psoriasis vulgaris can flare to erythroderma following use of systemic glucocorticoids. The most common cause of erythroderma, or redness over 80% body surface area, is a preexisting condition. Peripheral edema, erosions from excoriations due to severe pruritus, and scaling are common findings. Owing to compromise of the skin barrier, affected patients are at risk for dehydration, electrolyte abnormalities, protein loss, heat loss, and infection, which can be fatal. Short courses of systemic glucocorticoids in a patient with psoriasis can result in a striking increase in skin disease upon abrupt cessation. The presence of lamellar scale that bleeds when peeled away (Auspitz sign) and nail pitting support the diagnosis of erythrodermic psoriasis.

Drug reaction with eosinophilia and systemic symptoms (DRESS) can also present with erythroderma. This represents a delayed response to a medication several weeks after initiation. Patients present with rash, striking facial edema, peripheral eosinophilia (or less common atypical

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lymphocytosis), lymphadenopathy, and evidence of organ involvement such as acute kidney injury or abnormal liver chemistry tests.

Sézary syndrome is an acute leukemic variant of cutaneous T-cell lymphoma. Patients often present with erythroderma, ectropion, and lymphadenopathy. The absence of a preceding history of cutaneous T-cell lymphoma makes this diagnosis unlikely.

Stevens-Johnson syndrome may cause erythroderma, but it manifests as epidermal necrosis with dusky plaques that slough rather than scale. Mucous membrane involvement is a keystone of diagnosis and is absent in this patient. Most cases of Stevens-Johnson syndrome are caused by a medication.

KEY POINT

- Psoriasis can flare to erythroderma following brief use of systemic glucocorticoids.

Bibliography

Mistry N, Gupta A, Alavi A, Sibbald RG. A review of the diagnosis and management of erythroderma (generalized red skin). Adv Skin Wound Care. 2015;28:228-36; quiz 237-8. [PMID: 25882661] doi:10.1097/01.ASW.0000463573.40637.73

Item 47 Answer: A

Educational Objective: Evaluate an annular, scaly patch with a potassium hydroxide examination.

The most appropriate diagnostic test to perform on this patient is the potassium hydroxide (KOH) examination. This patient's skin lesions are erythematous annular patches with noticeable surface scale. When confronted with an annular scaly patch, the most common diagnosis is tinea from a dermatophyte infection. Direct microscopic examination of KOH-prepared specimens is the simplest, cheapest method used for the diagnosis of dermatophyte infections of the skin. After scraping the leading edge of scale with a number 15 blade or the edge of the glass slide, apply 2 to 3 drops of KOH on the debris and then apply a coverslip. Evaluate the specimen initially with 10 power magnification. Tinea is confirmed by the presence of septated branching hyphae.

A scabies preparation is used when the patient has burrows. Burrows are pathognomonic for a scabies infection and are most frequently found along the wrists, fingers, and palms. To obtain the specimen, place a drop of mineral oil on the burrow and scrape the area with a number 15 blade. After placing the specimen on a glass slide, apply the cover slip, and examine with 10 power magnification to identify mites, eggs, and/or feces.

A Tzanck preparation should be performed on patients when the skin findings are concerning for a herpes virus infection. Grouped vesicles on an erythematous base or tender vesicles in a dermatomal distribution are both primary skin findings in which a Tzanck preparation can be performed. This is done by deroofing the blister and scraping the base of the blister. The scraping is smeared on a glass microscope slide and stained with an appropriate stain (Tzanck or Giemsa). The presence of multinucleated giant cells is diagnostic for herpes viral infections. This finding, however, cannot distinguish the responsible virus. Viral culture or direct immunofluorescence can be used to identify the specific virus, if needed.

A Wood lamp is an ultraviolet light source that can be used to evaluate hypo- and depigmentation lesions as seen in vitiligo. Vitiligo will appear bright white and sharply delineated when examined with a Wood light and is most helpful in fair-skinned persons where depigmentation may not otherwise be visible. A Wood lamp can also detect skin fluorescence associated with erythrasma and the urine fluorescence in patients with porphyria cutanea tarda.

KEY POINT

- Diagnosis of dermatophyte infection can be performed by examination of the scale with potassium hydroxide; the presence of branching hyphae is diagnostic.

Bibliography

Levitt JO, Levitt BH, Akhavan A, Yanofsky H. The sensitivity and specificity of potassium hydroxide smear and fungal culture relative to clinical assessment in the evaluation of tinea pedis: a pooled analysis. Dermatol Res Pract. 2010;2010:764843. [PMID: 20672004] doi:10.1155/2010/764843

Item 48 Answer: A

H

Educational Objective: Diagnose calciphylaxis.

This patient has calciphylaxis. Patients with calciphylaxis present with angulated, lacy, or netlike retiform purpuric patches with areas of central dusky or black necrotic tissue that may form bullae, ulcerate, and leave a hard eschar. For unknown reasons, calcium is deposited in the medial layer of small arteries, which leads to thrombus, infarction of the overlying skin, and significant pain. The thighs and lower abdomen have been reported as the most frequent areas of involvement. Calciphylaxis typically occurs in patients who have underlying end-stage kidney disease; however, only 1% to 2% of patients on dialysis will develop calciphylaxis. Persons with calciphylaxis will usually have a corrected calcium-phosphorus product greater than 60 to 70 mg^2/dL^2.

Therapy is difficult and multifactorial. It includes surgery to debride any areas of potential infection and parathyroidectomy in those patients with hyperparathyroidism. Medical therapies are dialysis, intravenous sodium thiosulfate, decreasing calcium intake, bisphosphonates, and meticulous wound care. Infection leading to sepsis is the leading cause of death. Prevention of infection is critically important.

Kyrle disease is most frequently seen in persons with diabetes and end-stage kidney disease. It can present with an individual papule or numerous widespread hyperpigmented papules. The papules have an umbilicated central core. Kyrle disease is caused by collagen extrusion from the dermis into and through the epidermis.

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Nephrogenic systemic fibrosis is characterized by yellowish, thickened papules and nodules with progressive skin tightening and sclerosis. If biopsied, the skin findings mimic those of scleromyxedema. This condition has been seen in patients undergoing dialysis for end-stage kidney disease who were exposed to gadolinium-containing contrast dyes.

Progressive systemic sclerosis presents similarly to nephrogenic systemic fibrosis. It is an autoimmune disease with cutaneous and systemic findings. The cutaneous findings are thickening of the skin, which results in lack of joint mobility, dilated periungual capillary loops, Raynaud phenomenon, digital ulcerations, and digital infarcts.

Ulcerations and eschar formation on the upper thighs do not occur in Kyrle disease, nephrogenic systemic sclerosis, or progressive systemic sclerosis.

KEY POINT

- Calciphylaxis lesions are intensely painful, angulated, retiform purpuric patches with areas of black necrotic tissue that may form bullae, ulcerate, and leave a hard, firm eschar in patients with end-stage kidney disease.

Bibliography

Nigwekar SU, Kroshinsky D, Nazarian RM, Goverman J, Malhotra R, Jackson VA, et al. Calciphylaxis: risk factors, diagnosis, and treatment. Am J Kidney Dis. 2015;66:133-46. [PMID: 25960299] doi:10.1053/j.ajkd.2015.01.034

H

Item 49 Answer: B

Educational Objective: Treat a cutaneous abscess.

This patient has an abscess with no systemic signs of infection, so the most appropriate treatment would be incision and drainage. Gram stain and culture of pus from carbuncles and abscesses are strongly recommended, but treatment without these studies is reasonable in typical cases. Treatment with antibiotics is not indicated unless there are systemic signs of infection including fever (38 °C [100.4 °F]), tachycardia (>90/min), tachypnea (>24/min), an abnormal leukocyte count (>12,000/µL or <400/µL), or immunocompromise. This patient does not present with any of these indications for antibiotic therapy. If antibiotic therapy is indicated, empiric treatment of purulent skin and soft tissue infection (furuncle, carbuncle, and abscess) should include an agent that is active against methicillin-resistant *Staphylococcus aureus* (MRSA), for example, trimethoprim-sulfamethoxazole or doxycycline.

Antibiotic therapy based on culture results is an inappropriate choice for this cutaneous abscess. Bacterial cultures should be obtained from the abscess, but treatment with incision and drainage should proceed before the culture results return. Antibiotics should be added to incision and drainage if there are systemic symptoms. If antibiotic therapy is indicated, it should be initiated empirically prior to obtaining culture results. The culture results can be used to modify the antibiotic selection if necessary.

Incision and drainage plus oral cephalexin should not be used for abscesses without systemic signs of infection. In addition, if antibiotic therapy were indicated, cephalexin lacks MRSA activity and would be an inappropriate antibiotic selection for an abscess.

Oral trimethoprim-sulfamethoxazole would be an appropriate choice for an abscess if antibiotic therapy were indicated. Because this patient's skin and soft tissue infection is categorized as mild (no systemic signs or symptoms), antibiotic therapy is not indicated.

KEY POINT

- Primary treatment for abscess with no systemic signs of infection is incision and drainage; antibiotics should be added only if systemic symptoms or signs are present.

Bibliography

Stevens DL, Bisno AL, Chambers HF, Dellinger EP, et al. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the Infectious Diseases Society of America. Clin Infect Dis. 2014 Jul 15;59(2):e10-52. [PMID: 24973422]

Item 50 Answer: C

Educational Objective: Diagnose halo nevus.

This patient has a halo nevus. Halo nevi are benign melanocytic nevi that are in the process of being attacked and eliminated by the immune system. They are characterized by a pigmented macule or papule with a surrounding "halo" of hypopigmented or depigmented skin. The halo gradually enlarges, and the mole shrinks until all that is left is a depigmented area on the skin that resembles a small area of vitiligo. These lesions are particularly common on the back in children, teenagers, and young adults.

Melanocytic nevi are benign neoplasms comprising melanocytes, commonly referred to as "moles." They vary in clinical appearance depending on the location of melanocytes within the skin. Junctional nevi are flat and often dark brown in color. Compound nevi are raised (papules) and may be irregularly pigmented. Dermal nevi are soft and flesh colored and may resemble skin tags. The terms "junctional," "compound," and "dermal" refer to the location of the melanocytic nests: junctional nevi have nests located at the dermal-epidermal junction, compound nevi have nests at the dermal-epidermal junction and in the dermis, and dermal nevi have nests in the dermis. Nevi undergo a benign maturation process from junctional to compound to dermal over a period of many years.

Dysplastic nevi can display one or more of the identifying characteristics of melanoma, making an accurate clinical diagnosis difficult; however, a biopsy of the lesion can typically exclude melanoma. They are often asymmetric, irregularly bordered, and more than one shade of brown, and they may be quite large in diameter. Many dysplastic nevi have a dark brown center and a surrounding ring of light brown, a pattern that is often referred to as a "fried egg"

appearance. Patients with multiple dysplastic nevi are at risk for developing melanoma and should be monitored closely. Melanoma can arise within any melanocytic nevi including dysplastic nevi; therefore, biopsy should be limited to clinically worrisome or changing lesions.

Malignant melanoma presents as macules, papules, or plaques typically larger than 6 mm in diameter and shows asymmetry and irregular boarders, as well as color variation within the lesion. The surrounding skin can show erythema or hypopigmentation.

KEY POINT

- Halo nevi are benign pigmented macules or papules with a surrounding "halo" of hypopigmented or depigmented skin, most frequently presenting on the back of teenagers and young adults.

Bibliography

Weyant GW, Chung CG, Helm KF. Halo nevus: review of the literature and clinicopathologic findings [Letter]. Int J Dermatol. 2015;54:e433-5. [PMID: 26146814] doi:10.1111/ijd.12843

Item 51 Answer: C

Educational Objective: Diagnose inverse psoriasis.

Based on the finding of the well-demarcated, erythematous plaques in intertriginous areas, this patient has inverse psoriasis. Psoriasis is a chronic inflammatory dermatosis that manifests with scaling, variably pruritic plaques that may be recalcitrant to topical therapy. There are many different patterns of psoriasis including classic psoriasis vulgaris (erythematous patches with a thick, adherent scale), inverse psoriasis (red, thin plaques with variable amount of scale in the axillae, under the breasts or pannus, intergluteal cleft, and perineum), sebopsoriasis (red, thin plaques in the scalp, eyebrows, nasolabial folds, central chest, and pubic area), and guttate psoriasis (0.5- to 2-cm red plaques that erupt suddenly on the trunk often after a group A streptococcal infection). Psoriasis can also involve the nails presenting as pit-like indentations and "oil spots" often involving multiple nails. Inverse psoriasis can be difficult to diagnosis because it often lacks the classic silvery scale. It also resembles other common dermatologic conditions such as tinea, intertrigo, and allergic contact dermatitis.

Allergic contact dermatitis, while possible in these locations, would be less likely without history of exposure to an allergen. Allergic contact dermatitis does not explain the patient's erythematous plaques with scale on the scalp.

Candida is frequently found in the flexures of obese patients, but typically presents with a bright red plaque with satellite papules and pustules. *Candida* would also respond to topical antifungal treatment.

Seborrheic dermatitis can be found in the scalp, face, chest, and groin. It is more prevalent in those with HIV/AIDS or neurologic diseases such as Parkinson disease. This rash usually has a greasy, sometimes yellow scale and improves with antifungal medications.

Tinea cruris is also commonly found in the inguinal folds. It typically presents as an annular plaque with an active, scaly border. The lack of scale and lack of response to antifungal therapy makes tinea cruris an unlikely diagnosis.

KEY POINT

- Inverse psoriasis is characterized by red, thin plaques with variable amounts of scale in the axillae, intergluteal cleft, and perineum, and under the breasts and pannus.

Bibliography

Omland SH, Gniadecki R. Psoriasis inversa: A separate identity or a variant of psoriasis vulgaris? Clin Dermatol. 2015 Jul-Aug;33(4):456-61. [PMID: 26051061]

Item 52 Answer: B

Educational Objective: Treat dermatitis herpetiformis.

This patient has dermatitis herpetiformis (DH), and the most appropriate treatment is a gluten-free diet and dapsone. DH is a subepidermal autoimmune bullous disorder that is extremely pruritic. There are small tense vesicles and papules, which are rarely intact, so the usual presentation is excoriations on the elbows, knees, and buttocks. The diagnosis can be confirmed with skin biopsy for routine and direct immunofluorescence testing. Deposition of granular IgA in the dermal papillary tips is pathognomonic of dermatitis herpetiformis. While dapsone is effective in inducing a clinical remission of DH, a gluten-free diet is the preferred long-term therapy. DH has a strong association with celiac disease. Dapsone will successfully treat the skin symptoms of dermatitis herpetiformis, but does not treat the associated gastrointestinal disease. A gluten-free diet treats both the cause and the symptoms of both diseases. In patients with celiac disease, failure to maintain a gluten-free diet increases the risk for small bowel lymphoma. Prior to initiating therapy with dapsone, patients should be checked for glucose-6-phosphate dehydrogenase deficiency because these patients have a high risk of hemolysis on dapsone therapy.

Potent topical glucocorticoids, such as betamethasone valerate, may help alleviate pruritus associated with DH but are not adequate monotherapy and should always be used in combination with dapsone and a gluten-free diet. Long-term side effects of topical glucocorticoids include cutaneous atrophy, striae, and hypopigmentation.

Numerous oral antihistamines are available for the treatment of pruritus, and anecdotal experience suggests that the more sedating antihistamines such as diphenhydramine may have a better antipruritic effect than the less-sedating products. However, DH is not a histamine-mediated disease, and the use of antihistamines for this condition is not very effective and may result in intolerable sedation in some patients.

In addition to the significant complications associated with the long-term use of prednisone, it is not effective in inducing or maintaining clinical remission in patients with DH and should not be used.

For patients who cannot tolerate dapsone, other sulfonamide drugs are a potential treatment option for DH. Case reports suggest that sulfasalazine is effective. While sulfasalazine does not cause hemolysis, there is an increased risk for agranulocytosis and hypersensitivity reactions. As with dapsone, periodic laboratory monitoring for significant side effects is recommended.

KEY POINT

- Dapsone should be used in conjunction with a gluten-free diet as first-line treatment of dermatitis herpetiformis.

Bibliography

Jakes AD, Bradley S, Donlevy L. Dermatitis herpetiformis. BMJ. 2014;348:g2557. [PMID: 24740905] doi:10.1136/bmj.g2557

H

Item 53 Answer: A

Educational Objective: Manage contact dermatitis in the setting of stasis dermatitis.

The most appropriate initial management is to discontinue application of the neomycin/polymyxin B/bacitracin ointment. This patient has contact dermatitis from the topical antibiotic in the setting of chronic stasis dermatitis with venous stasis ulcerations. Neomycin and bacitracin are usually the causative agents. Topical antibiotics applied to venous stasis ulcers commonly lead to the development of allergic contact dermatitis. This often presents with worsening erythema and weeping of the lower extremities. It is often mistaken for cellulitis.

Intravenous vancomycin is an antibiotic used for the treatment of severe skin infections. It is often combined with surgical debridement to treat hospitalized patients with complicated skin and soft tissue infection defined as deeper soft tissue infections, surgical/traumatic wound infection, major abscesses, cellulitis, and infected ulcers and burns. This patient does not have a complicated skin infection, and intravenous vancomycin is not needed.

Mild cellulitis (no focus of purulence or systemic symptoms) can be treated with oral clindamycin, penicillin, dicloxacillin, or a cephalosporin. In this patient, the cause of the worsening erythema is most likely contact dermatitis and not infection, and discontinuation of the topical antibiotic is the best management before initiation of any antimicrobial therapy.

Oral terbinafine is the treatment for fungal infections such as tinea capitis or onychomycosis. There is reason to suspect a fungal infection in this patient.

Topical triamcinolone ointment is a glucocorticoid preparation commonly used in the treatment of stasis dermatitis and for allergic contact dermatitis; however, the best initial management in allergic contact dermatitis is removal of the offending agent. Adding a topical glucocorticoid without stopping the contact allergen is unlikely to result in clinical improvement. A topical glucocorticoid is often used as an adjunctive therapy after stopping the topical antibiotic.

KEY POINT

- Neomycin and bacitracin can cause allergic contact dermatitis that mimics a wound infection; the most appropriate initial management is to discontinue its use.

Bibliography

Spring SI, Pratt M, Chaplin A. Contact dermatitis to topical medicaments: a retrospective chart review from the Ottawa Hospital Patch Test Clinic. Dermatitis. 2012 Sep-Oct;23(5):210-3. [PMID: 23010827]

Item 54 Answer: D

Educational Objective: Treat hand dermatitis.

This patient has hand dermatitis likely caused by an irritant contact dermatitis from frequent water exposure, and the most appropriate management would be to minimize hand washing and to apply thick emollients such as petrolatum to repair the skin barrier. Hand dermatitis is characterized by inflamed, scaling, and sometimes fissured skin on the palmar or dorsal hand. The most common causes are over washing, allergic or irritant contact dermatitis, atopic dermatitis, dyshidrotic eczema (pompholyx), and tinea. Repeated or extended washing with soap causes hand dermatitis by friction, removal of the protective skin barrier, and irritation from the surfactant properties of the soap. People who are required to repeatedly wash their hands (such as medical professionals) or those who wash repeatedly because of obsessive-compulsive or autism spectrum disorders often have extremely pronounced hand dermatitis. This type of irritant dermatitis will be especially marked on the dorsal hands where the stratum corneum is thinner than that of the palms. For irritant hand dermatitis due to over-washing, avoiding the irritant by washing less and moisturizing more can prevent development of a rash. Topical petrolatum jelly is an inexpensive and effective way of repairing the damaged skin barrier. A topical glucocorticoid may be necessary for a short period while the triggers are identified or if the skin is very inflamed.

Epicutaneous patch testing can be used to help determine causes of hand dermatitis due to allergic contact dermatitis. In this patient, the most likely cause is hand dermatitis from frequent hand washing, so patch testing would not be the most appropriate management. It could be considered if there was no improvement after minimizing hand washing and the application of emollients.

Oral fluconazole is a treatment for fungal infections such as candidiasis. It can be effective in cases of tinea manuum. "Two feet, one hand" tinea is a common presentation of concomitant tinea pedis and tinea manuum. In this patient, the potassium hydroxide was negative and her feet were clear, so treatment with antifungal therapy would be inappropriate.

Oral prednisone can improve acute flares of hand dermatitis but often results in relapses of chronic hand dermatitis. Because there are also significant side effects of oral

prednisone, it would not be the most appropriate initial treatment for this patient.

KEY POINT

- Treatment of hand dermatitis includes topical emollients such as petrolatum to repair the skin barrier; hand washing should be minimized.

Bibliography

Perry AD, Trafeli JP. Hand Dermatitis: A review of etiology, diagnosis, and treatment. J Am Board Fam Med. 2009 May Jun;22(3): 325 30. [PMID: 19429739]

Item 55 Answer: D

Educational Objective: Treat comedonal acne.

This patient has comedonal acne and should be treated with a topical retinoid. Treatment begins by considering the types and distribution of lesions, as well as the pregnancy status of the female patient. Interventions are selected with the goal of modifying the main causal factors, such as follicular occlusion, sebum production, *Propionibacterium acnes* proliferation, and inflammation. Comedonal acne consists of open and closed comedones (blackheads and whiteheads, respectively) with no inflammatory papules or pustules. First-line treatment for most patients with comedonal acne is topical retinoid. Topical retinoids are the only choice that is comedolytic and normalizes keratinization of the hair follicle. Topical retinoids are also effective in treating inflammatory acne. Because retinoids are preventive, they need to be applied to the entire acne-prone area and not used as a spot treatment. The most common adverse effects are dryness and irritation.

Isotretinoin is an oral retinoid used to treat severe nodulocystic acne with scarring or when other traditional therapies have failed. This patient does not have evidence of scarring or cystic lesions and has not previously failed any other prescription therapies. Isotretinoin is teratogenic, and use requires that providers, patients, and pharmacies must be registered in the iPLEDGE program, an FDA-approved regulatory program to prevent birth defects, and complete monthly reports. Patients must use two forms of birth control in order to be eligible for isotretinoin therapy.

Oral contraceptive pills are more effective in inflammatory and adult acne, which is characterized by inflammatory papules and cystic lesions along the jawline. Oral contraceptive pills have been shown to reduce comedones, but are not as effective as topical retinoids for comedonal acne.

Topical antibiotics are important in inflammatory acne when pustules and inflammatory papules are present. They work to inhibit *P. acnes* and decrease inflammation. They are not comedolytic and would not be effective in treating comedonal acne. Owing to the increased incidence of antibiotic resistance, topical antibiotics should not be used as monotherapy. Benzoyl peroxide is available over the counter and is an excellent complement to treatment with an oral or topical antibiotic, as it reduces the development of bacterial resistance.

KEY POINT

- Topical retinoids are first-line treatment for comedonal acne because they are comedolytic and normalize keratinization of the hair follicle.

Bibliography

Zaenglein AL, Pathy AL, Schlosser BJ, et al. Guidelines of care for the management of acne vulgaris. J Am Acad Dermatol. 2016 May;74(5):945-973. e33. [PMID: 26897386]

Item 56 Answer: A

Educational Objective: Treat postscabetic pruritus.

This patient has postscabetic pruritus, which follows an infestation caused by the ectoparasite *Sarcoptes scabiei* resulting in intense pruritus. Treatment of the patient and close contacts is required to eliminate the original infestation. Topical application of permethrin 5% cream is a first-line therapy. The cream is applied overnight to the entire body surface from neck to toes, including genitals and under fingernails. The lotion is removed by showering or bathing 8 to 14 hours following application. Repeat treatment in 7 to 10 days is usually recommended. Clothing, linens, and anything that has had contact with skin within the preceding 1 to 2 weeks must be thoroughly washed. Itching can persist for several weeks following treatment, and this alone does not constitute a treatment failure; however, treatment failure or reinfestation should be considered if new lesions continue to develop. The persistence of pruritus in the absence of reinfection or treatment failure, termed "postscabetic pruritus" can be treated with antihistamines, topical glucocorticoids, and, if severe, oral glucocorticoids can be used.

Two doses of oral ivermectin separated by 7 to 10 days appears to be as effective as permethrin but is contraindicated in pregnant and breastfeeding women. Safety in children has not been established. Ivermectin is often reserved for patients that are intolerant of other therapies, for treatment failures, and when topical application of permethrin is impractical such as outbreaks in nursing homes. Crusted scabies, a complication usually seen in patients with HIV or other immunodeficiencies, should be treated with both 5% permethrin and oral ivermectin.

Lindane 1% lotion has been associated with neurotoxicity and is typically reserved as third-line therapy in patients who cannot intolerant of other therapies or for treatment failures.

KEY POINT

- Itching can persist for several weeks following treatment of scabies and does not constitute a treatment failure; persistent itching can be treated with antihistamines, topical glucocorticoids, and, if severe, oral glucocorticoids.

Bibliography

Rosamilia LL. Scabies. Semin Cutan Med Surg. 2014;33:106-9. [PMID: 25577847]

Item 57 Answer: C

Educational Objective: Diagnose ocular rosacea.

The most likely diagnosis is ocular rosacea. This patient presents with the facial erythema, telangiectasias, and papulopustules that are characteristic of rosacea. Rosacea is a common chronic condition of the facial skin characterized by pink papules, pustules, erythema, and telangiectasias. It is typically found in a bilaterally symmetric distribution on the convexities of the face, namely the forehead, cheeks, nose, and chin. Both acne and rosacea have inflammatory papules and pustules, but comedones are not seen in rosacea. Ocular rosacea is seen in more than 50% of patients with cutaneous rosacea. Symptoms are burning or a foreign body sensation in the eye. Blepharitis, chalazia, and chronic eye infections can develop. This patient has anterior blepharitis, which is characterized by anterior lid margin edema and hyperemia and accumulated squamous debris around the lash bases. Eyelid thickening and loss of eyelashes can be seen in chronic cases. An ophthalmology consultation is recommended, and treatments include topical ophthalmic cyclosporine, topical erythromycin, or systemic tetracyclines.

Anterior scleritis is inflammation of the superficial sclera and deep vessels of the episclera. It is often associated with systemic inflammatory disorders. Patients may present with severe ocular pain, photophobia, tearing, and vision changes. On examination, the sclera may have a blue or violet coloration and be tender to palpation.

Episcleritis is an abrupt localized inflammation of the superficial vessels of the episclera. The cause is often unclear, but occasional association with rheumatic diseases is noted. Patients with episcleritis frequently present without pain or decreased visual acuity. On examination, the inflammation appears more localized than with conjunctivitis, which is typically diffuse.

Viral conjunctivitis, typically caused by an adenovirus, is often acute, unilateral, and associated with antecedent upper respiratory tract infection and exposure to infected persons. Symptoms are itching, foreign body sensation, and crusting of the eyelids following sleep. Viral conjunctivitis typically resolves in 3 to 7 days. Viral conjunctivitis does not typically cause blepharitis.

Anterior episcleritis, scleritis, or viral conjunctivitis is not associated with rosacea.

KEY POINT

- Ocular rosacea is characterized by burning, itching, dryness, or a foreign body sensation; blepharitis, chalazia, and chronic eye infections can develop.

Bibliography

Webster G, Schaller M. Ocular rosacea: a dermatologic perspective. J Am Acad Dermatol. 2013 Dec;69(6 Suppl 1):S42-3. [PMID: 24229636]

Item 58 Answer: A

Educational Objective: Diagnose erythema nodosum.

This patient has erythema nodosum, a form of panniculitis that affects women more frequently than men. Patients present with tender pink-to-red nodules on their lower extremities, most frequently the anterior lower legs. Erythema nodosum has been associated with many different medical conditions, medications, and hormones, including pregnancy, oral contraceptive pills, and hormone replacement therapy. All women of childbearing age who present with erythema nodosum should be evaluated for pregnancy. Those taking oral contraceptive pills should discontinue use.

Other associations have been reported in persons with erythema nodosum, including tubercular, streptococcal, HIV, fungal infections (coccidioidomycosis), sarcoidosis, and inflammatory bowel disease. A thorough history, physical examination, and targeted testing should be done.

Most cases of erythema nodosum are self-limited and will resolve within 6 to 9 months. Patients benefit from compression stockings, NSAIDs, rest, and elevation. A saturated solution of potassium iodide has been used successfully, as has prednisone, dapsone, and colchicine.

Granuloma annulare is a chronic dermatosis of unknown cause consisting of erythematous annular nonscaling plaques usually on the dorsal hands, feet, elbows, and knees. Generalized granuloma annulare is associated with diabetes mellitus. Usually asymptomatic, this dermatosis will resolve spontaneously after several months to years.

Lipodermatosclerosis is a fibrosing panniculitis of the subcutaneous tissue associated with chronic venous insufficiency. Characteristic findings include a woody induration of the subcutaneous tissues in association with findings of chronic venous stasis including varicosities, edema, ulcerations, and brown discoloration of the skin.

Necrobiosis lipoidica presents as atrophic, orange-colored patches often associated with visible vasculature from skin thinning; the lesions may ulcerate. Necrobiosis lipoidica may develop in patients with diabetes mellitus, and when present may be a sign of end-organ damage, as such patients are more likely to have retinopathy or nephropathy.

Pyoderma gangrenosum is an uncommon inflammatory process that typically occurs on the pretibial aspects of the lower legs and is often associated with an underlying systemic disease, such as inflammatory bowel disease. The ulcers are very deep and painful, with a dusky or violet-colored undermined border.

KEY POINT

- Erythema nodosum, a form of panniculitis, is often triggered by hormones, including oral contraceptives, hormone replacement therapy, and pregnancy, as well as certain infections and other inflammatory diseases.

Bibliography

Acosta KA, Haver MC, Kelly B. Etiology and therapeutic management of erythema nodosum during pregnancy: an update. Am J Clin Dermatol. 2013;14:215-22. [PMID: 23625180] doi:10.1007/s40257-013-0024-x

Item 59 Answer: D

Educational Objective: Treat arterial insufficiency ulcers.

This patient has an arterial insufficiency ulcer characterized by a well-demarcated painful ulcer with a dry wound bed; surgical revascularization will improve lower extremity circulation and facilitate wound healing. Arterial ulcers are most commonly found on the tips of and between the digits, but they can also form at sites of increased pressure, such as the lateral malleolus and metatarsal heads, or at sites of previous trauma. Arterial ulcers tend to be painful; discomfort may increase with elevation of the legs, compression, or any other maneuver that further limits circulation. Unlike venous stasis ulcers, which often have somewhat irregular borders and a significant amount of surrounding post-inflammatory hyperpigmentation, arterial insufficiency ulcers have a "punched out" appearance with surrounding erythema. The extremities as a whole often appear pale, and the skin is thin, taut, and shiny, and lacks hair. Pedal pulses are often difficult to appreciate; the toes are cold, and capillary refill is poor. If arterial insufficiency is suspected, diagnosis can be confirmed by measuring the ankle-brachial index (ABI). An ABI less than 0.9 is indicative of peripheral artery disease. Basic care of arterial ulcers includes debridement of necrotic tissue and proper dressings, but the most beneficial treatment is restoration of adequate circulation to the extremity. Surgical revascularization, percutaneous angioplasty, or stent placement are all options to restore blood flow to the affected area.

Compression stockings are a preferred treatment for venous stasis ulcerations. They should not be applied to a patient with arterial insufficiency ulcerations because of the risk of further ischemia.

Oral cilostazol is a phosphodiesterase inhibitor with antiplatelet activity and vasodilatory properties. When combined with a structured exercise program, cilostazol can improve maximum and pain-free treadmill-walking distance and quality-of-life measures in patients with peripheral artery disease. There is limited evidence of its benefit in arterial insufficiency ulcers.

Skin grafting is a procedure often used for the treatment of recalcitrant venous ulcers that fail to respond to compression and usual wound care. Revascularization, not skin grafting, is the primary treatment of arterial ulcers.

KEY POINT

- In patients with arterial insufficiency ulcers, surgical revascularization to improve the lower extremity circulation is often necessary to facilitate wound healing.

Bibliography

Kirsner RS, Vivas AC. Lower-extremity ulcers: diagnosis and management. Br J Dermatol. 2015 Aug;173(2):379-90. [PMID: 26257052]

Item 60 Answer: E

Educational Objective: Diagnose porphyria cutanea tarda.

This patient has porphyria cutanea tarda (PCT). Skin findings seen early in the disease include fragile skin with vesicles and bulla associated with milia (tiny proteinaceous cysts) formation on sun-exposed skin, particularly on the dorsal hands. PCT is caused by an accumulation of photosensitive porphyrins within the bloodstream and tissue. These photosensitizers enter the skin and upon exposure to ultraviolet A light in the 400- to 410-nm range cause damage to the skin. Later in the course of the disease, patients may develop hypo- or hyperpigmentation and hypertrichosis of the face. In some patients, scarring may result in thickening and calcification of the skin. Persons diagnosed with PCT should be evaluated for underlying liver disease, especially hepatitis C and hemochromatosis. Therapy is usually focused on avoiding sun exposure and decreasing the iron overload with phlebotomy, as well as treating the underlying cause of liver disease. Susceptibility factors that can exacerbate PCT to be avoided include alcohol use, smoking, and estrogens. The diagnosis can be made by finding elevated levels of porphyrins in the urine. A 24-hour urine evaluation will show elevated levels of uroporphyrin and coproporphyrin.

Bullous pemphigoid is the most frequent cause of autoimmune blistering disease. Patients will have pruritic urticarial red plaques that eventually develop large bullae. These blisters are subepidermal in nature, and milia may occasionally be seen. The blisters occur most frequently on the trunk and can be quite large and tense.

Bullous tinea is typically unilateral and associated with an annular scaly patch or patches. A potassium hydroxide examination will reveal fungal hyphae. The blisters are intraepidermal in nature, and milia will not be seen.

Dermatitis herpetiformis presents with tiny fragile vesicles or small erosions on the elbows, knees, or scalp. Itching is pronounced, and the condition is worsened by consumption of food containing gluten. Involvement of the dorsal hands would be an unusual clinical finding.

Persons with pemphigus vulgaris develop fragile vesicles and bulla without milia formation. The oral mucosa is frequently involved and is often the site of first involvement.

Patients with bullous pemphigoid, pemphigus vulgaris, and dermatitis herpetiformis do not develop hypertrichosis.

KEY POINT

- Porphyria cutanea tarda presents with skin fragility and small, transient, easily ruptured vesicles in sun-exposed areas, mainly on the hands; these eventually rupture, forming erosions, dyspigmentation, and scarring.

Bibliography

Balwani M, Desnick RJ. The porphyrias: advances in diagnosis and treatment. Blood. 2012;120:4496-504. [PMID: 22791288] doi:10.1182/blood-2012-05-423186

H

Item 61 Answer: A

Educational Objective: Diagnose melanoma during pregnancy.

The patient has a changing mole that is very suspicious for melanoma on her left leg. It needs to be biopsied promptly as not to delay the diagnosis of melanoma. The skin biopsy is an important part of the diagnostic work-up for melanoma. Ideally, an atypical pigmented lesion should be removed using an excisional biopsy, in which the entire lesion is removed. Since this is not always practical or possible, additional options are sometimes used. These include punch biopsy, in which a sample of the lesion is removed using a cylindrical blade and sent for analysis. Although this type of biopsy generally provides a sample of adequate depth, there is concern about sampling error given that the area removed may not necessarily be representative of the remainder of the lesion. Similarly, although shave biopsies are often readily available and easy to perform, this technique carries the risk of transecting the melanoma if a deep enough sample is not taken. This would result in an underestimate of the true depth of the lesion, which could have implications regarding further work-up and management.

There is no reason to delay the biopsy in a suspicious melanocytic lesion during pregnancy. Lidocaine is classified by the FDA as pregnancy category B and can be safely used as local anesthesia during pregnancy. It is controversial to use epinephrine as it is FDA classified as category C. Although no adverse events have been documented in humans, in vitro studies of human uterine arteries have shown that in high doses, epinephrine can cause spasms and reduce flow through the uterine artery. Obtaining a biopsy from a changing mole in a pregnant woman should be done promptly as not to delay the diagnosis of melanoma.

It is not appropriate to treat a highly suspicious lesion with cryotherapy. The depth of invasion (Breslow depth) of a melanoma is the most important prognostic feature and correlates most strongly with the risk of recurrence and metastasis. Destruction of a pigmented lesion removes the possibility of making a proper diagnosis and prognosis for a potential melanoma.

Providing reassurance and thereby delaying diagnosis of melanoma could result in poor prognosis for the mother and child. Malignant melanoma is the most common malignancy during pregnancy. Studies show that changes in size in nevi during pregnancy occur on the front of the body owing to the stretching of the skin as the pregnancy progresses. Nevi on other locations, such as the leg, typically do not change during pregnancy, and this development is a red flag for possible melanoma.

KEY POINT

- A suspicious melanocytic lesion should be biopsied promptly during pregnancy because dermatologic surgery under local anesthesia is safe during pregnancy; a diagnosis of melanoma should not be delayed.

Bibliography

Bieber AK, Martires KJ, Driscoll MS, Grant-Kels JM, Pomeranz MK, Stein JA. Nevi and pregnancy. J Am Acad Dermatol. 2016;75:661-6. [PMID: 27646736] doi:10.1016/j.jaad.2016.01.060

H

Item 62 Answer: C

Educational Objective: Treat pyoderma gangrenosum.

This patient has pyoderma gangrenosum, and a glucocorticoid, such as prednisone, is the preferred initial treatment. Typically required in doses of 1 mg/kg, prednisone is often effective in controlling pyoderma. To protect from long-term side effects of prolonged glucocorticoid use, steroid-sparing agents, immunosuppressants, intralesional glucocorticoids, or high-potency topical glucocorticoids are frequently used. Pyoderma gangrenosum is commonly associated with inflammatory bowel disease, hematologic abnormalities, and malignancies. The disease predominately affects the lower legs, but can be seen at any location. The beginning sign is often a tender pustule or red papule or nodule. This will quickly erode into an ulcer. Classic cases will have a rolled purplish border and undermined edges. As the ulcer resolves, it tends to heal with atrophic scarring in a cross-like or cribriform pattern. The ulcer is extremely painful. The diagnosis is one of exclusion, and other causes of ulceration need to be ruled out. Skin biopsies are not diagnostic. Surface cultures will grow myriad bacteria, which are most likely colonizing the ulcer and not causative.

Compression can be used in patients with extensive edema, but it is not a mainstay of therapy. Compression is often not tolerated because of pain. Good wound care with nonadherent dressings is important. Avoiding tape on the skin is necessary to prevent pathergy, the occurrence of lesions at sites of trauma, from the skin tape.

Dapsone has been used with some success, likely because of its anti-neutrophil effects, but it is not used as first-line treatment of pyoderma.

Pyoderma gangrenosum often occurs in the site of trauma (pathergy). For this reason, surgical debridement should be avoided unless a life-threatening infection is suspected. One exception is peristomal pyoderma gangrenosum. Surgical reanastomosis and closure of the ostomy site often results in healing of peristomal pyoderma. Relocating the stoma to another skin site will often result in resolution of the original peristomal ulcer; however, pyoderma will likely develop at the new ostomy site.

Potent topical glucocorticoids have been used for small lesions, but topical hydrocortisone is of no benefit as it is a low-potency glucocorticoid. Patients with underlying disease (inflammatory bowel disease, hematologic malignancy,

H CONT

rheumatoid disease) often improve with therapy that is directed at the underlying disease. Active pyoderma in persons with underlying disease often means that the underlying disease is not adequately controlled.

KEY POINT

- Prednisone is the preferred initial treatment for pyoderma gangrenosum.

Bibliography

Herberger K, Dissemond J, Hohaus K, Schaller J, Anastasiadou Z, Augustin M. Treatment of pyoderma gangrenosum: retrospective multicentre analysis of 121 patients [Letter]. Br J Dermatol. 2016;175:1070-1072. [PMID: 27060666] doi:10.1111/bjd.14619

Item 63 Answer: D

Educational Objective: Treat severe allergic contact dermatitis.

This patient has severe contact dermatitis from poison ivy (*Toxicodendron* genus), and the most appropriate treatment is a 21-day taper of oral prednisone. There are two types of contact dermatitis: allergic and irritant. Allergic contact dermatitis is a type IV delayed hypersensitivity reaction. With repeated exposure, a pruritic eczematous dermatitis develops on the exposed area. In exuberant cases, the localized inflammation can lead to a secondary "id" reaction, a generalized acute cutaneous reaction in which pinpoint flesh-colored to red papules develop diffusely on the body. Irritant contact dermatitis is caused by a direct toxic effect on the epidermis from exposure to a chemical such as a cleaning agent, other caustic substances, or repeated wetting and drying, and it is not mediated by the immune system. Urushiol is an allergen in the *Toxicodendron* genus of plants. Examples of these plants include poison ivy, poison oak, and poison sumac. Typically this rash presents with geometric lines or splatters of red papules and vesicles, with surrounding erythema, especially on exposed areas. In severe cases involving multiple body areas or the face, systemic glucocorticoids are the best treatment. Two- to 3-week courses of glucocorticoids are preferred over shorter courses in order to decrease the risk of rebound dermatitis.

A 7-day course of oral acyclovir is the treatment for herpes zoster. Herpes zoster typically presents with painful clusters of vesicles in a dermatomal distribution. The widespread clinical presentation of a pruritic vesicular rash is not consistent with herpes zoster.

Oral doxycycline is an antibiotic often combined with incision and drainage for the empiric treatment of moderate purulent skin infections such as furuncles, carbuncles, and abscesses. Although allergic contact dermatitis can become secondarily infected with *Staphylococcus aureus* or streptococcus, there is no evidence of infection in this patient (for example, extensive and spreading erythema, warmth, drainage, and increasing pain).

A 6-day taper of methylprednisolone would increase the risk of rebound dermatitis after completion of the short taper. A longer 14- to 21-day taper of systemic glucocorticoids is preferred.

Hydrocortisone 1% is a low potency topical glucocorticoid and would be ineffective for treating this severe case of contact dermatitis. High potency glucocorticoids such as clobetasol propionate 0.05% or betamethasone dipropionate 0.05% can be helpful in early and localized disease.

KEY POINT

- Severe allergic contact eruptions such as those from poison ivy may necessitate a 2- to 3-week taper of systemic glucocorticoids; because of the risk of rebound dermatitis, shorter courses are not recommended.

Bibliography

Usatine RP1, Riojas M. Diagnosis and management of contact dermatitis. Am Fam Physician. 2010 Aug 1;82(3):249-55. [PMID: 20672788]

Item 64 Answer: A

Educational Objective: Treat tinea pedis.

Dermatophytosis or tinea of non-hair-bearing skin with limited involvement can be treated with imidazole cream applied once to twice daily for 2 to 4 weeks. Application should extend a few centimeters beyond the advancing border. For tinea pedis, the web spaces between the toes should be treated. Other topical agents including miconazole, clotrimazole, ketoconazole, ciclopirox, or terbinafine can also be used. Over-the-counter preparations are cost-effective options with good efficacy. Most infections will resolve but may recur and require retreatment. In immunosuppressed patients, recognition and treatment of superficial skin fungal infections is essential, as fungal infections can lead to epidermal breakdown and create a portal of entry for invasive pathogens. Tinea pedis is also a potential cause of recurrent bacterial cellulitis.

Dermatophytes do not respond to topical nystatin, which is used to treat infections caused by *Candida* species.

Oral antifungal therapy with terbinafine or an azole antifungal agent such as itraconazole or fluconazole may be necessary for treating tinea capitis, onychomycosis, Majocchi granuloma (a granulomatous response to dermatophyte infection in the dermis and hair follicles), or extensive infection. Oral ketoconazole no longer has an indication for superficial fungal infection because of severe and sometimes fatal idiosyncratic liver toxicity. In addition, ketoconazole is a potent inhibitor of CYP3A4 resulting in significant drug interactions. Prolonged use of ketoconazole also may result in adrenal gland suppression.

Combination therapy with potent topical glucocorticoids, such as betamethasone, and antifungal creams, such as clotrimazole, should be avoided because of an increased risk of treatment failures, development of skin atrophy with prolonged use, and increased cost without increased efficacy.

KEY POINT

- Treatment of tinea of non-hair-bearing skin includes topical antifungal agents such as imidazole, miconazole, clotrimazole, ketoconazole, ciclopirox, or terbinafine; topical nystatin is not effective, and oral ketoconazole should be avoided.

Bibliography

Jewell JR, Myers SA. Topical Therapy Primer for Nondermatologists. Med Clin North Am. 2015;99:1167-82. [PMID: 26476246] doi:10.1016/j.mcna.2015.06.001

H

Item 65 Answer: A

Educational Objective: Diagnose drug reaction with eosinophilia and systemic symptoms (DRESS).

This patient's symptoms are characteristic of drug reaction with eosinophilia and systemic symptoms (DRESS) or drug hypersensitivity syndrome. DRESS is a severe, life-threatening, idiosyncratic medication reaction. The most common culprit medications include sulfonamide antibiotics, allopurinol, and anticonvulsants, but many more have been implicated. DRESS is unique in that the onset is usually 2 to 6 weeks after exposure to a causative medication. Because of this delayed onset, DRESS is often underrecognized or misdiagnosed. The eruption is usually an exuberant morbilliform eruption with prominent facial edema, lymphadenopathy, fever, and, in severe cases, hypotension. Typical laboratory findings include leukocytosis with eosinophilia and increased serum alanine aminotransferase levels. Cessation of the causative agent and systemic glucocorticoids with a long taper are the best treatment. DRESS reactions with carbamazepine may cross-react with phenytoin and phenobarbital, but not levetiracetam or valproic acid.

The term *retiform purpura* describes the angulated or netlike configuration that reflects the underlying vascular structure in the skin. Various conditions can cause retiform purpura, many of which disrupt arterial blood flow such as thrombosis and embolization.

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are both severe drug reactions, but these reactions happen closer to the start date of the offending agent than DRESS syndrome. SJS/TEN lack the facial edema of DRESS syndrome, and DRESS syndrome lacks the epidermal necrosis of SJS/TEN. DRESS can cause mucositis in the minority of cases. Both SJS/TEN and DRESS can result in liver or kidney function abnormalities, but eosinophilia is strongly indicative of DRESS.

KEY POINT

- Drug reaction with eosinophilia and systemic symptoms (DRESS) is a systemic drug hypersensitivity reaction that presents with rash, prominent facial edema, lymphadenopathy, and fever 2 to 6 weeks after the initiation of the causative drug.

Bibliography

Darlenski R, Kazandjieva J, Tsankov N. Systemic drug reactions with skin involvement: Stevens-Johnson syndrome, toxic epidermal necrolysis, and DRESS. Clin Dermatol. 2015;33:538-41. [PMID: 26321400] doi:10.1016/j.clindermatol.2015.05.005

Item 66 Answer: B

H

Educational Objective: Evaluate the cause of pruritus in the absence of skin findings.

The most appropriate initial management for this patient is to discontinue hydrochlorothiazide. Pruritus in the absence of skin findings should be evaluated for underlying systemic causes. These include kidney disease, hyperthyroidism, hepatobiliary diseases, HIV infection, lymphoproliferative disorders (lymphoma), and myeloproliferative disorders (polycythemia vera). Drug-induced pruritus should also be considered. This patient has a normal complete blood count, liver chemistry tests, thyroid-stimulating hormone levels, serum creatinine, and sedimentation rate, making many of the systemic diseases unlikely. However, this patient is taking hydrochlorothiazide for hypertension. Hydrochlorothiazide, calcium channel blockers, opiates, and NSAIDs are all medications that can cause generalized pruritus without skin findings. In patients taking multiple medications, it can be challenging to determine which drug(s) may be contributing to pruritus, as patients may develop medication-induced itch even after months or years on a drug. The most appropriate management in this patient would be to discontinue hydrochlorothiazide and monitor for 2 to 4 weeks to detect improvement of his pruritus.

Hodgkin lymphoma is the malignant disease most strongly associated with pruritus. CT of the chest and abdomen could be ordered to evaluate for Hodgkin disease, but he has no other symptoms to suggest lymphoma, such as fever or weight loss, and no lymphadenopathy on physical examination. The high cost of CT imaging and radiation exposure would make this an inappropriate initial management option for this patient. A plain chest radiograph would be a better initial imaging test if Hodgkin lymphoma were suspected.

Topical permethrin is prescribed for the treatment of scabies. Although scabies should be considered in any patient with pruritus, there are no skin findings to suggest scabies in this patient, such as erythematous papulonodules and scaling patches, especially in web spaces, wrists, axillae, nipples, waistline, and genitals.

Topical triamcinolone can be used for pruritus associated with inflammatory skin conditions, such as atopic dermatitis or psoriasis. This patient has no evidence of atopic dermatitis or psoriasis, such as inflamed, dry, red, itchy skin, or thick silvery scale on erythematous patches.

KEY POINT

- Pruritus in the absence of skin findings should be evaluated for underlying systemic causes; many medications such as hydrochlorothiazide, calcium channel blockers, opiates, or NSAIDs can also cause generalized pruritus without skin findings.

Bibliography

Silverberg JI. Practice gaps in pruritus. Dermatol Clin. 2016 Jul;34(3):257-601. [PMID: 27363881]

H

Item 67 Answer: A

Educational Objective: Treat low-risk basal cell carcinoma.

Electrodesiccation and curettage (ED&C) is a widely used treatment for noninfiltrating basal cell carcinomas on low-risk anatomic sites (trunk and extremities). Treatment of basal cell carcinomas depends on many factors, including the histologic subtype, location, size, cosmetic considerations, and patient's age and comorbidities. Nodular and superficial basal cell carcinomas on the trunk and extremities are often treated with ED&C. Infiltrative and micronodular basal cell carcinomas, especially on the face, are not appropriate for ED&C. For this patient, his lesion is a small, histologically low-risk subtype of basal cell carcinoma on the back that can be treated with ED&C.

Mohs micrographic surgery is a specialized surgical procedure that provides margin control while sparing as much normal skin as possible. Indications for Mohs micrographic surgery include tumors with aggressive histologic subtypes (micronodular, morpheaform, infiltrative, perineural involvement); high-risk and cosmetically sensitive locations (face, genitals); large tumors or tumors arising in scar tissue; and tumors in patients who are immunosuppressed. This patient's lesion would not be an appropriate use of Mohs surgery.

Radiation therapy for skin cancers is appropriate for patients who refuse surgery or are not optimal surgical candidates. The patient will be able to tolerate an ED&C without any difficulty.

Vismodegib is an oral medication that inhibits the hedgehog signaling pathway; this signaling pathway is aberrant in most basal cell carcinomas. It is reserved for locally advanced or metastatic basal cell carcinomas.

KEY POINT

- Noninfiltrating basal cell carcinomas on low-risk areas such as the trunk and extremities are best treated with electrodesiccation and curettage.

Bibliography

Connolly SM, Baker DR, Coldiron BM, Fazio MJ, Storrs PA, Vidimos AT, et al; American Academy of Dermatology. AAD/ACMS/ASDSA/ASMS 2012 appropriate use criteria for Mohs micrographic surgery: a report of the American Academy of Dermatology, American College of Mohs Surgery, American Society for Dermatologic Surgery Association, and the American Society for Mohs Surgery. Dermatol Surg. 2012;38:1582-603. [PMID: 22958088] doi:10.1111/j.1524-4725.2012.02574.x

Item 68 Answer: A

Educational Objective: Diagnose alopecia areata.

This patient has alopecia areata, a patchy, nonscarring alopecia. It most often occurs in early adulthood and is associated with autoimmune disorders such as type 1 diabetes mellitus, thyroid disease, and vitiligo. Alopecia areata tends to have an acute onset. It appears as round or oval patches of hair loss with the periphery studded with exclamation point hairs. These are hair shafts that narrow as they approach the skin surface. The scalp is most often affected with severe 2- to 3-cm patches of hair loss. The clinical course of alopecia areata is variable and unpredictable with spontaneous recovery for most patients with localized disease. Treatment is dependent on the area involved. In localized disease, high-potency topical glucocorticoids are first-line treatment.

Discoid lupus erythematosus is a form of patchy scarring alopecia. It is characterized by oval plaques that may have a pink, active rim with a white atrophic center. A biopsy of the scalp would confirm the diagnosis. Local treatment involves high-potency topical or intralesional glucocorticoids.

Secondary syphilis can cause patchy nonscarring alopecia ("moth eaten"). Alopecia is seen in approximately 7% of patients with secondary syphilis. There are other syphilids in secondary syphilis such as copper-colored macules and papules on the trunk and extremities, including palms and soles. Serology would aid in diagnosis. Treatment involves intramuscular benzathine penicillin.

Tinea capitis is a superficial infection of the scalp, seen mostly in school-aged children. It can appear as a patchy, nonscarring alopecia with broken hair shafts. Occipital lymph nodes can often be palpated. As there is often scale, it can look like seborrheic dermatitis. A potassium hydroxide microscopic examination and culture of broken hairs can confirm the diagnosis. Treatment involves systemic antifungal agents.

Trichotillomania, alopecia from compulsive twisting and pulling, is in the differential diagnosis for patchy nonscarring alopecia; however, on physical examination, the patches are often more irregular and ill-marginated with broken hairs. Patients with trichotillomania often have a history of psychiatric conditions and anxiety.

KEY POINT

- Alopecia areata is a chronic autoimmune disease that results in smooth, hairless patches of skin, most commonly appearing on the scalp.

Bibliography

Mubki T, Rudnicka L, Olszewska M, Shapiro J. Evaluation and diagnosis of the hair loss patient: part I. History and clinical examination. J Am Acad Dermatol. 2014;71:415.e1-415.e15. [PMID: 25128118] doi:10.1016/j.jaad.2014.04.070

Item 69 Answer: A

Educational Objective: Diagnose amyloidosis.

This patient likely has amyloidosis. Amyloid light chain amyloidosis is the most common type of amyloidosis; it is a plasma cell dyscrasia-related disease characterized by end-organ damage secondary to tissue deposition of monoclonal free λ or κ light-chain fibrils. Clinical symptoms and manifestations vary and are dictated by the tissue tropism of the amyloidogenic light chain. If amyloid deposits are identified on tissue biopsy, other types of amyloidosis should be excluded by typing,

which can be done by κ/λ light-chain immunohistochemistry. Major clinical manifestations include proteinuria with worsening kidney function, restrictive cardiomyopathy, and hepatomegaly. Neurologic findings include a symmetric, distal sensorimotor neuropathy, carpal tunnel syndrome, and autonomic neuropathy with orthostatic hypotension. Skin manifestations are present in 30% to 40% of patients and include generalized waxy appearance, ecchymoses with minor pressure ("pinch purpura"), ecchymoses around the eyes ("raccoon eyes"), yellow waxy papules and plaques especially in a periorbital location, dystrophic nails, and macroglossia. Bleeding caused by acquired factor X deficiency may also occur.

A pathognomonic cutaneous feature of dermatomyositis is a heliotrope rash, a distinctive purple or lilac erythema of the eyelids that may be accompanied by edema. It is not yellow or papular as seen in this patient.

Xanthelasma is a type of plane xanthoma localized to the periorbital area, most commonly on the upper medial eyelid, and it is characterized by soft, nontender, nonpruritic plaques. Xanthelasma can occur without hyperlipidemia, particularly in older persons, but it is often associated with familial dyslipidemias when seen in a younger person. This patient's periorbital lesions are not consistent with xanthelasma.

Classic cutaneous sarcoidosis appears as violaceous papules around the nose including the ala, or periorbitally and around the oropharynx and nasal openings. This patient's yellow periorbital papules are not consistent with sarcoidosis.

The combination of the patient's periorbital skin findings, easy bruising and bleeding, hepatomegaly, and proteinuria cannot be explained by dermatomyositis, hyperlipidemia, or sarcoidosis.

KEY POINT

- Skin manifestations of amyloid light chain amyloidosis are present in 30% to 40% of patients and include generalized waxy appearance, ecchymoses with minor pressure ("pinch purpura"), ecchymoses around the eyes ("raccoon eyes"), yellow waxy papules and plaques especially in a periorbital location, dystrophic nails, and macroglossia.

Bibliography

Wechalekar AD, Gillmore JD, Hawkins PN. Systemic amyloidosis. Lancet. 2016;387:2641-54. [PMID: 26719234] doi:10.1016/S0140-6736(15)01274-X

Item 70 Answer: C

Educational Objective: Diagnose eruptive xanthoma associated hypertriglyceridemia.

This patient has eruptive xanthomas, which are characterized by a rapid onset of numerous yellow papules with surrounding erythema found primarily on the extensor surfaces of the extremities and buttocks. Xanthomas are localized lipid deposits whose presence is suggested by characteristic cutaneous papules, plaques, or nodules.

Cutaneous xanthomas can be idiopathic and not associated with an underlying disorder or an indication of a primary dyslipidemia, hyperlipidemia secondary to another disorder, medication effect (estrogens, prednisone, protease inhibitors), or hematologic disease. The ability to diagnose the xanthoma subtype will direct the proper testing and treatment. When necessary, diagnosis can be confirmed with a skin biopsy that shows lipid-laden macrophages in the dermis. Eruptive xanthomas are pathognomonic of hypertriglyceridemia, and a vast number of these patients also have a diagnosis of diabetes mellitus. Eruptive xanthomas have also been reported as a complication of hypertriglyceridemia-induced pancreatitis.

Tuberous xanthomas are associated with markedly elevated low-density lipoprotein levels (familial hypercholesterolemia) and elevated intermediate-density lipoprotein and triglyceride levels (familial dysbetalipoproteinemia). Tuberous xanthomas present as yellow to red papules or nodules up to 3 cm in size located over joints and extensor surfaces of the elbows and knees. The location and size of tuberous xanthomas distinguish them from eruptive xanthomas.

Tendinous xanthomas are skin-colored nodules most commonly located over the Achilles tendon. They are smooth, firm, and mobile and are attached to and move with the tendon. Tendon xanthomas are typically associated with familial hypercholesterolemia and familial defective apo B 100. The location, size, and color of these tumors distinguish them from eruptive xanthomas.

Plane xanthomas may occur in the absence of lipid disorders in approximately 50% of adults or can be associated with familial dysbetalipoproteinemia, homozygous familial hypercholesterolemia, and hypercholesteremia associated with primary biliary cirrhosis. Plane xanthomas are recognized as yellow thin plaques most commonly found around the eyelids (xanthelasma), neck, trunk, shoulders, axillae, and in some cases, palms. The flat plaque-like appearance and location of plane xanthomas distinguishes them from eruptive xanthomas.

KEY POINT

- Eruptive xanthomas, characterized by yellow papules with surrounding erythema, are pathognomonic of hypertriglyceridemia, with a number of these patients also having a diagnosis of diabetes mellitus.

Bibliography

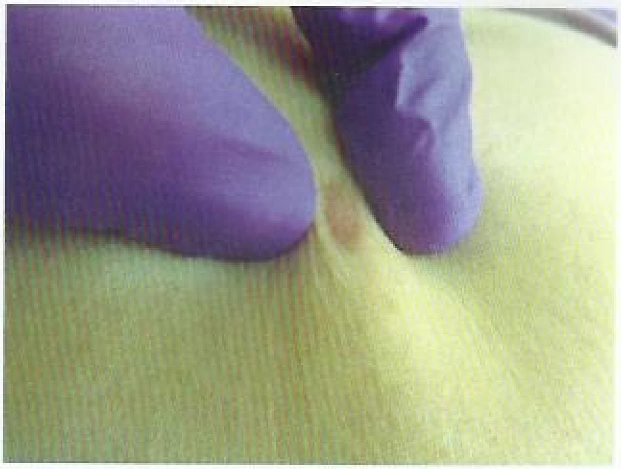
Roga G, Jithendriya M. Eruptive xanthoma: Warning sign of systemic disease. Cleve Clin J Med. 2016;83:715-716. [PMID: 27726830] doi:10.3949/ccjm.83a.15126

Item 71 Answer: B

Educational Objective: Diagnose dermatofibroma.

Dermatofibromas are benign, fibrohistiocytic lesions common on the extremities of young adults, in particular women, but they also occur on the trunk in both men and women. Diagnosed clinically, dermatofibromas are tan-to-brown or reddish discrete papules about the size of a pencil eraser. They "dimple" when lateral pressure is applied to the lesion with the thumb and first finger as shown (see top of next page).

Multiple lesions may be present in some persons. They are thought to arise from minor injury, including insect



bites, shaving injuries, or folliculitis. Dermatofibromas are benign and do not require treatment.

Acrochordons or "skin tags" are skin-colored, pedunculated papules. They are most commonly seen on the neck and skin folds in older adults. They are harmless but often bothersome from a cosmetic standpoint. They may also occasionally become tender when traumatized. The presence of numerous lesions, particularly in the setting of obesity and acanthosis nigricans, is associated with insulin resistance.

Neurofibromas are asymptomatic, benign nerve sheath tumors that present as soft skin-colored papules, which show invagination of the papule with lateral pressure ("buttonhole" sign). Isolated lesions are common in the general population and are not associated with any underlying disease. The presence of numerous neurofibromas suggests a diagnosis of neurofibromatosis type 1. Additional findings that suggest this diagnosis include multiple café-au-lait macules, Lisch nodules (raised, pigmented hamartomas of the iris), and axillary freckling. Neurofibromas are benign and do not require treatment.

Pyogenic granulomas are bright red vascular lesions that arise suddenly and grow rapidly; they often appear during pregnancy or in the setting of certain medications (such as antiretroviral therapy). The name is misleading, as they are neither pyogenic nor granulomatous. They resemble cherry hemangiomas, but are often more friable and tend to bleed more easily. They are benign lesions that do not have any systemic disease associations; they are treated with biopsy or electrocautery.

KEY POINT

- Dermatofibromas are benign firm brown or reddish papules about the size of a pencil eraser that most commonly occur on the lower extremities; they "dimple" when lateral pressure is applied to the lesion with the thumb and first finger.

Bibliography

Higgins JC, Maher MH, Douglas MS. Diagnosing Common Benign Skin Tumors. Am Fam Physician. 2015;92:601-7. [PMID: 26447443]

Item 72 Answer: A

Educational Objective: Evaluate the cause of acanthosis nigricans.

This patient has acanthosis nigricans (AN), and he should be screened for insulin resistance with a fasting blood glucose measurement. AN presents as velvety-to-verrucous, gray-to-brown thickening with accentuation of skin marking seen in the intertriginous folds and neck. AN is more common in persons of color. It can be benign and associated with diabetes or present as a paraneoplastic syndrome. Benign AN is characteristically seen in patients with type 2 diabetes mellitus and obesity; however, it can be seen in patients with other endocrine abnormalities that involve insulin resistance. Therefore, a diagnosis of AN should prompt screening for diabetes. If symptoms are extensive and of acute onset, in particular involving the palms and tongue, a screening for malignancy is indicated with a thorough review of systems and a complete physical examination.

Acanthosis nigricans is associated with endocrinopathies other than diabetes that can cause insulin resistance, including Cushing syndrome. This patient has some elements of Cushing syndrome including obesity and truncal acne, but the absence of hypertension and striae make this diagnosis less likely, and a 24-hour urine cortisol measurement is therefore not the next diagnostic test.

A thyroid-stimulating hormone and serum thyroxine measurement should be performed in patients with pretibial myxedema. Pretibial myxedema presents with firm nodules and plaques with a "peau d'orange" appearance on the pretibial area. Pretibial myxedema is almost always associated with the signs and symptoms of hyperthyroidism. Extrathyroidal manifestations of Graves disease include Graves orbitopathy, pretibial myxedema (thyroid dermopathy), and acropachy. Acropachy is swelling of the soft tissues on the hands and feet with digital clubbing. This patient has no findings consistent with pretibial myxedema.

Erythrasma is a superficial infection with *Corynebacterium minutissimum*. Its growth is encouraged by a warm, moist environment, such as intertriginous areas. Erythrasma causes well-defined, pink-to-brown patches with fine scale, located in the axillae, groin, or inframammary regions. A unique feature of this infection is that it fluoresces a bright coral-red color when illuminated with a Wood lamp. The location, morphology, and color of this patient's skin findings are not consistent with erythrasma.

KEY POINT

- Acanthosis nigricans presents as skin thickening and darkening of the intertriginous areas, particularly the axillae and neck; it can be associated with insulin resistance or present as a paraneoplastic syndrome.

Bibliography

Murphy-Chutorian B, Han G, Cohen SR. Dermatologic manifestations of diabetes mellitus: a review. Endocrinol Metab Clin North Am. 2013;42:869-98. [PMID: 24286954] doi:10.1016/j.ecl.2013.07.004

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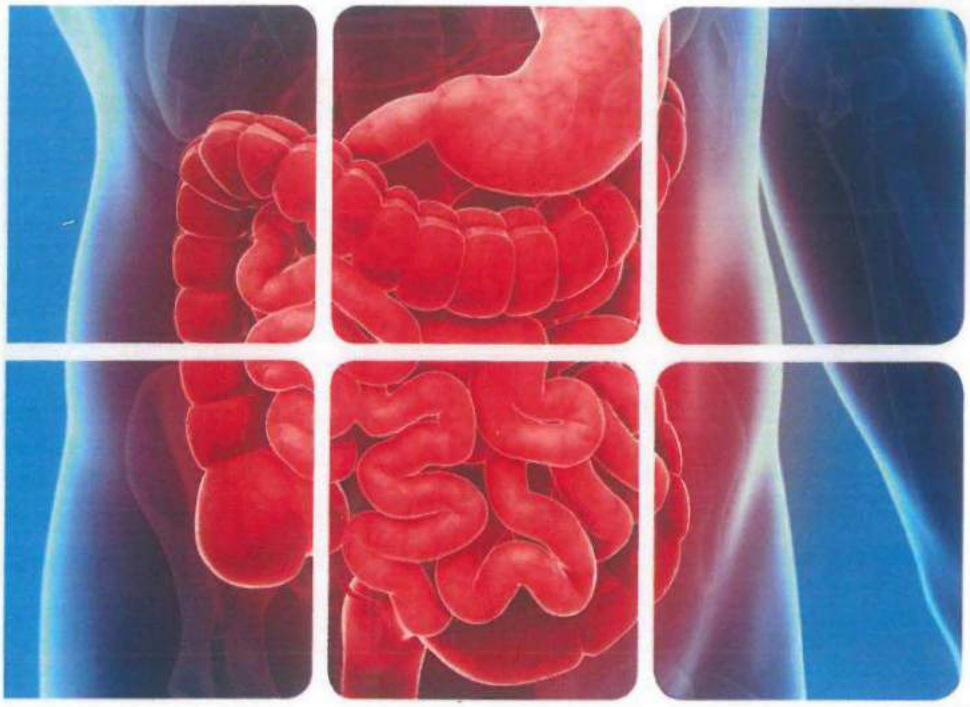

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Gastroenterology and Hepatology High Value Care Recommendations

The American College of Physicians, in collaboration with multiple other organizations, is engaged in a worldwide initiative to promote the practice of High Value Care (HVC). The goals of the HVC initiative are to improve health care outcomes by providing care of proven benefit and reducing costs by avoiding unnecessary and even harmful interventions. The initiative comprises several programs that integrate the important concept of health care value (balancing clinical benefit with costs and harms) for a given intervention into a broad range of educational materials to address the needs of trainees, practicing physicians, and patients.

HVC content has been integrated into MKSAP 18 in several important ways. MKSAP 18 includes HVC-identified key points in the text, HVC-focused multiple choice questions, and, for subscribers to MKSAP Digital, an HVC custom quiz. From the text and questions, we have generated the following list of HVC recommendations that meet the definition below of high value care and bring us closer to our goal of improving patient outcomes while conserving finite resources.

High Value Care Recommendation: A recommendation to choose diagnostic and management strategies for patients in specific clinical situations that balance clinical benefit with cost and harms with the goal of improving patient outcomes.

Below are the High Value Care Recommendations for the Gastroenterology and Hepatology section of MKSAP 18.

- In patients with gastroesophageal reflux symptoms without alarm features, empiric proton pump inhibitor therapy is the first therapeutic and diagnostic step.
- Attempts to stop or reduce long-term proton pump inhibitor therapy for uncomplicated gastroesophageal reflux disease should be considered at least annually (see Item 59).
- Women with gastroesophageal reflux disease do not require screening for Barrett esophagus.
- Patients 60 years and older with dyspepsia should undergo upper endoscopy.
- Patients younger than age 60 years with dyspepsia should be tested and treated for *Helicobacter pylori* infection.
- Enteral nutrition is preferred in patients with acute pancreatitis (see Item 26).
- Same-admission cholecystectomy reduces rates of gallstone-related complications for patients with mild gallstone pancreatitis (see Item 20).
- Asymptomatic patients with walled-off necrosis of the pancreas require no intervention (see Item 95).
- Biopsy and endoscopic retrograde cholangiopancreatography are not indicated in the diagnosis of chronic pancreatitis.
- Evaluation with imaging, endoscopy, and other testing is not indicated for irritable bowel syndrome or functional diarrhea.
- Irritable bowel syndrome can often be managed with reassurance, lifestyle modifications, and dietary modifications.
- The evaluation for centrally mediated pain syndrome does not require extensive laboratory testing or imaging.
- Acute diverticulitis usually does not require abdominal imaging.
- Patients with small hyperplastic polyps should undergo repeat colonoscopy no sooner than 10 years (see Item 11).
- Patients with uncomplicated diverticulitis should be treated with oral antibiotics (see Item 74).
- Ultrasonography is the most effective means of diagnosing ascites.
- Asymptomatic hepatic cysts require no follow-up.
- Focal nodular hyperplasia does not require follow-up.
- Incidentally diagnosed gallstones do not require cholecystectomy.
- The diagnosis of acute cholecystitis can be made by ultrasonography.
- In patients with upper gastrointestinal bleeding, a transfusion threshold of less than 7 g/dL (70 g/L) with a target hemoglobin level of 7-9 g/dL (70-90 g/L) is associated with decreased mortality and length of hospital stay (see Item 83).

Gastroenterology and Hepatology

Disorders of the Esophagus

Symptoms of Esophageal Disease

Dysphagia

Dysphagia represents a disruption in the swallowing mechanism, resulting in food not passing from the mouth to the stomach. Common descriptions of the sensations of dysphagia include food "hanging up" or feeling "lodged" or "stuck" during a meal. Determining whether the underlying cause is oropharyngeal or esophageal is important in developing a differential diagnosis and management plan. **Table 1** highlights the common causes of dysphagia.

Oropharyngeal Dysphagia

Oropharyngeal dysphagia, also known as transfer dysphagia, occurs when the patient is unable to transfer the food bolus

TABLE 1. Causes of Dysphagia

Condition	Diagnostic Clues
Oropharyngeal Dysphagia	
Structural disorders	
Cervical osteophytes	High dysphagia, degenerative joint disease
Cricoid webs	High dysphagia, iron deficiency
Pharyngoesophageal (Zenker) diverticulum	Aspiration, neck mass, and regurgitation of foul-smelling food
Goiter	Neck mass
Neurologic/myogenic disorders	
Amyotrophic lateral sclerosis	Upper and lower motoneuron signs, fasciculations
Central nervous system tumor	Headache, vision changes, nausea, seizures, balance problem
Stroke	Focal neurologic deficits
Muscular dystrophy	Slow progression of muscular weakness over years
Myasthenia gravis	Weakness with repetitive activity
Multiple sclerosis	Episodes of neurologic dysfunction with variable degrees of recovery
Parkinson disease	Bradykinesia, rigidity, tremor
Dementia	Altered cognition
Sjögren syndrome	Dry mouth, dry eyes
Esophageal Dysphagia	
Structural disorders	
Dysphagia lusoria (vascular dysphagia)	Vascular extrinsic compression on the esophagus on imaging
Epiphrenic/traction diverticulum	Outpouching of the esophagus at any level on imaging
Esophageal strictures	Intermittent dysphagia, especially for solid food; history of reflux
Eosinophilic esophagitis	Food impactions, atopic history, rings or strictures on endoscopy
Esophageal webs or rings	Upper esophageal webs may be associated with iron deficiency anemia
Neoplasms	Rapidly progressive dysphagia for solids, then liquids; anorexia; weight loss
Motility disorders	
Achalasia	Concomitant liquid and solid dysphagia
Diffuse esophageal spasm	Chest pain
Systemic sclerosis	Tight skin, telangiectasias, sclerodactyly, gastroesophageal reflux disease, Raynaud phenomenon

from the mouth into the upper esophagus by swallowing. Symptoms commonly reported include choking, coughing, and nasal regurgitation of food. Patients are at risk for aspiration pneumonia. Other presenting symptoms include hoarseness (resulting from laryngeal nerve damage) and dysarthria (from weakness of the soft palate or pharyngeal constrictors), both representing an underlying neurologic disorder. A pharyngoesophageal (Zenker) diverticulum should be considered when undigested food is brought up several hours after a meal or if a patient reports hearing a gurgling noise in the chest.

The initial study for suspected oropharyngeal dysphagia is a modified barium swallow, with both a liquid and a solid phase to help identify the underlying cause. Management strategies include dietary changes and a swallowing exercise program implemented with a speech pathologist.

Esophageal Dysphagia

Patients with esophageal dysphagia are able to initiate the swallowing process, but often feel discomfort in the mid to lower sternum as the food bolus passes through the esophagus. Esophageal dysphagia is the result of one of two underlying causes: a mechanical obstruction or a motility disorder. Dysphagia occurring with solids alone suggests a mechanical obstruction, whereas dysphagia with either liquids alone or the combination of liquids and solids favors a motility disorder. Dysphagia that progresses from occurring with solids only to occurring with both solids and liquids suggests malignancy.

Achalasia often presents with nonacidic regurgitation of undigested food. Chest pain while taking liquids that are very hot or very cold may indicate esophageal spasm. Mechanical esophageal obstruction may be benign or malignant and may be caused by strictures, masses, esophageal ring (for example, a Schatzki ring [**Figure 1**]), or webs. Upper endoscopy allows for diagnostic (biopsy and inspection) and therapeutic intervention (dilation). Clinical management is based on the underlying cause.

FIGURE 1. Barium esophagram showing a Schatzki ring, a subtype of esophageal ring located at the squamocolumnar junction and a common cause of dysphagia.

Reflux and Chest Pain

The development of chest pain from an esophageal cause can mimic chest pain from cardiac disease. Reports of heartburn with history of Raynaud phenomenon could signify a systemic condition, such as scleroderma.

Once a cardiac cause is ruled out, the most common cause of chest pain is gastroesophageal reflux disease (GERD). Starting a course of an acid-reducing agent, such as an H_2 blocker or proton pump inhibitor (PPI), can be both diagnostic and therapeutic. Patients whose symptoms do not respond require further evaluation, including upper endoscopy and possibly ambulatory pH testing with or without esophageal manometry.

See Gastroesophageal Reflux Disease for information about diagnosis and management.

Odynophagia

A presentation of pain while swallowing defines odynophagia, which suggests active mucosal inflammation and ulceration in the esophagus. Odynophagia is commonly associated with pill-induced damage, infection, or caustic ingestion, and is less commonly caused by GERD or esophageal cancer. Upper endoscopy with biopsies is the most appropriate diagnostic test to determine the degree of inflammation and underlying cause.

Globus Sensation

Patients commonly report globus sensation as a "lump in the throat" or "throat tightness," usually not linked to meals. Causes of globus include GERD (with or without heartburn), stress, and psychiatric conditions (anxiety, panic disorders, somatization). A diagnosis of globus should not be made if the patient reports other esophageal symptoms, such as dysphagia or odynophagia. Evaluation to determine the underlying cause should include evaluation for thyroid goiter and an underlying pharyngeal lesion, which can be diagnosed by transnasal endoscopy or barium swallow.

Treatment with acid suppression or cognitive behavioral therapy should be initiated once a structural cause has been ruled out.

KEY POINTS

- Oropharyngeal dysphagia occurs when the patient is unable to transfer the food bolus from the mouth into the upper esophagus by swallowing and should be evaluated with a modified barium swallow.
- Esophageal dysphagia occurring with solids alone suggests a mechanical obstruction, whereas dysphagia with either liquids alone or the combination of liquids and solids favors a motility disorder.
- Upper endoscopy is diagnostic and may be therapeutic for esophageal dysphagia.
- Chest pain is common in patients with gastroesophageal reflux disease, but a cardiac cause of chest pain must be ruled out first.

Nonmalignant Disorders of the Esophagus

Gastroesophageal Reflux Disease

GERD is characterized by food and acid refluxing from the stomach into the esophagus and throat. Its prevalence is 10% to 20% in the Western world, and there is a strong relationship between GERD and obesity. The most common symptoms reported are heartburn, regurgitation, and chest pain, for which a cardiac cause must be excluded. Reflux can be triggered by a number of factors (**Table 2**). Protective mechanisms to minimize the esophagus' exposure to acid consist of peristalsis, a competent lower esophageal sphincter (LES), and gastric emptying; reflux occurs when these physiologic protectors become ineffective. Uncontrolled GERD can negatively affect quality of life due to poor sleep, low productivity, and work absences. Longstanding GERD can lead to complications, including erosive esophagitis, stricture, Barrett esophagus, and esophageal cancer (**Figure 2**). Pregnant women may experience GERD during any trimester of pregnancy, but symptoms may worsen as the pregnancy progresses. Heartburn symptoms resolve after delivery.

TABLE 2. Factors Associated with Reflux

Category	Factor
Lifestyle	Cigarette smoking
	Obesity
Eating habits	Eating large meals
	Eating late at night
	Lying supine shortly after eating
Foods and beverages	Alcohol
	Chocolate
	Citrus fruits and juices
	Coffee
	Fatty and fried foods
	Onions
	Peppermint
Medications	Anticholinergic agents
	Aspirin and NSAIDs
	Calcium channel blockers
	Nitrates
	Progesterone
	Opioids (due to delayed gastric emptying)
Body position	Bending over, exercising (both result in increased intra-abdominal pressure)
Other	Pregnancy
	Tight-fitting clothing
	Hiatal hernia

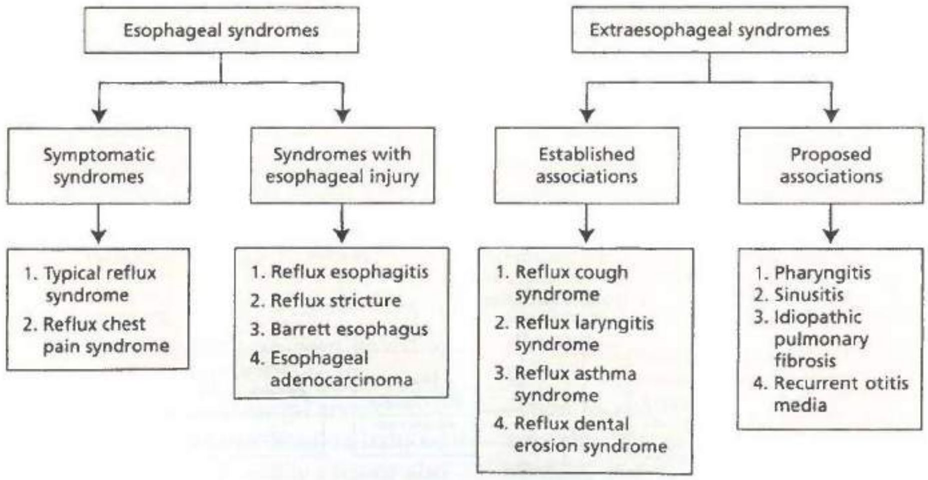

FIGURE 2. Classification of gastroesophageal reflux disease and its subsets.

Reprinted with permission from Vakil N, van Zanten SV, Kahrilas P, Dent J, Jones R; Global Consensus Group. The Montreal definition and classification of gastroesophageal reflux disease: a global evidence-based consensus. Am J Gastroenterol. 2006;101:1900-20; quiz 1943. [PMID: 16928254]. Copyright 2006, Springer Nature.

Diagnosis

Strategies for diagnosing GERD include use of clinical history, response to medical therapy, and testing, including endoscopy and ambulatory pH monitoring; there is no single gold-standard diagnostic test. Clinical symptoms of heartburn and regurgitation strongly suggest GERD. Patients with GERD symptoms, but without alarm features (such as dysphagia, unintentional weight loss, hematemesis, or melena) may undergo an empiric trial of a PPI. Symptom relief from medical therapy can confirm the diagnosis.

Upper endoscopy is warranted in patients reporting dysphagia to rule out an underlying ring, web, or malignancy, and in patients with suspected erosive esophagitis, stricture, or Barrett esophagus. Most patients with GERD have a normal upper endoscopy examination.

Ambulatory pH monitoring can assess the degree of acid exposure in the esophagus, especially in patients unresponsive to acid-reducing therapy. Impedance-pH testing can help differentiate between acid and nonacid reflux. Testing to detect active acid reflux can be done with a 24-hour transnasal catheter or a 48-hour wireless capsule, which patients generally tolerate better. Esophageal manometry has limited value in diagnosing GERD, but should be considered as part of the evaluation for antireflux surgery to rule out motility disorders such as achalasia.

Treatment

An algorithm outlining the management of GERD is presented in **Figure 3**.

Lifestyle Changes

Patients with recent weight gain or who are overweight should develop a weight-loss plan. Patients with nocturnal GERD should eat at least 2 to 3 hours before going to sleep and should consider raising the head of the bed.

Dietary modification should focus on eliminating foods that trigger an individual patient's GERD symptoms, rather than globally eliminating all common trigger foods (caffeine, chocolate, spicy foods, acidic foods such as citrus fruits, and fatty foods). Cessation of alcohol and tobacco use is universally supported.

Medical Therapy

Pharmacologic therapy includes antacids, H_2 blockers, and PPI therapy. A PPI once daily for 8 weeks is the therapy of choice for symptom relief, as well as for treatment of erosive esophagitis. PPI therapy is superior to H_2 blocker therapy for GERD with or without erosive esophagitis. The PPI should be taken once daily, 30 to 60 minutes before the first meal of the day. Patients with partial response to PPI therapy should increase the dosage to twice daily. Patients requiring long-term maintenance therapy should be placed on the lowest effective PPI dose, including on-demand or intermittent usage, and for patients with uncomplicated GERD, an attempt to stop or reduce chronic PPI therapy should be made once a year. Adverse effects of PPIs are shown in **Table 3**. Switching to a different PPI may be warranted for adverse reactions or for unresponsive symptoms. Initial studies suggested an interaction with clopidogrel; however, subsequent data suggest that

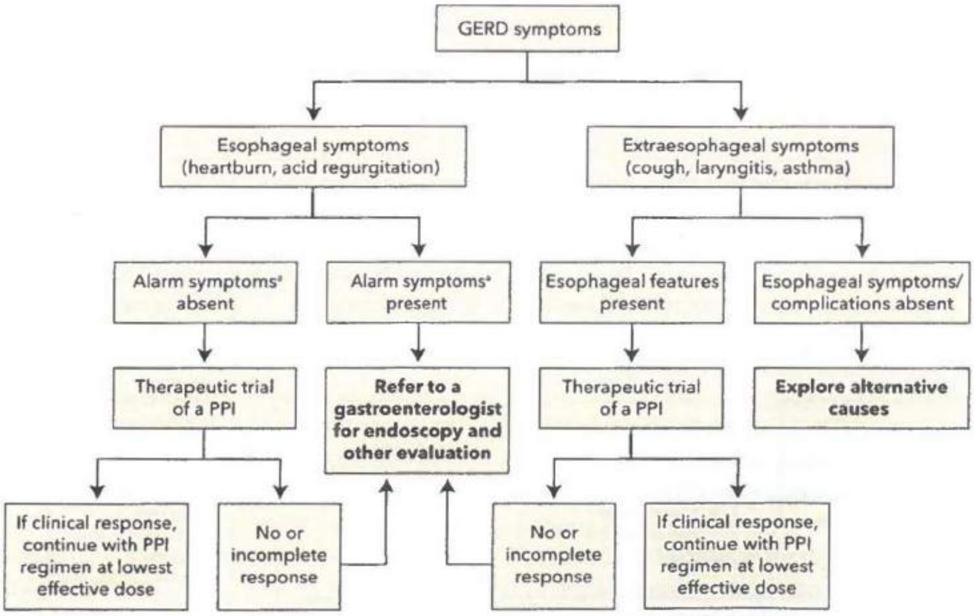

FIGURE 3. Management of gastroesophageal reflux disease.

GERD = gastroesophageal reflux disease; PPI = proton pump inhibitor.

*Alarm symptoms include dysphagia, unintentional weight loss, hematemesis, and melena.

TABLE 3. Adverse Effects of Proton Pump Inhibitors

Common	Unusual	Proposed Associations
Headache	Vitamin B_{12} deficiency	Kidney injury
Diarrhea	Hypomagnesemia	Dementia
Dyspepsia	Community-acquired pneumonia	
	Clostridium difficile infection	
	Hip fracture	

concurrent use does not increase risk for a cardiac event. PPIs are safe in pregnant patients.

Sucralfate has no role in the treatment of GERD. Prokinetic agents such as metoclopramide should not be used to treat GERD unless gastroparesis is present.

Antireflux Surgery

Surgical treatments for GERD are laparoscopic fundoplication or bariatric surgery for obese patients, as well as magnetic sphincter augmentation, a newer technique in which a magnetic ring is placed around the LES without surgical alteration of the stomach. Surgery is infrequently required; indications include failure of optimal therapy, wanting to stop medication, and intolerable medication side effects. Patients should undergo objective testing, such as impedance-pH monitoring, to confirm true acid reflux and correlation with symptoms before surgery. Surgery is most effective in patients with typical symptoms of heartburn and regurgitation that are responsive to therapy. However, about one third of patients require resumption of a PPI 5 to 10 years after surgery. Postoperative complications include dysphagia, diarrhea, and inability to belch from a tight fundoplication.

Endoscopic Therapy

Endoscopy-based therapies for GERD include thermal radiofrequency to augment the LES, silicone injection to the LES, and suturing of the LES. Early relief of reflux symptoms has been seen with these therapies, but long-term benefits have not been proven. None of these therapies has been associated with normalized esophageal pH levels. Newer approaches include transoral incisionless fundoplication, which is a full-thickness suture to create an endoscopic fundoplication, but there are no long-term data on its efficacy.

Extraesophageal Manifestations

Asthma, chronic cough, and laryngitis have been linked to GERD (see Figure 3). It is important to eliminate other non-GERD causes when these symptoms are present. Laryngoscopy often shows edema and erythema as signs of reflux-induced laryngitis. However, more than 80% of healthy persons also have these findings; therefore, laryngoscopy should not be used to diagnose GERD-related laryngitis. A PPI trial is recommended in patients who also have typical GERD symptoms. If a patient has atypical symptoms only, ambulatory esophageal pH monitoring should be considered before a PPI trial. Surgery is less effective in this group and should be considered only in patients whose symptoms respond to PPI therapy.

Refractory GERD

The first step in addressing refractory GERD is to optimize PPI therapy by emphasizing the importance of taking medication 30 to 60 minutes before eating, increasing the dosage to twice daily, or switching to another PPI. If symptoms are still unresponsive, alternative causes must be considered. For typical symptoms, use endoscopy to rule out eosinophilic esophagitis or erosive esophagitis. Esophageal impedance-pH testing may also be useful and should be performed while the patient is receiving optimized PPI therapy. For atypical symptoms, refer the patient to otorhinolaryngology, pulmonary, or allergy specialists to identify and treat the underlying cause. In these patients, medical therapy should be stopped before impedance-pH testing. A negative impedance-pH test likely means that the patient does not have GERD and PPI therapy should be discontinued. For patients with both types of symptoms, if further evaluation is unremarkable, impedance-pH testing should be performed.

Eosinophilic Esophagitis

Eosinophilic esophagitis (EE) is a condition commonly associated with dysphagia and food bolus obstruction. Most patients are diagnosed between the second and fifth decades of life, and EE is more commonly seen in men. Patients often have other atopic conditions such as asthma, rhinitis, dermatitis, and seasonal or food allergies. The reported prevalence is as high as 40 to 90 per 100,000 in the United States. The diagnostic criteria for EE are esophageal symptoms (dysphagia), esophageal biopsies showing 15 eosinophils/hpf or greater, persistent mucosal eosinophilia despite a trial of PPI therapy, and exclusion of other causes of eosinophilia. EE is a diagnosis made in the absence of peripheral eosinophilia.

Endoscopic findings include rings, longitudinal furrows, luminal narrowing, and white exudates and plaques. Patients with GERD may have elevated numbers of eosinophils in mucosal biopsies. Therefore, patients with prominent esophageal mucosal eosinophils should first undergo an 8-week trial of a PPI to rule out GERD. If there is no clinical improvement, repeat endoscopy with biopsy is recommended. If biopsies continue to show 15 eosinophils/hpf or greater, EE can be diagnosed and appropriate therapy initiated, with swallowed aerosolized topical glucocorticoids (fluticasone or budesonide). Diet modification has been suggested as a treatment option to prevent EE flares. An empiric elimination diet—removing the foods most commonly associated with food allergies, such as egg, soy, wheat, peanuts, cow's milk, and fish/shellfish—has been used. Endoscopic dilation should be considered in patients with continued dysphagia caused by esophageal stricture not responding to medical therapy.

Infectious Esophagitis

Infectious esophagitis can be caused by fungal, viral, bacterial (uncommon), and parasitic pathogens. Patients most commonly present with odynophagia or dysphagia. *Candida* esophagitis most commonly causes dysphagia, while viral esophagitis produces odynophagia. Other organisms associated with esophagitis include *Lactobacillus*, B-hemolytic streptococci, *Cryptosporidium*, *Pneumocystis jirovecii*, *Mycobacterium avium* complex, and *Mycobacterium tuberculosis*.

Candida infection can occur in immunocompetent or immunocompromised hosts. Diagnosis is usually made clinically based on the presence of compatible symptoms and oral candidiasis. Endoscopy and biopsy can be considered for patients who do not respond to empiric therapy or have atypical symptoms. Endoscopy shows small, white, raised plaques, and esophageal brushings confirm the diagnosis (**Figure 4**). The most common species is *Candida albicans*, treated with oral fluconazole.

Herpes simplex virus and cytomegalovirus are seen in immunodeficient or immunosuppressed individuals, but rarely in immunocompetent patients. Endoscopy with biopsy is needed to confirm the diagnosis. Herpes simplex virus infection is treated with acyclovir, and cytomegalovirus infection with ganciclovir.

Pill-Induced Esophagitis

Medications can cause esophageal injury resulting in esophagitis. Risk factors associated with pill-induced esophagitis include decreased salivary output, esophageal dysmotility, large pills, medications that increase the LES tone (opioids), and ingestion of medications in the supine position. Patients commonly report chest pain, dysphagia, and odynophagia occurring several hours to days after taking medication. Pill-induced esophagitis has been observed with alendronate, quinidine, tetracycline, doxycycline, potassium chloride, ferrous sulfate, and mexiletine. Medications associated with stricture formation include alendronate, ferrous sulfate, NSAIDs, and potassium chloride. Preventive strategies include drinking sufficient water with medication and remaining in an upright position for 30 minutes after pill ingestion.

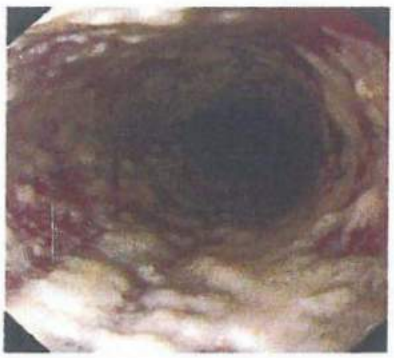

FIGURE 4. Upper endoscopy showing white adherent plaques suggestive of *Candida* esophagitis.

Esophageal Motility Disorders

The esophagus is a muscle that passes a food bolus from the hypopharynx to the stomach through peristalsis. The upper third of the esophagus is composed of skeletal muscle innervated by axons of lower motoneurons. The lower two thirds is smooth muscle innervated by the vagus nerve. The upper and lower esophageal sphincters relax during swallowing.

Additional peristaltic activity occurs when the esophagus is distended. High-resolution esophageal manometry is used to evaluate suspected esophageal motility disorders.

GERD is the most common cause of noncardiac chest pain. However, hypercontractile disorders of the esophagus should also be considered in patients with noncardiac chest pain. Esophageal manometry is used to differentiate these disorders.

Hypertonic Motility Disorders

Hypertonic motility disorders are characterized by dysphagia with both liquids and solids. Other symptoms can include regurgitation of undigested food, in particular when in a recumbent position. Treatment of hypertonic disorders of the esophagus is aimed at relieving symptoms.

Achalasia and Pseudoachalasia

Achalasia is a hypertonic motility condition defined by inadequate relaxation of the LES and aperistalsis. Achalasia can be idiopathic or associated with viral, autoimmune, and neurodegenerative disorders and infection (Chagas disease). Damage to the ganglion cells and myenteric plexus in the esophageal body and LES leads to uncontested cholinergic nerve activation, which prevents LES relaxation. Achalasia affects men and women equally, with an annual incidence of 1 in 100,000 individuals. It commonly occurs between 30 and 60 years of age. Patients present with dysphagia occurring with both solids and liquids along with nonacidic regurgitation of undigested food. Additional symptoms include heartburn, weight loss, and chest pain unresponsive to acid-reducing agents. Extrinsic compression from surgical procedures, such as fundoplication or bariatric surgery (gastric band), can also cause secondary achalasia. Barium esophagography is the initial diagnostic test, which shows dilation of the esophagus with narrowing at the gastroesophageal junction (GEJ), known as a "bird's beak" (**Figure 5**). Upper endoscopy reveals retained food and saliva, no signs of mechanical obstruction or mass, and "tightness" at the GEJ while advancing the scope into the stomach. Esophageal manometry showing incomplete LES relaxation and aperistalsis confirms the diagnosis of achalasia.

Pseudoachalasia is a result of malignant tumor infiltration or other secondary causes, and can present similarly to achalasia causing myenteric plexus damage. Unlike achalasia, this condition has been associated with sudden weight loss later in life, usually after age 50 years. Suspected pseudoachalasia should be evaluated with CT or endoscopic ultrasound.

Approaches to treatment of achalasia include endoscopic or surgical intervention with the goal of lowering LES

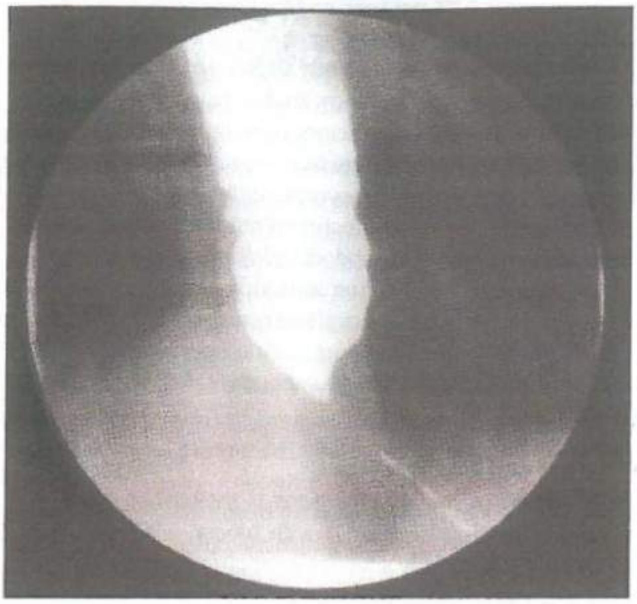

FIGURE 5. Barium esophagram showing the typical appearance of a dilated esophagus and "bird's beak" narrowing at the gastroesophageal junction in a patient with achalasia.

pressure, which relieves symptoms. Medical therapy is uncommonly used.

Endoscopic therapy involves injection of botulinum toxin, pneumatic dilation, or peroral endoscopic myotomy. Botulinum toxin injection into the LES inhibits acetylcholine release, causing LES relaxation. However, after 1 year, only 40% of patients have continued relief of symptoms. Botulinum toxin injection can be repeated, but successive treatments are often less effective for symptom management. Pneumatic dilation is an effective nonsurgical therapy. Dilators ranging from 30 mm to 40 mm in size are used to disrupt the circular muscle. Clinical symptom improvement ranges from 50% to 90%, and the most common complication is perforation. Peroral endoscopic myotomy is a newer endoscopic procedure in which the physician creates an esophageal submucosal tunnel extending to the level of the LES and then performs a myotomy. Studies have shown resolution of symptoms in over 80% of patients. Surgical treatment consists of laparoscopic myotomy of the circular muscle fibers. Fundoplication is also recommended to avoid reflux symptoms after myotomy. Determining whether a patient should receive endoscopic or surgical therapy often depends on local expertise.

Medical therapy is reserved for patients who are poor candidates for endoscopic or surgical therapy. LES pressure can be reduced with medical therapy, including calcium channel blockers (nifedipine) or long-acting nitrates.

Patients with achalasia for more than 10 years have increased risk for squamous cell carcinoma and may benefit from surveillance endoscopy, but there are no established guidelines for frequency of surveillance.

Diffuse Esophageal Spasm and Nutcracker Esophagus

Diffuse esophageal spasm is a hypercontractile state presenting with chest pain or dysphagia. Symptoms often respond to nitroglycerin, suggesting a flaw in esophageal nitric-oxide production. The esophagus has a "corkscrew" (**Figure 6**) or "rosary bead" appearance on esophagography. Esophageal manometry shows simultaneous high-amplitude (>30 mm Hg) esophageal contractions with intermittent aperistaltic contractions. Medical therapy with antidepressants (trazadone and imipramine) or a phosphodiesterase inhibitor (sildenafil) can relieve chest pain. Dysphagia may respond to calcium channel blockers. Botulinum toxin injection has been reported to alleviate dysphagia symptoms.

"Nutcracker" or "jackhammer" esophagus is found in patients with high-amplitude peristaltic contractions of greater than 220 mm Hg.

Hypotonic Motility Disorders

Hypotonic disorders of the esophagus are marked by lack of contractility and incomplete peristalsis. Patients may report symptoms of GERD, which result from decreased LES pressure or dysphagia from incomplete peristalsis. In most cases, the cause of hypotonic esophageal disease is unknown. However, secondary causes include smooth-muscle relaxants, anticholinergic agents, estrogen, progesterone, connective tissue disorders (scleroderma), and pregnancy. Esophageal manometry shows hypotonic, weak nonperistaltic contractions in the distal esophagus. Findings can mimic achalasia.

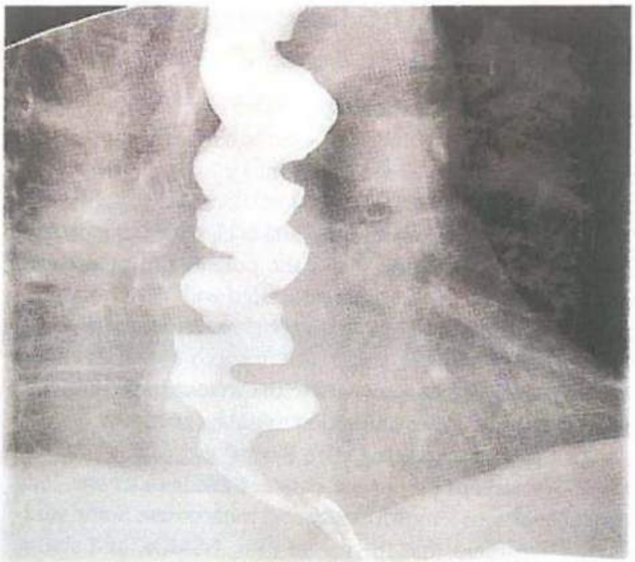

FIGURE 6. Findings of a "corkscrew esophagus" (caused by multiple simultaneous contractions) on esophagography are typical of diffuse esophageal spasm.

Treatment includes lifestyle changes, such as eating upright and eating liquid or semisolid rather than solid food. Medical therapy includes acid-reducing agents for GERD and low-dose antidepressants to reduce chest discomfort. Prokinetic agents, such as metoclopramide, are not recommended for treatment.

KEY POINTS

HVC

- In patients with symptoms of gastroesophageal reflux disease but without alarm features, an empiric trial of a proton pump inhibitor can relieve symptoms and confirm the diagnosis.
- Most patients with gastroesophageal reflux disease do not require surgery; indications include failure of optimal proton pump inhibitor therapy, wanting to stop medication, and intolerable medication side effects.
- The diagnostic criteria for eosinophilic esophagitis are esophageal symptoms (most commonly dysphagia), esophageal biopsies showing persistent counts of 15 eosinophils/hpf or greater despite a trial of proton pump inhibitor therapy, and exclusion of other causes of eosinophilia.
- Odynophagia and dysphagia are the most common presenting symptoms of infectious esophagitis.
- To prevent pill-induced esophagitis, patients should drink water with medication and remain upright for at least 30 minutes after ingestion.

Metaplastic and Neoplastic Disorders of the Esophagus

Barrett Esophagus

Epidemiology and Screening

Barrett esophagus is defined as the extension of the metaplastic columnar epithelium above the GEJ into the esophagus. Barrett esophagus is a consequence of GERD, even in patients who experience no clinical symptoms, and is classified as a premalignant condition because it has the potential to progress to esophageal cancer. Risk factors associated with Barrett esophagus include chronic GERD (for more than 5 years), age older than 50 years, male sex, white race, tobacco use, and obesity. Drinking alcohol is not associated with increased risk for Barrett esophagus, and wine consumption might be protective.

Risk factors associated with Barrett esophagus progression to dysplasia or esophageal cancer include older age, long Barrett esophagus length, obesity, and tobacco use. Some studies have suggested that the use of PPIs, NSAIDs, and statins may be protective; however, this has not been established, and the use of these agents for prevention of progression to dysplasia is not recommended. The annual cancer risk associated with Barrett esophagus without dysplasia is 0.2% to 0.5% per year. For Barrett esophagus with low-grade dysplasia, annual risk for cancer is 0.7% per year, and for Barrett esophagus with high-grade dysplasia, 7% per year.

About 10% of patients with GERD are found to have Barrett esophagus on endoscopy. Studies have suggested individuals with multiple risk factors for esophageal carcinoma and chronic GERD might benefit from screening. Men older than age 50 years with GERD symptoms for more than 5 years and additional risk factors (nocturnal reflux symptoms, hiatal hernia, elevated BMI, intra-abdominal distribution of body fat, tobacco use) may benefit from screening endoscopy. Women do not require routine endoscopic screening for Barrett esophagus. Evidence does not support routine screening for Barrett esophagus based on GERD symptoms for the general population.

Diagnosis and Management

The diagnosis of Barrett esophagus is established based on endoscopic findings (**Figure 7**) with biopsy, which are then confirmed by pathology showing specialized intestinal metaplasia with acid-mucin–containing goblet cells. Endoscopy measurements have categorized Barrett esophagus into short-segment (≤3 cm) or long-segment (>3 cm). The Prague classification more accurately assesses a segment of Barrett esophagus using the degree of circumferential disease (C followed by a number indicating the length in cm) along with maximal Barrett esophagus segment length (M followed by a number indicating the length in cm). For example, a patient with Barrett esophagus extending circumferentially for 2 cm above the squamocolumnar junction but with tongues of Barrett

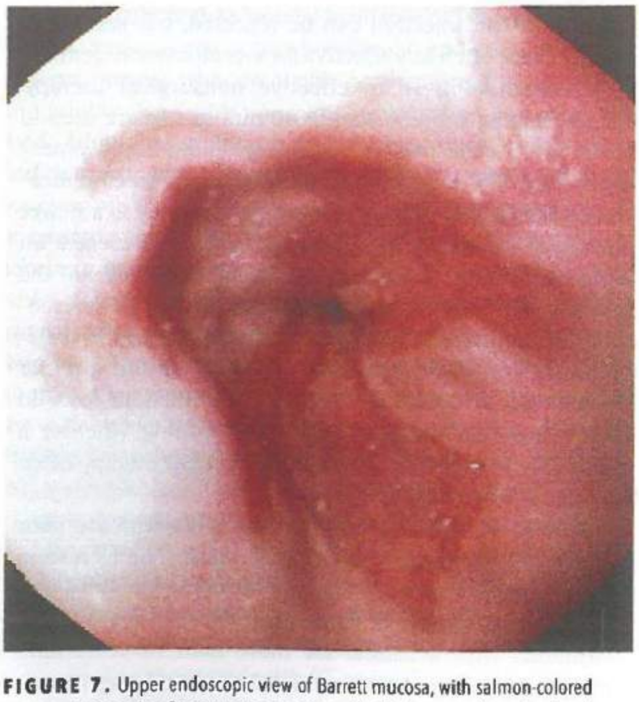

FIGURE 7. Upper endoscopic view of Barrett mucosa, with salmon-colored mucosa representing Barrett mucosa compared with the normal pearl-colored squamous mucosa.

esophagus extending 5 cm above the squamocolumnar junction would have a Prague classification of C2M5.

Barrett esophagus progresses along a pathway from intestinal metaplasia, to indefinite for dysplasia, to low-grade dysplasia, to high-grade dysplasia, to invasive adenocarcinoma. Surveillance and treatment recommendations are based on grade of Barrett esophagus and the presence of dysplasia (**Table 4**).

Chemoprevention is recommended in the form of PPI therapy, but dosing should be based on symptom control and healing of erosive esophagitis. Initial dosing is once daily. There is no strong evidence that antireflux surgery can prevent the progression of Barrett esophagus to adenocarcinoma when compared to medical therapy with PPIs. NSAIDs and aspirin should not be prescribed as an antineoplastic strategy.

Patients with a diagnosis of Barrett esophagus indefinite for dysplasia should start or optimize PPI therapy, followed by repeat upper endoscopy. Treatment to remove Barrett esophagus is recommended for patients with high-grade dysplasia and confirmed low-grade dysplasia. Endoscopy-based therapies include radiofrequency ablation and endoscopic mucosal resection, possibly used in combination. Endoscopic therapies have had similar outcomes to surgery (esophagectomy) in patients with high-grade dysplasia, but local expertise and patient preference will determine the best course of therapy. The Prague classification is useful to more accurately assess response to endoscopic therapy.

Esophageal Carcinoma

Epidemiology

The incidence of esophageal cancer varies widely between regions of the world; high-prevalence areas include Asia and southern and eastern Africa. Worldwide, squamous cell carcinoma comprises about 90% of all esophageal cancers, but incidence has been decreasing in Western countries as the incidence of adenocarcinoma is rising. Esophageal cancer occurs in the fifth to seventh decade of life and is three to four times more common in men. In the United States, about 16,000 new cases are reported annually, with 15,000 deaths occurring within the same year. The overall 5-year survival rate ranges from 15% to 25%, depending on the stage of the cancer at the time of initial presentation. The rate has remained relatively unchanged since 2000.

Risk Factors

Risk factors for the development of adenocarcinoma include GERD, Barrett esophagus, obesity, tobacco use, past thoracic radiation, a diet low in fruits and vegetables, older age, male sex, and the use of medications that relax the LES. Risk factors for squamous cell carcinoma include tobacco and alcohol use, caustic injury, achalasia, past thoracic radiation, nutritional deficiencies (zinc, selenium), poor socioeconomic status, poor oral hygiene, nonepidermolytic palmoplantar keratoderma (an autosomal dominant disorder associated with yellow, waxlike hyperkeratosis on the palms and soles, also known as tylosis), human papillomavirus infection, and nitrosamine exposure.

Diagnosis and Staging

The most common initial presentation of esophageal carcinoma is dysphagia with solid foods, but asymptomatic individuals have been diagnosed based on surveillance endoscopy. Other symptoms include weight loss, anorexia, anemia (secondary to gastrointestinal bleeding), and chest pain. Upper endoscopy with biopsy is the preferred diagnostic test.

Squamous cell carcinoma is most commonly located in the proximal esophagus, and adenocarcinoma is usually found in the distal esophagus.

TNM staging is often done with endoscopic ultrasound for locoregional disease and with CT and PET to identify metastatic disease. For treatment of esophageal carcinoma, see MKSAP 18 Hematology and Oncology.

KEY POINTS

- Barrett esophagus is a premalignant condition caused by longstanding gastroesophageal reflux disease.
- Women with gastroesophageal reflux disease do not require routine screening for Barrett esophagus. **HVC**
- Patients with Barrett esophagus should receive proton pump inhibitor therapy with dosing based on symptom relief and healing of erosive esophagitis.
- Dysphagia with solid foods is the most common presenting symptom of esophageal cancer.

TABLE 4. Practice Guidelines for Endoscopic Surveillance of Barrett Esophagus

Dysplasia Grade	Recommendation
None	If no dysplasia is present, repeat upper endoscopy every 3 to 5 years
Indefinite	Start or adjust proton pump inhibitor therapy, then repeat endoscopy in 3 to 6 months
	If still present, then repeat endoscopy in 1 year
Low-grade	Confirmation by expert pathologist, then proceed to endoscopic eradication therapy (surveillance endoscopy in 12 months is an alternative)
High-grade	Confirmation by expert pathologist
	Endoscopic eradication therapy is preferred

Adapted with permission from Shaheen NJ, Falk GW, Iyer PG, Gerson LB; American College of Gastroenterology. ACG clinical guideline: diagnosis and management of Barrett's esophagus. Am J Gastroenterol. 2016;111:30-50; quiz 51. [PMID: 26526079] doi:10.1038/ajg.2015.322.

Disorders of the Stomach and Duodenum

Dyspepsia

Clinical Features

Dyspepsia is a term used to describe epigastric pain. Associated symptoms can include early satiety, epigastric burning, nausea, and postprandial symptoms, including pain, bloating, or belching. Coexistent heartburn may be present, but it is not a primary symptom of dyspepsia. Recurrent or bothersome vomiting should raise concern for other conditions.

The list of possible organic causes of dyspepsia is extensive (**Table 5**); the most common conditions are peptic ulcer disease and gastroesophageal reflux disease (20% of patients with erosive esophagitis present with dyspepsia). If no organic cause of dyspepsia symptoms is identified after testing, the term *functional dyspepsia* applies.

Functional dyspepsia represents a heterogeneous group of functional gastrointestinal disorders predominated by one or more upper gastrointestinal symptoms. Diagnostic criteria from the fourth Rome working group for functional gastrointestinal disorders are shown in **Table 6**. Functional dyspepsia can be further categorized into postprandial distress syndrome if the patient's predominant symptoms are meal-induced (**Table 7**), or epigastric pain syndrome if the predominant symptoms of epigastric pain or burning are unrelated to meals (**Table 8**).

Evaluation and Management

The approach to testing for dyspepsia should be based on patient age, severity of symptoms, and risk for gastric cancer. Upper endoscopy is commonly ordered to exclude upper gastrointestinal neoplasia; however, it is invasive and costly. Given the low incidence of malignancy and consideration for cost effectiveness in the evaluation of dyspepsia in younger adults, the American College of Gastroenterology (ACG) and the Canadian Association of Gastroenterology (CAG) have jointly recommended routine use of upper endoscopy only in patients aged 60 years and older to exclude malignancy. The ACG/CAG guidelines recommend against the routine use of upper endoscopy in patients younger than age 60 years, even in the presence of alarm features including weight loss, anemia, dysphagia,

TABLE 5. Organic Causes of Dyspepsia

Gastroesophageal	Gastroesophageal reflux disease, peptic ulcer disease, *Helicobacter pylori* gastritis, gastric cancer/lymphoma, gastric amyloidosis, Ménétrier disease, gastroparesis
Small bowel	Celiac disease, Crohn disease
Pancreatic	Pancreatitis, pancreatic cancer
Infectious	*Giardia lamblia, Strongyloides stercoralis*, tuberculosis, syphilis
Common medications	NSAIDs, aspirin, iron, antibiotics (erythromycin, ampicillin), narcotics, estrogens and oral contraceptives, theophylline, levodopa, digitalis
Other systemic conditions	Coronary artery disease, kidney disease, thyroid dysfunction, adrenal insufficiency, hyperparathyroidism, pregnancy

TABLE 6. Rome 4 Diagnostic Criteria for Functional Dyspepsia

One or more of the following:[a]

- Bothersome postprandial fullness
- Bothersome early satiation
- Bothersome epigastric pain
- Bothersome epigastric burning

No evidence of structural disease (including upper endoscopy) that is likely to explain the symptoms

[a]Criteria fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis.

Reprinted with permission from Stanghellini V, Chan FK, Hasler WL, Malagelada JR, Suzuki H, Tack J, et al. Gastroduodenal disorders. Gastroenterology. 2016;150:1380-92. [PMID: 27147122] doi:10.1053/j.gastro.2016.02.011. Copyright 2016, The AGA Institute.

TABLE 7. Rome 4 Diagnostic Criteria for Postprandial Distress Syndrome

Criteria[a]	Supportive Remarks
Must include one or both of the following at least 3 days per week:	Postprandial epigastric pain or burning, epigastric bloating, excessive belching, and nausea can also be present
Bothersome postprandial fullness (i.e., severe enough to affect usual activities)	Vomiting warrants consideration of another disorder Heartburn is not a dyspeptic symptom but may often coexist
Bothersome early satiation (i.e., severe enough to prevent finishing a regular-sized meal)	Symptoms that are relieved by evacuation of feces or gas should generally not be considered as part of dyspepsia
No evidence of organic, systemic, or metabolic disease that is likely to explain the symptoms on routine investigations (including upper endoscopy)	Other individual digestive symptoms or groups of symptoms, such as from gastroesophageal reflux disease and irritable bowel syndrome, may coexist

[a]Criteria fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis.

Reprinted with permission from Stanghellini V, Chan FK, Hasler WL, Malagelada JR, Suzuki H, Tack J, et al. Gastroduodenal disorders. Gastroenterology. 2016;150:1380-92. [PMID: 27147122] doi:10.1053/j.gastro.2016.02.011. Copyright 2016, The AGA Institute.

TABLE 8. Rome 4 Diagnostic Criteria for Epigastric Pain Syndrome

Criteria[a]	Supportive Remarks
Must include the following symptoms at least 1 day per week:	Pain may be induced by ingestion of a meal, relieved by ingestion of a meal, or may occur while fasting
Bothersome epigastric pain and/or burning (i.e., severe enough to affect usual activities)	Postprandial epigastric bloating, belching, and nausea can also be present
No evidence of organic, systemic, or metabolic disease that is likely to explain the symptoms on routine investigations (including upper endoscopy)	Persistent vomiting suggests another disorder
	Heartburn is not a dyspeptic symptom but may often coexist
	The pain does not fulfill biliary pain criteria
	Symptoms that are relieved by evacuation of feces or gas should generally not be considered as part of dyspepsia
	Other individual digestive symptoms or groups of symptoms, such as from gastroesophageal reflux disease and irritable bowel syndrome, may coexist

[a]Criteria fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis.

Reprinted with permission from Stanghellini V, Chan FK, Hasler WL, Malagelada JR, Suzuki H, Tack J, et al. Gastroduodenal disorders. Gastroenterology. 2016;150:1380-92. [PMID: 27147122] doi:10.1053/j.gastro.2016.02.011. Copyright 2016, The AGA Institute.

persistent vomiting, a family history of gastric cancer, immigration from a region with increased risk for gastric cancer (Asia, Russia, and South America), and severe symptoms, because these features are poor predictors of organic pathology, such as malignancy, peptic ulcer disease, or esophagitis. The ACG/CAG guidelines also state that upper endoscopy can be considered regardless of age in patients with a combination of alarm features.

For patients younger than age 60 years with dyspepsia symptoms, the ACG/CAG guidelines recommend noninvasive testing for *Helicobacter pylori*. Other testing, such as routine laboratory testing, screening for celiac disease, abdominal imaging, or gastric emptying, should be considered on an individual basis.

Management of dyspepsia is directed at treatment of the underlying cause. Patients who test positive for *H. pylori* should receive eradication therapy. If *H. pylori* testing is negative or *H. pylori* eradication fails to relieve the dyspepsia, an empiric trial of a proton pump inhibitor (PPI) should be pursued for 4 weeks. Patients whose symptoms are not alleviated with PPI therapy should undergo further evaluation with an upper endoscopy. Patients diagnosed with functional dyspepsia after the exclusion of organic disease can be treated with a variety of interventions (**Figure 8**).

KEY POINTS

HVC • For patients with dyspepsia, routine upper endoscopy to exclude malignancy is reserved for patients older than age 60 years.

• Upper endoscopy should be considered for patients with alarm features such as a family history of gastric cancer, immigration from a region with increased risk for gastric cancer, or severe symptoms, regardless of age.

HVC • Patients younger than age 60 years with dyspepsia symptoms should be tested and treated for *Helicobacter pylori* infection.

Peptic Ulcer Disease

Clinical Features, Diagnosis, and Complications

The most frequently reported symptom of peptic ulcer disease (PUD) is epigastric pain, frequently described as worse during fasting and improved with eating or use of antacid or antisecretory therapy. Pain may be accompanied by other dyspeptic symptoms, such as early satiety, abdominal bloating, nausea, belching, or heartburn (from coexistent esophagitis). Epigastric pain may be minimal or absent in the elderly, immunosuppressed patients, and chronic NSAID users.

NSAIDs and *H. pylori* infection are the two most common causes of PUD, although idiopathic (NSAID-negative, *H. pylori*-negative) PUD is becoming more common in the United States. The causes of idiopathic PUD remain unclear; however, cocaine, methamphetamine, bisphosphonates, selective serotonin reuptake inhibitors, smoking, excessive alcohol consumption, and stress have been implicated. Rare causes of PUD include gastrinoma (Zollinger-Ellison syndrome), systemic mastocytosis, α_1-antitrypsin deficiency, COPD, chronic kidney disease, gastric cancer, gastric lymphoma, Crohn disease, eosinophilic gastroenteritis, or cytomegalovirus (in immunocompromised patients).

The diagnosis of PUD is most often made by upper endoscopy. Abdominal CT is the diagnostic study of choice for suspected perforating PUD, with a sensitivity of 98%.

Complications of PUD include bleeding, perforation, and obstruction. PUD is the most common cause of upper gastrointestinal bleeding. Overt bleeding presents with melena, hematemesis, and/or hematochezia, whereas obscure bleeding presents with iron deficiency anemia and/or stool positive for occult blood. Perforation is likely to present with sudden, severe epigastric pain that can become more generalized, along with peritoneal findings. Symptoms associated with obstruction may include vomiting, early satiety, abdominal distension, and weight loss.

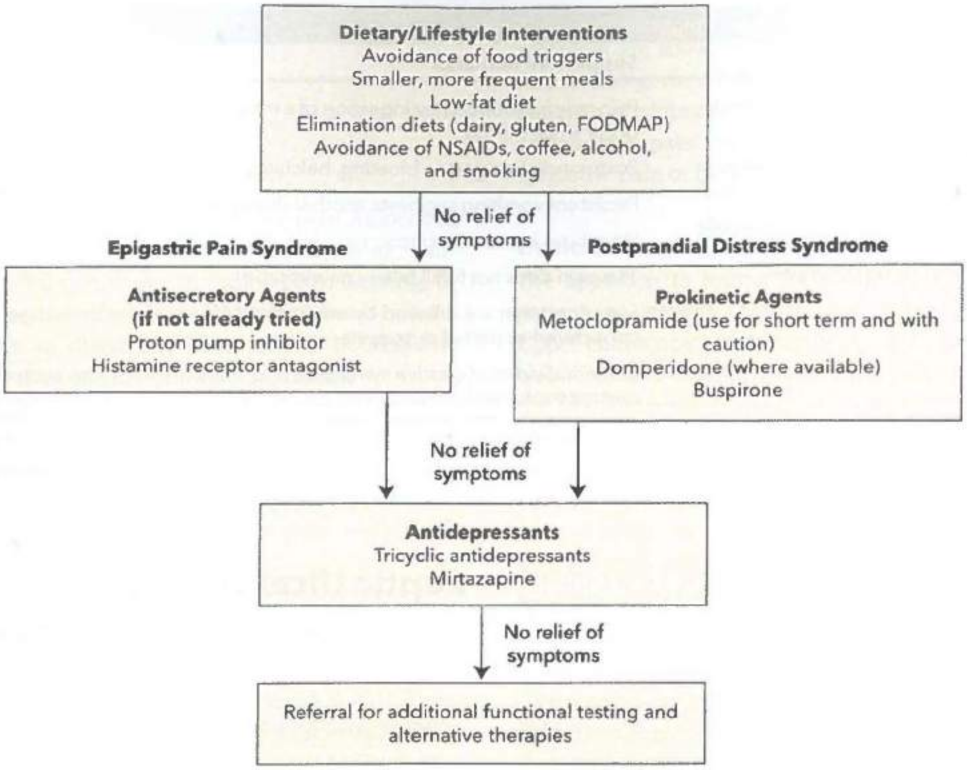

FIGURE 8. Treatment of functional dyspepsia.

FODMAP = Fermentable Oligosaccharides, Disaccharides, Monosaccharides, And Polyols.

Management

Following confirmation of uncomplicated PUD by upper endoscopy, *H. pylori* infection should be treated if identified and eradication confirmed after treatment. If *H. pylori* testing is negative, a once-daily PPI should be initiated and any agent causing PUD (such as an NSAID) should be discontinued.

In patients with bleeding PUD, risk factors that increase the risk for recurrent bleeding and death include tachycardia, hypotension, age older than 60 years, hemoglobin level less than 7 g/dL (70 g/L) (8 g/dL [80 g/L] in patients with cardiovascular disease), and comorbid illness. Interventions to address the modifiable risks should be pursued before upper endoscopy.

Upper endoscopy should be performed within 24 hours. The use of PPIs before upper endoscopy reduces the need for endoscopic therapy only in patients with high-risk ulcer findings. An intravenous dose of erythromycin 30 minutes before upper endoscopy reduces the need for repeat endoscopy by improving gastroduodenal visualization. Nasogastric tube placement is not required before upper endoscopy.

In patients with bleeding PUD related to low-dose aspirin use for secondary cardiovascular prevention, aspirin should be restarted 1 to 7 days after cessation of bleeding. PPI therapy can be discontinued after confirmation of *H. pylori* eradication in patients with *H. pylori*–associated bleeding PUD. NSAIDs should be discontinued in patients with NSAID-induced bleeding PUD. If there is no effective alternative to NSAIDs, a selective cyclooxygenase-2 inhibitor plus a once-daily PPI should be used. Patients with idiopathic ulcers that have bled should receive once-daily PPI therapy indefinitely because of the significant risk for rebleeding.

Repeat upper endoscopy is not performed routinely. Reasons for a follow-up upper endoscopy may include persistent symptoms after 8 to 12 weeks of therapy, ulcers of unknown cause, and if gastric ulcer biopsy was not performed during the initial upper endoscopy.

Perforated PUD is a surgical emergency with a mortality rate of up to 30%; older age, comorbidity, and delayed surgery confer increased risk. Prompt identification, urgent surgical intervention, and proper pre- and postoperative management of sepsis are essential. Postoperative upper endoscopy to rule out gastric cancer should be considered for patients with perforating gastric ulcers.

Gastric outlet obstruction resulting from inflammation or scarring at the pylorus or proximal duodenum should be biopsied at the time of diagnosis to exclude malignancy. For mild symptoms, PPI therapy, treatment of *H. pylori* infection if identified, and/or cessation of NSAIDs may be effective. For severe or persistent symptoms, endoscopic dilation should be pursued, reserving surgery for obstruction that persists after more than two attempts at endoscopic dilation.

KEY POINTS

- NSAIDs and *Helicobacter pylori* infection are the two most common causes of peptic ulcer disease.
- Upper endoscopy is the diagnostic test of choice for peptic ulcer disease.
- Repeat upper endoscopy is reserved for patients with persistent symptoms after 8 to 12 weeks of therapy, ulcers of unknown cause, or if gastric ulcer biopsy was not performed during the initial upper endoscopy.

Helicobacter pylori Infection

Indications for *Helicobacter pylori* Testing

Indications for *H. pylori* testing include active PUD, history of PUD without documented cure of *H. pylori* infection, gastric mucosa-associated lymphoid tissue lymphoma, or history of endoscopic resection of early gastric cancer. Other conditions in which *H. pylori* testing should be considered include dyspepsia in patients younger than age 60 years without alarm features warranting early upper endoscopy, before long-term low-dose aspirin or NSAID use, unexplained iron deficiency anemia, and idiopathic thrombocytopenic purpura in adult patients with gastrointestinal symptoms. Routine testing for *H. pylori* is not indicated in patients with typical gastroesophageal reflux disease symptoms, lymphocytic gastritis, hyperplastic gastric polyps, or hyperemesis gravidarum, or in asymptomatic individuals with a family history of gastric cancer.

Diagnosis

The diagnosis of *H. pylori* infection can be made with gastric biopsies during upper endoscopy, or noninvasively using ^{13}C-urea breath, stool antigen, or serologic testing. The ^{13}C-urea breath and the monoclonal stool antigen are the preferred noninvasive tests because both have sensitivity and specificity greater than 95% for evidence of active infection. Serologic testing for IgG antibodies against *H. pylori* is the cheapest and most convenient method; however, it has the significant disadvantage of being unable to distinguish between active and previous infection. Although the negative predictive value of serologic testing is reasonably high, a positive serologic result in a population with low prevalence of *H. pylori* infection, such as in the United States, requires confirmation with the ^{13}C-urea breath test, stool antigen test, or gastric biopsy. Also, conditions that lower the *H. pylori* density, such as PPI use, recent antibiotic use, atrophic gastritis, intestinal metaplasia, or mucosa-associated lymphoid tissue lymphoma, can result in false-negative results for any of the noninvasive studies. Serologic testing is most useful as an adjunct test in patients with bleeding PUD because of the decreased sensitivity of biopsy in the setting of acute bleeding. Any upper endoscopy for the evaluation of dyspepsia, or with the finding of gastric erosions or ulcers, should include gastric biopsies for *H. pylori* testing by histology or a rapid urea test.

Treatment

Any patient with a test result that is positive for active infection requires treatment with the goal of *H. pylori* eradication. The first course of treatment offers the best chance of eradication and should be carefully chosen. Several first-line treatments are available, with the choice based on resistance patterns of *H. pylori*, previous antibiotic use by the patient, and antibiotic allergies (**Table 9**). In most cases, duration of therapy is 14 days. Second-line therapy in the event of treatment failure should be for a minimum of 14 days, ideally using antibiotics different from those used for initial treatment (**Table 10**).

Eradication Testing

Testing for eradication of *H. pylori* should be done after completion of eradication therapy, using a ^{13}C-urea breath test, fecal antigen test, or biopsies obtained during upper endoscopy at least 4 weeks after completion of eradication therapy. Serologic testing is not used to confirm *H. pylori* eradication because it can remain positive in the absence of active infection.

KEY POINTS

- Patients with active peptic ulcer disease, history of peptic ulcer disease without documented cure of *Helicobacter pylori* infection, gastric mucosa-associated lymphoid tissue lymphoma, or history of endoscopic resection of early gastric cancer must be tested for *H. pylori* and treated if positive.
- Gastric biopsies during upper endoscopy or noninvasive testing methods, including ^{13}C-urea breath and stool antigen testing, can confirm the presence of *H. pylori* infection; negative serologic testing can exclude infection, but a positive serologic result requires confirmation.
- Treatment regimens for *H. pylori* consist of a minimum of three agents, including two antimicrobial agents and one antisecretory agent; treatment duration is 14 days in most cases.
- Testing for eradication of *H. pylori* is performed using a ^{13}C-urea breath test, fecal antigen test, or biopsies obtained during upper endoscopy at least 4 weeks after completion of eradication therapy.

Miscellaneous Gastropathy

Atrophic Gastritis

Chronic atrophic gastritis can present as either an environmental metaplastic atrophic gastritis (EMAG), also called multifocal atrophic gastritis, or an autoimmune atrophic gastritis (AMAG). EMAG is the result of *H. pylori* infection, and typically improves after *H. pylori* eradication. AMAG is caused by autoantibody formation to parietal cell antigens, and is

TABLE 9. First-Line Treatment Options for *Helicobacter pylori* Infection

Treatment Regimen	Duration of Therapy	Clinical Indicators
PPI, standard[a] or double dose twice daily (esomeprazole, once daily only) Clarithromycin, 500 mg twice daily Amoxicillin, 1 g twice daily	14 days	*H. pylori* clarithromycin resistance is known to be <15% No previous history of macrolide exposure for any reason
PPI, standard or double dose twice daily Clarithromycin, 500 mg twice daily Metronidazole, 500 mg three times daily	14 days	*H. pylori* clarithromycin resistance is known to be <15% No previous history of macrolide exposure for any reason Penicillin allergy
PPI, standard dose twice daily Bismuth subcitrate, 120-300 mg or subsalicylate, 300 mg four times daily Tetracycline, 500 mg three times daily Metronidazole, 250 mg four times daily or 500 mg three times daily	10-14 days	Previous macrolide exposure Penicillin allergy
PPI, standard dose twice daily Clarithromycin, 500 mg twice daily Amoxicillin, 1 g twice daily Nitroimidazole, 500 mg twice daily	10-14 days	May be an alternative to standard clarithromycin triple therapy Not validated in North America
PPI, standard dose twice daily Levofloxacin, 500 mg twice daily Amoxicillin, 1 g twice daily	10-14 days	May be an alternative to standard clarithromycin triple therapy Not validated in North America

PPI = proton pump inhibitor.

[a]Standard dose PPIs: esomeprazole, 40 mg; lansoprazole, 30 mg; omeprazole, 20 mg; pantoprazole, 40 mg; rabeprazole, 20 mg.

Adapted with permission from Chey WD, Leontiadis GI, Howden CW, Moss SF. ACG clinical guideline: treatment of *Helicobacter pylori* infection. Am J Gastroenterol. 2017;112:212-239. [PMID: 28071659] doi:10.1038/ajg.2016.563.

TABLE 10. Second-Line Treatment for *Helicobacter pylori* Infection after Failure of Initial Treatment

Treatment Regimen	Duration of Therapy	Clinical Indicators
PPI, standard dose twice daily Bismuth subcitrate, 120-300 mg, or subsalicylate, 300 mg four times daily Tetracycline, 500 mg three times daily Metronidazole, 250 mg four times daily, or 500 mg three times daily	14 days	Failure of clarithromycin-based or levofloxacin-based therapy
PPI, standard dose twice daily Levofloxacin, 500 mg twice daily Amoxicillin, 1 g twice daily	14 days	Failure of bismuth-based or clarithromycin-based therapy
PPI, standard or double dose twice daily Clarithromycin, 500 mg twice daily Amoxicillin, 1 g twice daily	14 days	Failure of bismuth-based therapy
PPI, standard or double dose twice daily Clarithromycin, 500 mg twice daily Metronidazole, 500 mg three times daily	14 days	Failure of bismuth-based therapy Penicillin allergy

PPI = proton pump inhibitor.

Adapted with permission from Chey WD, Leontiadis GI, Howden CW, Moss SF. ACG clinical guideline: treatment of *Helicobacter pylori* infection. Am J Gastroenterol. 2017;112:212-239. [PMID: 28071659] doi:10.1038/ajg.2016.563.

commonly associated with pernicious anemia. The achlorhydria from chronic atrophic gastritis can lead to iron deficiency, small intestinal bacterial overgrowth, and enteric infections. The hypergastrinemia associated with AMAG can promote the development of gastric carcinoid. Goals of therapy for patients with AMAG include the prevention of pernicious anemia and iron deficiency with vitamin B_{12} supplementation and iron replacement, and surveillance for gastric neoplasm. There are no universally accepted surveillance protocols for gastric neoplasm in the United States. A screening upper endoscopy with gastric biopsy is recommended in the setting of pernicious anemia.

Intestinal Metaplasia

Gastric intestinal metaplasia is a preneoplastic gastropathy arising from chronic inflammation associated with *H. pylori* infection. Other causes of chronic inflammation, including other gastric infections, chemical agents, and autoimmune disease, may also promote progression to gastric intestinal metaplasia. There is no conclusive evidence that long-term PPI use promotes the development of intestinal metaplasia. Gastric intestinal metaplasia is believed to be an intermediary stage in the multistage progression from chronic atrophic gastritis to gastric adenocarcinoma. Given the rare occurrence of gastric adenocarcinoma in the United States, there are no universally accepted surveillance strategies. Surveillance programs do exist in other parts of the world, and endoscopic surveillance should be considered in patients at increased risk, such as those with a family history of gastric cancer or who have immigrated from East Asia, Russia, or South America.

Eosinophilic Gastritis

Eosinophilic gastritis is a rare gastropathy characterized by infiltration of eosinophils in the stomach. Secondary causes of eosinophilia should first be excluded, including parasitic and bacterial infections of the stomach, inflammatory bowel disease, hypereosinophilic syndrome, myeloproliferative disorders, polyarteritis, allergic vasculitis, scleroderma, drug injury, and drug hypersensitivity. The cause of primary eosinophilic gastritis is unknown, but believed to be an allergic process. Symptoms vary widely based on depth of eosinophilia and organ involvement, as the small bowel may also be involved. Treatment includes avoidance of food allergens and use of elemental diets and/or glucocorticoids.

Lymphocytic Gastritis

Lymphocytic gastritis is a rare gastropathy typically presenting with mild, nonspecific dyspeptic symptoms and a normal-appearing stomach on endoscopy. On occasion, the stomach may have thickened folds covered by small nodules and aphthous ulceration. Celiac disease is the most common cause of lymphocytic gastritis. Other causes include HIV infection, Crohn disease, common variable immunodeficiency, and, rarely, *H. pylori* infection.

KEY POINTS

- Autoimmune atrophic gastritis is associated with pernicious anemia, iron deficiency, small intestinal bacterial overgrowth, and gastric cancer.
- *Helicobacter pylori* is associated with upper gastrointestinal conditions other than peptic ulcer disease including environmental metaplastic atrophic gastritis, gastric intestinal metaplasia, and, rarely, lymphocytic gastritis.

Gastrointestinal Complications of NSAIDs

Epidemiology and Risk Factors

Upper gastrointestinal complications associated with NSAID use can occur with short- or long-term NSAID use and are dose dependent, with a linear increase in incidence over time with chronic NSAID use. Nearly 1% to 2% of chronic NSAIDs users suffer a clinically significant upper gastrointestinal event (such as a bleeding ulcer, perforation, or obstruction) annually. The rate of upper gastrointestinal adverse events rises to 14% for elderly NSAID users. The greatest risk factor for an NSAID-related upper gastrointestinal bleed is a history of gastrointestinal bleeding. Other risk factors are listed in **Table 11**.

The use of low-dose aspirin for cardioprophylaxis is associated with a two- to fourfold increase in risk for upper gastrointestinal complications including bleeding ulcer, perforation, and obstruction. Use of enteric-coated aspirin does not lower this risk, and an increase in aspirin dosage is associated with an increased risk for upper gastrointestinal complications.

Prevention of NSAID-Induced Injury

Treatment strategies for the prevention of NSAID-related upper gastrointestinal adverse events include the avoidance of NSAIDs, addressing modifiable risk factors, use of a selective cyclooxygenase (COX)-2 inhibitor, or coadministration of gastroprotective agents, such as PPIs, misoprostol, or H_2 blockers. PPIs are the preferred gastroprotective agent for the treatment and prophylaxis of NSAID-related (including aspirin-related) upper

TABLE 11. Risk Factors for NSAID-Related Upper Gastrointestinal Complications

History of upper gastrointestinal bleeding
History of peptic ulcer disease
Helicobacter pylori infection
Age older than 65 years
Hemodialysis or peritoneal dialysis
Use of high-dose or multiple NSAIDs
Concomitant use of aspirin (even low-dose), nonaspirin antiplatelet agents, anticoagulants, oral glucocorticoids, selective serotonin reuptake inhibitors

gastrointestinal complications, and are specifically superior to H_2 blockers in the prevention of PUD and bleeding related to low-dose aspirin use. Misoprostol may be used instead of PPIs in patients with intolerance or unwillingness to take PPIs. However, side effects of misoprostol, such as diarrhea, abdominal discomfort, and nausea, can be limiting, particularly at therapeutic doses, and it is contraindicated in pregnancy.

When coadministered with aspirin, a selective COX-2 inhibitor provides no advantage over an NSAID in the prevention of an upper gastrointestinal adverse event. Given the increased risk for PUD with the concomitant use of either an NSAID or selective COX-2 inhibitor with low-dose aspirin, at-risk individuals should receive gastroprotective therapy. Compared to an NSAID plus a PPI in patients at high risk, a selective COX-2 inhibitor plus a PPI offers a lower risk for perforation, obstruction, and bleeding, as well as for NSAID and COX-2 withdrawal due to gastrointestinal adverse events.

After an NSAID-induced bleeding peptic ulcer, the safest strategy is avoidance of future NSAID use. If an NSAID must be used, the combination of a selective COX-2 inhibitor plus a PPI provides the best gastrointestinal protection, as this combination is more likely to prevent a rebleed than a selective COX-2 inhibitor alone or an NSAID plus a PPI. A treatment approach based on risk for NSAID-related ulcer complications and the need for low-dose aspirin for cardioprophylaxis is provided in **Table 12**.

KEY POINTS

- Upper gastrointestinal complications, such as bleeding, are common with the use of NSAIDs (both short- and long-term) and low-dose aspirin.
- Proton pump inhibitors are the preferred agent for the prevention and treatment of NSAID-related (including aspirin-related) upper gastrointestinal complications.
- In high-risk individuals without cardiovascular disease, including those with previous NSAID-induced gastrointestinal bleeding, the combination of a selective cyclooxygenase-2 inhibitor plus a proton pump inhibitor provides the best gastrointestinal protection if avoidance of NSAIDs is not possible.

Gastroparesis

Presentation

Gastroparesis is a heterogeneous clinical syndrome with three components to the diagnosis: the presence of specific symptoms, absence of mechanical outlet obstruction, and objective evidence of delay in gastric emptying into the duodenum. The most commonly reported symptoms in order of prevalence are nausea (90%), vomiting (84%), upper abdominal pain (72%), and early satiety (60%). Other symptoms may include abdominal fullness and bloating. Symptoms may be chronic or persistent, or may occur intermittently. More severe cases may involve weight loss and evidence of malnutrition and/or dehydration. A viral prodrome, such as gastroenteritis or respiratory infection before symptom onset, may suggest postviral gastroparesis, a condition that frequently resolves over time. Gastroparesis can result from a variety of causes (**Table 13**).

Diagnostic Testing

The first study performed to evaluate suspected gastroparesis is an upper endoscopy to exclude a gastric outlet obstruction. Once a structural cause for symptoms has been excluded, an objective test to assess gastric emptying is performed. There are three testing modalities available to assess gastric emptying: gastric scintigraphy, wireless motility capsule, and the radiolabeled carbon breath test using ^{13}C-labeled *Spirulina platensis* (**Table 14**). Gastric scintigraphy is the most commonly used modality. Narcotic and anticholinergic agents must be stopped at least 72 hours before a gastric emptying study. Once delayed emptying is objectively confirmed, additional testing maybe required to determine the underlying cause of the gastroparesis.

Management

The severity of gastroparesis-related symptoms does not correlate with the severity of delayed gastric emptying, particularly with regard to the symptoms of abdominal bloating and epigastric pain. This suggests that gastroparesis is not simply

TABLE 12. Strategies for Prevention of NSAID-Related Ulcer Complications

	No GI Risk Factors[a]	One to Two GI Risk Factors[a,b]	More than Two GI Risk Factors[a]
No aspirin	NSAID	NSAID plus PPI	Ideally, avoidance of NSAIDs If no alternative to NSAIDs, then a selective COX-2 inhibitor plus a PPI
Low-dose aspirin (81 mg/d) for cardiovascular prophylaxis	Naproxen plus PPI	Naproxen plus PPI	Avoid selective COX-2 inhibitors and use alternative analgesic

COX-2 = cyclooxygenase-2; GI = gastrointestinal; NSAID = nonsteroidal anti-inflammatory drug; PPI = proton pump inhibitor.

[a]GI risk factors: history of GI bleeding; history of peptic ulcer disease; concurrent use of NSAIDs and aspirin (including low-dose aspirin), nonaspirin antiplatelets, anticoagulants, or glucocorticoids; age older than 65 years; any chronic, debilitating illness.

[b]With no prior NSAID-related upper GI bleeding.

Adapted with permission from Lanza FL, Chan FK, Quigley EM; Practice Parameters Committee of the American College of Gastroenterology. Guidelines for prevention of NSAID-related ulcer complications. Am J Gastroenterol. 2009;104:728-38. [PMID: 19240698] doi:10.1038/ajg.2009.115.

TABLE 13. Causes of Gastroparesis

Common causes	Diabetes mellitus (40% in long-standing type 1 diabetes mellitus, 20% in type 2 diabetes mellitus)
	Postsurgical (e.g., Nissen fundoplication, bariatric surgery, pancreatic surgery)
	Idiopathic (e.g., postviral)
Infrequent causes	Connective tissue disease (e.g., systemic sclerosis)
	Neurologic disease (e.g., Parkinson disease)
	Eating disorders
	Hypothyroidism
	Amyloidosis
	Paraneoplastic syndromes (e.g., small cell lung cancer)
	Mesenteric ischemia
	Medications (e.g., opiates, anticholinergic agents)

a motility disorder but one of altered sensation as well. Because poor glycemic control (blood glucose level >200 mg/dL [11.1 mmol/L]) can worsen symptoms as well as gastric emptying, tight glycemic control is the most important element of treatment of diabetic gastroparesis. Initial management also includes correction of dehydration and electrolyte abnormalities, and nutritional support if needed. Initial dietary intervention should consist of small, frequent meals that are low in fat and soluble fiber. Referral to a dietician may be beneficial.

Pharmacologic therapy is used to improve gastric emptying and to treat symptoms. Metoclopramide is the only prokinetic approved in the United States for the treatment of gastroparesis. To minimize the significant risk for neurologic side effects, including dystonia, Parkinsonian movements, and tardive dyskinesia, the lowest effective dose should be used. Therapy must be stopped immediately if neurologic side effects develop.

Erythromycin improves gastric emptying, but its use should be limited to the treatment of flares or short-term use (2 to 3 weeks) due to the risk for tachyphylaxis.

Antiemetics for treatment of nausea and vomiting as well as centrally acting modulators, including tricyclic antidepressants and mirtazapine, can also provide relief of symptoms but have no beneficial effect on gastric emptying.

Interventional therapy, such enteral feeding via jejunostomy, gastric stimulator placement, pyloroplasty, and subtotal or total gastrectomy, can be considered in patients who do not respond to dietary and pharmacologic therapy.

KEY POINTS

- Gastroparesis is a heterogeneous clinical syndrome with three components to the diagnosis: the presence of specific symptoms, absence of mechanical outlet obstruction, and objective evidence of delay in gastric emptying into the duodenum.
- Initial management of gastroparesis includes correction of dehydration and electrolyte abnormalities; nutritional support; small, frequent meals that are low in fat and soluble fiber; and improved glycemic control in patients with diabetes mellitus.
- Metoclopramide is a prokinetic drug that improves gastric emptying but is associated with dystonia, tardive dyskinesia, and Parkinsonism.

Gastric Polyps and Subepithelial Lesions

Gastric Polyps

Polyps in the stomach include fundic gland polyps, hyperplastic polyps, and adenomas. All gastric polyps should be biopsied to determine polyp histology. Fundic gland polyps and

TABLE 14. Diagnostic Tests Assessing Gastric Emptying

Test Modality	Advantages	Disadvantages	Clinical Pearls
Gastric scintigraphy	Considered the gold standard	Radiation exposure (technetium radiolabeled meal) Requires specially trained personnel Cost	4-Hour study is most accurate Assesses solid emptying (liquid emptying is less accurate) Blood sugar should be less than 275 mg/dL (15.3 mmol/L)
Wireless motility capsule	Can also assess small bowel, colon, and whole gut transit No radiation Ambulatory study	Cost Can't be used with pacemaker or defibrillator Risk for capsule retention	Consider in a patient with suspected global motility problem Stop antisecretory agents as study relies on measurement of pH
Gastric emptying breath test	Low cost	Only recently commercially available Efficacy and accuracy limited to clinical trials	—

hyperplastic polyps account for 70% to 90% of stomach polyps. Fundic gland polyps have no potential for malignancy and are commonly seen in the setting of PPI use. Multiple fundic gland polyps are also found in patients with familial adenomatous polyposis.

Hyperplastic polyps of the stomach are thought to have malignant potential, with 5% to 19% harboring dysplasia or malignancy. Risk factors for malignant potential of hyperplastic polyps include size greater than 1 cm and pedunculated morphology. All hyperplastic polyps greater than 0.5 to 1.0 cm in size should be resected.

Adenomas found in the stomach can be sporadic or associated with hereditary syndromes, including familial adenomatous polyposis and Lynch syndrome. Adenomas in the stomach should be resected and endoscopic surveillance should be performed 1 year after resection and then every 3 to 5 years thereafter.

Gastric Subepithelial Lesions

Gastrointestinal Stromal Tumors

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the stomach. GISTs may present with symptoms, such as bleeding or abdominal pain, but are also found incidentally. Endoscopic ultrasonography is the best diagnostic modality for evaluation of a GIST. High-risk features on endoscopic ultrasonography include size greater than 2 cm, lobulated or irregular borders, invasion into adjacent structures, and heterogeneity. Biopsies of a GIST can be done, but the high-risk endoscopic features are better predictors of malignant potential. Treatment consists of surgical excision if the GIST is symptomatic or high-risk features are present. For GISTs without high-risk features, yearly endoscopic surveillance is indicated. See MKSAP 18 Hematology and Oncology for staging and treatment of GISTs.

Carcinoid Tumors

A carcinoid tumor is a well-differentiated neuroendocrine tumor originating in the digestive tract, lungs, or, rarely, the kidneys or ovaries. Carcinoid tumors can be encountered throughout the gastrointestinal tract, including the stomach. They may present symptomatically or may be found incidentally. Carcinoid tumors are usually sporadic but can be seen in the setting of Zollinger-Ellison syndrome, atrophic gastritis, and rare syndromes, such as multiple endocrine neoplasia type 1 and neurofibromatosis type 1. Carcinoid tumors are classified by their size, number, and anatomic distribution. Management includes endoscopic surveillance for lesions smaller than 1 cm in size, especially when multiple lesions are present. Endoscopic or surgical excision is indicated for carcinoid tumors with high-risk features, such as solitary lesions not found in the setting of atrophic gastritis or Zollinger-Ellison syndrome. See MKSAP 18 Hematology and Oncology for treatment of gastric neuroendocrine tumors.

KEY POINTS

- Polyps in the stomach include fundic gland polyps, which have no malignant potential; hyperplastic polyps; and, less commonly, adenomas, which should be resected.
- Gastrointestinal stromal tumors should be evaluated with endoscopic ultrasonography and excised if symptoms or high-risk features are present.
- Carcinoid tumors are well-differentiated neuroendocrine tumors that can occur throughout the gastrointestinal tract, including the stomach.

Gastric Adenocarcinoma

Epidemiology and Risk Factors

Stomach adenocarcinoma has an incidence rate of 6.7 in 100,000 persons and a mortality rate of 3.4 per 100,000 persons in the United States. Rates have steadily decreased since the 1990s. There are two types of gastric cancer: intestinal-type, which is more common, and diffuse-type. *H. pylori* is a recognized risk factor for both types of cancer. Other risk factors primarily associated with intestinal-type gastric adenocarcinoma include male sex; ethnicity (incidence is highest in persons of Asian and Pacific Island descent, and mortality is highest in non-Hispanic white persons); geography (the highest rates worldwide occur in Asia, Eastern Europe, and Central and South America); diet high in smoked, salted, and pickled foods as well as nitrates and nitrites; smoking; and obesity. Additional risk factors include previous stomach surgery, pernicious anemia, and hereditary syndromes such as hereditary diffuse gastric cancer (associated with the diffuse type), Lynch syndrome, and familial adenomatous polyposis. Gastric intestinal metaplasia and dysplasia are also risk factors for gastric adenocarcinoma.

Screening and Surveillance

There is no recommendation for population-based screening for gastric adenocarcinoma in countries with a low incidence of gastric cancer, such as the United States. If intestinal metaplasia with high-grade dysplasia is identified, it should be resected because 25% of cases progress to adenocarcinoma. Screening and surveillance is indicated for patients with familial adenomatous polyposis and Lynch syndrome.

Clinical Manifestations and Diagnosis

Symptoms of gastric adenocarcinoma may be vague. They include poor appetite, weight loss, abdominal pain, early satiety, nausea, and vomiting. Signs of gastric adenocarcinoma include iron deficiency anemia. Diagnosis is typically made by upper endoscopy with biopsies.

For treatment of gastric cancer, see MKSAP 18 Hematology and Oncology.

KEY POINTS

- In countries with a low incidence of gastric cancer, screening for gastric cancer should be reserved for patients with genetic cancer syndromes.
- The primary nongenetic risk factor for gastric cancer is *Helicobacter pylori* infection.
- Upper endoscopy with biopsy is the diagnostic test of choice for gastric cancer.

Gastric Surgery Complications

For complications of bariatric surgery, see MKSAP 18 General Internal Medicine.

Partial or complete gastric resections are performed for benign and malignant disease. The extent of resection, type of reconstruction, and nature of the disease affect postoperative morbidity and mortality. Partial gastric resection allows for preservation of some function of the stomach, but in the setting of malignancy, it requires lifelong surveillance of the remaining stomach for recurrence. Patients who undergo partial gastrectomy for benign disease have an increased risk for cancer in the gastric remnant 15 to 20 years after surgery, with reported frequency ranging from 0.8% to 8.9%.

Dumping syndrome, which results from rapid gastric emptying after gastric surgery, can cause significant postprandial gastrointestinal and vasomotor symptoms. Clinical features of early dumping syndrome occur within 30 minutes of eating due to gastrointestinal hormone hypersecretion, autonomic dysregulation, and bowel distention. Symptoms include palpitations, flushing or pallor, diaphoresis, lightheadedness, hypotension, and fatigue, followed by diarrhea, nausea, abdominal bloating, cramping, and borborygmus. Late symptoms occur 1 to 3 hours after meals because of reactive hypoglycemia and can include decreased concentration, faintness, and altered consciousness. In severe cases, protein-wasting malnutrition can occur. It is estimated that 25% to 50% of all patients who have undergone gastric surgery experience some symptoms of dumping syndrome, but severe, persistent symptoms occur in only about 10%. Oral glucose challenge testing is useful to make the diagnosis, with a sensitivity as high as 100% and a specificity of 94%.

First-line treatment for dumping syndrome is dietary, with smaller, more frequent meals and ingestion of liquids after meals. Decreasing carbohydrate intake, especially simple carbohydrates, and increasing protein and fiber intake may also alleviate symptoms.

Acarbose, an α-glycosidase hydrolase inhibitor that interferes with the digestion of polysaccharides to monosaccharides, can be used for late symptoms of dumping syndrome. Other pharmacologic therapies include anticholinergics to slow gastric emptying, and antispasmodics. Severe cases of dumping rarely require octreotide. If a trial of subcutaneous injections is effective, monthly intramuscular injections of long-acting octreotide can be used.

KEY POINTS

- Patients who undergo partial gastrectomy for malignancy require lifelong surveillance for recurrence of cancer.
- Dumping syndrome results from rapid gastric emptying after gastric surgery; first-line treatment is smaller, more frequent meals with liquids taken following meals.

Disorders of the Pancreas

Acute Pancreatitis

Acute pancreatitis is an inflammatory process involving the pancreas and extrapancreatic organs. It is the most common gastrointestinal cause of hospitalization in the United States. Passage of gallstones, sludge, or biliary crystals (microlithiasis) is the most common cause of acute pancreatitis (**Table 15**).

TABLE 15. Causes of Acute Pancreatitis
Common
Biliary disease
Gallstones
Microlithiasis (1- to 2-mm stones that are not detected by imaging studies)
Alcohol use
Post-endoscopic retrograde cholangiopancreatography
Occasional
Medications
Furosemide
Didanosine
Asparaginase
Mesalamine
Hydrochlorothiazide
6-Mercaptopurine/azathioprine
Simvastatin
Hypertriglyceridemia
Hypercalcemia
Choledochocele
Rare
Autoimmune
Infectious
Viral (mumps, coxsackie B virus, cytomegalovirus)
Parasitic (*Toxoplasma* species, *Ascaris lumbricoides*)
Ischemia
Trauma
Neoplasia
Celiac disease
Genetic (only if attacks are recurrent)

Premature activation of digestive enzymes and release of cytokines cause "autodigestion" of the pancreas and inflammation, which may involve surrounding tissues and distant organs.

Acute pancreatitis is classified as mild, moderately severe, or severe. Mild acute pancreatitis does not involve organ failure or local or systemic complications, usually resolves within 1 week, and has a low mortality rate. Twenty percent of patients with acute pancreatitis develop moderately severe or severe disease. Moderately severe acute pancreatitis involves local or systemic complications such as necrosis or transient organ failure (for less than 48 hours). Severe acute pancreatitis involves systemic inflammatory response syndrome (SIRS), persistent organ failure (usually kidney or respiratory failure), duration longer than 48 hours, and one or more local complications; it has a mortality rate as high as 50%.

Clinical Presentation and Diagnosis

The diagnosis of acute pancreatitis requires two of the following three criteria: (1) acute-onset abdominal pain characteristic of pancreatitis (severe, persistent for hours to days, and epigastric in location, often radiating to the back); (2) serum lipase or amylase levels elevated to three to five times the upper limit of normal; and (3) characteristic radiographic findings on contrast-enhanced CT (**Figure 9**), MRI, or transabdominal ultrasonography. The presence of high fever and leukocytosis is part of the cytokine cascade and does not necessarily indicate infection.

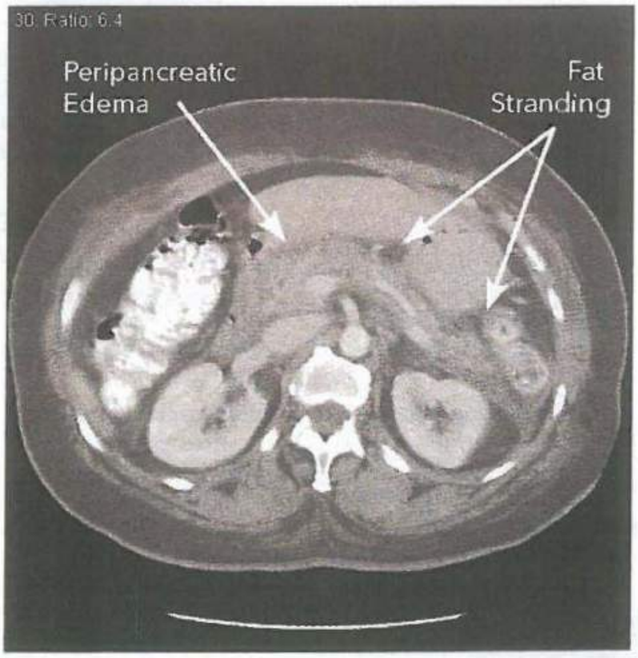

FIGURE 9. CT scan showing acute pancreatitis with peripancreatic fat stranding and inflammation. The hazy appearance of the mesenteric fat surrounding the pancreas in this image is called fat stranding, and the blurring of the margins of the pancreas is consistent with peripancreatic edema, features seen with inflammatory changes of acute pancreatitis.

Because acute pancreatitis is most commonly caused by biliary disorders, patients with acute pancreatitis should undergo transabdominal ultrasonography. Transabdominal ultrasonography is preferred over CT because it has a higher sensitivity for detection of gallstones, avoids the risks associated with intravenous contrast, and is more cost effective. However, abdominal air can limit the visualization of the pancreas in patients with acute pancreatitis. Magnetic resonance cholangiopancreatography (MRCP) may be considered in patients who do not have abnormal findings on ultrasonography. CT may be indicated if the diagnosis is in question or if clinical symptoms are not alleviated within the first 48 hours.

Acute liver-enzyme elevation at presentation suggests biliary obstruction. Serum amylase and lipase levels may be elevated in conditions other than acute pancreatitis, such as kidney disease, acute appendicitis, cholecystitis, intestinal obstruction or ischemia, peptic ulcer, or gynecologic disorders. Enzyme levels may be falsely low or normal in patients with hypertriglyceride-induced pancreatitis because of lipemic-serum interference with laboratory assays. Triglyceride levels should be measured in patients without a biliary cause of acute pancreatitis, and if the triglyceride level is greater than 1000 mg/dL (11.3 mmol/L), it can be considered the cause of the acute pancreatitis.

Prognostic Criteria

Risk factors for severe disease include age older than 55 years, medical comorbidities, BMI greater than 30, the presence of SIRS, signs of hypovolemia on presentation (for example, a serum blood urea nitrogen level greater than 20 mg/dL [7.1 mmol/L] and rising, a hematocrit greater than 44%, or an elevated serum creatinine), the presence of pleural effusions and/or infiltrates, and altered mental status. A systematic review of 18 multiple-factor scoring systems, including the Ranson criteria and the Acute Physiologic Assessment and Chronic Health Evaluation (APACHE) II score, for predicting outcome in acute pancreatitis found these systems to have limited clinical value and accuracy. Scoring systems only identify severe disease as it develops, without enough lead time for intervention, and they are too cumbersome for routine use. Data suggest serum hematocrit, elevated blood urea nitrogen levels, and the presence of SIRS to be as accurate as complex scoring systems in predicting outcome, and they are easier to use.

Management

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Mainstays of management include fluid resuscitation, pain management, and antinausea medication.

Aggressive hydration (250-500 mL/h of intravenous lactated Ringer solution) should be given to patients with acute pancreatitis on presentation and is most beneficial in the first 12 to 24 hours. More rapid fluid resuscitation (boluses) may be needed in patients with severe volume depletion. Patients with organ failure or SIRS should be admitted to an ICU or

CONT.

intermediary care setting, with reassessment of fluid requirements every 6 hours for the first 24 to 48 hours.

Routine use of antibiotics is not warranted in acute pancreatitis, unless there is evidence of extrapancreatic infection, such as ascending cholangitis, bacteremia, urinary tract infection, or pneumonia. Use of prophylactic antibiotics in patients with sterile pancreatic necrosis to prevent infected necrosis is not recommended.

In mild acute pancreatitis, oral feedings can be started as soon as nausea and vomiting are controlled and clinical symptoms begin to subside. Enteral feeding should begin within 72 hours if oral feeding is not tolerated; it is usually required in patients with moderately severe or severe acute pancreatitis. Feeding with a nasojejunal tube has traditionally been preferred, but data suggest that nasogastric feedings are likely equally effective and easier to administer. Enteral feeding promotes a healthy gut-mucosal barrier to prevent translocation of bacteria into inflamed tissues.

If a biliary cause of acute pancreatitis is suspected, serial liver chemistry tests and clinical symptoms can show whether the biliary obstruction is ongoing or resolving. Endoscopic retrograde cholangiopancreatography (ERCP) is not indicated in patients with gallstone pancreatitis unless there is persistent elevation of liver chemistries or if choledocholithiasis is seen on imaging studies. Patients with cholangitis should undergo ERCP within 24 hours of admission. Patients with uncomplicated gallstone pancreatitis should be considered for cholecystectomy before discharge.

There is no value in rechecking serum amylase and lipase levels after the diagnosis is established.

Complications

There are two overlapping phases of acute pancreatitis with two peaks in mortality. The early phase is the first week of the disease, when the body is responding to local pancreatic injury and the cytokine cascade, and SIRS and organ failure are possible. The late phase occurs after the first week and may persist for weeks to months in patients with moderately severe or severe acute pancreatitis. Significant risk for infection in peripancreatic fluid collections and necrosis occurs in the late phase.

Proper classification of fluid collections in acute pancreatitis is important to guide management. An international consensus group updated the Atlanta classification and definitions of acute pancreatitis and its complications in 2012 to try to promote consistency in diagnosis and management. Four types of fluid collections were defined:

1. Acute peripancreatic fluid collections are collections that occur in edematous interstitial pancreatitis (no necrosis) within the first 4 weeks, are thought to occur because of rupture of main or side branch ducts as a result of inflammation, are sterile, and usually resolve spontaneously.
2. Pancreatic pseudocysts are acute peripancreatic fluid collections that have persisted for longer than 4 weeks, developed a well-defined wall, and contain no solid debris (necrosis).
3. Acute necrotic collections (**Figure 10**) are areas of necrosis in the pancreatic parenchyma and/or peripancreatic tissues within the first 4 weeks of acute pancreatitis.
4. Walled-off necrosis (**Figure 11**) occurs after 4 weeks, when the body liquifies the necrosis and contains it within a well-defined wall.

Contrast-enhanced CT may not be able to distinguish solid from liquid content in fluid collections; therefore, necrotic collections are frequently misdiagnosed as pancreatic pseudocysts. Pancreatic pseudocysts do not require drainage

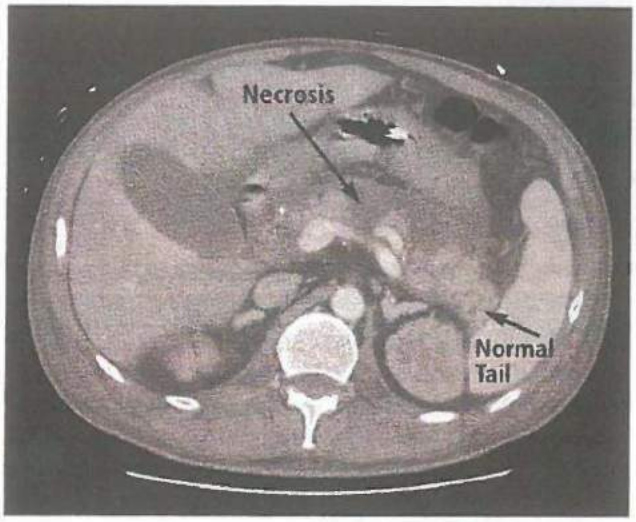

FIGURE 10. CT scan showing acute pancreatitis with hypoperfusion of the body of the pancreas as indicated by lack of enhancement following intravenous contrast infusion (necrosis) and normal perfusion of the pancreatic tail.

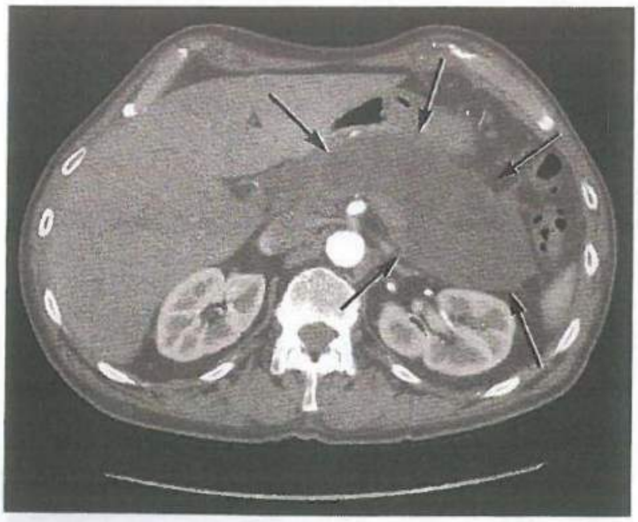

FIGURE 11. CT scan showing maturation and liquefaction of pancreas necrosis of nearly the entire pancreas over 4 weeks in duration with a well-defined rim or wall (*arrows*), known as walled-off necrosis.

H CONT.

unless they cause significant symptoms, regardless of size. Because they contain only fluid, pseudocysts are easily drained under endoscopic or radiographic guidance. Walled-off necrosis is not as amenable to percutaneous or endoscopic drainage due to solid necrotic debris within the cavity and may require endoscopic, radiologic, or surgical debridement.

The management of suspected infected necrosis includes initiation of antibiotics (for example, imipenem-cilastatin, meropenem, or ciprofloxacin plus metronidazole) with consideration of fine-needle aspiration with Gram stain and culture under CT guidance. Drainage procedures or debridement should be delayed for at least 4 weeks if possible to allow encapsulation of the necrosis with a fibrous wall. H

KEY POINTS

- Biliary disease, such as gallstone or microlithiasis, is the most common cause of acute pancreatitis.
- Diagnosis of acute pancreatitis requires two of three criteria: (1) acute-onset upper abdominal pain, (2) serum lipase or amylase levels elevated at least three times greater than the upper limit of normal, and (3) characteristic findings on imaging.
- Patients with acute pancreatitis should undergo transabdominal ultrasonography to evaluate for biliary disease.
- Patients with acute pancreatitis should be hospitalized for fluid administration and close monitoring of cardiovascular, respiratory, and kidney status.

Chronic Pancreatitis

Chronic pancreatitis is thought to develop when the inflammatory response to acute pancreatitis persists and ongoing inflammation activates stellate cells, resulting in a fibroinflammatory response. This causes distorted tissue architecture, loss of normal parenchyma, activation of pancreatic nociceptors, and loss of acinar and islet cell function. Genetic variants affecting inflammatory response, enzyme activation, and tissue repair are thought to play important roles in the pathogenesis of chronic pancreatitis. Many genes have been identified as disease modifiers in chronic pancreatitis, but the gene-environment interaction is not fully understood.

Alcohol use has long been described as a risk factor for chronic pancreatitis, but less than 3% of heavy alcohol users develop pancreatic disease. Patients who drink more than five drinks per day (or 35 drinks per week) seem to be more susceptible to chronic pancreatitis. In the largest study of patients with chronic pancreatitis in North America, only 46% had a history of significant alcohol use. The higher prevalence of alcohol-associated pancreatitis among men could be partially explained by an X chromosome–linked genetic variant, the *CLDN2* gene. Tobacco is considered an independent risk factor. **Table 16** lists common causes of chronic pancreatitis.

Clinical Presentation and Diagnosis

Abdominal pain is the most common presenting symptom of chronic pancreatitis (seen in 85% of patients), but some patients have no pain. Pain patterns can vary from constant, daily pain to intermittent attacks of severe pain. Pancreatic enzyme levels may not increase during attacks of pain because of fibrosis and atrophy of acinar cells and decreased enzyme production. Constant daily pain in chronic pancreatitis causes significant reduction in quality of life, with increased use of health care resources, disability benefits, and time away from employment. Exocrine or endocrine insufficiency occurs in some patients as a result of significant tissue destruction.

Diagnosis of chronic pancreatitis remains challenging because hallmark anatomic features, such as pancreatic calcifications (**Figure 12**), only occur in 25% of patients, and other features of atrophy or duct dilation can occur normally with aging or other disease processes. If pancreatic calcifications are not present on CT imaging of the abdomen, diagnosis usually requires a combined approach in patients with symptoms,

TABLE 16. Causes of Chronic Pancreatitis

Toxic or metabolic
Alcohol, tobacco, hypercalcemia, hypertriglyceridemia, chronic kidney disease
Genetic
Mutations or polymorphisms of the *CFTR, PRSSI, SPINKI, CTRC, CASR, CLDN2* genes
Recurrent and severe acute pancreatitis
Vascular disease/ischemia
Obstructive
Pancreatic tumor, intraductal papillary mucinous neoplasm
Posttraumatic (pancreatic duct stricture)
Autoimmune (type 1 and type 2)
Idiopathic

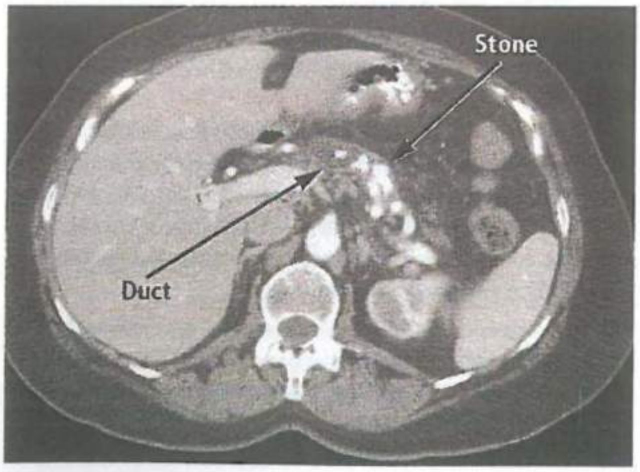

FIGURE 12. CT scan showing chronic calcific pancreatitis with multiple stones in the main duct and side branches of the pancreas.

with advanced imaging using MRI, MRCP, or endoscopic ultrasonography and evidence of pancreatic dysfunction. Pancreatic biopsy is not indicated. ERCP is no longer used as a diagnostic tool for chronic pancreatitis. MRI and MRCP are safer and more readily available; however, sensitivity and specificity are variable. Endoscopic ultrasonography for the diagnosis of chronic pancreatitis has relatively high sensitivity but low specificity, and is not reliable as a single diagnostic test.

Management

The management of chronic pancreatitis focuses on treating symptoms. No effective treatment exists to reverse or halt disease progression. Patients should be counseled to avoid alcohol and tobacco, as this may lessen attacks of inflammation and pain. Intermittent attacks of severe acute pain are treated as in acute pancreatitis. Complications of chronic pancreatitis, including pseudocyst, pancreatic duct stones causing upstream obstruction, and malignancy, should be evaluated with imaging when a patient's symptom pattern changes. Constant, daily pain is more challenging to manage and frequently involves the use of medications such as tramadol, gabapentinoids, and possibly narcotics, although long-term use of narcotics should be avoided due to hyperesthesia and development of tolerance or addiction. Pancreatic enzymes are used to treat steatorrhea but have not been shown to effectively treat pain or prevent attacks of pancreatitis. Two large randomized trials using antioxidants to treat chronic pancreatitis pain showed conflicting results, and guidelines do not support their use. Nerve blocks and neurolysis procedures are not recommended because the response rate is low, and pain relief, if achieved, only lasts a few weeks.

Surgery offers the best long-term results for chronic, refractory pain management and, depending on anatomy and cause, may include lateral pancreaticojejunostomy, duodenal-preserving pancreatic head resection, pancreaticoduodenectomy, distal pancreatectomy, or even total pancreatectomy with or without auto-islet cell transplantation. These procedures have been shown to improve outcomes in patients at high-volume pancreas referral centers. Pancreatic endocrine insufficiency may require specialty referral for labile diabetes management and nutritional consultation.

KEY POINTS

- Abdominal pain, which may occur as intermittent attacks or as ongoing, daily pain, is the most common symptom of chronic pancreatitis.
- HVC Pancreatic biopsy and endoscopic retrograde cholangiopancreatography are not indicated in the diagnosis of chronic pancreatitis.
- Symptomatic management is the cornerstone of treatment for chronic pancreatitis, including patients with refractory pain.
- Patients with chronic pancreatitis should be counseled to avoid alcohol and tobacco use.

Autoimmune Pancreatitis and IgG4 Disease

Autoimmune pancreatitis (AIP) is a frequent manifestation of IgG4-related disease. Other organs that can be affected include the lacrimal and salivary glands, central nervous system, kidneys, thyroid gland, lungs, biliary tract and liver, prostate gland, retroperitoneum, and lymph nodes. Storiform fibrosis and obliterative phlebitis are characteristics seen in the pancreas and biliary tract. The most common pancreatic manifestation of IgG4-related disease is type 1 AIP, with abundant infiltration of IgG4-positive plasma cells and lymphocytes. Type 2 AIP has no or few IgG4-positive cells but is characterized by idiopathic duct-centric neutrophil infiltration, known as a granulocytic epithelial lesion. Type 2 AIP is a pancreas-specific disease with occasional association with ulcerative colitis. The 2011 International Consensus of Diagnostic Criteria for Autoimmune Pancreatitis endorsed the concept of type 1 and type 2 disease, but there is some debate over whether type 2 should be considered an IgG4-related disease.

For more information on IgG4-related disease, see MKSAP 18 Rheumatology.

Clinical Presentation and Diagnosis

Diagnostic criteria for AIP require image findings of a narrowed main pancreatic duct and parenchymal swelling (the "sausage-shaped" pancreas [**Figure 13**]) and response to glucocorticoids. Patients with type 1 AIP have elevated levels of IgG4-positive cells in pancreatic tissue (>10 IgG4-positive cells/hpf), and 60% to 80% of patients have associated sclerosing cholangitis, sclerosing sialoadenitis, or retroperitoneal fibrosis. A significant elevation of serum IgG4 level is helpful in diagnosing type 1 AIP. Patients with type 2 AIP will have no elevation of IgG4-positive cells in pancreatic tissue. Patients with both types may present with abdominal pain or

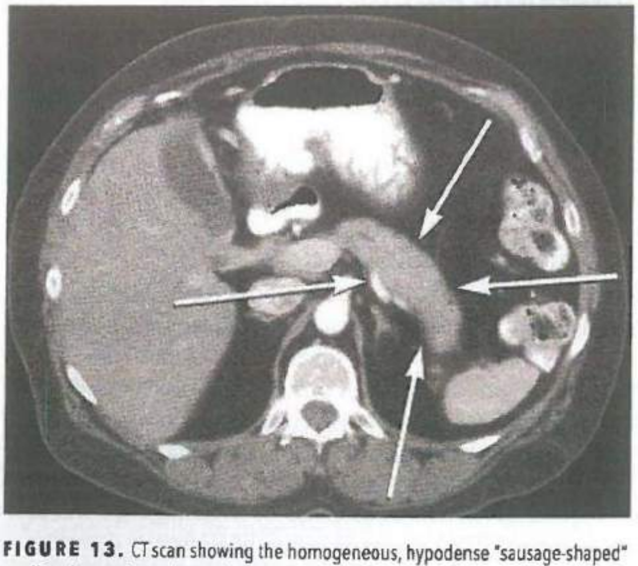

FIGURE 13. CT scan showing the homogeneous, hypodense "sausage-shaped" swelling (*arrows*) seen in autoimmune pancreatitis.

obstructive jaundice with or without a mass. In patients presenting with obstructive jaundice or with a mass, pancreatic malignancy must be considered. Many patients with malignancy have a dilated upstream main pancreatic duct, whereas patients with AIP may have a narrow main duct. Endoscopic ultrasonography and biopsy may be required to differentiate AIP and pancreas neoplasm. Ten percent of patients with type 1 AIP may develop chronic pancreatitis or pancreatic stone formation.

Treatment

Glucocorticoids are effective treatment for types 1 and 2 AIP, starting with oral prednisolone, 0.6 to 1.0 mg/kg/d, and tapered over 2 to 3 months. Response is determined by symptom relief and imaging features. Failure of clinical symptoms to respond to glucocorticoids suggests an incorrect diagnosis, and other causes should be investigated. Up to 60% of patients may relapse. Readministration of glucocorticoids or immunomodulators, such as 6-mercaptopurine, azathioprine, mycophenolate, or rituximab, may be used to treat recurrent AIP.

KEY POINTS

- Diagnosis of autoimmune pancreatitis requires the presence of a narrowed main pancreatic duct and parenchymal swelling ("sausage-shaped" pancreas) on imaging and disease response to glucocorticoids.
- Type 1 autoimmune pancreatitis is characterized by elevated numbers of IgG4-positive cells in pancreatic tissue; most patients also have a significant elevation of IgG4 in serum.
- Patients with type 2 autoimmune pancreatitis have normal IgG4-positive cell counts.
- Types 1 and 2 autoimmune pancreatitis are treated with glucocorticoids, with a relapse rate of up to 60%.

Pancreatic Adenocarcinoma

Pancreatic ductal adenocarcinoma has a poor prognosis and increasing incidence. In 2015, there were approximately 49,000 cases diagnosed in the United States and 41,000 deaths. It is predicted to become the second leading cause of cancer-related death in the United States over the next decade, with an overall 5-year survival rate of less than 6%.

Epidemiology and Risk Factors

Risk factors for pancreatic cancer include age older than 50 years, smoking history, obesity, chronic pancreatitis, and mucinous cystic lesions of the pancreas. Inherited conditions associated with pancreatic cancer include Peutz-Jeghers syndrome, *BRCA2* germline mutations, hereditary pancreatitis, familial atypical multiple mole melanoma, Lynch syndrome, and familial pancreatic cancer with at least two affected first-degree relatives.

There are no standard guidelines for screening high-risk or average-risk patients because no means of accurately detecting tumors at a curable stage has been identified.

Clinical Presentation

Symptoms in patients with pancreatic adenocarcinoma include abdominal pain, back pain, weight loss, and jaundice if the lesion is located in the head of the pancreas obstructing the common bile duct. Pancreatic cancer is highly associated with diabetes mellitus, and two thirds of patients develop new-onset diabetes mellitus in the 36 months surrounding the diagnosis. Venous thromboembolic events and depression have been observed to occur at higher rates in patients with pancreatic adenocarcinoma than in patients with other malignancies.

Diagnosis

Pancreas protocol CT uses multiphasic arterial and venous phases with thin cuts (3 mm) through the abdomen to view the primary tumor's relationship to mesenteric vasculature and to detect metastatic lesions. Some studies suggest that pancreas protocol MRI may be superior to CT for pancreatic disease. Histopathologic confirmation of pancreatic adenocarcinoma is increasingly recommended before initiation of therapy. Endoscopic ultrasound-guided biopsy is preferable to CT-guided biopsy in patients with potentially resectable disease because of ultrasonography's higher diagnostic yield, safety, and lower risk for peritoneal seeding. Patients are considered for primary surgical resection if they have no involvement of mesenteric vasculature or metastatic disease and are healthy enough for major intra-abdominal surgery. Preoperative chemotherapy and/or radiotherapy may be recommended for patients with locally advanced disease.

For staging and treatment of pancreatic adenocarcinoma, see MKSAP 18 Hematology and Oncology.

KEY POINTS

- Diagnosis of pancreatic cancer is suggested by weight loss, abdominal pain, jaundice, and new-onset diabetes mellitus; pancreas protocol CT or MRI help support the diagnosis and delineate the extent of disease.
- Endoscopic ultrasound-guided fine-needle aspiration of the pancreas is recommended to provide histological confirmation of cancer.

Ampullary Adenocarcinoma

Adenocarcinoma of the ampulla of Vater accounts for 0.2% of gastrointestinal malignancies and usually presents early because of obstruction of the biliary system. Endoscopic ultrasonography with biopsy is the preferred method for staging and tissue diagnosis, with 90% accuracy. At least 50% of patients with familial adenomatous polyposis syndrome develop adenomatous changes of the periampullary region; upper endoscopy screening in patients with this syndrome should begin at age 25 to 30 years. See Colorectal Neoplasia for more information on adenomatous polyposis syndromes.

Cystic Lesions of the Pancreas

Pancreatic cysts are found incidentally in 15% of patients undergoing abdominal imaging. The detection of a cystic lesion in the pancreas causes anxiety in patients and clinicians and is a growing driver of health care use in the United States.

Cystic neoplasms of the pancreas are subcategorized as mucin-producing and non-mucin-producing cysts. Mucin-producing cysts are thought to have malignant potential, but most never become malignant. Intraductal papillary mucinous neoplasms (IPMNs) are the most commonly found cystic lesions of the pancreas. Most IPMNs arise from a branched duct and have a very low rate of malignant transformation. In contrast, the rate of malignant transformation is greater than 65% in IPMNs involving the main pancreatic duct (**Figure 14**). Other high-risk features are the presence of symptoms, cyst size greater than 3 cm, and a solid component to the cyst.

Mucinous cystic neoplasms are mucin-producing cysts seen almost exclusively in women (more than 98%) and found in the pancreas body or tail in 90% of cases. They have a thick fibrous capsule with epithelioid cells similar to ovarian stroma surrounding the tumor. Differentiating mucinous cysts from serous cysts, pseudocysts, and cystic neuroendocrine tumors of the pancreas can be challenging, as there is no definitive test with high sensitivity and specificity. Endoscopic ultrasonography with fine-needle aspiration is used for cyst fluid analysis in worrisome lesions; carcinoembryonic antigen levels are frequently elevated in patients with mucinous cysts, whereas serum amylase levels are often elevated in patients with pseudocysts. Cytology of cyst fluid has a low sensitivity (<60%) and is an unreliable predictor of malignant transformation.

Surgical resection of high-risk cysts is currently the only option for treatment. In 2018, the American Gastroenterological Association published guidelines based on expert opinion for the management of asymptomatic cystic neoplasms of the pancreas. Worrisome features include symptoms related to the cyst (jaundice, pancreatitis), size of 3 cm or greater, dilated main pancreatic duct, and a solid component. MRI is preferred for surveillance. Surveillance can be discontinued if no worrisome features develop over 5 years or if the patient is no longer a surgical candidate.

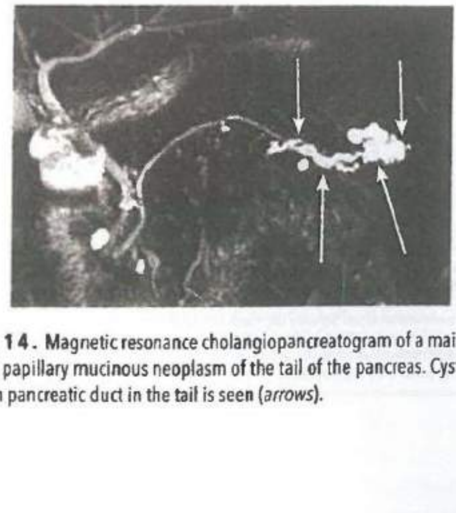

FIGURE 14. Magnetic resonance cholangiopancreatogram of a main-duct intraductal papillary mucinous neoplasm of the tail of the pancreas. Cystic dilation of the main pancreatic duct in the tail is seen (*arrows*).

KEY POINTS

- Most pancreatic cysts never become malignant, with the exception of intraductal papillary mucinous neoplasms involving the main pancreatic duct.
- Cystic lesions are managed with surveillance and surgical resection of high-risk cysts.

Pancreatic Neuroendocrine Tumors

Pancreatic neuroendocrine tumors are rare, representing 3% of primary pancreatic neoplasms. Ten to twenty-five percent of pancreatic neuroendocrine tumors are functional and hypersecrete hormones. Tumors may be sporadic or part of an inherited disorder. Initial evaluation includes blood and urine tests for chromogranin A, 5-hydroxyindoleacetic acid, gastrin, glucagon, insulin and proinsulin (if clinically indicated; requires fasting with concurrent glucose), pancreatic polypeptide, and vasoactive intestinal polypeptide to determine functional status. Most functional pancreatic neuroendocrine tumors secrete gastrin (gastrinoma) or insulin (insulinoma). Genetic testing for multiple endocrine neoplasia type 1 is recommended in all young patients with gastrinomas or insulinomas, and in any patient with a family or personal history of other endocrinopathies or multiple pancreatic neuroendocrine tumors. Genetic testing for other associated inherited disorders, such as von Hippel-Lindau syndrome, tuberous sclerosis, or neurofibromatosis-1, should be considered based on clinical and family history.

Imaging is recommended with multiphasic CT or MRI of the abdomen. Endoscopic ultrasonography (90% sensitive) or octreotide scintigraphy may be needed to detect small lesions. For functional pancreatic neuroendocrine tumors, surgery is recommended if more than 90% of the tumor can be resected. For nonfunctional tumors associated with multiple endocrine neoplasia type 1 and von Hippel-Lindau syndrome, surgery is usually recommended if the tumors are greater than 2 to 3 cm in size. Medical management of gastrinomas includes oral proton pump inhibitors two or three times daily or somatostatin analogs. High-volume or progressive disease is best managed in conjunction with a gastroenterologist.

KEY POINTS

- Ten to twenty-five percent of pancreatic neuroendocrine tumors are functional and hypersecrete hormones, most commonly gastrin or insulin.
- Genetic testing for inherited tumor syndromes should be considered based on patient age and history.

Disorders of the Small and Large Bowel

Diarrhea

Classification

Diarrhea is a condition marked by passage of a greater number of less-formed stools than normal. The classification of diarrhea as acute or chronic is determined by duration of symptoms: acute diarrhea is defined by duration of less than 2 weeks, whereas chronic diarrhea is defined by duration of at least 4 weeks. Acute diarrhea is usually caused by infectious agents; chronic diarrhea is most commonly noninfectious.

Acute Diarrhea

Causes

Causes of acute diarrhea are primarily infectious, including bacteria, viruses, and parasites. These can be divided into noninvasive and invasive causes. Noninvasive causes lead to watery diarrhea; they include *Clostridium difficile*, viruses (such as norovirus and rotavirus), *Escherichia coli*, cholera, cryptosporidia, and *Giardia lamblia*. Invasive causes lead to dysentery or bloody diarrhea and include *Campylobacter*, hemorrhagic *E. coli*, *Entamoeba histolytica*, *Shigella*, and *Salmonella*. Persistent diarrhea (lasting between 14 and 30 days) is usually caused by a parasitic infection. For example, *Giardia lamblia* can begin as an acute infection but then become persistent or even chronic. See MKSAP 18 Infectious Disease for further discussion of infectious diarrhea.

Evaluation

Acute diarrhea may be accompanied by abdominal cramping, tenesmus, flatulence, fever, nausea, and vomiting. For all patients with acute diarrhea, evaluation of hydration status is important. Stool testing for infectious causes depends on many factors, including suspicion of disease outbreak, severity of symptoms, duration of symptoms (>7 days), and whether an individual is considered at increased risk for infectious diarrhea (such as a worker in day care, health care, or food preparation). For example, individuals with *Giardia* present with watery diarrhea that can be explosive and is associated with bloating due to malabsorption. A stool enzyme-linked immunosorbent assay is the best diagnostic test for *Giardia* infection.

Management

Fluid therapy is the mainstay of treatment for acute diarrhea. In patients with severe diarrhea or travelers with cholera-like diarrhea, balanced electrolyte rehydration solutions should be used. Confirmed infection with *C. difficile* should be treated with metronidazole, vancomycin, or other agents, depending on patient comorbidities and clinical severity (see MKSAP 18 Infectious Disease for discussion of *C. difficile* infection). Treatment of diarrhea in travelers includes bismuth and loperamide to relieve symptoms and consideration of empiric antibiotics if symptoms are moderate or severe.

Chronic Diarrhea

Causes

Chronic diarrhea can be grouped into six categories according to type of cause: (1) osmotic, (2) secretory, (3) steatorrhea, (4) inflammatory, (5) motility, and (6) miscellaneous (**Table 17**). These categories may overlap because some diseases have multiple mechanisms that cause diarrhea. The most common

TABLE 17. Types of Chronic Diarrhea

Diarrhea Type	Causes (examples)
Osmotic	Medications (laxatives)
	Undigested sugars (lactose, fructose, sorbitol, mannitol)
Secretory	Medications (nonosmotic laxatives, antibiotics)
	Endocrine (carcinoid, gastrinoma, VIPoma, adrenal insufficiency, hyperthyroidism)
	Bile salt malabsorption (ileal resection, cholecystectomy)
	Noninvasive infections (giardiasis, cryptosporidiosis)
	Small intestinal bacterial overgrowth
Steatorrhea	Maldigestion (decreased bile salts, pancreatic dysfunction)
	Malabsorption (celiac disease, tropical sprue, giardiasis, Whipple disease, chronic mesenteric ischemia, short bowel syndrome, bacterial overgrowth, lymphatic obstruction)
Inflammatory	Inflammatory bowel disease (ulcerative colitis, Crohn disease, microscopic colitis)
	Malignancy (colorectal cancer, lymphoma)
	Invasive infections (*Clostridium difficile*, cytomegalovirus, *Entamoeba histolytica*, tuberculosis)
	Ischemia
	Radiation colitis/enteritis
Motility	Postsurgical (vagotomy, dumping)
	Endocrine (diabetes mellitus, hyperthyroidism)
	Scleroderma
Miscellaneous	Irritable bowel syndrome
	Functional diarrhea[a]
	Factitious
	Overflow
	Fecal incontinence

[a]Frequent or loose or watery stools without abdominal discomfort in the absence of other identifiable causes.

Adapted with permission from Schiller LR, Pardi DS, Spiller R, Semrad CE, Surawicz CM, Giannella RA, et al. Gastro 2013 APDW/WCOG Shanghai working party report: chronic diarrhea: definition, classification, diagnosis. J Gastroenterol Hepatol. 2014;29:6-25. [PMID: 24117999] doi:10.1111/jgh.12392.

causes of chronic diarrhea are irritable bowel syndrome with predominant diarrhea (IBS-D) and functional causes. Medications are also an important cause of chronic diarrhea (**Table 18**).

Evaluation

The evaluation of chronic diarrhea includes a careful history and physical examination. Because IBS-D and functional causes are the most common causes, further diagnostic studies should be reserved for patients whose symptoms suggest another cause.

History and Physical Examination

The pattern of diarrhea can help determine the most likely diagnosis. Steatorrhea is often described as malodorous, greasy, or oily stools that float. The relation of symptoms to eating can also provide clues to the cause of diarrhea. Osmotic diarrhea occurs with eating and subsides with fasting, whereas secretory diarrhea does not subside with fasting. Information about specific dietary factors that commonly cause osmotic diarrhea, such as lactose, fructose, or artificial sweeteners (sorbitol) should be obtained. The patient should be asked about new medications (both prescription and nonprescription) and the timing of the initiation of medication in relation to the onset of diarrhea. Nocturnal symptoms are often related to inflammatory conditions, such as inflammatory bowel disease (IBD). Abdominal pain accompanying diarrhea suggests IBS-D, especially when a bowel movement relieves the pain. In evaluating chronic diarrhea, special attention should be given to features suggestive of malignancy, including rectal bleeding, weight loss, and age older than 50 years. Conditions such as IBS and microscopic colitis are more common in women than in men. IBS is most common in the third and fourth decades of life, whereas microscopic colitis is most common in the seventh and eighth decades.

Physical examination should assess for hydration and nutrition status, perineal disease suggestive of Crohn disease, and sphincter defects suggestive of fecal incontinence.

TABLE 18. Medications that Cause Diarrhea

Common
Antacids, proton pump inhibitors
Chemotherapy
Antibiotics
Colchicine
Metformin
NSAIDs, mesalamine
Cholesterol-lowering drugs
Rarer
ACE inhibitors
Angiotensin receptor blockers
β-adrenergic receptor antagonists
Carbamazepine
Lipase inhibitors
Lithium
Prostaglandin
Vitamin/mineral supplements

Adapted with permission from Schiller LR, Pardi DS, Spiller R, Semrad CE, Surawicz CM, Giannella RA, et al. Gastro 2013 APDW/WCOG Shanghai working party report: chronic diarrhea: definition, classification, diagnosis. J Gastroenterol Hepatol. 2014;29:6-25. [PMID: 24117999] doi:10.1111/jgh.12392.

Additional Testing

The decision to do additional testing, including serologies, stool studies, imaging, and endoscopy, depends on the clinical scenario and likelihood of disease.

Evaluation of the small intestine may include imaging with small-bowel radiography, CT enterography, or MR enterography to identify conditions that could lead to bacterial overgrowth, such as small intestinal diverticular disease, inflammation, or strictures. Upper endoscopy is indicated when small-bowel mucosal disease (such as celiac disease or chronic infection) is suspected. Capsule endoscopy can be used to visualize the small intestine but does not allow for sampling. Device-assisted enteroscopy (balloon or spiral overtubes) can be used in selected patients who require sampling of small-intestinal tissue based on abnormalities found on imaging or capsule endoscopy. The diagnostic yields for capsule endoscopy and device-assisted enteroscopy are low in patients with chronic diarrhea and normal laboratory or imaging studies.

Colonoscopy is the primary diagnostic tool for evaluating causes of diarrhea related to the colon, such as IBD, microscopic colitis, chronic colonic infections, and malignancy. By definition, colon biopsies are required to exclude microscopic colitis. Colonoscopy is especially important in patients with rectal bleeding and/or age older than 50 years.

In cases of chronic diarrhea without an underlying diagnosis, stool studies can help clarify the cause. Analysis of stool includes fecal weight, stool electrolytes, fecal pH, fat content, fecal calprotectin, and presence of blood and leukocytes. In watery stools, fecal electrolytes can be used to calculate the fecal osmotic gap:

$$290 - (2 \times [\text{stool sodium} + \text{stool potassium}])$$

An osmotic gap of less than 50 mOsm/kg (50 mmol/kg) suggests secretory diarrhea, and a gap greater than 100 mOsm/kg (100 mmol/kg) suggests osmotic diarrhea.

The presence of blood or leukocytes in the stool suggests an inflammatory cause. A positive 72-hour stool collection for fecal fat confirms steatorrhea; a random fecal fat assessment may be helpful if a timed collection is not possible. When laxative abuse is suspected, a stool or urine laxative screen can aid in the diagnosis.

Additional testing may be warranted in immunocompromised patients, patients with secretory diarrhea, and those in

whom celiac disease is suspected. Patients found to have a small-bowel tumor in the setting of diarrhea should be considered for additional testing including radioimmunoassays for peptides and/or 24-hour urine 5-hydroxyindoleacetic acid measurement for carcinoid tumors. Testing for carcinoid tumors should be limited to patients with chronic diarrhea and flushing.

Management

The management of chronic diarrhea is determined by its underlying cause. IBS-D and chronic diarrhea with a functional cause are treated with various medications aimed at slowing motility (loperamide), binding bile acids (cholestyramine), altering the gut microbiome (rifaximin), decreasing bowel contractions (eluxadoline), and modulating neurotransmitters (antidepressants).

Treatment of osmotic diarrhea requires avoiding offending agents, such as following a low-Fermentable Oligosaccharides, Disaccharides, Monosaccharides, And Polyols (FODMAP) (**Table 19**) and lactose-free diet.

Treatment of secretory diarrhea is aimed at identification of the underlying cause as well as careful management of hydration. Repletion of fat-soluble vitamins is important in cases of fat malabsorption. Probiotics are not recommended for treatment of diarrhea.

Diarrhea induced by medications necessitates changing medications unless the benefits exceed the potential harms and the diarrhea is manageable from the standpoint of the patient.

KEY POINTS

- Acute diarrhea (of less than 2 weeks' duration) is usually caused by infectious agents; chronic diarrhea (of more than 4 weeks' duration) is most commonly noninfectious.
- Maintaining hydration is the primary goal of treatment for acute diarrhea.
- The primary causes of chronic diarrhea are irritable bowel syndrome with predominant diarrhea, functional causes, and medications.
- HVC Evaluation with imaging, endoscopy, and additional testing should be reserved for patients whose symptoms do not suggest irritable bowel syndrome or a functional cause of chronic diarrhea.

TABLE 19. Sources of FODMAP Carbohydrates

Fructose: honey, apples, pears, peaches, mangos, fruit juice, dried fruit
Lactose: milk, custard, ice cream, yogurt, soft cheeses
Fructans: wheat, rye, onions, leeks, zucchini
Galactans: legumes
Sugar alcohols: xylitol, sorbitol, maltitol, mannitol

FODMAP = Fermentable Oligosaccharides, Disaccharides, Monosaccharides, And Polyols.

Celiac Disease and Nonceliac Gluten Sensitivity

Celiac disease is an immune-mediated disease that primarily affects the small intestine in response to dietary gluten. It is one of the most common causes of malabsorption, and only affects individuals who are genetically predisposed. The immune reaction leads to destruction of the small intestinal villi starting in the proximal duodenum. Although antibodies are produced as part of the immune reaction, they are not thought to be involved in the pathogenesis of celiac disease.

Testing

Testing should be pursued in patients with typical gastrointestinal symptoms or extraintestinal manifestations, and in those with increased risk (patients with type 1 diabetes mellitus, autoimmune thyroid disease, or a first-degree family member with celiac disease). Gastrointestinal symptoms of celiac disease typically include chronic diarrhea, bloating, and weight loss, but may also include atypical symptoms, such as constipation and dyspepsia. Other manifestations include iron deficiency anemia, bone loss, abnormal liver aminotransferase levels, neurologic symptoms, and dermatitis herpetiformis (**Figure 15**). Patients may also be asymptomatic.

Ideally, testing for celiac disease should be done while the patient is on a gluten-containing diet. The best initial step is to test for IgA tissue transglutaminase antibodies. Because IgA deficiency is more common in patients with celiac disease, total IgA levels may also need to be measured. Testing for anti-deamidated gliadin peptide IgG antibodies may also be used. Anti-endomysial antibodies are highly specific and can be

FIGURE 15. Dermatitis herpetiformis, a manifestation of celiac disease, is characterized by pruritic papules and transient, almost immediately excoriated blisters on the elbows, knees, and buttocks.

helpful in making the diagnosis of celiac disease, but measurement with immunofluorescent microscopy is not reliable. Testing for anti-gliadin antibodies (IgA and IgG) should not be used because of low sensitivity and specificity. If clinical suspicion is high and initial testing is negative, additional testing should be pursued. Antibody testing is less reliable if the patient is on a gluten-free diet. In such patients, genetic testing for *HLA-DQ2* or *HLA-DQ8* should be considered.

The vast majority of patients with celiac disease carry *HLA-DQ2* or *HLA-DQ8* genetic susceptibility; however, these genes can be found in up to 40% of the general population. Therefore, genetic testing can rule out disease but not confirm it.

Diagnosis

A positive serologic test for celiac disease requires upper endoscopy with biopsies from the duodenum for confirmation of the disease. There are specific recommendations for the biopsy procedure to minimize false-negative results. Celiac disease is confirmed by the presence of increased intraepithelial lymphocytosis and villous blunting or atrophy of the duodenal villi.

Management and Monitoring

Patients with a diagnosis of celiac disease should be educated about the gluten-free diet by a knowledgeable registered dietician. The treatment of celiac disease is lifelong avoidance of wheat, rye, and barley. Patients should be aware of gluten in medications and over-the-counter products. Dietary oats are generally safe in patients with celiac disease. Monitoring includes clinical assessment of symptoms and signs of celiac disease, assessment of dietary adherence, and confirmation of normalization of antibody levels. Repeat upper endoscopy with biopsies should be considered for individuals with ongoing symptoms while adhering to a gluten-free diet. Assessment of bone density at the time of diagnosis should be considered to ensure adequate bone health.

Nonresponsive Celiac Disease

The most common cause of refractory celiac disease symptoms is gluten exposure. When a patient's symptoms do not resolve completely with adherence to a gluten-free diet, the accuracy of the original diagnosis of celiac disease should be reassessed. Other conditions that may account for ongoing symptoms include IBS, lactose or fructose intolerance, bacterial overgrowth, microscopic colitis, or IBD. Additional evaluation to exclude these as causes is critical before considering the patient to have refractory celiac disease.

A very small number of patients develop refractory celiac disease, in which small-intestinal inflammation persists despite adherence to a strict gluten-free diet. Individuals with refractory sprue are typically older than age 65 years and present with diarrhea, weight loss, dehydration, and nutritional deficiencies. Possible medication-induced sprue should be managed by discontinuing the offending medication. Patients with refractory celiac disease should be managed in a specialized celiac disease center.

Nonceliac Gluten Sensitivity

Nonceliac gluten sensitivity is defined by gastrointestinal and extraintestinal symptoms that occur with gluten ingestion and subside with avoidance of gluten. By definition, celiac disease must be excluded. Because gluten is a nonabsorbable carbohydrate, it can cause gastrointestinal symptoms due to osmotic mechanisms, as well as fermentation by colonic bacteria. Other than assessing symptom response after withdrawal of gluten, there is no diagnostic test for nonceliac gluten sensitivity.

KEY POINTS

- The best initial test for celiac disease is testing for IgA tissue transglutaminase antibodies.
- Up to 40% of the general population carries the *HLA-DQ2* or *HLA-DQ8* mutation, so genetic testing alone cannot be used to diagnose celiac disease. **HVC**
- The treatment of celiac disease is lifelong avoidance of gluten.
- The most common cause of refractory celiac disease symptoms is gluten exposure.

Malabsorption

Small Intestinal Bacterial Overgrowth

Small intestinal bacterial overgrowth (SIBO) is caused by various conditions, including impaired motility, strictures (for example, in Crohn disease), or blind loops (for example, small-bowel diverticula). There is some evidence that SIBO could contribute to symptoms in IBS-D.

Classically, SIBO is defined by the presence of more than 10^5 colony-forming units per mL of jejunal aspirate. Based on its use in research studies, jejunal aspirate is considered the gold standard but is often not used in clinical practice due to the requirement for endoscopy to obtain cultures, the patchy nature of small intestinal overgrowth, and oropharyngeal contamination of the specimen. Glucose and lactulose breath tests have acceptable specificity (around 80%) but poor sensitivity (30%-40%) for diagnosing SIBO. Diagnosis requires typical symptoms and a confirmatory test, usually breath testing. Treatment consists of antibiotic therapy and often requires repeated courses if the underlying condition cannot be resolved.

Short Bowel Syndrome

Short bowel syndrome is defined by a small-intestine length of less than 200 cm, with loss of absorptive area leading to maldigestion, malabsorption, and malnutrition. Surgery for strangulated bowel, Crohn disease, ischemia, trauma, and weight loss can all lead to short bowel syndrome.

Treatment depends on whether the patient has an intact ileocecal valve and colon or an ostomy. Patients with short

bowel syndrome and an ostomy usually require parenteral nutrition and hydration. Those with extensive ileal resection should be tested and treated for vitamin B_{12} deficiency. Adjunctive therapies include antimotility and antisecretory drugs. Glucagon-like peptide 2 and its analog, teduglutide, are new pharmacologic agents for treatment of short bowel syndrome. Both have been evaluated in randomized trials and found to increase intestinal wet weight absorption and decrease parenteral fluid support in patients with short bowel syndrome.

Carbohydrate Malabsorption

Carbohydrates can be classified as monosaccharides (glucose, fructose), disaccharides (lactose, sucrose), oligosaccharides (maltodextrose), or polyols (sorbitol, mannitol). These short-chain carbohydrates are osmotically active and can lead to increased luminal water retention and gas production through colonic fermentation. These two actions can cause gastrointestinal symptoms, including gas, bloating, and diarrhea.

Lactose malabsorption is commonly due to loss of the brush border lactase enzyme in adulthood. Fructose malabsorption can also lead to gastrointestinal symptoms such as bloating and diarrhea. Although both lactose and fructose breath tests are available, testing is often not required, as symptoms subside with exclusion of the sugar from the diet and recur with ingestion.

KEY POINTS

- Small intestinal bacterial overgrowth is caused by various conditions, including impaired motility, strictures, or blind loops, and is treated with antibiotic therapy.
- Short bowel syndrome is defined by a small-intestine length of less than 200 cm, resulting in maldigestion, malabsorption, and malnutrition.
- Lactose malabsorption is common, with symptoms occurring when lactose is ingested and subsiding with exclusion of lactose from the diet.

Inflammatory Bowel Disease

IBD is an idiopathic chronic inflammatory condition of the gut that includes ulcerative colitis and Crohn disease. In addition, microscopic colitis is considered a type of IBD with distinct clinical and pathologic features. The pathogenesis of IBD likely involves host genetic predisposition and abnormal immunologic responses to endogenous gut bacteria.

Risk Factors

The primary risk factor for development of IBD is family history, with a risk of approximately 10% for first-degree relatives of affected patients. Individuals of Ashkenazi Jewish descent have increased risk for IBD. Tobacco smoking increases the risk for Crohn disease and is protective for ulcerative colitis.

IBD has a bimodal age presentation, with an initial peak incidence in the second to fourth decades of life followed by a less prominent second peak in the seventh and eighth decades.

Clinical Manifestations

Ulcerative Colitis

The major symptoms of ulcerative colitis include diarrhea, abdominal discomfort, rectal bleeding, and tenesmus, with symptoms varying depending on the extent and severity of disease. Symptoms typically have a slow, insidious onset and often have been present for weeks or months by the time the patient seeks care, although ulcerative colitis may present acutely, mimicking infectious colitis.

Rectal inflammation (proctitis) causes frequent defecatory urges and passage of small liquid stools containing mucus and blood. Although bloody diarrhea is considered the hallmark presentation of ulcerative colitis, diarrhea is not always present. Patients with proctitis or proctosigmoiditis may have constipation. Abdominal pain is usually not a prominent symptom of ulcerative colitis; however, most patients with active disease experience vague lower-abdominal discomfort relieved with defecation. Physical examination in patients with mild or moderate ulcerative colitis is usually normal but may reveal mild lower-abdominal discomfort over the affected colonic segment. The presence of fever, nausea, vomiting, or severe abdominal pain indicates a severe attack or complication such as superimposed infection or toxic megacolon.

Crohn Disease

The clinical presentation of Crohn disease may be subtle and varies depending on the location and severity of inflammation along the gut axis as well as the presence of intestinal complications such as abscess, stricture, or fistula. Compared with ulcerative colitis, abdominal pain is a more common symptom of Crohn disease. The ileocecal area is the most common bowel segment affected by Crohn disease, and it often presents insidiously with mild diarrhea and abdominal cramping. Abdominal examination may reveal fullness or a tender mass in the right hypogastrium. Some patients present initially with a small-bowel obstruction caused by impaction of indigestible vegetables or fruit. Occasionally, the main presenting symptom is acute pain in the right lower quadrant, mimicking appendicitis. In patients with Crohn colitis, tenesmus is less common than in patients with ulcerative colitis because the rectum is often less inflamed than other colonic segments. Perianal disease is a common presentation of Crohn disease with anal fissures, ulcers, and stenosis.

Fistulae are a frequent manifestation of the transmural nature of Crohn disease and consist of abnormal connections between two epithelial surfaces (perianal, enteroenteric, enterocutaneous, rectovaginal, enterovesical). Drainage of fecal material from fistulae leads to symptoms such as passage of feces through the vagina (rectovaginal fistula). Intra-abdominal

abscesses may form; the classic presentation is spiking fevers and focal abdominal tenderness, which may be masked by the use of glucocorticoids. Strictures represent long-standing inflammation and may occur in any segment of the gastrointestinal tract, although the terminal ileum is the most common site. Strictures may be secondary to fibrosis or severe inflammatory luminal narrowing. Patients with intestinal strictures often initially present with colicky postprandial abdominal pain and bloating that may progress to complete intestinal obstruction.

Table 20 summarizes the features of ulcerative colitis and Crohn disease.

Extraintestinal Manifestations

Inflammatory conditions involving extraintestinal structures, including the joints, eyes, liver, and skin, may occur in patients with IBD. These extraintestinal manifestations are categorized as either associated with active bowel disease or independent of bowel inflammation. Up to 30% of patients with IBD experience an extraintestinal manifestation at some time during the course of their disease; peripheral arthritis is the most common. See MKSAP 18 Rheumatology for discussion of IBD-related arthritis.

The two most common dermatologic extraintestinal manifestations are erythema nodosum and pyoderma gangrenosum. Erythema nodosum most commonly presents as single or multiple tender nodules on extensor surfaces of the lower extremities (**Figure 16**). Pyoderma gangrenosum typically presents as a papule that rapidly develops into an ulcer with undermined and violaceous borders (**Figure 17**). Both manifestations usually correspond to underlying IBD activity. See MKSAP 18 Dermatology for discussion of cutaneous manifestations of IBD.

Ocular extraintestinal manifestations of IBD include episcleritis and uveitis. Episcleritis is more common and consists of injection of the sclera and conjunctiva. It does not affect visual acuity and occurs in association with active bowel disease. Uveitis presents with headache, blurred vision, and

TABLE 20. Features of Ulcerative Colitis and Crohn Disease

Feature	Ulcerative Colitis	Crohn Disease
Depth of inflammation	Mucosal	Transmural
Pattern of disease	Contiguous and symmetric	Skips areas and asymmetric
Location	Colorectum	Mouth to anus
Rectal involvement	Nearly 100%	Less common
Ileal disease	Backwash ileitis (15%)	Common
Fistulas, abscess, and strictures	Rare	Common
Perianal disease	Rare	Common
Granulomas	Unlikely	In approximately 30%
Overt rectal bleeding	Common	Less common
Tobacco use	Protective	Exacerbates

FIGURE 16. Erythema nodosum, a manifestation of inflammatory bowel disease, typically appears as ill-defined erythema overlying subcutaneous, tender nodules most commonly symmetrically located on the anterior shins.

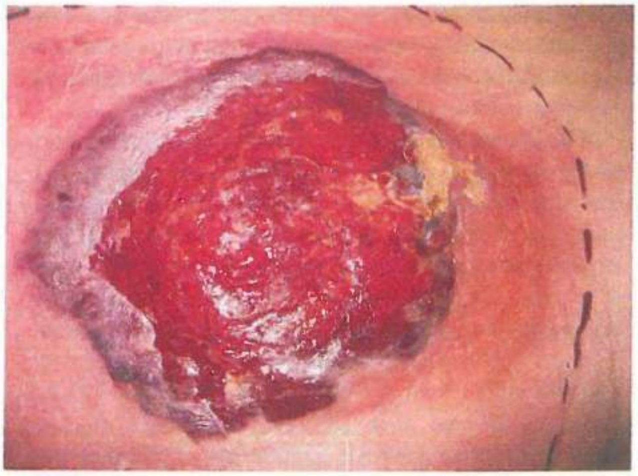

FIGURE 17. Pyoderma gangrenosum, a manifestation of inflammatory bowel disease, typically begins as a small pustule or red nodule that rapidly expands with an edematous, infiltrated, actively inflamed border and a painful, exudative wet ulcer. The border is characteristically violaceous with an edge that overhangs the ulcer.

photophobia. Uveitis is an ocular emergency requiring prompt referral to an ophthalmologist. See MKSAP 18 General Internal Medicine for discussion of episcleritis and uveitis.

Primary sclerosing cholangitis is a major liver manifestation of IBD, occurring in 5% of patients. Patients most often present with isolated elevations in the serum alkaline phosphatase level. The liver disease is typically progressive and independent of the outcome of the IBD. See Disorders of the Liver for discussion of primary sclerosing cholangitis.

Diagnosis

The diagnosis of IBD relies on the integration of the clinical presentation, exclusion of infectious enteropathogens, endoscopic appearance, histologic assessment of mucosal biopsies, and radiologic features. IBD should be considered in any patient with chronic or bloody diarrhea. It is paramount to exclude infection, particularly with *C. difficile* and Shiga toxin-producing *E. coli*, by stool tests, especially in patients with acute onset of symptoms. Fecal calprotectin should be considered to help differentiate IBD from irritable bowel syndrome. Laboratory testing helps to assess disease activity. Common findings include anemia and hypoalbuminemia. Many patients develop iron deficiency anemia from chronic blood loss. Hematologic changes, such as thrombocytosis and leukocytosis, reflect active inflammatory disease. Persistently abnormal serum alkaline phosphatase levels should prompt further investigation for primary sclerosing cholangitis.

Endoscopy (either sigmoidoscopy or colonoscopy) with biopsy is needed to help make the diagnosis of IBD. Colonoscopy is most commonly used to assess the extent and severity of disease. At presentation, 50% of patients with ulcerative colitis have disease limited to the rectum and sigmoid (proctosigmoiditis), 20% have left-sided disease (to the splenic flexure), and 30% present with pancolitis (to the cecum). Endoscopic findings range from decreased vascular pattern with erythema and edema in mild disease to large and deep ulcerations in severe disease. Histopathology characteristically shows features of chronic colitis with distorted and branching colonic crypts along with crypt abscesses.

Crohn disease has a different pattern of distribution from ulcerative colitis: 50% of patients have ileocolonic disease, 30% have isolated small bowel disease, and 20% have colonic disease. A minority of patients have isolated upper gastrointestinal tract or perianal disease in the absence of inflammation in the small bowel or colon. The earliest endoscopic findings of Crohn disease include aphthous ulcers, which can coalesce to form stellate ulcers, and a "cobblestone" mucosal appearance. A characteristic mucosal feature of Crohn disease is the so-called "skip lesion," consisting of affected areas separated by normal mucosa. Granulomatous inflammation is characteristic of Crohn disease but uncommonly found on mucosal biopsies. Histopathology in small-intestinal Crohn disease will show chronic jejunitis or ileitis, and Crohn colitis will have histology similar to that in ulcerative colitis, with exception of granulomas.

Radiographic studies establish the location, extent, and severity of IBD. Patients with a severe attack of IBD require a plain abdominal radiograph to assess for a dilated colon (indicative of evolving toxic megacolon) or small-bowel obstruction (**Figure 18**). CT or MR enterography provides information about the location and severity of small bowel disease and the presence of complicating fistula, abscess, or stricture. Video capsule endoscopy is a highly sensitive modality for detection of small inflammatory lesions of the intestine, although it is not commonly required.

Treatment

The goals of therapy for IBD are to induce and maintain remission, and to prevent disease- and treatment-related complications. Four categories of drugs are used to treat IBD: 5-aminosalicylates, glucocorticoids, immunomodulators, and biologics. Stratification based on clinical severity is important in guiding IBD management. Currently, there are no validated or consensus definitions of mild, moderate, or severe IBD. However, three domains are relevant to the evaluation of disease severity in IBD: impact of the disease on the patient (clinical symptoms, quality of life, and disability); inflammatory burden (extent, location, and severity of bowel involvement); and disease course, including structural

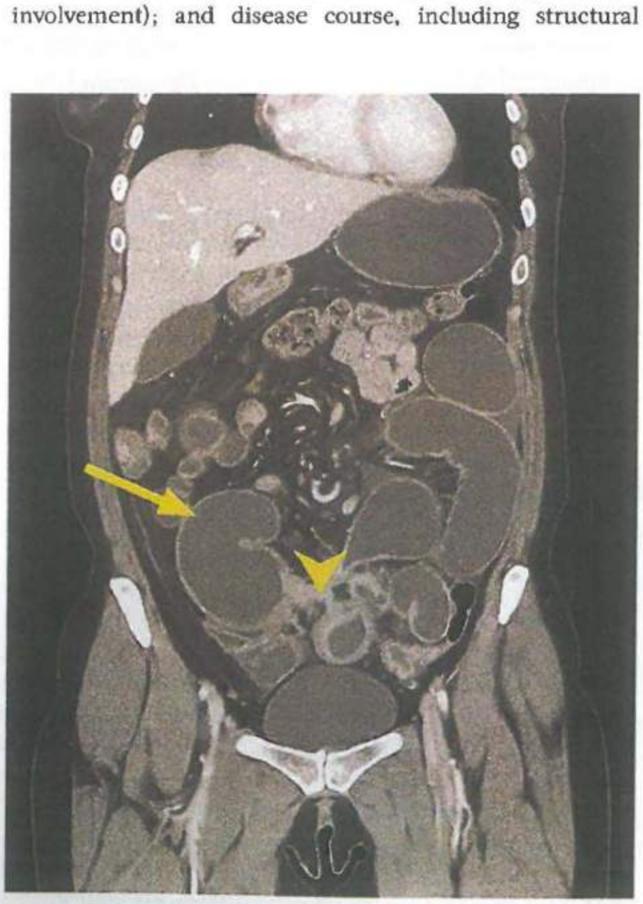

FIGURE 18. CT scan of the abdomen and pelvis in a patient with Crohn disease, showing small-bowel obstruction with dilated loops of small intestine (*arrow*) and matted loops of bowel (*arrowhead*) in the pelvis.

damage. Surgery is reserved for refractory symptoms and complications.

Patients with IBD are at markedly increased risk for venous thromboembolism. The cause of thromboembolism is multifactorial and related to severity of disease, immobilization, and hospitalization. It is important that all hospitalized patients with IBD be given venous thromboembolism prophylaxis with subcutaneous heparin. Only in cases of massive gastrointestinal bleeding with severe anemia, tachycardia, and hypotension should nonpharmacologic prophylaxis with intermittent pneumatic compression of the lower extremities be used.

Pharmacotherapy

5-Aminosalicylates

5-Aminosalicylates (5-ASAs) are believed to have an anti-inflammatory mechanism of action. Various formulations and controlled-release systems are available, with some preparations purported to deliver 5-ASAs to the small bowel.

5-ASAs are the mainstay of treatment of mild to moderate ulcerative colitis, with a dose-dependent response when used to induce disease remission. Three major factors need to be considered when choosing therapy for ulcerative colitis (**Figure 19**). Patients with proctitis or left-sided disease should receive topical therapy with 5-ASA suppositories and enemas. In mild to moderate ulcerative colitis, combined 5-ASA therapy (oral and topical) is superior for induction of remission compared with oral or topical therapies alone. Once remission is achieved, 5-ASAs are effective in maintaining it. Of the available agents, sulfasalazine has the most adverse effects, including fever, rash, nausea, vomiting, and headache. In addition, sulfasalazine may cause reversible sperm abnormalities and impair folate absorption.

Despite the availability of several formulations designed to deliver the drug to the small bowel, 5-ASAs have not proved to be efficacious in small-bowel Crohn disease.

Glucocorticoids

Oral and intravenous glucocorticoids are commonly used to treat moderate to severe flares of IBD and are effective in inducing remission. However, glucocorticoids are not effective for maintenance therapy and have significant adverse effects. One formulation of oral budesonide is a controlled-release glucocorticoid with high first-pass metabolism in the liver and minimal systemic adverse effects. It is effective in inducing remission in mild to moderate ileocolonic Crohn disease. Another oral formulation is multimatrix (MMX) budesonide, designed to release the drug throughout the colon. It is effective in inducing remission in mild to moderate ulcerative colitis.

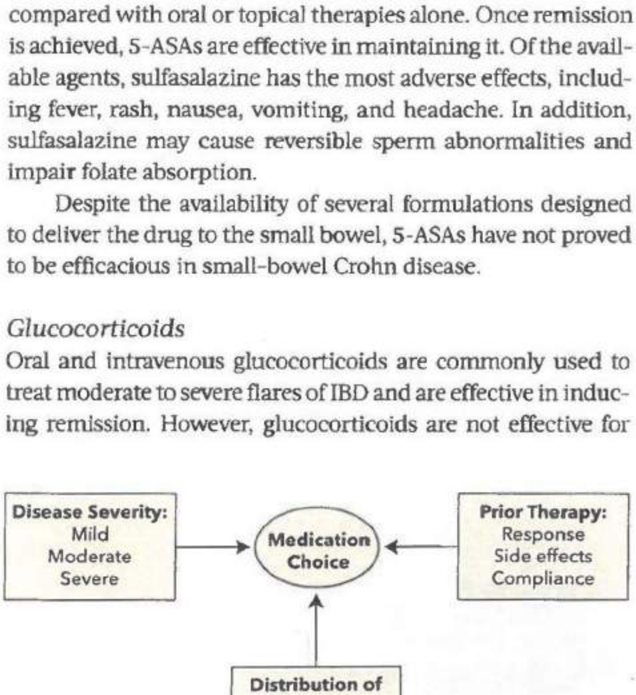

FIGURE 19. Factors to consider when choosing medical therapy for ulcerative colitis.

Immunomodulators

Thiopurines (azathioprine and mercaptopurine [6-MP]) are immunomodulators used as glucocorticoid-sparing agents. They have a slow onset of action (2-3 months) and patients require a tapering glucocorticoid regimen to bridge the time interval until the thiopurines take effect. Thiopurine methyltransferase, a key enzyme involved in the metabolism of azathioprine and 6-MP, exhibits a population polymorphism that greatly increases the risk for bone marrow toxicity with use of these agents. Therefore, before initiation of thiopurine therapy, testing for the *TPMT* genotype or phenotype (enzyme activity) is recommended to help prevent toxicity by identifying individuals with low or absent *TPMT* enzyme activity. However, regardless of *TPMT* status, all patients require monitoring with complete blood counts and liver chemistry testing because 70% of patients who develop leukopenia while using these agents do not have *TPMT* mutations. Azathioprine and 6-MP are reported to cause the rare hepatosplenic T-cell lymphoma. Azathioprine and 6-MP are effective in maintaining remission in patients with ulcerative colitis and should be considered in glucocorticoid-dependent patients. This includes patients who require two courses of glucocorticoids for induction of remission within 1 year, or patients who require intravenous glucocorticoids for acute disease flare.

Methotrexate is an immunomodulator that is beneficial in inducing and maintaining remission in Crohn disease but not in ulcerative colitis. Side effects of methotrexate include hepatotoxicity and interstitial pneumonitis, which can manifest with cough and dyspnea of insidious onset.

Biologic Agents

Tumor necrosis factor (TNF)-α is a proinflammatory cytokine that plays a critical role in the pathogenesis of both Crohn disease and ulcerative colitis. The anti-TNF agents infliximab, adalimumab, and certolizumab are used to treat moderate to severe Crohn disease. Infliximab is administered by intravenous infusion; adalimumab and certolizumab are given subcutaneously. Combination therapy with infliximab and azathioprine is more efficacious than monotherapy with either agent alone in achieving glucocorticoid-free remission and mucosal healing. There is increasing evidence for the use of biologic agents early in the course of disease. Before initiation of anti-TNF agents, patients should undergo testing for latent tuberculosis because of an increased risk for reactivation of tuberculosis during therapy. If latent tuberculosis is present,

treatment with isoniazid should occur for at least 2 months before initiation of anti-TNF therapy. Patients should also be assessed for chronic hepatitis B viral infection before starting anti-TNF therapy and receive treatment if needed.

The anti-TNF agents infliximab, adalimumab, and golimumab are used to treat moderate to severe ulcerative colitis. Combination therapy with infliximab and azathioprine is more effective than monotherapy with either agent in achieving glucocorticoid-free remission and mucosal healing.

The anti-adhesion agents natalizumab and vedolizumab are effective in inducing and maintaining remission for moderate to severe Crohn disease. Ustekinumab, a monoclonal antibody that blocks the biologic activity of interleukin-12 and -23 by inhibiting receptors for these cytokines on T-cells, is efficacious in severe Crohn disease. These agents are typically used after anti-TNF therapies prove ineffective.

Surgery

Indications for surgery in patients with Crohn disease include medically refractory fistula, fibrotic stricture with obstructive symptoms, symptoms refractory to medical therapy, and cancer. The guiding principle of surgery in Crohn disease is the preservation of bowel length and function, as the rate of disease recurrence after segmental resection is high. Patients with Crohn disease who undergo surgery require aggressive pharmacologic treatment with anti-TNF agents and/or immunomodulators to decrease the rate of postoperative recurrence of Crohn disease.

In patients with ulcerative colitis, total proctocolectomy with end-ileostomy or ileal pouch-anal anastomosis is performed for medically refractory disease, toxic megacolon, or carcinoma.

Health Care Considerations

Patients with IBD are at increased risk for vaccine-preventable illnesses, and vaccines are underutilized in this patient population. Inactivated vaccines can be safely administered to all patients with IBD, regardless of immunosuppression. Patients with IBD should receive a seasonal influenza vaccine as well as the 13-valent pneumococcal conjugate vaccine and the 23-valent pneumococcal polysaccharide vaccine. Ideally, pneumococcal vaccination should occur before beginning immunosuppressive therapy. Live vaccines such as measles, mumps, rubella; varicella; and herpes zoster are contraindicated in immunosuppressed patients with IBD. See MKSAP 18 General Internal Medicine for discussion of vaccination strategies.

Women with IBD are at increased risk for developing cervical dysplasia; this risk is greater in women with Crohn disease than in those with ulcerative colitis, and is also greater in women using immunosuppressive therapy. Women with IBD should undergo Pap testing annually, and human papillomavirus vaccination is recommended.

All patients with IBD should be encouraged to stop smoking. Smoking increases Crohn disease activity and the risk for extraintestinal manifestations. Patients with IBD are at increased risk for metabolic bone disease due to use of glucocorticoids and diminished vitamin D and calcium absorption. Patients with Crohn disease are at greater risk than those with ulcerative colitis. Screening for osteoporosis should be considered in patients at increased risk.

Patients with IBD are at increased risk for developing cancers of the colorectum, cervix, and skin. Longstanding inflammation of the colorectum increases the risk for cancer. In patients with IBD (ulcerative colitis with disease proximal to the sigmoid colon and Crohn disease with more than one third of the colon involved), surveillance colonoscopy should begin 8 years after diagnosis and recur every 1 to 2 years thereafter. Primary sclerosing cholangitis increases the risk for colorectal cancer, and surveillance colonoscopy should begin at the time of diagnosis and recur yearly thereafter.

Patients with IBD are at increased risk for both melanoma and nonmelanoma skin cancers. Most of the risk has been associated with specific treatments; however, there is some evidence that IBD is associated with an increased risk for melanoma, independent of treatment. All patients with IBD should be advised to use sunscreen, wear protective clothing, avoid tanning beds, and have a yearly skin examination.

Microscopic Colitis

Microscopic colitis is a distinct type of IBD characterized by macroscopically normal mucosa with inflammatory changes seen only on histopathology of colon biopsies. It is subclassified into lymphocytic colitis and collagenous colitis (**Figure 20**) based on predominating histologic features. It predominantly affects middle-aged women and is associated with other autoimmune conditions, particularly celiac disease. It presents with abrupt or gradual onset of watery diarrhea that has a relapsing and remitting course over months to years, sometimes accompanied by mild weight loss.

Several classes of medications, including NSAIDs, selective serotonin reuptake inhibitors, and proton pump inhibitors

FIGURE 20. Collagenous colitis: colon mucosal biopsy showing a pink, abnormal subepithelial collagen band (*arrowhead*) and lamina propria expanded by inflammatory cells (*arrow*).

have been associated with development of microscopic colitis. The first step in management is to discontinue any potentially causative medication. First-line treatments include supportive treatment with antidiarrheal agents such loperamide or bismuth subsalicylate. The next step is oral budesonide, which is efficacious but has a high rate of recurrent symptoms when discontinued. Unlike Crohn disease and ulcerative colitis, there is no long-term increased risk for colorectal cancer in patients with microscopic colitis.

KEY POINTS

- The major symptoms of ulcerative colitis include diarrhea, abdominal discomfort, rectal bleeding, and tenesmus, with a slow onset of symptoms.
- Fistula, abscess, and stricture are characteristic complications of Crohn disease.
- Endoscopy with biopsy is needed to help make the diagnosis of inflammatory bowel disease.
- The goals of therapy are to induce and maintain remission of inflammatory bowel disease, and to prevent disease- and treatment-related complications.
- Unlike patients with Crohn disease or ulcerative colitis, patients with microscopic colitis are not at increased risk for colorectal cancer.

Constipation

Constipation is one of the most common gastrointestinal symptoms, affecting 20% of the general population. Constipation can present with symptoms including infrequent, difficult, or incomplete defecation. It can be acute or chronic, and either secondary or idiopathic in nature. Medications are the most common cause of secondary constipation; other causes include mechanical obstruction, systemic illnesses, altered physiologic states, and psychosocial conditions (**Table 21**).

Once secondary causes have been excluded, chronic constipation is considered to be functional (idiopathic). The definition of functional constipation has been refined by the fourth Rome working group for functional gastrointestinal disorders. Functional constipation is subtyped into categories of slow transit, normal transit, or dyssynergic defecation. Slow transit constipation is defined as the delayed passage of fecal contents through the colon based on objective transit testing (radiopaque marker study, scintigraphy, or the wireless motility capsule). Normal transit constipation is idiopathic constipation in which colonic transit times are adequate based on objective transit testing. Dyssynergic defecation (also termed pelvic floor dyssynergia, obstructed defecation, or outlet obstruction) refers to difficulty with or inability to expel stool as a result of some combination of abnormalities in contraction and/or relaxation of the muscles of the pelvic floor during defecation. In some cases, functional constipation can be the result of slow transit constipation and coexistent dyssynergic defecation.

TABLE 21. Secondary Causes of Constipation
Medications
Opioids
Antidiarrheals
Anticholinergics (antispasmodics, antiparkinsonian drugs, tricyclic antidepressants, antipsychotics)
Antihistamines
NSAIDs
Iron supplements
Calcium supplements
Bismuth
Antihypertensives (calcium channel blockers, diuretics, clonidine)
Serotonergic antagonists (ondansetron)
Mechanical Causes
Colorectal cancer
Rectocele
Rectal intussusception
Rectal prolapse
Sigmoidocele
Enterocele
Anastomotic stricture
Anal stenosis/stricture
Extrinsic compression from pelvic/abdominal process
Systemic Illnesses
Endocrinologic
Diabetes mellitus
Hypothyroidism
Panhypopituitarism
Pheochromocytoma
Glucagonoma
Neuropathy/myopathy
Altered Physiologic State
Hypercalcemia
Hypokalemia
Pregnancy
Porphyria
Heavy-metal poisoning (arsenic, lead, mercury)
Psychosocial
Depression
Cognitive impairment
Immobility

Evaluation

A careful medical, surgical, and medication history identifies most causes of secondary constipation. The medication history should focus on the temporal relationship between medications and the development of constipation symptoms. The history should include an assessment for the presence of alarm features: hematochezia, acute constipation in elderly patients, unintentional weight loss, family history of colorectal cancer, unexplained anemia, and age older than 50 years with no previous colonoscopy. Anorectal examination, including a digital examination during Valsalva maneuver, is an important part of the physical examination because it may identify anatomic or functional causes of an evacuation disorder.

A flat plate radiograph of the abdomen is the most useful initial study because it can assess for the presence and distribution of excessive stool in the colon and/or rectum. Colonoscopy is used to assess blood in the stool, a sudden change in bowel habits, or unexplained anemia. It is also used for colon cancer screening in patients at average and increased risk due to family history of colorectal cancer. Additional imaging or laboratory studies should only be considered if clinically indicated. Physiologic testing, including colon transit testing, anorectal manometry, balloon expulsion testing, or defecography, is reserved for patients with constipation symptoms that do not respond to initial trials of laxative therapy.

Functional (idiopathic) constipation is diagnosed once secondary causes have been excluded.

Management

Various treatment strategies may benefit patients with constipation when lifestyle and dietary interventions have been ineffective. Treatment options include bulking agents, stimulant laxatives, osmotic laxatives, stool softeners, secretagogues, and/or biofeedback (**Table 22**). The evidence for treatment

TABLE 22. Treatments for Constipation

Intervention	Mechanism of Action	Considerations
Bulk Laxative Soluble fiber (psyllium, methylcellulose, calcium polycarbophil, wheat dextrin) Insoluble fiber (bran, rye, flax seed)	Increases ability of stool to retain water Bulks stool Speeds movement of stool through colon	Start with a low dose and increase slowly Soluble fiber works better than insoluble fiber Bloating, distension, flatulence, and cramping may be limiting
Stool Softener Docusate sodium, docusate calcium	A detergent that allows water to penetrate the stool	Minimal effectiveness in clinical trials Only role is in mild constipation symptoms Well tolerated Few side effects
Osmotic Laxative Polyethylene glycol 3350 Lactulose Magnesium hydroxide/magnesium citrate Sorbitol	Poorly absorbed compounds Creates an osmotic gradient Water moves into the bowel lumen	Polyethylene glycol 3350 and lactulose improve stool frequency and consistency; others have not been tested in clinical trials Bloating and gas can be limiting Caution with use of magnesium in renal insufficiency
Stimulant Laxative Anthraquinones (senna, cascara) Diphenylmethanes (bisacodyl, sodium picosulfate)	Irritates the colon wall, increasing contractions Stimulates sensory nerves lining the colon May inhibit water absorption in the colon	Quickest acting (works within 8-12 hours of ingestion) Senna can cause melanosis coli (benign pigmentation of the colon) Diarrhea, cramping, bloating, and nausea can be limiting
Secretagogue Lubiprostone Linaclotide Plecanatide	Lubiprostone activates type-2 chloride channels on enterocytes lining the gut lumen, causing chloride ions to move into the colonic lumen with sodium and water following the ionic gradient Linaclotide and plecanatide activate guanylate cyclase C receptors on enterocytes, leading to chloride channel activation through a series of processes within the cell	Lubiprostone improves stool form and frequency, straining, and abdominal pain; nausea is a common side effect Linaclotide and plecanatide improve stool form and frequency, straining, bloating, and abdominal pain; diarrhea is a common side effect
Serotonergic Agent Prucalopride	Increases intestinal contractions Increases intestinal secretion	Not available in the United States Available in Canada and Europe
Neuromuscular Reeducation (biofeedback)	Retrains the skeletal muscle involved in defecation (abdominal wall, pelvic floor, anorectal) Corrects altered rectal sensation	Effective for dyssynergic defecation Requires a specially trained physical therapist

efficacy is strongest for polyethylene glycol, lubiprostone, and linaclotide. Fiber supplements, polyethylene glycol, magnesium, senna, docusate, and bisacodyl have the advantage of being available without a prescription. For refractory cases of constipation, combination therapy should include agents with different mechanisms of action, such as an osmotic plus a stimulant laxative.

Although lubiprostone has an FDA indication for the treatment of opioid-induced constipation, initial treatment should be the same as for other forms of constipation. Three peripherally acting μ-opioid receptor antagonists (methylnaltrexone, naloxegol, and alvimopan) have also been approved for the treatment of opioid-induced constipation in selected patients.

KEY POINTS

- The most common cause of secondary constipation is medication.
- Treatment strategies include dietary and lifestyle modification, addressing causes of secondary constipation, and various pharmacologic agents.

Irritable Bowel Syndrome

IBS represents a heterogeneous group of functional bowel disorders defined by the presence of abdominal pain in association with defecation and/or a change in bowel habits. Abdominal pain may worsen or subside with defecation. The altered bowel habits may include constipation, diarrhea, or a mix of both types. Other commonly reported symptoms include abdominal bloating and abdominal distention. The exact cause of IBS remains unknown, and there are no all-encompassing pathophysiologic mechanisms to explain the symptoms. IBS is more common in women and adults younger than age 50 years, and is frequently seen in association with psychosocial disturbance. There are no specific anatomic or physiologic abnormalities, nor are there any reliable biomarkers to define IBS. The diagnosis of IBS requires symptoms of recurrent abdominal pain at least 1 day a week for a period of 3 months, along with at least two of the following three additional criteria: pain related to defecation, change in stool frequency, or change in stool consistency. IBS can then be further subtyped into IBS with predominant constipation (IBS-C), IBS with predominant diarrhea (IBS-D), IBS with mixed bowel habits, or IBS unclassified.

Evaluation

The diagnosis of IBS is no longer one of exclusion; instead, the diagnosis can reliably be made by clinical criteria in the absence of alarm features. Therefore, evaluation for IBS relies on a comprehensive history and physical examination.

Management

Management of IBS includes lifestyle and dietary modifications, and reassurance that the disease is benign. The focus is control of symptoms. There is limited evidence to suggest that exercise, stress management, and correction of impaired sleep can alleviate the symptoms of IBS.

The most common dietary intervention is an increase in fiber, either through diet or use of fiber supplements. Water-soluble fiber supplements such as psyllium are more effective than insoluble dietary fiber such as bran. Dietary restrictions can include avoidance of trigger foods, gluten (in the absence of celiac disease), dairy products, and FODMAPs (see Table 19). Randomized trials have shown that a low-FODMAP diet alleviates symptoms in patients with IBS. When these initial measures fail to relieve symptoms, medications, typically directed at the primary symptoms of IBS such constipation, diarrhea, or abdominal pain, are employed. The evidence supporting the use of the various agents is variable, with few rigorous studies showing long-term effectiveness.

Therapy for Irritable Bowel Syndrome with Predominant Constipation

Several peripherally acting medications have demonstrated efficacy and safety in the treatment of IBS-C (see Table 22). The American Gastroenterological Association (AGA) has given a strong recommendation based on high-quality evidence for the use of linaclotide, followed by a conditional recommendation for the use of lubiprostone based on moderate-quality evidence and a conditional recommendation for the use of polyethylene glycol based on low-quality evidence in the treatment of IBS-C. Probiotics may offer benefit particularly for symptoms of pain, bloating, and flatulence, although specifics regarding the most beneficial species and strains is unknown.

Therapy for Irritable Bowel Syndrome with Predominant Diarrhea

Prescription medications with FDA approval for the treatment of IBS-D include rifaximin, eluxadoline, and alosetron. A 14-day course of rifaximin has shown superiority to placebo in relieving the global symptoms, bloating, abdominal pain, and loose stools associated with IBS-D for up to 10 weeks after treatment. A retreatment study of patients with recurring IBS-D symptoms after an initial course of rifaximin showed that a second 14-day treatment of rifaximin was superior to placebo in relieving abdominal pain and improving stool frequency for 4 weeks after treatment.

Eluxadoline (combination of a μ-opioid receptor agonist and a δ-opioid receptor antagonist) was superior to placebo in the treatment of men and women with IBS-D for up to 26 weeks based on a composite response of decreased abdominal pain and improved stool consistency in two randomized trials. Use of eluxadoline is contraindicated in patients without a gallbladder and in those with known or suspected biliary obstruction, Sphincter of Oddi disease or dysfunction, ingestion of three or more alcoholic beverages a day, history of pancreatitis or structural disease of the pancreas, severe hepatic impairment, or history of severe constipation.

Alosetron (a selective 5-HT_3 antagonist) has alleviated abdominal pain and the global symptoms of women with IBS-D in pooled data from several randomized trials. The AGA has given it a conditional recommendation for the treatment of women with IBS-D based on moderate-quality evidence. Due to the risk for severe constipation and ischemic colitis, prescribers must be enrolled in an FDA-mandated risk evaluation and mitigation strategy program in order to prescribe alosetron.

Other medications with clinical evidence for the treatment of IBS-D include loperamide, antispasmodics, and tricyclic antidepressants. The AGA has given a conditional recommendation for loperamide use in patients with IBS-D. Although loperamide has not demonstrated global relief of IBS-D symptoms, this recommendation is based on its ability to reduce stool frequency in other diarrheal conditions, as well as its low cost, favorable safety profile, and wide availability. Antispasmodics (for example, cimetropium-dicyclomine, peppermint oil, pinaverium, and trimebutine) decreased abdominal pain and global symptoms of IBS in a meta-analysis of 22 randomized trials. Although the overall quality of studies was low, the AGA gave a conditional recommendation for the use of antispasmodics in IBS-D. Based on data from several randomized trials, tricyclic antidepressants offer modest relief of the abdominal pain and global symptoms of IBS-D. The AGA has given a conditional recommendation based on low-quality evidence for the use of tricyclic antidepressants in the treatment of IBS-D.

KEY POINTS

- Irritable bowel syndrome is diagnosed based on clinical criteria and is no longer a diagnosis of exclusion.
- **HVC** Many cases of irritable bowel syndrome can be effectively managed with reassurance, lifestyle modifications, and dietary modifications.
- Pharmacotherapy should target predominant symptoms and be used if conservative treatment is not effective.

Management of Patients with Indeterminate Abdominal Pain

When abdominal pain is the primary symptom and is unrelated to food intake and defecation, centrally mediated abdominal pain syndrome (CAPS) should be considered. Abdominal pain is described as constant, nearly constant, or frequently recurring. The pain is not localized and may include extraintestinal symptoms such as musculoskeletal pain. It can be associated with impairment in activities of daily living and psychosocial issues. CAPS is a result of central sensitization with disinhibition of pain signals. Limited evaluation is needed in the setting of chronic pain meeting the diagnostic criteria for CAPS. Initial evaluation should include a detailed medical and psychosocial history, physical examination, and limited laboratory studies to exclude gastrointestinal bleeding and inflammation.

Successful treatment depends on the patient-physician relationship, and should focus on setting appropriate goals and expectations. A combination of pharmacologic and/or psychological therapies may be needed, including tricyclic antidepressants, selective serotonin reuptake inhibitors, or serotonin-norepinephrine reuptake inhibitors. Four classes of psychotherapy have shown benefits in CAPS when combined with medical therapy: cognitive-behavioral therapy, psychodynamic-interpersonal therapy, mindfulness- and acceptance-based therapy, and hypnotherapy.

Narcotic bowel syndrome, also known as opiate-induced gastrointestinal hyperalgesia, is characterized by the paradoxical increase in abdominal pain with increasing doses of narcotics despite clinical evidence showing improvement or stability of the underlying condition. Often these patients fear tapering off narcotics and believe the narcotics are "the only thing that helps." The only treatment is complete detoxification and cessation of narcotic use, which requires a trusting patient-physician relationship and understanding of the pathophysiology of the pain. Enrollment in a supervised detoxification program is recommended.

KEY POINTS

- The evaluation for centrally mediated pain syndrome in the setting of chronic abdominal pain requires a detailed medical and psychosocial history and physical examination with limited laboratory testing. **HVC**
- Narcotic bowel syndrome, also known as opiate-induced gastrointestinal hyperalgesia, is characterized by the paradoxical increase in abdominal pain with increasing doses of narcotics.

Diverticular Disease

A diverticulum is the herniation of the mucosa and submucosa through a weakness in the muscle wall. Diverticulosis (the presence of diverticula) is the most common finding identified during colonoscopy. Most patients with diverticulosis are asymptomatic, but 15% will develop complications. The causative mechanism is thought to be multifactorial, involving diet, microbiota, genetics, and colonic motility. The incidence of diverticulosis continues to rise in the Western world and increases with age, with a reported prevalence of 80% in persons aged 85 years and older. Diverticulosis may also cause bleeding, more commonly in the right colon, which often resolves spontaneously.

Diverticulitis is the consequence of a diverticulum becoming blocked, trapping bacteria, and subsequently developing inflammation. Diverticulitis can be classified as uncomplicated or complicated. In some patients, a focal area of colitis can develop in a segment of diverticulosis, called segmental colitis associated with diverticulosis.

The clinical presentation of uncomplicated diverticulitis is colicky abdominal pain that is relieved with flatus or a bowel movement. On physical examination, left-lower-quadrant abdominal tenderness is often present. Patients with complicated diverticulitis may present with dysuria, urinary frequency, pneumaturia, fecaluria, and recurrent urinary infection concerning for colovesical fistula. It is uncommon for patients with diverticulitis to present with rectal bleeding.

Acute diverticulitis is often a clinical diagnosis, usually not requiring imaging. However, a CT scan will help to differentiate uncomplicated from complicated diverticulitis.

The medical management of diverticulitis is based on the degree of the patient's symptoms and severity of diverticular disease. Uncomplicated diverticulitis is treated with oral antibiotics (ciprofloxacin or metronidazole) and a liquid diet. Intravenous antibiotics and hospitalization are required in patients unable to tolerate an oral diet; patients with severe comorbidities, advanced age, or immunosuppression; and patients for whom oral antibiotics have been ineffective.

Treatment of complicated diverticulitis depends on the severity of illness and CT findings. If the CT scan shows a large (>5 cm) abscess, CT-guided drainage may be needed. Surgery is indicated for patients presenting with, or who develop, peritonitis or persistent sepsis.

A high-fiber diet is recommended to prevent recurrence of diverticulitis. There is no evidence supporting restriction of foods such as nuts, berries, and seeds to prevent recurrent diverticulitis.

KEY POINTS

- Diverticulitis is the consequence of a diverticulum becoming blocked, trapping bacteria, and subsequently developing inflammation.
- The main presenting symptom of diverticulitis is colicky abdominal pain that is relieved with flatus or a bowel movement.
- **HVC** Acute diverticulitis is often a clinical diagnosis, usually not requiring abdominal imaging.

Ischemic Bowel Disease

Ischemic bowel disease is a broad term describing a decrease in blood flow to the small or large intestine, which is insufficient to meet intestinal cellular metabolic function. It represents a spectrum of conditions that can be related to acute or chronic alterations of arterial or venous intestinal blood flow. Ischemic bowel disease can be broadly subcategorized into three major clinical syndromes: acute mesenteric ischemia, chronic mesenteric ischemia, and colonic ischemia.

Acute Mesenteric Ischemia

Clinical Features

Acute mesenteric ischemia (AMI) is a rare condition caused by an abrupt decrease in blood flow to the small intestine that can be obstructive or nonobstructive in nature. Obstructive causes of AMI include emboli from a cardiac source (such as atrial or ventricular thrombus) or thrombosis related to underlying atherosclerotic disease. Nonobstructive AMI is most commonly caused by vasoconstriction of the mesenteric vasculature in the setting of severe sepsis or marked reduction in effective circulating volume (low-flow states). Mesenteric vein thrombosis may cause AMI and often is associated with malignancy, hypercoagulable states, or intra-abdominal inflammatory conditions. If the reduction of blood flow is prolonged, bowel infarction occurs, which is the most important prognostic factor for adverse outcome.

AMI most commonly presents with abrupt onset of severe, periumbilical abdominal pain followed by the urge to defecate. The abdominal pain is constant and the patient may subsequently have loose, nonbloody stools. Hematochezia occurs in a minority of cases of AMI (15%) and its presence signifies concomitant right colon ischemia. In the early course of AMI, the abdominal examination may be falsely reassuring: despite the patient's reporting severe abdominal pain, the physical examination reveals a soft, nontender, nondistended abdomen without peritoneal signs. This is called "pain out of proportion to physical examination findings" and should immediately raise suspicion for early AMI. With delayed or late presentation, intestinal ischemia progresses to infarction and peritoneal signs develop. This represents late AMI, which carries a high mortality rate.

Diagnosis

Laboratory studies and abdominal imaging findings in the early course of AMI, before the development of intestinal infarction, are nonspecific. Most patients with AMI will have elevated leukocyte counts. A serum lactate concentration may be normal, and this should not exclude the diagnosis.

CT angiography is the recommended method of imaging for the diagnosis of AMI. CT angiography depicts the vessel origins and length of vessels, and characterizes the occlusion. While MR angiography avoids the risks of radiation and contrast exposure, it takes longer and is less sensitive for distal and nonocclusive disease. Duplex ultrasonography is an effective, low-cost method to assess the proximal mesenteric vessels, but an adequate ultrasound examination often cannot be performed in patients with AMI. The classic angiographic finding in obstructive AMI is either an embolus or thrombus in the superior mesenteric artery.

Treatment

After aggressive resuscitation and administration of broad-spectrum antibiotics, angiography with selective catheterization of the mesenteric vessels is indicated. Findings signifying mesenteric infarction, such as pneumatosis intestinalis (presence of gas within the wall of the intestine) or portal venous gas, require emergent surgery.

Chronic Mesenteric Ischemia

Clinical Features

Chronic mesenteric ischemia (CMI) is an uncommon condition that involves a gradual decrease in blood flow to the small intestine over months to years. It most commonly results from atherosclerotic narrowing of the mesenteric arteries. CMI occurs when two of the three adjacent mesenteric vessels (celiac, superior mesenteric, and inferior mesenteric) are severely narrowed.

The classic symptom triad of CMI is postprandial abdominal pain, sitophobia (fear of eating), and weight loss. However, this triad is seen in only 30% of patients with CMI, and CMI should be suspected in the setting of recurrent postprandial abdominal pain. The pain begins approximately 30 minutes after food ingestion and results from "shunting of blood" away from the small intestine to meet the increased functional demand of the stomach. Due to fixed narrowing of the mesenteric arteries, blood flow cannot increase sufficiently to meet the intestinal metabolic demand and ischemia results.

Diagnosis

The diagnosis of CMI requires symptoms (the CMI triad), exclusion of alternative causes of postprandial abdominal pain and weight loss, and compatible radiographic findings. Imaging modality should be chosen based on patient characteristics and availability. CT or MR angiogram findings suggestive of CMI include severe stenosis (>70%) of two of the three mesenteric arteries. If the patient has compatible symptoms and suggestive angiographic findings, and alternative explanations for postprandial abdominal pain have been excluded, then the diagnosis of CMI is secure.

Treatment

CMI is treated with percutaneous endovascular stenting or surgical revascularization. Choice of therapy depends on operative risk and occlusive lesion characteristics. Periprocedural morbidity and mortality are lower with endovascular stenting; however, it is less durable than surgical revascularization.

Colonic Ischemia

Colonic ischemia is the most common form of ischemic bowel disease. It most commonly results from a nonocclusive low-flow state in microvessels, which occurs in the setting of hypovolemia or hypotension. Risk factors include age (older than 60 years), female sex, vasoconstrictive medications, constipation, thrombophilia, and COPD.

Clinical Features

Colonic ischemia presents with the abrupt onset of lower abdominal discomfort that is mild to moderate and cramping, and is followed within 24 hours by hematochezia. The onset of bleeding often prompts the patient to seek medical attention.

Diagnosis

Physical examination most commonly reveals mild lower abdominal tenderness over the involved bowel segment without peritoneal signs. Laboratory studies may show a mild elevation in the leukocyte count and blood urea nitrogen level.

Abdominal CT is indicated to assess the severity, phase, and distribution of colonic ischemia. CT findings in colonic ischemia are nonspecific and include bowel-wall thickening (**Figure 21**) and pericolonic fat stranding (increase in density within the pericolonic fat secondary to inflammation). Infections that can mimic colonic ischemia, such as cytomegalovirus, *C. difficile*, and enterohemorrhagic *E. coli*, must be excluded. Colonoscopy with biopsy is the test of choice to confirm the diagnosis of colonic ischemia.

Because colonic ischemia is most commonly caused by a nonocclusive low-flow state, dedicated imaging of the mesenteric vasculature is of low yield and generally not indicated. The exception to this rule is right-sided colonic ischemia, which can be the harbinger of AMI caused by a focal thrombus or embolus of the superior mesenteric artery. Therefore, patients with right-sided colonic ischemia require noninvasive imaging of the mesenteric vasculature to exclude occlusive process of the superior mesenteric artery.

Treatment

Most cases of colonic ischemia are mild and transient with rapid spontaneous resolution. Patients with more severe

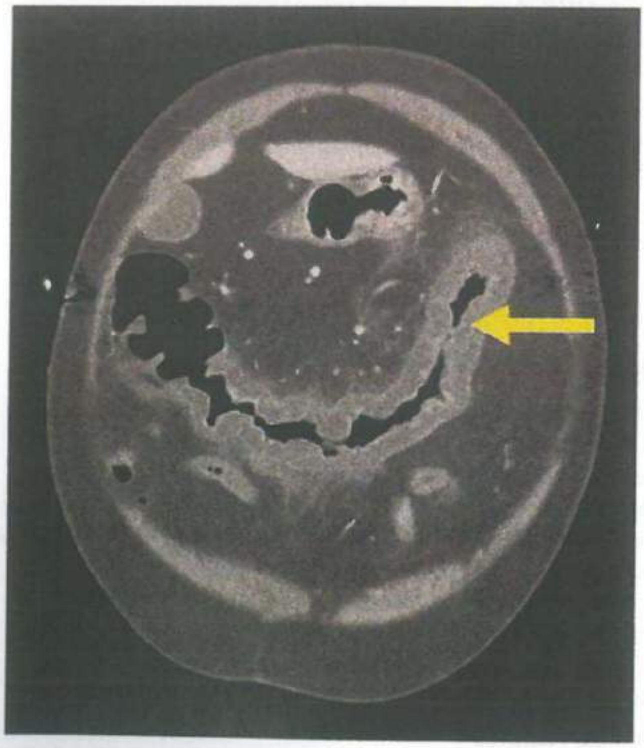

FIGURE 21. Colon ischemia causing segmental thickening (*arrow*) of the transverse colon wall on CT.

disease require hospitalization for supportive care with bowel rest, restoration of intravascular volume, antimicrobial therapy in select cases, and close observation. Only a small percentage of patients require operative intervention for necrotic bowel or irreversible complications such as stricture.

KEY POINTS

- Acute abdominal pain out of proportion to physical examination findings should immediately raise suspicion for early acute mesenteric ischemia.
- CT angiography is the recommended imaging method for the diagnosis of acute mesenteric ischemia.
- The classic symptom triad of chronic mesenteric ischemia is postprandial abdominal pain, sitophobia (fear of eating), and weight loss.
- Colonic ischemia is the most common form of ischemic bowel disease, and most cases resolve spontaneously and rapidly.

Anorectal Disorders

Perianal Disorders

Perianal disorders can range from relatively common and benign disorders, such as hemorrhoids, to potentially disabling conditions, such as anal fissure or fecal incontinence, to the life-threatening condition of anal cancer. Perianal symptoms, including bright red blood per rectum, anal pain, anal itching, or a reported anal mass, should prompt a detailed evaluation of the anus, anal canal, and rectum that includes visual inspection of the anus and digital rectal examination. Further evaluation with anoscopy or proctoscopy may be required to establish the diagnosis. Colonoscopy is indicated when additional alarm features are present; these include age older than 50 years, altered bowel habits, anemia, IBD, unexplained weight loss, and/or family history of colorectal cancer.

Hemorrhoids

Hemorrhoids are submucosal, arteriovenous sinusoids that are part of normal anorectal anatomy and are believed to play an important role in anal canal function. Risk factors for symptomatic hemorrhoids include ascites, pregnancy, excessive sitting or squatting, systemic rheumatic disorders, low dietary-fiber intake, obesity, and sedentary lifestyle. Recurrent straining and persistent bowel alterations (either constipation or diarrhea) can lead to engorgement of hemorrhoid plexuses, causing symptoms of bleeding, prolapse, and swelling. Age-related changes can cause the hemorrhoid beds to slide back and forth during defecation, resulting in mucoid anal discharge, as well as perianal wetness, soiling, irritation, and/or pruritus. Pain is not a common symptom of uncomplicated hemorrhoids and should raise suspicion for hemorrhoid complications, including thrombosis, ischemia, or incarceration from prolapse, or for an alternative diagnosis such as anal fissure, perirectal infection, or perianal abscess.

Other conditions to consider in the differential diagnosis are perianal dermatitis, lichen sclerosis, condyloma, solitary rectal ulcer syndrome, colorectal or anal polyps or cancer, and IBD. Hemorrhoids are categorized as internal if proximal to the dentate line, external if distal to the dentate line, or mixed if crossing the dentate line.

The evaluation of hemorrhoids should always include a careful perianal and digital rectal examination. Symptomatic hemorrhoids can be confused with rectal mucosal prolapse, full thickness rectal prolapse, or a prolapsed rectal polyp. The presence of prolapsed concentric folds indicates rectal prolapse as opposed to a prolapsed hemorrhoid or anal polyp (**Figure 22**). Further direct evaluation of the anorectum can be considered with anoscopy or flexible sigmoidoscopy.

First-line therapy for hemorrhoids includes increased fiber intake, adequate liquid intake, and avoidance of straining. Although various topical agents may reduce hemorrhoid symptoms, they are not necessary for curative therapy. Patients with internal hemorrhoids unresponsive to medical therapy should be considered for banding. Other options, including sclerotherapy and infrared coagulation, are less effective.

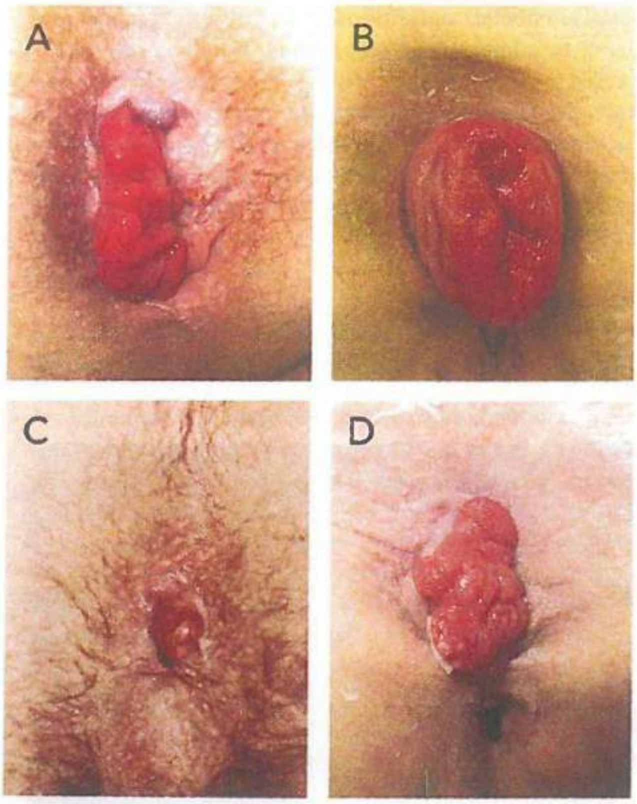

FIGURE 22. Hemorrhoids are vascular cushions that support the muscles of the anal sphincter by swelling up as needed to maintain stool continence. Prolapsed hemorrhoids (*A*) are internal hemorrhoids that protrude out of the rectum. The hallmark of rectal prolapse (*B*) is the identification of concentric rings of the rectum protruding through the anus. Prolapsed polyps (*C, D*) present as mucosa-covered globular masses protruding from the anus.

Images courtesy of Richard E. Burney, MD, Professor of Surgery, Michigan Medicine at the University of Michigan.

Thrombosed external hemorrhoids are best treated with surgical excision within 72 hours of symptom onset. Surgical hemorrhoidectomy should be reserved for refractory hemorrhoids, large external hemorrhoids, or combined internal and external hemorrhoids with rectal prolapse.

Anal Fissure

Anal fissures are longitudinal mucosal tears in the anal canal characterized by anorectal pain worsened by bowel movements and sitting (**Figure 23**). Rectal bleeding with bowel movements or wiping is frequently reported. Anal fissures are either idiopathic or the result of trauma due to the passage of hard stool, receptive anal intercourse, or the insertion of a foreign body such as an enema or endoscope. Anal fissures occurring laterally should raise concern for other entities including Crohn disease, ulcerative colitis, tuberculosis, syphilis, HIV, psoriasis, or anal cancer. Anal fissures lasting more than 8 to 12 weeks are considered chronic and may be characterized by edema and fibrosis as well as the presence of a sentinel pile (appearing as a skin tag) or hypertrophied anal papilla within the anal canal.

Acute anal fissures generally resolve within a few weeks with the use of sitz baths, psyllium, and bulking agents. Topical anesthetics and anti-inflammatory agents can be considered to address pain or bleeding, but their use is not required to promote fissure healing. Rectal spasm is the major reason for anal fissures becoming chronic and should be treated with either topical calcium channel blockers or nitrates. Patients with chronic fissures unresponsive to these measures should be referred for internal sphincter botulinum toxin injection or surgical sphincterotomy.

Fecal Incontinence

Fecal incontinence, also called accidental bowel leakage, is defined as the recurrent, uncontrolled passage of fecal material of at least 3 months' duration. Fecal incontinence does not include the passage of clear mucus or flatus incontinence. Fecal incontinence is grossly underreported due to associated embarrassment, and health care providers should inquire about it during clinic visits, particularly in patients at risk. Fecal incontinence is more common in multiparous women and in patients with advanced age, obesity, diarrhea or urinary incontinence, or history of obstetric complications, anorectal surgery or anorectal disease. Various factors can contribute to fecal incontinence, including loose stool, impairment of rectal storage capacity, altered rectal sensation, and reduced anal sphincter tone. Constipation with resultant fecal loading and overflow diarrhea can also cause fecal incontinence.

A digital rectal examination is essential in the evaluation. This can identify reduced anal sphincter tone, prolapse of hemorrhoids or rectum, or rectal stool impaction. Additional diagnostic testing is determined by the history and rectal examination. If fecal loading is suspected, an abdominal radiograph can be diagnostic. If diarrhea is present, stool testing and/or colonoscopy should be considered. If weak sphincter tone is appreciated or rectal urgency is reported, evaluation may include anorectal manometry to assess anal sphincter pressure and rectal sensation, anal endosonography for anal sphincter defects, or defecography for structural evaluation of the pelvic floor.

Initial treatment should be directed at the treatment of reversible factors such as diarrhea, constipation, offending medications, smoking, obesity, and physical inactivity. Effective dietary modifications include fiber supplementation and avoidance of trigger foods. If there is lack of response to conservative measures, the next step is pelvic floor muscle training with specially trained physical therapists. In the event of lack of response to biofeedback therapy, other treatment options include the use of anal plugs, anal wicking, various minimally invasive procedures (for example, the use of injectable bulking agents or sacral nerve stimulation), or surgery such as sphincteroplasty.

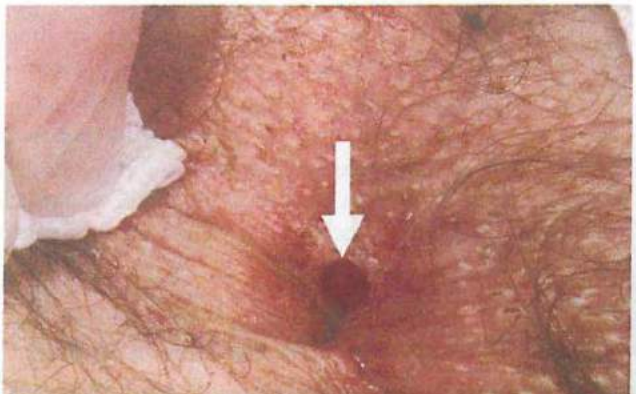

FIGURE 23. Anal fissures are painful longitudinal mucosal tears in the anal canal.
Image courtesy of Richard E. Burney, MD, Professor of Surgery, Michigan Medicine at the University of Michigan.

Anal Cancer

Anal cancer (**Figure 24**) is rare, with a yearly incidence of 8000 cases in the United States. Squamous cell cancer is the most common type, representing 80% of all anal cancers. The incidence has been rising by 2.2% each year for the last decade. Delayed diagnosis by up to 2 years in more than half of cases has resulted in increased need for aggressive surgical intervention.

Human papillomavirus infection and presence of intraepithelial neoplasia are strongly linked with anal cancer. Risk is increased in men who have sex with men, in patients with HIV infection, history of condylomata, and kidney or liver transplantation. Presenting symptoms of anal cancer may include bleeding, pain, or pruritus; however, 25% of cases present without any anorectal symptoms. Anal squamous cell cancer occurs in patients with IBD or ulcerative colitis at a rate of 1 in 100,000, and at a rate of 2 in 100,000 in patients with Crohn disease, largely in those with perianal disease, warranting

FIGURE 24. Anal cancer presenting as an ulcerated mass protruding from the anal canal. The presentation of anal cancer can vary from an obstructing anal mass to a nonprotruding polyp or flat growth in the anal canal.

Image courtesy of Richard E. Burney, MD, Professor of Surgery, Michigan Medicine at the University of Michigan.

heightened vigilance in patients with longstanding perianal disease. Cancer occurs at a young age in patients with Crohn disease (mean age of 42 years) with a typical presentation of anal pain. Anal cancer is aggressive in patients with Crohn disease; most patients require radical surgery, and cumulative overall and disease-free survival is 37% at 5 years.

Although no formal recommendations address screening for anal dysplasia in at-risk populations, screening modalities to consider include digital rectal examination, anal Pap test, human papillomavirus testing, and high-resolution anoscopy.

Biopsy is required to make the diagnosis of anal cancer. Unlike colorectal cancer, staging of anal cancer is based on tumor size and does not involve depth of invasion. Only anal cancers involving the vagina, urethra, or bladder are classified as T4 lesions, regardless of size. Invasion of the rectum, skin, or sphincter muscles does not classify lesions as T4. Lymph node metastasis is divided into perirectal, iliac, and/or inguinal lymph nodal involvement.

For treatment and follow-up of anal cancer, see MKSAP 18 Hematology and Oncology.

KEY POINTS

- First-line therapy for hemorrhoids includes increased fiber intake, adequate liquid intake, and avoidance of straining.
- Fecal incontinence is grossly underreported due to embarrassment, and health care providers should inquire about it during clinic visits, particularly in patients at risk.
- Presenting symptoms of anal cancer may include bleeding, pain, or pruritus; however, 25% of cases present without any anorectal symptoms.
- Patients with Crohn disease with longstanding perianal disease are particularly at risk for anal cancer.

Colorectal Neoplasia

Epidemiology

Colorectal cancer is the third most common cancer and second most common cause of cancer-related mortality among men and women in the United States. Its annual incidence rate among adults in the United States is 42 cases per 100,000, and its mortality rate is 15.5 deaths per 100,000. The incidence of colorectal cancer is approximately 25% higher in men than in women.

The incidence and mortality rates for colorectal cancer have decreased over the past 30 years, largely because of early detection through screening and changes in risk factors (such as decreased smoking). However, there has been a steady increase in the number of colorectal cancer cases in patients younger than age 50 years, for unknown reasons. Survival rates are greater than 90% when the disease is localized, underscoring the importance of early detection. Between 20% and 53% of adults older than age 50 years have premalignant adenomas of the colon detected on screening, and 3% to 8% of the adenomas have advanced histological features. Despite strong evidence supporting colorectal cancer screening, only about 59% of Americans older than age 50 years are up-to-date for recommended testing.

KEY POINT

- Colorectal cancer is the third most common cancer and second most common cause of cancer-related mortality among men and women in the United States.

Pathogenesis

Colorectal cancer develops through one of three mechanisms: chromosomal instability, microsatellite instability, and serrated neoplasia.

Chromosomal instability is the most common mechanism, accounting for approximately 85% of colorectal cancers. Chromosomal instability is characterized by cancer cells that gain or lose whole chromosomes or large fractions of chromosomes (aneuploidy) at an increased rate compared with normal cells. Stepwise accumulation of mutations leads to progression from normal colon to adenoma to cancer. The most commonly mutated gene in this pathway is the adenomatous polyposis coli (*APC*) gene, a multifunctional tumor suppressor gene. Deregulation caused by mutations in *APC* is implicated in the development and spread of colon cancer. Germline mutations in the *APC* gene lead to hereditary familial adenomatous polyposis.

Microsatellites are dozens to hundreds of repetitive nucleotide sequences seen throughout the human genome. The term *microsatellite instability* refers to the presence of mismatched bases at repeated DNA microsatellites. Microsatellite instability accounts for about 15% of colorectal cancers and is characterized by defective DNA mismatch repair, leading to

multiple mutations, adenomas, and cancer. Defective mismatch repair can occur if there is a germline mutation in one of the mismatch repair genes in Lynch syndrome (including *MLH1, MSH2, MSH6, PMS2*) or in the epithelial cell adhesion molecule gene (*EPCAM*), or as a result of sporadic methylation of the *MLH1* promoter.

A more recently described mechanism involves hypermethylation of tumor suppressor genes and the development of serrated polyps and cancer. Serrated polyps are a heterogeneous group of lesions classified by their saw-toothed appearance on histology. Serrated polyps are often found in the proximal colon and may be flat and difficult to distinguish from normal mucosa (**Figure 25**). Hyperplastic polyps that are benign also develop through this mechanism. Interval colon cancers, which are defined as cancers that develop after a negative colonoscopy and before the next recommended screening colonoscopy, most commonly develop through the serrated neoplasia mechanism. A hereditary condition called serrated polyposis syndrome has been described, but its genetic basis has not been elucidated.

KEY POINT

- Chromosomal instability is the most common mechanism responsible for the development of colorectal cancer, accounting for 85% of cases.

Risk Factors

Several risk factors have been established for colorectal cancer. Nonmodifiable risk factors include age (50 years and older), male sex, black race, and a personal or family history of colon adenomas or colorectal cancer. The risk doubles with a family history of colorectal cancer in a first-degree relative.

Long-standing (≥8 years) colonic inflammatory bowel disease (both Crohn disease and ulcerative colitis) is associated with about a 2.7-fold increased risk and is dependent on the severity and extent of bowel involvement. Patients with ureterocolic anastomoses after extensive bladder surgeries and adult survivors of childhood malignancy who received abdominal radiation are also at increased risk for colorectal cancer.

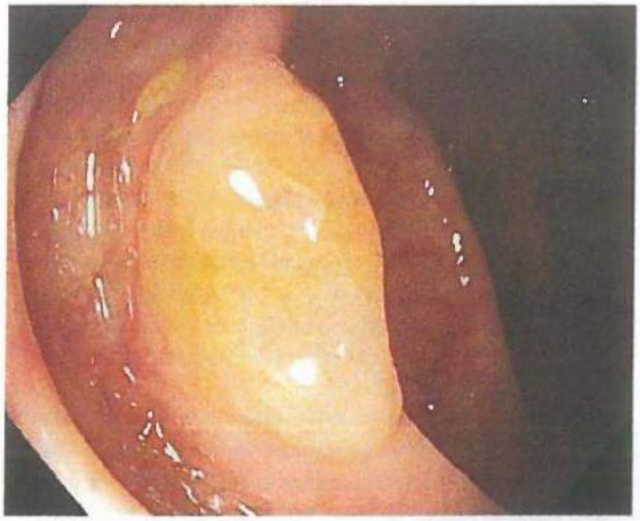

FIGURE 25. A serrated polyp in the ascending colon, showing flat morphology that can make these polyps difficult to identify on colonoscopy.

Modifiable risk factors associated with increased risk include diets high in red and processed meat; low intake of fruits, vegetables, fiber, and dairy; use of alcohol and tobacco; type 2 diabetes mellitus; sedentary lifestyle; and obesity.

KEY POINTS

- Nonmodifiable risk factors for colorectal cancer include age (50 years and older), male sex, black race, and a personal or family history of colorectal cancer.
- Modifiable risk factors for colorectal cancer include diets high in red and processed meat; low intake of fruits, vegetables, fiber, and dairy; use of alcohol and tobacco; type 2 diabetes mellitus; sedentary lifestyle; and obesity.
- Longstanding inflammatory bowel disease (both ulcerative colitis and Crohn disease) is associated with increased risk for colorectal cancer.

Chemoprevention

Substantial epidemiological and experimental data show that aspirin use prevents colorectal cancer. The U.S. Preventive Services Task Force updated their guidelines in 2015 to include the use of low-dose aspirin (81 mg/d) for preventing colorectal cancer and cardiovascular disease in individuals aged 50 and 59 years who are at increased risk for cardiovascular disease. Aspirin use is associated with a 30% decreased risk for colorectal cancer based on cohort and case-control studies. However, randomized controlled trials have not shown a benefit of aspirin in prevention of colorectal cancer. Randomized controlled trials have shown that aspirin decreases the risk for recurrent adenomas.

Studies of other NSAIDs for prevention of colon cancer and adenomas have also yielded positive results; however, benefits of aspirin and other NSAIDs must be weighed against harms, most notably gastrointestinal bleeding.

Some evidence suggests that selective cyclooxygenase-2 inhibitors prevent recurrent adenomas and decrease the incidence of advanced lesions; however, the associated increased cardiovascular risk confounds a recommendation of their use for chemoprevention.

KEY POINT

- The U.S. Preventive Services Task Force recommends the use of low-dose aspirin for preventing colorectal cancer and cardiovascular disease in individuals aged 50 and 59 years who are at increased risk for cardiovascular disease.

Screening

Screening individuals at average risk is discussed in MKSAP 18 General Internal Medicine.

Screening strategies for individuals at increased risk for colorectal cancer are described in **Table 23**.

Key quality indicators for screening colonoscopy are adequate bowel preparation, preparation sufficient to identify polyps 6 mm in size or larger, visualization of the entire colon to the cecum, and longer duration of colonoscopy.

Because adenomas are an intermediary step in the progression from normal colonic mucosa to colon cancer, the identification and management of polyps is critical. Adenomas can be found throughout the colon. They are classified based on morphology, histology, and degree of dysplasia (**Table 24**). Adenomas with any degree of villous histology or high-grade dysplasia have greater malignant potential. Risk is also substantially increased in polyps larger than 1 cm in size. The progression of adenoma to carcinoma takes approximately 8 to 10 years.

KEY POINTS

- Screening for colon cancer should be individualized in patients at increased risk.
- The risk for colon cancer depends on the size of the adenoma, degree of villous histology, and presence of dysplasia.

Clinical Presentation

Colorectal cancer may be asymptomatic, or it may present with iron deficiency anemia, gastrointestinal bleeding, altered bowel habits, abdominal pain, colonic obstruction, and weight loss in more advanced cases.

Diagnosis and Staging

The diagnosis of colorectal cancer is usually made by colonoscopy with biopsy. Staging is based on tumor size and extent of invasion into local tissues, lymph node involvement, and evidence of metastasis (TNM system). Cross-sectional imaging of the chest, abdomen, and pelvis is used for staging in the initial evaluation after diagnosis. Management of colon cancer depends on stage, evidence of microsatellite instability, and presence of specific mutations, including *KRAS/NRAS* and *BRAF*.

For treatment of colorectal cancer, see MKSAP 18 Hematology and Oncology.

Favorable characteristics include stage 1 to 2, lack of angiolymphatic involvement, and negative margins after polyp removal. Endoscopic resection of polyps is curative in some cases. Malignant sessile or flat polyps are associated with higher risk for recurrence and local or distant spread.

KEY POINTS

- The diagnosis of colorectal cancer is usually made by colonoscopy with biopsy.
- Staging of colon cancer is based on tumor size and extent of invasion into local tissues, lymph node involvement, and evidence of metastasis.

TABLE 23. Screening for Colorectal Cancer in Individuals at Increased Risk

Risk Category	Criteria	Screening Recommendations (age; modality; interval)
Increased	Family history of CRC:	
	CRC diagnosed in FDR <60 years old or two or more FDRs at any age	Begin at age 40 years or 10 years earlier than age of youngest FDR at diagnosis, whichever comes first; colonoscopy; repeat every 5 years[a]
	CRC diagnosed in FDR >60 years old	Begin at age 50 years; any modality; repeat every 10 years[a]
	Personal history of CRC	Perform at time of diagnosis; colonoscopy; repeat at 1 year, 3 years, and, if normal, every 5 years thereafter until the benefit of continued screening is outweighed by risks
High	Familial adenomatous polyposis	Begin at age 10-12 years; flexible sigmoidoscopy or colonoscopy; repeat every 1-2 years until colectomy
	Lynch syndrome	Begin at age 20-25 years or 10 years earlier than youngest cancer in family; colonoscopy; repeat every 1-2 years
	Inflammatory bowel disease (Crohn disease or ulcerative colitis)	Begin after 8 years of chronic colitis; colonoscopy with biopsies; repeat every 1-2 years

CRC = colorectal cancer; FDR = first-degree relative (parent, sibling, or child).

[a]If baseline examination is normal.

Data from Rex DK, Johnson DA, Anderson JC, Schoenfeld PS, Burke CA, Inadomi JM; American College of Gastroenterology. American College of Gastroenterology guidelines for colorectal cancer screening 2009 [corrected]. Am J Gastroenterol. 2009;104:739-50. [PMID: 19240699] doi:10.1038/ajg.2009.104; Rubenstein JH, Enns R, Heidelbaugh J, Barkun A; Clinical Guidelines Committee. American Gastroenterological Association Institute Guideline on the Diagnosis and Management of Lynch Syndrome. Gastroenterology. 2015;149:777-82; quiz e16-7. [PMID: 26226577] doi:10.1053/j.gastro.2015.07.036; Syngal S, Brand RE, Church JM, Giardiello FM, Hampel HL, Burt RW; American College of Gastroenterology. ACG clinical guideline: Genetic testing and management of hereditary gastrointestinal cancer syndromes. Am J Gastroenterol. 2015;110:223-62; quiz 263. [PMID: 25645574] doi:10.1038/ajg.2014.435.

TABLE 24. Classification of Colorectal Polyps
Adenomatous Polyps[a]
Tubular adenoma
Tubulovillous adenoma
Villous adenoma
Serrated Polyps
Hyperplastic polyp
Sessile serrated polyp with or without cytologic dysplasia
Traditional serrated adenoma
Other
Hamartomatous polyp
Inflammatory polyp

[a]With or without high-grade dysplasia.

Surveillance

Surveillance for colorectal cancer after screening or polypectomy is based on findings on the baseline examination (**Table 25**).

Hereditary Colorectal Cancer Syndromes

Lynch Syndrome

Lynch syndrome is characterized by germline mutations in the mismatch repair genes (*MLH1*, *MSH2*, *MSH6*, *PMS2*) or the epithelial cell adhesion molecule gene (*EPCAM*), leading to an increased risk for neoplasia of the colon and other organs. Another name for this syndrome, hereditary nonpolyposis colorectal cancer, is no longer used because the syndrome is associated with colorectal polyps as well as extracolonic cancers. The syndrome follows an autosomal dominant inheritance pattern and new mutations are rare.

Individuals with Lynch syndrome are at increased risk for colorectal and endometrial cancers (most common), as well as other cancers, including tumors of the stomach, ovary, hepatobiliary and urinary tracts, small bowel, brain, and pancreas, and sebaceous skin adenoma or cancer.

In persons with Lynch syndrome, the lifetime risk for colorectal cancer depends on the location of the gene mutation, and the risk can be as high as 50% to 80%. Colorectal cancer in Lynch syndrome is more likely to occur in the proximal colon and can display characteristic pathological features, such as tumor-infiltrating lymphocytes and medullary growth pattern. Colorectal tumors in Lynch syndrome result from microsatellite instability that can be assessed using polymerase chain reaction or immunohistochemistry (see Pathogenesis). All colorectal cancers should be screened for Lynch-syndrome genetic mutations or microsatellite instability.

Clinical criteria to evaluate for Lynch syndrome include the Amsterdam and Bethesda criteria, as well as newer models such as the PREdiction Model for gene Mutations 5 ($PREMM_5$). The Amsterdam II criteria follow the "3-2-1-1-0 rule," which states that a diagnosis is warranted if all of the following criteria are met:

- Three family members are affected with a Lynch syndrome-associated cancer
- Two successive generations are affected
- One affected family member is a first-degree relative of the other two affected family members
- One of the cancers was diagnosed before age 50 years
- A familial polyposis syndrome has been ruled out
- Tumors have been verified histologically

These criteria are specific but not sensitive for the diagnosis of Lynch syndrome. The Bethesda criteria have good sensitivity but poor specificity. Genetic counseling and testing should be offered to patients with a personal and/or family history consistent with Lynch syndrome, as well as patients whose tumor shows evidence of microsatellite instability or loss of mismatch repair protein expression. When a mutation is identified in a family, testing of first-degree relatives should be performed and surveillance instituted.

Screening for colorectal cancer in patients with Lynch syndrome should begin at age 20 to 25 years (or 2-5 years

TABLE 25. Surveillance for Colorectal Cancer After Screening or Polypectomy

Adenomatous Polyps	Interval to Next Colonoscopy
1-2 tubular adenomas <10 mm in size	5-10 years
3-10 adenomas ≥10 mm in size, villous histology, or high grade dysplasia	3 years
≥10 adenomas on single examination	<3 years; a genetic cause of disease should be investigated
Serrated Polyps	**Interval to Next Colonoscopy**
Rectosigmoid hyperplastic polyps <10 mm in size	10 years
SSP <10 mm in size	5 years
SSP ≥10 mm in size or SSP with dysplasia or TSA	3 years
Serrated polyposis syndrome	1 year

SSP = sessile serrated polyps; TSA = traditional serrated adenomas.

before the age of diagnosis of the earliest cancer in the family). Screening should be done by colonoscopy and repeated every 1 to 2 years. Risk-reducing total hysterectomy and bilateral salpingo-oophorectomy should be considered starting at age 40 to 45 years after childbearing is completed in women who carry Lynch syndrome mutations.

Screening with upper endoscopy for stomach and small-bowel cancers can be considered starting at age 30 to 35 years and repeated every 2 to 5 years. Testing for *Helicobacter pylori* is also recommended in patients at risk for or with Lynch syndrome.

Adenomatous Polyposis Syndromes

Syndromes that predispose to multiple adenomatous polyps in the colon include familial adenomatous polyposis (FAP), *MutYH*-associated polyposis (MAP), and polymerase proofreading-associated polyposis (PPAP).

Familial Adenomatous Polyposis

FAP is an inherited disorder characterized by multiple (usually more than 100) adenomatous colon polyps. FAP is caused by germline mutations in the *APC* gene that are inherited in an autosomal dominant pattern, although *de novo* mutations occur in about 25% of cases. Adenomas in classic FAP are more numerous in the distal colon than in the proximal colon. Adenoma and cancer develop in 100% of classic FAP cases if surgery is not performed. The average age of colorectal cancer onset is 39 years, with a risk of 93% by age 50 years. An attenuated form of FAP (AFAP) causes fewer polyps (<100 synchronous polyps) with more proximal colonic distribution. The risk for colon cancer in patients with AFAP is about 70% by age 80 years, with an average age of onset of 58 years.

Both FAP and AFAP are associated with extracolonic intestinal manifestations (**Figure 26**). Duodenal adenomas require surveillance because the lifetime risk for duodenal adenocarcinoma is estimated at 4%. Fundic gland polyps of the stomach do not have malignant potential but can mask gastric adenomas and cancer. Risk for gastric cancer is estimated at less than 1%. Risk for desmoid tumors is increased, especially after surgery to remove the colon. Risk for papillary thyroid cancer is also increased, especially in women. Nonmalignant findings include extra teeth, cysts, osteomas, and congenital hypertrophy of the retinal pigmented epithelium.

Screening in classic FAP mutation carriers should begin at age 10 to 12 years with sigmoidoscopy or colonoscopy and repeated every 1 to 2 years. Screening in patients with AFAP can be delayed until age 20 to 25 years and should be performed with colonoscopy. For individuals with FAP and AFAP, screening with upper endoscopy should begin at age 25 to 30 years and include visualization of the papilla with a duodenoscope. Fundic gland polyps in the stomach should be randomly sampled. Surveillance of the upper gastrointestinal tract is determined by findings in the duodenum. Annual thyroid ultrasound is also recommended.

Colectomy is the treatment of choice for classic FAP and may be pursued in patients with AFAP. Absolute indications for surgery include cancer and significant symptoms such as rectal bleeding. Relative indications include multiple adenomas greater than 6 mm size, increase in number of polyps, an adenoma with high-grade dysplasia, and multiple diminutive polyps, which can prevent identification of adenomas. The type of surgery depends on the polyp burden in the rectum; total colectomy with ileorectal anastomosis is indicated for patients with a small rectal polyp burden, and total proctocolectomy with ileo-pouch anastomosis is indicated for patients with a large rectal polyp burden. Postsurgical surveillance is yearly sigmoidoscopy for those with an intact rectum and ileoscopy every 2 years for patients with an ileostomy.

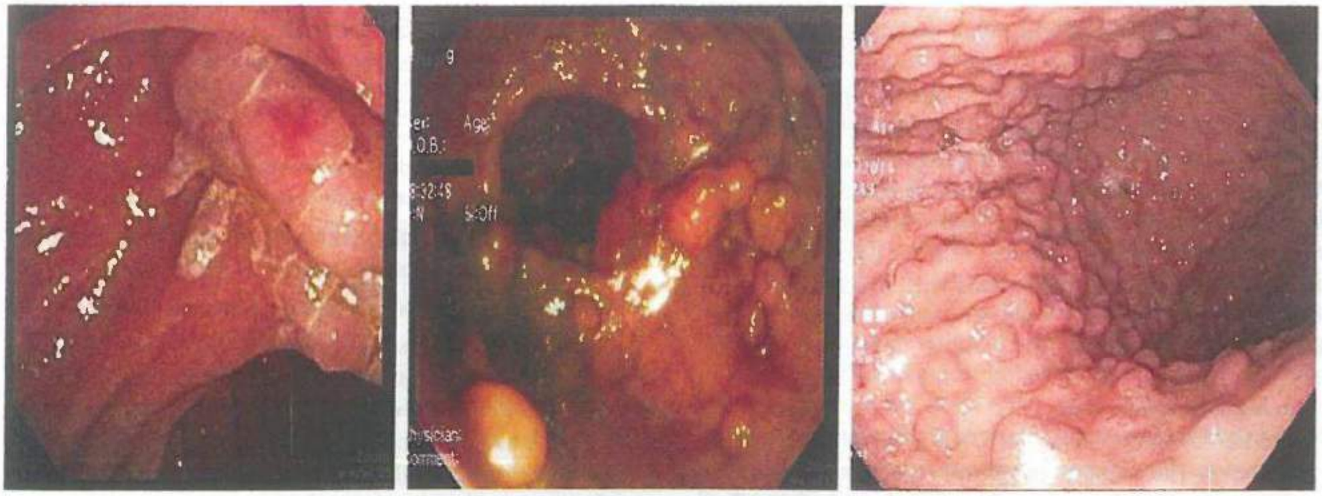

FIGURE 26. Intestinal features of familial adenomatous polyposis (FAP). Patients with FAP can develop polyps throughout the gastrointestinal tract. Adenomatous polyps always develop in the colon. Duodenal adenomas can also develop in patients with FAP, especially involving the ampulla of Vater. Regular upper endoscopic surveillance is indicated to remove polyps larger than 10 mm (*left*). If a patient with FAP has had surgery and has an ileorectal anastomosis, that patient must continue to be surveyed regularly because rectal polyps can develop in the remaining rectum (*center*). Numerous fundic gland polyps of the stomach can develop in FAP (*right*).

MutYH-Associated Polyposis

MAP is an inherited syndrome characterized by fewer adenomas than classic FAP. MAP is caused by mutations in the *MutYH* gene, a component of base excision repair. MAP is a recessive condition in which an affected patient has inherited two mutated copies from their parents. Most patients have between 20 and 99 adenomatous colon polyps. Some individuals can develop cancer with only a few or no synchronous adenomas. Mean age of cancer onset is about 52 years. In addition, other polyp types can be encountered in patients with MAP, including serrated and hyperplastic polyps. Duodenal cancer risk in MAP is estimated at 4% and surveillance with upper endoscopy is similar to that indicated in patients with FAP. Surgical management of the colon is similar to that of FAP.

Polymerase Proofreading-Associated Polyposis

This more recently described syndrome is inherited in an autosomal dominant manner. PPAP appears to have features of both FAP and Lynch syndrome and is caused by mutations in polymerase proofreading genes *POLE* and *POLD1*. Endometrial cancer has been described in this syndrome, and tumor testing has been reported to show microsatellite instability. Management guidelines have not been established for PPAP, but management of colonic polyps follows similar principles as for other adenomatous polyp syndromes.

Hamartomatous Polyposis Syndromes

Hamartomas refer to polyps caused by overgrowth of normal tissue. There are three primary syndromes associated with hamartomas in the gastrointestinal tract: juvenile polyposis syndrome (JPS), Peutz-Jeghers syndrome (PJS), and *PTEN* hamartoma syndrome, also known as Cowden syndrome.

Juvenile Polyposis Syndrome

JPS is caused by mutations in the *BMPR1A* and *SMAD4* genes. It has an incidence of approximately 1 in 130,000 live births. Multiple juvenile polyps (>5 polyps) are found in the colon (98%), stomach (14%), and small bowel (14%) of patients with JPS (**Figure 27**). Sporadic juvenile polyps can be found in up to 1% of children and are not considered syndromic. The average age of patients at the time JPS is diagnosed is 18.5 years, and rectal bleeding is the most common symptom. Patients with JPS are at increased risk for colon, stomach, and small-bowel cancer. Individuals with mutations in the *SMAD4* gene can also have hereditary hemorrhagic telangiectasia.

Peutz-Jeghers Syndrome

PJS is caused by mutations in the *STK11* gene. Its incidence is approximately 1 in 200,000 live births. PJS hamartomas are found primarily in the small bowel but can also develop in the stomach and colon (**Figure 28**). PJS is also characterized by hyperpigmented mucocutaneous macules on the lips and buccal mucosa (**Figure 29**).

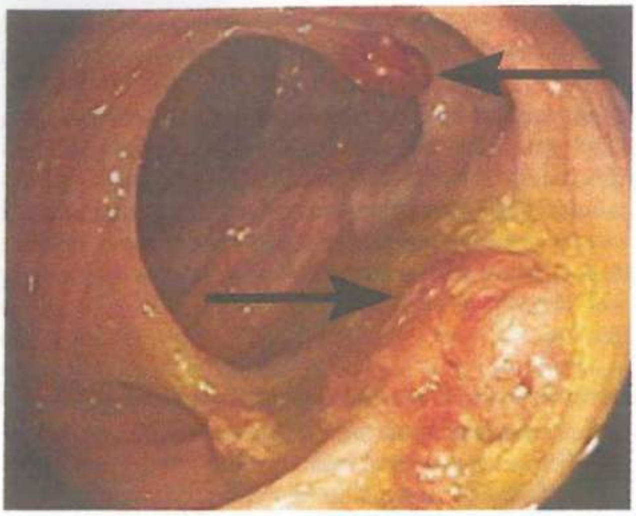

FIGURE 27. Juvenile polyps in the colon of a patient with juvenile polyposis syndrome, on endoscopy. Juvenile polyps can have an erythematous and waxy appearance.

Small bowel hamartomas develop at a young age in patients with PJS, and may present with intussusception, obstruction and bleeding. Patients with PJS have increased risk for cancer in the colon, stomach, small bowel, breast, ovary, cervix, uterus, testicles, lung, and pancreas.

PTEN Hamartoma Syndrome

Also known as Cowden syndrome, this syndrome is caused by germline mutations in the tumor suppressor gene *PTEN*. It is characterized by gastrointestinal hamartomas associated with a number of cancers, such as breast, thyroid, kidney, and colon cancer, as well as macrocephaly, esophageal glycogenic acanthosis, and dermatological manifestations. Colorectal cancer prevalence is estimated at 9% to 18%.

Serrated Polyposis Syndrome

Serrated polyposis syndrome is characterized by numerous serrated polyps in the colon. The definition is based on having any of the following:

- Five or more serrated polyps proximal to the sigmoid colon, with two or more greater than 10 mm in size
- Any number of serrated polyps in patients with first-degree relatives with serrated polyposis syndrome
- More than 20 serrated polyps throughout the colon

Estimates suggest that the prevalence of serrated polyposis syndrome is between 0.3% and 0.6%. Risk for colon cancer in patients with this syndrome is increased, and smoking appears to be a risk factor. Colonoscopy is recommended every 1 to 3 years with removal of all polyps greater than 5 mm in size. Surgery may be considered if the polyps cannot be managed endoscopically. No extracolonic manifestations have been noted in serrated polyposis syndrome. The genetic basis of the syndrome is unknown.

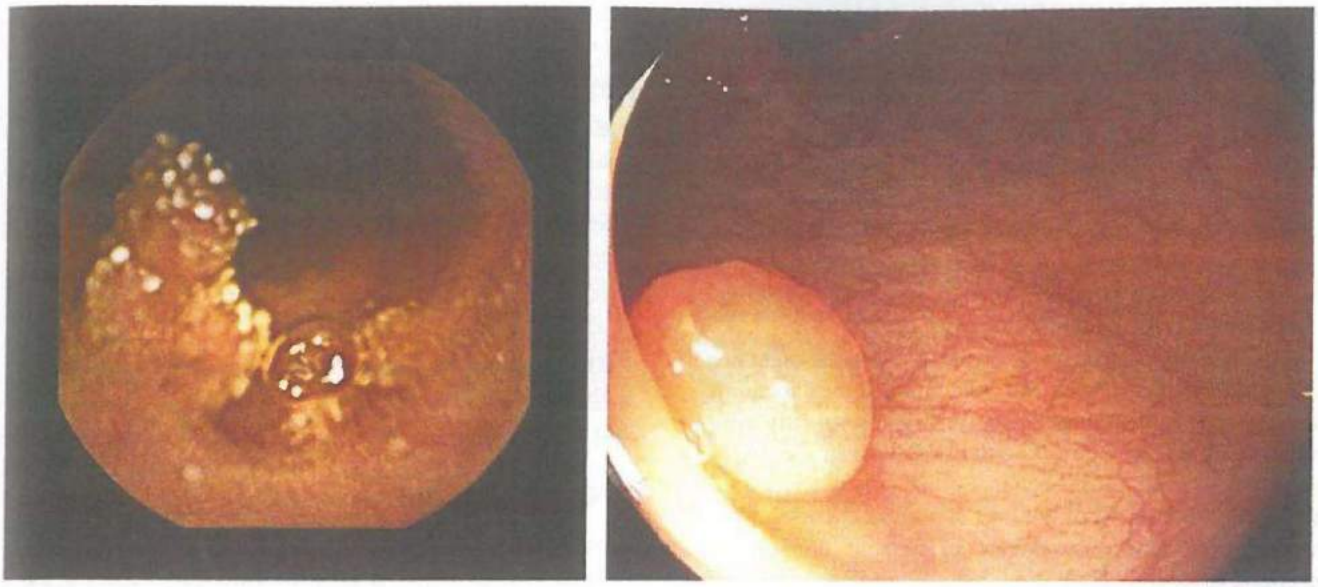

FIGURE 28. Peutz-Jeghers syndrome (PJS) polyps. Capsule endoscopy showing a PJS hamartomatous polyp in the small intestine (*left*); polyps in the small intestine can cause bleeding and/or obstructions. Colonoscopy showing a hamartomatous polyp in the colon of a patient with PJS (*right*).

FIGURE 29. Peutz-Jeghers syndrome is associated with multiple hamartomatous polyps in the gastrointestinal tract and distinctive mucocutaneous pigmentations. The pigmented lesions occur most commonly on the lips and perioral region but can also occur on the nose, perianal area, and genitals.

KEY POINTS

- Lynch syndrome is caused by germline mutations in the mismatch repair genes and carries a lifetime risk for colorectal cancer of 50% to 80%.
- Syndromes that predispose persons to multiple adenomatous polyps in the colon include familial adenomatous polyposis, *MutYH*-associated polyposis, and polymerase proofreading-associated polyposis.
- Hamartomatous polyposis syndromes are associated with increased risk for multiple cancers, including colon cancer.

Disorders of the Liver

Approach to the Patient with Abnormal Liver Chemistry Studies

Basic metabolic panels commonly include liver chemistry tests. Liver chemistry tests are often abnormal (10% to 20% of the time); therefore, it is important to take a systematic approach to their evaluation. The patterns of the elevations of liver tests can be used to group causes into categories; however, these patterns are not specific. Elevations of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels represent hepatic parenchymal inflammation. Elevated ALT levels are more specific for hepatic inflammation because AST is also found in other tissues such as heart and muscle.

Elevations in alkaline phosphatase (ALP) and bilirubin levels result from inflammation of the biliary tree or bile flow abnormalities. ALP is also produced in bone and placenta and high levels are seen in pregnancy. Elevation of ALP and other liver chemistries typically reflects liver injury. Fractionation of ALP levels can be performed to determine the source of elevation. Bilirubin can be divided into conjugated and unconjugated forms. Elevation of conjugated bilirubin reflects a liver disorder, whereas elevation of unconjugated bilirubin is seen in hematological disease or in benign alterations of bilirubin conjugation, such as Gilbert syndrome.

The prothrombin time and serum albumin levels reflect the synthetic function of the liver. Albumin levels are decreased in the setting of malnourishment, the nephrotic syndrome, acute inflammation, and protein-losing enteropathies. Prothrombin time can be prolonged in vitamin K deficiency, warfarin therapy, coagulopathy of liver disease, inherited or

acquired factor deficiency, and the antiphospholipid antibody syndrome. In patients with abnormal liver enzyme levels, thrombocytopenia may be a clue to the presence of portal hypertension.

The relative levels and severity of elevations of AST, ALT, and ALP provide clues about the cause of the liver inflammation (**Table 26**). The duration of abnormal liver tests is also important in evaluating the causes of liver injury. Acute liver inflammation is defined as less than 6 months in duration, whereas chronic hepatitis is defined as elevated liver chemistries of greater than 6 months' duration.

Abdominal imaging can be helpful in the assessment of a patient with abnormal liver tests. Abdominal ultrasonography may show increased echogenicity, consistent with fatty infiltration of the liver, as well as nodularity of the liver seen in the setting of cirrhosis. Cross-sectional imaging may show findings of fatty infiltration of the liver as well as changes of cirrhosis. Noninvasive assessments of hepatic fibrosis are becoming more frequently used. Ultrasound-based transient elastography and magnetic resonance (MR) elastography measure tissue stiffness. Tissue stiffness correlates with stages of hepatic fibrosis, although high stiffness values may also occur with hepatic congestion, infiltrative disorders, and bile duct obstruction.

KEY POINTS

- Elevations of aspartate aminotransferase and alanine aminotransferase levels represent hepatic parenchymal inflammation; alanine aminotransferase levels are more specific for hepatic inflammation.
- Elevations in alkaline phosphatase and bilirubin levels result from inflammation of the biliary tree or bile flow abnormalities.
- The prothrombin time and serum albumin levels reflect the synthetic function of the liver.

Viral Hepatitis

Hepatitis A

Hepatitis A virus (HAV) is an RNA virus that causes acute hepatitis mediated by the host immune response. HAV infection is a self-limited illness, but atypical forms exist, including a relapsing, remitting infection with cholestatic features and,

TABLE 26. Typical Liver Chemistry Studies in Common Hepatobiliary Disorders

Disease	AST	ALT	ALP	Bilirubin	Other Features
Acute viral hepatitis	↑↑↑	↑↑↑	Normal to ↑	Normal to ↑↑↑	Exposure history, fatigue, nausea
Chronic viral hepatitis	↑	↑↑	Normal to ↑	↑ if advanced	History of exposure to infected blood or body fluids
Nonalcoholic steatohepatitis	↑	↑	Normal to ↑	Normal	Metabolic syndrome
Alcoholic hepatitis	↑↑	Normal or ↑	↑	Normal to ↑↑↑	Excess alcohol intake
Acute autoimmune hepatitis	↑↑↑	↑↑↑	Normal to ↑	Normal to ↑↑	Autoantibodies
Chronic autoimmune hepatitis	↑	↑↑	Normal to ↑	Normal	Autoantibodies
Wilson disease	↑	↑	Low	↑ and often unconjugated	Hemolysis if acute, neurologic symptoms if chronic
α_1-Antitrypsin deficiency	↑	↑	Normal	↑ if advanced	May have pulmonary disease
Hemochromatosis	Normal	Normal	Normal	Normal	Joint symptoms, family history, other organ involvement
Primary biliary cholangitis	↑	↑	↑↑↑	↑ if advanced	Female, sicca symptoms, antimitochondrial antibody
Primary sclerosing cholangitis	↑	↑	↑↑↑	↑ if advanced or dominant stricture is present	Ulcerative colitis, abnormal cholangiogram
Large duct obstruction	↑(↑↑ if acute)	↑(↑↑ if acute)	↑↑	↑↑	Pain if acute, dilated ducts on imaging
Infiltrative liver disease	↑	↑	↑↑↑	Normal	Features of malignancy, sarcoid, amyloid, or mycobacterial or fungal infection
Hepatic ischemia	↑↑↑	↑↑↑	Normal	Normal	AST >5000 U/L, history of hypotension
Celiac disease	Normal or ↑	Normal or ↑	Normal or ↑	Normal	Usually other features of celiac disease

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase.

rarely, acute liver failure. HAV is transmitted by the fecal-oral route. Risk factors include international travel, contacts with household members with HAV infection, men who have sex with men, and exposure to day care or institutionalized settings. The incidence of HAV infection declined dramatically after introduction of the HAV vaccination (see MKSAP 18 Infectious Diseases). Mortality is rare but may be increased in patients with preexisting chronic liver disease. The incubation period for HAV is 15 to 50 days. A prodrome of malaise, nausea, vomiting, fever, and right-upper-quadrant pain is followed by development of jaundice, with physical examination findings of jaundice and hepatomegaly. HAV can be transmitted during the prodrome stage and up to 1 week after development of jaundice. Laboratory studies may show aminotransferase levels greater than 1000 U/L and total bilirubin level of 10 mg/dL (171 µmol/L) or higher, mostly direct (conjugated). A positive test for IgM antibodies to HAV is suggestive of acute illness, although false positives may occur in the setting of other viral infections. The presence of IgG antibodies to HAV indicates previous infection or vaccination and provides immunity from reinfection. Treatment is supportive, and 90% of patients or more recover fully within 3 to 6 months of infection. Postexposure vaccination is sufficient for immunocompetent patients, and HAV immunoglobulin can be administered to immunocompromised patients.

Hepatitis B

Hepatitis B virus (HBV) is a DNA virus affecting 240 million persons worldwide and 2.2 million in the United States. See MKSAP 18 General Internal Medicine for HBV vaccination strategies. HBV can be transmitted vertically, through sexual exposure, percutaneously, or by close person-to-person contact. The risk for developing chronic HBV infection differs by age. Newborns acquiring HBV have the highest risk (90%), whereas adults have an approximately 5% risk. Testing for HBV is recommended in individuals with risk factors (**Table 27**).

HBV infection presents as acute hepatitis in a minority of patients. Approximately 30% of adults may develop jaundice as a result of acute infection with aminotransferase levels as high as 3000 U/L and nonspecific symptoms including malaise, nausea, and right-upper-quadrant pain. Acute liver failure (ALF) develops in approximately 0.5% of patients. Typically, adult patients recover within 1 to 4 months. Chronic HBV infection is diagnosed after 6 months in patients with persistent hepatitis B surface antigen (HBsAg) detected in serum.

Interpretation of HBV serologies is shown in **Table 28**. There are four phases of chronic HBV infection: immune tolerant, immune active, immune control, and reactivation (**Figure 30**). Patients who have acquired HBV through vertical transmission remain in the immune-tolerant phase for the first two to three decades. This stage does not require treatment except in specific cases (patients older than 40 years with an HBV DNA level of at least 1 million IU/mL and significant inflammation or fibrosis).

Patients transition to hepatitis B e antigen (HBeAg)–positive, immune-active hepatitis later in life. Hallmarks of the immune-active phase include elevated ALT levels, an HBV DNA level of at least 20,000 IU/mL, and a positive HBeAg test. Moderate to severe inflammation can occur, fibrosis can progress, and treatment is warranted in this phase.

Spontaneous seroconversion to the immune-control (inactive) phase with a loss of HBeAg and development of anti-HBe occurs at a rate of 10% per year. To be considered inactive, the ALT level must be normal and the HBV DNA level must be 2000 IU/mL or lower when measured every 3 to 4 months for 1 year.

Approximately 60% to 80% of cases remain in the inactive phase, but up to 20% can revert to the HBeAg-positive, immune-active phase. In addition, the HBeAg-negative reactivation phase can develop in 10% to 30% of cases; this phase is marked by fluctuating elevations in ALT levels and an HBV DNA level that is low but at least 2000 IU/mL, accompanied by ongoing inflammation and fibrosis that require treatment. Not all patients progress through each one of these phases or in sequence.

TABLE 27. Risk Factors Requiring Testing for Hepatitis B Virus
Individuals born or raised in regions with high rates of hepatitis B virus infection, including Asia, Africa, the South Pacific, European Mediterranean countries, Eastern Europe, most of South America, Honduras, Guatemala, and the Middle East (except Israel and Cyprus)
U.S.-born persons not vaccinated as infants whose parents were born in endemic areas
Household or sexual contact with hepatitis B surface antigen-positive persons
Intravenous drug use
Multiple sex partners or history of sexually transmitted infection
Men who have sex with men
History of incarceration
History of hepatitis C virus or HIV infection
Hemodialysis
Pregnancy
Elevated aminotransferase levels of unknown cause

TABLE 28. Interpretation of Hepatitis B Virus Test Results

Clinical Scenario	HBsAg	Anti-HBs	IgM anti-HBc	IgG anti-HBc	HBeAg	Anti-HBe	HBV DNA (IU/mL)
Acute hepatitis B; occasionally reactivation of chronic hepatitis B	+	−	+	−	+	−	>20,000
Resolved previous infection	−	+	−	+	−	+/−	Undetected
Immunity due to previous vaccination	−	+	−	−	−	−	Undetected
False positive anti-HBc or resolved previous infection	−	−	−	+	−	−	Undetected
Immune-tolerant chronic hepatitis B (perinatally acquired, age <30 years)	+	−	−	+	+	−	>1 million
Inactive chronic hepatitis B	+	−	−	+	−	+	<10,000
HBeAg-positive immune-active chronic hepatitis B	+	−	−	+	+	−	>10,000
HBeAg-negative immune-reactive chronic hepatitis B	+	−	−	+	−	+	>10,000

Anti-HBc = hepatitis B core antibody; anti-HBe = hepatitis B e antibody; anti-HBs = hepatitis B surface antibody; HBeAg = hepatitis B e antigen; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus.

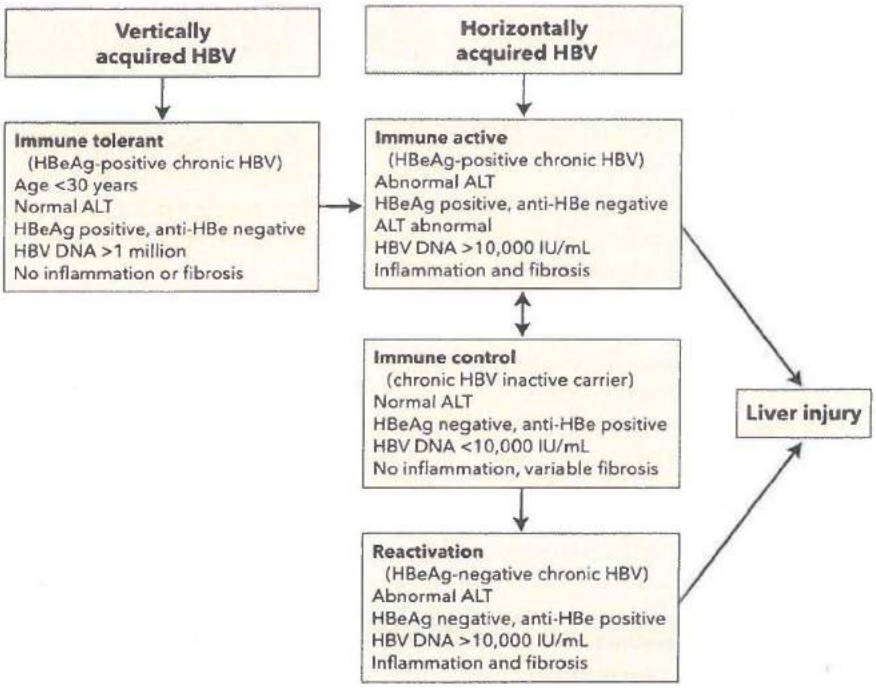

FIGURE 30. Phases of chronic hepatitis B infection. It is assumed that patients progress through the phases in sequence, although not all patients develop HBeAg-negative chronic hepatitis B, and only patients with vertical transmission of hepatitis B have a clinically recognized immune-tolerant phase. All phases have positive HBsAg, negative anti-HBs, and positive IgG anti-HBc.

ALT = alanine aminotransferase; anti-HBc = hepatitis B core antibody; anti-HBe = hepatitis B e antibody; anti-HBs = hepatitis B surface antibody; HBeAg = hepatitis B e antigen; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HBV DNA = hepatitis B virus DNA.

Risk factors for the development of cirrhosis and hepatocellular carcinoma in patients with chronic HBV infection are listed in **Table 29**.

Treatment is advised for patients with acute liver failure, infection in the immune-active phase or reactivation phase, and cirrhosis, and in immunosuppressed patients. Treatment thresholds in chronic immune-active or reactivation HBV infection are an ALT level at least twice the upper limit of normal and an HBV DNA level of at least 20,000 IU/mL (HBeAg-positive, immune-active phase), or an HBV DNA level of at least 2000 IU/mL (HBeAg-negative, reactivation phase). First-line treatment is entecavir or tenofovir. Lamivudine, adefovir, and telbivudine are less commonly used due to resistance. Pegylated interferon can be used for 48 weeks in patients with

TABLE 29. Risk Factors for Developing Cirrhosis or Hepatocellular Carcinoma in Patients with Chronic Hepatitis B Virus Infection
Age older than 40 years
Hepatitis B virus DNA level >2000 IU/mL
Elevated alanine aminotransferase level
Genotype C infection
Heavy alcohol use
Development of hepatitis B e antigen-negative reactivation phase of chronic hepatitis B virus infection
HIV infection
Hepatitis C virus or hepatitis D virus infection

high ALT levels, low HBV DNA levels, and without cirrhosis. Candidates for interferon are those who have a desire for finite therapy, are not pregnant, and do not have significant psychiatric disease, cardiac disease, seizure disorder, cytopenia, or autoimmune disease.

Treatment goals for patients in the HBeAg-positive, immune-active phase are HBeAg loss and anti-HBe seroconversion, which should be followed by an additional 12 months of treatment. Goals of treatment in the HBeAg-negative, reactivation phase are HBV DNA suppression and ALT normalization; oral antiviral agents are generally continued indefinitely. Patients with cirrhosis should continue oral antiviral medications indefinitely. HBsAg seroconversion rarely occurs with oral antiviral treatment and, therefore, is not a goal of treatment. Regression of fibrosis and even of cirrhosis can occur with treatment.

Prophylactic oral antiviral therapy should be given to patients who are HBsAg-positive or isolated core antibody-positive and receiving B-cell depleting therapy (for example, rituximab, or ofatumumab), prednisone (≥10 mg/d for at least 4 weeks), or anthracycline derivatives. Patients undergoing therapy with tumor necrosis factor-α or tyrosine kinase inhibitors should be considered for prophylaxis.

Rarely, patients with HBV infection develop polyarteritis nodosa or cryoglobulinemia, which should prompt treatment with oral antiviral therapy. Membranous glomerulonephritis is a rare extrahepatic association.

The survival rate after liver transplantation for end-stage liver disease from HBV infection is greater than 90% at 1 year. Recurrence of HBV infection in transplant recipients is prevented with HBV immunoglobulin and/or oral antiviral therapy.

The prognosis for untreated individuals with HBV infection worsens with age, particularly with age older than 40 years. Approximately 40% of deaths in HBV-infected persons older than age 40 years are related to hepatocellular carcinoma or decompensated cirrhosis. The following characteristics are associated with an increased risk for hepatocellular carcinoma in patients with HBV infection and are indications for surveillance with ultrasound or cross-sectional imaging every 6 months: (1) cirrhosis; (2) Asian descent plus male sex plus age older than 40 years; (3) Asian descent plus female sex plus age older than 50 years; (4) sub-Saharan African descent plus age older than 20 years; (5) persistent inflammatory activity (defined as an elevated ALT level and HBV DNA levels greater than 10,000 IU/mL for at least a few years); and (6) a family history of hepatocellular carcinoma.

Hepatitis C

Worldwide, 130 to 150 million individuals are infected with hepatitis C virus (HCV), with 2.7 to 3.9 million individuals with HCV infection in the United States. HCV is most commonly transmitted through intravenous or intranasal drug use, blood transfusions before 1992, or sexual intercourse. The efficiency of the virus' spread through vaginal intercourse is low. Individuals born between 1945 and 1965 require one-time HCV testing, as the prevalence is nearly 3% in this group and these individuals account for 75% of cases of HCV infection. Patients with risk factors should be tested (**Table 30**).

Acute HCV infection is asymptomatic in most patients. Jaundice, nausea, right-upper-quadrant pain, dark urine, and acholic stools can occur in the symptomatic cases. Evaluation of suspected acute infection includes HCV antibody and RNA tests. The HCV RNA test becomes positive first, and the HCV antibody test becomes positive within 1 to 3 months. HCV antibody seroconversion within 12 weeks in the presence of an initial positive HCV RNA test confirms an acute HCV infection. Infection that clears spontaneously, usually within 6 months, is more common in patients with symptoms, high ALT levels, female sex, younger age, and the *IL-28 CC* genotype. Monitoring HCV RNA quantification for clearance for 6 months is recommended in patients with acute infection.

TABLE 30. Conditions Requiring Testing for Hepatitis C Virus
Birth year 1945-1965
Injection-drug use or intranasal illicit-drug use (ever)
Long-term hemodialysis (ever)
Percutaneous/parenteral exposures in an unregulated setting (nonsterile technique)
Needlesticks, sharps, or mucosal exposure to hepatitis C virus-infected blood
Children born to women infected with hepatitis C virus
Receipt of blood or blood-components transfusion or organ transplantation before 1992
Receipt of clotting-factor concentrates produced before 1987
History of incarceration
HIV infection
Sexually active persons about to start preexposure prophylaxis for HIV
Undiagnosed chronic liver disease
Elevated alanine aminotransferase level
Living organ donors, before donation

HCV results in chronic infection in 60% to 80% of patients, with up to 30% progressing to cirrhosis over two to three decades. Patients with cirrhosis have a 2% to 4% risk per year for developing hepatocellular carcinoma.

The first step in the diagnosis of chronic HCV infection is HCV antibody testing, and if positive, a HCV RNA quantification. Patients with positive HCV antibody and RNA tests have active infection, and a genotype test should be performed. Asymptomatic patients with a positive HCV antibody and a negative HCV RNA test, and without recent exposure to HCV, do not have active infection and generally do not require further testing.

All patients infected with HCV should be tested for HBV and HIV because of the potential shared routes of transmission. HBV testing should include HBsAg to assess for active infection (followed by HBV DNA if positive) and antibodies to hepatitis B antigens (anti-HBs and anti-HBc) to assess for past infection. Susceptible patients should receive HBV vaccination. HBV reactivation can be seen during treatment of HCV infection with direct-acting antiviral therapy. Patients who test positive for HBsAg with detectable HBV DNA and who do not meet standard HBV treatment criteria should undergo HBV DNA monitoring approximately every 4 weeks until 12 weeks after completion of treatment for HCV infection, or they can be treated with oral HBV therapy prophylactically.

Patients with chronic HCV infection require a fibrosis assessment with a transient or MRI elastography or liver biopsy, unless they have a documented short duration of disease, decompensated cirrhosis, or a radiologic diagnosis of cirrhosis.

All patients infected with HCV should be considered for treatment unless there are significant life-limiting comorbidities or major barriers to adherence to treatment.

Treatment regimens include a combination of direct-acting antivirals, using different mechanisms to prevent viral reproduction (**Table 31**). Regimens are chosen based on genotype, previous treatment experience and response, and fibrosis status. Patients whose infection does not respond to newer regimens are generally managed by a hepatologist or infectious disease specialist because resistance-associated substitution-guided retreatment may be necessary. Patients with decompensated cirrhosis should see a hepatologist before treatment and be considered for liver transplantation. Post–liver transplantation recurrence of HCV infection is universal in treatment-naïve patients. Success rates of HCV treatment after liver transplantation are excellent.

TABLE 31. Treatment Regimens for Hepatitis C Virus Infection

Drug Treatment Regimens
Grazoprevir[a] + elbasvir[b]
Paritaprevir[a] + ombitasvir[b] + dasabuvir[c]
Simeprevir[a] + sofosbuvir[d]
Daclatasvir[b] + sofosbuvir[d]
Ledipasvir[b] + sofosbuvir[d]
Velpatasvir[b] + sofosbuvir[d]

[a]Drug class: NS3/4A protease inhibitor (-previr)

[b]Drug class: NS5A inhibitor (-asvir)

[c]NS5B non-nucleoside polymerase inhibitor (-buvir)

[d]NS5B nucleotide polymerase inhibitor (-buvir)

Cure is defined by the absence of HCV RNA in blood 12 weeks after completion of treatment. HCV antibodies remain positive indefinitely and should not be rechecked. Patients can become reinfected after new exposures, and HCV RNA testing is appropriate to identify new infection. Cure rates exceed 90% in the majority of patients. Virologic cure reduces the risk for progression to cirrhosis, complications of cirrhosis, hepatocellular carcinoma, and liver-related mortality. Patients with stage F3 fibrosis or cirrhosis require ongoing surveillance for hepatocellular carcinoma even after virologic cure. Patients with cryoglobulinemic vasculitis and non-Hodgkin lymphoma are more likely to experience remission when HCV is eradicated.

Hepatitis D

Hepatitis D virus (HDV) is a defective RNA virus that requires HBV for human infection. HDV is endemic in the Mediterranean basin and Pacific islands and uncommon in Western countries. The diagnosis of HDV infection is made through detection of HDV IgG. The clinical course can range from inactive disease to progressive liver disease (in the case of simultaneous HBV-HDV coinfection) to fulminant hepatitis in HDV superinfection. Patients infected with HDV with evidence of progressive liver disease should receive treatment with pegylated interferon for 12 months; cure rates are 25% to 45%.

Hepatitis E

Hepatitis E virus (HEV) is an RNA virus with worldwide distribution. There are four different genotypes: genotypes 1 and 2 are more common in developing countries and are transmitted by the fecal-oral route through contaminated water; genotypes 3 and 4 are more common in developed countries where transmission occurs through contaminated food, mostly pork or deer meat. In developing countries, HEV infection generally occurs in young adults and can occur in large epidemics. In developed countries, HEV generally affects males older than age 40 years. The incubation period is 2 to 5 weeks. Approximately 50% of cases are asymptomatic. Symptoms of HEV infection are jaundice, malaise, nausea, vomiting, anorexia, and right-upper-quadrant pain. Aminotransferase levels are usually elevated to 1000 to 3000 U/L. Diagnosis relies on detection of HEV IgM or RNA. Treatment is supportive, and recovery is expected within 4 to 6 weeks. HEV infection should be considered in patients with an unknown cause of acute hepatitis and in immunocompromised patients with chronic hepatitis. Solid-organ transplant recipients with chronic hepatitis E have response rates of 70% with ribavirin treatment.

Other Viruses

Other viruses can causes hepatitis, including Epstein-Barr virus (EBV), cytomegalovirus (CMV), herpes simplex virus (HSV), varicella zoster virus, and parvovirus. Approximately 90% of EBV-infected individuals have mild hepatitis, occasionally developing jaundice and elevated ALP levels. Diagnostic testing includes heterophile antibody testing or checking EBV serologies, which may demonstrate a positive viral-capsid antigen IgM. Treatment is supportive.

CMV can cause a syndrome that mimics EBV-related mononucleosis. CMV infection can cause mild aminotransferase elevations. Diagnosis is made with CMV serologies in the immunocompetent host. Treatment is supportive, and spontaneous recovery is the norm. CMV infection in solid-organ transplant recipients can cause CMV syndrome, marked by fever and myelosuppression, or tissue-invasive CMV infection involving the gastrointestinal tract, liver, lungs, and retina. Treatment with intravenous ganciclovir is required in immunocompromised hosts. Without treatment, CMV infection carries a high mortality rate in immunocompromised hosts.

HSV-caused hepatitis in women in the third trimester of pregnancy manifests with fever, altered mental status, right-upper-quadrant pain, hepatomegaly, and a presentation similar to sepsis. Aminotransferase levels are commonly elevated to 5000 U/L or higher with a disproportionately low bilirubin level, accompanied by coagulopathy. Diagnosis can be confirmed with polymerase chain reaction testing for HSV (when available) or a liver biopsy showing intranuclear inclusions, multinucleated giant cells, and coagulative necrosis with minimal inflammation. Intravenous acyclovir is the treatment of choice. The case fatality rate is approximately 80% in untreated patients.

In adults, primary varicella zoster virus is a very rare cause of acute hepatitis. Primary infection in organ transplant recipients can cause acute liver failure. Diagnosis in immunocompromised patients requires a biopsy of the skin or of the affected organ. Treatment is intravenous acyclovir.

Parvovirus B19 can result in transient elevation of aminotransferase levels but has also been associated with fulminant hepatic failure in very rare instances.

Other viruses associated with elevated liver chemistries include human herpes virus 6, 7, and 8, as well as adenoviruses.

KEY POINTS

- Treatment of hepatitis A virus infection is supportive, and 90% of patients or more recover fully within 3 to 6 months of infection.
- Treatment of hepatitis B virus infection is advised for patients with acute liver failure, infection in the immune-active phase or the reactivation phase, cirrhosis, and in immunosuppressed patients.
- Individuals born between 1945 and 1965 require one-time testing for hepatitis C virus.
- Up to 95% of patients with hepatitis C virus infection can be cured with direct-acting antiviral agents.

Autoimmune Hepatitis

Autoimmune hepatitis is a chronic inflammatory hepatitis that is four times more common in women than in men and can be associated with other autoimmune diseases (most commonly autoimmune thyroiditis, synovitis, or ulcerative colitis). It can affect individuals at any age but most commonly occurs in middle-aged adults. The presentation of autoimmune hepatitis can vary from asymptomatic elevation of transaminase levels to extrahepatic symptoms such as myalgia and malaise to acute liver failure. Diagnosis is made based on laboratory results (including positive antinuclear and smooth-muscle antibodies and elevated IgG levels), exclusion of other diagnoses (such as Wilson disease, viral hepatitis, and drug-induced liver injury), and histologic findings on liver biopsy.

Treatment includes prednisone and azathioprine for most patients. For uncomplicated autoimmune hepatitis without cirrhosis, budesonide can be considered in place of prednisone, but its role is not established. Prednisone monotherapy is less preferable due to adverse effects. Azathioprine requires monitoring for cytopenia. Typically, biochemical response occurs within 3 to 8 months for the 85% of patients whose disease responds to standard treatment. Histologic response can lag by many months. Duration of treatment should be 2 to 3 years before consideration of withdrawal. A liver biopsy is recommended to determine histologic response before consideration of drug withdrawal. High rates of relapse after discontinuation of treatment underscore the need for serial monitoring of liver tests. Patients with a severe acute form of autoimmune hepatitis presenting with jaundice should be managed by a hepatologist, and patients with features of acute liver failure require urgent transfer to a transplant center.

KEY POINTS

- Diagnosis of autoimmune hepatitis is made based on the presence of elevated aminotransferase levels, positive antinuclear antibody and smooth-muscle antibody, elevated levels of IgG, and compatible findings on liver biopsy.
- Wilson disease, viral hepatitis, and drug-induced liver injury need to be excluded before making the diagnosis of autoimmune hepatitis.

Alcohol-Induced Liver Disease

Alcohol-induced liver disease is the second most common reason for liver transplantation in the United States. Alcohol injury to the liver may take the form of steatosis, steatohepatitis, or severe steatohepatitis, also known as alcoholic hepatitis. Approximately 25% of heavy drinkers develop cirrhosis. History of alcohol use is the most important component in making the diagnosis, although not all patients are forthcoming about alcohol use. See MKSAP 18 General Internal Medicine for more information about screening for alcohol abuse. Most patients with alcoholic liver disease have consumed more than

100 g of alcohol daily for 20 years. The Alcoholic Liver Disease/Nonalcoholic Fatty Liver Disease Index score (www.mayoclinic.org/medical-professionals/model-end-stage-liver-disease/alcoholic-liver-disease-nonalcoholic-fatty-liver-disease-index) can be helpful in distinguishing alcoholic liver disease from nonalcoholic fatty liver disease. It includes the following variables: AST, ALT, mean corpuscular volume, age, height, weight, and sex. Physical examination may show evidence of hepatomegaly in patients with steatosis or steatohepatitis. In patients with alcoholic hepatitis or cirrhosis, findings of advanced liver disease may be present, including muscle wasting, scleral icterus, jaundice, spider angiomata, gynecomastia, left hepatic lobe hypertrophy, testicular atrophy, or palmar erythema. Laboratory evaluation of alcohol-related liver disease may show an elevated mean corpuscular volume, AST:ALT ratio greater than 2, elevated γ-glutamyl transferase level, and in advanced cases, elevated INR and thrombocytopenia.

H Manifestations of alcoholic hepatitis include fever, jaundice, tender hepatomegaly, and leukocytosis. Ultrasound or cross-sectional imaging may reveal evidence of steatosis, cirrhosis, and findings consistent with portal hypertension. The diagnosis is most often made clinically, with liver biopsy reserved for cases with diagnostic uncertainty. Severity of alcoholic hepatitis is determined by the Maddrey discriminant function (MDF) score, which is calculated as follows:

$$\text{MDF score} = 4.6\ (\text{prothrombin time [s]} - \text{control prothrombin time [s]}) + \text{total bilirubin (mg/dL)}$$

In severe cases, as defined by an MDF score of 32 or greater or the presence of hepatic encephalopathy, treatment with prednisolone is recommended by the American College of Gastroenterology (ACG) guideline. The STOPAH trial showed a trend toward improvement in 28-day mortality with the use of prednisolone, but results were not statistically significant. However, a meta-analysis of randomized studies (including the STOPAH study) showed that glucocorticoids were effective in reducing short-term mortality by 46%. Pentoxifylline can be used in patients with contraindications to steroids, including active infection, gastrointestinal bleeding, or kidney failure, but data supporting its benefit are inconclusive. Pentoxifylline is not effective in patients whose symptoms do not respond to prednisone. The ACG guideline makes a conditional recommendation against the use of pentoxifylline for patients with severe alcoholic hepatitis based on a low level of evidence. Due to risk for infection, prednisolone should be discontinued if the bilirubin level does not decrease by day 7. If the bilirubin level decreases, treatment should be continued for 28 days. Nonsevere alcoholic hepatitis (MDF score <32) requires supportive measures and should not be treated with prednisolone or pentoxifylline. All patients require assessment for nutritional deficiencies, thiamine replacement, and alcohol treatment with a goal of abstinence. H

Alcoholic cirrhosis can be diagnosed on clinical and radiologic grounds in patients with obvious evidence of portal hypertension and a history of consistent alcohol intake. Occasionally a liver biopsy is necessary in cases with diagnostic ambiguity. In patients who drink alcohol, inflammation of the liver increases stiffness, making transient and MR elastography inaccurate. Nutritional assessments and alcohol treatment are required. Alcohol abstinence can result in significant stabilization of liver function and reversal of portal hypertension. Liver transplantation is reserved for appropriate candidates who are abstinent from alcohol for approximately 6 months.

KEY POINTS

- The Alcoholic Liver Disease/Nonalcoholic Fatty Liver Disease Index score can be helpful in distinguishing alcoholic liver disease from nonalcoholic fatty liver disease.
- Manifestations of alcoholic hepatitis include fever, jaundice, tender hepatomegaly, and leukocytosis.
- Severity of alcoholic hepatitis is determined by the Maddrey discriminant function score; patients with a score of 32 or greater or with hepatic encephalopathy may be considered for prednisone therapy.

Drug-Induced Liver Injury

H Drug-induced liver injury encompasses a spectrum of liver injury and can be induced by many medications. Prescription, over-the-counter, and herbal medications have been implicated. Acetaminophen is the most recognized medication to have intrinsic hepatotoxicity, and its pattern of liver injury is easily recognizable. People who chronically drink alcohol can develop acetaminophen hepatotoxicity even when taking therapeutic doses of acetaminophen. The early recognition of acetaminophen-induced liver injury is critical so that *N*-acetylcysteine can be administered promptly to prevent liver failure.

Antibiotic (particularly amoxicillin-clavulanate) and antiepileptic medications (phenytoin and valproate) are among the most common medications associated with drug-induced liver injury, representing 60% of cases. The most common drugs that cause acute liver failure in the United States are antituberculosis drugs, sulfa-containing antimicrobial agents, and antifungal agents. The pattern of liver test abnormalities and histological injury can be unpredictable. Some medications, such as amoxicillin-clavulanate, can cause a cholestatic hepatitis, whereas others, such as erythromycin, can cause differing patterns of liver pathology. Patients should be asked about exposure within the past 6 months to medications, both prescription and nonprescription as well as herbal and dietary supplements. Withdrawal of the potentially offending drug with resolution of liver injury supports the diagnosis. Re-exposure to the drug to demonstrate recurrence is not advisable, due to the risk of severe hepatitis upon rechallenge. H

Jaundice that occurs in the setting of cholestatic drug reactions can take months to resolve. An elevated bilirubin level in the setting of increased hepatic transaminases greater than three times the upper limit of normal is associated with mortality rates as high as 14%. Until resolution occurs, there is potential for progression to liver failure and a need for liver transplantation.

KEY POINTS

- Acetaminophen, antibiotics (particularly amoxicillin-clavulanate), and antiepileptic agents (phenytoin and valproate) are the most common causes of drug-induced liver injury.
- Liver injury typically resolves after discontinuation of the offending drug.

H Acute Liver Failure

Acute liver failure is defined as the onset of hepatic encephalopathy and a prolonged prothrombin time within 26 weeks of occurrence of jaundice or other symptoms of liver inflammation in the absence of chronic liver disease. The most common cause of acute liver failure in the United States is acetaminophen overdose. Other widely recognized causes are presented in **Table 32**. The diagnosis requires immediate referral to a liver transplant center.

Patients with acute liver failure require careful monitoring of mental status because progressive hepatic encephalopathy can result in cerebral edema (see Hepatic Encephalopathy). Kidney injury is common, and continuous renal replacement therapy is better tolerated than intermittent hemodialysis. Patients with acute liver failure are at risk for hypoglycemia and infection.

Specific treatment is based on the cause: *N*-acetylcysteine is used for acetaminophen intoxication; antiviral medications for HBV infection and herpes simplex hepatitis; penicillin G for *Amanita* mushroom poisoning; and delivery of the fetus for acute fatty liver of pregnancy. Prompt treatment is crucial. For example, mortality rates for acetaminophen intoxication are lowest when *N*-acetylcysteine is administered within 12 hours of ingestion. H

TABLE 32. Causes of Acute Liver Failure
Acetaminophen
Hepatitis A virus
Herpes simplex virus
Autoimmune hepatitis
Other medications (antituberculosis drugs, sulfa-containing antimicrobial agents, antifungal agents, and herbal supplements)
Hepatitis B virus
Amanita phalloides mushrooms
Acute fatty liver of pregnancy

KEY POINTS

- The most common cause of acute liver failure in the United States is acetaminophen overdose.
- The diagnosis of acute liver failure requires immediate referral to a liver transplant center.

Metabolic Liver Diseases

Nonalcoholic Fatty Liver Disease

Nonalcoholic fatty liver disease (NAFLD) is the most common cause of liver disease in the world. Some 30% of the U.S. population may be affected by this condition. Most patients with NAFLD do not have liver inflammation. In these patients, the presence of fat in the liver without inflammation or fibrosis is considered a benign condition. Patients who have fatty liver with inflammation (nonalcoholic steatohepatitis [NASH]) have progressive disease that can lead to fibrosis and cirrhosis. NAFLD usually develops due to the metabolic syndrome, leading to triglyceride accumulation within the liver. The mechanisms by which patients with NAFLD develop NASH are not fully understood. Metabolic, genetic, and environmental factors likely play a role. Patients with NAFLD are often diagnosed by abdominal imaging. Ultrasound, CT, and MRI can detect the presence of hepatic fat. Symptoms of NAFLD are nonspecific and include fatigue and vague right-upper-quadrant abdominal pain. NASH is characterized by inflammation, risk for progressive fibrosis, and development of cirrhosis. NASH may affect 5% of the U.S. population. Mildly elevated hepatic transaminases are common in NASH. Unrecognized NASH is likely a major cause of cryptogenic cirrhosis.

There are no tests that can diagnose NASH as a cause of chronically elevated liver chemistries. Patients with elevated liver chemistries, a negative serological evaluation for alternative causes, clinical features of the metabolic syndrome, and characteristic abdominal imaging are presumed to have NASH. Low titers of autoantibodies are observed in 20% of patients with NAFLD. The NAFLD fibrosis score (www.nafldscore.com) uses clinical data to identify patients at risk for severe disease. Transient elastography can be used to determine whether patients with NASH have developed significant hepatic fibrosis. Liver biopsy is indicated when the diagnosis is in doubt, or if the presence of hepatic fibrosis cannot otherwise be determined.

The management of NAFLD is focused on weight loss through diet and lifestyle modification. No specific diet for NAFLD is recommended, although carbohydrate-restricted diets may result in greater reduction in liver fat than other diets. Bariatric surgery and concomitant weight loss results in improvement of inflammation and fibrosis associated with NAFLD. No drugs have been approved by the FDA for the treatment of NAFLD. Cardiovascular disease is the leading cause of death in patients with NASH, and therapy with statins should be considered.

α_1-Antitrypsin Deficiency

α_1-Antitrypsin deficiency is an autosomal recessive genetic disorder that results in accumulation of a variant protein in the liver. Homozygosity for this condition may result in liver injury and eventual cirrhosis. The hepatic accumulation of α_1-antitrypsin results in decreased circulating α_1-antitrypsin, leading to lung disease. Supplemental α_1-antitrypsin prevents progressive lung injury but does not affect the progression of cirrhosis. Patients with heterozygosity for α_1-antitrypsin deficiency are at increased risk for liver injury in the setting of other liver diseases, including viral hepatitis or fatty liver disease. Liver transplantation is required to treat liver failure resulting from α_1-antitrypsin deficiency.

Hereditary Hemochromatosis

Hereditary hemochromatosis is a condition characterized by excessive accumulation of iron in the liver due to a mutation in the genes that control the synthesis of hepcidin. Several genetic conditions can cause clinically significant iron overload; hereditary hemochromatosis typically results from homozygosity of the *C282Y* polymorphism of the *HFE* gene. Cirrhosis can develop in untreated patients with hereditary hemochromatosis and is associated with an increased risk for hepatocellular carcinoma.

Elevated transferrin saturation and elevated serum ferritin levels can suggest a diagnosis of hereditary hemochromatosis; transferrin saturation is recommended as the initial diagnostic test. Elevations in either test can be seen in other liver diseases, so confirmation of the diagnosis requires genetic testing.

Removal of excessive iron, usually by phlebotomy, effectively prevents the development of cirrhosis. Cirrhosis may be clinically apparent. If it is not apparent based on imaging or physical examination findings, it should be suspected in all patients with hereditary hemochromatosis who have a serum ferritin level greater than 1000 ng/mL (1000 µg/L). Confirmation of cirrhosis is important because surveillance for hepatocellular cancer is recommended in these patients. Patients with cirrhosis should undergo iron-lowering therapy to stabilize liver disease and to prevent other organ manifestations of iron overload. Liver failure resulting from hereditary hemochromatosis is treated by liver transplantation.

First-degree relatives of patients with hereditary hemochromatosis should be screened with iron studies as well as testing for the *HFE* gene mutation. Children of affected patients can be reassured that they do not have hemochromatosis if the other parent is tested for the *HFE* gene mutation and has a normal genotype, as this would mean that the children are obligate heterozygotes.

Hemochromatosis is discussed further in MKSAP 18 Hematology and Oncology.

Wilson Disease

Wilson disease is a rare autosomal recessive disorder that causes accumulation of copper in the liver. The accumulation of copper can result in sudden liver failure and the need for emergent liver transplantation, especially in younger patients. Unexplained liver disease or liver failure in any patient younger than age 40 years should prompt an investigation for Wilson disease, although older patients with Wilson disease have also been described.

H

Decompensated Wilson disease presents with Coombs-negative hemolytic anemia due to the sudden release of copper from hepatocytes. Laboratory findings include high levels of urinary copper and low levels of ceruloplasmin and ALP. Neurological changes can be seen in patients with Wilson disease (tremor, early-onset Parkinson disease, dystonia). Kayser-Fleischer rings can be seen on slit-lamp examination of patients with Wilson disease and neurologic findings. Histological changes on liver biopsy can be nonspecific, although levels of hepatic copper are typically high. Genetic testing for mutations in the *ATP7B* gene confirms Wilson disease. H

Treatment is lifelong and involves administration of copper chelators. Trientine is preferred over penicillamine due to a lower rate of adverse effects. Zinc supplements can be administered to decrease the intestinal absorption of copper.

KEY POINTS

- Nonalcoholic fatty liver disease is the commonest cause of liver disease in the world.
- Management of nonalcoholic liver disease is focused on weight loss through dietary and lifestyle modification.
- α_1-Antitrypsin deficiency is an autosomal recessive genetic disorder that results in accumulation of a variant protein in the liver; homozygosity can result in liver injury and cirrhosis.
- Hereditary hemochromatosis is a condition characterized by excessive iron absorption that results in accumulation of iron in the liver and the development of cirrhosis.
- Wilson disease is a rare autosomal recessive disorder that causes accumulation of copper in the liver.

Cholestatic Liver Disease

Primary Biliary Cholangitis

Primary biliary cholangitis (PBC), previously termed primary biliary cirrhosis, is an autoimmune disease affecting the small and medium bile ducts with a female to male predominance of 9 to 1. It is more common in individuals of European descent. PBC can present with fatigue and pruritus, but many patients are asymptomatic, with the diagnosis suggested by elevated ALP levels. Diagnosis does not require liver biopsy when the ALP is at least 1.5 times the upper limit of normal and antimitochondrial antibody testing is positive. In patients with negative antimitochondrial antibody test results and strong suspicion for PBC, a liver biopsy is necessary. Transient or MRI elastography can be used for fibrosis staging.

The initial treatment is ursodeoxycholic acid. Response to treatment is defined by improvement of ALP level to less than 1.67 times the upper limit of normal. Patients whose disease does not respond to ursodeoxycholic acid should receive obeticholic acid. Dose reductions are required for obeticholic acid use in patients with decompensated cirrhosis to avoid worsening liver failure. Ursodeoxycholic acid treatment results in histologic improvement, better survival rates, and diminished need for liver transplantation. Patients who present with normal bilirubin and albumin levels and respond to treatment have a life expectancy similar to that of individuals without PBC.

PBC is associated with other autoimmune conditions, particularly autoimmune thyroid disease. Therefore, in patients with PBC, thyroid-stimulating hormone level should be checked on a yearly basis. In patients with a PBC score of 4.1 or greater (www.mayoclinic.org/medical-professionals/model-end-stage-liver-disease/updated-natural-history-model-for-primary-biliary-cirrhosis), upper endoscopy is indicated to assess for esophageal varices. First-degree relatives of patients with PBC, especially women, should be screened by checking their ALP level periodically. Patients with advanced disease should be managed like other patients with cirrhosis and portal hypertension (see Complications of Advanced Liver Disease). Liver transplant outcomes for patients with PBC are excellent, with a 1-year survival rate greater than 90% and a recurrence rate of approximately 20% at 5 years after liver transplantation.

Primary Sclerosing Cholangitis

Primary sclerosing cholangitis (PSC) is an autoimmune fibroinflammatory disease of the large bile ducts, but it can also affect the small bile ducts (small-duct PSC). It is more common in men than in women, which is unique among the autoimmune liver diseases. PSC is associated with inflammatory bowel disease (IBD) in about 85% of cases; up to 7.5% of patients with ulcerative colitis have PSC. All patients with PSC and without known IBD should have a colonoscopy at the time of PSC diagnosis. Patients with concomitant IBD may have a unique PSC-IBD phenotype, characterized by rectal sparing, mild pancolitis, and backwash ileitis; this carries a higher risk for colon cancer, requiring colonoscopy with surveillance biopsies every 1 to 2 years, as well as a higher risk for pouchitis after total colectomy. The diagnosis of PSC can be made noninvasively through MR cholangiopancreatography (MRCP) (**Figure 31**). Endoscopic retrograde cholangiopancreatography (ERCP) should be considered in patients with jaundice, worsening pruritus, bacterial cholangitis, or a dominant stricture or bile duct mass seen on MRCP. Diagnosis of PSC does not usually require liver biopsy; small-duct PSC, which cannot be diagnosed by MRCP, is an exception.

PSC often requires liver transplantation and has the highest case-based mortality rate among the autoimmune liver diseases. Median transplant-free survival for patients with PSC is 12 years. There is no current medical therapy for PSC. ERCP to dilate strictures and remove stones is used in symptomatic patients.

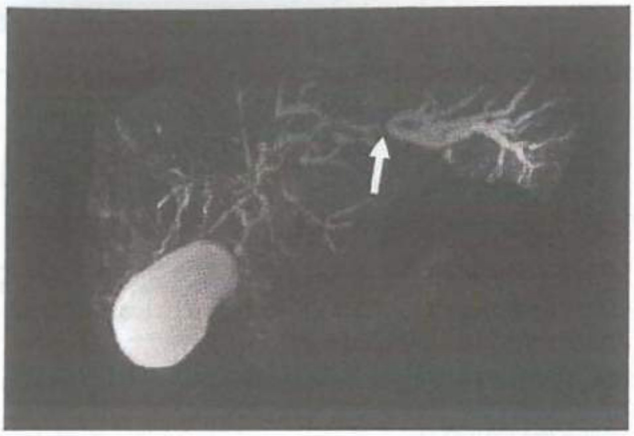

FIGURE 31. Magnetic resonance cholangiopancreatography showing multifocal intra- and extrahepatic bile-duct stricturing with a dominant left-lobe stricture (*arrow*) and upstream bile-duct dilation consistent with the diagnosis of primary sclerosing cholangitis.

Patients with PSC have a 15% lifetime risk for cholangiocarcinoma. Yearly MRCP and measurement of the carbohydrate 19-9 level is recommended for cholangiocarcinoma surveillance. The incidence of cholangiocarcinoma is highest in the first 2 years after diagnosis of PSC is made.

Liver transplantation should be considered for patients with decompensated cirrhosis, recurrent bacterial cholangitis, and hilar cholangiocarcinoma. Transplant outcomes for patients with PSC are excellent, with 1-year survival rates of at least 90% and recurrence rates of approximately 20% at 5 years after liver transplantation.

KEY POINTS

- In patients with primary biliary cholangitis, ursodeoxycholic acid treatment results in histologic improvement, better survival rates, and diminished need to for liver transplantation.
- Primary sclerosing cholangitis is associated with inflammatory bowel disease in about 85% of cases; these patients have an increased risk for colorectal cancer and require surveillance colonoscopy every 1 to 2 years.
- Primary sclerosing cholangitis often requires liver transplantation and has the highest case-based mortality rate among the autoimmune liver diseases.

Determining Prognosis

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The Child-Turcotte-Pugh (CTP) score (**Table 33**) and Model for End-Stage Liver Disease (MELD) score are prognostic in patients with cirrhosis. The 1-year survival rates for patients with CTP class A, B, and C cirrhosis are 100%, 80%, and 45%, respectively.

The MELD formula includes bilirubin level, INR, and creatinine level, and is accurate in predicting 3-month mortality. Another version of the MELD score, the MELD-Na

TABLE 33. Child-Turcotte-Pugh Score[a]	1 Point	2 Points	3 Points
Encephalopathy	None	Grade I-II	Grade III-IV
Ascites	None	Mild/moderate	Severe
Bilirubin	<2 mg/dL (34.2 µmol/L)	2-3 mg/dL (34.2-51.3 µmol/L)	>3 mg/dL (51.3 µmol/L)
Albumin	>3.5 g/dL (35 g/L)	2.8-3.5 g/dL (28-35 g/L)	<2.8 g/dL (28 g/L)
Prothrombin time/INR	<4 s/<1.7	4-6 s/1.7-2.3	>6 s/>2.3

[a]5-6 points = Child-Turcotte-Pugh class A; 7-9 points = Child-Turcotte-Pugh class B; 10-15 points = Child-Turcotte-Pugh class C.

H CONT.

(https://optn.transplant.hrsa.gov/resources/allocation-calculators/meld-calculator/), adds sodium to the formula. The MELD score has been the basis for liver transplant allocation since 2002. In 2016, the allocation system was changed to include the MELD-Na score, which was found to be a better predictive model for 3-month mortality.

The MELD score can estimate postoperative mortality in patients with cirrhosis (www.mayoclinic.org/medical-professionals/model-end-stage-liver-disease/post-operative-mortality-risk-patients-cirrhosis). H

KEY POINT

- The Model for End-Stage Liver Disease-sodium formula accurately predicts 3-month mortality and is used for liver transplant allocation.

Complications of Advanced Liver Disease

Patients with chronic liver disease from any cause are at risk for the development of cirrhosis. Uncomplicated cirrhosis is referred to as "compensated cirrhosis" and may be asymptomatic or associated with nonspecific symptoms. Decompensated cirrhosis includes patients with complications such as ascites, jaundice, hepatocellular carcinoma, hepatorenal syndrome, variceal hemorrhage, spontaneous bacterial peritonitis, and hepatic encephalopathy.

Portal Hypertension

Portal venous hypertension develops in the setting of advanced cirrhosis due to obstruction of blood flow caused by intrahepatic fibrosis, the development of regenerating liver nodules, and increased intrahepatic vascular resistance. Prehepatic causes, including portal vein thrombosis, and posthepatic causes, such as Budd-Chiari syndrome, can also result in portal hypertension in the absence of cirrhosis. Hypersplenism, often also associated with thrombocytopenia, further increases flow within the portal vein, exacerbating portal hypertension. Complications of portal hypertension include gastroesophageal varices, ascites, and hepatic encephalopathy due to poor hepatic clearance of absorbed nitrogenous compounds from the intestines. These complications of portal hypertension herald a high rate of further complications and mortality, leading to consideration for liver transplantation.

Esophageal Varices

H

Esophageal varices are enlarged vessels within the lumen of the lower esophagus that provide extrahepatic pathways of blood flow from the portal circulation to the systemic circulation. Over time, esophageal varices enlarge and may spontaneously rupture, leading to bleeding and possible death. The mortality rate for acute variceal hemorrhage has been significantly reduced with treatment. Upper endoscopy should be performed on all patients with cirrhosis to assess for the presence of varices. Management of varices in patients with cirrhosis depends on size of the varix and whether the cirrhosis is compensated (**Table 34**).

See Gastrointestinal Bleeding for discussion of management and secondary prophylaxis of variceal hemorrhage.

Gastric Varices and Portal Hypertensive Gastropathy

Gastric varices are seen in as many as 20% of patients with cirrhosis and are responsible for 10% to 30% of variceal

TABLE 34. Management of Esophageal Varices in Patients with Cirrhosis

Findings	Management
No varices	Repeat upper endoscopy in 3 years (unless decompensation occurs)
Small varices (<5 mm)	Repeat upper endoscopy in 2 years (unless decompensation occurs)
Small varices with red wale marks (erythematous raised areas)	Initiate nonselective β-blocker therapy (propranolol, nadolol, or carvedilol)
Large varices (>5 mm)	Initiate nonselective β-blocker therapy or endoscopic variceal ligation
Varices in patients unable to tolerate β-blockers	Endoscopic variceal ligation

H CONT.

hemorrhage. Varices that extend from the esophagus into the cardia of the stomach are treated with band ligation, like esophageal varices. Varices of the gastric fundus, or isolated varices in other parts of the stomach, are not treated with band ligation. Bleeding varices in these areas should be treated with hemodynamic resuscitation, antibiotic therapy, and octreotide. Cyanoacrylate glue injection can be injected into bleeding gastric varices but is not FDA-approved for this indication. A transjugular intrahepatic portosystemic shunt (TIPS) should be considered for bleeding from gastric varices. Splenic vein thrombosis can cause isolated gastric varices and is treated with splenectomy.

Hepatic Encephalopathy

Hepatic encephalopathy is characterized by brain dysfunction ranging from minimal abnormalities to frank coma. It occurs due to insufficient hepatic function and porto-systemic shunting of blood caused by portal hypertension or vascular shunting. The development of hepatic encephalopathy can be spontaneous or precipitated by other conditions such as infection, sedating medications, volume depletion, or gastrointestinal bleeding, and heralds worsening of liver function.

Minimal manifestations of hepatic encephalopathy can be detected on neuropsychiatric testing, although overt changes of hepatic encephalopathy, ranging from personality changes to frank coma, are common in the setting of advanced cirrhosis (**Table 35**). Asterixis, a flapping hand tremor, is typically present in middle stages of hepatic encephalopathy. Asterixis is typically absent in subclinical stages of hepatic encephalopathy and is lost as patients progress to later stages of hepatic encephalopathy, including coma.

Patients with hepatic encephalopathy should be monitored in an ICU. Diminishing consciousness should prompt consideration of intubation because airway-protective reflexes can be lost in the advanced stage of hepatic encephalopathy. Measures to reduce intracranial hypertension include elevation of the head of the bed and increasing serum osmolality with mannitol infusions.

The treatment of hepatic encephalopathy is multifaceted. Precipitating causes, such as infection or gastrointestinal bleeding, should be promptly treated. The nonabsorbed disaccharide lactulose is typically administered to decrease absorption of nitrogenous substances. If a suboptimal response is seen with lactulose therapy, rifaximin can be administered to alter bacterial flora in the intestinal lumen. While rifaximin is better tolerated than lactulose, it is more expensive. Initial treatment with lactulose is preferred.

Ascites

Ascites occurs in 50% of patients within 10 years of diagnosis of cirrhosis and is the most common complication of cirrhosis. The finding of a fluid wave on physical examination can detect ascites; other findings are less reliable. Ultrasound is useful for identifying the presence of ascites. When ascites is first detected, diagnostic paracentesis should be performed. The serum-ascites albumin gradient is measured by subtracting the level of albumin in the ascitic fluid from a concurrent serum albumin measurement:

$$\text{serum-ascites albumin gradient} = \text{serum albumin} - \text{ascites albumin}$$

Total protein levels in ascitic fluid also assist in determining the cause of the ascites. The differential diagnosis of ascites is presented in **Table 36**.

Cirrhosis is the cause in 85% of patients with ascites. The management of ascites involves a sodium-restricted diet (<2 g/d) and diuretic therapy, typically with spironolactone and furosemide. Kidney function and electrolyte levels are typically checked 7 to 10 days after changes to diuretic regimens.

Serial paracenteses can be performed if ascites does not resolve with sodium restriction and diuretic therapy. If more than 5 L of ascitic fluid is removed at one time, supplemental 25% albumin, at a dose of 7 to 9 g/L of ascitic fluid removed, should be administered to prevent circulatory dysfunction after paracentesis.

Patients with ascites should discontinue ACE inhibitors and NSAIDs. TIPS or intermittent paracentesis can be considered in patients with refractory ascites and a low MELD score. Indwelling drains in ascites due to portal hypertension are associated with high rates of complications and are not recommended.

Spontaneous Bacterial Peritonitis

Spontaneous bacterial peritonitis (SBP) is an infection of ascitic fluid in the setting of portal hypertension. SBP has a

TABLE 35. Hepatic Encephalopathy Classification

Severity of Encephalopathy	Description	Findings
Minimal	Detected only on neuropsychiatric testing	Few or absent clinical manifestations
Grade 1	Mild lack of awareness, sleep disturbances	Oriented to time and place, but with psychomotor slowing
Grade 2	Lethargic, disoriented, and with personality change	Disoriented to time, with asterixis
Grade 3	Somnolence, confusion, and significant disorientation	Disoriented to time, place, and situation, with asterixis
Grade 4	Coma	Lack of response even to painful stimuli

Adapted with permission from Vilstrup H, Amodio P, Bajaj J, Cordoba J, Ferenci P, Mullen KD, et al. Hepatic encephalopathy in chronic liver disease: 2014 practice guideline by the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver. Hepatology. 2014;60:715-35. [PMID: 25042402] doi:10.1002/hep.27210.

TABLE 36. Characteristics of Ascites

	SAAG	Ascitic Fluid Total Protein Level	Other Characteristics
Cirrhosis	High[a]	Low[c]	Clear, straw-colored
Heart failure	High[a]	High[d]	—
Chylous ascites	Low[b] or high[a]	High[d]	High triglycerides SAAG can be high if caused by portal hypertension SAAG is low if caused by lymphatic disruption
Tuberculosis	Low[b]	High[d]	Peritoneal biopsy may be required to confirm diagnosis of tuberculosis
Malignancy	Low[b]	High[d]	Positive cytology
Nephrotic syndrome	Low[b]	Low[c]	Proteinuria and edema

SAAG = serum-ascites albumin gradient.

[a]≥1.1 g/dL (11 g/L)

[b]<1.1 g/dL (11 g/L)

[c]<2.5 g/dL (25 g/L)

[d]≥2.5 g/dL (25 g/L)

H CONT.

high mortality rate, and patients who develop SBP should be considered for liver transplantation. SBP can present with fever, abdominal pain, and kidney disease, but its presence should be considered in any patient with ascites who experiences a decline in condition. Patients with very low total protein levels in their ascitic fluid (<1.5 g/dL [15 g/L]) in conjunction with hyponatremia, kidney dysfunction, or CTP class B or C cirrhosis are at high risk for development of SBP and should be given long-term primary prophylaxis with a fluoroquinolone antibiotic (for example, norfloxacin or ciprofloxacin).

The diagnosis of SBP is established by an ascitic-fluid neutrophil count of 250/µL or higher on diagnostic paracentesis. Bacterial culture of ascitic fluid should also be obtained. Prompt initiation of therapy with a third-generation cephalosporin (for example, cefotaxime) is the initial treatment of SBP. If patients have kidney dysfunction, or significant hepatic dysfunction as measured by a serum bilirubin level greater than 4 mg/dL (68 µmol/L), adjunctive therapy with albumin (1.5 g/kg body weight on day 1, as well as 1 g/kg on day 3) should be administered; such treatment has a demonstrated survival benefit.

Follow-up paracentesis to demonstrate improvement in inflammation can be performed if clinical improvement is not obvious. Indefinite secondary prophylactic therapy should be offered to patients after resolution of SBP and typically consists of once-daily fluoroquinolone therapy.

Hepatorenal Syndrome

Hepatorenal syndrome (HRS) occurs in the setting of portal hypertension and results from a reduction in renal blood flow during simultaneous dilatation of the splanchnic vasculature. Most patients who develop HRS have cirrhosis, although alcoholic hepatitis and acute liver failure are also associated with this syndrome. Type 1 HRS is characterized by a rise in serum creatinine of at least 0.3 mg/dL (26.5 µmol/L) and/or ≥50% from baseline within 48 hours, bland urinalysis, normal kidney ultrasound, and exclusion of other causes of acute kidney injury. Often patients also have low fractional excretion of sodium and oliguria. Type 2 HRS is characterized by a more gradual decline in kidney function associated with refractory ascites.

Serum creatinine level is one of the most important predictors of death in patients with cirrhosis, and a rapid rise should prompt evaluation for infections and causes of hypovolemia.

Treatment of HRS involves withdrawal of diuretics, volume expansion, with intravenous albumin, and vasoconstrictors. Treatment may also include midodrine and octreotide with intravenous albumin to raise mean arterial pressure and improve kidney perfusion. Hemodialysis while awaiting liver transplantation may be required for patients whose kidney function does not improve with therapy.

Hepatopulmonary Syndrome

Hepatopulmonary syndrome is characterized by dilation of intrapulmonary vessels in patients with portal hypertension, resulting in right-to-left shunting of blood and hypoxemia. Features of hepatopulmonary syndrome include orthodeoxia (worsening oxygen saturation while upright) and platypnea (worsening sense of dyspnea when upright). The diagnosis should be suspected in patients with portal hypertension who have symptoms of dyspnea and evidence of hypoxia. Findings of intrapulmonary shunting with agitated saline administration during echocardiography confirm the diagnosis. Macroaggregated albumin perfusion studies can also aid in diagnosis. Hepatopulmonary syndrome is initially treated with supplemental oxygen, but it is uniformly fatal without liver transplantation.

H CONT.

Portopulmonary Hypertension

Patients with cirrhosis and portal hypertension who present with dyspnea on exertion should be suspected of having portopulmonary hypertension. While less common than hepatopulmonary syndrome, portopulmonary hypertension is a complication of advanced cirrhosis with a high mortality rate. Echocardiography demonstrates right ventricular systolic pressures greater than 50 mm Hg, which should prompt right-heart catheterization to confirm the diagnosis. Although portopulmonary hypertension was formerly considered a contraindication to liver transplantation, patients with preserved right ventricular function who can attain a mean pulmonary artery pressure of less than 35 mm Hg with the use of vasodilator therapies can benefit from liver transplantation. Prostacyclin analogues, phosphodiesterase inhibitors, and endothelin receptor antagonists have been used to successfully treat portopulmonary hypertension. H

KEY POINTS

- Upper endoscopy should be performed on all patients with cirrhosis to assess for the presence of varices; primary prophylaxis to prevent bleeding includes nonselective β-blocker therapy (propranolol, nadolol, or carvedilol) or endoscopic variceal ligation.
- Precipitating causes of hepatic encephalopathy may include infection, sedating medications, volume depletion, or gastrointestinal bleeding; treatment involves addressing the precipitating cause and lactulose.
- HVC Ultrasound is the most effective means of ascertaining the presence of ascites; the serum-ascites albumin gradient and total protein levels in ascitic fluid assist in determining the cause of ascites.
- The management of ascites involves a sodium-restricted diet and diuretic therapy with spironolactone.
- An ascitic-fluid neutrophil count of 250/µL or greater confirms the diagnosis of spontaneous bacterial peritonitis; patients who develop this condition have a high mortality rate and should be considered for liver transplantation.
- Hepatopulmonary syndrome should be suspected in patients with portal hypertension who have symptoms of dyspnea and evidence of hypoxia; the diagnosis is confirmed by demonstrating intrapulmonary shunting with agitated saline administration during echocardiography.

Health Care Maintenance in Patients with Chronic Liver Disease

Patients with chronic liver disease are at risk for severe complications if they develop acute hepatitis and should be vaccinated against HAV and HBV if they are not immune. Nonresponse to vaccinations is more common in patients with cirrhosis, and postvaccination immunity should be assessed. Patients with chronic liver disease should receive annual influenza vaccination and recommended pneumococcal vaccinations. Other vaccinations should be given based on current recommendations (see MKSAP 18 General Internal Medicine).

Patients with cirrhosis should be counseled to avoid the use of alcohol. Sedating medications such as opiates and benzodiazepines should be avoided because they can precipitate symptoms of hepatic encephalopathy. Raw shellfish can transmit *Vibrio vulnificus*, which can be fatal in patients with cirrhosis; therefore, patients with cirrhosis should be counseled to avoid the consumption of raw shellfish.

Patients with cirrhosis should be screened for osteoporosis. Cholestasis results in decreased absorption of vitamin D, and all causes of cirrhosis can be associated with osteoporosis. The cause of osteoporosis in patients with cirrhosis is multifactorial and is associated with jaundice, hypogonadism, and decreased levels of insulin-like growth factor that are common in cirrhosis. Patients with osteoporosis should be treated with bisphosphonates. Patients with esophageal varices should receive intravenous rather than oral bisphosphonates. Patients with identified osteopenia should be treated with supplemental calcium plus vitamin D. Weight-bearing exercise should be encouraged in all patients with cirrhosis.

Protein-calorie malnutrition is common in patients with cirrhosis. Protein consumption is essential to prevent the catabolic effects of chronic liver disease. Daily protein intake of 1.5 g/kg body weight should be administered to patients with chronic liver disease.

Medications that are metabolized by the liver may require dosage adjustments depending on the severity of the cirrhosis. Patients with advanced cirrhosis (CTP class B or C) often require dosage adjustments, whereas patients with well-compensated cirrhosis (CTP class A) may not.

KEY POINTS

- Patients with cirrhosis should avoid alcohol, sedating drugs including opioids, and raw shellfish.
- Patients with cirrhosis should be screened for osteoporosis; confirmed osteoporosis should be treated with either oral or intervenous bisphosphonates.
- Patients with chronic liver disease should be vaccinated against hepatitis A and B viruses and should receive annual influenza vaccination and recommended pneumococcal vaccinations.

Hepatic Tumors, Cysts, and Abscesses

Benign liver masses are typically discovered incidentally on abdominal imaging. These findings are usually asymptomatic, with the exception of liver abscesses or lesions greater than 5 cm in size. Most liver lesions can be characterized and diagnosed noninvasively with CT or MRI. Percutaneous

fine-needle aspiration of lesions is reserved for cases in which imaging is nondiagnostic and in which the information obtained will prompt a change in management. Risks associated with liver biopsy, including a 1% risk for serious complication, such as bleeding or perforation, and a 1-in-10,000 risk for death, need to be considered.

Hepatic Cysts

Hepatic cysts are a common radiological finding on abdominal imaging. Simple cysts are smooth with thin walls and anechoic features on ultrasonography. Patients with polycystic liver disease or autosomal dominant polycystic kidney disease can present with numerous liver cysts. Asymptomatic cysts are benign and require no follow-up. Large cysts, rarely presenting with abdominal pain, can be treated with surgical defenestration or, when surgery is contraindicated, with cyst aspiration and sclerotherapy. Rarely, polycystic liver disease with extensive cystic liver involvement may lead to portal hypertension and/or malnutrition. Obstruction of the portal vein or inferior vena cava can occur due to mass effect. Options for management include surgery, and if that is not technically feasible, liver transplantation. Cystadenomas with thick, irregular walls can be distinguished from simple cysts by ultrasonography; they require surgical resection due to risk for malignancy.

Hepatic Adenomas

Hepatic adenomas are rare liver neoplasms. Despite the benign nature of these lesions, adenomas that are greater than 5 cm in size have potential for risk for hemorrhage or malignant transformation. Hepatic adenomas are associated with oral contraception use and occur eight times more frequently in women than in men. Other risk factors include androgen treatment, type 1 and 3 glycogen storage disease, and obesity. Increasingly, hepatic adenoma is an incidental finding on abdominal ultrasound, CT, or MRI. Hepatic adenomas can be differentiated from focal nodular hyperplasia using MRI with gadobenate dimeglumine or gadoxetate disodium contrast. Biopsy is indicated when there is diagnostic uncertainty but may increase the risk for bleeding; therefore, it should only be performed if the diagnosis will result in a meaningful change in management. Hepatic adenomas 5 cm in size or smaller can be managed with serial imaging every 6 months for a 2-year period. For patients with hepatic adenomas larger than 5 cm in size, the risk for hemorrhage or malignant transformation is elevated and surgical resection should be considered.

Oral contraceptives should be discontinued in all patients with hepatic adenomas with follow-up CT or MRI at 6- to 12-month intervals to confirm stability or regression in the size of the lesion. The duration of surveillance depends on subsequent imaging findings. Biopsy to risk-stratify hepatic adenomas can be considered on a case-by-case basis. Hepatic adenomas with β-catenin activation are at higher risk for malignant transformation into hepatocellular carcinoma. Men with hepatic adenomas are at increased risk for malignant transformation, and resection is recommended.

Focal Nodular Hyperplasia

Focal nodular hyperplasia is the most common benign liver tumor and a frequent incidental finding. It is caused by a congenital arterial anomaly leading to a focal area of regeneration that can cause the formation of a stellate scar seen on CT or MRI. CT or MRI with and without contrast is recommended to confirm the diagnosis. Focal nodular hyperplasia does not have malignant potential or a risk for bleeding and does not require follow-up. In women with focal nodular hyperplasia who continue to use oral contraceptives, there is limited evidence to recommend liver ultrasonography every 2 to 3 years to assess for growth. MRI with a hepatobiliary contrast agent can be used to distinguish between focal nodular hyperplasia and hepatic adenomas.

Hepatic Hemangiomas

Hepatic hemangiomas are common and more frequent in women. Up to 20% of affected patients have multiple hemangiomas. In most cases, symptoms that might be ascribed to hemangioma are due to other causes. Kasabach-Merritt syndrome is a rare syndrome that develops with particularly large hemangiomas that develop consumptive coagulopathy with thrombocytopenia and sometimes disseminated intravascular coagulation. Hemangiomas do not have potential for malignancy, and spontaneous bleeding is rare. The diagnosis should be confirmed with MRI or CT with contrast, which typically shows peripheral nodular enhancement and progressive centripetal fill-in. Biopsies should be avoided due to bleeding risk. Hepatic hemangiomas are benign lesions that do not require intervention or follow-up except in the rare instance when they cause symptoms.

Hepatic Abscesses

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Pyogenic Liver Abscesses

Pyogenic liver abscesses are complications of biliary tract infections or portal venous spread of intra-abdominal infections such as diverticulitis. Patients with pyogenic liver abscesses present with fever, right-upper-quadrant abdominal pain, and malaise. Liver abscesses are typically polymicrobial, and the diagnosis is confirmed by radiologically guided aspiration. Small abscesses (<3 cm) can be successfully treated by administration of broad-spectrum antibiotics. Larger abscesses are treated by aspiration or longer-term percutaneous tube drainage in addition to broad-spectrum antibiotics. The success of radiologically guided aspiration and tube drainage has resulted in only rare need for surgical excision of pyogenic hepatic abscesses.

Amebic Liver Abscesses

Amebic abscesses of the liver are found in developing areas of the world or in migrants from countries in which amebiasis is

H CONT. endemic. Intestinal infection with amoebae can result in invasion of the portal vein and migration to the liver. Typical symptoms of amebic liver abscesses include right-upper-quadrant abdominal pain and fever. Hepatic imaging and serological testing make the diagnosis of amebic liver abscess. Treatment of the hepatic infection with metronidazole or tinidazole should be accompanied by eradication of the coexistent intestinal infection with paromomycin. H

Hepatocellular Carcinoma

Hepatocellular carcinoma is the most common liver tumor arising in patients with cirrhosis, the fifth most common cause of cancer worldwide, and the second most common cause of cancer-related deaths worldwide. Approximately 85% of patients with hepatocellular carcinoma have cirrhosis.

Patients with cirrhosis, regardless of the cause, require surveillance liver ultrasound with or without α-fetoprotein measurement every 6 months, which leads to early diagnosis, increased rate of curative treatment, and improved 3-year survival rates. Patients with HBV infection can develop hepatocellular carcinoma even in the absence of cirrhosis; therefore, surveillance for hepatocellular carcinoma is recommended even in the absence of cirrhosis in individuals at high risk (individuals with HBV who are from sub-Saharan Africa and older than age 20 years, Asian men older than age 40 years, and Asian women older than age 50 years). The diagnosis of hepatocellular carcinoma can usually be made without biopsy using multiphase contrast-enhanced CT or MRI in patients with cirrhosis and a lesion at least 1 cm in size. Biopsy may be needed for lesions that are large, growing, or indeterminant on imaging.

Many specialty societies have issued guidelines for the management of hepatocellular carcinoma. Patients with CTP class A cirrhosis, without significant portal hypertension or jaundice, and a singular lesion 5 cm in size or smaller should be considered for resection. Liver transplantation should be considered in patients with hepatocellular carcinoma within the Milan criteria and with portal hypertension or jaundice. The Milan criteria are as follows: up to three liver lesions 3 cm in size or smaller or one lesion 5 cm in size or smaller, without macrovascular invasion, and without extrahepatic spread. Patients who are not surgical or liver transplantation candidates should be considered for locoregional therapy in the absence of macrovascular invasion (tumor thrombus) or extrahepatic spread. Locoregional therapies include radiofrequency ablation, microwave ablation, transarterial chemoembolization, and transarterial radioembolization. Decisions about locoregional therapy are increasingly made through multidisciplinary tumor boards. Sorafenib is used for advanced hepatocellular carcinoma, which includes cases with macrovascular invasion or extrahepatic spread. In 2017, the FDA approved two drugs for second-line therapy: regorafenib, an oral multi-kinase inhibitor, and nivolumab, an intravenous humanized monoclonal antibody against the programmed cell death receptor.

KEY POINTS

- Asymptomatic hepatic cysts are benign and require no follow-up. **HVC**
- Focal nodular hyperplasia, a common incidental finding, does not have malignant potential or a risk for bleeding, and does not require follow-up. **HVC**
- Hepatic adenomas 5 cm in size or smaller can be managed with serial imaging; hepatic adenomas larger than 5 cm in size should be considered for surgical resection.
- Patients with cirrhosis and high-risk patients with hepatitis B virus infection require hepatocellular carcinoma surveillance using liver ultrasound with or without α-fetoprotein measurement every 6 months.

Liver Transplantation

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Referral for liver transplantation is indicated in patients whose MELD score is 15 or greater because liver transplantation provides a survival advantage in these patients. Patients with decompensated cirrhosis, including ascites, esophageal variceal bleeding, hepatic encephalopathy, jaundice, or hepatocellular carcinoma, should also be considered for referral. Patients should generally abstain from alcohol for at least 6 months, although transplant centers may differ in their requirements for sobriety duration and chemical-dependency treatment. Other factors important in candidate selection are adequate social support, adherence to treatment, and absence of significant cardiopulmonary, psychiatric, and active infectious diseases.

Appropriate candidates are placed on the national waiting list, with the highest priority given to patients with acute liver failure and high MELD-Na scores. In some conditions, the most common being hepatocellular carcinoma, exception points are added to the MELD score, resulting in increased scores every 3 months. Other conditions eligible for MELD exception points include portopulmonary hypertension, hepatopulmonary syndrome, familial amyloidotic polyneuropathy, primary hyperoxaluria, cystic fibrosis, and cholangiocarcinoma.

The average 1- and 5-year survival rates after liver transplantation are 92% and 75% to 85%, respectively. Recipients require lifelong immunosuppression, most commonly using tacrolimus, and less often, cyclosporine. Both drugs are metabolized by cytochrome P450 3A isozymes and pose a risk for drug-drug interactions. Recipients are at increased risk for developing diabetes, hypertension, hyperlipidemia, chronic kidney disease, and malignancy secondary to immunosuppressive medications. H

KEY POINT

- Referral to a transplant center is indicated for patients with acute liver failure or for patients with cirrhosis with a Model for End-Stage Liver Disease score of 15 or greater or decompensated cirrhosis.

Pregnancy-Related Liver Diseases

During pregnancy, physiological changes occur that mimic chronic liver disease. Altered hormonal states and increasing circulatory volume can lead to lower-extremity edema, palmar erythema, and spider angiomata.

In pregnant women with preexisting chronic liver disease, HBV and HCV can be transmitted to the newborn. There are no specific steps that can be taken to eliminate the risk for vertical transmission of HCV; however, vertical transmission is relatively rare, with less than 5% of women with HCV viremia transmitting the virus to their children.

HBV carries a higher risk for vertical transmission. Among women with replicating HBV infection, the vertical transmission rate can be as high as 90%. Pregnant women with an HBV DNA level greater than 200,000 IU/mL between gestational weeks 24 and 28 should start oral antiviral treatment to prevent vertical transmission. Oral antiviral agents approved in pregnancy include lamivudine, telbivudine, and tenofovir. Breastfeeding is not contraindicated during treatment. Passive immunization with HBV immune globulin and active HBV vaccination should be administered to newborns within 12 hours of delivery. These measures can reduce vertical transmission rates by 95%. Administration of antiviral medications in the third trimester to pregnant women with high HBV viremia can further reduce the risk for vertical transmission.

Women with autoimmune hepatitis who become pregnant typically continue the use of prednisone and/or azathioprine, which are generally felt to be safe during pregnancy.

Several diseases of the liver are unique to pregnancy and can affect the health of both the mother and fetus. During the first trimester, hyperemesis gravidarum occurs when prolonged, intractable vomiting results in fluid and electrolyte abnormalities. Elevated hepatic transaminase levels are seen in up to 50% of cases of hyperemesis gravidarum, but jaundice is rare. Laboratory abnormalities typically resolve when vomiting abates. Pyridoxine and antiemetic medications can resolve symptoms of hyperemesis gravidarum.

Intrahepatic cholestasis of pregnancy is presumed to result from cholestatic effects of increased levels of pregnancy-related hormones. Increased risk for this condition can be seen in women of South American descent, twin pregnancies, and in women with a history of liver disease. Intrahepatic cholestasis of pregnancy typically presents in the second to third trimesters of pregnancy. Symptoms include pruritus in most patients and jaundice in 10% to 25% of patients. Serum bile acid levels are elevated and help to establish the diagnosis. Fetal complications, including placental insufficiency, premature labor, and sudden fetal death, are more common in intrahepatic cholestasis of pregnancy. Ursodeoxycholic acid produces relief of pruritus and improves fetal outcomes. Increased fetal mortality is noted to occur late in gestation. Delivery is typically induced at 36 to 38 weeks of gestation in women with proven disease.

H The most serious pregnancy-related liver diseases occur in the third trimester of pregnancy and are associated with high rates of maternal and fetal mortality. In these conditions, the only definitive therapy is delivery of the fetus. HELLP (Hemolysis, Elevated Liver enzymes, and Low Platelets) syndrome is a severe complication of preeclampsia. HELLP typically presents with nonspecific symptoms such as abdominal pain, nausea with vomiting, pruritus, and jaundice. Rates of maternal and fetal morbidity and mortality are high. Patients with HELLP syndrome should, therefore, be managed in high-risk obstetrical units. Blood pressure, fluid and electrolytes, kidney function, and coagulopathy may require careful management in the perinatal state. Although delivery is the definitive therapy for HELLP syndrome, the maternal condition may continue to worsen in the immediate postpartum period. Resolution is typically seen within days after delivery. Rarely, liver transplantation may be required if liver recovery is not seen. HELLP can reoccur in as many as 25% of subsequent pregnancies.

Acute fatty liver of pregnancy is a rare but serious condition that also occurs late in pregnancy. It presents with symptoms similar to those of HELLP syndrome. Indicators of liver failure, including hypoglycemia and coagulopathy, are often worse in acute fatty liver of pregnancy than in HELLP syndrome; both conditions require close monitoring to prevent adverse maternal and fetal outcomes. Acute fatty liver of pregnancy is a potential cause of acute liver failure. Affected patients may require transfer to a liver transplant center. Prompt delivery of the fetus once the diagnosis is recognized typically results in improvement of the mother's medical condition within 48 to 72 hours. Acute fatty liver of pregnancy can reoccur in subsequent pregnancies. It is also associated with long-chain 3-hydroxyacyl CoA dehydrogenase deficiency, and affected women and their offspring should be screened for this deficiency. H

KEY POINTS

- Measures to reduce vertical transmission of hepatitis B virus include administration of hepatitis B virus immune globulin to newborns and immediate vaccination of newborns.
- The most serious liver complications of pregnancy occur in the third trimester and include HELLP (Hemolysis, Elevated Liver enzymes, and Low Platelets) syndrome and acute fatty liver of pregnancy; both are managed in high-risk obstetrical units and with early delivery.

Vascular Diseases of the Liver

Portal Vein Thrombosis

Portal vein thrombosis is common in patients with decompensated cirrhosis and is a consequence of poor flow through the portal veins. The diagnosis is typically established by

abdominal Doppler ultrasonography or contrast-enhanced CT or MRI. Hypercoagulable states are typically not present in patients with cirrhosis who develop portal vein thrombosis. Chronic portal vein thrombosis is typically asymptomatic and does not require anticoagulation therapy. Acute portal vein thrombosis can be symptomatic with the development of ascites or variceal hemorrhage. Anticoagulation can be considered if there is concern that portal vein thrombosis has extended into the superior mesenteric vein risking intestinal ischemia.

Budd-Chiari Syndrome

Budd-Chiari syndrome describes any disease process that obstructs the normal outflow of blood from the liver, usually as thrombosis of the hepatic veins. Causes vary, but it may occasionally be associated with hypercoagulable states such as in patients with a myeloproliferative neoplasm, pregnancy, oral contraceptive use, IBD, or inherited thrombophilias. Underlying malignancy, especially hepatocellular carcinoma, must be considered. Typical symptoms of Budd-Chiari syndrome include hepatomegaly, ascites, and right-upper-quadrant abdominal pain. Budd-Chiari syndrome is typically diagnosed by ultrasound with Doppler evaluation in the appropriate clinical setting. The caudate lobe of the liver is hypertrophied due to the presence of venous outflow channels distinct from the hepatic veins. Long-term anticoagulation is required in patients with Budd-Chiari syndrome, although bleeding risks are significant in patients with acute or chronic liver disease, portal hypertension, and esophageal varices. Angioplasty of the hepatic veins and/or TIPS placement can be used to reestablish adequate hepatic venous drainage. If liver failure develops, liver transplantation should be considered.

KEY POINTS

- Portal vein thrombosis is common in patients with decompensated cirrhosis and is a consequence of poor flow through the portal veins.
- The classic presentation of Budd-Chiari syndrome includes hepatomegaly, ascites, and right-upper-quadrant abdominal pain.

Disorders of the Gallbladder and Bile Ducts

Asymptomatic Gallstones

Gallstones can be characterized as either cholesterol stones or pigment stones, which are black or brown. Cholesterol stones are the result of supersaturation of the bile with cholesterol; they account for approximately 75% of cases in the United States. Risk factors for cholesterol cholelithiasis include older age, female sex (twice as likely as in men), American Indian ethnicity, Western diet, pregnancy, rapid weight loss, obesity, total parenteral nutrition, and drugs such as estrogen and somatostatin analogues. Black pigment stones, usually composed of calcium bilirubinate, can form in patients with chronic hemolytic disease states, ineffective erythropoiesis, ileal disease such as Crohn disease, and cirrhosis. Brown pigment stones are composed of unconjugated bilirubin and varying amounts of other substances, such as cholesterol, but also contain bacteria. These are typically found in patients with biliary stasis and bacterial biliary infection, as can be seen in chronic biliary obstruction.

Gallstones are commonly discovered when patients undergo abdominal imaging for unrelated reasons. Ultrasound and CT can identify gallstones, whereas plain radiography identifies gallstones uncommonly.

Gallstones that are found incidentally do not typically cause any symptoms, and cholecystectomy is generally not recommended because most stones remain asymptomatic. Cholecystectomy is indicated in asymptomatic patients at high risk for gallbladder cancer, including patients with gallstones larger than 3 cm in size, porcelain gallbladder (intramural calcification of the gallbladder wall), gallbladder adenomas or polyps larger than 1 cm in size, or anomaly of pancreatic ductal drainage.

KEY POINT

- Gallstones that are found incidentally do not typically cause any symptoms, and cholecystectomy is generally not recommended because most stones remain asymptomatic. **HVC**

Biliary Colic

Biliary colic pain results from stimulation of the gallbladder in the presence of an obstructive cystic duct from gallstones or sludge. This pain is typically of relatively acute onset, is fairly severe and steady, and is located in the right upper quadrant or epigastrium. Pain may radiate to the right scapula and can be associated with nausea, vomiting, and diaphoresis, lasting 2 to 6 hours. This symptom complex may be precipitated by eating a fatty meal, which causes gallbladder contraction. Patients with unrelenting right-upper-quadrant or epigastric pain generally do not have biliary colic.

Patients with typical biliary colic symptoms and gallstones on imaging should undergo cholecystectomy, as the risk for complications from gallstones is approximately 2% to 3% per year. Complications include choledocholithiasis, cholangitis, and pancreatitis. Patients with atypical symptoms should be evaluated for other causes.

KEY POINT

- Patients with typical biliary colic symptoms and gallstones on imaging should undergo cholecystectomy.

Acute Cholecystitis

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Acute cholecystitis develops in the setting of cystic-duct obstruction and gallbladder inflammation. In many patients,

H CONT.

infection of the gallbladder ensues. Patients typically present with severe right-upper-quadrant or epigastric pain lasting longer than 6 hours, accompanied by fever and localized peritoneal signs in the right upper quadrant. A positive Murphy sign (arrested inspiration upon contact of the gallbladder wall with the examiner's fingers) may be seen on physical examination. Laboratory studies may show leukocytosis; liver chemistries are not usually elevated in uncomplicated acute cholecystitis. The diagnosis can be made by ultrasonography showing gallbladder wall thickening and/or edema and a sonographic Murphy sign. A hepatobiliary iminodiacetic acid scan can be used when the diagnosis is unclear, such as when symptoms suggest cholecystitis but the sonogram is normal.

Treatment includes pain control, intravenous antibiotics with gram-negative and anaerobic coverage (monotherapy with a β-lactam or β-lactamase, or combination therapy with a third-generation cephalosporin plus metronidazole), and cholecystectomy. Timing of cholecystectomy depends on the patient's surgical risk and response to antibiotics. An emergency operation is necessary in cases of suspected gallbladder perforation or emphysematous cholecystitis (infection of the gallbladder wall with gas-forming organisms such as *Clostridium perfringens*). For patients with low surgical risk, cholecystectomy, preferably laparoscopic, should be performed during the initial hospitalization. Patients who are deemed high-risk for surgery and who respond to antibiotics can be reassessed at a later time to determine if their surgical risk has decreased. In patients who are not good candidates for cholecystectomy and do not respond to antibiotics, percutaneous cholecystostomy tube or endoscopic drainage can be pursued. H

KEY POINTS

HVC
- The diagnosis of acute cholecystitis can be made by ultrasonography showing gallbladder wall thickening and/or edema and sonographic Murphy sign.
- Treatment of acute cholecystitis includes pain control, intravenous antibiotics with gram-negative and anaerobic coverage, and cholecystectomy during the initial hospitalization in good candidates for surgery.

H Acalculous Cholecystitis

Acalculous cholecystitis typically occurs in critically ill patients and is a result of gallbladder ischemia that can be complicated by enteric bacterial infection. Risk factors for this condition include cardiac and aortic surgery, sepsis, burns, and vasculitis. The presentation depends on whether the patient is alert or sedated and mechanically ventilated. In alert patients, the presentation is pain, as seen in cholecystitis related to gallstones. In sedated or mechanically ventilated patients, it may present with leukocytosis, jaundice, and sepsis. The diagnosis is made using ultrasonography, which may show gallbladder wall thickening, pericholecystic fluid, gallbladder distention, or gallbladder-wall pneumatosis in the absence of calculi. In this setting, the gallbladder may not be visualized on a hepatobiliary iminodiacetic acid scan.

Treatment consists of empiric intravenous antibiotics to cover enteric bacteria and cholecystectomy. A cholecystostomy tube may be needed if the patient is unstable or a poor candidate for surgery. The role of endoscopic gallbladder drainage is evolving. The mortality rate for untreated acalculous cholecystitis is as high as 75%. H

KEY POINTS

- Acalculous cholecystitis typically occurs in critically ill patients and is a result of gallbladder ischemia that can be complicated by enteric bacterial infection.
- Left untreated, the mortality rate for acalculous cholecystitis is as high as 75%.

Functional Gallbladder Disorder

The Rome 4 criteria for gallbladder disorders suggest that evaluation for functional gallbladder disorder is appropriate in patients with typical biliary pain in the absence of gallstones or structural pathology. Typical biliary pain is located in the epigastrium and/or right upper quadrant; is intermittent; lasts ≥30 minutes; crescendos and then plateaus; is severe enough to interrupt normal activities or results in an emergency department visit; and is not relieved by bowel movements, positional changes, or acid suppression. Supportive features include a gallbladder ejection fraction of less than 40% measured by cholecystokinin-stimulated cholescintigraphy and normal liver chemistry tests and pancreatic enzymes. Other causes of upper abdominal discomfort, including functional dyspepsia, peptic ulcer disease, and angina, should be carefully considered. Gallstones should be excluded by transabdominal ultrasonography. Endoscopic ultrasonography may be helpful if the transabdominal ultrasound is normal. If no other cause of pain is found and the gallbladder ejection fraction is less than 40%, cholecystectomy can be considered. The data supporting cholecystokinin-stimulated cholescintigraphy is poor. In clinical practice, it is not uncommon to see patients who have met these criteria and undergo cholecystectomy, but continue to have the same upper-abdominal symptoms postoperatively.

Common Bile Duct Stones and Cholangitis

Stones in the common bile duct are a leading cause of obstructive jaundice. Complications in patients with common bile duct stones are more common than in those with gallstones, but 20% of patients spontaneously pass the stones, and less than 50% of patients develop symptoms. Symptomatic common bile duct stones present with jaundice, abdominal pain, or pruritus due to obstruction of bile flow. Abdominal imaging, including CT, ultrasonography, or magnetic resonance

cholangiopancreatography (MRCP), can detect dilation of extrahepatic and intrahepatic bile ducts, indicating the presence of stones. Endoscopic retrograde cholangiopancreatography (ERCP) is the preferred therapeutic method for relieving obstruction of the common bile duct by stones.

The presence of cholangitis is heralded by the onset of the Charcot triad (fever, jaundice, and right-upper-quadrant abdominal pain) or Reynold pentad (Charcot triad plus hypotension and altered mental status). Cholangitis is potentially life-threatening, and antibiotic therapy targeting gram-negative *Enterobacteriaceae* should be administered. Identified common bile duct stones should be removed urgently with ERCP in patients with cholangitis, after which elective cholecystectomy should be performed within 6 weeks to reduce the risk for complications. In patients who are not surgical candidates, endoscopic sphincterotomy can be performed to facilitate the passage of additional common bile duct stones.

KEY POINTS

- Endoscopic retrograde cholangiopancreatography is the preferred therapeutic method for relieving obstruction due to a common bile duct stone.
- Cholangitis (heralded by the onset of fever, jaundice, and right-upper-quadrant abdominal pain) is potentially life-threatening; antibiotic therapy targeting gram-negative *Enterobacteriaceae* should be administered, and identified common bile duct stones should be removed urgently.

Gallbladder Polyps

Gallbladder polyps, usually incidental findings, can be seen on 1% to 5% of gallbladder ultrasounds. They can be neoplastic, such as an adenoma, or nonneoplastic, such as cholesterol polyps or adenomyomas. The best predictor of a malignant or premalignant lesion is size of the gallbladder polyp, with polyps greater than 1 cm in size being more likely to be neoplastic. Gallbladder polyps associated with gallbladder stones or primary sclerosing cholangitis are also more likely to be neoplastic. Management of gallbladder polyps is outlined in **Figure 32.**

KEY POINT

- Gallbladder polyps greater than 1 cm in size and those associated with gallbladder stones or primary sclerosing cholangitis are more likely to be neoplastic.

Gallbladder Cancer

Gallbladder cancer is the most common biliary cancer in the United States, but it is rare, with 3700 new cases per year. Risk factors include female sex, ethnicity or race (American Indian, Alaskan native, black), cholelithiasis, gallbladder polyps, porcelain gallbladder, anomalous pancreaticobiliary junction, and obesity. The gallbladder serves as a reservoir for *Salmonella typhi* in chronically infected patients, and patients with this organism are at higher risk for gallbladder cancer.

Presenting symptoms may include right-upper-quadrant pain, nausea, vomiting, weight loss, or jaundice in advanced cancers, and biliary colic in early cancers. Gallbladder cancer should be suspected if an enhancing gallbladder mass is seen on CT or MRI.

Early gallbladder cancer is most commonly diagnosed incidentally at the time of cholecystectomy performed for biliary colic. Incidental tumors found to invade the lamina propria (stage T1a) do not require further treatment, whereas more advanced lesions require extended cholecystectomy.

The treatment of choice for gallbladder cancer is surgery. Treatment for unresectable disease can include chemotherapy with or without radiation, or palliative care.

Prophylactic cholecystectomy is recommended for patients with an anomalous pancreaticobiliary junction, gallbladder polyps 1 cm in size or larger, or gallbladder polyp(s) in the presence of biliary colic or gallstones; it is also recommended for patients with primary sclerosing cholangitis and a gallbladder polyp larger than 8 mm in size. Prophylactic cholecystectomy can be considered for porcelain gallbladder or for gallstones larger than 3 cm in size.

Cholangiocarcinoma

Cholangiocarcinoma, although rare, is an increasingly recognized malignancy. It is classified as (1) intrahepatic—seen in the smaller bile ducts entirely within the liver parenchyma; (2) hilar—most commonly arising from confluence of right and left hepatic ducts (Klatskin tumor); or (3) distal—arising distal to the cystic-duct entrance. Risk factors include primary sclerosing cholangitis, choledochal cysts, liver flukes (*Opisthorchis*), exposure to thorium dioxide (contrast medium), and hepatolithiasis. Symptoms vary with tumor location and may include jaundice, pain in the right upper quadrant, and constitutional symptoms.

Intrahepatic, hilar, and distal cholangiocarcinomas can occur in patients without liver disease. Intrahepatic

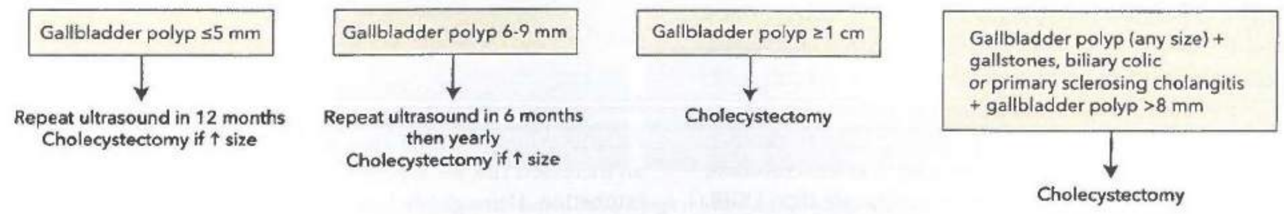

FIGURE 32. Management of gallbladder polyps.

cholangiocarcinoma can complicate cirrhosis, and hilar cholangiocarcinoma can complicate primary sclerosing cholangitis.

Diagnosis of intrahepatic cholangiocarcinoma requires imaging with CT or MRI, and usually a biopsy. An elevated CA 19-9 level is supportive but insufficient for diagnosis. First-line therapy for intrahepatic cholangiocarcinoma is resection. Locoregional and/or systemic chemotherapy are appropriate for patients who are not candidates for resection.

Diagnosis of hilar cholangiocarcinoma can be challenging and is made by a combination of MRCP and ERCP. During ERCP, bile-duct brushings should be obtained for cytologic examination and fluorescence in situ hybridization testing. The latter test uses DNA probes to evaluate for gain or loss of chromosomes or loci, which are often present in biliary cancer. An elevated CA 19-9 level is supportive, but repeat ERCP is often required every 2 to 3 months to make the diagnosis. First-line therapy for hilar cholangiocarcinoma is resection. Patients with obstructive jaundice may require ERCP with stent placement to allow for biliary drainage. Patients with unresectable hilar cholangiocarcinoma smaller than 3 cm in size and without extrahepatic spread can be evaluated for liver transplantation at select centers with neoadjuvant chemoradiation protocols. However, percutaneous or transluminal biopsy of hilar cholangiocarcinoma excludes a patient for liver transplantation due to the risk for tumor seeding.

The preferred treatment for distal cholangiocarcinoma is a Whipple resection.

Metastatic cholangiocarcinoma of any variety should be treated with gemcitabine-cisplatin.

The 5-year survival rate for patients with cholangiocarcinoma (excluding liver transplant recipients), including those who undergo resection, is 20% to 30%.

KEY POINTS

- Resection is first-line treatment for cholangiocarcinoma.
- Selected patients with unresectable hilar cholangiocarcinoma smaller than 3 cm in size and without extrahepatic spread may be candidates for liver transplantation.

Gastrointestinal Bleeding

Overview

In the United States, gastrointestinal bleeding is a common gastrointestinal cause of hospitalization. Upper gastrointestinal bleeding (UGIB) is defined as bleeding from the esophagus, stomach, or duodenum. The mortality rate for patients with UGIB varies from 2% to 10% but is usually due to other factors related to comorbid diseases. Lower gastrointestinal bleeding (LGIB) occurs from the colon or anorectum. It is less common, typically less severe, and has a lower mortality rate than UGIB. Small-bowel bleeding, formerly called obscure gastrointestinal bleeding, is bleeding that does not appear to originate from the upper or lower gastrointestinal tract; it is relatively uncommon.

KEY POINT

- Upper gastrointestinal bleeding is more common, more severe, and has a higher mortality rate than lower gastrointestinal bleeding.

Upper Gastrointestinal Bleeding

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UGIB can present in various ways, including hematemesis, "coffee-ground" emesis, melena, or hematochezia. Hematemesis is vomiting of bright red blood or clots. Coffee-ground emesis is the vomiting of dark, digested blood. Melena is black, tarry stool with a distinctive odor. Hematochezia is the passage of fresh blood or clots from the rectum.

Causes

Common causes of UGIB include peptic ulcer disease, gastroesophageal varices, and Mallory-Weiss tear. Peptic ulcer disease is the most common cause (50%), with most gastroduodenal ulcers caused by *Helicobacter pylori* or NSAID use. Erosive esophagitis is a common endoscopic finding but only rarely causes clinically important UGIB. Therefore, in a patient with UGIB and erosive esophagitis, alternative causes for the bleeding should be excluded.

Bleeding gastroesophageal varices typically occur in the distal esophagus or proximal stomach in individuals with advanced liver disease. Bleeding risk of varices is proportional to varix size.

A Mallory-Weiss tear consists of a mucosal disruption at the gastroesophageal junction and typically forms after repeated episodes of severe vomiting or retching.

Less common causes of UGIB include Cameron erosions, Dieulafoy lesion, gastric antral vascular ectasia, aortoenteric fistula, hemosuccus pancreaticus, hemobilia, and upper gastrointestinal tumors (**Table 37**).

Evaluation

The initial step in the approach to UGIB is a risk assessment to determine the severity of UGIB. This risk assessment includes the measurement of vital signs and reviewing patient factors. Tachycardia (pulse rate >100/min), hypotension (systolic blood pressure <100 mm Hg), age older than 60 years, and major comorbid medical conditions are all associated with increased risk for rebleeding and death.

Findings of stigmata of chronic liver disease suggest a possible variceal source of bleeding.

Management

Patients with altered mental status, massive hematemesis, or an increased risk for aspiration should undergo endotracheal intubation. Hemoglobin levels should be measured. A restrictive transfusion strategy is recommended and initiated when

TABLE 37. Less Common Causes of Upper Gastrointestinal Bleeding

Lesion	Pathogenesis	Presentation	Treatment
Cameron erosion	Mechanical trauma to mucosal folds of hiatal hernia	Typically chronic GI bleeding presenting as iron deficiency anemia	Includes medical therapy with PPI and iron, and surgical repair of hiatal hernia
Dieulafoy lesion	Dilated, aberrant submucosal vessel	Included in differential diagnosis of recurrent, often massive bleeding without clear source	Endoscopic
Gastric antral vascular ectasia	Most idiopathic; associated with cirrhosis and systemic sclerosis	Acute bleeding or iron deficiency anemia	Endoscopic
Aortoenteric fistula	Direct communication between aorta and GI tract	"Herald" bleed followed by massive exsanguination	Surgical
Hemosuccus pancreaticus	Erosion of pancreatic pseudocyst or tumor into a vessel with bleeding into pancreatic duct	Upper GI bleeding in setting of pancreatic disease	Mesenteric angiography with coil embolization
Hemobilia	Bleeding from the hepatobiliary tract often caused by arteriobiliary fistula from trauma or liver biopsy	Triad of jaundice, biliary colic, and GI bleeding	Angiography or surgical
Upper GI tumors	Benign or malignant neoplasms	Slow or massive hemorrhage	Palliative radiographic and endoscopy for malignant tumors, surgical resection for benign tumors

GI = gastrointestinal; PPI = proton pump inhibitor.

the hemoglobin level is below 7 g/dL (70 g/L) in hemodynamically stable patients without preexisting cardiovascular disease. Patients with hypotension due to severe, ongoing UGIB and those with concomitant cardiovascular disease should be transfused before the hemoglobin level decreases below 7 g/dL (70 g/L) to prevent the decreases below 7 g/dL (70 g/L) that may occur with fluid resuscitation alone.

For variceal bleeding, resuscitative measures need to be initiated with the goal of hemodynamic stabilization. Two large-bore peripheral intravenous catheters (minimum 18 gauge) are required with initiation of crystalloid fluids, either normal saline or lactated Ringer solution, to maintain adequate blood pressure. See Disorders of the Liver for discussion of variceal bleeding, including prophylaxis.

Pre-endoscopic Care

Intravenous proton pump inhibitor (PPI) therapy initiated before endoscopy decreases high-risk endoscopic stigmata seen (**Figure 33** and **Figure 34**) but does not influence outcome. Octreotide and antibiotics should be initiated if variceal

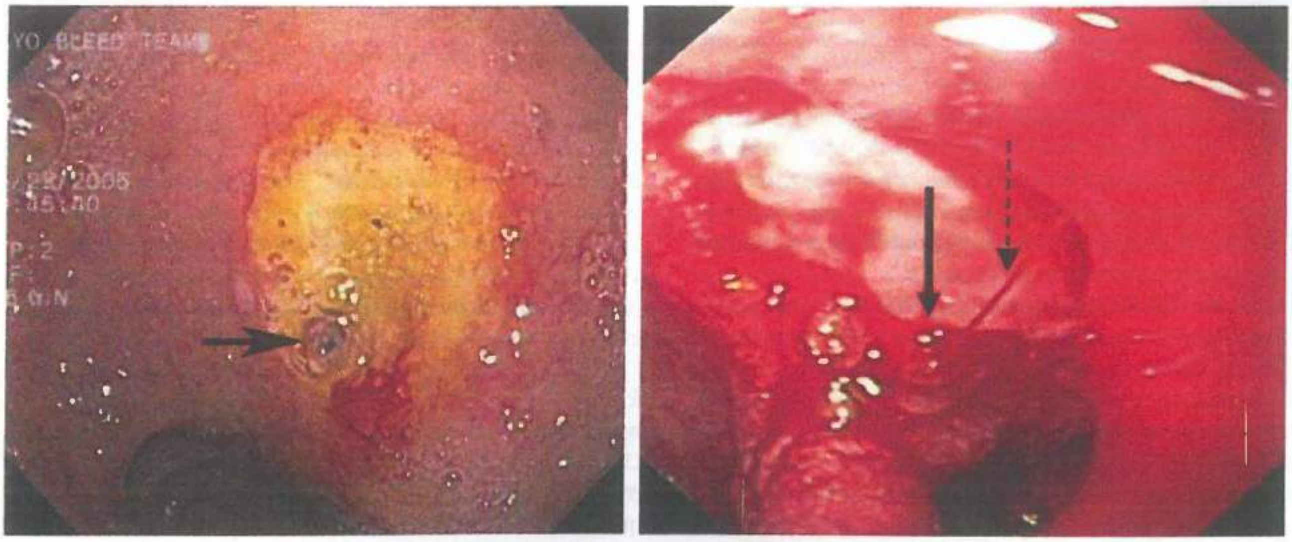

FIGURE 33. *Left:* Duodenal ulcer with nonbleeding visible vessel (*arrow*) that is at high risk for rebleeding and must be treated endoscopically. *Right:* Active arterial spurting (*dotted arrow*) from a duodenal ulcer (*solid arrow*). This lesion is at the highest risk for rebleeding and must be treated endoscopically.

Courtesy of Louis M. Wong Kee Song, MD, Mayo Clinic.

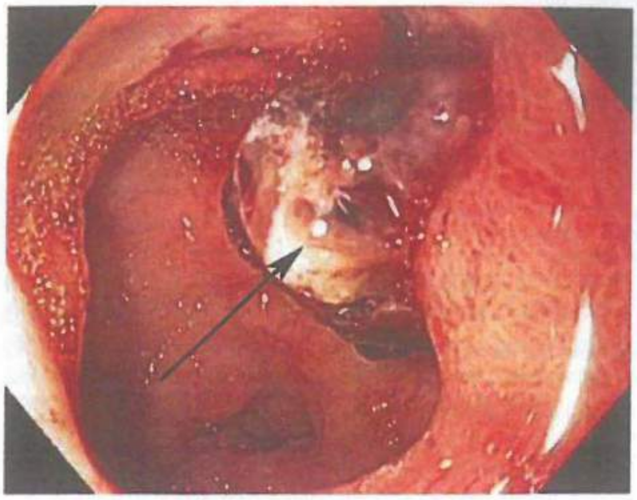

FIGURE 34. Duodenal ulcer with adherent clot (*arrow*) that is at risk for rebleeding. This can be treated medically or by clot removal and endoscopic therapy in addition to standard medical therapy.

Courtesy of Louis M. Wong Kee Song, MD, Mayo Clinic.

H CONT.

hemorrhage is suspected. Intravenous erythromycin given before endoscopy improves gastric visualization and decreases the need for repeat endoscopy, but it should be administered only when requested by the endoscopist, not routinely. Nasogastric tube lavage is not required, as it has shown no evidence of clinical benefit.

Vitamin K and 4-factor prothrombin complex concentrate should be administered to patients on anticoagulation with a supratherapeutic INR. The risk for continued bleeding on anticoagulation therapy should be weighed against the risk associated with stopping therapy. Furthermore, endoscopy should not be delayed for anticoagulation reversal unless the INR is greater than 3.0.

Decisions regarding discontinuing antiplatelet therapy are based on whether the therapy is for primary or secondary prophylaxis. If aspirin is being taken for primary prophylaxis, then it should be discontinued because the risk for recurrent bleeding outweighs the benefit. Aspirin for secondary prophylaxis can be discontinued for 3 days but needs to be promptly resumed when hemostasis is secure. Decisions regarding discontinuing clopidogrel and other antiplatelet agents should be made in conjunction with a cardiologist.

Patients with hemodynamic instability or active bleeding (hematemesis or recurrent large-volume hematochezia) should be admitted to an ICU for resuscitation. Other patients can be admitted to a regular hospital ward. Several decision rules and predictive models have been developed to identify patients who are at low risk for recurrent or life-threatening UGIB. The modified Glasgow-Blatchford bleeding score is calculated using the blood urea nitrogen level, hemoglobin level, systolic blood pressure, and pulse rate. It predicts the need for clinical intervention, rebleeding, and mortality. Patients at low risk according to the modified Glasgow-Blatchford score may be considered for early discharge or outpatient treatment.

Endoscopic Evaluation and Treatment

Upper endoscopy is the primary diagnostic modality for evaluating UGIB. For patients hospitalized with UGIB, endoscopy should be performed within 24 hours of resuscitation; in those with rapid bleeding or suspected variceal hemorrhage, it should be done more emergently. The possibility of aortoenteric fistula should always be considered in patients who have had previous aortic graft surgery and who present with gastrointestinal bleeding because aortoenteric fistula is life-threatening, with a mortality rate of 50% even with surgical intervention. When there is a high degree of suspicion for an aortoenteric fistula, CT with intravenous contrast should be performed before endoscopy or other types of gastrointestinal evaluation.

Endoscopy can determine the cause of bleeding and helps to risk-stratify the patient. Lesions at high risk for recurrent bleeding that require endoscopic treatment include: actively bleeding peptic ulcers, ulcers with nonbleeding visible vessels (see Figure 33), and ulcers with adherent clots (see Figure 34). An adherent clot should be irrigated with the intention of removing the clot; if clot removal is successful, the ulcer is then considered low-risk for rebleeding. Lesions at low risk for rebleeding (clean-based ulcers, ulcers with pigmented spots, and Mallory-Weiss tears) do not require endoscopic treatment (**Figure 35**). Most Mallory-Weiss tears (**Figure 36**) stop bleeding spontaneously. Endoscopic techniques such as injection therapy, thermal devices, and endoclips can be used for actively bleeding tears.

The initial therapy for acute esophageal variceal hemorrhage (**Figure 37**) is resuscitation in an ICU with the goal of maintaining hemodynamic stability and a hemoglobin of 7 g/dL (70 g/L). Overtransfusion can precipitate variceal rebleeding due to increased portal pressure.

The most effective approach for control of acute variceal hemorrhage is combined therapy with octreotide (somatostatin analog) and endoscopic therapy. Octreotide decreases splanchnic blood flow and lowers portal pressure; it should be initiated before endoscopic evaluation and continued for 3 to 5 days after variceal hemorrhage. Endoscopic variceal ligation within 12 hours of presentation is the endoscopic treatment of choice for hemostasis of active variceal hemorrhage, with a success rate of 90%. Subsequent endoscopy with further band ligation as needed to obliterate varices should be performed every 2 to 4 weeks.

Patients who develop variceal hemorrhage are at high risk for infection, such as pneumonia and urinary tract infection, and nearly 50% of patients with cirrhosis who are hospitalized with UGIB have a bacterial infection. Rates of rebleeding and death are reduced with prophylactic antibiotics (such as ceftriaxone or quinolone). Initiation of antibiotics at the time of hospitalization is recommended in all patients with cirrhosis and gastrointestinal bleeding, and antibiotic therapy should continue for 7 days after variceal hemorrhage, even in the absence of ascites.

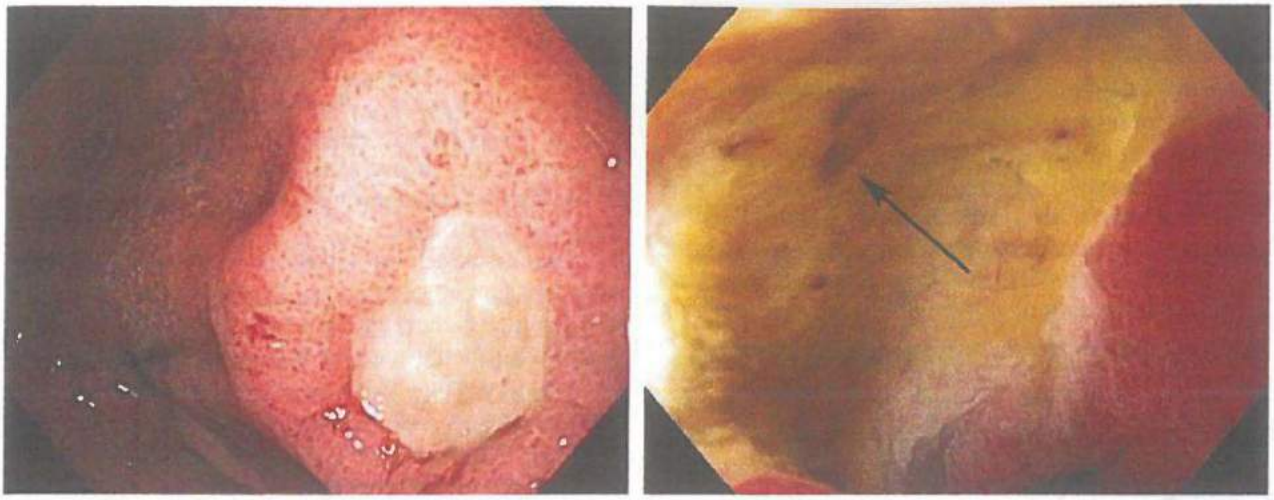

FIGURE 35. Ulcers at low risk for rebleeding, for which endoscopic therapy is not indicated. *Left*: Clean-based gastric ulcer with no blood vessels, pigmented spots/protuberances, or clots noted in the base. *Right*: Nonprotuberant pigmented spot (*arrow*) in a duodenal ulcer bed.

Courtesy of Louis M. Wong Kee Song, MD, Mayo Clinic.

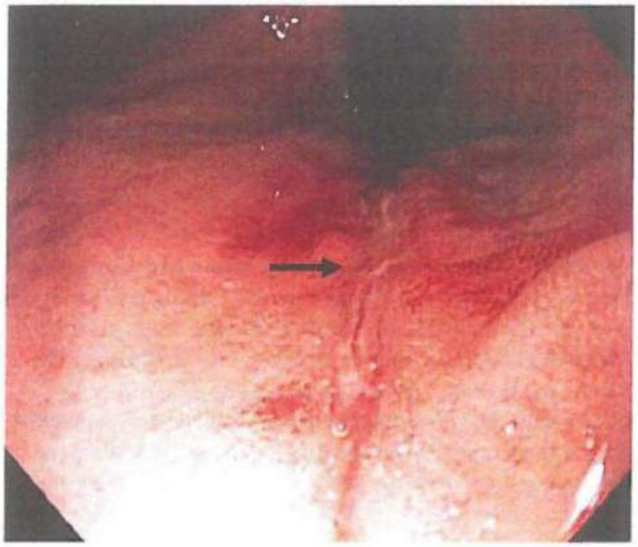

FIGURE 36. Mallory-Weiss tear. A superficial linear mucosal tear (*arrow*) seen on endoscopic retroflexion in the proximal stomach.

Courtesy of Louis M. Wong Kee Song, MD, Mayo Clinic.

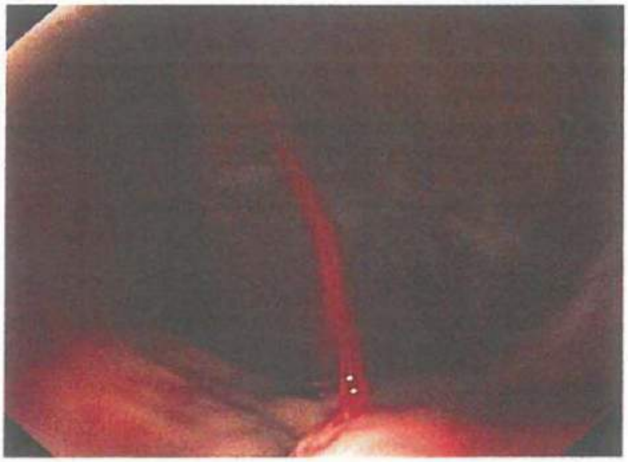

FIGURE 37. Acute esophageal variceal hemorrhage. A varix in the distal esophagus is seen spurting bright red blood.

H CONT.

Nonselective β-blocker therapy (propranolol, nadolol, or carvedilol) should be initiated in addition to endoscopic band ligation for secondary prophylaxis of variceal hemorrhage. The dosage of β-blockers should be increased as tolerated to obtain a resting pulse rate of 55 to 60/min.

If bleeding recurs, endoscopic therapy should be repeated, but routine second-look endoscopy is not recommended. Interventional radiology or surgery is reserved for cases of rebleeding despite endoscopic treatment. For variceal bleeding, placement of a transjugular intrahepatic portocaval shunt is reserved for bleeding that is not controlled by drug and endoscopic therapy.

Postendoscopic Care

Patients with low-risk stigmata (see Figure 35) can be fed within 24 hours of endoscopy, receive once-daily oral PPI therapy, and be discharged from the hospital. Patients with high-risk lesions and those with adherent clots requiring endoscopic treatment should receive intravenous PPI therapy for 72 hours to decrease risk for rebleeding and remain in the hospital for this interval.

When hemostasis is secure, antithrombotic agents can be restarted while continuing high-dose oral PPI therapy twice daily. Patients with idiopathic peptic ulcer disease, unrelated to NSAID use or *Helicobacter pylori* infection, should continue once-daily oral PPI therapy indefinitely because of the high risk for recurrent bleeding.

For discussion of management of peptic ulcer disease, see Disorders of the Stomach and Duodenum. H

KEY POINTS

- The most common causes of upper gastrointestinal bleeding include peptic ulcer disease, gastroesophageal varices, and Mallory-Weiss tear.
- Tachycardia (pulse rate >100/min), hypotension (systolic blood pressure <100 mm Hg), age older than 60 years, and major comorbid medical conditions are all associated with increased risk for rebleeding and death in patients with upper gastrointestinal bleeding.
- Upper endoscopy is the primary diagnostic modality for evaluating upper gastrointestinal bleeding.
- Management of an ulcer depends on the endoscopic appearance and risk for rebleeding.

H Lower Gastrointestinal Bleeding

Twenty percent of all cases of gastrointestinal bleeding originate in the colon or rectum. Most cases of LGIB stop spontaneously and have good outcomes; however, higher rates of morbidity and mortality are seen in older patients and in those with comorbid conditions. Patients with LGIB usually present with sudden onset of hematochezia (maroon or red blood per rectum). Occasionally, bleeding from the cecum or right colon may appear black and tarry, like melena. LGIB may present with additional symptoms of pain, diarrhea, or change in bowel movements.

Causes

The most common cause of minor LGIB is hemorrhoidal bleeding. Hemorrhoidal bleeding is usually characterized by a small volume of bright red blood and does not cause hemodynamic instability or significant volume loss (see Disorders of the Small and Large Bowel for discussion of hemorrhoids). Causes of severe LGIB that may lead to clinical instability include diverticular bleeding, colonic angiodysplasia, postpolypectomy bleeding, Dieulafoy lesion, solitary rectal ulcer syndrome, rectal varices, or malignancy (**Table 38**). Fifteen percent of patients with a presumed lower gastrointestinal source of bleeding are found to have an upper gastrointestinal source.

TABLE 38. Causes of Severe Lower Gastrointestinal Bleeding

Diverticulosis
Aortoenteric fistula
Colonic or rectal varices
Dieulafoy lesions
Neoplasm
Colitis
Ischemic
Inflammatory bowel disease
Infectious
Intussusception
Meckel diverticulum
Angiodysplasia

Diverticular bleeding is arterial, usually painless, occurs in the neck or dome of a diverticulum, and stops spontaneously in 75% of cases. In patients with diverticulosis, the risk for bleeding is estimated at 0.5 per 1000 person-years. For further discussion of diverticular disease, see Disorders of the Small and Large Bowel.

Angiodysplasia, also known as angiectasia or arteriovenous malformation, can occur throughout the colon but is most common in the right colon. Elderly patients and patients on anticoagulation therapy are at highest risk.

Postpolypectomy bleeding can occur immediately after polyp removal or days or weeks later. Risk is increased in patients with polyps larger than 2 cm in size, with polyps located in the right colon, and with resumption of antithrombotic therapy.

Patients with ischemic colitis usually present with severe abdominal pain, often out of proportion to physical findings. Diarrhea, abdominal pain, and hematochezia can occur with inflammatory bowel disease and infectious colitis. LGIB from a colon malignancy may be painless or associated with obstructive symptoms. Patients with cardiac disease, such as valve dysfunction or dilated cardiomyopathy, are at risk for acquired von Willebrand disease and gastrointestinal bleeding.

Evaluation

An initial patient assessment and hemodynamic resuscitation should be performed simultaneously. The timing and quality of any previous colonoscopy should be assessed, as should whether or not polypectomy or biopsies were performed. The patient's medication history, especially use and dosing of antithrombotic agents, should be assessed, as well as personal history, risk factors for liver disease, other comorbidities, and recent illness.

Management

Resuscitation goals for patients with LGIB should be normalization of blood pressure and heart rate, as well as the transfusion of packed red blood cells if needed to maintain the hemoglobin level above 7 g/dL (70 g/L), with a threshold of 9 g/dL (90 g/L) in patients with massive bleeding, or when treatment may be delayed. Platelet transfusion to maintain counts above 50,000 cells/µL (50×10^9/L) is recommended in patients with active bleeding. The decision to discontinue or reverse anticoagulant agents should balance the risk of ongoing bleeding with the risk of thromboembolic events and often requires a multidisciplinary approach.

Colonoscopy is the initial diagnostic test in the majority of patients with LGIB and should be performed within 24 hours of presentation after adequate colon preparation in patients with significant bleeding. Colonoscopy identifies a source of LGIB in two thirds of patients. Hematochezia with

H CONT.

hemodynamic instability may indicate a rapid UGIB source, and upper endoscopy may be indicated.

Radiographic interventions should be considered in patients with ongoing bleeding who do not respond to resuscitation, patients who cannot tolerate colonoscopy or colon preparation, or patients in whom a source of bleeding is not identified endoscopically. Techniques include CT angiography, angiography, and, less frequently, tagged red blood cell scintigraphy.

Angiography with embolization is frequently used to stop persistent or recurrent diverticular bleeding because endoscopic approaches are limited due to the typical location of the vessel inside a thin-walled diverticulum. Surgical consultation is usually reserved for patients who do not respond to endoscopic or radiographic measures.

The risk for rebleeding is highest in patients with diverticular bleeding (9% to 47%) and angiodysplasia bleeding (37% to 64%). For prevention of recurrent LGIB, nonaspirin NSAIDs should be avoided, particularly after diverticular or angiodysplasia bleeding. The continued use of antiplatelet or anticoagulants needs to be weighed against the risk for rebleeding. Aspirin for secondary prevention in patients with high-risk cardiovascular disease should not be discontinued. Decisions about discontinuation of dual antiplatelet therapy in patients with an acute coronary syndrome or coronary stent placement should be made in conjunction with a cardiologist. Anticoagulation use for other medical indications should be resumed as soon as possible, within at least 7 days for most patients. H

KEY POINTS

- Patients with lower gastrointestinal bleeding usually present with sudden onset of hematochezia (maroon or red blood per rectum).
- Most cases of lower gastrointestinal bleeding stop spontaneously and have good outcomes; however, higher rates of morbidity and mortality are seen in older patients and in those with comorbid conditions.
- Colonoscopy identifies a source of lower gastrointestinal bleeding in two thirds of patients.

H Small-Bowel Bleeding

The term *small-bowel bleeding* is preferred to *obscure gastrointestinal bleeding* because in many clinical situations the cause of the bleeding can now be identified. Patients with small-bowel bleeding often have normal results on upper endoscopy and colonoscopy. Small-bowel bleeding can be characterized as overt or occult. In patients with visible bleeding (either melena or hematochezia), it is overt. In patients who present with anemia but no gross signs of bleeding, the bleeding is considered occult. It is estimated that 5% to 10% of gastrointestinal bleeding occurs between the ligament of Treitz and the ileocecal valve; this is also known as midgastrointestinal bleeding.

Causes

The likely underlying cause of small-bowel bleeding varies with patient age (**Table 39**). Patients younger than age 40 years are likely to have bleeding due to inflammatory bowel disease, Dieulafoy lesions, neoplasia (leiomyoma, carcinoid, lymphoma, or adenocarcinoma), Meckel diverticulum, or a polyposis syndrome. Patients older than age 40 years are likely to have bleeding due to angiodysplasia, Dieulafoy lesion, neoplasia, or NSAID-related ulcers. Angiodysplasia (**Figure 38**) is the most common cause of small-bowel bleeding. It is found in 40% of cases and is often seen in elderly patients. Rare causes of bleeding include Henoch-Schönlein purpura, small-bowel varices or portal hypertensive enteropathy, amyloidosis, blue rubber bleb nevus syndrome, hematobilia, aortoenteric fistula, and hemosuccus entericus.

Evaluation

A detailed medical history and physical examination are needed to narrow the differential diagnosis to a small-bowel source. Patients should be asked about NSAID use to evaluate for NSAID-induced small-bowel ulcers, aortic aneurysm

TABLE 39. Causes of Small-Bowel Gastrointestinal Bleeding

Differential Diagnosis	Patient Age (Years)	Clinical Clues
Angiodysplasia	>60	Intermittent, usually occult bleeding; may also occur in the colon
Peutz-Jeghers syndrome	<20	Perioral pigmentation, obstructive symptoms
Meckel diverticulum	20-60	Possible abdominal pain
Hemangioma	<20	Possible cutaneous hemangiomas
Malignancy	>50	Weight loss, abdominal pain
Hereditary hemorrhagic telangiectasia	>50	Mucocutaneous telangiectasias

FIGURE 38. Capsule endoscopy image of angiodysplasia. The lesion (*arrow*) has a fernlike pattern and is red in color. Angiodysplasia can have no bleeding or active bleeding.

H CONT.

repair (which raises concern for an aortoenteric fistula), necrotizing pancreatitis (which causes hemosuccus pancreaticus), or liver damage (such as trauma, tumor, or recent biopsy causing hemobilia). The presence of skin lesions may help determine an underlying diagnosis, including mucocutaneous telangiectasia (hereditary hemorrhagic telangiectasia, also known as Osler-Weber-Rendu syndrome [**Figure 39**]) or dermatitis herpetiformis (celiac disease).

If the bleeding source is not identified, but clinical suspicion suggests that the cause of the bleeding is discoverable by a conventional endoscopic examination, a second-look endoscopy or colonoscopy should be done. The diagnostic yield is up to 25% with this approach.

Angiography

Conventional angiography is a diagnostic and therapeutic test. However, it is limited to detecting bleeding at rates greater than 0.5 mL/min. Clinical predictors of successful angiography include hemodynamic instability and the need for transfusion of more than 5 units of blood. Potential complications of angiography include acute kidney injury, systemic embolism, hematoma, and vascular dissection or aneurysm.

CT angiography uses multiple phases of contrast enhancement, including arterial enhancement. It can identify bleeding at rates as low as 0.3 mL/min, but its usefulness is limited because the patient must have active bleeding to identify the location.

Technetium-Labeled Nuclear Scan

Technetium 99m-labeled red blood cell or sulfur colloid nuclear scans are able to detect bleeding rates between 0.1 to 0.4 mL/min. Their accuracy in identifying a source of bleeding varies, ranging from 24% to 91%, and they do not provide for therapeutic intervention. A nuclear scan is often done before angiography to confirm the presence of active bleeding.

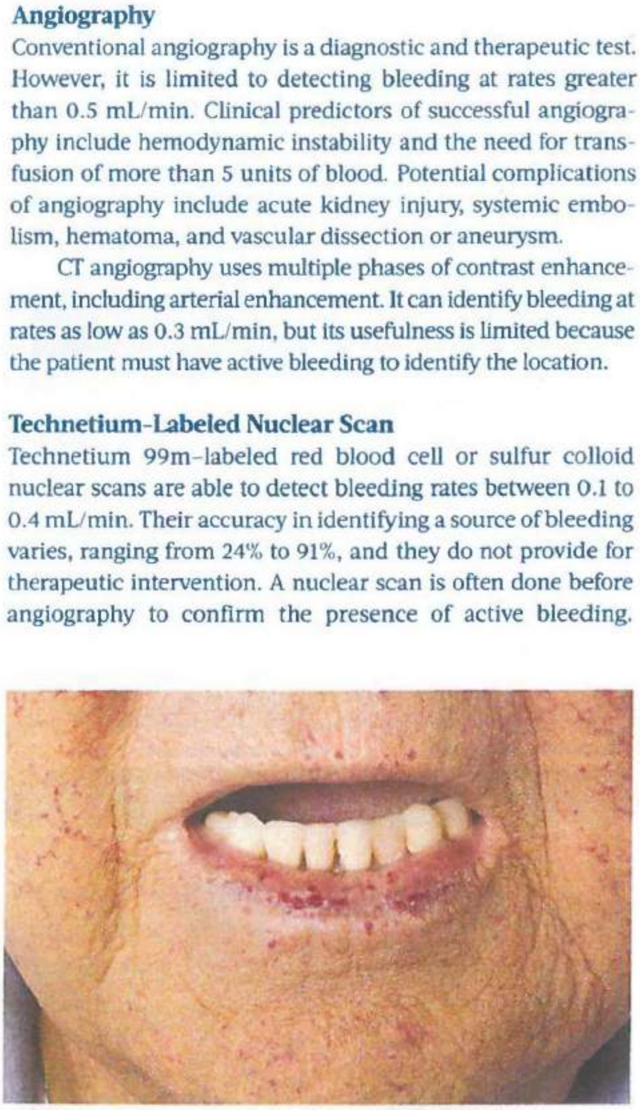

FIGURE 39. Hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu syndrome) is a disorder of development of the vasculature characterized by telangiectases and arteriovenous malformations in specific locations. It is one of the most common monogenic disorders, but affected individuals are frequently not diagnosed. The most common features of the disorder—nosebleeds and telangiectases on the lips, hands, and oral mucosa—are often quite subtle.

Follow-up studies after a positive scan can include repeat endoscopy or angiography, both of which can offer more accurate localization and therapy.

Wireless Capsule Endoscopy

Capsule endoscopy employs a wireless capsule camera (**Figure 40**) that is swallowed by the patient to take images of the small bowel. The images are transmitted to a radiofrequency receiver worn by the patient. Capsule endoscopy is the preferred test for evaluating stable patients for causes of small-bowel bleeding after normal results on upper endoscopy and colonoscopy. Capsule endoscopy is able to visualize the entire small bowel in up to 90% of cases, with a diagnostic yield as high as 83%. Limitations of capsule endoscopy include the inability for therapeutic intervention and difficulty with localization of the lesion. The primary complication is possibility of capsule retention due to obstruction or strictures. The capsule can be retrieved by deep enteroscopy or surgery.

If there is continued concern for bleeding from the small bowel, specialized types of enteroscopy may be considered, including push, spiral, and balloon enteroscopy. These techniques allow visualization beyond the ligament of Treitz for diagnosis and the opportunity for therapeutic intervention. In general, the rates of complications are low, but complications can include perforation and in the case of balloon enteroscopy, ileus and pancreatitis.

Small-Bowel Imaging

Endoscopy has replaced imaging for the initial evaluation of suspected bleeding from the small bowel.

Barium-based examinations are no longer recommended for the evaluation of small-bowel bleeding because of low diagnostic yields. CT enterography is beneficial in diagnosing small-bowel masses and has shown a diagnostic yield of 40% for bleeding. Due to insufficient data, MR enterography is not recommended for the evaluation of small-bowel bleeding. However, it can be considered in patients younger than age 40 years, and it offers lower exposure to radiation than CT.

FIGURE 40. Endoscopy capsule.

Courtesy of Elizabeth Rajan, MD, Mayo Clinic.

Intraoperative Endoscopy

CONT.

Intraoperative endoscopy occurring during laparotomy is often a last resort because it is the most invasive modality available. The diagnostic yield for small-bowel bleeding has been reported in the range of 58% to 88%; however, its use should be reserved for patients in whom all other diagnostic modalities have failed.

Management

After achieving hemodynamic stabilization, therapy is guided by the underlying source of bleeding. Vascular lesions (angiodysplasia) should be treated with electrocautery, argon plasma coagulation, injection therapy, mechanical hemostasis (hemoclips or banding), or a combination of these techniques. Medical therapy for vascular lesions may require a somatostatin analog, such as octreotide. Hormonal therapy no longer has a role in the medical management of small-bowel bleeding.

Tumors or masses require surgical intervention, and if massive bleeding is present, embolization of the bleeding vessel may be needed with the assistance of interventional radiology.

Anemia should be treated with blood transfusion acutely if needed and iron supplementation. If a causative agent is identified, such as an NSAID, the agent should be stopped. Patients with angiodysplasia in the setting of aortic stenosis (known as Heyde syndrome) benefit from valve replacement surgery. While not FDA approved, thalidomide, which inhibits vascular endothelial growth factor, has shown some benefit in decreasing bleeding in patients with vascular malformations of the gut.

KEY POINTS

- Capsule endoscopy is the preferred test for evaluating stable patients for small-bowel bleeding after normal results on endoscopy and colonoscopy.
- After achieving hemodynamic stabilization, therapy for small-bowel bleeding is guided by the underlying source of bleeding.

Bibliography

Disorders of the Esophagus

Bowers SP. Esophageal motility disorders. Surg Clin North Am. 2015;95:467-82. [PMID: 25965124] doi:10.1016/j.suc.2015.02.003

Ganz RA. A review of new surgical and endoscopic therapies for gastroesophageal reflux disease. Gastroenterol Hepatol (N Y). 2016;12:424-31. [PMID: 27489524]

Gunasingam N, Perczuk A, Talbot M, Kaffes A, Saxena P. Update on therapeutic interventions for the management of achalasia. J Gastroenterol Hepatol. 2016;31:1422-8. [PMID: 27060999] doi:10.1111/jgh.13408

Katz PO, Gerson LB, Vela MF. Guidelines for the diagnosis and management of gastroesophageal reflux disease. Am J Gastroenterol. 2013;108:308-28; quiz 329. [PMID: 23419381] doi:10.1038/ajg.2012.444

Kavitt RT, Hirano I, Vaezi MF. Diagnosis and treatment of eosinophilic esophagitis in adults. Am J Med. 2016;129:924-34. [PMID: 27155108] doi:10.1016/j.amjmed.2016.04.024

Pandolfino JE, Kahrilas PJ; American Gastroenterological Association. AGA technical review on the clinical use of esophageal manometry. Gastroenterology. 2005;128:209-24. [PMID: 15633138]

Shaheen NJ, Falk GW, Iyer PG, Gerson LB; American College of Gastroenterology. ACG clinical guideline: diagnosis and management of Barrett's esophagus. Am J Gastroenterol. 2016;111:30-50; quiz 51. [PMID: 26526079] doi:10.1038/ajg.2015.322

Vaezi MF, Pandolfino JE, Vela MF. ACG clinical guideline: diagnosis and management of achalasia. Am J Gastroenterol. 2013;108:1238-49; quiz 1250. [PMID: 23877351] doi:10.1038/ajg.2013.196

Zerbib F, Roman S. Current therapeutic options for esophageal motor disorders as defined by the Chicago Classification. J Clin Gastroenterol. 2015;49:451-60. [PMID: 25844840] doi:10.1097/MCG.0000000000000317

Disorders of the Stomach and Duodenum

American Cancer Society. Cancer facts & figures 2016. Atlanta: American Cancer Society; 2016.

Berg P, McCallum R. Dumping Syndrome: A Review of the Current Concepts of Pathophysiology, Diagnosis, and Treatment. Dig Dis Sci. 2016;61:11-8. [PMID: 26396002] doi:10.1007/s10620-015-3839-x

Camilleri M, Parkman HP, Shafi MA, Abell TL, Gerson L; American College of Gastroenterology. Clinical guideline: management of gastroparesis. Am J Gastroenterol. 2013;108:18-37; quiz 38. [PMID: 23147521] doi:10.1038/ajg.2012.373

Chey WD, Leontiadis GI, Howden CW, Moss SF. ACG clinical guideline: treatment of *Helicobacter pylori* infection. Am J Gastroenterol. 2017;112:212-239. [PMID: 28071659] doi:10.1038/ajg.2016.563

Evans JA, Chandrasekhara V, Chathadi KV, Decker GA, Early DS, Fisher DA, et al; ASGE Standards of Practice Committee. The role of endoscopy in the management of premalignant and malignant conditions of the stomach. Gastrointest Endosc. 2015;82:1-8. [PMID: 25935705] doi:10.1016/j.gie.2015.03.1967

Ingle SB, Hinge Ingle CR. Eosinophilic gastroenteritis: an unusual type of gastroenteritis. World J Gastroenterol. 2013;19:5061-6. [PMID: 23964139] doi:10.3748/wjg.v19.i31.5061

Laine L. Clinical Practice. Upper gastrointestinal bleeding due to a peptic ulcer. N Engl J Med. 2016;374:2367-76. [PMID: 27305194] doi:10.1056/NEJMcp1514257

Lanza FL, Chan FK, Quigley EM; Practice Parameters Committee of the American College of Gastroenterology. Guidelines for prevention of NSAID-related ulcer complications. Am J Gastroenterol. 2009;104:728-38. [PMID: 19240698] doi:10.1038/ajg.2009.115

Moayyedi PM, Lacy BE, Andrews CN, Enns RA, Howden CW, Vakil N. ACG and CAG Clinical guideline: management of dyspepsia. Am J Gastroenterol. 2017;112:988-1013. [PMID: 28631728] doi:10.1038/ajg.2017.154

Park JY, Lam-Himlin D, Vemulapalli R. Review of autoimmune metaplastic atrophic gastritis. Gastrointest Endosc. 2013;77:284-92. [PMID: 23199649] doi:10.1016/j.gie.2012.09.033

Stanghellini V, Chan FK, Hasler WL, Malagelada JR, Suzuki H, Tack J, et al. Gastroduodenal disorders. Gastroenterology. 2016;150:1380-92. [PMID: 27147122] doi:10.1053/j.gastro.2016.02.011

Syngal S, Brand RE, Church JM, Giardiello FM, Hampel HL, Burt RW; American College of Gastroenterology. ACG clinical guideline: genetic testing and management of hereditary gastrointestinal cancer syndromes. Am J Gastroenterol. 2015;110:223-62; quiz 263. [PMID: 25645574] doi:10.1038/ajg.2014.435

Talley NJ, Ford AC. Functional dyspepsia. N Engl J Med. 2015;373:1853-63. [PMID: 26535514] doi:10.1056/NEJMra1501505

Zong L, Chen P. Billroth I vs. Billroth II vs. Roux-en-Y following distal gastrectomy: a meta-analysis based on 15 studies. Hepatogastroenterology. 2011;58:1413-24. [PMID: 21937419] doi:10.5754/hge10567

Disorders of the Pancreas

Banks PA, Bollen TL, Dervenis C, Gooszen HG, Johnson CD, Sarr MG, et al; Acute Pancreatitis Classification Working Group. Classification of acute pancreatitis—2012: revision of the Atlanta classification and definitions by international consensus. Gut. 2013;62:102-11. [PMID: 23100216] doi:10.1136/gutjnl-2012-302779

Canto MI, Hruban RH, Fishman EK, Kamel IR, Schulick R, Zhang Z, et al; American Cancer of the Pancreas Screening (CAPS) Consortium. Frequent detection of pancreatic lesions in asymptomatic high-risk individuals. Gastroenterology. 2012;142:796-804; quiz e14-5. [PMID: 22245846] doi:10.1053/j.gastro.2012.01.005

Di MY, Liu H, Yang ZY, Bonis PA, Tang JL, Lau J. Prediction models of mortality in acute pancreatitis in adults: a systematic review. Ann Intern Med. 2016;165:482-490. [PMID: 27454310]

Elta GH, Enestvedt BK, Sauer BG, Marie Lennon A. ACG Clinical Guideline: Diagnosis and management of pancreatic cysts. Am J Gastroenterol. 2018 Feb 27. doi:10.1038/ajg.2018.14. [Epub ahead of print] [PMID: 29485131]

Khorana AA, Mangu PB, Berlin J, Engebretson A, Hong TS, Maitra A, et al. Potentially curable pancreatic cancer: American Society of Clinical Oncology clinical practice guideline. J Clin Oncol. 2016;34:2541-56. [PMID: 27247221] doi:10.1200/JCO.2016.67.5553

Kunz PL, Reidy-Lagunes D, Anthony LB, Bertino EM, Brendtro K, Chan JA, et al; North American Neuroendocrine Tumor Society. Consensus guidelines for the management and treatment of neuroendocrine tumors. Pancreas. 2013;42:557-77. [PMID: 23591432] doi:10.1097/MPA.0b013e31828e34a4

Majumder S, Chari ST. Chronic pancreatitis. Lancet. 2016;387:1957-66. [PMID: 26948434] doi:10.1016/S0140-6736(16)00097-0

Okano K, Oshima M, Yachida S, Kushida Y, Kato K, Kamada H, et al. Factors predicting survival and pathological subtype in patients with ampullary adenocarcinoma. J Surg Oncol. 2014;110:156-62. [PMID: 24619853] doi: 10.1002/jso.23600

Okazaki K, Uchida K. Autoimmune Pancreatitis: the past, present, and future. Pancreas. 2015;44:1006-16. [PMID: 26355544] doi:10.1097/MPA.0000000000000382

Tenner S, Baillie J, DeWitt J, Vege SS; American College of Gastroenterology. American College of Gastroenterology guideline: management of acute pancreatitis. Am J Gastroenterol. 2013;108:1400-15; 1416. [PMID: 23896955] doi:10.1038/ajg.2013.218

Vaughn VM, Shuster D, Rogers MAM, Mann J, Conte ML, Saint S, et al. Early versus delayed feeding in patients with acute pancreatitis: a systematic review. Ann Intern Med. 2017;166:883-892. [PMID: 28505667]

Disorders of the Small and Large Bowel

Brandt LJ, Feuerstadt P, Longstreth GF, Boley SJ; American College of Gastroenterology. ACG clinical guideline: epidemiology, risk factors, patterns of presentation, diagnosis, and management of colon ischemia (CI). Am J Gastroenterol. 2015 Jan;110(1):18-44; quiz 45. doi: 10.1038/ajg.2014.395. [PMID: 25559486]

Brenner DM, Shah M. Chronic constipation. Gastroenterol Clin North Am. 2016 Jun;45(2):205-16. doi: 10.1016/j.gtc.2016.02.013. [PMID: 27261894]

Clair DG, Beach JM. Mesenteric ischemia. N Engl J Med. 2016 Mar 10; 374(10):959-68. [PMID: 26962730]

Downey L, Houten R, Murch S, et al.; Guideline Development Group. Recognition, assessment, and management of coeliac disease: summary of updated NICE guidance. BMJ. 2015 Sep 2;351:h4513. doi: 10.1136/bmj.h4513. [PMID: 26333593]

Ford AC, Moayyedi P, Lacy BE, et al.; Task Force on the Management of Functional Bowel Disorders. American College of Gastroenterology monograph on the management of irritable bowel syndrome and chronic idiopathic constipation. Am J Gastroenterol. 2014 Aug;109 Suppl 1:S2-26; quiz S27. [PMID: 25091148]

Freeman A, Menees S. Fecal incontinence and pelvic floor dysfunction in women: a review. Gastroenterol Clin North Am. 2016 Jun;45(2):217-37. [PMID: 27261895]

Keefer L, Drossman DA, Guthrie E, et al. Centrally mediated disorders of gastrointestinal pain. Gastroenterology. 2016 Feb 19. pii: S0016-5085(16)00225-0. [PMID: 27144628]

Kornbluth A, Sachar DB; Practice Parameters Committee of the American College of Gastroenterology. Ulcerative colitis practice guidelines in adults: American College of Gastroenterology, Practice Parameters Committee. Am J Gastroenterol. 2010 Mar;105(3):501-23; quiz 524. Erratum in: Am J Gastroenterol. 2010 Mar;105(3):500. [PMID: 20068560]

Leeds IL, Fang SH. Anal cancer and intraepithelial neoplasia screening: a review. World J Gastrointest Surg. 2016 Jan 27;8(1):41-51. [PMID: 26843912]

Lichtenstein GR, Hanauer SB, Sandborn WJ; Practice Parameters Committee of American College of Gastroenterology. Management of Crohn's disease in adults. Am J Gastroenterol. 2009 Feb;104(2):465-83; quiz 464, 484. [PMID: 19174807]

Mearin F, Lacy BE, Chang L, et al. Bowel disorders. Gastroenterology. 2016 Feb 18. pii: S0016-5085(16)00222-5. [PMID: 27144627]

Nikaki K, Gupte GL. Assessment of intestinal malabsorption. Best Pract Res Clin Gastroenterol. 2016 Apr;30(2):225-35. [PMID: 27086887]

Pardi DS, Tremaine WJ, Carrasco-Labra A. American Gastroenterological Association Institute technical review on the medical management of microscopic colitis. Gastroenterology. 2016 Jan;150(1):247-274.e11. [PMID: 26584602]

Riddle MS, DuPont HL, Connor BA. ACG clinical guideline: diagnosis, treatment, and prevention of acute diarrheal infections in adults. Am J Gastroenterol. 2016 May;111(5):602-22. [PMID: 27068718]

Rubio-Tapia A, Hill ID, Kelly CP, et al: American College of Gastroenterology. ACG clinical guidelines: diagnosis and management of celiac disease. Am J Gastroenterol. 2013 May;108(5):656-76; quiz 677. [PMID: 23609613]

Schiller LR, Pardi DS, Spiller R, et al. Gastro 2013 APDW/WCOG Shanghai working party report: chronic diarrhea: definition, classification, diagnosis. J Gastroenterol Hepatol. 2014 Jan;29(1):6-25. [PMID: 24117999]

Shepherd SJ, Lomer MC, Gibson PR. Short-chain carbohydrates and functional gastrointestinal disorders. Am J Gastroenterol. 2013 May;108(5):707-17. [PMID: 23588241]

Tursi A, Papa A, Danese S. Review article: the pathophysiology and medical management of diverticulosis and diverticular disease of the colon. Aliment Pharmacol Ther. 2015 Sep;42(6):664-84. [PMID: 26202723]

Wald A, Bharucha AE, Cosman BC, Whitehead WE. ACG clinical guideline: management of benign anorectal disorders. Am J Gastroenterol. 2014 Aug;109(8):1141-57; (Quiz) 1058. [PMID: 25022811]

Colorectal Neoplasia

American Cancer Society. Colorectal Cancer Facts and Figures 2014-2016. Atlanta: American Cancer Society, 2014.

American Gastroenterology Association. AGA institute guidelines for colonoscopy surveillance after cancer resection: clinical decision tool. Gastroenterology. 2014 May;146(5):1413-4. [PMID: 24742563]

Bibbins-Domingo K; U.S. Preventive Services Task Force. Aspirin use for the primary prevention of cardiovascular disease and colorectal cancer: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2016 Jun 21;164(12):836-45. [PMID: 27064677]

Bouvard V, Loomis D, Guyton KZ, et al.; International Agency for Research on Cancer Monograph Working Group. Carcinogenicity of consumption of red and processed meat. Lancet Oncol. 2015 Dec;16(16):1599-600. [PMID: 26514947]

Giardiello FM, Allen JI, Axilbund JE, et al. Guidelines on genetic evaluation and management of Lynch syndrome: a consensus statement by the US Multi-Society Task Force on Colorectal Cancer. Dis Colon Rectum. 2014 Aug;57(8):1025-48. [PMID: 25003300]

Lieberman DA, Rex DK, Winawer SJ, et al.; United States Multi-Society Task Force on Colorectal Cancer. Guidelines for colonoscopy surveillance after screening and polypectomy: a consensus update by the US Multi-Society Task Force on Colorectal Cancer. Gastroenterology. 2012 Sep;143(3):844-57. [PMID: 22763141]

Provenzale D, Gupta S, Ahnen DJ, Bray T, Cannon JA, Cooper G, et al. Genetic/Familial High-Risk Assessment: Colorectal Version 1.2016, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2016;14:1010-30. [PMID: 27496117]

Rubenstein JH, Enns R, Heidelbaugh J, Barkun A; Clinical Guidelines Committee. American Gastroenterological Association Institute guideline on the diagnosis and management of Lynch Syndrome. Gastroenterology. 2015 Sep;149(3):777-82; quiz e16-7. [PMID: 26226577]

Syngal S, Brand RE, Church JM, et al.; American College of Gastroenterology. ACG clinical guideline: genetic testing and management of hereditary gastrointestinal cancer syndromes. Am J Gastroenterol. 2015 Feb;110(2):223-62; quiz 263. [PMID: 25645574]

Disorders of the Liver

AASLD-IDSA. Recommendations for testing, managing, and treating hepatitis C. https://www.hcvguidelines.org/. Accessed February 14, 2018.

Chalasani NP, Hayashi PH, Bonkovsky HL, Navarro VJ, Lee WM, Fontana RJ; Practice Parameters Committee of the American College of Gastroenterology. ACG clinical guideline: the diagnosis and management of idiosyncratic drug-induced liver injury. Am J Gastroenterol. 2014;109:950-66; quiz 967. [PMID: 24935270] doi:10.1038/ajg.2014.131

Chalasani N, Younossi Z, Lavine JE, Charlton M, Cusi K, Rinella M, et al. The diagnosis and management of nonalcoholic fatty liver disease: practice guidance from the American Association for the Study of Liver Diseases. Hepatology. 2017. [PMID: 28714183] doi:10.1002/hep.29367

European Association for the Study of the Liver. EASL clinical practice guidelines: autoimmune hepatitis. J Hepatol. 2015;63:971-1004. [PMID: 26341719] doi:10.1016/j.jhep.2015.06.030

Heimbach J, Kulik LM, Finn R, Sirlin CB, Abecassis M, Roberts LR, et al. AASLD guidelines for the treatment of hepatocellular carcinoma. Hepatology. 2017. [PMID: 28130846] doi:10.1002/hep.29086

Ilyas JA, Kanwal F. Primary prophylaxis of variceal bleeding. Gastroenterol Clin North Am. 2014;43:783-94. [PMID: 25440925] doi:10.1016/j.gtc.2014.08.008

Kamar N, Bendall R, Legrand-Abravanel F, Xia NS, Ijaz S, Izopet J, et al. Hepatitis E. Lancet. 2012;379:2477-88. [PMID: 22549046] doi:10.1016/S0140-6736(11)61849-7

Lindor KD, Gershwin ME, Poupon R, Kaplan M, Bergasa NV, Heathcote EJ; American Association for Study of Liver Diseases. Primary biliary cirrhosis. Hepatology. 2009;50:291-308. [PMID: 19554543] doi:10.1002/hep.22906

Lindor KD, Kowdley KV, Harrison ME; American College of Gastroenterology. ACG clinical guideline: primary sclerosing cholangitis. Am J Gastroenterol. 2015;110:646-59; quiz 660. [PMID: 25869391] doi:10.1038/ajg.2015.112

Radcke S, Dillon JF, Murray AL. A systematic review of the prevalence of mildly abnormal liver function tests and associated health outcomes. Eur J Gastroenterol Hepatol. 2015;27:1-7. [PMID: 25380394] doi:10.1097/MEG.0000000000000233

Singal AK, Bataller R, Ahn J, Kamath PS, Shah VH. ACG Clinical Guideline: Alcoholic Liver Disease. Am J Gastroenterol. 2018. [PMID: 29336434] doi:10.1038/ajg.2017.469

Terrault NA, Bzowej NH, Chang KM, Hwang JP, Jonas MM, Murad MH; American Association for the Study of Liver Diseases. AASLD guidelines for treatment of chronic hepatitis B. Hepatology. 2016;63:261-83. [PMID: 26566064] doi:10.1002/hep.28156

Thursz MR, Richardson P, Allison M, Austin A, Bowers M, Day CP, et al; STOPAH Trial. Prednisolone or pentoxifylline for alcoholic hepatitis. N Engl J Med. 2015;372:1619-28. [PMID: 25901427] doi:10.1056/NEJMoa1412278

Westbrook RH, Dusheiko G, Williamson C. Pregnancy and liver disease. J Hepatol. 2016;64:933-45. [PMID: 26658682] doi:10.1016/j.jhep.2015.11.030

Disorders of the Gallbladder and Bile Ducts

Cotton PB, Elta GH, Carter CR, Pasricha PJ, Corazziari ES. Rome IV. Gallbladder and sphincter of Oddi disorders. Gastroenterology. 2016. [PMID: 27144629] doi:10.1053/j.gastro.2016.02.033

European Association for the Study of the Liver (EASL). Clinical Practice Guidelines on the prevention, diagnosis and treatment of gallstones. J Hepatol. 2016;65:146-181. [PMID: 27085810] doi:10.1016/j.jhep.2016.03.005

Razumilava N, Gores GJ. Cholangiocarcinoma. Lancet. 2014;383:2168-79. [PMID: 24581682] doi:10.1016/S0140-6736(13)61903-0

Gastrointestinal Bleeding

Fisher L, Lee Krinsky M, Anderson MA, Appalaneni V, Banerjee S, Ben-Menachem T, et al; ASGE Standards of Practice Committee. The role of endoscopy in the management of obscure GI bleeding. Gastrointest Endosc. 2010;72:471-9. [PMID: 20801285] doi:10.1016/j.gie.2010.04.032

Gerson LB, Fidler JL, Cave DR, Leighton JA. ACG clinical guideline: diagnosis and management of small bowel bleeding. Am J Gastroenterol. 2015;110:1265-87; quiz 1288. [PMID: 26303132] doi:10.1038/ajg.2015.246

Laine L. Clinical practice. Upper gastrointestinal bleeding due to a peptic ulcer. N Engl J Med. 2016;374:2367-76. [PMID: 27305194] doi:10.1056/NEJMcp1514257

Laine L, Jensen DM. Management of patients with ulcer bleeding. Am J Gastroenterol. 2012;107:345-60; quiz 361. [PMID: 22310222] doi:10.1038/ajg.2011.480

Leighton JA. The role of endoscopic imaging of the small bowel in clinical practice. Am J Gastroenterol. 2011;106:27-36; quiz 37. [PMID: 20978483] doi:10.1038/ajg.2010.410

Liu K, Kaffes AJ. Review article: the diagnosis and investigation of obscure gastrointestinal bleeding. Aliment Pharmacol Ther. 2011;34:416-23. [PMID: 21692820] doi:10.1111/j.1365-2036.2011.04744.x

Strate LL, Gralnek IM. ACG clinical guideline: management of patients with acute lower gastrointestinal bleeding. Am J Gastroenterol. 2016;111:459-74. [PMID: 26925883] doi:10.1038/ajg.2016.41

Teshima CW. Small bowel endoscopy for obscure GI bleeding. Best Pract Res Clin Gastroenterol. 2012;26:247-61. [PMID: 22704568] doi:10.1016/j.bpg.2012.01.020

Villanueva C, Colomo A, Bosch A, Concepción M, Hernandez-Gea V, Aracil C, et al. Transfusion strategies for acute upper gastrointestinal bleeding. N Engl J Med. 2013;368:11-21. [PMID: 23281973] doi:10.1056/NEJMoa1211801

Gastroenterology and Hepatology Self-Assessment Test

This self-assessment test contains one-best-answer multiple-choice questions. Please read these directions carefully before answering the questions. Answers, critiques, and bibliographies immediately follow these multiple-choice questions. The American College of Physicians (ACP) is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

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CME credits and MOC points are available from the publication date of July 31, 2018, until July 31, 2021. You may submit your answer sheet or enter your answers online at any time during this period.

Directions

*Each of the numbered items is followed by lettered answers. Select the **ONE** lettered answer that is **BEST** in each case.*

Item 1

A 60-year-old woman is evaluated for persistent constipation symptoms of 2 years' duration. She has reflex sympathetic dystrophy syndrome involving the right arm and neck that began 3 years earlier and requires chronic opioid analgesic therapy. She reports passing two hard bowel movements per week. Trials of several fiber supplements caused severe bloating and abdominal distention without relieving symptoms. A trial of polyethylene glycol (PEG) has not been effective; the patient reports that her stool is soft, but she still has no more than two bowel movements per week. Adding bisacodyl caused severe abdominal cramping, prompting its discontinuation. Colonoscopy at the onset of constipation was unremarkable. In addition to PEG, her medications are gabapentin, hydrocodone, fentanyl patch, and a calcium supplement with vitamin D.

On physical examination, vital signs and other findings are normal.

Which of the following is the most appropriate treatment for her constipation?

(A) Add docusate sodium
(B) Add lactulose
(C) Increase PEG dosage
(D) Switch to naloxegol

Item 2

A 29-year-old woman is evaluated during a new-patient appointment. She was diagnosed with hepatitis B virus (HBV) infection 10 years ago; her mother had HBV infection, and it was presumed that the patient acquired the infection at birth. She reports feeling well. Her medical history is otherwise unremarkable and she takes no medication.

On physical examination, vital signs are normal, as is the remainder of the examination.

Laboratory studies are positive for hepatitis B surface antigen and positive for hepatitis B e antigen. The serum HBV DNA level is 20,000,000 IU/mL. Alanine aminotransferase and aspartate aminotransferase levels are within normal limits.

Which of the following is the most appropriate next step in management?

(A) Entecavir
(B) Hepatic ultrasonography
(C) Pegylated interferon
(D) Repeat liver chemistry tests in 6 months
(E) Tenofovir

Item 3

A 58-year-old man is counseled before undergoing colonoscopy and polypectomy in 10 days' time. A routine screening CT colonography showed two polyps in the descending colon, 10 mm and 8 mm in size. Two years earlier, he had an inferior wall myocardial infarction. His medications are low-dose aspirin, atorvastatin, metoprolol, and enalapril.

Which of the following is the most appropriate management of his aspirin therapy?

(A) Continue aspirin use until the day of the polypectomy; resume in 48 hours
(B) Discontinue aspirin use 7 days before the polypectomy; resume immediately after
(C) Discontinue aspirin use 7 days before the polypectomy; resume in 48 hours
(D) Do not discontinue aspirin

Item 4

A 48-year-old woman is evaluated at a follow-up appointment for elevated liver chemistry tests over the preceding 6 months. She reports no symptoms. She has type 2 diabetes mellitus and hypertension. Her family history is unremarkable. She drinks two glasses of wine one or two times per month. Her medications are metformin and lisinopril.

On physical examination, vital signs are normal; BMI is 31. No spider angiomata, palmar erythema, splenomegaly, abdominal distention, or lower-extremity edema is noted.

Laboratory studies:

Alkaline phosphatase	96 U/L
Alanine aminotransferase	85 U/L
Aspartate aminotransferase	74 U/L
Anti-smooth muscle antibody	Positive (1:20 titer)

Results of other studies, including hepatitis C antibody, hepatitis B surface antigen, iron saturation, α1-antitrypsin phenotype, tissue transglutaminase IgA antibody, antimitochondrial antibody, and IgG, are within normal limits.

On ultrasonography, the liver is hyperechoic and enlarged.

Which of the following is the most likely diagnosis?

(A) Antimitochondrial antibody-negative primary biliary cholangitis
(B) Autoimmune hepatitis
(C) Nonalcoholic fatty liver disease
(D) Primary sclerosing cholangitis

Item 5

A 75-year-old man is evaluated for progressive dysphagia of 8 months' duration for both solid food and water, and the necessity to induce vomiting several times each month to relieve his symptoms. He also has experienced chest pain and heartburn symptoms. He has lost approximately 6 kg (13 lb) of weight over the preceding 3 months and a total of 9 kg (20 lb) since his symptoms began. He has a long history of cigarette and alcohol use. His medical history and review of systems is otherwise negative. He has no travel history outside the northeastern United States. He takes no medication.

On physical examination, vital signs are normal; BMI is 23. He appears thin and tired. The remainder of the physical examination is unremarkable.

Upper endoscopic findings reveal retained saliva, liquid, and food in the esophagus without mechanical obstruction. Manometry demonstrates incomplete lower esophageal relaxation and aperistalsis.

Which of the following is the most likely diagnosis?

(A) Achalasia

(B) Chagas disease

(C) Eosinophilic esophagitis

(D) Pseudoachalasia

Item 6

A 35-year-old man is evaluated for a 1-year history of near-daily postprandial diarrhea, episodic abdominal cramping relieved with a bowel movement, and abdominal bloating. He is otherwise healthy, and his only medication is loperamide. This treatment has not been consistently effective in reducing diarrhea symptoms and has had no effect on the cramping and bloating, despite increased frequency of dosing.

Vital signs are normal. Diffuse tenderness to abdominal palpation is noted. Other physical examination findings are normal.

Stool testing for infection and celiac antibody testing are negative.

Colonoscopy findings are unremarkable.

Which of the following is the most appropriate treatment?

(A) Alosetron

(B) Linaclotide

(C) Low-FODMAP (Fermentable Oligosaccharides, Disaccharides, Monosaccharides, And Polyols) diet

(D) Lubiprostone

Item 7

A 52-year-old man is evaluated for dysphagia of 3 months' duration. He reports regurgitating undigested food soon after eating solid food, occasional coughing and choking after swallowing, and chronic halitosis. He reports no weight loss or chest pain. He drinks two beers weekly and does not smoke.

On physical examination, vital signs are normal; BMI is 25. The remainder of the examination, including abdominal examination, is unremarkable.

Which of the following is the most appropriate diagnostic test to perform next?

(A) Barium esophagography

(B) Esophageal manometry

(C) 24-Hour esophageal pH monitoring

(D) Upper endoscopy

Item 8

A 48-year-old woman is evaluated for shortness of breath of 6 weeks' duration. She has cirrhosis due to primary biliary cholangitis.

On physical examination, vital signs are normal. Spider nevi are present on the skin. The cardiopulmonary examination is normal. There is no edema. When the patient is supine, oxygen saturation is 98% breathing ambient air, but oxygen saturation drops to 92% with standing.

A radiograph of the chest is normal.

Which of the following is the most appropriate diagnostic test?

(A) Bronchoscopy

(B) CT angiography

(C) Echocardiography with agitated saline

(D) Pulmonary function testing

Item 9

H

A 72-year-old woman is evaluated in the hospital for new-onset abdominal pain in the right upper quadrant and fever that developed abruptly on hospital day 5. She was hospitalized 5 days earlier for altered mental status. In the emergency department, she was found to be confused, hypotensive, and tachycardic. She was transferred to the ICU, where she was diagnosed and treated for urosepsis. Within 24 hours, she was hemodynamically stable and the sepsis syndrome resolved. She also has type 2 diabetes mellitus, hypertension, and hyperlipidemia. Her medications are insulin glargine, insulin aspart, lisinopril, atorvastatin, and piperacillin-tazobactam.

On physical examination, the patient is alert. Temperature is 38.2 °C (100.8 °F), blood pressure is 90/62 mm Hg, pulse rate is 110/min, and respiration rate is 20/min. Abdominal examination is notable for tenderness to palpation of the right upper quadrant. A soft palpable mass is felt in this area.

Laboratory studies show a leukocyte count of 20,000/µL (20×10^9/L) and a serum total bilirubin level of 5 g/dL (85.5 µmol/L).

Ultrasonography shows a distended gallbladder with wall thickening and pericholecystic fluid. No gallstones are seen and bile ducts are normal.

Which of the following is the most appropriate next step in management?

(A) Cholecystostomy tube placement

(B) Endoscopic retrograde cholangiopancreatography

(C) Hepatobiliary iminodiacetic acid scan

(D) MR cholangiopancreatography

Item 10

A 45-year-old man is evaluated for severe lower back and hip pain related to degenerative joint disease. His pain responds to naproxen, but he was hospitalized 6 months earlier for a bleeding gastric ulcer attributed to daily naproxen use. Naproxen was stopped, and twice-daily omeprazole was initiated at that time. Three months later, the ulcer had healed completely and omeprazole was discontinued. The patient's pain did not respond to trials of acetaminophen. He did not tolerate tramadol. The patient has no other medical problems and currently takes only acetaminophen.

Which of the following is the most appropriate treatment regimen?

(A) Celecoxib

(B) Celecoxib and omeprazole

(C) Ibuprofen and misoprostol

(D) Naproxen and ranitidine

Item 11

A 55-year-old woman is evaluated after screening colonoscopy showed three polyps at the rectosigmoid junction. The three polyps were 3 mm, 5 mm, and 6 mm in size. All three polyps were completely excised and pathology showed them to be hyperplastic. Colonoscopy preparation was excellent and the procedure was complete to the cecum. Family history is significant for colon cancer diagnosed in her paternal grandfather at age 80 years.

All physical examination findings, including vital signs, are normal.

When should this patient next undergo colonoscopy?

(A) 1 year

(B) 3 years

(C) 5 years

(D) 10 years

Item 12

A 62-year-old woman is evaluated in the emergency department for a 12-hour history of fever, dark urine, and abdominal pain in the right upper quadrant.

On physical examination, temperature is 39.7 °C (103.5 °F); other vital signs are normal. Her mental status is normal. Scleral icterus is noted. The abdomen is tender to palpation in the right upper quadrant.

Laboratory studies:

Hematocrit	36%
Leukocyte count	14,600/µL (14.6×10^9/L)
Platelet count	350,000/µL (350×10^9/L)
Alanine aminotransferase	453 U/L
Total bilirubin	3.5 mg/dL (59.9 µmol/L)

An abdominal ultrasound shows a stone in the common bile duct and intrahepatic biliary dilation. Gallbladder stones are also noted.

Antibiotic therapy is initiated.

Which of the following is the most appropriate next step in management?

(A) Cholecystectomy

(B) Endoscopic retrograde cholangiopancreatography

(C) MR cholangiopancreatography

(D) Percutaneous cholecystostomy

Item 13

A 30-year-old man is evaluated for ongoing symptoms of dysphagia. He was previously diagnosed with eosinophilic esophagitis on upper endoscopy and has completed an 8-week course of swallowed aerosolized fluticasone, which did not alleviate his symptoms. He takes no other medications.

On physical examination, vital signs are normal; BMI is 25. Other findings, including those of an abdominal examination, are unremarkable.

Upper endoscopy shows an area of high-grade stenosis in the distal esophagus.

Which of the following is the most appropriate treatment?

(A) Increase fluticasone

(B) Endoscopy with dilation

(C) Omeprazole

(D) Oral prednisone

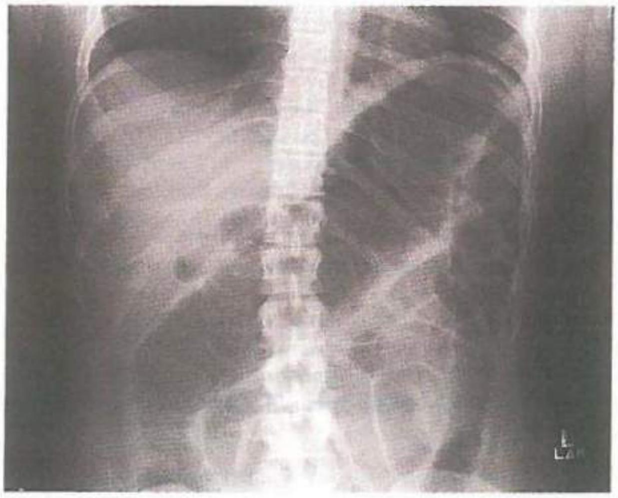
Item 14

A 24-year-old man is evaluated in the emergency department for a 2-week history of worsening bloody diarrhea with up to 10 bloody bowel movements per day. He also reports increasing lower abdominal pain and distension and that stool frequency has decreased over the past day. He has extensive ulcerative colitis of 5 years' duration. His medications are infliximab and azathioprine.

On physical examination, the patient appears ill. Temperature is 38.3 °C (101 °F), blood pressure is 90/60 mm Hg, and pulse rate is 110/min; other vital signs are normal. The abdomen is distended with guarding. Bowel sounds are hypoactive.

Laboratory studies show a hemoglobin level of 10 g/dL (100 g/L), leukocyte count of 16,000/µL (16×10^9/L), and blood urea nitrogen level of 26 mg/dL (9.3 mmol/L).

An abdominal radiograph is shown.



Which of the following is the most appropriate next step in management?

(A) Colectomy

(B) Colonoscopy

(C) CT of the abdomen

(D) Stool culture

Item 15

A 65-year-old woman is evaluated for watery, nonbloody diarrhea of 8 months' duration. She reports up to six bowel movements per day with nocturnal awakenings, but no

abdominal pain, bloating, flatulence, or weight loss. Her last screening colonoscopy at age 60 years was normal. She has no personal or family history of colon cancer or polyps. She also has osteoarthritis, and her only medication is ibuprofen approximately three times weekly. The patient is not exposed to children and has no recent travel history or engagement in outdoor recreational activities.

On physical examination, vital signs are normal. The remainder of the physical examination, including abdominal examination, is normal.

Laboratory studies show hemoglobin, serum albumin, total IgA, and tissue transglutaminase IgA levels to be within normal limits.

Which of the following is the most likely diagnosis?

(A) *Giardia lamblia* infection
(B) Microscopic colitis
(C) Small intestinal bacterial overgrowth
(D) Ulcerative colitis

H Item 16

A 78-year-old man is evaluated in the emergency department for worsening jaundice of 2 weeks' duration, dry mouth, dark urine, and light stools. He has also noticed swelling under his jaw bilaterally. He reports no abdominal pain or weight loss.

On physical examination, vital signs are normal. Swollen submandibular glands bilaterally and jaundice are noted.

Laboratory studies:

Alkaline phosphatase	180 U/L
Alanine aminotransferase	66 U/L
Aspartate aminotransferase	55 U/L
Total bilirubin	6.2 mg/dL (106.0 µmol/L)
Direct bilirubin	4.8 mg/dL (82.1 µmol/L)

A CT scan of the abdomen shows a narrowed pancreatic duct and enlargement of the pancreas parenchyma, described as a "sausage-shaped" pancreas, as well as findings consistent with retroperitoneal fibrosis. Endoscopic ultrasound-guided biopsy of the pancreas shows more than 10 IgG4-positive cells/hpf and no evidence of malignancy.

Which of the following is the most appropriate treatment?

(A) Azathioprine
(B) Endoscopic retrograde cholangiopancreatography with bile-duct stenting
(C) Pancreaticoduodenectomy
(D) Prednisone

H Item 17

A 25-year-old woman is evaluated in the hospital for right-upper-quadrant abdominal pain, jaundice, and nausea of 10 days' duration. She is in her 35th week of pregnancy. Her only medication is a prenatal vitamin.

On physical examination, the patient is drowsy. Temperature is normal. Blood pressure is 95/60 mm Hg, pulse rate is 108/min, and respiration rate is 22/min. Jaundice is apparent. Abdominal examination shows tenderness to palpation in the right upper quadrant. The uterus is of appropriate size for gestation.

Laboratory studies:

Hematocrit	34%
Leukocyte count	6000/µL (6×10^9/L)
Platelet count	155,000/µL (155×10^9/L)
INR	2.2
Alanine aminotransferase	115 U/L
Aspartate aminotransferase	130 U/L
Total bilirubin	6.2 mg/dL (106.0 µmol/L)
Glucose	55 mg/dL (3.1 µmol/L)

On abdominal ultrasonography, the liver is hyperechoic. Hepatic vasculature is patent, and there is no bile-duct dilation.

She is transferred to an ICU setting, and intravenous fluids with glucose are administered.

Which of the following is the most appropriate next step in management?

(A) Endoscopic retrograde cholangiopancreatography
(B) Immediate delivery of the fetus
(C) Lactulose
(D) Ursodeoxycholic acid

Item 18

A 65-year-old man is evaluated after a screening ultrasound for abdominal aortic aneurysm showed incidental gallbladder findings. He reports no symptoms. He continues to smoke cigarettes, 1 pack per day. He has no other medical problems and takes no medications.

On physical examination, vital signs are normal, as is the remainder of the examination.

The results of all laboratory studies, including a complete blood count and alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, and total bilirubin levels, are within normal limits.

The abdominal ultrasound shows numerous layering gallstones and an immobile 8-mm gallbladder polyp.

Which of the following is the most appropriate next step in management?

(A) Cholecystectomy
(B) MR cholangiopancreatography
(C) Repeat ultrasonography in 6 months
(D) Ursodeoxycholic acid

Item 19

A 60-year-old woman is evaluated 1 month after completing a 14-day course of *Helicobacter pylori* eradication therapy consisting of amoxicillin, clarithromycin, and omeprazole. Initial upper endoscopy before treatment showed patchy gastric erythema with no ulcers or erosions, and biopsies revealed *H. pylori* gastritis. Currently, she reports alleviated symptoms. She is otherwise healthy and takes no medication.

Which of the following is the most appropriate test to perform next?

(A) Serologic antibody testing for *H. pylori*
(B) Upper endoscopy with gastric biopsy
(C) Urea breath test
(D) No further testing

Item 20

A 36-year-old woman is evaluated 3 days after being hospitalized for gallstone pancreatitis. An abdominal ultrasound showed multiple gallstones in the gallbladder and a normal-diameter common bile duct. She was treated with intravenous hydration and pain medication. Over the course of 3 days, she tolerated eating and her pain subsided.

On physical examination, vital signs are normal; BMI is 32. Minimal tenderness to palpation is noted on abdominal examination. All other findings are unremarkable.

All laboratory studies have returned to baseline normal values.

Which of the following is the most appropriate treatment?

(A) Endoscopic retrograde cholangiopancreatography
(B) Laparoscopic cholecystectomy before discharge from the hospital
(C) Laparoscopic cholecystectomy 4 weeks after discharge from the hospital
(D) MR cholangiopancreatography
(E) Ursodeoxycholic acid

Item 21

A 48-year-old man is hospitalized with a fever and rigors. He has primary sclerosing cholangitis and ulcerative colitis. His only medication is mesalamine.

On physical examination, temperature is 38.6 °C (101.5 °F), blood pressure is 118/75 mm Hg, pulse rate is 95/min, and respiration rate is 18/min. Abdominal examination is notable for right-upper-quadrant tenderness to palpation. The remainder of the examination is normal.

Laboratory studies show a leukocyte count of 14,000/µL (14×10^9/L). Blood cultures are pending.

A 1-L bolus of intravenous normal saline is administered, and intravenous piperacillin-tazobactam is given.

Which of the following is the most appropriate test to perform next?

(A) CA 19-9 measurement
(B) Endoscopic retrograde cholangiopancreatography
(C) IgG4 measurement
(D) Percutaneous transhepatic biliary tube placement
(E) PET scan

Item 22

A 39-year-old woman is evaluated for fatigue, intermittent rectal bleeding, and abdominal pain over the past 2 months. She reports that the bleeding is not accompanied by anal pain or itching. She has experienced an unintentional 2.3-kg (5.1-lb) weight loss since her symptoms started. She has no personal or family history of colon cancer or other cancers. She takes no medication.

On physical examination, her pulse rate is 102/min; other vital signs are normal. BMI is 22. Abdominal examination reveals mild tenderness in the left lower quadrant with no rebound or guarding. Rectal examination shows no masses. Large, friable hemorrhoids are present.

Laboratory studies show a hemoglobin level of 10.5 g/dL (105 g/L) and a serum ferritin level of 5 ng/mL (5 µg/L).

Which of the following is the most appropriate next step in management?

(A) Anoscopy
(B) Colonoscopy
(C) Flexible sigmoidoscopy
(D) Topical hemorrhoid treatment

Item 23

A 52-year-old woman is evaluated for midabdominal pain and nausea. These symptoms worsen after eating large meals. The pain does not alleviate after bowel movements, and she reports frequent constipation. She has gained 2.3 kg (5.1 lb) over the past year. The pain began 1 year earlier, after she was hospitalized with an episode of gallstone pancreatitis for which she underwent laparoscopic cholecystectomy. After cholecystectomy, she had persistent abdominal pain. Over the next several weeks she had upper and lower endoscopies, a CT scan of the abdomen and pelvis, and multiple laboratory tests; all were normal. She states that the only thing that helps the pain is hydrocodone, but as the dose of hydrocodone has increased, so has her pain intensity.

On physical examination, vital signs are normal; BMI is 26. Tenderness to palpation in all quadrants is noted on abdominal examination. Other findings are unremarkable.

Which of the following is the most likely diagnosis?

(A) Chronic pancreatitis
(B) Distal intestinal obstruction syndrome
(C) Irritable bowel syndrome
(D) Narcotic bowel syndrome

Item 24

A 60-year-old man is evaluated for constant low-grade epigastric pain radiating to his back that worsens after he eats fatty foods. He has a 2-year history of chronic pancreatitis. The pain has progressively worsened over the preceding 6 months. His weight is stable. He has a normal bowel movement once every other day. He does not drink alcohol. He continues to smoke 2 packs of cigarettes per day as he has done for 30 years. The patient has a remote history of opioid abuse.

On physical examination, vital signs are normal. Abdominal examination shows tenderness to palpation in the epigastrium.

A contrast-enhanced CT scan of the abdomen shows calcifications throughout the pancreas with no pancreatic mass, no dilated pancreatic duct, and no cystic lesions.

Which of the following is the most appropriate initial treatment?

(A) Celiac plexus block
(B) NSAIDs, low-fat diet, and smoking cessation
(C) Oxycodone
(D) Pancreatic enzyme replacement therapy

Item 25

A 43-year-old man is evaluated for 4 days of fever and arthralgia, as well as a raised purple rash over his lower extremities of 1 week's duration. He is a current intravenous drug user. He has no other medical problems and takes no medications.

On physical examination, temperature is 37.8 °C (100 °F) and blood pressure is 132/85 mm Hg; other vital signs are normal. The large and small joints are tender to palpation without evidence of synovitis. The abdomen is not tender to palpation. The liver edge is palpable below the right costal margin. The skin findings are shown.

Laboratory studies:

Alanine aminotransferase	143 U/L
Aspartate aminotransferase	130 U/L
Total bilirubin	2.2 mg/dL (37.6 µmol/L)
Creatinine	1.0 mg/dL (88.4 µmol/L)
Hepatitis B surface antigen	Positive
IgM antibody to hepatitis B core antigen	Positive
Hepatitis B e antigen	Positive
HBV DNA	10,000,000 IU/mL
Hepatitis C antibody	Negative
HIV-1/HIV-2 antigen and antibody combination immunoassay	Negative
Cryoglobulin	Normal
Urinalysis	Normal

Which of the following is the most appropriate treatment?

(A) Entecavir
(B) Plasma exchange
(C) Prednisone and cyclophosphamide
(D) Sofosbuvir and ledipasvir
(E) Tenofovir, emtricitabine, and raltegravir

Item 26

H

A 34-year-old woman is evaluated 4 days after being hospitalized for severe epigastric abdominal pain associated with nausea and vomiting. At the time of hospitalization, her serum lipase level was 4650 U/L and an abdominal ultrasound examination showed cholelithiasis. She has taken nothing by mouth (NPO) since hospitalization and reports having no appetite. She is being treated with intravenous fluids and opioid pain medication. A CT scan of the abdomen and pelvis with contrast showed changes consistent with pancreatic necrosis. Her medical history is unremarkable and she took no medication before hospitalization.

On physical examination, temperature is 38 °C (100.4 °F), blood pressure is 130/70 mm Hg, pulse rate is 90/min, and respiration rate is 15/min. Abdominal examination shows tenderness in the epigastrium with no abdominal distention.

Which of the following is the most appropriate next step in management of her nutrition?

(A) Initiate enteral feeding
(B) Initiate total parenteral nutrition
(C) Maintain NPO status until cholecystectomy is performed
(D) Maintain NPO status until the lipase level normalizes

Item 27

H

A 55-year-old man is evaluated in the hospital for new-onset ascites. He has a history of cirrhosis due to hepatitis C viral infection. His only medication is propranolol.

On physical examination, pulse rate is 58/min; other vital signs are normal. The abdomen is soft and distended consistent with ascites.

Laboratory studies show a serum albumin level of 2.5 g/dL (25 g/L), serum total bilirubin level of 3.6 mg/dL (61.6 µmol/L), and serum creatinine level of 1.4 mg/dL (123.8 µmol/L).

Paracentesis with analysis of ascitic fluid shows a leukocyte count of 200/µL with 30% neutrophils, albumin level of 0.4 g/dL (4 g/L), and total protein level of 0.9 g/dL (9 g/L).

Which of the following is the most appropriate next step in management?

(A) Increase propranolol therapy
(B) Initiate albumin infusion
(C) Initiate ciprofloxacin therapy
(D) Initiate lisinopril therapy

Item 28

A 53-year-old woman is evaluated for an 8-month history of palpitations, tachycardia, lightheadedness, and sweating with explosive diarrhea and nausea within 15 to 30 minutes of eating. She has lost 6.8 kg (15 lb) during this time period and describes feeling better if she eats smaller portions. She reports no vomiting. Upper endoscopy performed 1 year earlier for refractory gastroesophageal reflux disease incidentally found a small gastrointestinal stromal tumor in her stomach, and she underwent a partial gastrectomy with gastrojejunostomy. Her only medication is omeprazole.

On physical examination, vital signs are normal; BMI is 28. Abdominal examination shows a well-healed scar with no abdominal pain on palpation and no organomegaly.

Which of the following is the most likely diagnosis?

(A) Dumping syndrome
(B) Gastroparesis
(C) Irritable bowel syndrome
(D) Small intestinal bacterial overgrowth

Item 29

A 35-year-old woman is evaluated for constipation. She reports passage of hard stool every 3 to 4 days and associated bloating. Her symptoms have been present for more than 10 years and have progressed gradually. Trials of over-the-counter fiber supplementation and polyethylene glycol worsened the bloating, prompting discontinuation. Senna tea was ineffective. Bisacodyl caused abdominal cramping. She is otherwise healthy and currently takes no medication.

On physical examination, vital signs and other findings are normal.

Which of the following is the most appropriate treatment?

(A) Lactulose
(B) Linaclotide
(C) Methylnaltrexone
(D) Rifaximin

Item 30

A 28-year-old woman is evaluated at 28 weeks' gestation. This is her first pregnancy. She has chronic hepatitis B virus (HBV) infection acquired through vertical transmission. The patient reports feeling well. Her only medication is a prenatal vitamin.

On physical examination, vital signs are normal. The uterus is enlarged, consistent with 28-week intrauterine gestation. No stigmata of chronic liver disease are noted.

Laboratory studies are positive for hepatitis B surface antigen and hepatitis B e antigen. The HBV DNA level is 300,000 IU/mL. The results of other studies, including alanine aminotransferase, aspartate aminotransferase, and total bilirubin levels, are within normal limits.

Which of the following is the most appropriate next step in management?

(A) Cesarean delivery at term
(B) HBV DNA measurement in 3 months
(C) Pegylated interferon
(D) Tenofovir

Item 31

A 60-year-old man is evaluated following the diagnosis of acute pancreatitis. Abdominal ultrasonography showed a normal gallbladder, biliary system, and liver, but the pancreas was not well visualized due to overlying loops of bowel. He reports decreased appetite, vague new back pain, and an unintentional 6.9-kg (15.2-lb) weight loss over the preceding 6 months. He does not smoke or drink alcohol. He takes no medication.

On physical examination, vital signs are normal; BMI is 20. Abdominal examination shows a thin abdomen with tenderness to deep palpation in the epigastrium. No jaundice is noted.

Which of the following is the most appropriate next step in management?

(A) CT of the abdomen with contrast
(B) Endoscopic retrograde cholangiopancreatography
(C) Endoscopic ultrasound
(D) Clinical observation

Item 32

H

A 75-year-old man is evaluated after hospitalization for an episode of hematemesis. Upon admission, his INR was 2.5. Intravenous proton pump inhibitor therapy was initiated, and his warfarin was held. Endoscopy showed a large duodenal bulb ulcer with an actively bleeding visible vessel; endoscopic hemostasis was achieved. Vital signs have been normal for 24 hours after endoscopy. The patient also has hypertension and atrial fibrillation and a history of transient ischemic attack. His daily medications are warfarin, losartan, and metoprolol.

On physical examination, vital signs are normal; BMI is 32. Other than an irregularly irregular heart rhythm, the physical examination is normal.

Which of the following is the most appropriate management of the patient's warfarin therapy?

(A) Restart warfarin therapy now
(B) Restart warfarin therapy in 10 days
(C) Restart warfarin therapy in 30 days
(D) Hold warfarin therapy indefinitely

Item 33

A 32-year-old woman is evaluated for a 6-month history of loose stools, bloating, and a 3.2-kg (7-lb) weight loss. Her medical history is otherwise unremarkable. Her brother has type 1 diabetes mellitus, and her mother has autoimmune thyroid disease. She reports no other symptoms and takes no medication.

On physical examination, vital signs and other findings are normal; BMI is 19.

Laboratory studies:

Hemoglobin	11.0 g/dL (110 g/L)
Alanine aminotransferase	60 U/L
Aspartate aminotransferase	42 U/L
Total bilirubin	0.9 mg/dL (15.4 µmol/L)
Ferritin	6 ng/mL (6 µg/L)

Which of the following is the most appropriate test to perform next?

(A) Anti-gliadin IgA antibody
(B) Anti-*Saccharomyces cerevisiae* IgA antibody
(C) Anti-smooth muscle antibody
(D) Anti-tissue transglutaminase IgA antibody

Item 34

A 63-year-old woman is evaluated at a follow-up appointment after undergoing right hemicolectomy for colon cancer 1 year earlier. Her paternal grandfather had colon cancer diagnosed at age 75 years. She reports that she has been feeling well and takes no medication.

All physical examination findings, including vital signs, are normal.

When should this patient's next surveillance colonoscopy take place?

(A) Now
(B) In 1 year
(C) In 3 years
(D) In 5 years

Item 35

A 60-year-old man is evaluated for epigastric pain that occurs intermittently after eating. He was hospitalized twice in the preceding year for idiopathic recurrent acute pancreatitis. He is a former smoker and reports no alcohol use.

On physical examination, vital signs are normal, as is the remainder of the examination.

Contrast-enhanced CT of the abdomen shows a diffusely dilated main pancreatic duct with normal intrahepatic and extrahepatic bile ducts and a normal gallbladder. No tumor is seen in the pancreas or liver, and there is no peripancreatic inflammation or necrosis. Endoscopic ultrasonography confirms no evidence of a tumor or gallstone, but the main pancreatic duct appears dilated throughout the pancreas. Mucin is seen exuding from the ampulla of Vater during the endoscopy.

Which of the following is the most appropriate next step in management?

(A) Endoscopic ultrasonography in 1 year
(B) MRI of the abdomen in 1 year
(C) Oral prednisone
(D) Pancreatic resection

H Item 36

A 36-year-old man is evaluated in the emergency department after passing three bowel movements of red to maroon-colored blood. He recently injured his knee playing soccer and has been taking ibuprofen three times a day for a week. He has no other relevant medical history and does not smoke or drink alcohol.

On physical examination, he is lightheaded but alert. His blood pressure is 80/60 mm Hg, pulse rate is 126/min, respiratory rate is 12/min, and oxygen saturation is 98% breathing ambient air. Cardiac examination shows tachycardia. Rectal examination shows maroon-colored stool. All other findings are unremarkable.

The patient's vital signs improve after he is given intravenous hydration.

Laboratory studies show a hemoglobin level of 9 g/dL (90 g/L) upon presentation. Six hours later, the hemoglobin level is 7.4 g/dL (74 g/L).

Which of the following is the most appropriate test to perform next?

(A) Angiography
(B) Capsule endoscopy
(C) Colonoscopy
(D) Upper endoscopy

Item 37

A 72-year-old woman is evaluated for a 3-month history of large-volume, watery, nonbloody diarrhea with mucus, which occurs even when she is fasting. She reports no abdominal pain or flushing but has experienced an unintentional 3-kg (6.6-lb) weight loss. She has never had a colonoscopy.

On physical examination, blood pressure is 100/50 mm Hg and pulse rate is 95/min; other vital signs and examination findings are normal.

Laboratory studies show a serum sodium level of 130 mEq/L (130 mmol/L) and a serum potassium level of 3.3 mEq/L (3.3 mmol/L). Hemoglobin and serum creatinine levels are within normal limits.

Which of the following types of diarrhea is most compatible with the patient's findings?

(A) Infectious
(B) Inflammatory
(C) Osmotic
(D) Secretory

Item 38

A 25-year-old woman is evaluated for a 1-month history of intermittent, loose, bloody bowel movements associated with pain in the left lower quadrant before defecation. The bleeding occurs with and without bowel movements. She reports no fever, chills, night sweats, arthralgia, eye pain, or rash. The patient works in a day care center and has not traveled or used antibiotics recently. She takes no medication.

On physical examination, vital signs are normal. The abdomen is scaphoid and soft, with suprapubic tenderness. The remainder of the physical examination is normal.

Stool testing for bacterial enteropathogens, including *Clostridium difficile*, is negative.

Colonoscopy results show patchy erythema and ulceration in the cecum, ascending colon, descending colon, and sigmoid colon with no involvement of the transverse colon or rectum. Mucosal biopsies of the involved mucosa reveal distorted and branching colonic crypts with lymphocytic and neutrophilic infiltration. Ileal examination is normal.

Which of the following is the most likely diagnosis?

(A) Crohn disease
(B) Giardiasis
(C) Microscopic colitis
(D) Ulcerative colitis

Item 39

A 55-year-old man is evaluated at a follow-up appointment 4 days after being diagnosed with acute sigmoid diverticulitis.

He is on day 4 of oral antibiotics and reports that his pain is almost gone. He has no other symptoms and has never had a colonoscopy. He takes no other medication.

His vital signs are normal. Abdominal examination is positive for minimal tenderness on deep palpation in the left lower quadrant without rebound or guarding.

The CT scan of the abdomen from the emergency department shows mild sigmoid diverticulitis with no abscess.

When should this patient undergo colonoscopy?

(A) Now
(B) In 1 to 2 months
(C) In 6 months
(D) In 12 months

Item 40

A 65-year-old woman is reevaluated following an initial evaluation for anemia. Other than a gradually increasing sense of fatigue, she has no symptoms. Her only other medical problem is autoimmune thyroid disease, which is being treated with levothyroxine. Her last screening colonoscopy, done 4 years earlier, was normal.

Physical examination reveals normal vital signs. There is evidence of conjunctival rim pallor. The remainder of the examination, including thyroid and neurologic examinations, is normal.

At the time of her initial evaluation, laboratory studies showed a hemoglobin level of 10 g/dL (100 g/L) and mean corpuscular volume of 104 fL. Serum cobalamin and ferritin levels were low. An antiparietal cell antibody test was positive. Stool testing revealed no evidence of blood.

Which of the following is the most appropriate test to perform next?

(A) Capsule endoscopy
(B) Glucose hydrogen breath test
(C) Serum gastrin measurement
(D) Upper endoscopy

Item 41

A 28-year-old woman is evaluated for 2 weeks of intense rectal pain that occurs with most bowel movements. She also reports periodic rectal bleeding and occasional constipation symptoms that have worsened since a recent shoulder surgery. Over-the-counter hemorrhoid cream has not alleviated her symptoms. Family history includes colon cancer diagnosed in her grandmother at age 74 years. The patient's medications are acetaminophen with codeine and an over-the-counter stool softener as needed.

On physical examination, vital signs are normal. Rectal examination findings are shown (see top of next column).

Which of the following is the most appropriate next step in management?

(A) Anal botulinum toxin injection
(B) Flexible sigmoidoscopy

(C) Prednisone suppository
(D) Sitz baths and psyllium
(E) Topical hydrocortisone and lubiprostone

Item 42

A 25-year-old man is evaluated for worsening heartburn of 4 months' duration, despite treatment with twice-daily omeprazole. He has no pertinent personal or family medical history and takes no other medication.

On physical examination, vital signs and other findings are normal.

Upper endoscopy shows a normal esophagus with a normal gastroesophageal junction. The stomach has 30 small (<10 mm) sessile polyps seen in the fundus. The duodenum is normal. Pathology of a polyp shows it to be a fundic gland polyp.

Which of the following is the most appropriate next step in evaluation of this patient?

(A) Colonoscopy
(B) Gastrectomy
(C) Repeat upper endoscopy in 3 months
(D) No further evaluation

Item 43

A 44-year-old man is evaluated after his routine yearly follow-up for ulcerative colitis showed elevated liver chemistry test results. He was diagnosed with ulcerative colitis 5 years ago. He reports that he passes solid, formed stool every 1 to 2 days without abdominal pain. His only medication is mesalamine.

On physical examination, vital signs are normal; BMI is 26. Hepatomegaly and palmar erythema are noted.

Laboratory studies:

Alkaline phosphatase	412 U/L
Alanine aminotransferase	78 U/L
Aspartate aminotransferase	62 U/L
Total bilirubin	2 mg/dL (34.2 µmol/L)
Direct bilirubin	1.5 mg/dL (25.7 µmol/L)

A complete blood count and serum creatinine level are normal, and an antimitochondrial antibody titer is negative.

MR cholangiopancreatography shows hepatomegaly but is otherwise normal.

Liver biopsy is pending.

Which of the following is the most likely diagnosis?

(A) Antimitochondrial antibody–negative primary biliary cholangitis
(B) Drug-induced liver injury
(C) Nonalcoholic fatty liver disease
(D) Primary sclerosing cholangitis

Item 44

A 45-year-old man is evaluated for a 2-month history of a burning sensation starting in his stomach and radiating into his chest, usually occurring 4 to 5 times weekly. He says that he usually eats dinner late and then goes to sleep. He often wakes up with a sour taste in his mouth. He reports no dysphagia or unintentional weight loss. He takes no medication.

On physical examination, vital signs are normal; BMI is 34. The remainder of the examination, including abdominal examination, is unremarkable.

Which of the following is the most appropriate next step in management?

(A) Ambulatory pH testing
(B) Barium esophagography
(C) Empiric trial of a proton pump inhibitor
(D) Upper endoscopy

Item 45

A 45-year-old woman is evaluated during a routine follow-up appointment for cirrhosis due to primary biliary cholangitis. She has chronic symptoms of fatigue that are unchanged since her previous visits. She has no other new symptoms of advancing liver dysfunction, including no ascites, jaundice, or hepatic encephalopathy. A recent upper endoscopy showed small esophageal varices without red wale marks. Her only medication is ursodeoxycholic acid. She is up to date for her influenza, 23-valent polysaccharide pneumococcal, and hepatitis A and B immunizations.

On physical examination, vital signs are normal. Scattered spider angiomas are seen on her chest and upper back. The remainder of the examination is normal.

An abdominal ultrasound shows changes in the liver consistent with cirrhosis. No liver masses are seen.

Which of the following is the most appropriate intervention to perform next?

(A) Bone densitometry
(B) Colonoscopy
(C) Contrast-enhanced abdominal CT
(D) Herpes zoster immunization

Item 46

H

A 30-year-old man is evaluated after being hospitalized for an acute flare of extensive ulcerative colitis. He reports six to eight bloody bowel movements daily with prominent urgency and lower abdominal cramping for the past 2 weeks. He has been taking prednisone daily for 1 week. His only other medication is mesalamine.

On physical examination, vital signs are normal. Abdominal examination reveals lower abdominal tenderness. The abdomen is not distended and bowel sounds are normal. Blood is seen on digital rectal examination.

Hemoglobin level is 10 g/dL (100 g/L). He remains hemodynamically stable.

Which of the following is the most appropriate venous thromboembolism prophylaxis for this patient?

(A) Aspirin
(B) Graduated compression stockings
(C) Heparin
(D) Intermittent pneumatic compression
(E) Low-dose warfarin

Item 47

A 37-year-old man is evaluated during a follow-up appointment after resection of a well-differentiated adenocarcinoma of the ascending colon, which was diagnosed 1 month earlier. His family history is significant for endometrial cancer diagnosed in his mother at age 50 years and colon cancer diagnosed in his maternal grandfather at age 49 years. The patient reports that he has been feeling well and takes no medication.

All physical examination findings, including vital signs, are normal.

Which of the following is the most appropriate next step in management?

(A) Colonoscopy in 3 years
(B) Fecal immunochemical testing in 1 year
(C) Genetic counseling
(D) Upper endoscopy and capsule endoscopy

Item 48

A 35-year-old man is evaluated during a follow-up appointment for persistent heartburn with chronic cough. He has a 1-year history of gastroesophageal reflux disease and takes pantoprazole twice daily. He reports no nausea, vomiting, or dysphagia. Upper endoscopy performed 1 year earlier showed no abnormal findings.

His vital signs and physical examination are normal. Results of an ear, nose, and throat evaluation are noncontributory.

Which of the following is the most appropriate next diagnostic test?

(A) Ambulatory pH testing
(B) Barium esophagography
(C) Esophageal manometry
(D) Upper endoscopy

Item 49

A 55-year-old man is evaluated for ascites. He recently went to the emergency department, where paracentesis was performed. He was then discharged for outpatient follow-up. He has a history of cirrhosis due to nonalcoholic steatohepatitis and also has hypertension. Endoscopy 3 months earlier showed small varices without stigmata, making prophylaxis for esophageal variceal bleeding unnecessary. His only medication is lisinopril.

On physical examination, vital signs are normal; BMI is 28. Abdominal examination shows abdominal distention without tenderness.

Laboratory studies of the ascitic fluid show a leukocyte count of 80/µL with 20% neutrophils and protein level of 1.6 g/dL (16 g/L). Serum studies show a creatinine level of 1.3 mg/dL (114.9 µmol/L) and sodium level of 134 mEq/L (134 mmol/L).

An abdominal ultrasound from the emergency department shows changes consistent with cirrhosis. The portal vein and hepatic veins are patent with normal flow direction. A moderate amount of free-flowing ascites is seen.

In addition to initiating a sodium-restricted diet, which of the following is the most appropriate next step in management?

(A) Discontinue lisinopril
(B) Initiate free-water restriction
(C) Initiate propranolol
(D) Insert an indwelling drain into the peritoneal cavity

H Item 50

A 30-year-old man is evaluated in the emergency department for the recent onset of confusion and jaundice of 6 weeks' duration. His medical history is unremarkable.

On physical examination, the patient is confused. His temperature is 36.9 °C (98.4 °F), blood pressure is 102/60 mm Hg, pulse rate is 115/min, and respiration rate is 22/min. Jaundice and asterixis are noted. No organomegaly is noted.

Laboratory studies:

Hematocrit	38%
Leukocyte count	11,000/µL (11×10^9/L)
Platelet count	350,000/µL (350×10^9/L)
INR	2.6
Alanine aminotransferase	200 U/L
Aspartate aminotransferase	150 U/L
Total bilirubin	18.6 mg/dL (318.1 µmol/L)
Creatinine	3.0 mg/dL (265.2 µmol/L)

On abdominal ultrasound, the liver appears normal with intact vasculature. No splenomegaly or dilation of bile ducts is noted.

Which of the following is the most appropriate next step in management?

(A) Administer fresh frozen plasma
(B) Initiate hemodialysis
(C) Perform endoscopic retrograde cholangiopancreatography
(D) Refer for liver transplantation

Item 51

A 21-year-old woman is evaluated for a 6-week history of frequent bowel movements (three times daily) with intermittent passage of small amounts of blood and mucus. She also reports suprapubic cramping pain that is relieved with passage of stool. She reports no fever, chills, nausea, vomiting, or weight loss. She is otherwise healthy and takes no medication.

On physical examination, vital signs are normal. The abdomen is scaphoid, with tenderness to palpation in the suprapubic area. Rectal examination is notable for a small amount of blood on the examining finger.

Laboratory studies show a normal complete blood count and C-reactive protein level. Stool testing for enteropathogens, including *Clostridium difficile*, is negative.

Results of colonoscopy show continuous, symmetric rectal and sigmoid inflammation characterized by erythema, edema, and friable mucosa. The remainder of the colonic mucosa and distal ileum is normal. Biopsy specimens from the rectum and sigmoid colon show evidence of mildly active chronic colitis.

Which of the following is the most appropriate treatment?

(A) Mesalamine enema
(B) Mesalamine suppository
(C) Oral mesalamine
(D) Oral mesalamine and mesalamine enema

Item 52

A 20-year-old man is evaluated for epigastric pain that has gradually increased in severity over 8 months. The pain worsens with eating and is not relieved by antacids. The patient reports no melena, diarrhea, or constipation. The patient's personal medical history is unremarkable and he takes no medication.

On physical examination, vital signs are normal. Epigastric tenderness to palpation is noted. Other findings are normal.

A complete blood count is normal.

Which of the following is the most appropriate next step in management?

(A) Initiation of omeprazole
(B) Stool antigen testing for *Helicobacter pylori*
(C) Ultrasonography of the right upper quadrant
(D) Upper endoscopy

Item 53

A 46-year-old man is evaluated for abdominal pain in the right upper quadrant and fever of 1 month's duration. He recently emigrated from Mexico. His medical history is unremarkable, and he takes no medication.

On physical examination, temperature is 37.7 °C (99.9 °F); other vital signs are normal. Abdominal examination shows tenderness to palpation of the right upper quadrant. No scleral icterus is noted. The remainder of the examination is normal.

An ultrasound of the liver shows a fluid-containing structure and complex wall consistent with hepatic abscess.

Laboratory studies show a leukocyte count of 10,600/µL (10.6×10^9/L). Testing for *Entamoeba histolytica* IgG is positive.

Which of the following is the most appropriate treatment?

(A) Meropenem
(B) Metronidazole and paromomycin
(C) Percutaneous drainage of the abscess
(D) Surgical resection

Item 54

A 26-year-old woman is evaluated for a 2-month history of diarrhea characterized by two to three semibloody stools per day associated with cramping lower abdominal pain. She reports no fever, chills, nausea, vomiting, or weight loss. She has not traveled internationally. She takes no medication.

On physical examination, vital signs are normal. Abdominal examination shows left and right lower abdominal tenderness to palpation. Rectal examination is remarkable for bright red blood.

Stool testing for enteric pathogens is negative.

Results of colonoscopy show inflamed mucosa characterized by granularity, erythema, friability, and loss of vascular pattern that starts at the anorectal verge and extends proximally in a continuous and symmetric fashion to the splenic flexure where there is an abrupt transition from affected to normal mucosa. The terminal ileum is normal. Biopsy results for the inflamed mucosa reveal crypt abscesses along with distorted and branching colonic crypts.

Which of the following is the most likely diagnosis?

(A) Chronic *Entamoeba histolytica* infection
(B) Crohn colitis
(C) Cytomegalovirus infection
(D) Ulcerative colitis

Item 55

A 26-year-old woman is evaluated for the new onset of jaundice. She reports no fever or abdominal pain. Her medical history is unremarkable and she takes no medication.

On physical examination, vital signs are normal. Scleral icterus and psychomotor slowing are noted.

Laboratory studies:

Hemoglobin	10.2 g/dL (102 g/L)
Reticulocyte count	8% of total erythrocyte count
Alkaline phosphatase	26 U/L
Alanine aminotransferase	78 U/L
Aspartate aminotransferase	156 U/L
Total bilirubin	6.4 mg/dL (109.4 µmol/L)
Conjugated bilirubin	2.6 mg/dL (44.5 µmol/L)

Testing for hepatitis A, B, and C viral infections is negative for acute infection.

On abdominal ultrasonography, the liver is small and nodular. Splenomegaly is noted.

Which of the following is the most appropriate test to perform next?

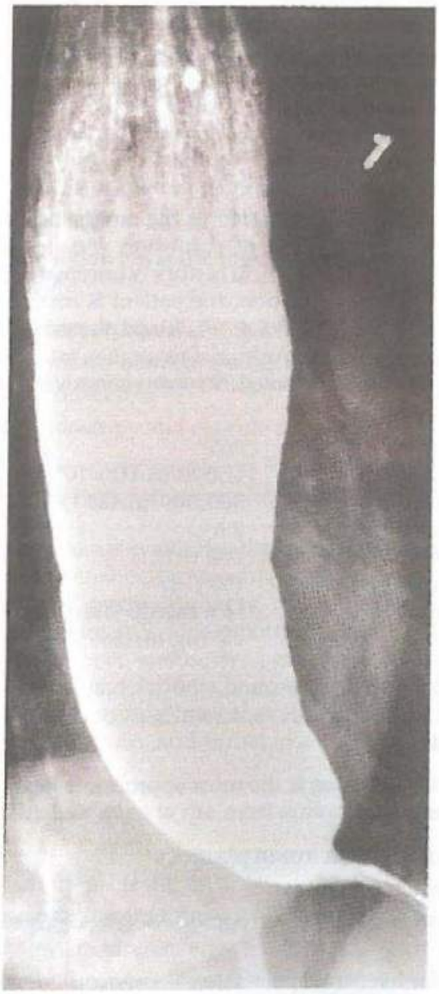
(A) Antimitochondrial antibody test
(B) Hepatitis B virus DNA measurement
(C) Serum ceruloplasmin measurement
(D) Transferrin saturation measurement

Item 56

A 55-year-old man is evaluated for progressive dysphagia of 2 years' duration. He reports dysphagia to both solid food and liquids. He has cardiomyopathy, with an ejection fraction of 15%. His medications are pantoprazole, furosemide, valsartan, digoxin, metoprolol, low-dose aspirin, and amiodarone. He is unable to walk up two flights of stairs without stopping. He does not drink or smoke.

On physical examination, his blood pressure is 100/65 mm Hg, pulse rate is 90/min, and respiratory rate is 22/min; BMI is 32. His examination is remarkable for fine crackles at the lung bases posteriorly, a third heart sound, and 2+ pitting edema to the knees.

Upper endoscopy shows no masses. A barium esophagram is shown.



Which of the following is the most appropriate treatment?

(A) Botulinum toxin injection
(B) Calcium channel blockers
(C) Endoscopic pneumatic dilation
(D) Laparoscopic surgical myotomy

Item 57

A 56-year-old woman is evaluated for chest discomfort after meals occurring intermittently over the preceding month. She describes a sensation of heaviness on her chest, and says that she also notices this pain sometimes while walking up stairs. She reports no nausea, dysphagia, or reflux. She has been taking ranitidine with minimal relief of symptoms. She also takes atorvastatin for hyperlipidemia. She smokes half a pack of cigarettes daily.

On physical examination, her blood pressure is 140/90 mm Hg and other vital signs are normal; BMI is 34. The remainder of the examination, including abdominal examination, is unremarkable.

Which of the following is the most appropriate next step in management?

(A) Barium esophagography
(B) Electrocardiography
(C) Empiric trial of a proton pump inhibitor
(D) Upper endoscopy

Item 58

A 32-year-old woman is evaluated for arthralgia and jaundice. Three months earlier, she traveled to Mexico for a 2-week vacation and developed nausea, vomiting, abdominal pain, fever, and jaundice approximately 3 weeks after returning to the United States. Testing for hepatitis A virus IgM was positive, and she was treated with supportive measures. Her symptoms and jaundice resolved within 3 weeks. A few weeks later, jaundice reappeared along with arthralgia. The patient's medical history is otherwise unremarkable, and she takes no medication.

On physical examination, vital signs are normal; BMI is 27. Jaundice is noted. The remainder of the examination is unremarkable.

Laboratory studies:

Alkaline phosphatase	272 U/L
Alanine aminotransferase	775 U/L
Aspartate aminotransferase	672 U/L
Total bilirubin	5.8 mg/dL (99.2 µmol/L)

The results of other studies, including a complete blood count, INR, serum creatinine level, antinuclear antibody, anti–smooth muscle antibody, and total IgG level, are within normal limits.

Ultrasonography of the liver is normal.

Which of the following is the most likely diagnosis?

(A) Autoimmune hepatitis
(B) Leptospirosis
(C) Malaria
(D) Relapsing, remitting hepatitis A viral infection

Item 59

A 75-year-old woman with longstanding gastroesophageal reflux disease (GERD) comes to the office with concerns related to her new diagnosis of osteopenia. Her GERD is well controlled with once-daily pantoprazole, which she has taken without side effects for 1 year. She also takes calcium and vitamin D supplements. Other than her age, she has no additional risk factors for osteoporosis.

Her vital signs and the remainder of the physical examination are normal.

Which of the following is the most appropriate next step in management?

(A) Attempt to discontinue or reduce pantoprazole
(B) Continue pantoprazole at current dose
(C) Obtain an upper endoscopy
(D) Switch to ranitidine and metoclopramide
(E) Switch to sucralfate

Item 60

A 22-year-old woman is evaluated for intractable pruritus that keeps her awake at night. She is in her 25th week of pregnancy. Her medications are a prenatal vitamin and a folate supplement.

On physical examination, vital signs are normal. Scleral icterus is noted. Excoriations are seen on the arms, chest, abdomen, and legs.

Laboratory studies:

Hematocrit	35%
Platelet count	370,000/µL (370×10^9/L)
Alanine aminotransferase	55 U/L
Aspartate aminotransferase	30 U/L
Bile acids	Elevated
Total bilirubin	2.5 mg/dL (42.8 µmol/L)

Testing for hepatitis C and hepatis B viral infections is negative.

An ultrasound shows a normal liver with no dilated bile ducts.

Which of the following is the most appropriate next step in management?

(A) Liver biopsy
(B) Peripheral blood smear
(C) Topical glucocorticoids
(D) Ursodeoxycholic acid

Item 61

H

A 60-year-old woman is admitted to the hospital with sudden-onset, cramping abdominal pain of moderate severity in the right lower quadrant, followed several hours later by a bloody bowel movement. She has coronary artery disease; medications are atorvastatin, metoprolol, sublingual nitroglycerin, and low-dose aspirin.

On physical examination, the patient appears comfortable. Pulse rate is 110/min; BMI is 35. Other vital signs are normal. The abdomen is nondistended with normal bowel sounds. Deep palpation elicits tenderness in the right lower quadrant with no rebound or guarding.

H CONT.

A CT scan without contrast shows thickening of the ascending colon. Colonoscopy results show a segment of subepithelial hemorrhage, edema, and erythema from the cecum to the hepatic flexure.

Which of the following is the most appropriate test to perform next?

(A) CT angiography
(B) Doppler ultrasonography of mesenteric vessels
(C) MR angiography
(D) Selective catheter angiography

H

Item 62

A 73-year-old man is evaluated in the hospital for lightheadedness. He also reports nonbloody, watery diarrhea of 4 months' duration and an unintentional 4.5-kg (9.9-lb) weight loss over the same time period. He has hypertension and hyperlipidemia. His medications are olmesartan and atorvastatin.

On physical examination, blood pressure is 100/50 mm Hg and pulse rate is 108/min; other vital signs are normal. Physical examination findings are unremarkable.

Results of laboratory studies, including serum creatinine, total IgA, and tissue transglutaminase IgA, are within normal limits.

The patient responds to fluid resuscitation with normalization of his pulse and blood pressure. Colonoscopy is grossly normal, and biopsy samples show no evidence of microscopic colitis. Upper endoscopy with duodenal biopsies shows villous flattening and increased intraepithelial lymphocytes.

Which of the following is the most appropriate next step in management?

(A) Discontinue atorvastatin
(B) Discontinue olmesartan
(C) Start a gluten-free diet
(D) Start prednisone

Item 63

A 65-year-old man is evaluated with upper endoscopy in follow-up for Barrett esophagus. He has had heartburn for more than 15 years, but his symptoms have been well controlled with daily omeprazole. He reports no weight loss or pain with swallowing and has no history of anemia. He stopped smoking 5 years earlier, but has a 40-pack-year history.

Vital signs and the remainder of the physical examination are normal.

On upper endoscopy, an area of salmon-colored mucosa is seen in the esophagus. Biopsies confirm evidence of Barrett esophagus with low-grade dysplasia. The pathology slides were reviewed by a second pathologist, confirming the presence of low-grade dysplasia.

Which of the following is the most appropriate next step in management?

(A) Endoscopic ablation
(B) Esophagectomy
(C) Fundoplication
(D) Repeat endoscopy in 6 months

Item 64

A 45-year-old man is evaluated for watery diarrhea accompanied by nausea and bloating. Symptoms began 4 weeks earlier with abdominal cramping and explosive watery stools. Now, he reports up to five loose bowel movements per day, with no blood and no nocturnal symptoms. He also describes generalized abdominal discomfort that is not relieved after a bowel movement. He works at a child care center. He is otherwise healthy and takes no medication.

On physical examination, vital signs are normal. Abdominal examination shows periumbilical tenderness with no rebound or guarding. The remainder of the examination is unremarkable.

Results of laboratory studies, including hemoglobin level and a comprehensive metabolic panel, are within normal limits.

Which of the following is the most appropriate next step in management?

(A) Colonoscopy
(B) CT scan of the abdomen and pelvis
(C) 24-Hour urine 5-hydroxyindoleacetic acid measurement
(D) Stool testing for *Giardia lamblia*

Item 65

A 45-year-old woman is evaluated for episodic nausea, bloating, and epigastric pain of 5 years' duration. In the past 3 months, the nausea has been accompanied by occasional vomiting. She also reports near-daily heartburn symptoms that have not responded to daily omeprazole. She has a 10-year history of type 2 diabetes mellitus that is treated with metformin and glyburide.

On physical examination, vital signs are normal; BMI is 29. Abdominal examination shows diffuse tenderness to deep palpation with no guarding. Other findings are normal.

Laboratory studies show a blood hemoglobin A_{1c} level of 7.5%. The basic metabolic panel is normal. A complete blood count and liver chemistry tests are normal.

Upper endoscopy shows a moderate amount of retained food in the stomach and patchy erythema of the gastric mucosa. Biopsies of the stomach are normal.

Which of the following is the most appropriate next step in management?

(A) Gastric emptying scintigraphy
(B) 24-Hour pH probe
(C) Initiation of domperidone
(D) Initiation of metoclopramide

Item 66

H

A 55-year-old man is evaluated after emergent treatment for an episode of hematemesis. Emergency endoscopy was performed in the emergency department, and the bleeding was successfully treated with band ligation. The endoscopy

H CONT.

revealed esophageal varices, one of which had stigmata of recent hemorrhage. Treatment with octreotide and a proton pump inhibitor was initiated. The patient has a history of cirrhosis due to hepatitis C viral infection. He has no other medical problems and takes no medication.

On physical examination, vital signs and other findings are normal.

Laboratory studies show a hemoglobin level of 8.9 g/dL (89 g/L), leukocyte count of 3600/μL (3.6×10^9/L), and platelet count of 80,000/μL (80×10^9/L).

Which of the following is the most appropriate next treatment?

(A) Blood transfusion
(B) Ciprofloxacin
(C) Platelet transfusion
(D) Transjugular intrahepatic portosystemic shunt placement

H

Item 67

A 56-year-old man is evaluated in the emergency department for altered mental status of 18 hours' duration. He has a history of cirrhosis due to hepatitis C viral infection and also has anxiety. He has not changed his diet recently, and he has no symptoms suggestive of gastrointestinal bleeding. His bowel movements have been regular and unchanged. His only medication is alprazolam started 2 weeks earlier, after a visit to an urgent care center.

On physical examination, vital signs are normal. Oxygen saturation is 96% breathing ambient air. Abdominal examination is unremarkable; there is no evidence of ascites. Psychomotor slowing and asterixis are noted. There are no focal neurologic findings. The remainder of the examination is unremarkable.

Complete blood count, serum electrolytes and creatinine, and blood glucose are normal.

In addition to starting lactulose, which of the following is the most appropriate next step in management?

(A) CT of the head
(B) Initiate a protein-restricted diet
(C) Initiate rifaximin
(D) Withdraw alprazolam

Item 68

A 38-year-old man is evaluated during a new-patient appointment. The patient reports no rectal bleeding or other gastrointestinal symptoms. His family history includes colon cancer diagnosed in his father at age 52 years. His personal medical history is unremarkable and he takes no medication.

All physical examination findings, including vital signs, are normal.

When should this patient undergo his first screening colonoscopy?

(A) Now
(B) Age 40 years
(C) Age 42 years
(D) Age 50 years

Item 69

A 64-year-old man is evaluated for hepatitis C virus–related cirrhosis with decompensation, including previous variceal hemorrhage, and ascites. His medications are furosemide, spironolactone, and nadolol.

On physical examination, vital signs are normal; BMI is 25. Spider angiomata are seen over the chest, and palmar erythema is noted. The abdomen is distended with flank dullness to percussion. The left liver lobe is palpable 5 cm below the xiphoid process. The spleen is palpable. Bilateral lower-extremity edema is noted. The remainder of the examination is normal.

A screening ultrasound examination shows a 3-cm mass with poorly defined margins and coarse, irregular internal echoes in the right hepatic lobe. A CT scan of the abdomen with contrast shows a 3-cm arterial enhancing lesion with portal venous phase washout in the periphery of the right lobe. The chest is normal on CT.

Which of the following is the most appropriate next step in management?

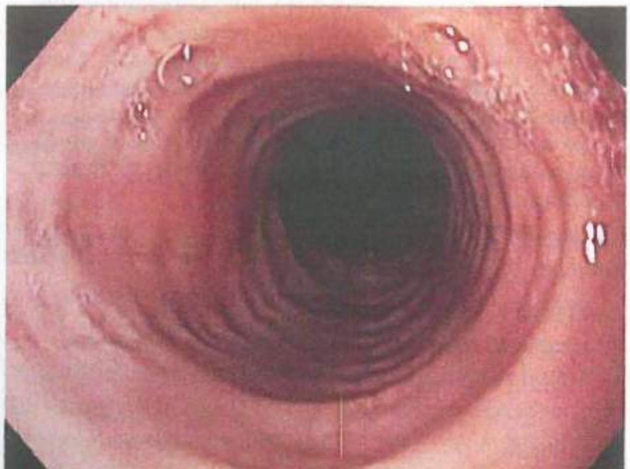
(A) Biopsy of the lesion
(B) Liver transplantation
(C) Sorafenib
(D) Surgical resection

Item 70

A 25-year-old man is evaluated for a sensation of solid food "sticking" several times per week. He reports that he sometimes forces himself to vomit when he feels food "stuck" in the esophagus, but he has never gone to the emergency department. He takes a multivitamin and is generally healthy.

On physical examination, vital signs and other findings, including those of an abdominal examination, are unremarkable.

Upper endoscopy findings are shown.



Biopsies of the esophagus show more than 18 eosinophils/hpf.

Which of the following is the most likely diagnosis?

(A) Achalasia

(B) *Candida* esophagitis

(C) Eosinophilic esophagitis

(D) Pill-induced esophagitis

Item 71

A 65-year-old man undergoes screening with ultrasonography for abdominal aortic aneurysm. He has no symptoms, his medical history is unremarkable, and he takes no medication.

Vital signs and other findings of the physical examination are normal.

On the abdominal ultrasound, the abdominal aorta appears normal. Multiple gallstones smaller than 1 cm in size are seen in the gallbladder. The liver has normal echogenicity, and there are no dilated bile ducts. No abnormalities are seen in the gallbladder wall.

Which of the following is the most appropriate management of this patient's gallstone disease?

(A) Cholecystectomy

(B) Endoscopic retrograde cholangiopancreatography

(C) Repeat ultrasonography in 6 months

(D) Clinical observation

H

Item 72

An 80-year-old man is evaluated in the emergency department after a bowel movement with initial passage of brown soft stool followed by a large volume of red blood. He reports intermittent chills and fevers over the past week. He also has peripheral vascular disease, hypertension, and hypercholesterolemia. His history includes an aortoiliac aneurysm treated with an aortic bifurcation graft 3 years earlier. His medications are atorvastatin, hydrochlorothiazide, losartan, and low-dose aspirin.

On physical examination, the patient is comfortable. His temperature is 38 °C (100.4 °F), blood pressure is 108/60 mm Hg, pulse rate is 112/min, and respiration rate is 18/min. Cardiopulmonary examination is unremarkable. There is midabdominal tenderness to palpation. Rectal examination reveals bright red blood mixed with brown stool.

Laboratory studies show a hemoglobin level of 9 g/dL (90 g/L). Leukocyte count is 14,000/µL (14×10^9/L) with neutrophilia.

Which of the following is the most appropriate test to perform next?

(A) CT scan with contrast

(B) Mesenteric angiogram

(C) Tagged red blood cell scintigraphy

(D) Upper endoscopy

H

Item 73

A 72-year-old woman is evaluated after being hospitalized for gastrointestinal bleeding. She went to the emergency department after passing a large amount of bright red blood per rectum at home and became lightheaded. She had a second bloody bowel movement in the emergency department. She is otherwise healthy and takes no medication.

Findings on physical examination, including vital signs, are normal.

Laboratory studies show a hemoglobin level of 9 g/dL (90 g/L).

Which of the following is the most appropriate next step in management?

(A) Angiography and arterial embolization

(B) Colonoscopy within 8 hours with cleansing enemas

(C) Colonoscopy within 24 hours with oral bowel preparation

(D) Tagged red blood cell scintigraphy

(E) Transfusion of packed red blood cells

H

Item 74

A 58-year-old woman is evaluated in the emergency department for sharp, nonradiating pain in the left lower quadrant that has persisted for 2 days. She reports no fever, diarrhea, or blood in stools, and has not traveled recently. Her last colonoscopy, performed 1 year earlier, showed pandiverticulosis.

On physical examination, her temperature is 37.2 °C (99.0 °F), blood pressure is 130/85 mm Hg, pulse rate is 88/min, and respiratory rate is 18/min; BMI is 26. Abdominal examination is positive for left-lower-quadrant tenderness on palpation with no rebound or guarding.

Results of laboratory studies show an elevated leukocyte count; other findings are normal.

Abdominal CT shows focal diverticulitis in the sigmoid colon, without abscess.

Which of the following is the most appropriate next step in management?

(A) Colonoscopy

(B) Intravenous antibiotics

(C) Oral antibiotics

(D) Surgery

Item 75

A 66-year-old man is evaluated for breakthrough symptoms of gastroesophageal reflux disease (GERD) despite once-daily pantoprazole. He has a 5-year history of GERD.

On physical examination, his blood pressure is 118/70 mm Hg, pulse rate is 76/min, and respiratory rate is 18/min; BMI is 30. The abdomen is soft, nontender, and nondistended. Bowel sounds are hyperactive. The remainder of the examination is unremarkable.

Upper endoscopy shows Barrett esophagus. Biopsy results are indefinite for dysplasia.

Which of the following is the most appropriate next step in management?

(A) Endoscopic ablation therapy

(B) Esophagectomy

(C) Optimization of medical therapy followed by repeat upper endoscopy

(D) Repeat upper endoscopy in 1 year

Item 76

A 78-year-old woman is evaluated for frequent rectal urgency with the passage of explosive, loose to watery stool. She says she is often unable to get to the bathroom in time. Episodes have occurred after meals and in the early morning over the past 3 months. She has Alzheimer dementia and lives with her daughter. She also has hypertension and chronic back pain. Her history includes occasional constipation that resolves when treated with docusate. Her last screening colonoscopy at age 70 years showed diffuse diverticulosis. Her medications are lisinopril, acetaminophen, memantine, docusate as needed, and a calcium supplement with vitamin D.

On physical examination, vital signs are normal. Fecal soiling is noted. Rectal examination shows normal anal tone and brown stool in the rectal vault.

A complete blood count and thyroid-stimulating hormone level are normal.

Which of the following is the most appropriate next step in management?

(A) Abdominal radiograph
(B) Anorectal manometry
(C) Loperamide
(D) Psyllium

Item 77

H

A 68-year-old man is evaluated in the ICU for cramping abdominal pain in the left lower quadrant, which began approximately 3 hours before the evaluation. Twenty minutes before the evaluation, he had a loose stool with hematochezia. The patient has been in the ICU for 24 hours, after being admitted with fever and hypotension secondary to urosepsis. He was treated with intravenous fluids, vasopressors, and piperacillin-tazobactam. His medical history includes hypertension, benign prostatic hypertrophy, and hyperlipidemia. His daily medications are chlorthalidone, atorvastatin, and low-dose aspirin.

On physical examination, the patient is alert. Temperature is 38.7 °C (101.7 °F), blood pressure is 106/60 mm Hg, pulse rate is 90/min, respiration rate is 18/min, and oxygen saturation is 96% breathing ambient air. There is tenderness to palpation over the left side of the abdomen without guarding. The remainder of the examination is unremarkable.

Colonoscopy findings are shown.

Which of the following is the most likely diagnosis?

(A) Acute mesenteric ischemia
(B) Diverticular bleeding
(C) Enterohemorrhagic *Escherichia coli*
(D) Ischemic colitis

Item 78

A 26-year-old woman with Crohn disease is evaluated for a 2-week history of worsening abdominal pain in the right lower quadrant. She reports passage of one to two formed and nonbloody stools per day with no changes in bowel habits. The patient has required three courses of prednisone for disease flares over the past year. Her only medication is azathioprine.

On physical examination, temperature is 37.7 °C (99.9 °F) and pulse rate is 115/min; other vital signs are normal. Abdominal examination shows fullness and tenderness in the right lower quadrant with no distinct mass. The remainder of the examination is unremarkable.

Laboratory studies show a hemoglobin level of 10.5 g/dL (105 g/L) and a C-reactive protein level of 32 mg/dL (320 mg/L). Leukocyte count and liver chemistry tests are normal.

CT enterography shows asymmetric mural thickening and mucosal inflammation of a long segment of distal ileum without luminal narrowing.

Which of the following is the most appropriate treatment?

(A) Budesonide
(B) Infliximab
(C) Mesalamine
(D) Prednisone

Item 79

A 30-year-old woman is evaluated during a new-patient appointment. Her personal medical history is unremarkable and she takes no medication. Her family history includes colon cancer diagnosed in her mother at age 48 years, endometrial cancer diagnosed in a maternal aunt at age 51 years, and colon cancer diagnosed in her maternal grandfather at age 55 years.

All physical examination findings, including vital signs, are normal.

Genetic testing for *MSH2* mutation is positive, consistent with Lynch syndrome.

Which of the following is the most appropriate next step?

(A) Colectomy
(B) Colonoscopy at age 38
(C) Colonoscopy at age 40
(D) Colonoscopy now

Item 80

A 38-year-old man is evaluated for epigastric discomfort and early satiety associated with an unintentional 4.5-kg (9.9-lb) weight loss over the preceding 5 months. His

family history includes lobular breast cancer diagnosed in his mother at age 45 years, stomach cancer diagnosed in his maternal grandfather at age 48 years, and stomach cancer diagnosed in his maternal uncle at age 52 years. The patient's medical history is unremarkable, and he takes no medication.

On physical examination, vital signs are normal. Abdominal examination shows epigastric tenderness to palpation and normal bowel sounds.

Which of the following is the most appropriate diagnostic test to perform next?

(A) Colonoscopy
(B) Gastric emptying study
(C) *Helicobacter pylori* serology
(D) Upper endoscopy
(E) Upper gastrointestinal radiograph series

Item 81

A 32-year-old man is evaluated for a 1-week history of jaundice and pruritus. One month earlier, he completed treatment for sinusitis with amoxicillin-clavulanate. His sinusitis symptoms resolved with therapy.

On physical examination, vital signs are normal. BMI is 26. Jaundice is noted. Excoriations are seen on the extremities. The abdominal examination is normal.

Laboratory studies:

INR	1.0
Albumin	3.8 g/dL (38 g/L)
Alkaline phosphatase	580 U/L
Alanine aminotransferase	42 U/L
Aspartate aminotransferase	38 U/L
Total bilirubin	8.6 mg/dL (147.1 µmol/L)

Hepatitis A, B, and C virus and Epstein-Barr virus studies show no evidence of current or previous infection. Testing for antinuclear antibody and anti-smooth muscle antibody is negative. The ceruloplasmin level is normal.

Results of abdominal ultrasonography are normal, with no evidence of biliary dilation, gallstones, or hepatic parenchymal abnormalities.

Which of the following is the most appropriate next step in management?

(A) Endoscopic retrograde cholangiopancreatography
(B) Liver biopsy
(C) Prednisone administration
(D) Continued observation

Item 82

A 54-year-old woman is evaluated for a 1-year history of generalized abdominal pain that is constant throughout the day, every day. The pain is not triggered by eating and is not relieved by bowel movements. She reports no weight loss and no change in bowel habits. She also has depression. A screening colonoscopy done 8 months earlier was normal. Her only medication is escitalopram.

On physical examination, vital signs are normal; BMI is 28. The abdomen is tender to palpation in all quadrants without guarding. The remainder of the examination is normal.

Results of laboratory studies, including a complete blood count and liver chemistry tests, are normal.

Which of the following is the most appropriate treatment?

(A) Alosetron
(B) Budesonide
(C) Cognitive-behavioral therapy
(D) Linaclotide

Item 83

H

A 55-year-old man is evaluated after being hospitalized for epigastric pain of 1 month's duration and melenic stools over the past 3 days associated with fatigue. He reports no hematochezia, hematemesis, chest pain, or shortness of breath. He has osteoarthritis treated with ibuprofen. He received an intravenous fluid bolus in the emergency department.

On physical examination, blood pressure is 135/75 mm Hg and other vital signs are normal, with no orthostatic changes. Abdominal examination reveals epigastric tenderness but is otherwise unremarkable. No stigmata of chronic liver disease are seen.

Laboratory studies show a hemoglobin level of 7.3 g/dL (73 g/L).

Upper endoscopy shows a 1.5-cm duodenal bulb ulcer with a clean base.

Which of the following is the most appropriate resuscitation measure?

(A) Transfuse red blood cells to a goal hemoglobin level of 8 g/dL (80 g/L)
(B) Transfuse red blood cells to a goal hemoglobin level of 9 g/dL (90 g/L)
(C) Transfuse red blood cells to a goal hemoglobin level of 10 g/dL (100 g/L)
(D) No transfusion

Item 84

A 28-year-old man is evaluated after hospitalization for lower gastrointestinal bleeding 6 weeks earlier. At that time, he was found to have innumerable adenomatous colon polyps during colonoscopy. He underwent total colectomy, and pathology showed a 2-cm adenocarcinoma in the transverse colon. There was no evidence of metastatic disease. Genetic testing confirmed a germline mutation in the adenomatous polyposis coli (*APC*) gene consistent with familial adenomatous polyposis syndrome. Family medical history is unremarkable.

On physical examination, vital signs are normal. Abdominal examination shows a well-healed scar and no tenderness to palpation.

Which of the following is the most appropriate test to perform next?

(A) Barium upper gastrointestinal series
(B) Double-balloon enteroscopy

(C) Upper endoscopy
(D) No further testing

Item 85

A 52-year-old man is evaluated after screening colonoscopy revealed three polyps in the descending colon, measuring 5 mm, 8 mm, and 3 mm in size. Colonoscopy preparation was excellent, and the procedure was complete to the cecum. The polyps were completely excised, and pathology showed all three to be tubular adenomas. The patient has no personal or family history of colorectal cancer. He reports no symptoms and takes no medication.

All physical examination findings, including vital signs, are normal.

Based on his colonoscopy findings, when should this patient next undergo surveillance colonoscopy?

(A) 1 year
(B) 3 years
(C) 5 years
(D) 10 years

Item 86

A 55-year-old woman is evaluated for a 6-month history of throbbing and sometimes burning epigastric pain. The pain occurs 2 to 3 times per week and often subsides with eating. She reports no weight loss, nausea, or vomiting, and no bowel symptoms. She tested negative for *Helicobacter pylori* infection. Her pain did not respond to a 4-week trial of omeprazole. The patient also has anxiety, hypothyroidism, and type 2 diabetes mellitus controlled by diet. Her family medical history is unremarkable. Her medications are lorazepam and levothyroxine.

On physical examination, vital signs are normal. Epigastric tenderness to palpation is noted. Other findings are normal.

A complete blood count, liver chemistry tests, and thyroid-stimulating hormone level are normal. Hemoglobin A_{1C} level is 6.7%.

Upper endoscopy findings are normal. Gastric and small-bowel biopsies are normal.

Which of the following is the most appropriate next step in management?

(A) CT scan of the abdomen
(B) Gastric emptying test
(C) Initiation of a tricyclic antidepressant
(D) Twice-daily proton pump inhibitor therapy
(E) Ultrasonography of the right upper quadrant

Item 87

A 61-year-old woman is evaluated for joint pain, a rash on her legs, and weakness. She has chronic genotype 1 hepatitis C viral infection. She takes no medication.

On physical examination, vital signs are normal. The lower extremities are shown (see top of next column). No evidence of muscle weakness, joint swelling or warmth is

noted on musculoskeletal exam. The liver edge is palpable at the costal margin. The remainder of the physical examination is unremarkable.

Laboratory studies:

Complete blood count	Normal
Alanine aminotransferase	112 U/L
Aspartate aminotransferase	84 U/L
Total bilirubin	1 mg/dL (17.1 µmol/L)
Creatinine	Normal
Urinalysis	Normal

Which of the following is the most appropriate treatment?

(A) Cyclophosphamide
(B) Glucocorticoids
(C) Ledipasvir and sofosbuvir
(D) Pegylated interferon and ribavirin
(E) Rituximab

Item 88

A 63-year-old woman is evaluated for diarrhea characterized by three to four large-volume, watery stools per day over a period of 14 months with gradually increasing severity and frequency. She now reports occasional urge fecal incontinence and nocturnal diarrhea but no abdominal pain, bloody stools, or weight loss. She has been taking loperamide up to five times daily, but symptoms have persisted.

On physical examination, vital signs are normal; BMI is 26. Abdominal examination is normal with no tenderness or distention. Rectal examination reveals no blood or masses.

Results of routine laboratory studies are normal. Polymerase chain reaction testing of the stool for *Clostridium difficile* is negative.

Colonoscopy results are normal. Random colon biopsy specimens show lymphocytic infiltration of the mucosa with a subepithelial collagen band.

Which of the following is the most appropriate treatment?

(A) Bismuth subsalicylate
(B) Budesonide
(C) Mesalamine
(D) Prednisone
(E) Probiotics

Item 89

A 33-year-old woman is evaluated following an incidentally discovered hepatic adenoma. One week earlier, she was evaluated for nephrolithiasis with CT urogram. A 4-cm right-lobe liver lesion was also seen. Follow-up MRI identified findings consistent with hepatic adenoma. She is experiencing no symptoms now but has noted a sense of right-upper-quadrant abdominal discomfort in the past. Her only medication is an oral contraceptive agent.

All physical examination findings are normal.

Which of the following is the most appropriate management?

(A) Discontinue the oral contraceptive agent
(B) Radiofrequency ablation
(C) Surgical resection
(D) Observation

Item 90

A 75-year-old man is evaluated during a follow-up appointment for newly diagnosed iron deficiency anemia and stool testing positive for occult blood. He has undergone upper endoscopy and colonoscopy twice with no cause found for his gastrointestinal bleeding.

On physical examination, vital signs and other findings are unremarkable.

Laboratory studies show a serum ferritin level of 6 ng/mL (6 µg/L), a hemoglobin level of 9.9 g/dL (99 g/L), and a mean corpuscular volume of 78 fL.

Which of the following is the most appropriate next step in management?

(A) Capsule endoscopy
(B) CT enterography
(C) Push enteroscopy
(D) Small-bowel follow-through radiography

Item 91

A 40-year-old woman is evaluated at a follow-up appointment for hepatitis B virus (HBV) infection, which was diagnosed at age 23 years. The patient also has psoriasis. She is married and is sexually active. Medications are topical clobetasol and an oral contraceptive agent.

On physical examination, vital signs are normal. Psoriatic lesions are present on the elbows and knees. No hepatosplenomegaly is noted.

Laboratory studies:

Alanine aminotransferase	125 U/L
Aspartate aminotransferase	112 U/L
Hepatitis B surface antigen	Positive
Hepatitis B e antigen	Positive
HBV DNA	41,326 IU/mL

Which of the following is the most appropriate treatment?

(A) Adefovir
(B) Lamivudine
(C) Pegylated interferon
(D) Tenofovir
(E) No treatment

Item 92

A 40-year-old woman is evaluated for intermittent lower abdominal pain, daily bloating, and constipation. Her lower abdominal pain initially worsens then subsides after a bowel movement; it occurs nearly daily. She has bowel movements every 2 to 3 days and reports that most bowel movements are hard. The patient reports that adherence to a gluten-free diet has helped the bloating, but other symptoms have not responded. A twice-daily soluble fiber supplement has not affected symptoms. Her last thyroid-stimulating hormone measurement and complete blood count 6 months earlier were normal. Family history includes colon cancer diagnosed in her grandfather at age 60 years and a first cousin with celiac disease.

On physical examination, BMI is 29; all other findings are unremarkable.

Which of the following is the most appropriate next step in management?

(A) Colonoscopy
(B) Glucose breath test
(C) Polyethylene glycol 3350
(D) Serum tissue transglutaminase antibody measurement

Item 93

A 65-year-old man is evaluated after a positive stool antigen test for *Helicobacter pylori* infection obtained to confirm eradication after therapy. *H. pylori* gastritis was diagnosed in the setting of a duodenal ulcer. Four weeks ago, he completed a 10-day course of eradication therapy consisting of amoxicillin, clarithromycin, and omeprazole. He reports taking all medications as prescribed during treatment and reports no upper gastrointestinal symptoms or melena. The patient does not smoke cigarettes or drink alcohol. He has no known drug allergies.

Which of the following is the most appropriate 14-day treatment regimen?

(A) Amoxicillin, clarithromycin, and omeprazole
(B) Amoxicillin, metronidazole, and omeprazole
(C) Bismuth, metronidazole, omeprazole, and tetracycline
(D) Clarithromycin, metronidazole, and omeprazole

Item 94

H

A 61-year-old woman is evaluated in the hospital for abdominal discomfort and worsening ascites. She reports a significant decrease in urine output over the preceding 3 days. She has a history of cirrhosis due to primary biliary cholangitis. Her medications are furosemide and spironolactone.

On physical examination, blood pressure is 90/58 mm Hg; other vital signs are normal. The abdomen is distended with a positive fluid wave.

H CONT.

Laboratory studies show a serum creatinine level of 2.8 mg/dL (247.5 µmol/L) (3 weeks ago, 1.2 mg/dL [106.1 µmol/L]) and a serum sodium level of 133 mEq/L (133 mmol/L).

Urine studies show a sodium level of less than 10 mEq/L (10 mmol/L) and no protein, leukocytes, erythrocytes, or casts.

Analysis of ascitic fluid shows a leukocyte count of 180/µL with 30% neutrophils. Cultures of ascitic fluid are negative.

A kidney ultrasound shows no evidence of obstruction or kidney parenchymal disease.

Which of the following is the most likely diagnosis?

(A) Acute interstitial nephritis
(B) Acute tubular necrosis
(C) Hepatorenal syndrome
(D) Membranous glomerulonephritis

H

Item 95

A 48-year-old man is evaluated in the emergency department for left flank pain and dysuria. Six months earlier, the patient was hospitalized for severe acute gallstone pancreatitis. Contrast-enhanced CT of the pancreas showed lack of perfusion in the body of the pancreas. He recovered with supportive care and was discharged 2 weeks later. He had an uncomplicated laparoscopic cholecystectomy 4 weeks after discharge. He reports that he has felt well until the sudden onset of left flank pain today.

On physical examination, blood pressure is 130/80 mm Hg and pulse rate is 90/min; other vital signs are normal. Abdominal examination is notable for pain in the left lower quadrant on palpation. The remainder of the examination is normal.

Urinalysis shows hematuria.

A CT scan identifies nephrolithiasis and a small stone in the left ureter. The CT scan also shows a 6-cm fluid collection with solid debris in the body of the pancreas with a well-defined wall.

Which of the following is the most appropriate management of the fluid collection?

(A) Antibiotic therapy
(B) CT-guided fine-needle aspiration
(C) Drainage procedure
(D) Observation

Item 96

A 62-year-old woman is evaluated during a follow-up appointment 12 weeks after she completed treatment for genotype 1a hepatitis C virus (HCV) infection. She has Child-Turcotte-Pugh Class A cirrhosis (well-compensated cirrhosis). Small esophageal varices were noted on upper endoscopy 1 year earlier.

On physical examination, vital signs are normal; BMI is 26. Palmar erythema, spider angiomata over the chest, a firm liver edge 3 cm below the costal margin, and a palpable spleen tip are noted. The examination is otherwise normal.

Her HCV RNA is undetectable and her calculated Model for End-Stage Liver Disease score is 8.

Which of the following is the most appropriate management for this patient?

(A) Liver transplantation evaluation
(B) Measurement of HCV RNA in 12 weeks
(C) Ultrasonography of the liver every 6 months
(D) Upper endoscopy

Answers and Critiques

Item 1 Answer: D

Educational Objective: Treat opioid-induced constipation.

Switching to naloxegol is the most appropriate treatment for this patient. The clinical definition of constipation (as defined by the Rome 4 international working group) is a symptom complex that includes at least two of the following: straining during defecation, passage of lumpy or hard stool, sensation of incomplete defecation, use of manual maneuvers to facilitate a bowel movement, and/or frequency of fewer than three bowel movements per week. Oral naloxegol is a peripherally acting μ-opioid receptor antagonist that is FDA-approved for the treatment of opioid-induced constipation in adults with chronic noncancer pain. This patient's constipation can be classified as opioid-induced because her constipation symptoms developed after the initiation of chronic opioid analgesic therapy for reflex sympathetic dystrophy syndrome. First-line laxative therapies, including over-the-counter stool softeners, bulk laxatives (fiber supplements), a stimulant laxative (bisacodyl), and an osmotic laxative (polyethylene glycol [PEG]), have all been ineffective. Current maintenance laxative therapy should be stopped before the initiation of naloxegol and can be added to the naloxegol after 3 days of monotherapy as symptoms dictate.

Surfactants such as docusate sodium or docusate calcium are weak laxatives with an excellent safety profile. As such, they are most appropriate for very mild, intermittent constipation and will not be effective in this patient.

Adding a second osmotic agent such as lactulose is unlikely to improve the patient's reduced stool frequency, which is the result of slowed colonic motility caused by her chronic opioid analgesic use. Also, lactulose use is likely to lead to bloating.

Increasing the dose of PEG will not provide any additional benefit because the patient reports soft stool with the current dose. The patient's altered colonic motility will not improve with additional PEG. Furthermore, an increased dose of PEG is likely to cause bloating.

KEY POINT

- Oral naloxegol is a peripherally acting μ-opioid receptor antagonist that is FDA-approved for the treatment of opioid-induced constipation in adults with chronic noncancer pain.

Bibliography

Chey WD, Webster L, Sostek M, Lappalainen J, Barker PN, Tack J. Naloxegol for opioid-induced constipation in patients with noncancer pain. N Engl J Med. 2014;370:2387-96. [PMID: 24896818] doi:10.1056/NEJMoa1310246

Item 2 Answer: D

Educational Objective: Manage the immune-tolerant phase of hepatitis B viral infection.

Repeat liver chemistry testing in 6 months is the most appropriate next step in the management of this patient. The patient has hepatitis B virus (HBV) infection in the immune-tolerant phase, which can be determined by the likely vertical transmission and the patient's young age, positive hepatitis B e antigen (HBeAg), high viral load, and normal aminotransferase levels. Therefore, the patient only requires serial monitoring of aminotransferase levels. There are four typical phases of HBV infection: (1) immune tolerant; (2) immune active, HBeAg positive; (3) immune control (inactive); and (4) reactivation, HBeAg negative. Not all patients go through each phase. Patients with infection in the immune-tolerant phase do not have significant hepatic inflammation and have no fibrosis, and, therefore, do not require treatment. However, infection can progress to the immune-active, HBeAg-positive phase, in which hepatic inflammation, elevated aminotransferase levels, and fibrosis develop, underscoring the need for surveillance of aminotransferase levels.

Patients with HBV infection in the immune-active, HBeAg-positive and reactivation, HBeAg-negative phases require treatment if the alanine aminotransferase level is elevated. Antiviral therapy is also required for patients who present with acute liver failure, all patients with cirrhosis, and patients undergoing treatment with certain immunosuppressive or chemotherapy regimens. None of these scenarios apply to this patient, so she does not require antiviral treatment such as tenofovir, entecavir, or pegylated interferon.

Patients with HBV infection are at increased risk for hepatocellular carcinoma, even in the absence of cirrhosis. Patients from Southeast Asia should undergo hepatocellular carcinoma surveillance with ultrasonography starting at age 40 years for men and at age 50 years for women, and patients from sub-Saharan Africa should begin at age 20 years. Other indications include persistent inflammatory activity (defined as an elevated alanine aminotransferase level and HBV DNA levels greater than 10,000 IU/mL for at least a few years) and a family history of hepatocellular carcinoma. The preferred surveillance strategy is liver ultrasonography with or without α-fetoprotein measurement. This patient is not yet old enough to warrant hepatocellular carcinoma surveillance, so hepatic ultrasonography is not indicated.

KEY POINT

- Patients with hepatitis B infection in the immune-tolerant phase require serial monitoring of aminotransferase levels.

Bibliography

Terrault NA, Bzowej NH, Chang KM, Hwang JP, Jonas MM, Murad MH; American Association for the Study of Liver Diseases. AASLD guidelines for treatment of chronic hepatitis B. Hepatology. 2016;63:261-83. [PMID: 26566064] doi:10.1002/hep.28156

Item 3 Answer: D

Educational Objective: Manage aspirin use before and after polypectomy.

This patient should not discontinue aspirin use. Aspirin does not need to be discontinued before colonoscopy in any scenario, and data from studies of patients who have undergone polypectomy show no difference in the risk for postprocedure bleeding with discontinuation or continuation of aspirin use. The American College of Gastroenterology's 2016 guidelines for management of lower gastrointestinal bleeding (LGIB) recommend the continuation of aspirin for secondary cardiovascular prophylaxis after polypectomy. Discontinuing aspirin is recommended after polypectomy in patients without established cardiovascular disease who are using aspirin as primary prophylaxis. In patients with established cardiovascular disease, such as this patient, the risks of a potential cardiovascular event outweigh those of potential gastrointestinal bleeding.

Holding aspirin for a period of time after a polypectomy, such as 48 hours, has not been shown to reduce postprocedure LGIB and may increase risk for a thromboembolic event in a patient with established cardiovascular disease.

KEY POINT

- Aspirin for secondary prophylaxis in patients with established cardiovascular disease should be continued after colonoscopy with polypectomy.

Bibliography

Strate LL, Gralnek IM. ACG clinical guideline: management of patients with acute lower gastrointestinal bleeding. Am J Gastroenterol. 2016;111:459-74. [PMID: 26925883] doi:10.1038/ajg.2016.41

Item 4 Answer: C

Educational Objective: Diagnose nonalcoholic fatty liver disease.

The most likely diagnosis is nonalcoholic fatty liver disease (NAFLD). Up to 108 million Americans have NAFLD, which far exceeds the prevalence of any other form of chronic liver disease. Risk factors include obesity, diabetes mellitus, insulin resistance, hypertension, and hyperlipidemia. This patient has three risk factors for NAFLD, as well as an enlarged liver on physical examination. Her elevated alanine aminotransferase and aspartate aminotransferase levels are within the typical range for patients with NAFLD. Alkaline phosphatase (ALP) levels may be slightly elevated as well, typically less than 2 to 2.5 times the upper limit of normal. The finding of a hyperechoic liver on ultrasonography is also consistent with NAFLD. Because other liver diseases may also result in hepatic steatosis, patients with elevated liver chemistries and suspected nonalcoholic steatohepatitis should be evaluated to exclude other causes of chronic liver disease.

The diagnosis of primary biliary cholangitis (PBC) is generally made on the basis of a cholestatic liver enzyme profile in the setting of a positive antimitochondrial antibody test. The predominant liver enzyme abnormality is an increase in serum ALP levels, but a mild to moderate increase in aminotransferase levels is also seen. Antimitochondrial antibody-negative PBC accounts for about 10% of cases of PBC. This patient's liver chemistry profile is hepatocellular (elevations primarily of aminotransaminase levels), not cholestatic, making PBC unlikely.

Although this patient has a positive anti–smooth muscle antibody test, the low titer alone is not diagnostic of autoimmune hepatitis. Autoimmune hepatitis is typically accompanied by higher autoantibody titers and elevated γ-globulin levels. It requires a liver biopsy to establish the diagnosis. Between 20% and 30% of patients with NAFLD exhibit low-titer autoantibodies.

This patient has a minimally elevated ALP level, which helps to exclude primary sclerosing cholangitis (PSC) or PBC. In addition, the patient's risk factors and ultrasound findings make these diagnoses unlikely. MR cholangiopancreatography is required to diagnose PSC.

KEY POINT

- Nonalcoholic fatty liver disease is the most common cause of abnormal liver test results in the United States.

Bibliography

Chalasani N, Younossi Z, Lavine JE, Diehl AM, Brunt EM, Cusi K, et al. The diagnosis and management of non-alcoholic fatty liver disease: practice guideline by the American Association for the Study of Liver Diseases, American College of Gastroenterology, and the American Gastroenterological Association. Hepatology. 2012;55:2005-23. [PMID: 22488764] doi:10.1002/hep.25762

Item 5 Answer: D

Educational Objective: Diagnose pseudoachalasia.

This patient likely has pseudoachalasia, and endoscopic ultrasound should be used to diagnose a possible tumor of the distal esophagus or gastric cardia. The other causes of pseudoachalasia are benign disease, such as amyloidosis and sarcoidosis, and postsurgical status (for example, after Nissen fundoplication or bariatric surgery). The clinical presentation of achalasia consists of dysphagia to both solids and liquids along with regurgitation of undigested food and saliva. Other conditions can mimic achalasia and can have identical clinical, barium-imaging, and manometric findings, as well as identical endoscopic appearance. These include pseudoachalasia, secondary achalasia, and Chagas disease. Pseudoachalasia is caused by a tumor at the gastroesophageal junction infiltrating the myenteric plexus causing esophageal motor abnormalities. Tumors capable

of infiltrating the myenteric plexus include those of the distal esophageus, gastric cardia, pancreatic, breast, lung, and hepatocellular. Patients with pseudoachalasia are often in their sixth decade of life or older, have a short duration of symptoms, and experience sudden and profound weight loss. Endoscopic ultrasonography can exclude an infiltrating tumor, and guidelines recommend its use in patients with a strong suspicion for malignancy.

Achalasia affects men and women equally, with an annual incidence of 1 in 100,000 individuals. It tends to occur between the ages of 30 and 60 years. Typical achalasia has an insidious onset and long duration of symptoms, often measured in years, before patients seek medical attention. This patient's age, short duration of symptoms, and rapid weight loss argue against the diagnosis of achalasia.

Chagas disease is caused by infection with the vector-borne parasite *Trypanosoma cruzi* in rural areas of Latin America. The major manifestations of Chagas disease include enteric myenteric destruction, resulting in achalasia, megacolon, heart disease, and other neurologic disorders. The lack of travel and absence of other manifestations of Chagas disease make this diagnosis unlikely.

Eosinophilic esophagitis is inconsistent with this patient's symptoms and endoscopic examination. Its typical presentation is in younger patients with food bolus obstruction. Endoscopy findings in eosinophilic esophagitis include rings and furrows.

KEY POINT

- Pseudoachalasia is caused by a tumor at the gastroesophageal junction infiltrating the myenteric plexus causing esophageal motor abnormalities; symptoms, barium-imaging and manometric findings, and endoscopic appearance are similar to achalasia.

Bibliography

Vaezi MF, Pandolfino JE, Vela MF. ACG clinical guideline: diagnosis and management of achalasia. Am J Gastroenterol. 2013;108:1238-49; quiz 1250. [PMID: 23877351] doi:10.1038/ajg.2013.196

Item 6 Answer: C

Educational Objective: Treat diarrhea-predominant irritable bowel syndrome.

A low-FODMAP (Fermentable Oligosaccharides, Disaccharides, Monosaccharides, And Polyols) diet is the most appropriate treatment for this patient. FODMAPs consist of short-chain carbohydrates that are poorly absorbed and rapidly fermented by gut bacteria, resulting in the production of gas and an increased osmotic fluid load within the gut lumen. The patient has diarrhea-predominant irritable bowel syndrome (IBS-D). IBS is a heterogeneous symptom complex characterized by abdominal pain and altered bowel habits. The diagnosis of IBS requires symptoms of recurrent abdominal pain or discomfort at least 1 day a week for a period of 3 months, along with two of the following three additional criteria: pain relieved by defecation, change in stool frequency, or change in bowel consistency. IBS can then be further subtyped into IBS with predominant constipation (IBS-C), predominant diarrhea, mixed bowel habits, or unclassified.

The effects of dietary FODMAPs may contribute to the symptoms of IBS-D. A randomized controlled trial involving 84 adults with IBS-D compared a low-FODMAP diet to a diet based on modified National Institute for Health and Care Excellence (mNICE) guidelines. In this study, more patients on the low-FODMAP diet reported adequate relief of their IBS-D symptoms (52% versus 41%) and response in abdominal pain (51% versus 23%) than those on the mNICE diet.

Alosetron is a peripherally acting serotonin type 3-receptor antagonist approved by the FDA for the treatment of IBS-D in women aged 18 years or older after failure of conventional therapy. Due to the risk for adverse events with the use of alosetron, including serious complications of constipation and ischemic colitis, a prescriber must first complete an FDA-mandated Risk Evaluation and Mitigation Strategy training program that is available online (www.alosetronrems.com). Alosetron is not FDA-approved for the treatment of men with IBS-D due to the small number of men involved in the pivotal clinical trials, and it would not be appropriate as an initial treatment for IBS in this male patient.

Linaclotide is a peripherally acting guanylate cyclase-C activator approved by the FDA for the treatment of IBS-C. Lubiprostone is a peripherally acting chloride channel activator that is approved by the FDA for the treatment of IBS-C in women aged 18 years or older. In this patient whose predominant bowel symptom is diarrhea, use of either of these agents will worsen his diarrhea and is therefore not indicated.

KEY POINT

- A low-FODMAP (Fermentable Oligosaccharides, Disaccharides, Monosaccharides, And Polyols) diet can reduce abdominal pain and bloating and improve stool consistency, frequency, and urgency in patients with diarrhea-predominant irritable bowel syndrome.

Bibliography

Eswaran SL, Chey WD, Han-Markey T, Ball S, Jackson K. A randomized controlled trial comparing the low FODMAP diet vs. modified NICE guidelines in US adults with IBS-D. Am J Gastroenterol. 2016;111:1824-1832. [PMID: 27725652] doi:10.1038/ajg.2016.434

Item 7 Answer: A

Educational Objective: Diagnose a Zenker diverticulum.

Barium esophagram is the most appropriate next diagnostic test for this patient. The patient's primary symptom of dysphagia associated with regurgitation of undigested food is the classic presentation of a Zenker diverticulum. Other commonly reported symptoms include halitosis, aspiration, and gurgling in the chest, but esophageal dysphagia is the most common symptom, reported by the majority of patients with a Zenker diverticulum. This type of diverticulum is located

in the cervical esophagus and may lead to complications such as aspiration and pneumonia. The best initial test is a barium esophagram, which will identify the diverticulum. Treatment is reserved for symptomatic patients and endoscopic diverticulectomy is favored where surgical expertise is available. In medical centers without such expertise, surgery by external neck incision is used.

Esophageal manometry is used when there is concern for a motility disorder, such as achalasia. Patients with motility disorders commonly report dysphagia to liquids or both solids and liquids; this patient's dysphagia to solid food does not suggest a motility disorder.

Ambulatory pH testing and impedance-pH testing can be valuable tools in identifying acid exposure within the esophagus. Impedance-pH testing can identify both acid and nonacid reflux. Testing can be done with a 48-hour wireless capsule or 24-hour transnasal catheter to detect active acid reflux. The wireless capsule has been shown to have better patient tolerability. A 24-hour pH manometry test is often used to further evaluate a patient with symptoms of gastroesophageal reflux disease that have not responded to medical therapy (usually a trial of an acid-reducing agent such as a proton pump inhibitor). A peptic stricture causing solid-food dysphagia may result from untreated reflux, but this patient reports dysphagia and regurgitation of undigested food, symptoms strongly suggestive of Zenker diverticulum.

Endoscopy is used to inspect the mucosal surface of the esophagus, stomach, and duodenum to identify conditions within the upper gastrointestinal tract. Because this patient's symptoms are consistent with the presentation of a Zenker diverticulum, a barium esophagram is a more appropriate choice than upper endoscopy. Although endoscopy may identify the diverticulum, there is risk for perforation if the endoscope enters the diverticulum.

KEY POINT

- Patients with dysphagia associated with regurgitation of undigested food should be evaluated with a barium esophagram for the presence of a Zenker diverticulum.

Bibliography

Smith CD. Esophageal strictures and diverticula. Surg Clin North Am. 2015;95:669-81. [PMID: 25965138] doi:10.1016/j.suc.2015.02.017

Item 8 Answer: C

Educational Objective: Diagnose hepatopulmonary syndrome.

Echocardiography with agitated saline is the most appropriate next test for this patient. Hepatopulmonary syndrome is a complication of cirrhosis caused by dilation of the pulmonary vasculature in the setting of advanced liver disease and portal hypertension. A high alveolar-arterial oxygen gradient results from functional shunting. Patients with hepatopulmonary syndrome usually have a preexisting diagnosis of liver disease and present with shortness of breath. Dilation of pulmonary vasculature occurs at the base of the lungs, so hypoxemia is most noted when patients are upright or sitting, when shunting is maximal. Classic features are platypnea (worsening shortness of breath in the upright position) and orthodeoxia (worsening arterial oxygen saturation in the upright position). Pulse oximetry is often used to screen for changes in the arterial oxygen saturation level with changes of position. The diagnosis is made by demonstrating an arterial oxygen tension less than 80 mm Hg (10.7 kPa) breathing ambient air, or an alveolar-arterial gradient of 15 mm Hg (2 kPa) or greater, along with evidence of intrapulmonary shunting on echocardiography with agitated saline or macroaggregated albumin study. The detection of intrapulmonary shunting of blood is best confirmed by echocardiography with agitated saline (also known as a bubble study), during which bubbles are identified in the left side of the heart after 5 beats, demonstrating that the shunting of blood is not intracardiac. Clinically significant hepatopulmonary syndrome is treated with supplemental oxygen and liver transplantation. Hepatopulmonary syndrome is a progressive condition that is ultimately fatal without liver transplantation.

Bronchoscopy is of no value in the diagnosis of platypnea or shunting disorders. It is potentially useful in the diagnosis of a pulmonary infiltrate or relief of an airway obstruction.

CT angiography can demonstrate the presence of large vascular shunts in the lungs but is rarely required to establish the diagnosis of hepatopulmonary syndrome. An additional benefit of CT angiography is its ability to show pulmonary emboli. In this patient, the presence of orthopnea is not consistent with pulmonary embolism. Transthoracic echocardiography with agitated saline is the gold standard for detecting pulmonary vascular dilatation and diagnosing hepatopulmonary syndrome.

Pulmonary function testing is useful for evaluating the presence of obstructive lung disease as well as restrictive lung disease. The normal pulmonary examination and normal chest radiography suggest that neither restrictive nor obstructive lung disease is contributing to this patient's presentation.

KEY POINT

- The diagnosis of hepatopulmonary syndrome is made by demonstrating an arterial oxygen tension less than 80 mm Hg (10.7 kPa) breathing ambient air, or an alveolar-arterial gradient of 15 mm Hg (2 kPa) or greater, along with evidence of intrapulmonary shunting on echocardiography with agitated saline or macroaggregated albumin study.

Bibliography

Krowka MJ, Fallon MB, Kawut SM, Fuhrmann V, Heimbach JK, Ramsay MA, et al. International Liver Transplant Society practice guidelines: diagnosis and management of hepatopulmonary syndrome and portopulmonary hypertension. Transplantation. 2016;100:1440-52. [PMID: 27326810] doi:10.1097/TP.0000000000001229

H

Item 9 Answer: A

Educational Objective: Treat acalculous cholecystitis.

Cholecystostomy tube placement is the most appropriate next step in management for this patient. She has risk factors as well as clinical and radiologic findings that are consistent with acalculous cholecystitis. Cholecystectomy is the definitive treatment for acalculous cholecystitis in stable patients. However, this patient is now hemodynamically unstable and, therefore, requires a temporizing cholecystostomy tube to allow time for her to stabilize and for gallbladder inflammation to improve before cholecystectomy. Risk factors for acalculous cholecystitis include diabetes mellitus, sepsis, trauma, burns, vasculitis, cardiovascular disease, mechanical ventilation, and total parenteral nutrition. Acalculous cholecystitis can present with biliary colic symptoms in the alert patient or with unexplained leukocytosis, sepsis, and jaundice in the critically ill patient. On physical examination, a mass may be palpated in the right upper quadrant. Ultrasound may show some of the features seen in this patient (distended gallbladder with wall thickening and pericholecystic fluid), gas bubbles in the fundus ("champagne sign"), or nonvisualization of the gallbladder altogether. No stones or sludge are present in the gallbladder. Management includes bacterial cultures, intravenous antibiotics to cover gram-negative organisms, and cholecystostomy tube placement in the unstable patient or cholecystectomy in the stable patient.

The role of endoscopic retrograde cholangiopancreatography with stenting is evolving. It has been used in case series to decompress the gallbladder in patients with acalculous cholecystitis, but it is not yet considered a first- or second-line treatment option due to less robust evidence to support this practice and the need for experienced endoscopists to perform the procedure.

A hepatobiliary iminodiacetic acid scan may be used when ultrasonography is equivocal, and it would show nonopacification of the gallbladder in cases of cholecystitis. It is unnecessary in this patient who has clinical and radiologic features consistent with acalculous cholecystitis.

This patient's ultrasonographic findings of a distended and thick-walled gallbladder with associated pericholecystic fluid and a lack of gallstones, in addition to her risk factors for acalculous cholecystitis, make further imaging, such as MR cholangiopancreatography, unnecessary and possibly dangerous due to the need for urgent gallbladder decompression.

KEY POINT

- Acalculous cholecystitis can present with biliary colic symptoms in the alert patient or with unexplained leukocytosis, sepsis, and jaundice in the critically ill patient.

Bibliography

Huffman JL, Schenker S. Acute acalculous cholecystitis: a review. Clin Gastroenterol Hepatol. 2010;8:15-22. [PMID: 19747982] doi:10.1016/j.cgh.2009.08.034

Item 10 Answer: B

Educational Objective: Prevent recurrent NSAID-related peptic ulcer disease.

Celecoxib plus omeprazole is the most appropriate treatment regimen for this patient. Patients who have bleeding ulcers while taking NSAIDs should discontinue NSAIDs permanently if possible. In cases where this is not possible, strategies to reduce the risk for recurrent bleeding should be instituted. Selective cyclooxygenase-2 (COX-2) inhibitors, such as celecoxib, preferentially inhibit the COX-2 isoenzyme, which primarily modulates pain and inflammation, and minimally inhibit the COX-1 isoenzyme, which promotes generation of the gastric mucosal protective barrier, decreases gastric acid secretion, and helps to maintain good mucosal blood flow. The risk for gastroduodenal ulcers and ulcer complications is significantly lower in patients taking COX-2 inhibitors compared with nonselective NSAIDs such as naproxen; however, in high-risk patients, such as those with previous peptic ulcer disease, a COX-2 inhibitor alone is no better than a nonselective NSAID coadministered with a proton pump inhibitor in preventing ulcer complications, with rebleeding rates of approximately 4% to 6% within 6 months.

A single 12-month randomized study showed an ulcer rebleeding rate of 0% in patients treated with celecoxib plus omeprazole compared with 9% in patients treated with a celecoxib alone. A direct comparison of naproxen plus omeprazole to celecoxib plus omeprazole in the prevention of NSAID bleeding in high-risk patients has not been performed. There is also evidence that COX-2 inhibitors and nonselective NSAIDs, with the possible exception of naproxen, increase the risk for cardiovascular complications; therefore, the decision to use a COX-2 inhibitor requires a harm-benefit analysis that weighs the gastrointestinal risks of an NSAID with the potential cardiovascular risks of a COX-2 inhibitor.

The use of ibuprofen, a nonselective NSAID, is no safer than the use of naproxen for lessening the likelihood of development of peptic ulcers.

Other gastroprotective agents, such as H_2 blockers (including ranitidine) and misoprostol, have been ineffective in preventing NSAID-related peptic ulcers in patients at low or moderate risk; however, their efficacy in high-risk patients (such as this patient with a previous NSAID-induced gastric ulcer) has not been demonstrated. Misoprostol is associated with adverse effects, including diarrhea and abdominal pain. Also, the required twice-daily dosing for ranitidine and four-times-daily dosing for misoprostol may lead to patient nonadherence, which further reduces the efficacy of such therapy.

KEY POINT

- In patients requiring NSAIDs, an evidence-based treatment strategy to prevent recurrent NSAID-induced peptic ulcers is the use of a cyclooxygenase-2 selective NSAID plus a proton pump inhibitor.

Bibliography

Laine L. CLINICAL PRACTICE. Upper gastrointestinal bleeding due to a peptic ulcer. N Engl J Med. 2016;374:2367-76. [PMID: 27305194] doi:10.1056/NEJMcp1514257

Item 11 Answer: D

Educational Objective: Manage follow-up colonoscopy for hyperplastic polyps.

This patient should undergo colonoscopy in 10 years. Serrated polyps are classified into three histologic types: hyperplastic polyps, sessile serrated polyps, and traditional serrated adenomas. Hyperplastic polyps are the most common type of serrated polyp. They are non-neoplastic and are composed of normal mucosal elements; small hyperplastic polyps, often found in the rectosigmoid colon, are believed to have no clinical significance. As a result, the interval until the next screening examination is 10 years, the same as for patients who do not have polyps found on baseline examination. Sessile serrated polyps (also known as sessile serrated adenomas) and traditional serrated adenomas are both neoplastic and are precursors to colorectal cancer; they should be completely excised. Substantial variability has been demonstrated in the ability of a pathologist to differentiate a hyperplastic polyp from a sessile serrated polyp; therefore, guidelines recommend managing large (>10 mm) hyperplastic polyps as if they are sessile serrated polyps.

The patient's family history of a second-degree relative with colon cancer diagnosed at age 80 years does not increase her risk for colon cancer or indicate the need for more frequent or early colonoscopy.

A 1-year surveillance interval is not appropriate for this patient. It is indicated in patients with more than 10 adenomas found on colonoscopy, those with a diagnosed polyposis syndrome, or those with Lynch syndrome. *Lynch syndrome* is the term used to describe patients who meet the Amsterdam II criteria for hereditary nonpolyposis colorectal cancer and have an identified germline mutation in one of the four mismatch repair genes (*MLH1, MSH2, MSH6, PMS2*) or the epithelial cell adhesion molecule gene (*EPCAM*).

A 3-year surveillance interval is recommended for patients who have three or more adenomas (or sessile serrated polyps) found on baseline colonoscopy, one adenoma larger than 10 mm in size, or an adenoma with any degree of villous or high-grade dysplasia.

A surveillance interval of 5 years is recommended for patients with two or fewer adenomas (or sessile serrated polyps) found on baseline colonoscopy and for patients with a first-degree relative with colon cancer diagnosed at an age younger than 60 years. Sessile serrated polyps are more frequently found in the proximal colon and may be difficult to detect on colonoscopy due to their flat appearance. Like tubular adenomas, surveillance colonoscopy is based on size and presence of dysplasia.

KEY POINT

- Patients with small (<10 mm) hyperplastic polyps on baseline colonoscopic examination should undergo surveillance colonoscopy in 10 years.

Bibliography

Lieberman DA, Rex DK, Winawer SJ, Giardiello FM, Johnson DA, Levin TR; United States Multi-Society Task Force on Colorectal Cancer. Guidelines for colonoscopy surveillance after screening and polypectomy: a consensus update by the US Multi-Society Task Force on Colorectal Cancer. Gastroenterology. 2012;143:844-57. [PMID: 22763141] doi:10.1053/j.gastro.2012.06.001

Item 12 Answer: B

H

Educational Objective: Treat acute cholangitis with biliary obstruction.

Endoscopic retrograde cholangiopancreatography (ERCP) is the most appropriate next step in the management of this patient. The patient presents with the Charcot triad of symptoms–fever, abdominal pain in the right upper quadrant, and jaundice–which is consistent with a diagnosis of cholangitis. In patients with evidence of biliary obstruction (as seen in this patient's findings on ultrasonography) and more than mild disease, biliary decompression with ERCP is an essential component of therapy. Obstruction is typically indicated by a dilated bile duct and persistently elevated liver enzyme levels. Indications for urgent ERCP include ongoing septic physiology (persistently elevated leukocyte count and temperature greater than 38.9 °C [102 °F]) despite resuscitative measures and antibiotics, hyperbilirubinemia (>5 mg/dL [85.5 µmol/L]), and altered mental status, which may also herald a worsened prognosis.

When duct decompression with ERCP is not possible, percutaneous cholangiography with biliary tube placement can be performed. Most patients with cholangitis also have cholelithiasis, elevated aminotransferase levels, and hyperbilirubinemia. Acute cholangitis is usually caused by *Escherichia coli*, *Klebsiella* species, *Pseudomonas* species, and enterococci and can progress to septic shock with or without liver abscess formation. The mainstay of therapy for cholangitis is the initiation of antibiotic therapy targeting enteric organisms; for mild to moderate community-acquired disease, options include cefazolin, cefuroxime, or ceftriaxone.

Patients who have complicated gallstone disease with evidence of choledocholithiasis should be considered for cholecystectomy; however, in the acute setting, this intervention should be deferred until after antibiotic therapy and biliary decompression with ERCP. Cholecystectomy will remove the source of future gallstones, but it will not decompress this patient's obstructed common bile duct or reduce the risk for sepsis.

MR cholangiopancreatography is a diagnostic test that is unlikely to yield additional information other than what this patient's ultrasound has already shown. In this patient with a very high likelihood of finding a common bile duct stone, a therapeutic procedure such as ERCP is more appropriate.

H CONT.

A percutaneous cholecystostomy can be used to treat cholecystitis, but in the setting of cholangitis, as in this patient, percutaneous cholecystostomy would not necessarily provide decompression of the biliary obstruction if the bile duct is obstructed above the insertion point of the cystic duct. Due to their higher rates of morbidity, percutaneous approaches to decompression of the biliary system should only be considered if endoscopic approaches are unavailable or contraindicated.

KEY POINT

- Patients who have cholangitis with evidence of biliary obstruction should be treated with antibiotic therapy and biliary decompression with endoscopic retrograde cholangiopancreatography.

Bibliography

Demehri FR, Alam HB. Evidence-based management of common gallstone-related emergencies. J Intensive Care Med. 2016;31:3-13. [PMID: 25320159] doi:10.1177/0885066614554192

Item 13 Answer: B

Educational Objective: Treat an esophageal stricture.

Endoscopy with dilation is the most appropriate treatment for this patient, who has eosinophilic esophagitis, refractory symptoms of dysphagia despite fluticasone therapy, and the finding of an esophageal stricture on endoscopy. Eosinophilic esophagitis can cause patients to develop a fibrostenotic esophageal stricture, which can be treated using endoscopy with dilation. Endoscopic dilation relieves the dysphagia but has no effect on underlying inflammation; therefore, medical therapy must be maintained. For unclear reasons, patients with eosinophilic esophagitis are more prone to mucosal tears with dilation than are patients with other stricturing diseases. It is imperative that the extent of dilation be limited in amount to avoid these complications; multiple dilations may be required to adequately treat the dysphagia.

Most patients respond quickly after initiation of the fluticasone; therefore, continued or increased fluticasone alone will not alleviate the patient's dysphagia symptoms. Continued fluticasone may be necessary as maintenance therapy for this patient. Eosinophilic esophagitis is a chronic disease that often recurs after treatment is stopped; therefore, repeat or maintenance therapy may be needed.

Omeprazole and other proton pump inhibitors (PPIs) are not effective in relieving dysphagia due to stricture. PPIs can reduce inflammation and eosinophil count and are often used before initiating fluticasone therapy to determine if the patient has PPI-responsive eosinophilic esophagitis.

Limited data suggest that prednisone may be useful in patients with eosinophilic esophagitis who do not experience relief of symptoms with fluticasone therapy. However, like the swallowed aerosolized glucocorticoids, relapse is common when the medication is stopped, and relatively high doses are typically required, which carry associated risks of immunosuppression and other side effects. Additionally, this patient's esophageal stricture is fibrotic rather than inflammatory, so oral prednisone would not be effective for his dysphagia symptoms.

KEY POINT

- Esophageal stricture in patients with eosinophilic esophagitis requires treatment with endoscopic dilation when symptoms do not respond to medical therapy.

Bibliography

Dellon ES, Gonsalves N, Hirano I, Furuta GT, Liacouras CA, Katzka DA; American College of Gastroenterology. ACG clinical guideline: evidenced based approach to the diagnosis and management of esophageal eosinophilia and eosinophilic esophagitis (EoE). Am J Gastroenterol. 2013; 108:679-92; quiz 693 [PMID: 23567357] doi:10.1038/ajg.2013.71

Item 14 Answer: A

H

Educational Objective: Treat toxic megacolon.

This patient requires colectomy. He has a history of ulcerative colitis and presents with fever, tachycardia, hypotension, and a dilated colon on abdominal radiography; the diagnosis is toxic megacolon, a life-threatening condition that complicates approximately 5% of acute, severe cases of ulcerative colitis. Toxic megacolon is defined by the presence of toxicity (fever, tachycardia, hypotension, and leukocytosis) along with evidence of colonic dilation. Patients with this condition have an increased risk for complications such as colonic perforation. Intravenous fluid resuscitation, intravenous high-dose corticosteroids, and broad-spectrum antibiotics (for example, a third-generation cephalosporin with metronidazole) should be initiated in patients with toxic megacolon. Management requires close collaboration with a surgeon; therefore, emergent surgical consultation for consideration of subtotal colectomy is required because of the impending risk for perforation and peritonitis in patients with toxic megacolon. Some patients may respond to medical therapy with high-dose glucocorticoids (in addition to intravenous fluids and broad-spectrum antibiotics), but there should be a low threshold for surgical intervention due to the potential harms associated with toxic megacolon.

Colonoscopy is contraindicated because it would increase the risk for perforation and complications related to toxic megacolon.

CT of the abdomen and pelvis is the optimal imaging modality to evaluate suspected toxic megacolon and may better assess for the presence of colonic necrosis; however, in this case, the diagnosis of toxic megacolon can be confidently made based on the patient's presentation and abdominal radiography, and urgent surgical evaluation is necessary.

Stool studies for enteric pathogens may identify a precipitant of toxic megacolon but require a minimum of 24 hours before test results are received. Surgical consultation should not be delayed to wait for results of stool testing.

KEY POINT

- Toxic megacolon is defined by the presence of toxicity and evidence of colonic dilation; it requires prompt surgical treatment.

Bibliography

Seah D, De Cruz P. Review article: the practical management of acute severe ulcerative colitis. Aliment Pharmacol Ther. 2016;43:482-513. [PMID: 26725569] doi:10.1111/apt.13491

Item 15 Answer: B

Educational Objective: Diagnose microscopic colitis.

Based on the patient's age, sex, and clinical presentation, microscopic colitis is the most likely diagnosis. Microscopic colitis is the underlying cause in 10% to 15% of patients with chronic, watery diarrhea. In contrast to inflammatory bowel disease, microscopic colitis is more common in older persons and does not cause endoscopically visible inflammation. The symptoms of microscopic colitis are similar to other chronic causes of nonbloody diarrhea, such as celiac disease and irritable bowel syndrome; therefore, colonic mucosal biopsies are required for diagnosis. Lymphocytic and collagenous colitis are the two subtypes of microscopic colitis, and they are distinguishable only by histology. Random biopsies from multiple colonic segments are recommended to establish the diagnosis because the disease can be patchy. In some patients, certain medications (such as NSAIDs and proton pump inhibitors) have been implicated as causative agents. Microscopic colitis is associated with other autoimmune diseases such as diabetes mellitus and psoriasis. The association with celiac disease is of particular clinical importance because the symptoms of these conditions are similar. Therefore, in patients with celiac disease or microscopic colitis whose symptoms do not respond to appropriate therapy, the other condition must be ruled out.

Giardia lamblia is a common infectious cause of persistent diarrhea in immunocompetent patients in developed countries and should be considered in patients with exposure to young children or potentially contaminated water, such as lakes and streams. This patient has no risk factors for *Giardia* infection.

Small intestinal bacterial overgrowth (SIBO) causes diarrhea, often with bloating, flatulence, and weight loss. Several conditions can predispose patients to SIBO due to effects on stomach acid, intestinal transit, or disruption of normal antibacterial defense mechanisms. Gastric bypass surgery is an increasingly common cause of SIBO. The absence of malabsorption symptoms and weight loss make this diagnosis unlikely.

Ulcerative colitis typically presents with bloody diarrhea and abdominal discomfort, the severity of which is related to the extent and severity of inflammation. Because ulcerative colitis typically involves the rectum, patients with this condition commonly present with tenesmus, urgency, rectal pain, and fecal incontinence. Some patients with distal inflammation can present with constipation owing to rectal spasm and stasis of stool. Fever and weight loss suggest severe disease. The patient's symptoms are not typical for ulcerative colitis.

KEY POINT

- Microscopic colitis is a cause of nonbloody, watery diarrhea in older adults and is diagnosed by colonoscopy with random biopsies from multiple colonic segments.

Bibliography

Pardi DS. Diagnosis and management of microscopic colitis. Am J Gastroenterol. 2017;112:78-85. [PMID: 27897155] doi:10.1038/ajg.2016.477

Item 16 Answer: D

H

Educational Objective: Treat autoimmune pancreatitis.

Prednisone is the most appropriate treatment for this patient. Based on his typical symptom of painless jaundice and the characteristic "sausage-shaped" pancreas on imaging, the patient has type 1 autoimmune pancreatitis, a frequent manifestation of IgG4 disease. He also has associated IgG4-related conditions, sialadenitis, and probable retroperitoneal fibrosis. Autoimmune pancreatitis is rare and has an unclear pathogenesis. Type 1 autoimmune pancreatitis is a systemic fibroinflammatory disease, defined as an inflammatory condition causing tissue damage and scarring. Pancreatic involvement is only one manifestation of IgG4 disease, which is characterized by abundant IgG4-producing plasma cells seen on tissue biopsy. Most IgG4-related conditions are characterized by plasma-cell infiltration of the affected tissue and the clinical consequences that infiltration entails. Almost any organ can be involved; lymph nodes are frequently affected. The initial treatment is oral prednisone with a taper over 2 to 3 months, and symptoms usually resolve within 2 to 4 weeks with treatment. Almost all patients (>90%) enter clinical remission in response to glucocorticoids. Treatment response may be limited by the amount of fibrosis present before initiation of therapy. The relapse rate is approximately 30% in type 1 autoimmune pancreatitis.

Azathioprine is an immunosuppressive drug that has been used to treat relapsing IgG4-related disease and can be used as a glucocorticoid-sparing agent. It may take 6 to 8 weeks to reach a therapeutic drug level and provoke a clinical response. Therefore, it is not considered initial first-line therapy for symptomatic IgG4-related disease.

Endoscopic retrograde cholangiopancreatography with bile-duct stenting is usually not required in patients with autoimmune pancreatitis because most patients' symptoms respond quickly to oral prednisone. Glucocorticoid therapy also treats the underlying immunologic disorder, making it the preferred first-line treatment.

Pancreaticoduodenectomy (Whipple surgery) is not indicated in patients with autoimmune pancreatitis. It may be considered to treat pancreatic adenocarcinoma occurring in the head of the pancreas, which can be mistaken for autoimmune pancreatitis. Because this patient's histology findings confirm IgG4-related disease, a trial of immunosuppressive therapy is the most appropriate treatment.

KEY POINT

- Almost all patients (>90%) with autoimmune pancreatitis enter clinical remission in response to glucocorticoids.

Bibliography

Okazaki K, Uchida K. Autoimmune pancreatitis: the past, present, and future. Pancreas. 2015;44:1006-16. [PMID: 26355544] doi:10.1097/MPA.0000000000000382

H Item 17 Answer: B

Educational Objective: Treat acute fatty liver of pregnancy with immediate delivery of the fetus.

Immediate delivery of the fetus is the most appropriate next step in management. This patient has findings of acute fatty liver of pregnancy, which is a rare but serious condition occurring most commonly in the third trimester. Women with this condition typically present with a 1- to 2-week history of nausea and vomiting, right-upper-quadrant or epigastric pain, headache, jaundice, anorexia, and/or polyuria and polydipsia (due to associated transient diabetes insipidus). Maternal and neonatal mortality rates are high in this setting. This patient's presentation with coagulopathy, hypoglycemia, and somnolence consistent with hepatic encephalopathy are indications of acute liver failure, which can result from acute fatty liver of pregnancy. Immediate delivery of the fetus is indicated to prevent fetal mortality and to reverse the mother's liver failure and improve her condition. Prompt delivery typically results in improvement of the mother's medical condition within 48 to 72 hours. Acute fatty liver of pregnancy can reoccur in subsequent pregnancies. It is also associated with long-chain 3-hydroxyacyl CoA dehydrogenase deficiency, and affected women and their children should be screened for this deficiency. HELLP (Hemolysis, Elevated Liver enzymes, and Low Platelets) syndrome can also occur in the third trimester of pregnancy. It has similarly life-threatening consequences and also requires emergent delivery of the fetus to resolve the condition. HELLP syndrome can present similarly to acute fatty liver of pregnancy in that manifestations of liver failure are present.

This patient's ultrasound showed no dilation of bile ducts, and no stones were seen in the common bile duct; therefore, endoscopic retrograde cholangiopancreatography is not indicated.

This patient's drowsiness is due to impending liver failure. Lactulose, which is used for treatment of hepatic encephalopathy in patients with chronic liver disease, is not indicated for patients with acute liver failure because it may exacerbate symptoms of ileus, and there is no evidence of benefit in the acute setting. Any symptoms referable to hepatic encephalopathy will resolve with delivery of the fetus, which resolves acute fatty liver of pregnancy.

Intrahepatic cholestasis of pregnancy occurs during the second or third trimester and resolves after delivery. The most common laboratory findings are elevated bilirubin and alkaline phosphatase levels. The condition is believed to result from sex hormone–induced inhibition of bile salt export from hepatocytes. It is treated with ursodeoxycholic acid, which can result in alleviation of symptoms. Although the maternal effects of intrahepatic cholestasis of pregnancy are mild, it can cause fetal distress and premature labor. Because this patient's clinical profile is not compatible with intrahepatic cholestasis of pregnancy, ursodeoxycholic acid therapy is not indicated.

KEY POINT

- The fetus should be delivered immediately upon recognition of acute fatty liver of pregnancy.

Bibliography

Bacak SJ, Thornburg LL. Liver failure in pregnancy. Crit Care Clin. 2016;32:61-72. [PMID: 26600444] doi:10.1016/j.ccc.2015.08.005

Item 18 Answer: A

Educational Objective: Treat a gallbladder polyp.

Cholecystectomy is indicated for this patient with a gallbladder polyp and gallstones because of the increased risk for gallbladder cancer when the two conditions coexist. The finding of a gallbladder polyp larger than 1 cm in size is an indication for cholecystectomy, even if the patient is asymptomatic. An additional indication for prophylactic cholecystectomy is the presence of a gallbladder polyp larger than 8 mm in size in the setting of primary sclerosing cholangitis. Gallbladder polyps are found on approximately 5% of ultrasounds. Although only a small percentage of gallbladder polyps are neoplastic (adenoma or adenocarcinoma), the risk for neoplasia increases as polyp size increases.

Further evaluation of the polyp with abdominal CT, endoscopic retrograde cholangiopancreatography, or MR cholangiopancreatography is not indicated because gallbladder ultrasonography is adequately sensitive for the detection of gallbladder lesions. These tests could be considered if this patient had symptoms or elevated liver chemistry tests suggesting bile-duct obstruction or malignancy.

In a patient with an 8-mm gallbladder polyp in the absence of gallstones or primary sclerosing cholangitis, repeat ultrasonography in 6 months would be indicated. However, follow-up ultrasonography is not appropriate for this patient with a gallbladder polyp and gallstones, which increase the risk for gallbladder cancer.

Bile acids, such as ursodeoxycholic acid, work by reducing biliary cholesterol secretion, thereby increasing biliary bile-acid concentrations and, as a result, reducing the cholesterol saturation index and gallstone size. Bile-acid therapy works best for small, primarily cholesterol gallstones and is indicated in patients who cannot or will not undergo laparoscopic cholecystectomy. More importantly, ursodeoxycholic acid therapy would not address this patient's gallbladder polyp.

KEY POINT

- The finding of a gallbladder polyp larger than 1 cm in size, or a polyp of any size associated with gallstones, is an indication for cholecystectomy even if the patient is asymptomatic.

Bibliography

Gallahan WC, Conway JD. Diagnosis and management of gallbladder polyps. Gastroenterol Clin North Am. 2010;39:359-67, x. [PMID: 20478491] doi:10.1016/j.gtc.2010.02.001

Item 19 Answer: C

Educational Objective: Evaluate for *Helicobacter pylori* eradication following treatment.

A urea breath test is the most appropriate next test for this patient. Testing to confirm eradication should be pursued in all cases of identified and treated *Helicobacter pylori* infection because of the established risks for peptic ulcer disease and gastric malignancy in patients with chronic *H. pylori* infection. To maximize the accuracy of testing to confirm eradication, testing should be performed a minimum of 4 weeks after completion of *H. pylori* eradication therapy and after proton pump inhibitor therapy has been discontinued for 1 to 2 weeks and H_2-blockers for 1 to 2 days. The test chosen should be highly accurate in identifying active infection; appropriate tests include the urea breath test, fecal antigen test, or biopsy-based testing. The urea breath test is limited by need for specialized equipment and personnel and by its cost. The fecal antigen test is limited by the collection of stool but is less expensive than the urea breath test. Biopsy-based testing is expensive and invasive. Unless upper endoscopy is indicated for other reasons, noninvasive testing modalities (the urea breath test or the fecal antigen test) are more appropriate for confirmation of eradication or assessment for reinfection. Both testing modalities are equivalent with regard to accuracy; therefore, the specific test chosen should be based on patient preference and/or test availability.

Serologic antibody testing is an inaccurate means of testing to confirm eradication because antibodies can remain present despite successful eradication of active infection; therefore, serologic testing cannot distinguish between past and current *H. pylori* infection.

Invasive (endoscopic) tests for *H. pylori* include the rapid urease test, histology, and culture; all invasive testing modalities identify active infection. Due to its expense and invasive nature, biopsy-based testing should be reserved for patients requiring a repeat upper endoscopy for other reasons (for example, follow-up endoscopy for high-risk gastric ulcer). In this patient with no indications for repeat upper endoscopy, one of the two noninvasive tests, either the urea breath test or fecal antigen test, is preferable.

KEY POINT

- After eradication therapy for *Helicobacter pylori* infection, eradication should be confirmed using the urea breath test or fecal antigen test.

Bibliography

Lopes AI, Vale FF, Oleastro M. *Helicobacter pylori* infection–recent developments in diagnosis. World J Gastroenterol. 2014;20:9299-313. [PMID: 25071324] doi:10.3748/wjg.v20.i28.9299

Item 20 Answer: B

H

Educational Objective: Treat gallstone pancreatitis with prompt cholecystectomy.

Laparoscopic cholecystectomy before discharge from the hospital is the most appropriate treatment. Gallstone acute pancreatitis can be diagnosed based on elevated liver transaminases on presentation, a lipase level elevated to more than three times the upper limit of normal, characteristic severe abdominal pain, and ultrasonographic evidence of cholelithiasis. This patient showed clinical improvement within 3 days of hospitalization. Her laboratory values have normalized, suggesting spontaneous passage of a gallstone through the common bile duct, which occurs in most patients with gallstone pancreatitis. In a multicenter randomized controlled trial, same-admission cholecystectomy reduced rates of gallstone-related complications compared with interval cholecystectomy 25 to 30 days after hospital discharge for patients with mild gallstone pancreatitis.

Endoscopic retrograde cholangiopancreatography (ERCP) is indicated within the first 24 hours for patients with acute pancreatitis and ascending cholangitis (fever, abdominal pain, and jaundice) due to choledocholithiasis. If there is evidence of ongoing biliary obstruction in patients hospitalized with acute pancreatitis, ERCP may be indicated to remove a retained gallstone from the common bile duct. This patient's symptoms and laboratory abnormalities resolved quickly, which supports the spontaneous passage of a gallstone without evidence of ongoing biliary obstruction.

MR cholangiopancreatography (MRCP) can be used to identify causes of biliary obstruction. MRCP is not needed in this patient because she has normal-caliber bile ducts on abdominal ultrasonography and normal liver chemistry test results, indicating that a biliary obstruction is unlikely.

Ursodeoxycholic acid has been used to medically dissolve small cholesterol gallstones in patients who are not candidates for surgery. The medication works slowly and may take longer than 1 year to dissolve small stones, leaving patients at risk for recurrent attacks of gallstone pancreatitis or other gallstone-related complications. This patient is young and without comorbidities, making surgery a more appropriate treatment.

KEY POINT

- Same-admission cholecystectomy reduces rates of gallstone-related complications compared with cholecystectomy after hospital discharge for patients with mild gallstone pancreatitis.

Bibliography

da Costa DW, Bouwense SA, Schepers NJ, Besselink MG, van Santvoort HC, van Brunschot S, et al; Dutch Pancreatitis Study Group. Same-admission versus interval cholecystectomy for mild gallstone pancreatitis (PONCHO): a multicentre randomised controlled trial. Lancet. 2015;386:1261-8. [PMID: 26460661] doi:10.1016/S0140-6736(15)00274-3

H

Item 21 Answer: B

Educational Objective: Treat cholangitis using endoscopic retrograde cholangiopancreatography.

Endoscopic retrograde cholangiopancreatography (ERCP) is the most appropriate next test for this patient. This patient with primary sclerosing cholangitis (PSC) presents with fever, rigors, right-upper-quadrant pain, and leukocytosis, all of which are consistent with bacterial cholangitis. Indications for ERCP in patients with PSC are bacterial cholangitis (as in this patient), increasing jaundice, increasing pruritus, or a dominant stricture seen on imaging. Symptoms of bacterial cholangitis, increasing jaundice, and pruritus can signify strictures that may improve with dilation or stenting, or, alternatively, removing sludge or stone debris in the bile ducts via ERCP. A dominant stricture in a patient with PSC must be evaluated for cholangiocarcinoma by obtaining biliary brushings for cytologic examination, and, if available, fluorescent in situ hybridization to evaluate chromosomal abnormalities.

The CA 19-9 level will be elevated in the setting of bacterial cholangitis. The risk for false-positive results makes CA 19-9 measurement inappropriate in this context. CA 19-9 levels can be used as an adjunctive tool in the diagnosis of cholangiocarcinoma, but the diagnosis cannot be made based only on this marker.

IgG4 levels should be checked in patients with a new diagnosis of presumed PSC because IgG4 cholangitis is a steroid-responsive condition, whereas PSC is not. Testing for IgG4 does not assist in the management of this patient's cholangitis.

A percutaneous transhepatic biliary tube can be employed when ERCP is unsuccessful at traversing a biliary stricture, but because of its invasiveness and inconvenience, it would not be a first-line tool for assessing and treating a patient with bacterial cholangitis.

The role of PET in the evaluation and management of cholangiocarcinoma is evolving. However, this is not the test of choice in a patient with bacterial cholangitis because it does not allow for biliary intervention. Furthermore, PET scans can be associated with false-positive results for malignancy in the setting of bacterial cholangitis, and also with false-negative results due to the desmoplastic reaction of cholangiocarcinoma tumors.

KEY POINT

- Indications for endoscopic retrograde cholangiopancreatography in patients with primary sclerosing cholangitis are bacterial cholangitis, increasing jaundice, increasing pruritus, or a dominant stricture on imaging.

Bibliography

Lindor KD, Kowdley KV, Harrison ME; American College of Gastroenterology. ACG clinical guideline: primary sclerosing cholangitis. Am J Gastroenterol. 2015;110:646-59; quiz 660. [PMID: 25869391] doi:10.1038/ajg.2015.112

Item 22 Answer: B

Educational Objective: Evaluate rectal bleeding in a young patient.

Colonoscopy is the most appropriate next step in management for this patient. Her symptoms of weight loss, abdominal pain, and rectal bleeding with iron deficiency anemia warrant further evaluation with colonoscopy. Inflammatory bowel disease is a possibility in this patient; however, colon cancer also needs to be excluded. In the United States, the overall incidence of colon cancer has decreased by 3% to 4% since the early 2000s; however, in adults younger than age 50 years, the incidence of colorectal cancer is increasing at a rate of 2.1% per year.

Anoscopy enables a limited examination and would not assist in evaluating the patient's iron deficiency anemia and weight loss.

Flexible sigmoidoscopy allows examination of only the lower third of the colon, and if negative, a full colonoscopy would still be required. There has been a gradual shift from left-sided to right-sided colon cancers. A number of factors have been suggested to explain this, including inadequate colon preparation, incomplete colonoscopy, and difficulty recognizing serrated polyps that are typically flat and occur more often on the right side. However, there also appears to be a true increase in tumors of the proximal and right colon that may be missed if only a sigmoidoscopy is performed.

Hemorrhoids are arteriovenous communications covered by cushions of connective tissue in the anal canal. Internal hemorrhoids cause most hemorrhoidal symptoms (bright red blood dripping in the toilet bowl or seen on toilet paper, with no accompanying pain; a protrusion of tissue; itching; and pain). Patients with alarm features (such as unexplained weight loss, change in bowel movements, iron deficiency anemia, age older than 50 years, or personal or family history of colorectal cancer or inflammatory bowel disease) warrant colonoscopy. Initial treatment of internal and external hemorrhoids consists of dietary and lifestyle modifications to soften bowel movements and avoid constipation, straining, and prolonged time on the toilet. Increased fiber intake has been shown to reduce symptomatic prolapse and bleeding. Local therapy such as topical anesthetics and glucocorticoids may relieve pain and itching, but data to support their use are scant.

KEY POINT

- Red-flag symptoms such as rectal bleeding with iron deficiency anemia, abdominal pain, and weight loss should prompt evaluation by colonoscopy for colorectal cancer regardless of the patient's age or the presence of bleeding hemorrhoids.

Bibliography

Inra JA, Syngal S. Colorectal cancer in young adults. Dig Dis Sci. 2015;60:722-33. [PMID: 25480403] doi:10.1007/s10620-014-3464-0

Item 23 Answer: D

Educational Objective: Diagnose narcotic bowel syndrome.

Narcotic bowel syndrome is the most likely diagnosis in this patient. Narcotic bowel syndrome, also known as opiate-induced gastrointestinal hyperalgesia, is a centrally mediated disorder of gastrointestinal pain characterized by a paradoxical increase in abdominal pain with increasing doses of narcotics. Many patients are prescribed opioid pain medication for an unrelated medical condition but have increasing pain over time despite clinical evidence of improvement or resolution of the initial condition. Patients often fear tapering off opioids and believe the opioids are the only treatment that alleviates their pain.

Chronic pancreatitis may result from a severe episode of acute pancreatitis or recurrent episodes of acute pancreatitis. It may require opioid pain medication for flares of pain or for constant, daily pain, but the pain is usually relieved with opioids. This patient only had one episode of uncomplicated pancreatitis and has no other risk factors for chronic pancreatitis and no evidence of chronic pancreatitis (pancreatic calcifications) on abdominal imaging.

Distal intestinal obstruction syndrome is caused by thickened intestinal contents that completely or partially block the small intestinal lumen in patients with cystic fibrosis. It is characterized by progressive, crampy abdominal pain in the right lower quadrant, sometimes progressing to vomiting. This patient has no history of cystic fibrosis and no symptoms of a small-bowel obstruction making this an unlikely diagnosis.

The diagnosis of irritable bowel syndrome is typically made in the presence of recurrent abdominal pain or discomfort at least 3 days per month in the last 3 months that is associated with two or more of the following: relief with defecation, onset associated with a change in frequency of stool, or onset associated with a change in form (appearance) of stool. While this patient has abdominal pain and constipation, her symptoms are worsened with eating, not relieved with defecation, and the onset of pain is clearly tied to an acute abdominal diagnosis and treatment with an opioid, making IBS an unlikely diagnosis.

KEY POINT

- Narcotic bowel syndrome, also known as opiate-induced gastrointestinal hyperalgesia, is a centrally mediated disorder of gastrointestinal pain characterized by a paradoxical increase in abdominal pain with increasing doses of opioids.

Bibliography

Keefer L, Drossman DA, Guthrie E, Simrén M, Tillisch K, Olden K, et al. Centrally mediated disorders of gastrointestinal pain. Gastroenterology. 2016. [PMID: 27144628] doi:10.1053/j.gastro.2016.02.034

Item 24 Answer: B

Educational Objective: Treat pain in chronic pancreatitis.

The most appropriate initial treatment is the use of NSAIDs, a low-fat diet, and smoking cessation. The hallmark symptom of chronic pancreatitis is abdominal pain that often radiates to the back; however, pain can be absent. Pain is typically intermittent, with attacks interrupted by varying pain-free intervals. Constant pain may occur from local anatomic causes (compressing pseudocyst, biliary or pancreatic duct stricture) or from visceral hyperalgesia (increased sensation in response to stimuli) from chronic narcotic use and centralization of pain. Management focuses on reducing pain and detecting and treating complications. Unfortunately, the treatment of persistent pain is difficult, and the evidence supporting most treatment modalities is of low quality and often contradictory. Most authorities recommend that persistent pain be treated in a stepwise approach beginning with lifestyle modification (discontinue alcohol and cigarettes), use of simple analgesics, adding low-dose tricyclic antidepressants, and gabapentinoids (gabapentin and pregabalin). Smoking has been identified as an important and independent risk factor for chronic pancreatitis, and cessation of smoking and alcohol use is recommended to prevent recurrent attacks of pancreatitis. An important goal is to control pain with opioid-sparing adjunctive agents to minimize chronic opioid use, owing to concerns for opioid dependence and gastrointestinal side effects. This would especially be true in a patient with a history of opioid or other substance abuse, such as this patient.

Nerve blocks, such as celiac plexus blocks, and neurolysis procedures are not recommended for the management of pain related to chronic pancreatitis because the response rate is low (15%), and pain relief, if achieved at all, is short-lived.

Opioid pain medications, such as oxycodone, are used in acute pancreatitis and during acute flares of chronic pancreatitis, but they should be avoided in the long-term management of ongoing pain due to the risk for hyperesthesia and the development of tolerance and/or addiction.

Pancreatic enzyme replacement therapy is often recommended for the treatment of persistent pain associated with chronic pancreatitis. A large systematic review found conflicting evidence for the efficacy of pancreatic enzymes in relieving pain in patients with chronic pancreatitis but found that they may improve fat absorption. If used, acid suppression therapy with a proton pump inhibitor should be given as an adjunct to uncoated pancreatic enzymes in order to reduce the inactivation of enzymes by gastric acid. Simple analgesics and lifestyle modifications can be effective for some patients and should be initiated first.

KEY POINT

- Treatment of chronic pancreatitis-related persistent pain should proceed in a stepwise approach beginning with lifestyle modifications (discontinue alcohol and cigarettes) and the use of simple analgesics (acetaminophen, NSAIDs).

Bibliography

Majumder S, Chari ST. Chronic pancreatitis. Lancet. 2016;387:1957-66. [PMID: 26948434] doi:10.1016/S0140-6736(16)00097-0

Item 25 Answer: A

Educational Objective: Treat hepatitis B virus–related polyarteritis nodosa.

The most appropriate treatment is entecavir. Hepatitis B virus (HBV)–related polyarteritis nodosa (PAN) is the most likely diagnosis in this patient. The patient has fever, arthralgia, and evidence of cutaneous vasculitis (rash). There is also evidence of hepatitis (elevated bilirubin and aminotransferase levels) likely related to his use of intravenous drugs. Testing for hepatitis B surface antigen and hepatitis B e antigen is positive, as is IgM antibody to hepatitis B core antigen, with a significant HBV DNA viral load; all of these results are consistent with a recent HBV infection. PAN and mixed cryoglobulinemia are rare HBV-associated vasculitides. This patient has undetectable serum cryoglobulins, excluding the diagnosis of mixed cryoglobulinemia. There are no data from randomized trials to guide therapy in patients with HBV-related PAN. Patients with HBV infection and mild manifestations of PAN are usually treated with antiviral agents such as entecavir. Patients (such as this one) with mild PAN have constitutional symptoms, arthritis or arthralgia, anemia, and skin lesions. More severe disease is characterized by organ dysfunction (for example, myocarditis, kidney insufficiency and hypertension, mononeuritis multiplex) or life-threatening systemic manifestations. Patients with severe manifestations of PAN are often treated with an antiviral agent and a short course of prednisone and plasma exchange.

Prednisone and cyclophosphamide are agents typically used to treat mild and severe manifestations of idiopathic PAN, the most commonly recognized form of PAN. Because this patient has HBV-related PAN, treating the causative viral infection with an antiviral agent is the preferred management.

Sofosbuvir and ledipasvir are direct-acting antiviral agents used to treat hepatitis C virus (HCV) infection and would be an appropriate choice for mild HCV-related PAN. However, this patient's hepatitis C antibody is negative and these agents are not indicated.

Tenofovir, emtricitabine, and raltegravir are used to treat HIV infection. This drug combination would be an appropriate choice for HIV-related PAN, but the patient's HIV test is negative and these agents are not indicated. Tenofovir alone would be a reasonable treatment for this patient.

KEY POINT

- Mild hepatitis B virus–related polyarteritis nodosa is treated with antiviral agents.

Bibliography

Forbess L, Bannykh S. Polyarteritis nodosa. Rheum Dis Clin North Am. 2015;41:33-46, vii. [PMID: 25399938] doi:10.1016/j.rdc.2014.09.005

Item 26 Answer: A

H

Educational Objective: Treat acute necrotic pancreatitis with enteral feeding.

Placement of a nasoenteric tube for enteral feeding is the most appropriate next step in this patient's management. The patient has taken nothing by mouth (NPO) since hospitalization 4 days earlier and requires nutritional support. She continues to have abdominal pain requiring intravenous opioid pain medication, as well as nausea and no appetite. Enteral nutrition is preferred in patients with acute pancreatitis because of the benefit of maintaining a healthy mucosal barrier in the gut to prevent translocation of bacteria. Both nasogastric and nasojejunal enteral feeding are safe and have comparable effectiveness. Studies show nasogastric tube feeding is well tolerated in these patients, and placement of a nasogastric tube may be easier, more cost effective, and faster than placement of a nasojejunal tube.

Total parenteral nutrition (TPN) is discouraged in patients with acute pancreatitis because the mucosal barrier is not maintained when patients are NPO for prolonged periods, which may lead to higher rates of bacterial translocation into necrotic pancreatic tissue. TPN also increases the risk for bacterial and fungal bloodstream infections, as well as venous thrombosis associated with more proximal indwelling intravenous catheters required for TPN administration.

Cholecystectomy will not be an option for this patient in the near future (likely not during this hospitalization) because she has severe necrotic acute pancreatitis. Maintaining NPO status for a prolonged period of time before surgery is not appropriate clinical management of her nutritional needs.

There are no data to support withholding feeding in patients with acute pancreatitis based on enzyme levels. Lipase levels three to five times the upper level of normal are used as diagnostic criteria for acute pancreatitis but have no impact on clinical management decisions.

KEY POINT

- Enteral nutrition is preferred in patients with acute pancreatitis because of the benefit of maintaining a healthy gut mucosal barrier to prevent translocation of bacteria.

Bibliography

Forsmark CE, Vege SS, Wilcox CM. Acute pancreatitis. N Engl J Med. 2016;375:1972-1981. [PMID: 27959604]

Item 27 Answer: C

H

Educational Objective: Prevent spontaneous bacterial peritonitis.

Initiation of indefinite primary prophylaxis with ciprofloxacin is the most appropriate next step in the management of this patient with ascites. Patients with ascites are at risk for developing spontaneous bacterial peritonitis (SBP), a common infection in patients with cirrhosis. SBP has a mortality

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rate of 20%. Long-term primary antibiotic prophylaxis may reduce mortality in patients at high risk for SBP. Criteria for patients at high risk include an ascitic-fluid total protein level less than 1.5 g/dL (15 g/L) in conjunction with any of the following: serum sodium level less than or equal to 130 mEq/L (130 mmol/L), serum creatinine level greater than or equal to 1.2 mg/dL (106.1 µmol/L), blood urea nitrogen level greater than or equal to 25 mg/dL (8.9 mmol/L), serum bilirubin level greater than or equal to 3 mg/dL (51.3 µmol/L), or Child-Turcotte-Pugh class B or C cirrhosis. Patients who have had a bout of SBP should also receive lifelong antibiotic prophylaxis to reduce the risk for recurrence. In the setting of variceal hemorrhage, a limited 7-day course of antibiotics initiated at the time of bleeding is indicated to prevent infectious complications from intestinal bacterial translocation.

Increasing this patient's propranolol is not indicated because, although β-blocker therapy can reduce the risk for variceal bleeding, the patient already has a pulse rate of less than 60/min. Nonselective β-blockers such as propranolol may be associated with higher transplant-free survival in patients with cirrhosis overall but may decrease transplant-free survival in the first 6 months after SBP or in patients with refractory ascites, and discontinuation should be considered at that time.

Albumin infusion may decrease the frequency of hepatorenal syndrome and improves survival in patients with SBP, but its role in primary prevention of SBP is undefined and its use for primary prevention not recommended.

Systemic blood pressure decreases in patients with decompensated cirrhosis resulting in reductions in renal perfusion and glomerular filtration rate. This leads to elevated levels of vasopressin, angiotensin, and aldosterone. ACE inhibitors, such as lisinopril, and angiotensin receptor blockers impair these compensatory efforts to maintain blood pressure and can worsen kidney perfusion in the setting of ascites due to portal hypertension; therefore, initiating lisinopril is inappropriate in this patient.

KEY POINT

- Primary prophylactic antibiotic therapy is indicated for patients at high risk for the development of spontaneous bacterial peritonitis, including patients with very low ascitic-fluid protein levels and those with advanced liver failure.

Bibliography

Solà E, Solé C, Ginès P. Management of uninfected and infected ascites in cirrhosis. Liver Int. 2016;36 Suppl 1:109-15. [PMID: 26725907] doi:10.1111/liv.13015

Item 28 Answer: A

Educational Objective: Diagnose dumping syndrome after gastrojejunostomy.

Dumping syndrome is the most likely diagnosis in this patient. Rapid gastric emptying of hyperosmolar chyme into the small intestine after partial gastric resection can lead to postprandial vasomotor symptoms known as dumping syndrome. This patient had a gastrojejunostomy 1 year earlier, and her symptoms started after the surgery. Common early symptoms of dumping symptoms are palpitations, tachycardia, diaphoresis, and lightheadedness with abdominal pain and diarrhea presenting within 30 minutes of eating. Late symptoms can occur 1 to 3 hours after eating in 25% of patients and include sweating, tremor, hunger, and difficulty with concentration and cognition (hypoglycemia). A minority of patients have both early and late symptoms. The diagnosis is usually made based on clinical findings. Initial treatment for dumping syndrome is dietary: eating small frequent meals and saving liquids until after a meal, which this patient has already found to help her symptoms.

Dumping syndrome is misdiagnosed as gastroparesis in up to 37% of patients. Gastroparesis involves delayed gastric emptying and is typically associated with nausea and vomiting after eating. The prominent vasomotor symptoms this patient describes are uncommon in gastroparesis.

Irritable bowel syndrome is more common in younger patients, and rarely causes weight loss. Symptoms that occur after a gastrointestinal surgery should suggest an alternative diagnosis.

Small intestinal bacterial overgrowth (SIBO) is an excess number and alteration in type of bacteria cultured from the small intestine. Digestive enzymes and intestinal motility normally limit the growth of excessive bacteria, but SIBO can occur in conditions in which these functions are disrupted, including gastrojejunostomy, which creates a blind loop of small intestine. Clinical features of SIBO are diarrhea, bloating, and weight loss. Patients may have a combination of fat, protein, or carbohydrate malabsorption. Unlike in dumping syndrome, symptoms are not immediately related to eating and are not associated with prominent vasomotor symptoms such as palpitations, tachycardia, diaphoresis, and lightheadedness.

KEY POINT

- Rapid gastric emptying of hyperosmolar chyme into the small intestine after partial gastric resection can lead to postprandial vasomotor symptoms, abdominal pain, and diarrhea, collectively known as dumping syndrome.

Bibliography

Berg P, McCallum R. Dumping syndrome: a review of the current concepts of pathophysiology, diagnosis, and treatment. Dig Dis Sci. 2016;61:11-8. [PMID: 26396002] doi:10.1007/s10620-015-3839-x

Item 29 Answer: B

Educational Objective: Treat chronic idiopathic constipation unresponsive to first-line treatment.

Linaclotide is the most appropriate treatment for this patient. Linaclotide is a peripherally acting guanylate

cyclase-C receptor agonist that is FDA approved for the treatment of chronic idiopathic constipation in adults. Linaclotide increases intracellular and extracellular cyclic guanosine monophosphate, which results in chloride and bicarbonate secretion into intestinal lumen, increasing intestinal fluid content and accelerated transit time. Its superiority to placebo in the treatment of constipation was demonstrated in two 12-week, high-quality randomized controlled trials. Diarrhea occurred in 16% of patients receiving linaclotide (compared to 4.7% in those receiving placebo) in the 12-week clinical trials. The potential for diarrhea can be minimized by taking linaclotide on an empty stomach, ideally 30 minutes before the first meal of the day. Plecanatide is the second guanylate cyclase-C receptor agonist to receive FDA approval for the treatment of chronic idiopathic constipation. Diarrhea was also the most commonly reported side effect of plecanatide therapy in the 12-week clinical trials (5% versus 1% in the placebo group). Lubiprostone, a chloride channel agonist, is a third agent with FDA approval for the treatment of chronic idiopathic constipation. The most common side effects reported in clinical trials were nausea, reported by 29% of patients taking lubiprostone, and diarrhea, reported by 12%. The efficacy and safety of linaclotide, plecanatide, and lubiprostone have not been established in patients aged younger than 18 years nor in pregnant patients. Because of cost effectiveness, over-the-counter laxatives, such as fiber supplements, polyethylene glycol, and bisacodyl, should be pursued first in patients with constipation, but they were ineffective in this patient.

Osmotic laxatives include magnesium hydroxide, lactulose, sorbitol, and polyethylene glycol (PEG); clinical trials have demonstrated the superiority and safety of PEG. The patient tried over-the-counter PEG, and it was poorly tolerated due to bloating. Substituting another, less effective, osmotic agent (for example, lactulose) will lead to similar adverse effects without relieving constipation.

Methylnaltrexone, an injectable peripheral opioid antagonist that does not cross the blood-brain barrier, is very effective in treating opioid-induced constipation without adversely affecting analgesia. Bowel obstruction is an absolute contraindication to methylnaltrexone. Because this patient does not have opioid-induced constipation, methylnaltrexone is an inappropriate choice.

Rifaximin is a nonabsorbable antibiotic used in the treatment of irritable bowel syndrome predominated by diarrhea, hepatic encephalopathy, and travelers' diarrhea. It has no proven efficacy in chronic idiopathic constipation and is therefore not indicated in this patient.

KEY POINT

- Linaclotide is a peripherally acting guanylate cyclase-C receptor agonist that is FDA approved for the treatment of chronic idiopathic constipation in adults with symptoms refractory to first-line therapies.

Bibliography

Lembo AJ, Schneier HA, Shiff SJ, Kurtz CB, MacDougall JE, Jia XD, et al. Two randomized trials of linaclotide for chronic constipation. N Engl J Med. 2011;365:527-36. [PMID: 21830967] doi:10.1056/NEJMoa1010863

Item 30 Answer: D

Educational Objective: Prevent vertical transmission of hepatitis B viral infection.

Tenofovir is the most appropriate next step in management of this patient, with the goal of preventing vertical transmission of hepatitis B virus (HBV) infection from mother to child during the course of delivery. Guidelines recommend treatment with lamivudine, telbivudine, or tenofovir for the prevention of vertical transmission in pregnant women who have HBV DNA levels greater than 200,000 IU/mL at 24 to 28 weeks' gestation. There are no head-to-head data comparing these regimens, but tenofovir is preferred over telbivudine and lamivudine due to lower rates of resistance. Tenofovir and telbivudine are the only FDA pregnancy category B agents. Lamivudine and other oral drugs used to treat HBV are category C agents, though there are reasonable data on the safety of lamivudine use in pregnancy in the HIV population. Only a few patients will become hepatitis B surface antigen–negative with treatment; therefore, cure of HBV infection is an unrealistic goal for most chronically infected patients.

There are no data suggesting that cesarean delivery is effective at preventing vertical transmission of HBV. All babies born to mothers with chronic HBV infection should receive active HBV vaccination and passive immunization (HBV immune globulin). The risk for developing chronic HBV infection is high (90%) in newborns who acquire HBV.

Because the patient's HBV DNA level is high enough (>200,000 IU/mL) to warrant treatment to prevent vertical transmission of HBV, measuring her HBV DNA level again in 3 months would not be appropriate without first instituting treatment.

Pegylated interferon is not considered safe in pregnancy and, therefore, would be an inappropriate choice for this patient. Pegylated interferon can be used to treat HBV infection in patients with high alanine aminotransferase levels, low HBV DNA levels, and without cirrhosis. Candidates for interferon have a desire for finite therapy, do not have cirrhosis, are not pregnant, and do not have significant psychiatric disease, cardiac disease, seizure disorder, cytopenia, or autoimmune disease.

KEY POINT

- Pregnant women who have hepatitis B virus DNA levels greater than 200,000 IU/mL at 24 to 28 weeks' gestation should be treated with tenofovir to prevent vertical transmission during delivery.

Bibliography

Terrault NA, Bzowej NH, Chang KM, Hwang JP, Jonas MM, Murad MH; American Association for the Study of Liver Diseases. AASLD guidelines for treatment of chronic hepatitis B. Hepatology. 2016;63:261-83. [PMID: 26566064] doi:10.1002/hep.28156

Item 31 Answer: A

Educational Objective: Diagnose pancreatic cancer.

Contrast-enhanced CT of the abdomen is the most appropriate next step in this patient's management. Pancreatic neoplasm must be considered as a cause of acute pancreatitis in patients older than age 40 years when no other cause has been identified and/or when worrisome features such as weight loss or new onset of diabetes mellitus are present. This patient had no identifiable cause and has worrisome features of decreased appetite, back pain, and weight loss. Contrast-enhanced multidetector CT has a 90% sensitivity for detecting malignancy in patients in whom pancreatic cancer is suspected. CT also provides staging information.

Endoscopic retrograde cholangiopancreatography (ERCP) is not appropriate for this patient because laboratory data, abdominal ultrasound, and physical examination show no evidence of biliary obstruction. ERCP may be indicated in patients with biliary obstruction for stenting of the bile duct. This may occur in the setting of a neoplasm in the head of the pancreas.

Endoscopic ultrasound (EUS) examination resembles standard endoscopy, but the endoscope has an ultrasound transducer at the tip that emits acoustic waves to the surrounding tissues, allowing for the acquisition of real-time views of the pancreas, bile ducts, and blood vessels. In the diagnosis of pancreatic lesions, EUS is useful for the detection of small tumors that may be below the resolution of the CT scan and allows tissue diagnosis by fine-needle aspiration when required. In patients in whom pancreatic cancer is suspected, contrast-enhanced multidetector CT is the preferred initial diagnostic study.

No further testing is indicated for patients younger than age 40 years who are asymptomatic after treatment for a first case of mild acute pancreatitis in the absence of worrisome features. This patient's age, lack of an identifiable cause, and worrisome clinical features warrant further evaluation rather than continuing current management.

KEY POINT

- Pancreatic neoplasm must be considered as a cause of acute pancreatitis in patients older than age 40 years when no other cause has been identified and/or when worrisome features, such as weight loss or new onset of diabetes mellitus, are present.

Bibliography

Tenner S, Baillie J, DeWitt J, Vege SS; American College of Gastroenterology. American College of Gastroenterology guideline: management of acute pancreatitis. Am J Gastroenterol. 2013;108:1400-15; 1416. [PMID: 23896955] doi:10.1038/ajg.2013.218

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Item 32 Answer: A

Educational Objective: Manage antithrombotic therapy after gastrointestinal bleeding.

This patient's warfarin therapy should be restarted now. The risk for warfarin-associated bleeding is determined by the INR, patient comorbid conditions, and duration of therapy. For patients with an INR in or slightly above the therapeutic range (up to 2.7), normalization of the INR does not reduce rebleeding risk but delays endoscopy and decreases the sensitivity of endoscopy to identify important prognostic indicators related to risk for rebleeding. There are few data to guide the clinician's decision of when to resume antithrombotic therapy after gastrointestinal bleeding. In general, once endoscopic hemostasis has been achieved, anticoagulation should be reinitiated, and in most cases, this can be done on the same day as the procedure. After temporary discontinuation of warfarin, antithrombotic therapy should be reinitiated within 7 days of initial drug discontinuation to avoid an increased risk for a thromboembolic event. Hemostasis has been achieved in this patient, with no evidence of ongoing gastrointestinal bleeding seen for 24 hours after the procedure; therefore, it is appropriate to reinitiate warfarin therapy now.

Retrospective studies have shown that resumption of warfarin therapy is associated with a decreased risk for mortality and thrombosis without a significantly increased risk for recurrent hemorrhage in patients with gastrointestinal bleeding. Waiting 10 or 30 days to resume warfarin therapy increases the risk for a thromboembolic event with no reduction in risk for recurrent gastrointestinal bleeding.

This patient's CHA_2DS_2-VASc (Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, Stroke or transient ischemic attack or thromboembolism, Vascular disease, Age 65-74 years, Sex category) score is 5, predicting a nearly 7% annual risk for stroke and thromboembolism event at 1-year follow-up evaluation. This is a moderately high annual risk for thromboembolism; therefore, holding warfarin therapy indefinitely is inappropriate.

KEY POINT

- Once endoscopic hemostasis has been achieved in a patient with gastrointestinal bleeding, anticoagulation should be reinitiated, and in most cases, this can be done on the same day as the procedure.

Bibliography

Abraham NS. Management of antiplatelet agents and anticoagulants in patients with gastrointestinal bleeding. Gastrointest Endosc Clin N Am. 2015;25:449-62. [PMID: 26142031] doi:10.1016/j.giec.2015.02.002

Item 33 Answer: D

Educational Objective: Diagnose celiac disease.

Testing for anti-tissue transglutaminase (tTG) IgA antibody is the most appropriate next test for this patient, who has symptoms of celiac disease, including diarrhea, bloating, and weight loss. She is underweight due to malabsorption related to immune destruction of small intestinal villi, and she has laboratory abnormalities associated with celiac disease, including iron deficiency anemia and elevated liver transaminases. Her family history of autoimmune diseases is also consistent with celiac disease due to common genetic

predisposition (*HLA-DQ2* and *DQ8*). The best initial screening test for celiac disease is anti-tTg IgA antibody testing. Given increased prevalence of IgA deficiency in celiac disease, total IgA levels should be measured in patients with high suspicion for celiac disease. If patients are IgA deficient, IgG-based antibody testing (such as deamidated gliadin peptide [DGP] IgG) should be performed. Positive antibody screening for celiac disease should prompt upper endoscopy and biopsies of the duodenum for definitive diagnosis. Treatment is a lifelong, strict gluten-free diet.

Gliadin antibodies are neither sensitive nor specific for the diagnosis of celiac disease and are no longer recommended for the evaluation of celiac disease. Newer gliadin-based serology tests, anti–DGP IgA and anti–DGP IgG, have greater sensitivity and specificity than older antigliadin antibodies. Anti–DGP IgG is particularly useful in cases of total IgA deficiency for diagnosing celiac disease.

Anti-*Saccharomyces cerevisiae* antibodies have been proposed as a serologic method for differentiating Crohn disease from ulcerative colitis, but they are neither adequately sensitive nor specific and can lead to false-positive results if used as a screening test for gastrointestinal symptoms. In addition, the absence of fever, bloody diarrhea, or abdominal pain makes the diagnosis of inflammatory bowel disease unlikely in this patient.

Anti-smooth muscle antibody testing can be helpful in the diagnosis of autoimmune hepatitis. Autoimmune hepatitis is a chronic inflammatory liver disease that is usually seen in women and can be associated with other autoimmune diseases (most commonly autoimmune thyroiditis, synovitis, or ulcerative colitis). The disease presentation ranges from asymptomatic to acute liver failure. Serum aminotransferase levels are elevated and range from mild elevations to greater than 1000 U/L. Serum IgG levels are also elevated. Patients with autoimmune hepatitis do not present with loose stools, bloating, and weight loss.

KEY POINT

- Anti-tissue transglutaminase IgA antibody testing is the best screening test for celiac disease.

Bibliography

Rubio-Tapia A, Hill ID, Kelly CP, Calderwood AH, Murray JA; American College of Gastroenterology. ACG clinical guidelines: diagnosis and management of celiac disease. Am J Gastroenterol. 2013;108:656-76; quiz 677. [PMID: 23609613] doi:10.1038/ajg.2013.79

Item 34 Answer: A

Educational Objective: Monitor for colorectal neoplasia after colon cancer resection.

This patient's next surveillance colonoscopy should take place now (1 year after diagnosis) according to the American Gastroenterological Association (AGA) and American Society of Clinical Oncology (ASCO) guidelines. Patients who undergo a complete perioperative colonoscopy with clearing of synchronous neoplasia and curative surgical resection for colon cancer should have a subsequent surveillance colonoscopy within 1 year. If the colonoscopy is normal, the AGA recommends repeat examination in 3 years; ASCO recommends repeat examination in 5 years. If normal, colonoscopy should be repeated every 5 years thereafter until the benefit of continued surveillance is outweighed by risks and diminished life expectancy. If neoplasms are detected during any follow-up examination, then the surveillance interval should be adjusted based on polyp size, number, and histology.

Colonoscopy is the preferred modality for surveillance in patients with a personal history of colon cancer. There is insufficient evidence to support CT colonography, fecal immunochemical testing, or fecal DNA testing for surveillance after colon cancer.

Surveillance colonoscopy every 1 to 2 years is recommended in individuals with Lynch syndrome, regardless of whether the patient has a personal history of colon cancer. Lynch syndrome is unlikely because the patient's family history does not meet the Amsterdam II criteria, which require that three family members are affected by a Lynch syndrome–associated cancer, at least two successive generations are affected, one of the affected family members is a first-degree relative of the other two affected family members, and at least one cancer was diagnosed in a family member younger than age 50 years, with familial adenomatous polyposis excluded and tumors verified histologically.

A 5-year or 10-year interval is not appropriate for this patient because the risk for metachronous cancer (multiple primary tumors developing at different time intervals) is increased for about 2 to 3 years after colon cancer resection.

According the American Cancer Society's *Colorectal Cancer Survivorship Care Guidelines* published in 2015, a history and physical examination should be performed every 3 to 6 months for the first 2 years, then every 6 months for 5 years. After treatment for stages 1, 2, or 3 colorectal cancer, patients at high risk for recurrence (for example, with poorly differentiated histology, lymphatic or vascular invasions, or positive resection margins) should receive annual abdominal-pelvic and chest CT scans for 5 years after resection. A history and physical examination should also be performed every 3 to 6 months for 5 years. Carcinoembryonic antigen measurement is recommended every 3 to 6 months for the first 2 years, then every 6 months to 5 years if the patient is a potential candidate for further intervention. Follow-up evaluation recommendations from other expert organizations vary.

KEY POINT

- After treatment of colon cancer, patients should undergo surveillance colonoscopy 1 year after diagnosis.

Bibliography

American Gastroenterology Association. AGA institute guidelines for colonoscopy surveillance after cancer resection: clinical decision tool. Gastroenterology. 2014;146:1413-4. [PMID: 24742563] doi:10.1053/j.gastro.2014.03.029

Item 35 Answer: D

Educational Objective: Treat main-duct intraductal papillary mucinous neoplasm of the pancreas.

Pancreatic resection is the most appropriate next step in management. Pancreatic cysts are classified as pancreatic cystic neoplasms (the most common), nonneoplastic pancreatic cysts, and pseudocysts. The two most common pancreatic cystic neoplasms are mucinous cystic neoplasms (MCNs) and intraductal papillary mucinous neoplasms (IPMNs), which involve the main duct, branch ducts, or both. Most pancreatic cysts are branch-duct IPMNs. Main-duct IPMNs can be diagnosed based on diffuse dilation of the main pancreatic duct and the characteristic feature of mucin exuding from the ampulla during endoscopic visualization. Main-duct IPMNs carry a greater than 65% risk for malignant transformation. Surgical resection is the only option for treatment of these high-risk cystic lesions of the pancreas in patients who are appropriate surgical candidates.

Diagnosis of solitary cysts is challenging. It may require endoscopic ultrasonography and fine-needle aspiration to distinguish between cystic neoplasms (branch-duct IPMNs, MCNs, and serous tumors) and pseudocysts based on cytology. This patient has endoscopic ultrasonographic findings showing characteristic features of main-duct IPMN. The best course of action is pancreatic resection and not endoscopic ultrasound surveillance in 1 year.

MRI of the abdomen in 1 year is the standard surveillance recommendation for asymptomatic, low-risk cystic lesions of the pancreas. Main-duct IPMN is considered a high-risk cystic lesion and, therefore, MRI surveillance is not appropriate.

Oral prednisone is used to treat autoimmune pancreatitis, a frequent manifestation of IgG4-related disease. The characteristic finding of autoimmune pancreatitis on imaging is a narrowed main pancreatic duct with parenchymal swelling, known as the "sausage-shaped" pancreas, which is not consistent with this patient's findings.

KEY POINT

- Surgical resection is the best management option for high-risk cystic lesions of the pancreas, such as intraductal papillary mucinous neoplasms that involve the main duct.

Bibliography

Vege SS, Ziring B, Jain R, Moayyedi P; Clinical Guidelines Committee. American Gastroenterological Association Institute guideline on the diagnosis and management of asymptomatic neoplastic pancreatic cysts. Gastroenterology. 2015;148:819-22; quize12-3. [PMID: 25805375] doi:10.1053/j.gastro.2015.01.015

H Item 36 Answer: D

Educational Objective: Diagnose the cause of hematochezia.

Upper endoscopy is the most appropriate test to perform next. The patient's presentation is consistent with rapid upper gastrointestinal bleeding (UGIB), likely from an NSAID-induced peptic ulcer. Fifteen percent of patients with presumed lower gastrointestinal bleeding are found to have an upper gastrointestinal source. Factors in this patient that favor a diagnosis of UGIB include young age, hemodynamic instability on presentation, and NSAID use. Approximately 80% of UGIB is due to four causes: peptic ulcer disease, esophagogastric varices, esophagitis, and Mallory-Weiss tear. Bleeding typically stops spontaneously; however, 20% of patients have persistent or recurrent bleeding, which increases mortality. Guidelines recommend upper endoscopy within 24 hours of presentation in patients with features of UGIB.

Angiography is used to diagnose the cause of obscure gastrointestinal bleeding when more common sources are not found on routine upper and lower endoscopy. It is also used for treatment, such as embolization, when a bleeding source has been identified.

Capsule endoscopy employs a wireless capsule camera that is swallowed by the patient to take images of the small bowel. These images are transmitted to a radiofrequency receiver worn by the patient. Capsule endoscopy allows visualization of the entire small bowel. This patient's bleeding is very likely to be accessible by upper endoscopy, the preferred diagnostic test.

Colonoscopy requires bowel preparation for adequate visualization of bleeding sources, and in the setting of acute bleeding with hemodynamic instability, a more urgent diagnostic and therapeutic test is indicated. Colonoscopy would be indicated if the source of bleeding were not identified on upper endoscopy.

KEY POINT

- Hematochezia associated with hemodynamic instability in a young patient is likely due to an upper gastrointestinal source.

Bibliography

Strate LL, Gralnek IM. ACG clinical guideline: management of patients with acute lower gastrointestinal bleeding. Am J Gastroenterol. 2016;111:459-74. [PMID: 26925883] doi:10.1038/ajg.2016.41

Item 37 Answer: D

Educational Objective: Diagnose secretory diarrhea.

Secretory diarrhea is the diagnosis most compatible with the patient's presentation. In the evaluation of chronic diarrhea, it is often useful to categorize the condition as secretory or osmotic, as well as to determine whether the cause is due to chronic infection or an inflammatory condition, which will guide further evaluation and treatment. Secretory and osmotic diarrhea can often be distinguished by clinical history. Patients with secretory diarrhea may pass liters of stool daily, causing severe dehydration and electrolyte disturbances, with persistent stooling despite fasting. Patients with osmotic diarrhea often have stool volumes of less than 1 L/d and have cessation of stooling when they are fasting. This

patient's large-volume, watery diarrhea that persists despite fasting is compatible with secretory diarrhea. Another clue to this patient's diagnosis is hypokalemia. Hypokalemia from lower-gastrointestinal losses is most common when the losses occur over a prolonged period. Fecal electrolytes can be used to calculate the fecal osmotic gap:

$$290 - (2 \times [\text{stool sodium} + \text{stool potassium}])$$

An osmotic gap of less than 50 mOsm/kg suggests secretory diarrhea, and a gap greater than 75 mOsm/kg suggests osmotic diarrhea.

Examples of conditions that can cause a chronic secretory diarrhea include medications (colchicine, NSAIDs), hormone-producing tumors (carcinoid, gastrinoma, VIPoma), small intestinal bacterial overgrowth, bile acid malabsorption (short-bowel syndrome), and villous adenoma. Additional testing may be warranted in patients with secretory diarrhea. Patients found to have a small-bowel tumor in the setting of diarrhea as well as symptoms such as flushing should be considered for additional testing, including radioimmunoassays for peptides and/or 24-hour urine 5-hydroxyindoleacetic acid measurement for carcinoid tumors. Colonoscopy can be used to evaluate for villous adenomas and is also indicated if the patient is not up-to-date for colon cancer screening.

Infections leading to chronic diarrhea can be caused by parasites such as *Giardia*. *Giardia* leads to a malabsorptive condition; it would not present with large-volume diarrhea that persists despite fasting.

Inflammatory causes of chronic diarrhea include inflammatory bowel diseases (ulcerative colitis and Crohn disease) and microscopic colitis. Patients with inflammatory causes of chronic diarrhea present with bloody stools, nocturnal symptoms, and sometimes anemia. This patient is less likely to have an inflammatory cause for her chronic diarrhea given the absence of these signs and symptoms. Blood or leukocytes in the stool suggest an inflammatory cause.

Causes of chronic osmotic diarrhea include medications (laxatives), undigested sugars (lactose), celiac disease, and fat maldigestion or absorption leading to steatorrhea (chronic pancreatitis). When laxative abuse is suspected, a stool or urine laxative screen can aid in the diagnosis. Celiac disease can be evaluated with serology testing and small intestinal biopsy. A positive 72-hour stool collection for fecal fat confirms steatorrhea; a random fecal fat assessment may be helpful if a timed collection is not possible.

KEY POINT

- Patients with secretory diarrhea may pass liters of stool daily, causing severe dehydration and electrolyte disturbances, with persistent stooling despite fasting.

Bibliography

Schiller LR, Pardi DS, Spiller R, Semrad CE, Surawicz CM, Giannella RA, et al. Gastro 2013 APDW/WCOG Shanghai working party report: chronic diarrhea: definition, classification, diagnosis. J Gastroenterol Hepatol. 2014;29:6-25. [PMID: 24117999] doi:10.1111/jgh.12392

Item 38 Answer: A

Educational Objective: Diagnose Crohn disease.

The patient has Crohn colitis presenting as a chronic inflammatory diarrhea. Common symptoms are abdominal pain, diarrhea, and weight loss; overt gastrointestinal bleeding is a less common manifestation. Crohn disease has varied presentations that can make diagnosis difficult. The pattern of inflammation and histologic features in this case allow distinction of Crohn disease from other inflammatory conditions. Colonoscopy findings are consistent with Crohn colitis based on patchy distribution of mucosal inflammatory changes with normal intervening mucosa, called "skip areas." The biopsy results show distorted and branching colonic crypts, which are indicative of chronic colitis. The skip areas of normal intervening mucosa and biopsy results for involved mucosa showing features of chronicity (distorted and branching colonic crypts) make Crohn disease the most likely diagnosis.

The patient is at risk for *Giardia lamblia* infection because she works in a child care center. However, *Giardia* is a small-bowel protozoal pathogen and does not cause the symptoms of colonic inflammation with bloody diarrhea. Although most patients with giardiasis are asymptomatic, those with symptoms note abdominal pain and cramping with diarrhea, often consisting of large-volume, watery, and foul-smelling stools. Symptoms may be acute or chronic.

Microscopic colitis does not cause bloody diarrhea but rather is a cause of chronic watery diarrhea predominantly in women, with a peak onset between ages 60 and 70 years. Also, colonoscopy results are normal in patients with this condition, with inflammation only seen on biopsy.

Ulcerative colitis typically presents with bloody diarrhea and abdominal discomfort, the severity of which is related to the extent and severity of inflammation. Because ulcerative colitis typically involves the rectum, tenesmus, urgency, rectal pain, and fecal incontinence are common. Patients with ulcerative colitis have distorted and branching colonic crypts on biopsy, but the distribution of inflammation begins in the rectum and progresses up the colon in a continuous and symmetric pattern, without skip areas.

KEY POINT

- Colonoscopy results in Crohn disease show patchy distribution of mucosal inflammatory changes with "skip areas" of normal intervening mucosa, and biopsy results for involved mucosa show features of chronicity (distorted and branching colonic crypts).

Bibliography

Lee JM, Lee KM. Endoscopic diagnosis and differentiation of inflammatory bowel disease. Clin Endosc. 2016;49:370-5. [PMID: 27484813] doi:10.5946/ce.2016.090

Item 39 Answer: B

Educational Objective: Manage follow-up colonoscopy after uncomplicated diverticulitis.

This patient should undergo colonoscopy in 1 to 2 months following treatment of uncomplicated diverticulitis. According to the American Gastroenterological Association Institute Technical Review on the Management of Acute Diverticulitis, patients with a recent episode of acute diverticulitis should undergo colonoscopy 4 to 8 weeks after an episode of acute diverticulitis. Follow-up colonoscopy may identify a few cases of colorectal carcinoma. The risk for perforation after a case of diverticulitis is uncertain. The technical review estimated that 1 in 67 patients with confirmed acute diverticulitis would have a misdiagnosed colorectal cancer found on follow-up colonoscopy. Almost all of the misdiagnosed colorectal cancers included in the technical review were located in the area of diverticulitis. Assessing the patient for underlying inflammatory bowel disease is another reason for performing follow-up colonoscopy.

Colonoscopy during the acute phase of illness is contraindicated because acute diverticulitis causes acute colonic inflammation, which may increase the risk for perforation. The risk for perforation has been reported to be as high as 0.3%, but it is generally thought to be less than 0.1%, based on data from large populations undergoing screening colonoscopy. If the results of colonoscopy performed within the past 12 to 24 months are negative, then repeat colonoscopy is not needed.

Delaying colonoscopy beyond 1 to 2 months places the patient at risk for a missed diagnosis that could be important and time sensitive, such as a diagnosis of colon cancer.

KEY POINT

- Patients with uncomplicated diverticulitis should undergo colonoscopy 1 to 2 months after the episode of acute diverticulitis, when colonic inflammation has resolved.

Bibliography

Strate LL, Peery AF, Neumann I. American Gastroenterological Association Institute technical review on the management of acute diverticulitis. Gastroenterology. 2015;149:1950-1976.e12. [PMID: 26453776] doi: 10.1053/j.gastro.2015.10.001

Item 40 Answer: D

Educational Objective: Diagnose atrophic gastritis.

Upper endoscopy with gastric biopsy is the most appropriate next diagnostic study. The two forms of atrophic gastritis are *Helicobacter pylori*-associated and autoimmune. *H. pylori*-associated atrophic gastritis typically resolves with *H. pylori* eradication, whereas autoimmune atrophic gastritis has no cure. This patient's hematologic findings and positive testing for serum antiparietal antibodies confirm the diagnosis of pernicious anemia and suggest the presence of autoimmune atrophic gastritis. Iron deficiency anemia is a common comorbidity of autoimmune gastritis, as is autoimmune thyroid disease. Autoimmune gastritis is associated with parietal cell loss, reduced gastric acid production, and secondary hypergastrinemia. Hypergastrinemia is associated with an increased risk for the development of gastric carcinoid and adenocarcinoma. It is prudent to perform upper endoscopy and gastric biopsy at the time of pernicious anemia diagnosis to evaluate for these cancers; however, the benefit on ongoing surveillance endoscopy is unclear. Autoimmune-related pernicious anemia and associated iron deficiency anemia are likely to require lifelong vitamin B_{12} and iron replacement, respectively.

Capsule endoscopy is typically used to evaluate obscure causes of gastrointestinal bleeding. This patient had a normal colonoscopy 4 years earlier, and stool evaluation is negative for blood. Finally, this patient's iron deficiency anemia is most likely due to atrophic gastritis-related achlorhydria, which decreases iron absorption by impairing the conversion of ferric iron to absorbable ferrous iron; in many patients, iron deficiency precedes vitamin B_{12} deficiency. Additional testing for iron deficiency beyond upper endoscopy is likely unnecessary.

Although small intestinal bacterial overgrowth (SIBO) can be associated with anemia, the diagnosis is unlikely in this patient with no risk factors or typical symptoms of SIBO; therefore, a glucose breath test to assess for SIBO is likely to be of low yield.

The serum gastrin level is elevated in patients with any form of atrophic gastritis and has no diagnostic or prognostic value in this setting.

KEY POINT

- Patients with newly diagnosed pernicious anemia should be evaluated for gastric adenocarcinoma and gastric carcinoid with upper endoscopy and gastric biopsy.

Bibliography

Minalyan A, Benhammou JN, Artashesyan A, Lewis MS, Pisegna JR. Autoimmune atrophic gastritis: current perspectives. Clin Exp Gastroenterol. 2017;10:19-27. [PMID: 28223833] doi:10.2147/CEG.S109123

Item 41 Answer: D

Educational Objective: Treat acute anal fissure.

Sitz baths and psyllium are the most appropriate next step in the management of this patient, who has an acute anal fissure that is most likely the result of worsening constipation induced by the recent use of opioid analgesic therapy. Anal fissures are tears in the anoderm below the dentate line that can be seen on inspection of the perianal area, often unaided by the use of an anoscope. They are usually in the posterior position and are less often in the anterior midline. The classic symptom is pain with and after defecation, which may be associated with bright red blood on the toilet tissue. Most acute fissures heal spontaneously. The most effective treatment approach is daily warm-water sitz baths and the use of the bulk laxative psyllium. This combination therapy

was superior to topical lidocaine or hydrocortisone in a randomized clinical trial.

Anal botulinum toxin injection is reserved for chronic anal fissures that do not respond to more conservative treatment measures, including sitz baths, fiber supplementation, and topical therapy (nitroglycerin or calcium channel blocker) applied to the anal canal. This initial acute presentation of anal fissure is best managed by more conservative, less invasive treatment measures first.

A flexible sigmoidoscopy is not indicated because the diagnosis of anal fissure can be accurately made by history and examination. Furthermore, the patient's family history is not significant enough to warrant endoscopic evaluation.

Although topical anti-inflammatory therapy can alleviate the pain associated with anal fissure, the placement of a suppository may be uncomfortable. In addition, the patient has already tried over-the-counter topical hemorrhoid therapy with no relief of symptoms, so a glucocorticoid suppository is unlikely to help.

Topical glucocorticoid therapy is less effective in the treatment of anal fissure than sitz baths and fiber. Lubiprostone is a peripherally acting chloride channel activator with FDA approval for the treatment of opioid-induced constipation. This patient's opioid analgesic use is temporary after shoulder surgery, and lubiprostone use is more appropriate in the setting of more chronic opioid use.

KEY POINT

- The most effective treatment approach for anal fissure is daily warm-water sitz baths and the use of the bulk laxative psyllium.

Bibliography

Beaty JS, Shashidharan M. Anal fissure. Clin Colon Rectal Surg. 2016;29:30-7. [PMID: 26929749] doi:10.1055/s-0035-1570390

Item 42 Answer: A

Educational Objective: Diagnose familial adenomatous polyposis.

Colonoscopy is the best next step in the evaluation of this patient. The patient has multiple fundic gland polyps, which can be associated with familial adenomatous polyposis (FAP). Fundic gland polyps related to FAP are usually numerous (>30 polyps) and frequently harbor low-grade dysplasia, but they rarely progress to gastric cancer. Colonoscopy to rule out FAP is recommended in patients younger than age 40 years with dysplastic or numerous fundic gland polyps. Classic FAP results in the development of hundreds to thousands of colorectal adenomas that often manifest by the second decade of life. Without treatment, colorectal cancer typically develops in all patients by age 40 years. Therefore, a colonoscopy is indicated in this patient to evaluate for colonic polyposis. If colonic polyposis identified, the patient should undergo genetic testing to make the definitive diagnosis of FAP. FAP is caused by mutations in the *APC* gene. Mutations can be inherited in an autosomal dominant pattern with multiple generations affected, but de novo mutations account for up to 25% of cases. If FAP is confirmed in this patient, it is likely due to a de novo mutation because of his unremarkable family history.

There is no role for surgical management of fundic gland polyps because they rarely progress to gastric cancer, so gastrectomy is not indicated for this patient.

An upper endoscopy in 3 months is not indicated for diagnosis of FAP. If FAP is confirmed, the patient should have regular surveillance of the upper gastrointestinal tract with a forward and side-viewing scope to assess for duodenal polyps. Duodenal polyps occur commonly in FAP, and risk for duodenal cancer is elevated. The interval for surveillance upper endoscopy in FAP depends on the number, size, and pathology of the duodenal polyps. This upper endoscopy also includes surveillance for gastric adenomas and cancer.

For sporadic fundic gland polyps, no further evaluation would be needed. Sporadic fundic gland polyps can arise in the setting of proton pump inhibitor (PPI) therapy; however, this usually occurs with prolonged therapy. Because this patient has only been taking a PPI for 4 months, his fundic gland polyposis is unlikely to be caused by PPI therapy. The patient's young age and the number of gastric polyps should prompt evaluation by colonoscopy.

KEY POINT

- Patients with multiple fundic gland polyps found at a young age should be evaluated for familial adenomatous polyposis.

Bibliography

Syngal S, Brand RE, Church JM, Giardiello FM, Hampel HL, Burt RW; American College of Gastroenterology. ACG clinical guideline: genetic testing and management of hereditary gastrointestinal cancer syndromes. Am J Gastroenterol. 2015;110:223-62; quiz 263. [PMID: 25645574] doi:10.1038/ajg.2014.435

Item 43 Answer: D

Educational Objective: Diagnose primary sclerosing cholangitis.

Primary sclerosing cholangitis (PSC) is the most likely diagnosis in this patient. The patient has elevated liver chemistry test results in a predominantly cholestatic pattern and concomitant inflammatory bowel disease (IBD). Disorders are considered cholestatic when the most prominent abnormality of liver chemistry testing is an elevation of the serum alkaline phosphatase level. Approximately 5% of patients with IBD will develop PSC during the course of their disease. In most patients, PSC presents as a stricturing process in the medium to large bile ducts, readily identifiable by MR cholangiopancreatography (alternating strictures and dilations resulting in a "string of beads" pattern). However, a minority of patients may present with involvement of only the small bile ducts, called small-duct PSC. The cholangiogram is normal in these patients; the diagnosis of small-duct PSC can only be made by liver biopsy. Small-duct PSC is associated with a better prognosis than typical PSC, although 10% to

20% of patients with small-duct PSC eventually develop changes in the medium and large ducts.

The diagnosis of primary biliary cholangitis (PBC) is generally made on the basis of a cholestatic liver enzyme profile in the setting of a positive antimitochondrial antibody test. Case reports have described PBC associated with IBD, but the association between the two conditions is not well accepted, making the diagnosis of PBC unlikely. Although 10% of patients with PBC may test negative for antimitochondrial antibody, the absence of antibody makes this diagnosis less likely. A liver biopsy is required to establish the diagnosis of antimitochondrial antibody–negative PBC.

Drug-induced liver injury can occur in patients taking medications used to treat IBD, such as azathioprine and tumor necrosis factor-α inhibitors. Drug-induced liver injury is not a common adverse effect of mesalamine; therefore, this diagnosis is unlikely in this patient.

Nonalcoholic fatty liver disease is the most common liver disease in the United States. It is unlikely in this patient because it usually does not present with alkaline phosphatase levels greater than 2 to 2.5 times the upper limit of normal. Furthermore, MRI has a reasonable sensitivity (>80%) for the detection of fatty liver, which was not seen in this patient.

KEY POINT

- Approximately 5% of patients with inflammatory bowel disease will develop primary sclerosing cholangitis during the course of their disease, typically presenting as cholestatic liver injury with a characteristic imaging study showing bile duct strictures and dilations ("string of beads").

Bibliography

Lindor KD, Kowdley KV, Harrison ME; American College of Gastroenterology. ACG clinical guideline: primary sclerosing cholangitis. Am J Gastroenterol. 2015;110:646-59; quiz 660. [PMID: 25869391] doi:10.1038/ajg.2015.112

Item 44 Answer: C

Educational Objective: Treat gastroesophageal reflux disease.

The most appropriate next step in the management of this patient is the initiation of a proton pump inhibitor (PPI) in conjunction with lifestyle and dietary changes. The diagnosis of gastroesophageal reflux disease (GERD) is made clinically. This patient's symptoms of burning pain in his abdomen and chest and a sour taste in his mouth occurring more than a few times a week are consistent with GERD. Due to the frequency of his symptoms, the best initial treatment is a once-daily PPI for a period of up to 8 weeks. Weight reduction is suggested for patients with recent weight gain or who are overweight. Interventions such as raising the head of the bed and eliminating meals within 2 to 3 hours of bedtime are helpful for nocturnal GERD. Cessation of alcohol and tobacco use is universally supported. Treatment for less frequent symptoms could include famotidine or other H_2 blockers. Symptom relief with the use of a PPI confirms the diagnosis of GERD.

Ambulatory pH testing is used to determine acid exposure in the esophagus in patients considering antireflux surgery. Indications for surgery include patient preference to stop taking medication, medication side effects, and refractory symptoms despite optimized medical therapy. Laparoscopic fundoplication and bariatric surgery (in obese patients) are surgical methods used to treat GERD. This patient has no surgical indications.

A barium esophagram is the initial test for evaluation of achalasia. The main symptom of achalasia is dysphagia to both solids and liquids along with regurgitation of undigested food and saliva. Patients may also report unintentional weight loss, chest pain, and heartburn. A barium esophagram is not indicated because this patient's symptoms are more consistent with GERD than with achalasia.

Upper endoscopy is indicated in patients with alarm symptoms, such as dysphagia or weight loss, and in patients whose symptoms do not respond to a PPI. Upper endoscopy is not indicated in this patient with typical GERD symptoms because most patients with typical symptoms have normal upper-endoscopy findings. Upper endoscopy is useful for the evaluation of the esophagus to identify damage in the form of erosive esophagitis, stricture, or Barrett esophagus.

KEY POINT

- Patients with a clinical diagnosis of gastroesophageal reflux disease should start an empiric trial of a proton pump inhibitor in conjunction with lifestyle and dietary changes, with no further testing.

Bibliography

Katz PO, Gerson LB, Vela MF. Guidelines for the diagnosis and management of gastroesophageal reflux disease. Am J Gastroenterol. 2013 Mar;108(3):308-28; quiz 329. Erratum in: Am J Gastroenterol. 2013 Oct;108(10):1672. [PMID: 23419381]

Item 45 Answer: A

Educational Objective: Screen for osteoporosis in a patient with cirrhosis.

Bone densitometry to screen for osteoporosis is the most appropriate next intervention for this patient with cirrhosis. Patients with cirrhosis are at twice the risk for the development of osteoporosis as demographically similar patients without cirrhosis, and women (especially those who are postmenopausal) are at higher risk than men. Initial studies of metabolic bone disease in patients with cirrhosis focused on those with primary biliary cholangitis (PBC) or alcoholic liver disease. Subsequently, it has been recognized that all patients with cirrhosis are at increased risk for bone fractures due to osteoporosis. Standard evaluation should include measurement of serum calcium, phosphate, and vitamin D levels. Up to two thirds of patients with cirrhosis are deficient in vitamin D. Dual-energy x-ray absorptiometry

is recommended for patients with cirrhosis or PBC (even if noncirrhotic).

Patients with primary sclerosing cholangitis (PSC) have a high likelihood of ulcerative colitis with associated risk for colonic dysplasia and colon cancer. Eighty percent of patients with PSC have inflammatory bowel disease, usually ulcerative colitis. This association with ulcerative colitis is not seen in patients with PBC. This patient is at average risk for colorectal cancer, and colonoscopy is not indicated until age 50 years.

Contrast-enhanced abdominal CT with arterial and portal venous phase imaging can be helpful in evaluating for hepatocellular cancer; however, in this patient whose ultrasound showed no hepatic mass, a CT scan is not necessary.

Patients with cirrhosis who develop an infection have a 30% mortality rate at 1 month, and another 30% die within 12 months; this underscores the importance of preventing infection. However, the herpes zoster vaccine is not indicated in patients younger than age 60 years. It is recommended for individuals aged 60 years and older, regardless of whether they have had a previous zoster episode, but vaccination should be avoided in immunocompromised patients. Patients with decompensated cirrhosis are considered immunocompromised due to impaired reticuloendothelial cell function, impaired neutrophil function, and possible concomitant malnutrition.

KEY POINT

- Patients with cirrhosis are at increased risk for the development of osteoporosis and should be screened using bone densitometry.

Bibliography

Santos LA, Romeiro FG. Diagnosis and management of cirrhosis-related osteoporosis. Biomed Res Int. 2016;2016:1423462. [PMID: 27840821]

H

Item 46 Answer: C

Educational Objective: Prevent venous thromboembolism in a hospitalized patient with inflammatory bowel disease.

Subcutaneous heparin is the most appropriate venous thromboembolism (VTE) prophylaxis for this patient. VTE is a common clinical problem and is associated with substantial morbidity and mortality among hospitalized patients. Most medical patients have one or more risk factors for VTE. More than a quarter of patients with undiagnosed and untreated pulmonary embolism (PE) will have a subsequent fatal PE, and between 5% and 10% of all in-hospital deaths are a direct result of PE. VTE is one of the most common extraintestinal manifestations of inflammatory bowel disease (IBD); patients with IBD have a three-fold risk for VTE compared to patients without IBD. VTE represents a significant cause of morbidity and mortality in patients with IBD, and risk for VTE is highest at the time of disease flare. Although the incidence of VTE increases with age, the highest relative risk for VTE in IBD is observed in patients younger than 40 years old. Patients with IBD who develop VTE have an increased mortality rate, and the most important risk factor for development of VTE is active IBD. For these reasons, prevention of VTE in patients with IBD is essential. All hospitalized patients with IBD should be given pharmacologic VTE prophylaxis with subcutaneous heparin. Systematic reviews of trials comparing prophylactic low-molecular-weight heparin with unfractionated heparin have not shown a statistically significant difference for mortality or major bleeding events, although there was a nonsignificant trend favoring low-molecular-weight heparin in the prevention of PE.

Mechanical VTE prophylaxis with graduated compression stockings or intermittent pneumatic compression devices is not recommended either with or in place of pharmacologic prophylaxis, although intermittent pneumatic compression has shown some efficacy in surgical patients and may be an option for nonsurgical patients with a contraindication to pharmacologic therapy, such as severe gastrointestinal bleeding. Compression stocking are no more effective than placebo in preventing VTE and are associated with harm in the form of increased incidence of skin breakdown.

Aspirin and low-dose warfarin have no role in VTE prophylaxis for hospitalized medical patients or patients with IBD.

KEY POINT

- All hospitalized patients with inflammatory bowel disease should be given pharmacologic venous thromboembolism prophylaxis with subcutaneous heparin.

Bibliography

Seah D, De Cruz P. Review article: the practical management of acute severe ulcerative colitis. Aliment Pharmacol Ther. 2016;43:482-513. [PMID: 26725569] doi:10.1111/apt.13491

Item 47 Answer: C

Educational Objective: Diagnose Lynch syndrome.

This patient should be referred to a genetic counselor for genetic testing. The patient could have Lynch syndrome based on his personal history of colon cancer diagnosed before age 50 years and his family history of colon cancers. His family history meets the Amsterdam II criteria for Lynch syndrome because three individuals in the family are affected with a Lynch syndrome–associated cancer, at least two successive generations are affected, one of the affected family members is a first-degree relative of the other two affected family members, and at least one cancer was diagnosed in a family member younger than age 50 years (the "3-2-1-1" pattern). Additional criteria are that familial adenomatous polyposis has been excluded and tumors have been verified histologically. Guidelines recommend tumor testing (microsatellite instability testing or immunohistochemistry) to screen for Lynch syndrome in all colon cancers. The results of tumor testing can help determine if Lynch syndrome is likely and inform genetic testing. Lynch syndrome is only diagnosed in individuals who meet the Amsterdam criteria and have an

identified constitutional mutation in a mismatch repair gene (*MLH1*, *MSH2*, *MSH6*, or *PMS2*) or the epithelial cell adhesion molecule (*EPCAM*) gene. Diagnosis of Lynch syndrome will inform colonoscopy surveillance recommendations for this patient. Identification of a Lynch syndrome mutation will also affect the recommendation for screening of other cancers (gastric, skin, urinary tract, and, in women, ovarian and endometrial cancers). In addition, if he has an identifiable mutation associated with Lynch syndrome, genetic testing should be offered to his first-degree relatives.

A 3-year interval for colonoscopy cannot be recommended until the results of the genetic evaluation are available. If Lynch syndrome is confirmed, the screening interval is every 1 to 2 years, not every 3 years.

Colonoscopy is preferred for screening high-risk patients such as those with a previous colorectal cancer; therefore, screening using fecal immunochemical testing, other fecal-based testing, or colonic imaging is not appropriate.

In patients with Lynch syndrome, upper endoscopy is recommended to screen for upper gastrointestinal cancers and to sample for *Helicobacter pylori*. However, this cannot be recommended until results from genetic testing are available. Patients with Lynch syndrome have an increased risk for small-intestinal cancer. However, routine cancer screening with capsule endoscopy is controversial and not routinely recommended even in patients with confirmed Lynch syndrome.

KEY POINT

- Patients with a family history suggesting Lynch syndrome (three family members are affected with a Lynch syndrome-associated cancer, at least two successive generations are affected, one of the affected family members is a first-degree relative of the other two affected family members, and at least one cancer was diagnosed in a family member younger than age 50 years) should be referred for genetic counseling.

Bibliography

Syngal S, Brand RE, Church JM, Giardiello FM, Hampel HL, Burt RW; American College of Gastroenterology. ACG clinical guideline: genetic testing and management of hereditary gastrointestinal cancer syndromes. Am J Gastroenterol. 2015;110:223-62; quiz 263. [PMID: 25645574] doi:10.1038/ajg.2014.435

Item 48 Answer: A

Educational Objective: Evaluate persistent gastroesophageal reflux disease.

Ambulatory pH testing is the most appropriate next diagnostic test for this patient. The patient has persistent cough, which may be an extraesophageal symptom of gastroesophageal reflux disease (GERD) resulting from laryngopharyngeal reflux. Additional extraesophageal symptoms of GERD include asthma, globus sensation, hoarseness, throat clearing, and chronic laryngitis. It appears that the laryngopharynx is more sensitive to the erosive effects of acid, and small amounts of reflux may produce symptoms. The selection of a diagnostic test to confirm or exclude laryngopharyngeal reflux is controversial. Ambulatory pH testing, if positive, can help to confirm the diagnosis of GERD and supports the diagnosis of laryngopharyngeal reflux. Negative ambulatory pH testing suggests that the patient does not have GERD and that proton pump inhibitor therapy should be discontinued and another cause of the persistent hoarseness sought. Other experts propose laryngoscopy as the gold standard to diagnose laryngopharyngeal reflux. Common findings during laryngoscopy include edema and erythema, but these findings are also seen in 80% of healthy controls. While laryngoscopy should not be used as the sole test to diagnose extraesophageal GERD, abnormal findings in patients with an appropriate clinical history suggest that cough is related to GERD. Other causes of cough may include allergy, smoking, and voice abuse, and these should be ruled out with an ear, nose, and throat evaluation.

Barium esophagography should not be used as the initial diagnostic test for GERD and is not useful for evaluating this patient's symptoms, which primarily involve the laryngopharynx.

Esophageal manometry is used for patients suspected of having an underlying motility disorder involving peristalsis or lower esophageal sphincter dysfunction. This patient reports no dysphagia, a common presenting symptom of motility disorders, and his heartburn symptoms are controlled, so esophageal manometry is not indicated.

Upper endoscopy is the primary tool used to evaluate patients with GERD for complications such as erosive esophagitis, stricture, Barrett esophagus, and esophageal cancer. Because this patient does not have esophageal symptoms and had a normal endoscopy 1 year ago, upper endoscopy is not indicated.

KEY POINT

- Ambulatory pH testing can be a helpful diagnostic test in patients with suspected extraesophageal manifestations of gastroesophageal reflux disease.

Bibliography

Katz PO, Gerson LB, Vela MF. Guidelines for the diagnosis and management of gastroesophageal reflux disease. Am J Gastroenterol. 2013;108:308-28; quiz 329. [PMID: 23419381] doi:10.1038/ajg.2012.444

Item 49 Answer: A

Educational Objective: Treat ascites caused by portal hypertension.

Discontinuing lisinopril is the most appropriate next step in the management of this patient with ascites. Blood pressure falls with worsening cirrhosis, resulting in reduced renal blood flow and glomerular filtration. A compensatory upregulation of the renin-angiotensin system results in increased levels of vasoconstrictors, including vasopressin, angiotensin, and aldosterone, which support systemic blood pressure and kidney function. ACE inhibitors and

angiotensin receptor blockers impair the compensatory response to cirrhosis-related hypotension and thereby impair the ability to excrete excess sodium and water and may also affect survival. Medications that decrease kidney perfusion, including NSAIDs, ACE inhibitors such as lisinopril, and angiotensin receptor blockers, should be discontinued because their use often worsens ascites due to portal hypertension. The mainstay of therapy of ascites is to initiate dietary changes, restricting sodium intake to less than 2000 mg (87 mEq) daily. If sodium restriction does not result in significant improvement of ascites, the initiation of diuretic therapy with spironolactone with or without furosemide can be effective in increasing urinary sodium excretion.

Free-water restriction can be useful for the management of dilutional hyponatremia that is sometimes seen in patients with advanced liver dysfunction. This patient has a normal serum sodium concentration, so free-water restriction is not indicated.

Propranolol and other nonselective β-blockers are often used prophylactically for the prevention of variceal hemorrhage, but they do not have a role in the management of ascites. Furthermore, in some patients with ascites that is refractory to medical management, β-blockers may worsen clinical outcomes, including survival.

Indwelling drains for ascites have been used for patients with malignant ascites, but in the setting of portal hypertensive ascites, such as seen in this patient, indwelling drains are associated with a high risk for infection and their use is contraindicated.

KEY POINT

- Medications that decrease kidney perfusion, including NSAIDs, ACE inhibitors, and angiotensin receptor blockers, should be discontinued in patients with ascites.

Bibliography

Runyon BA; AASLD. Introduction to the revised American Association for the Study of Liver Diseases Practice Guideline management of adult patients with ascites due to cirrhosis 2012. Hepatology. 2013;57:1651-3. [PMID: 23463403] doi:10.1002/hep.26359

H

Item 50 Answer: D

Educational Objective: Treat acute liver failure.

Referral for liver transplantation is the most appropriate choice for this patient with acute liver failure. Acute liver failure is defined by the manifestation of hepatic encephalopathy within 26 weeks of developing symptoms of liver disease. The development of jaundice was this patient's first symptom of liver disease. Within 6 weeks, he developed coagulopathy, with an INR of 2.6, as well as symptoms of hepatic encephalopathy (confusion and asterixis). Liver injury is distinct from acute liver failure and presents with elevated liver test results and/or jaundice in the absence of evidence of liver function failure. The most common causes of acute liver failure are medications, especially acetaminophen, and viral infections, although many cases are due to indeterminate causes. The prompt recognition of acute liver failure is essential due to high rates of mortality. Patients require frequent monitoring for hypoglycemia, hypophosphatemia, acute kidney injury, infections, and progressive hepatic encephalopathy, which can be accompanied by cerebral edema and intracranial hypertension. Liver transplantation improves the survival rate; therefore, referral to a liver transplantation center is essential upon recognition of acute liver failure.

The presence of an elevated INR reflects decreased synthesis of liver-derived clotting factors, and the administration of fresh frozen plasma is not indicated in the absence of demonstrable bleeding or the need for invasive procedures.

Kidney failure is common in the setting of acute liver failure, and many patients require renal replacement therapy, which should be performed in a liver transplant center. Most patients requiring hemodialysis in this setting tolerate continuous renal replacement therapy better than intermittent hemodialysis.

There are several appropriate indications for endoscopic retrograde cholangiopancreatography (ERCP), and one of the most common is the evaluation of biliary obstruction. In these cases, ERCP can both be diagnostic and therapeutic if the obstruction can be removed or bypassed. In this patient, ERCP is not indicated because the ultrasound shows no signs of biliary obstruction.

KEY POINT

- Acute liver failure is an indication for immediate referral to a liver transplantation center.

Bibliography

Lee WM, Stravitz RT, Larson AM. Introduction to the revised American Association for the Study of Liver Diseases position paper on acute liver failure 2011. Hepatology. 2012;55:965-7. [PMID: 22213561] doi:10.1002/hep.25551

Item 51 Answer: D

Educational Objective: Treat left-sided ulcerative colitis.

Oral mesalamine with mesalamine enema is the most appropriate treatment. Ulcerative colitis typically presents with bloody diarrhea and abdominal discomfort, the severity of which is related to the extent and severity of inflammation. The distribution of ulcerative colitis is generally divided into proctitis (involving the rectum only), left-sided colitis (inflammation does not extend beyond the splenic flexure), and pancolitis (inflammation extends above the splenic flexure). The choice of treatment depends on the extent and severity of inflammation. This patient's stool passage frequency (three per day), intermittent hematochezia, normal blood count and C-reactive protein level, and normal vital signs categorize her disease as mild. Results of colonoscopy with biopsy show moderate inflammation of the rectum and

a sigmoid colon consistent with chronic idiopathic left-sided ulcerative colitis.

Mesalamine preparations are the mainstay of treatment in patients with mild to moderate disease. Mesalamine given orally or topically is effective in inducing and maintaining remission in ulcerative colitis. Evidence suggests that combined mesalamine therapy (oral and topical) is superior for induction of remission in mild to moderately active disease compared with oral or topical therapies alone; however, patient adherence to this dual treatment regimen can be difficult.

A mesalamine enema has topical effects up to the splenic flexure of the colon and would be a more effective topical agent when combined with oral mesalamine in this patient.

A mesalamine suppository is appropriate for treatment of ulcerative proctitis but is not effective for topical treatment of inflammation above the rectum.

KEY POINT

- Combined mesalamine therapy (oral and topical) is superior for induction of remission in mild to moderately active ulcerative colitis compared with oral or topical therapies alone.

Bibliography

Bressler B, Marshall JK, Bernstein CN, Bitton A, Jones J, Leontiadis GI, et al; Toronto Ulcerative Colitis Consensus Group. Clinical practice guidelines for the medical management of nonhospitalized ulcerative colitis: the Toronto consensus. Gastroenterology. 2015;148:1035-1058.e3. [PMID: 25747596] doi:10.1053/j.gastro.2015.03.001

Item 52 Answer: B

Educational Objective: **Evaluate dyspepsia.**

Stool antigen testing for *Helicobacter pylori* is the most appropriate next step in the management of this patient. The American College of Gastroenterology and Canadian Association of Gastroenterology have issued a joint recommendation that patients younger than age 60 years presenting with dyspepsia should first undergo a noninvasive test for *H. pylori* followed by eradication therapy if testing is positive. The committee gave a strong recommendation based on high-quality evidence for the "test and treat" strategy.

The pooled data from four trials including a total of 1608 patients with dyspepsia found no difference in the prevalence of dyspepsia at the end of 1 year of follow-up between patients undergoing the "test and treat" strategy versus those receiving a course of empirical proton pump inhibitor (PPI) therapy. Furthermore, there was a trend toward a reduction in cost for the "test and treat" strategy compared to empirical PPI therapy. For these reasons, testing for *H. pylori* is a more appropriate initial strategy for this patient than a course of omeprazole. In patients whose testing is negative for *H. pylori*, an empiric trial of PPI therapy (for example, omeprazole) can be considered before proceeding to any other testing.

Upper endoscopy should be performed in patients older than 60 years with persistent dyspeptic symptoms despite eradication of *H. pylori* and/or a trial of PPI therapy. Upper endoscopy could also be considered, regardless of age, in patients with a combination of alarm features, including a family history of gastric cancer, immigration from a region with increased risk for gastric cancer (Asia, Russia, and South America), and severe symptoms. Upper endoscopy is considered the gold standard for the exclusion of upper gastrointestinal structural causes of dyspepsia.

No other biochemical, structural (including right upper quadrant ultrasonography), or physiologic studies should be performed routinely for the evaluation of dyspepsia.

KEY POINT

- Patients younger than age 60 years presenting with dyspepsia should first undergo a noninvasive test for *Helicobacter pylori* followed by eradication therapy if testing is positive.

Bibliography

Moayyedi PM, Lacy BE, Andrews CN, Enns RA, Howden CW, Vakil N. ACG and CAG clinical guideline: management of dyspepsia. Am J Gastroenterol. 2017;112:988-1013. [PMID: 28631728] doi:10.1038/ajg.2017.154

Item 53 Answer: B

Educational Objective: **Treat amebic liver abscess.**

Metronidazole plus paromomycin is the most appropriate treatment for this patient with an amebic liver abscess. The two most common types of hepatic abscess are pyogenic and amebic. Pyogenic liver abscesses are the most common hepatic abscesses in the United States, whereas amebic abscesses are seen more frequently in the developing world. Pyogenic abscesses are typically polymicrobial, originating from gastrointestinal flora in the setting of intra-abdominal infections, malignancies, or procedures. Amebic abscesses are usually caused by the organism *Entamoeba histolytica*, and the mechanism of formation involves enteric infection with the invasion of amoeba through the intestinal mucosa and via the portal vein. With amebic abscesses, infection of the liver is asymptomatic until hepatic necrosis results in abscess development, at which time abdominal pain, fever, and leukocytosis develop. Amebic liver abscesses are seen in patients from endemic areas, such as India, Africa, or Central or South America, or in patients who have traveled to endemic areas. The typical presentation in travelers occurs 3 to 5 months after infection. Nearly all patients with an amebic abscess have positive serological studies for *E. histolytica*. The diagnosis is usually established with compatible imaging and serologic testing. Ultrasonography is less sensitive for the detection of pyogenic liver abscesses (CT is preferred) but may be equally sensitive for the detection of amebic abscesses. The mainstay of therapy for an amebic liver abscess is antibiotic therapy, such as metronidazole, plus a luminal agent, such as paromomycin, to eradicate the coexisting intestinal infection.

Meropenem is an effective broad-spectrum antibiotic that is often used to treat pyogenic liver abscesses. It has no role in the treatment of an amebic abscess.

Percutaneous drainage and surgical resection of an abscess are treatment options indicated for pyogenic liver abscesses. Surgical intervention is usually necessary for abscesses 5 cm or larger in size, complex abscesses, presence of gas-forming organisms, hemodynamic instability, biliary fistulization, or presence of a foreign body. These procedures are typically not needed in the treatment of amebic liver abscesses, which usually resolve with antimicrobial therapy.

KEY POINT

- The mainstay of therapy for amebic liver abscesses is antibiotic therapy, such as metronidazole, plus a luminal agent, such as paromomycin, to eradicate the coexisting intestinal infection.

Bibliography

Bonder A, Afdhal N. Evaluation of liver lesions. Clin Liver Dis. 2012;16:271-83. [PMID: 22541698] doi:10.1016/j.cld.2012.03.001

Item 54 Answer: D

Educational Objective: Diagnose ulcerative colitis.

Ulcerative colitis is the most likely diagnosis in this patient. The differential diagnosis of chronic bloody diarrhea includes inflammatory bowel disease (ulcerative colitis or Crohn colitis) and chronic ulcerating infections such as cytomegalovirus or *Entamoeba histolytica*. This patient's stool studies for enteric pathogens are negative, making Crohn colitis or ulcerative colitis the most likely cause of her symptoms. The mucosal biopsy results showing crypt architectural distortion confirm a chronic colitis such as ulcerative colitis or Crohn disease. The endoscopic description of inflammation beginning at the anorectal verge and extending proximally in a continuous fashion with transition to normal mucosa at splenic flexure is consistent with left-sided ulcerative colitis. Crohn disease characteristically has a patchy progression pattern resulting in "skip lesions" and may spare the rectum, making Crohn colitis less likely in this case.

Entamoeba histolytica causes amoebic dysentery. In the United States, amebiasis is usually diagnosed in immigrants or travelers returning from endemic areas, or in institutional settings. Although most infected persons are asymptomatic, others may develop bloody or watery diarrhea, abdominal pain, and fever. Rarely, a chronic syndrome of diarrhea, weight loss, and abdominal pain can mimic inflammatory bowel disease. Stool microscopy for ova and parasites can aid in the diagnosis by detecting the protozoa, but stool antigen testing is more sensitive. This patient's negative travel history and findings on colonoscopy and biopsy are not consistent with amebiasis.

Cytomegalovirus infection is an uncommon infection in immunocompetent patients but can occur and cause significant symptoms. The most common presenting symptoms are diarrhea, fever, and abdominal pain; half of patients have grossly bloody stools. The most common finding on endoscopy is well-demarcated ulcerations. On biopsy, histological findings include multinucleated giants cells with eosinophilic inclusions. The rarity of this condition coupled with the patient's colonoscopy and biopsy findings make cytomegalovirus infection an unlikely diagnosis.

KEY POINT

- Chronic bloody diarrhea and abdominal discomfort are typical presenting symptoms of inflammatory bowel disease; endoscopic findings help distinguish ulcerative colitis from Crohn disease.

Bibliography

Danese S, Fiocchi C. Ulcerative colitis. N Engl J Med. 2011;365:1713-25. [PMID: 22047562] doi:10.1056/NEJMra1102942

Item 55 Answer: C

Educational Objective: Test for Wilson disease.

Serum ceruloplasmin measurement is the most appropriate test for this patient. Wilson disease is an autosomal recessive disorder of copper excretion with subsequent accumulation of copper in the liver and central nervous system, cornea, kidney, joints, and cardiac muscle resulting in organ dysfunction. Children aged 10 years or younger with Wilson disease tend to present with acute liver failure; older patients (aged 30 years or younger) present with chronic liver disease and/or neurologic manifestations. Wilson disease should be considered in all patients younger than age 40 years who have unexplained liver disease. When Wilson disease causes acute hepatitis, usually in young patients, the sudden release of copper from liver cells can also induce hemolytic anemia. In this patient with evidence of hepatic encephalopathy, hemolytic anemia, low alkaline phosphatase level, and unconjugated bilirubinemia, the diagnosis of Wilson disease should be considered. The serum ceruloplasmin level is used to test for Wilson disease. Slit-lamp examination of the cornea can be performed to evaluate for Kayser-Fleischer rings, which most commonly occur in patients with neurologic manifestations of Wilson disease. A 24-hour urine copper assessment can be performed to confirm an excessive amount of copper excretion.

The diagnosis of primary biliary cholangitis is generally made on the basis of a cholestatic liver enzyme profile in the setting of a positive antimitochondrial antibody test. The predominant liver enzyme abnormality is an increase in serum alkaline phosphatase level. This patient's biochemical profile reflects hepatocellular injury, not cholestasis, and an antimitochondrial antibody test is not indicated.

With a negative test for hepatitis B virus surface antigen, this patient is very unlikely to have a hepatitis B viral infection and measurement of a hepatitis B virus DNA level is not indicated.

Symptomatic hereditary hemochromatosis is usually diagnosed after age 40 years and is often diagnosed later in women than in men, due to iron losses associated with menstruation, pregnancy, and lactation. The most sensitive initial diagnostic study is measurement of the serum transferrin saturation. The patient's sex, young age, and presence of a hemolytic anemia make the diagnosis of hereditary hemochromatosis unlikely and the measurement of a transferrin level unnecessary.

KEY POINT

- Wilson disease should be considered in all patients younger than age 40 years who have unexplained liver disease.

Bibliography

Eapen CE, Kumar S, Fleming JJ, Ramakrishna B, Abraham L, Ramachandran J. Copper and liver disease. Gut. 2012;61:63. [PMID: 22139599] doi:10.1136/gutjnl-2011-301743

Item 56 Answer: A

Educational Objective: Treat achalasia with botulinum toxin injection.

Endoscopic botulinum toxin injection is the best treatment option for this patient because his cardiac status places him at an unacceptable surgical risk. Achalasia is a motility disorder of the esophagus that results in aperistalsis and inadequate relaxation of the lower esophageal sphincter (LES). The cause of achalasia is unknown, but the pathophysiologic process involves ganglion cell and myenteric plexus degeneration in the esophageal body and LES. This nerve imbalance leads to uncontested action by cholinergic nerves and incomplete LES relaxation. The clinical presentation of achalasia consists of dysphagia to both solids and liquids. Additional symptoms may include regurgitation, chest pain, and heartburn. Standard treatments for achalasia include surgical myotomy and endoscopic pneumatic dilation. Botulinum toxin injection inhibits acetylcholine release, resulting in relaxation of the LES and relief of achalasia symptoms in up to 85% of patients. However, approximately 50% of patients will experience recurrent symptoms within 6 to 24 months after injection.

Medical therapy with calcium channel blockers or long-acting nitrates is considered third-line therapy because its effectiveness is limited. Medications may be used early in treatment, in patients who decline other interventions, before definitive treatment, and in patients who have a recurrence in symptoms after botulinum toxin injection for achalasia.

Studies have shown that endoscopic pneumatic dilation and surgical myotomy result in similar clinical outcomes in patients with achalasia, with choice of therapy depending on local expertise. Pneumatic dilation is the most effective nonsurgical treatment and is more cost-effective than surgical myotomy, but it is associated with serious complications, such as esophageal perforation. Therefore, patients who are not surgical candidates should not undergo endoscopic dilation treatment of achalasia.

KEY POINT

- Patients with achalasia who are at high surgical risk should be treated with endoscopic botulinum toxin injection.

Bibliography

Vaezi MF, Pandolfino JE, Vela MF. ACG clinical guideline: diagnosis and management of achalasia. Am J Gastroenterol. 2013;108:1238-49; quiz 1250. [PMID: 23877351] doi:10.1038/ajg.2013.196

Item 57 Answer: B

Educational Objective: Recognize atypical chest pain and evaluate before starting treatment for gastroesophageal reflux disease.

The most appropriate next step in management of this patient is electrocardiography followed by evaluation for cardiac disease. Although gastroesophageal reflux disease (GERD) can present with symptoms of chest pain, this patient's pain is also exertional (occurs while walking up stairs), which is not typical in GERD. Failure to identify underlying cardiac disease in the setting of atypical chest pain can be catastrophic. Although this patient may have GERD, it is essential to evaluate her for heart disease before beginning empiric treatment for GERD. GERD is the most common cause of noncardiac chest pain, and chest pain caused by esophageal disorders can be difficult to distinguish from cardiac chest pain because of the anatomic proximity and common innervation of the esophagus and the heart.

Barium esophagography is recommended as the initial test for evaluation of dysphagia but is not recommended for the evaluation of typical GERD symptoms.

In patients with typical GERD symptoms, no additional testing is required and an empiric trial of a proton pump inhibitor (PPI) can be initiated. Failure to improve after 8 weeks of standard therapy should prompt further evaluation. In patients with atypical chest pain, treatment with a PPI is appropriate after ruling out cardiac disease as a cause of the chest pain.

An upper endoscopy is indicated in patients with gastrointestinal alarm symptoms such as anemia, dysphagia, or unintentional weight loss. Upper endoscopy is the primary tool to evaluate mucosal inflammation in the upper gastrointestinal tract.

KEY POINT

- In patients with atypical chest pain, a cardiac cause must be ruled out before starting treatment for gastroesophageal reflux disease.

Bibliography

Katz PO, Gerson LB, Vela MF. Guidelines for the diagnosis and management of gastroesophageal reflux disease. Am J Gastroenterol. 2013;108:308-28; quiz 329. [PMID: 23419381] doi:10.1038/ajg.2012.444

Item 58 Answer: D

Educational Objective: Diagnose the relapsing, remitting variant of hepatitis A viral infection.

Relapsing, remitting hepatitis A virus (HAV) infection is the most likely diagnosis. This patient returned from Mexico with an icteric illness and tested positive for HAV IgM, consistent with acute HAV infection. Her HAV-infection symptoms resolved and liver chemistry tests normalized, but she developed an icteric illness 3 months later. This presentation is most consistent with an atypical course of HAV infection known as relapsing, remitting HAV infection. It is rare but was reported to occur in up to 10% of patients with HAV infection in one series. Patients may have multiple clinical or biochemical relapses but will spontaneously improve within months to 1 year without intervention. The relapses tend to be milder, are more likely to be associated with cholestasis, and may be associated with extrahepatic manifestations including nephritis, arthralgia, vasculitis, and cryoglobulinemia.

In rare cases, HAV infection has been observed to trigger autoimmune hepatitis. However, testing does not show the typical antibodies (anti-smooth muscle or antinuclear antibodies) or elevated IgG levels commonly seen in patients with autoimmune hepatitis.

Acute leptospirosis is manifested by high fever, headache, severe myalgia, conjunctival injection, abdominal pain, diarrhea, pharyngitis, and occasionally a pretibial rash. The patient's clinical course is not compatible with leptospirosis.

Malarial infection can result in jaundice due to hemolysis or, less commonly, cholestasis. However, Mexico is considered to be a very low-risk travel destination for acquisition of malaria.

KEY POINT

- The relapsing, remitting variant of hepatitis A viral infection is characterized by multiple clinical or biochemical relapses with spontaneous improvement within months to 1 year without intervention.

Bibliography

Matheny SC, Kingery JE. Hepatitis A. Am Fam Physician. 2012;86:1027-34; quiz 1010-2. [PMID: 23198670]

Item 59 Answer: A

Educational Objective: Manage chronic proton pump inhibitor therapy.

The most appropriate next step in management is an attempt to discontinue or reduce pantoprazole. Guidelines recommend that patients with symptomatic gastroesophageal reflux disease (GERD) syndromes without esophagitis be treated with a short course of a proton pump inhibitor (PPI) to achieve symptom control. Maintenance PPI therapy is recommended for patients with GERD who continue to have symptoms after the initial course of a PPI is discontinued, and for those who have erosive esophagitis or Barrett esophagus. In 2010, the FDA revised the prescription and nonprescription labels for PPIs to include possible increased risk for hip, wrist, and spine fractures. The FDA concluded that fracture risk was greatest with higher doses of PPIs or PPI exposure for 1 year or longer. The evidence associating PPI therapy with hip fracture was inconsistent, and guidelines recommend not stopping PPI therapy when it is otherwise indicated in patients at risk for osteoporosis. Other possible PPI-related adverse reactions include vitamin B_{12} and mineral (calcium and magnesium) malabsorption, as well as increased risk for community-acquired pneumonia, *Clostridium difficile* infection, and cardiovascular events. Many guidelines recommend that long-term PPI therapy be given at the lowest effective dose, which may include as-needed therapy. Other recommendations encourage an attempt to either reduce or stop chronic PPI therapy for uncomplicated GERD at least once per year.

Upper endoscopy is not indicated in patients whose GERD symptoms are controlled in the absence of alarm symptoms, such as dysphagia, weight loss, or anemia.

Prokinetic agents such as metoclopramide should not be used in the treatment of GERD unless gastroparesis is also present. Prokinetic drugs are no more effective than placebo, and these drugs can be associated with acute dystonic reaction and tardive dyskinesia. H_2 blockers, such as ranitidine, can be used alone in patients without erosive esophagitis whose symptoms respond to H_2-blocker therapy.

Sucralfate is sulfated sucrose complexed with aluminum hydroxide and can bind to damaged mucosa. It has been shown to prevent acute mucosal damage and heals chronic ulcers without altering gastric acid concentration or pepsin secretion. Sucralfate has no role in the treatment of GERD because, as with metoclopramide, studies have shown that it is no more effective than placebo.

KEY POINT

- Long-term proton pump inhibitor (PPI) therapy for uncomplicated gastroesophageal reflux disease should be given at the lowest effective dose possible, and consideration should be given to reducing or stopping PPI therapy at least once a year.

Bibliography

Katz PO, Gerson LB, Vela MF. Guidelines for the diagnosis and management of gastroesophageal reflux disease. Am J Gastroenterol. 2013;108:308-28; quiz 329. [PMID: 23419381] doi:10.1038/ajg.2012.444

Item 60 Answer: D

Educational Objective: Treat intrahepatic cholestasis of pregnancy with ursodeoxycholic acid.

Ursodeoxycholic acid therapy is the most appropriate management for this patient. Intrahepatic cholestasis of pregnancy is a liver condition that affects pregnant women in the second or third trimester. This condition spontaneously improves within 48 hours of delivery. Typical symptoms include diffuse pruritus, and there is typically a mild increase

in serum transaminase concentrations. Associated risks include premature delivery as well as higher rates of fetal death. Mutations in bile salt transporters have been implicated in the pathophysiology. The mainstay of therapy for intrahepatic cholestasis of pregnancy is ursodeoxycholic acid, which is associated with alleviated symptoms, improved fetal outcomes, and improved liver test abnormalities.

Cholestasis of pregnancy can be diagnosed in pregnant women with otherwise unexplained pruritus and abnormal liver chemistry tests. Elevated levels of total serum bile acid in a pregnant woman with pruritus are considered diagnostic for cholestasis of pregnancy in the absence of an alternative diagnosis. In this patient with findings compatible with intrahepatic cholestasis of pregnancy and a normal hepatic ultrasound, a liver biopsy is not needed.

HELLP (Hemolysis, Elevated Liver enzymes, and Low Platelets) syndrome presents during the third trimester and is an advanced complication of preeclampsia. HELLP syndrome typically presents with abdominal pain, new-onset nausea and vomiting, pruritus, and jaundice. A peripheral blood smear will reveal schistocytes. This patient is not anemic and does not have thrombocytopenia or hypertension; therefore, a peripheral blood smear to support the diagnosis of HELLP syndrome is not needed.

Pruritic urticarial papules and plaques of pregnancy (PUPPP) is the most common specific dermatosis of pregnancy. PUPPP is a clinical diagnosis confirmed by the appearance late in the third trimester of erythematous plaques in the distribution of striae. Persistent and bothersome pruritus is a symptomatic hallmark of the condition. It is not associated with jaundice or elevated transaminase levels. The condition usually resolves shortly after delivery. The first-line option for therapy is usually topical glucocorticoids of low to mid potency. Topical glucocorticoids are of no value in intrahepatic cholestasis of pregnancy.

KEY POINT

- The mainstay of therapy for intrahepatic cholestasis of pregnancy is ursodeoxycholic acid, which is associated with alleviated symptoms, improved fetal outcomes, and improved liver test abnormalities.

Bibliography

Bacq Y, le Besco M, Lecuyer AI, Gendrot C, Potin J, Andres CR, et al. Ursodeoxycholic acid therapy in intrahepatic cholestasis of pregnancy: results in real-world conditions and factors predictive of response to treatment. Dig Liver Dis. 2017;49:63-69. [PMID: 27825922] doi:10.1016/j.dld.2016.10.006

H

Item 61 Answer: A

Educational Objective: Evaluate isolated right-colon ischemia.

CT angiography is the best next test for this patient, whose clinical presentation with the sudden onset of right-sided, cramping abdominal pain followed by a bloody bowel movement is typical of isolated right-colon ischemia. A CT scan showing thickening of the ascending colon and the colonoscopy features are helpful in confirming this diagnosis. The most common cause of colon ischemia is a nonocclusive low-flow state in the colonic microvasculature. Most cases of colonic ischemia involve the left colon, which is supplied by the inferior mesenteric artery; as with ischemia involving the right colon, the diagnosis is clinical and supported by CT and colonoscopy. Patients with left-sided colonic ischemia tend to heal well with conservative therapy alone, whereas isolated right-colon ischemia can be the harbinger of acute mesenteric ischemia caused by a focal thrombus or embolus of the superior mesenteric artery. This artery supplies both the small intestine and right colon, and the consequences of acute mesenteric ischemia involving the small bowel are severe, with mortality rates that can approach 60%. For this reason, patients with isolated right-colon ischemia require urgent, noninvasive imaging of the mesenteric vasculature to assess the extent of ischemia and nature of the intervention. CT angiography is the recommended method of imaging for diagnosing acute mesenteric ischemia because it can be obtained rapidly. CT angiography visualizes the origins and length of the vessels, characterizes the extent of occlusion, and aids in planning revascularization.

Doppler ultrasonography of the mesenteric vessels is an effective, low-cost tool that can assess the proximal visceral vessels but has limited ability to visualize distal vessels. It is best reserved for the evaluation of patients with chronic mesenteric ischemia, which typically presents with postprandial abdominal pain, sitophobia, and weight loss.

MR angiography provides information about mesenteric arterial flow and avoids the potential harms of radiation and use of contrast that are associated with CT angiography; however, MR angiography takes longer to perform, lacks the required resolution to identify arterial occlusion, and can overestimate the severity of stenosis.

Selective catheter angiography was the standard method for diagnosing mesenteric ischemia; however, it is now used after a revascularization plan has been chosen because CT angiography can be obtained rapidly and is noninvasive.

KEY POINT

- Isolated right-colon ischemia may be a warning sign of acute mesenteric ischemia caused by embolism or thrombosis of the superior mesenteric artery and should be evaluated using CT angiography.

Bibliography

Clair DG, Beach JM. Mesenteric ischemia. N Engl J Med. 2016;374:959-68. [PMID: 26962730] doi:10.1056/NEJMra1503884

Item 62 Answer: B

H

Educational Objective: Diagnose medication-induced enteropathy.

Discontinuing olmesartan, an angiotensin II receptor blocker, is the most appropriate next step in the management of this patient. The patient's presentation is most consistent with drug-associated enteropathy related to

H CONT.

olmesartan. In 2013, the FDA issued a warning that olmesartan medoxomil can cause intestinal symptoms known as sprue-like enteropathy and approved labeling changes to include this concern. The enteropathy may develop months to years after starting olmesartan. Drug-associated enteropathy can mimic refractory celiac disease with findings of villous atrophy and increased intraepithelial lymphocytes in the first part of the duodenum. The clinical presentation can include severe diarrhea, weight loss, and dehydration requiring hospitalization. Most of the reported cases of drug-associated enteropathy are caused by olmesartan, although other angiotensin-receptor blocking drugs have been implicated. In addition to adequate fluid resuscitation, the offending medication should be discontinued. In most cases of drug-associated enteropathy, symptoms and pathological changes resolve when the drug is stopped.

Other medications, such as NSAIDs, proton pump inhibitors, antibiotics, colchicine, metformin, and cholesterol-lowering drugs (such as statins), can cause diarrhea and should be considered when evaluating a patient with symptoms of chronic diarrhea (>4 weeks' duration). However, because of the severity of the patient's presentation, the diarrhea is unlikely to be caused by atorvastatin. Additionally, atorvastatin and other statins are not linked to villous atrophy.

A gluten-free diet is the mainstay of treatment for celiac disease. Given the patient's normal celiac serology testing, his symptoms are unlikely to be caused by celiac disease and a gluten-free diet is not indicated. Villous atrophy and increased intraepithelial lymphocytes are not specific for celiac disease.

Other causes of villous atrophy, such as refractory celiac disease, Crohn disease, and autoimmune enteropathy, are treated with glucocorticoids such as prednisone. This patient's presentation and his older age are not consistent with these causes of villous atrophy, so glucocorticoids are not indicated.

KEY POINT

- Olmesartan causes medication-induced enteropathy that can mimic refractory celiac disease.

Bibliography

Ianiro G, Bibbò S, Montalto M, Ricci R, Gasbarrini A, Cammarota G. Systematic review: sprue-like enteropathy associated with olmesartan. Aliment Pharmacol Ther. 2014;40:16-23. [PMID: 24805127] doi:10.1111/apt.12780

Item 63 Answer: A

Educational Objective: Manage a patient with Barrett esophagus with low-grade dysplasia.

Endoscopic ablation therapy is the most appropriate next step in the management of this patient's Barrett esophagus with low-grade dysplasia. Barrett esophagus is a consequence of chronic reflux, regardless of the presence of gastroesophageal reflux disease (GERD) symptoms. The damage from GERD causes a change in the normal squamous lining of the distal esophagus to a specialized columnar epithelium visible on endoscopy. Barrett esophagus can present with no dysplasia, indefinite dysplasia, low-grade dysplasia, or high-grade dysplasia, and in some patients dysplasia progresses to adenocarcinoma of the esophagus. In the past, guidelines recommended a surveillance endoscopy in 6 months for patients with low-grade dysplasia. However, more recent guidelines recommend that patients with minimal comorbidities undergo endoscopic ablation therapy for permanent eradication of Barrett esophagus. Endoscopic ablation should be considered after confirmation of dysplasia by a second expert pathologist. If a patient is ineligible for or unwilling to undergo ablation therapy, annual surveillance endoscopy is recommended as an alternative. If two consecutive surveillance endoscopies show no dysplasia, the surveillance interval is changed every 3 to 5 years, the same interval used in patients with Barrett esophagus with no dysplasia. Patients with Barrett esophagus with high-grade dysplasia are also treated with endoscopic ablation.

Esophagectomy is reserved for patients in whom ablation does not result in eradication of the dysplasia or who have esophageal cancer.

Surgical treatments for GERD consist of laparoscopic fundoplication, an endoscopic procedure that does not cure Barrett esophagus or reduce the risk for progression of dysplasia or cancer, and bariatric surgery (for obese patients). Indications for surgery include patient preference to stop taking medication, medication side effects, large hiatal hernia, and refractory symptoms despite maximal medical therapy (although patients with medically refractory symptoms may be less likely to benefit from surgery). Approximately one third of patients require resumption of PPI therapy within 5 to 10 years after surgery. Postoperative complications include dysphagia, diarrhea, and inability to belch because of a tight fundoplication.

Guidelines recommend that patients with Barrett esophagus undergo surveillance only after adequate counseling regarding the risks and benefits of surveillance. Patients with nondysplastic Barrett esophagus should undergo endoscopic surveillance no more frequently than every 3 to 5 years.

KEY POINT

- Barrett esophagus with low-grade dysplasia should be treated with endoscopic ablation therapy in patients without significant comorbidities.

Bibliography

Shaheen NJ, Falk GW, Iyer PG, Gerson LB; American College of Gastroenterology. ACG Clinical guideline: diagnosis and management of Barrett's esophagus. Am J Gastroenterol. 2016;111:30-50; quiz 51. [PMID: 26526079] doi:10.1038/ajg.2015.322

Item 64 Answer: D

Educational Objective: Diagnose *Giardia lamblia* infection.

Stool testing for *Giardia* infection is the most appropriate next step in the management of this patient. The patient presents with persistent diarrhea, defined as lasting between

2 and 4 weeks, and because of his occupational exposure, the most likely cause is *Giardia lamblia* (also known as *Giardia intestinalis*). Transmission is waterborne or through the fecal-oral route. It occurs most commonly among children (especially in developing countries), child care workers, and backpackers or campers who drink untreated water from lakes, rivers, or wells. *Giardia* is a noninvasive organism that infects the small intestine and causes diarrhea associated with nausea, bloating, and foul-smelling gas due to malabsorption. Because *Giardia* cysts are intermittently shed, stool microscopy is less sensitive than stool antigen testing, and the recommended test is a stool enzyme-linked immunosorbent assay. Treatment options include tinidazole, metronidazole, and nitazoxanide. Treatment of giardiasis with metronidazole is curative in more than 85% of patients.

A colonoscopy is not indicated because this patient's diarrhea is not associated with weight loss, abdominal pain, or blood in the stool, making inflammatory bowel disease an unlikely diagnosis. Microscopic colitis would be an unlikely diagnosis in a 45-year-old man who is not taking any medications known to be associated with microscopic colitis, such as NSAIDs.

A CT scan of the abdomen and pelvis would be unlikely to suggest a cause for watery diarrhea of 4 weeks' duration. The patient's symptoms and occupation suggest a parasitic cause of diarrhea that would not be diagnosed with an imaging study.

A 24-hour 5-hydroxyindoleacetic acid measurement is used to evaluate for carcinoid tumors. Up to 85% of patients with gastrointestinal carcinoid syndrome experience intermittent flushing. In addition to flushing, diarrhea is prominent in most patients and is related to rapid intestinal transit time. Approximately 40% of patients also have right-sided valvular heart disease. This patient has no flushing or evidence of a heart murmur, making carcinoid syndrome unlikely and measurement of 5-hydroxyindoleacetic unnecessary.

KEY POINT

- *Giardia lamblia* infection is a common parasitic infection that occurs most often among children, child care workers, and backpackers or campers who drink untreated water from lakes, rivers, or wells.

Bibliography

DuPont HL. Persistent diarrhea: a clinical review. JAMA. 2016;315:2712-23. [PMID: 27357241] doi:10.1001/jama.2016.7833

Item 65 Answer: A

Educational Objective: Diagnose gastroparesis.

Gastric emptying scintigraphy is the most appropriate next step in management. The diagnosis of gastroparesis requires: (1) the presence of specific symptoms; (2) the absence of mechanical outlet obstruction; and (3) objective evidence of delay in gastric emptying into the duodenum. Commonly reported symptoms include early satiety, postprandial fullness, nausea, vomiting, upper abdominal pain, bloating, and weight loss, but these symptoms correlate poorly with the findings on objective gastric emptying tests. Various other upper gastrointestinal disorders can present with similar symptoms. Exclusion of other upper gastrointestinal disorders, objective documentation of delayed gastric emptying, and an attempt to identify the cause of the gastroparesis are essential before treatment. Retained food in the stomach during upper endoscopy is not objective evidence of delayed gastric emptying. The three tests to objectively demonstrate delayed gastric emptying are gastric scintigraphy, wireless motility capsule, and the gastric emptying breath test. If scintigraphy is pursued, the 4-hour study is preferred over 90- or 120-minute studies due to increased diagnostic accuracy.

A 24-hour pH probe may be considered when heartburn symptoms do not respond to a higher dose of acid suppression therapy, such as twice-daily proton pump inhibitor therapy or a proton pump inhibitor plus a histamine receptor antagonist. This patient's medical therapy for heartburn symptoms should be optimized before further testing is pursued, and this test will not explain the patient's predominant symptoms of nausea, bloating, and epigastric pain.

Both metoclopramide and domperidone are effective in the treatment of gastroparesis. Metoclopramide is the only FDA-approved agent for the treatment of gastroparesis. Domperidone can be used under a special program administered by the FDA. The side effects of metoclopramide include dystonia, Parkinson-type movements, and tardive dyskinesia. Domperidone can prolong the QT interval on electrocardiography, potentially leading to cardiac arrhythmia. Before initiating treatment for gastroparesis, it is necessary to confirm the diagnosis.

KEY POINT

- The diagnosis of gastroparesis requires the presence of specific symptoms, absence of mechanical outlet obstruction, and objective evidence of delay in gastric emptying into the duodenum.

Bibliography

Camilleri M, Parkman HP, Shafi MA, Abell TL, Gerson L; American College of Gastroenterology. Clinical guideline: management of gastroparesis. Am J Gastroenterol. 2013;108:18-37; quiz 38. [PMID: 23147521] doi:10.1038/ajg.2012.373

Item 66 Answer: B

H

Educational Objective: Treat bleeding esophageal varices.

Ciprofloxacin for 7 days is the most appropriate next treatment for this patient with variceal bleeding. Variceal bleeding is a life-threatening complication of portal hypertension. Risk factors for variceal hemorrhage are Child-Turcotte-Pugh class B and C cirrhosis, large varices (>5 mm), and the endoscopic finding of red markings on varices. Approximately 15% to 20% of patients die within 6 weeks of hemorrhage.

H CONT.

The mainstay of therapy for variceal hemorrhage is endoscopic therapy. Antibiotic therapy is an important adjunctive therapy for variceal bleeding because bacterial infection occurs in 30% to 40% of patients within 1 week of variceal bleeding. The most common infections seen are spontaneous bacterial peritonitis as well as bacteremia, urinary tract infections, and pneumonia. Antibiotic therapy after variceal bleeding reduces rates of infection and rebleeding as well as mortality after variceal bleeding. There is also benefit to administering antibiotics for patients with cirrhosis who present with nonvariceal upper gastrointestinal bleeding.

This patient does not require a blood transfusion. Hemodynamically stable patients with acute upper gastrointestinal bleeding, no acute coronary syndrome, and no history of peripheral vascular disease or stroke should be transfused when the hemoglobin level is 7 g/dL (70 g/L) or less. This transfusion threshold is associated with improved clinical outcomes compared to higher transfusion thresholds. The goal of transfusion is a hemoglobin level of 7 g/dL (70 g/L) to 9 g/dL (90 g/L). In the setting of hemodynamic stability, overtransfusion should be avoided because it can cause an increase of portal pressure and thereby precipitate rebleeding.

Platelet transfusion is not warranted because hemostasis has already been achieved. This patient has thrombocytopenia, but a transfusion of platelets also has the potential to cause volume overload leading to an increase in portal hypertension and rebleeding. Patients with thrombocytopenia with clinically significant active bleeding, as well as patients without bleeding in whom nonneuraxial surgery is planned, should be transfused to a target platelet count of 50,000 to 100,000/µL ($50\text{-}100 \times 10^9$/L) depending on the clinical circumstances.

Transjugular intrahepatic portosystemic shunt (TIPS) placement is useful in the 10% to 20% of patients with variceal bleeding in whom hemostasis is unable to be achieved by endoscopic therapy. In this patient in whom endoscopic therapy was successful, TIPS placement is not indicated.

KEY POINT

- The mainstay of therapy for variceal hemorrhage is endoscopic therapy, and adjunctive therapies such as antibiotic therapy improve outcomes.

Bibliography

Satapathy SK, Sanyal AJ. Nonendoscopic management strategies for acute esophagogastric variceal bleeding. Gastroenterol Clin North Am. 2014;43:819-33. [PMID: 25440928] doi:10.1016/j.gtc.2014.08.011

H

Item 67 Answer: D

Educational Objective: Manage hepatic encephalopathy.

Discontinuing alprazolam is the most appropriate next step in the management of this patient. Hepatic encephalopathy is a significant, potentially reversible, complication of cirrhosis, with cognitive impairment ranging from mild personality changes to overt coma. Hepatic encephalopathy is a clinical diagnosis and should be suspected in patients with cirrhosis who have changes in mental status, mood, or behavior. Hepatic encephalopathy can be seen in the setting of acute liver failure as well as cirrhosis. The initial management of hepatic encephalopathy centers on identifying and mitigating a precipitating factor. Up to 80% of patients have a precipitating factor, most commonly infection or gastrointestinal bleeding. Other precipitants include opioids, benzodiazepines, electrolyte abnormalities, hypoglycemia, hypoxia, transjugular intrahepatic portosystemic shunt placement, inappropriate lactulose dosing, and dehydration. In this patient who uses a benzodiazepine, alprazolam therapy should be discontinued and alternative means of managing anxiety must be sought. Tapering is likely unnecessary in this patient because the medication was initiated recently. All patients with overt episodic hepatic encephalopathy should undergo screening for infections, including diagnostic paracentesis when ascites is present.

CT of the head can be a useful study in patients with altered mental status of unknown cause, but in patients with hepatic encephalopathy without a history of head trauma or a focal neurological examination, head CT is unnecessary.

Early concerns regarding dietary protein consumption as a precipitant of hepatic encephalopathy have been largely debunked, and outside of rare circumstances, dietary protein restriction should not be undertaken, even in the setting of acute hepatic encephalopathy. Furthermore, due to the high risk for protein-calorie malnutrition in patients with cirrhosis, dietary protein restriction can result in worsened clinical outcomes.

Lactulose is first-line treatment and should be titrated to produce three stools per day. Rifaximin is added to lactulose for prevention of recurrent episodes after a second episode of hepatic encephalopathy. Due to its expense, it is not a first-line therapy for hepatic encephalopathy.

KEY POINT

- Up to 80% of patients with hepatic encephalopathy have a precipitating factor, most commonly infection or gastrointestinal bleeding.

Bibliography

Vilstrup H, Amodio P, Bajaj J, Cordoba J, Ferenci P, Mullen KD, et al. Hepatic encephalopathy in chronic liver disease: 2014 practice guideline by the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver. Hepatology. 2014;60:715-35. [PMID: 25042402] doi:10.1002/hep.27210

Item 68 Answer: B

Educational Objective: Screen for colorectal cancer in a high-risk individual.

This patient should undergo his first screening colonoscopy at age 40 years. Based on the patient's family history, he is at increased risk for colon cancer. Individuals with a first-degree relative with colon cancer or an advanced adenoma diagnosed at an age younger than 60 years, or two or more first-degree relatives with colon cancer or advanced

adenoma diagnosed at any age, should begin colon cancer screening at age 40 years (or 10 years earlier than the youngest age at which colon cancer was diagnosed in a first-degree relative, whichever is first). Colonoscopy, rather than imaging or stool-based testing, is the recommended screening modality. If colonoscopy is performed and findings are normal, the recommended interval for repeat screening is 5 years if the first-degree relative was younger than age 60 years at the time of diagnosis and 10 years if the first-degree relative was age 60 years or older at the time of diagnosis.

Although age 42 years is 10 years earlier than the age at which his father was diagnosed with colon cancer, guidelines recommend starting colon cancer screening at age 40 years or 10 years earlier than the family member's diagnosis, whichever comes first. Therefore, age 40 years is the appropriate age at which to begin screening in this patient.

In average-risk patients, 50 years is the recommended age to begin screening for colon cancer. Because of this patient's family history, waiting until age 50 years to begin screening for colon cancer is not appropriate.

KEY POINT

- Individuals with a first-degree relative with colon cancer or an advanced adenoma diagnosed at an age younger than 60 years, or two or more first-degree relatives with colon cancer or advanced adenoma diagnosed at any age, should begin colon cancer screening at age 40 years (or 10 years earlier than the youngest age at which colon cancer was diagnosed in a first-degree relative, whichever is first).

Bibliography

Lieberman DA, Rex DK, Winawer SJ, Giardiello FM, Johnson DA, Levin TR; United States Multi-Society Task Force on Colorectal Cancer. Guidelines for colonoscopy surveillance after screening and polypectomy: a consensus update by the US Multi-Society Task Force on Colorectal Cancer. Gastroenterology. 2012;143:844-57. [PMID: 22763141] doi:10.1053/j.gastro.2012.06.001

Item 69 Answer: B

Educational Objective: Treat hepatocellular carcinoma with liver transplantation.

Referral for liver transplantation is the most appropriate next step in management for this patient. A diagnosis of hepatocellular carcinoma can be made in a patient with cirrhosis in the presence of lesions larger than 1 cm that enhance in the arterial phase and have washout of contrast in the venous phase. This patient meets the Milan criteria (up to three hepatocellular carcinoma tumors ≤3 cm or one tumor ≤5 cm) for liver transplantation. Patients who meet the Milan criteria and have a tumor 2 cm or larger with arterial enhancement and venous washout on CT or MRI are eligible to receive Model for End-Stage Liver Disease exception points, placing them at a higher priority for liver transplantation.

Liver transplantation is the only curative therapy for hepatocellular carcinoma and for end-stage liver disease. Patients meeting the Milan criteria have excellent 5-year survival rates after liver transplantation.

Biopsy of the lesion is not indicated in this patient. In the context of cirrhosis, a lesion larger than 1 cm with contrast enhancement in the arterial phase and portal venous washout meets radiologic criteria for hepatocellular carcinoma and, therefore, does not require a lesion biopsy. Additionally, there is potential for harm from a lesion biopsy due to coagulopathy or the very small risk for tumor seeding.

Sorafenib is a multikinase inhibitor that is reserved for patients with advanced hepatocellular carcinoma with vascular invasion or extrahepatic spread that is not amenable to surgery, liver transplantation, or locoregional therapies. Treatment of these patients with sorafenib confers a survival benefit. This patient is not a candidate for resection and should be evaluated for liver transplantation; sorafenib is not indicated.

Surgical resection would be dangerous for this patient, given the evidence of portal hypertension, which confers increased risk for intraoperative bleeding as well as risk for postoperative liver failure.

KEY POINT

- Patients with cirrhosis and who meet the Milan criteria (up to three hepatocellular carcinoma tumors ≤3 cm or one tumor ≤5 cm) are best treated with liver transplantation and have excellent 5-year survival rates.

Bibliography

Heimbach J, Kulik LM, Finn R, Sirlin CB, Abecassis M, Roberts LR, et al. AASLD guidelines for the treatment of hepatocellular carcinoma. Hepatology. 2017. [PMID: 28130846] doi:10.1002/hep.29086

Item 70 Answer: C

Educational Objective: Diagnose eosinophilic esophagitis.

Eosinophilic esophagitis is the most likely diagnosis in this patient. Defined as esophageal squamous mucosal inflammation caused by eosinophilic infiltration, eosinophilic esophagitis is commonly seen in young men presenting with symptoms of dysphagia. It often co-occurs in patients with food allergies, asthma, and eczema. Rings and furrows in the esophagus are common findings on upper endoscopy. The diagnosis is confirmed with biopsies of the esophagus showing more than 15 eosinophils/hpf. Treatment begins with a trial of a proton pump inhibitor (PPI) for a period of 2 months. Clinical improvement with a PPI indicates gastroesophageal reflux disease–associated eosinophilia rather than eosinophilic esophagitis. In this case, repeat upper endoscopy with biopsies should be considered; if esophageal eosinophilia is still present, the diagnosis of eosinophilic esophagitis is confirmed. For patients with confirmed eosinophilic esophagitis, treatment includes restriction of dietary elements (elemental diet or targeted elimination diet) and swallowed aerosolized topical glucocorticoids. Patients should also be counseled that the condition may recur.

This patient's endoscopic findings are not consistent with a diagnosis of achalasia. In patients with achalasia, endoscopy often shows a dilated esophageal body with resistance at the gastroesophageal junction. A manometry test confirms the diagnosis of achalasia. The most effective treatment options include pneumatic dilation and surgical myotomy.

Candida esophagitis rarely occurs in immunocompetent patients but is seen more often in patients with HIV and other immunocompromised patients. The most common symptom is odynophagia rather than dysphagia. Oral thrush may also be present, but its absence does not exclude esophageal involvement. Endoscopic findings in patients with *Candida* esophagitis are small, raised, white plaques. It is treated with oral fluconazole and management of the immunocompromised state.

Because this patient takes only a multivitamin and has no ulcers seen on endoscopy, pill-induced esophagitis is unlikely. Pill-induced esophagitis has been observed with medications including alendronate, quinidine, tetracycline, doxycycline, potassium chloride, ferrous sulfate, and mexiletine. Pills typically cause local injury at sites of anatomic narrowing of the esophagus. Clinical symptoms include chest pain, dysphagia, and odynophagia. Symptoms may begin hours to days after starting therapy, and stopping the medication often leads to symptom relief.

KEY POINT

- Eosinophilic esophagitis typically presents in young men with symptoms of dysphagia and in patients with a history of food allergies, eczema, and asthma.

Bibliography

Dellon ES, Gonsalves N, Hirano I, Furuta GT, Liacouras CA, Katzka DA; American College of Gastroenterology. ACG clinical guideline: evidenced based approach to the diagnosis and management of esophageal eosinophilia and eosinophilic esophagitis (EoE). Am J Gastroenterol. 2013;108:679-92; quiz 693. [PMID: 23567357] doi:10.1038/ajg.2013.71

Item 71 Answer: D

Educational Objective: Manage asymptomatic gallstones.

This patient's asymptomatic gallstone disease requires no further intervention at this time but should be managed as symptoms arise. Gallstone disease is a common finding in up to 15% of patients in Western countries. Gallstones that are found incidentally during abdominal imaging performed for another reason do not usually require intervention. Stones that produce symptoms typical of biliary colic or cause symptoms due to passage of the stone into the common bile duct require intervention. This patient has no symptoms potentially attributable to gallstones, and the ultrasonographic findings do not suggest any complications of gallstones. Because there are no complications, no intervention is necessary at this time and clinical observation is the appropriate management.

Eighty percent of patients with asymptomatic gallstones remain asymptomatic over a 15-year period, and most serious complications of gallstone disease are preceded by an episode of biliary colic; therefore, cholecystectomy is not generally advised in asymptomatic patients. Indications for cholecystectomy include symptomatic disease such as biliary colic or cholecystitis. Prophylactic cholecystectomy is recommended for patients with an anomalous pancreaticobiliary duct junction, gallbladder polyps 1 cm or larger, gallbladder polyp(s) with concomitant gallstones, or polyps of any size in the setting of primary sclerosing cholangitis. Prophylactic cholecystectomy can also be considered in patients with a porcelain gallbladder or with gallstones larger than 3 cm. These patients are at increased risk for gallbladder cancer. In this patient with small, asymptomatic gallstones, there is no indication for surgical intervention.

Referral for endoscopic retrograde cholangiopancreatography (ERCP) is not warranted in this setting because the patient is asymptomatic. Patients with gallstones in the common bile duct or patients who are not candidates for cholecystectomy may benefit from ERCP with sphincterotomy to reduce the risk for recurrent bouts of cholangitis.

Serial abdominal imaging, such as ultrasonography, to monitor asymptomatic gallstones is not warranted. Patients with gallbladder polyps may benefit from monitoring with serial gallbladder ultrasound because gallbladder polyps are a risk factor for gallbladder cancer. Diagnosis at a late stage contributes to the poor prognosis of gallbladder cancer.

KEY POINT

- Incidentally found gallstones with no associated symptoms and no complications require no further intervention.

Bibliography

Warttig S, Ward S, Rogers G; Guideline Development Group. Diagnosis and management of gallstone disease: summary of NICE guidance. BMJ. 2014;349:g6241. [PMID: 25360037] doi:10.1136/bmj.g6241

Item 72 Answer: A

H

Educational Objective: Diagnose aortoenteric fistula.

A CT scan with intravenous contrast is the most appropriate next test for this patient. The patient presents with the classic "herald bleed" of aortoenteric fistula: a brisk bleed associated with hypotension that stops spontaneously and then is followed later by massive gastrointestinal hemorrhage. An aortoenteric fistula is a communication between the aorta and the gastrointestinal tract, most commonly located in the distal duodenum, especially the third portion, because the duodenum is fixed and located just anterior to the aorta. The possibility of an aortoenteric fistula must be considered in a patient with previous aortic graft surgery who presents with gastrointestinal bleeding. It is a life-threatening condition, with a mortality rate of 50% even with surgical intervention. In this setting, the aortoenteric fistula is most commonly due to graft infection, and associated fever and leukocytosis occurs. When there is a high degree of suspicion for aortoenteric fistula, CT with intravenous contrast should be performed before other

H CONT.

types of gastrointestinal evaluation because CT can be performed promptly and is noninvasive. CT can reveal evidence of graft infection, such as perigraft soft-tissue thickening or loss of tissue planes, and its reported sensitivity for aortoenteric fistula is 80% or greater.

Mesenteric angiogram can detect bleeding rates as slow as 1 mL/min compared with 0.2 mL/min for tagged red blood cell scintigraphy; however, given the intermittent nature of bleeding from an aortoenteric fistula, mesenteric angiogram and tagged red blood cell scintigraphy are rarely helpful in the diagnosis of this condition.

Upper endoscopy may be performed to rule out other more common sources of bleeding, but in this patient, the presence of fever, leukocytosis, and bleeding points to aortoenteric fistula as the most likely diagnosis, and CT angiogram is the most urgently needed test.

KEY POINT

- Gastrointestinal bleeding occurring in patients following aortic graft surgery should raise the possibility of aortoenteric fistula; CT with contrast is the initial test in appropriate patients.

Bibliography

Singh M, Koyfman A, Martinez JP. Abdominal vascular catastrophes. Emerg Med Clin North Am. 2016;34:327-39. [PMID: 27133247] doi:10.1016/j.emc.2015.12.014

H

Item 73 Answer: C

Educational Objective: Manage lower gastrointestinal bleeding.

Colonoscopy within 24 hours with adequate bowel preparation is the most appropriate next step in management. Almost 80% of lower gastrointestinal bleeding (LGIB) is due to diverticulosis, colitis, hemorrhoids, or postpolypectomy bleeding. LGIB typically stops within 24 hours. Colonoscopy is the recommended initial diagnostic test after hemodynamic resuscitation in most patients with significant LGIB. LGIB typically occurs in older individuals and presents as acute bright red blood per rectum or red- or maroon-colored stool (hematochezia). Colonoscopy is able to identify the source of bleeding in two thirds of patients. The American College of Gastroenterology's 2016 guidelines for LGIB recommend oral bowel preparation to increase colonoscopy's diagnostic yield. Randomized controlled trials have not shown a benefit in clinical outcomes or cost with rapid bowel preparation and colonoscopy within 8 to 12 hours compared with a standard oral bowel preparation and colonoscopy within 24 hours for patients with LGIB.

For patients who continue to bleed and have failed endoscopic hemostasis treatments (for example, electrocoagulation, hemoclips, submucosal epinephrine injection), the next therapeutic step is arterial embolization of the bleeding source. Major complications include contrast dye reactions, acute kidney injury, transient ischemic attack, bowel ischemia, hematoma formation, and femoral artery thrombosis. This patient should be evaluated first with colonoscopy before using a more invasive treatment strategy.

Radiographic techniques such as tagged red cell scintigraphy may be useful in evaluating overt gastrointestinal bleeding from an unknown source. Nuclear scans can identify only a general area where bleeding is occurring; they cannot offer accuracy or intervention. Follow-up studies after a positive scan can include repeat endoscopy or angiography; both can offer more accurate localization and therapy. Nuclear scans are often done before angiography.

Transfusion strategies specifically for patients with LGIB have not been developed. Data extrapolated from patients with upper gastrointestinal bleeding found that a restrictive transfusion strategy with a transfusion threshold of hemoglobin less than 7 g/dL (70 g/L) improved survival and decreased rebleeding when compared with a threshold of 9 g/dL (90 g/L). Patients with massive bleeding, acute coronary syndrome, symptomatic peripheral vascular disease, or a history of cerebrovascular disease were excluded from these studies and may benefit from a more lenient transfusion strategy.

KEY POINT

- Colonoscopy is the recommended initial diagnostic test after hemodynamic resuscitation in most patients with significant lower gastrointestinal bleeding.

Bibliography

Strate LL, Gralnek IM. ACG clinical guideline: management of patients with acute lower gastrointestinal bleeding. Am J Gastroenterol. 2016;111:459-74. [PMID: 26925883] doi:10.1038/ajg.2016.41

Item 74 Answer: C

H

Educational Objective: Treat uncomplicated diverticulitis.

The patient has uncomplicated diverticulitis that can be managed with oral antibiotics. Approximately 5% of patients with diverticula will experience an episode of diverticulitis. Symptoms include abdominal pain, fever, and altered bowel habits. Physical examination findings include fever, left-lower-quadrant tenderness, and/or a lower abdominal or rectal mass. If clinical features are highly suggestive of diverticulitis, imaging studies are unnecessary. If the diagnosis is not clear or if an abscess is suspected (severe pain, high fever, palpable mass), CT imaging is indicated. Although the use of a 7-day course of oral antibiotics does not shorten the clinical course of diverticulitis, it may prevent complications from diverticulitis, such as an abscess, and may help prevent a future episode of diverticulitis. The antimicrobial agents used should cover colonic organisms and include anaerobic coverage (such as ciprofloxacin and metronidazole). Treatment can be done on an outpatient basis with close monitoring, and the patient should adhere to a liquid diet for 2 to 3 days, then advance the diet as tolerated. The routine use of antibiotics in uncomplicated diverticulitis has been questioned because of overuse of antibiotics.

H CONT.

Colonoscopy should not be done during acute diverticulitis due to the risk for perforation. In patients who have not undergone screening colonoscopy within the past 3 years, colonoscopy should be done 4 to 8 weeks after resolution of symptoms to exclude colon malignancy.

Intravenous antibiotics are appropriate in patients who cannot take oral medications or who have complicated diverticulitis, such as abscess or fistula formation. Fistulas may form between the colon and other adjacent structures including the bladder, vagina, skin, or peritoneum. CT-guided percutaneous drainage of abscesses is preferred.

Surgery is required for diverticulitis complicated by peritonitis and may be lifesaving. Patients with recurrent diverticulitis may also benefit from surgical resection of the affected area of the colon.

KEY POINT

- Patients with uncomplicated diverticulitis should be treated conservatively with oral antibiotics.

Bibliography

Strate LL, Peery AF, Neumann I. American Gastroenterological Association Institute technical review on the management of acute diverticulitis. Gastroenterology. 2015;149:1950-1976.e12. [PMID: 26453776] doi: 10.1053/j.gastro.2015.10.001

Item 75 Answer: C

Educational Objective: Manage a patient with Barrett esophagus that is indefinite for dysplasia.

The most appropriate next step in managing this patient is to optimize medical therapy and then repeat upper endoscopy. This patient's Barrett esophagus is indefinite for dysplasia, which falls between nondysplastic Barrett esophagus and low-grade dysplasia. In patients whose Barrett esophagus is indefinite for dysplasia, medical therapy for gastroesophageal reflux disease (GERD) should be optimized (in this patient, proton pump inhibitor therapy would increase to twice daily) and then the patient should receive a repeat upper endoscopy. Guidelines do not specify a time for repeating the endoscopy; 6 months to 1 year after antisecretory therapy is optimized would be reasonable. If the repeat endoscopy still shows Barrett esophagus that is indefinite for dysplasia, the patient should continue medical therapy and undergo a repeat endoscopy in 1 year. If the endoscopy is normal at 1 year, a surveillance interval of 3 to 5 years can be resumed.

The patient has a history of GERD, which can lead to Barrett esophagus. Other risk factors for Barrett esophagus include male gender, age, current or past smoking, central obesity, and white race. Barrett esophagus is a precancerous condition that is classified with five levels of histologic findings, from no dysplasia to esophageal cancer. It may progress from intestinal metaplasia to low-grade dysplasia to high-grade dysplasia to invasive adenocarcinoma.

Endoscopic ablation therapy is indicated for patients with Barrett esophagus with low-grade or high-grade dysplasia, although continued endoscopic surveillance is also acceptable for patients with low-grade dysplasia. Because this patient's Barrett esophagus is indefinite for dysplasia, endoscopic ablation therapy is inappropriate.

Esophagectomy is considered for patients with a diagnosis of esophageal cancer.

A repeat endoscopy at 1 year without optimizing medical therapy for GERD is not recommended by current guidelines. Patients with nondysplastic Barrett esophagus should undergo a repeat surveillance endoscopy in 3 to 5 years. Patients with Barrett esophagus with low-grade dysplasia should undergo surveillance endoscopy in 6 to 12 months to detect prevalent dysplasia, and dysplasia should be confirmed by an expert pathologist.

KEY POINT

- Patients whose Barrett esophagus is indefinite for dysplasia should begin optimized antisecretory medical therapy and undergo a repeat endoscopy.

Bibliography

Shaheen NJ, Falk GW, Iyer PG, Gerson LB; American College of Gastroenterology. ACG Clinical Guideline: Diagnosis and Management of Barrett's Esophagus. Am J Gastroenterol. 2016;111:30-50; quiz 51. [PMID: 26526079]

Item 76 Answer: A

Educational Objective: Evaluate fecal incontinence in an elderly patient.

An abdominal radiograph is the most appropriate next step in management of this patient. Fecal incontinence is the involuntary loss of stool. Prevalence increases with age and is 16% in adults older than 70 years. Urge fecal incontinence is the inability to postpone defecation. This patient's explosive diarrhea is the likely source of her urge fecal incontinence. Before treating the diarrhea, it is essential to determine whether the diarrhea is due to overflow from fecal loading (excess stool in the colon). An abdominal radiograph is a simple, safe, and inexpensive diagnostic test. Fecal loading with resultant overflow diarrhea is a common cause of fecal incontinence in elderly patients, particularly those who are hospitalized or have degenerative neurologic disorders. This patient has several risk factors for developing fecal loading, including Alzheimer dementia, history of constipation, and use of constipating medications (memantine and calcium).

Anorectal manometry is useful in the diagnostic evaluation of fecal incontinence to help assess for anal sphincter weakness, rectal hypersensitivity, and/or dyssynergic defecation. Due to its limited availability, cost, and logistical considerations for the patient, its use is reserved for patients with rectal findings suggestive of anal sphincter weakness or dyssynergia, or patients with a lack of response to initial treatment measures.

A trial of loperamide may alleviate this patient's diarrhea in the short term; however, loperamide use will add to the underlying fecal loading, causing her diarrhea and fecal incontinence to worsen over time.

Use of psyllium is unlikely to alleviate the patient's symptoms and would add stool bulk to an already overloaded colon, which would likely worsen her urgency, explosive diarrhea, and fecal incontinence. Furthermore, the patient is likely to experience bloating and abdominal distention caused by the fermentation of the psyllium in the gastrointestinal tract.

KEY POINT

- Fecal loading (excess stool in the colon) with resultant overflow diarrhea is a common cause of fecal incontinence in elderly patients, particularly those who are hospitalized or have degenerative neurologic disorders.

Bibliography

Yu SW, Rao SS. Anorectal physiology and pathophysiology in the elderly. Clin Geriatr Med. 2014;30:95-106. [PMID: 24267605] doi:10.1016/j.cger.2013.10.003

H

Item 77 Answer: D

Educational Objective: Diagnose ischemic colitis.

Ischemic colitis is the most likely diagnosis in this patient. The patient initially presented in septic shock from a urinary tract infection. He was hypotensive and required intravenous fluids and vasopressor support, which are risk factors for ischemic colitis in elderly patients. Ischemic colitis is a low-flow state of the colon occurring most frequently in the left colon. Conditions that can alter circulation include hypotension, dehydration, strenuous physical activity, medications and illicit drugs, thrombophilia, aortic or cardiac bypass, vasculitis, or an obstructing colon lesion. Diarrhea with rectal bleeding is common. Colonoscopy may show sharply demarcated pale mucosa with petechial bleeding, as it does in this patient. Left colon inflammatory changes may be detected by colonoscopy or abdominal CT. Treatment is supportive care with normalization of blood pressure.

Acute mesenteric ischemia (AMI) is an uncommon vascular emergency. Embolism to the mesenteric arteries causes 50% of cases of AMI. Most emboli are from cardiac sources. Patients typically present in the seventh decade of life and often have associated cardiovascular comorbidities. The classic presentation of early AMI is central abdominal pain out of proportion to the physical examination findings. This patient's gradual onset of left-sided, moderate-intensity abdominal pain is not typical of AMI.

Diverticula represent herniation of mucosa or submucosa through the muscular layers of the colon, typically at the entry site of vasa recta (small arteries), which are a source for bleeding. Diverticular bleeding is usually painless with passage of large-volume red- to maroon-colored blood per rectum. It occurs spontaneously without associated infection or other illness, making it unlikely in this patient.

The most common initial symptoms of enterohemorrhagic *Escherichia coli* are bloody diarrhea and abdominal tenderness, without fever. The timing of this patient's development of gastrointestinal symptoms, 1 day after presentation with hypotension secondary to urosepsis, makes the diagnosis of ischemic colitis more likely.

KEY POINT

- Ischemic colitis is a low-flow state of the colon occurring most frequently in the left colon and characterized by moderate, left-sided, cramping abdominal pain followed by bloody diarrhea.

Bibliography

Trotter JM, Hunt L, Peter MB. Ischaemic colitis. BMJ. 2016;355:i6600. [PMID: 28007701] doi:10.1136/bmj.i6600

Item 78 Answer: B

Educational Objective: Treat ileal Crohn disease.

Infliximab is the most appropriate treatment for this patient. This patient has moderate to severe ileal Crohn disease that has required multiple courses of tapering prednisone for flares of disease over the last year, despite treatment with the immunomodulator azathioprine. Infliximab is an anti–tumor necrosis factor (TNF)-α antagonist effective in inducing and maintaining remission in moderate to severe Crohn disease. Other FDA-approved anti-TNF agents include adalimumab and certolizumab pegol. Evidence indicates that efficacy is better when an anti-TNF agent is used together with an immunomodulator. In addition, the risk for developing antibodies against the anti-TNF agent is lower with combination therapy. Patients whose disease does not respond to one anti-TNF agent are often switched to a second or third anti-TNF agent. Fibrostenosing Crohn disease in the absence of ongoing mucosal inflammation is unlikely to respond to any anti-TNF agent. Patients with no response to or intolerance of anti-TNF agents should be treated with either surgery or a leukocyte trafficking blocker (natalizumab or vedolizumab).

Budesonide is a potent glucocorticoid with high first-pass metabolism in the liver, which limits systemic side effects related to conventional glucocorticoids. Budesonide can be an effective therapy for treating mild flares of ileal Crohn disease, but it is unlikely to induce remission in more severe Crohn disease and cannot be used to maintain remission.

Mesalamine agents are mainly used to treat ulcerative colitis of mild to moderate severity. Mesalamine may have efficacy in treating mild to moderate Crohn colitis, but it is not efficacious in treating small-bowel Crohn disease.

Reinitiating prednisone may induce remission of the patient's current disease flare, but it would not be helpful for maintenance of remission. Because this patient has required three separate tapering doses of glucocorticoids over the last year, she requires a medication such as infliximab that can both induce remission and maintain Crohn disease in remission.

KEY POINT

- Anti-tumor necrosis factor agents such as infliximab are effective in inducing and maintaining remission in moderate to severe Crohn disease.

Bibliography

Lichtenstein GR, Hanauer SB, Sandborn WJ; Practice Parameters Committee of American College of Gastroenterology. Management of Crohn's disease in adults. Am J Gastroenterol. 2009;104:465-83; quiz 464, 484. [PMID: 19174807] doi:10.1038/ajg.2008.168

Item 79 Answer: D

Educational Objective: Manage Lynch syndrome.

This patient should undergo a screening colonoscopy now, and if it is normal, have a repeat colonoscopy every 1 to 2 years until age 40 years, and then yearly thereafter. The patient has Lynch syndrome based on her family history and the identification of a deleterious mutation in the *MSH2* gene. The Amsterdam II criteria (known as the "3-2-1-1-0 rule") can be used to screen for Lynch syndrome; a diagnosis is warranted if the following criteria are met:

- Three family members are affected with a Lynch syndrome–associated cancer
- At least two successive generations are affected
- One affected family member is a first-degree relative of the other two affected family members
- One of the cancers was diagnosed before age 50 years
- Familial adenomatous polyposis has been excluded
- Tumors have been verified histologically

The Amsterdam criteria are specific for Lynch syndrome but lack sensitivity. Additional clinical tools, such as the Bethesda criteria or clinical models such as the PREdiction Model for gene Mutations 5 ($PREMM_5$) (premm.dfci.harvard.edu), may be used to screen for Lynch syndrome.

Lynch syndrome is caused by germline mutation in one of the DNA mismatch repair genes (*MLH1, MSH2, MSH6, PMS2*) or the epithelial cell adhesion molecule (*EPCAM*) gene. The appropriate age to begin screening colonoscopy in patients with Lynch syndrome is between ages 20 and 25 years or 2 to 5 years before the earliest age of colorectal cancer diagnosis in the family, whichever comes first; thus, this patient should undergo a colonoscopy now. The risk for colorectal cancer in patients with Lynch syndrome is elevated significantly compared with the general population and is as high as 80% for some individuals. Women with Lynch syndrome are at increased risk for endometrial cancer. Additional cancers, such as gastric, small intestinal, urothelial, ovarian, and pancreaticobiliary cancers, are also associated with this syndrome.

Colectomy and continued annual endoscopic surveillance of the remaining rectum is the recommended management for patients with Lynch syndrome who are found to have colorectal cancer on screening colonoscopy. Colectomy is not a recommended option for managing patients with Lynch syndrome in the absence of a documented cancer.

Screening starting at age 40 years or 10 years earlier than the youngest age of colon cancer diagnosis in the family is appropriate for individuals with a family history of colon cancer that does not meet criteria for Lynch syndrome.

KEY POINT

- Patients with Lynch syndrome should begin screening colonoscopy between ages 20 and 25 years or 2 to 5 years before the earliest age of colorectal cancer diagnosis in the family, whichever comes first, and colonoscopy should be repeated every 1 to 2 years if the baseline examination is normal.

Bibliography

Rubenstein JH, Enns R, Heidelbaugh J, Barkun A; Clinical Guidelines Committee. American Gastroenterological Association Institute guideline on the diagnosis and management of lynch syndrome. Gastroenterology. 2015;149:777-82; quiz e16-7. [PMID: 26226577] doi:10.1053/j.gastro.2015.07.036

Item 80 Answer: D

Educational Objective: Diagnose hereditary diffuse gastric cancer.

Upper endoscopy is the most appropriate next test for this patient. The patient's presentation is suggestive of gastric cancer, specifically diffuse gastric cancer. Proposed criteria for selection of patients for genetic testing for hereditary diffuse gastric cancer include the following: family members with two or more documented cases of gastric cancer in first- or second-degree relatives, with at least one diffuse gastric cancer diagnosed before age 50 years; family members with multiple lobular breast cancers with or without diffuse gastric cancer in first- or second-degree relatives; and, a personal diagnosis of diffuse gastric cancer before age 35 years from a low-incidence population such as in Canada and the United States. Based on the patient's young age and history of multiple family members with gastric and lobular breast cancer, hereditary diffuse gastric cancer is a likely diagnosis. The best diagnostic test for gastric cancer is an upper endoscopy with multiple biopsies of the stomach. The syndrome of hereditary diffuse gastric cancer is associated with mutations in the *CDH1* gene. The risk for diffuse gastric cancer approaches 80% in carriers of the mutation, and prophylactic gastrectomy is recommended in mutation carriers who have not developed gastric cancer.

A colonoscopy is not indicated as the initial test because the patient has primarily upper gastrointestinal symptoms. Colon polyps and cancer have been associated with hereditary diffuse gastric cancer, and more frequent screening colonoscopy for colon polyps is indicated in mutation carriers.

Delayed gastric emptying can present with abdominal pain and early satiety but is also often accompanied by nausea and vomiting. The patient has no risk factors for gastroparesis, such as diabetes mellitus, so a gastric emptying study is not indicated.

While *Helicobacter pylori* can present with dyspeptic symptoms, serological testing is not the most appropriate next step for this patient because his weight loss and family history raise concern for gastric cancer.

An upper gastrointestinal radiograph series might show thickened gastric folds related to diffuse gastric cancer, but it cannot be used to obtain biopsies to diagnose cancer.

KEY POINT

- A history of multiple family members with gastric cancer, particularly before age 50 years, or multiple family members with lobular breast cancer with or without gastric cancer, suggest the possibility of hereditary diffuse gastric cancer and the need for upper endoscopy and testing for mutations of the *CDH1* gene.

Bibliography

Syngal S, Brand RE, Church JM, Giardiello FM, Hampel HL, Burt RW; American College of Gastroenterology. ACG clinical guideline: genetic testing and management of hereditary gastrointestinal cancer syndromes. Am J Gastroenterol. 2015;110:223-62; quiz 263. [PMID: 25645574] doi:10.1038/ajg.2014.435

Item 81 Answer: D

Educational Objective: Manage drug-induced liver injury.

Continued observation is the most appropriate management of this patient. Drug-induced liver injury is a rare adverse reaction to medication that can result in jaundice, liver failure, and, potentially, death. This patient meets the criteria for diagnosis, which requires a history of drug or supplement exposure within 6 to 12 months, a biochemical pattern that fits the hepatotoxicity profile of the causative agent (in this case, cholestatic for amoxicillin-clavulanate), improvement after drug removal (dechallenge), and the absence of underlying liver or biliary diseases. The most common medications associated with drug-induced liver injury are antibacterial agents (especially amoxicillin-clavulanate) as well as herbal and dietary supplements. In this patient with drug-induced liver injury and well-preserved liver function, the offending medication has already been discontinued, and observation until resolution of symptoms occurs is the best course of action. The prognosis of drug-induced liver injury is generally good, with 70% of patients recovering without needing hospitalization and 90% recovering without developing acute liver failure.

Endoscopic retrograde cholangiography (ERCP) is used to treat biliary obstruction. In this setting, ultrasound has confirmed the absence of biliary dilation, and therefore, ERCP would not be expected to provide benefit.

A liver biopsy is rarely necessary in patients with drug-induced liver injury but is helpful in cases of uncertainty or suspected drug-induced autoimmune hepatitis. Zone 3 necrosis and eosinophilia are classic histologic findings in drug-induced liver injury, but other findings may include hepatitis, cholestasis, steatosis, or granulomas. This patient has a classic presentation, and a cholestatic biochemical profile and negative antibody tests make autoimmune hepatitis unlikely.

No specific antidotes are available for idiosyncratic drug-induced liver injury. The administration of glucocorticoids like prednisone is not indicated unless there is suspicion for drug hypersensitivity reaction. The absence of a morbilliform rash, fever, facial swelling, lymphadenopathy, and substantially elevated aminotransferase levels make a hypersensitivity reaction unlikely and prednisone unnecessary in this patient.

KEY POINT

- In patients with well-preserved liver function, drug-induced liver injury should be managed with discontinuation of the offending medication and observation until resolution of symptoms occurs.

Bibliography

Chalasani NP, Hayashi PH, Bonkovsky HL, Navarro VJ, Lee WM, Fontana RJ; Practice Parameters Committee of the American College of Gastroenterology. ACG clinical guideline: the diagnosis and management of idiosyncratic drug-induced liver injury. Am J Gastroenterol. 2014;109:950-66; quiz 967. [PMID: 24935270] doi:10.1038/ajg.2014.131

Item 82 Answer: C

Educational Objective: Treat centrally mediated abdominal pain syndrome.

Cognitive-behavioral therapy is the most appropriate treatment for this patient. She meets the diagnostic criteria for centrally mediated abdominal pain syndrome (CAPS): near-constant abdominal pain lasting longer than 6 months, involving a large anatomic distribution, and without initiating triggers or alarm features. Treatment includes a combination of pharmacologic and/or psychological therapies. She already takes a selective serotonin reuptake inhibitor for depression, but it has not improved her abdominal pain syndrome. Four classes of psychotherapy have shown benefit in patients with CAPS when combined with medical therapy: cognitive-behavioral therapy, psychodynamic-interpersonal therapy, mindfulness- and acceptance-based therapy, and hypnotherapy.

Irritable bowel syndrome (IBS) is a symptom complex characterized by abdominal pain and altered bowel habits. The diagnosis is made by the fulfillment of symptom-based criteria, including the presence of recurrent abdominal pain or discomfort at least 3 days per month in the last 3 months that is associated with two or more of the following: relief with defecation, onset associated with a change in frequency of stool, or onset associated with a change in form of stool. IBS is further subtyped based on the predominant stool pattern as IBS with predominant constipation (IBS-C), IBS with predominant diarrhea (IBS-D), mixed IBS, or IBS unclassified. CAPS differs from IBS in that there are no consistent initiating triggers and symptoms are not alleviated with

bowel movements. The patient reports no constipation, and her pain is not relieved with bowel movements, so IBS is an unlikely diagnosis.

Alosetron is a 5-HT_3 antagonist available for women with IBS-D whose symptoms have not responded to conventional therapy; however, owing to an increased risk for severe constipation and ischemic colitis with its use, it is restricted by a mandatory prescribing program. Because this patient does not have IBS, alosetron is not indicated.

Budesonide is indicated in patients with inflammatory bowel disease. This patient reports no chronic diarrhea, a hallmark symptom of inflammatory bowel disease, and a colonoscopy earlier this year was normal, showing no inflammation.

Linaclotide is a guanylate cyclase-C activator used in the treatment of IBS-C after fiber supplementation or osmotic and stimulatory laxative therapy fails. It has no role in the treatment of CAPS.

KEY POINT

- Centrally mediated abdominal pain syndrome is characterized by near-constant abdominal pain lasting longer than 6 months, involving a large anatomic distribution, and without initiating triggers or alarm features.

Bibliography

Keefer L, Drossman DA, Guthrie E, Simrén M, Tillisch K, Olden K, et al. Centrally mediated disorders of gastrointestinal pain. Gastroenterology. 2016. [PMID: 27144628] doi:10.1053/j.gastro.2016.02.034

H

Item 83 Answer: D

Educational Objective: Treat upper gastrointestinal bleeding.

This patient does not require transfusion. For patients with upper gastrointestinal bleeding, initial resuscitation is the first priority and should include stabilization of blood pressure with infusion of sufficient volumes of crystalloid fluid and/or red blood cells. The decision to transfuse red blood cells is based mainly on the presenting hemoglobin level. In hemodynamically stable patients, a restrictive transfusion strategy (transfusion threshold of less than 7 g/dL [70 g/L] with a target hemoglobin level of 7-9 g/dL [70-90 g/L]) is associated with decreased mortality, length of hospital stay, and transfusion-related adverse events compared to a liberal transfusion strategy (transfusion threshold of less than 9 g/dL [90 g/L] with a target hemoglobin level of 9-10 g/dL [90-100 g/L]). This patient is hemodynamically and physiologically stable with no evidence of ongoing overt gastrointestinal blood loss or symptoms of tissue ischemia; therefore, it is appropriate to continue maintenance intravenous fluids because he is at an appropriate target hemoglobin level of 7 to 9 g/dL (70-90 g/L).

A modification of the restrictive transfusion threshold may be considered in specific subpopulations, such as patients with hypotension due to severe bleeding and patients with cardiovascular disease. It may be reasonable to give transfusions to patients who are hemodynamically unstable before a decline in hemoglobin level to less than 7 g/dL (70 g/L) to prevent complications of tissue underperfusion. There is uncertainty regarding the need for a higher transfusion threshold in patients with cardiovascular disease, but current guidelines recommend considering transfusion when hemoglobin levels decrease below 8 g/dL (80 g/L) or when cardiovascular symptoms develop (for example, chest pain, dyspnea) in patients who are otherwise hemodynamically stable.

KEY POINT

- In patients with upper gastrointestinal bleeding, a restrictive transfusion strategy (transfusion threshold of less than 7 g/dL [70 g/L] with a target hemoglobin level of 7-9 g/dL [70-90 g/L]) is associated with decreased mortality, length of hospital stay, and transfusion-related adverse events compared to a liberal transfusion strategy.

Bibliography

Fortinsky KJ, Bardou M, Barkun AN. Role of medical therapy for nonvariceal upper gastrointestinal bleeding. Gastrointest Endosc Clin N Am. 2015;25:463-78. [PMID: 26142032] doi:10.1016/j.giec.2015.02.003

Item 84 Answer: C

Educational Objective: Screen for duodenal cancer in a patient with familial adenomatous polyposis syndrome.

Upper endoscopy with duodenoscopy is the most appropriate next test for this patient. The adenomatous polyposis syndromes include familial adenomatous polyposis (FAP) and *MutYH*-associated polyposis (MAP). Patients with FAP and MAP should receive genetic counseling and should be offered genetic testing. Although an autosomal dominant disorder, a positive family history is found in only 54% to 78% of patients diagnosed with FAP. Upper endoscopy with duodenoscopy, using both a standard upper scope and a side viewing scope, is indicated to screen for periampullary and duodenal adenomas and adenocarcinoma. At least 50% of patients with FAP develop adenomatous changes of the periampullary region of the duodenum. Upper-endoscopy screening in patients with FAP should begin at the time of onset of colonic polyps or at age 25 to 30 years, whichever comes first. Upper endoscopy with duodenoscopy for surveillance of duodenal cancer is indicated every 1 to 5 years at an interval based on the stage of the duodenal polyposis.

A barium upper gastrointestinal series has a low sensitivity for periampullary and duodenal adenomas, which may be flat or sessile lesions, and it does not allow for tissue biopsy if lesions are found.

Double-balloon enteroscopy allows endoscopy to reach the entire small-bowel lumen and is used in patients with occult gastrointestinal blood loss to look for a source of bleeding and provide therapeutic options. It may also be used to remove small-bowel mucosal lesions such as adenomas

if they are located beyond the reach of a standard esophagogastroduodenoscopy (EGD). Double-balloon enteroscopy requires longer anesthesia time and is higher-risk than standard EGD, and its availability is limited. Therefore, it is not the standard recommended procedure for initial screening for duodenal and periampullary adenomas in patients with FAP.

Patients with FAP should undergo upper endoscopy because there is more than a 50% chance of discovering duodenal adenomas at the first upper endoscopy. Conducting no further tests in this patient would be an inappropriate approach, given the high probability of finding one or more potentially premalignant lesions.

KEY POINT

- Upper-endoscopy screening for duodenal cancer in patients with familial adenomatous polyposis should begin at onset of colonic polyposis or at age 25 to 30 years, whichever comes first.

Bibliography

Syngal S, Brand RE, Church JM, Giardiello FM, Hampel HL, Burt RW; American College of Gastroenterology. ACG clinical guideline: genetic testing and management of hereditary gastrointestinal cancer syndromes. Am J Gastroenterol. 2015;110:223-62; quiz 263. [PMID: 25645574] doi:10.1038/ajg.2014.435

Item 85 Answer: B

Educational Objective: Manage colonoscopy surveillance following polypectomy.

This patient should undergo surveillance colonoscopy in 3 years. Current recommendations emphasize that an adequate bowel preparation and a high-quality colonoscopy that reaches and examines the cecum are required for an adequate screening examination. Screening colonoscopy studies demonstrate that polyps are detected in approximately 60% of average-risk individuals. The prevalence of polyps on average-risk screening colonoscopy is 22% to 25% for adenomas, 12% for hyperplastic polyps, and 0.6% for sessile serrated polyps. The degree of dysplasia in a polyp is reported as high or low. Adenomatous polyps are neoplastic lesions and, therefore, have malignant potential; most colorectal cancers arise from adenomatous polyps. Adenomatous polyps are further defined by their glandular architecture: tubular, villous, or a combination of both. The most common pattern is tubular, followed by tubulovillous, with the least common pattern being villous. After neoplastic polyps (adenomas, sessile serrated polyps, or traditional serrated adenomas) are completely resected, postpolypectomy colonoscopy should be performed; the surveillance interval depends on the size, number, and pathology of the polyp. This patient was found to have three tubular adenomas smaller than 1 cm in size. The presence of three or more adenomas, any adenoma greater than or equal to 1 cm in size, or any adenoma with villous features or high-grade dysplasia has been associated with increased risk for metachronous neoplasia (multiple primary tumors developing at different time intervals), warranting a 3-year surveillance interval.

Guidelines recommend screening average-risk individuals beginning at age 50 years. Repeat colonoscopy is based on initial findings. Individuals with no adenomas should have a repeat colonoscopy in 10 years. Individuals who have two or fewer tubular adenomas are also considered low-risk for colon cancer and should repeat screening in 5 to 10 years. Appropriate follow-up recommendations after screening colonoscopy, including avoidance of inappropriate use of colonoscopy after removal of adenomatous polyps, are core gastroenterology quality measures.

High-risk findings include more than 10 polyps on baseline colonoscopic examination, which should prompt consideration for a polyposis syndrome. These individuals should have a follow-up colonoscopy in less than 3 years, depending on polyp burden and polyposis syndrome. Any patient who has a polyp removed piecemeal should return within 3 to 6 months for repeat colonoscopy, especially if there is any concern for incomplete polyp removal.

KEY POINT

- Patients with three or more adenomas on screening colonoscopy should undergo surveillance colonoscopy in 3 years.

Bibliography

Lieberman DA, Rex DK, Winawer SJ, Giardiello FM, Johnson DA, Levin TR; United States Multi-Society Task Force on Colorectal Cancer. Guidelines for colonoscopy surveillance after screening and polypectomy: a consensus update by the US Multi-Society Task Force on Colorectal Cancer. Gastroenterology. 2012;143:844-57. [PMID: 22763141] doi:10.1053/j.gastro.2012.06.001

Item 86 Answer: C

Educational Objective: Treat functional dyspepsia.

Starting a trial of a tricyclic antidepressant is the most appropriate next step in the management of this patient. The patient has functional dyspepsia meeting the diagnostic criteria for epigastric pain syndrome: (1) bothersome postprandial fullness; (2) early satiety; (3) epigastric pain; and/or (4) epigastric burning for at least 3 days per week. These criteria should be met for the 3 months leading up to diagnosis, with symptoms starting at least 6 months before diagnosis and with no evidence of structural disease to explain the symptoms. The absence of an underlying organic disease is demonstrated by this patient's normal upper endoscopy, including gastric and small-bowel biopsies, as well as normal laboratory testing and the lack of alarm features such as vomiting, weight loss, or family history of gastrointestinal malignancy. Because she tested negative for *Helicobacter pylori* infection and her symptoms did not respond to a trial of once-daily omeprazole for a minimum of 4 weeks, the recommended next step in the treatment of functional dyspepsia is a trial of a tricyclic antidepressant. In the treatment of functional dyspepsia, this class of antidepressants was found to be more effective than other classes, including selective serotonin reuptake inhibitors or serotonin-norepinephrine reuptake inhibitors.

Given this patient's absence of alarm symptoms and normal laboratory test results, further structural testing with CT imaging or abdominal ultrasonography is likely to be of low yield; therefore, such testing is neither clinically indicated nor cost effective.

A gastric emptying test is used to evaluate suspected gastroparesis. Gastroparesis commonly presents with symptoms of early satiety, postprandial fullness, nausea, vomiting, upper abdominal pain, bloating, and weight loss; this patient's lack of compatible symptoms makes the diagnosis unlikely.

There is no evidence that a higher dose of a proton pump inhibitor performs better in the treatment of functional dyspepsia than once-daily omeprazole, which did not alleviate the patient's symptoms.

KEY POINT

- First-line treatment for functional dyspepsia is once-daily omeprazole for at least 4 weeks; if symptoms do not respond, a tricyclic antidepressant is the next recommended treatment.

Bibliography

Moayyedi PM, Lacy BE, Andrews CN, Enns RA, Howden CW, Vakil N. ACG and CAG clinical guideline: management of dyspepsia. Am J Gastroenterol. 2017;112:988-1013. [PMID: 28631728] doi:10.1038/ajg.2017.154

Item 87 Answer: C

Educational Objective: Treat cryoglobulinemia in a patient with chronic hepatitis C viral infection.

A combination of ledipasvir and sofosbuvir is the most appropriate treatment for this patient. The patient has Meltzer triad–consisting of asthenia, arthralgia, and palpable purpura–which is the classic presentation of type II mixed cryoglobulinemia, a vasculitis that most often arises in the context of chronic hepatitis C virus (HCV) infection. Meltzer triad is seen in less than 30% of patients, but nearly all patients with type II cryoglobulinemia develop cutaneous findings, as seen in this patient. Other findings may include peripheral neuropathy; membranoproliferative glomerulonephritis; and pulmonary, central nervous system, or gastrointestinal vasculitis. Urinalysis may show dysmorphic erythrocytes and proteinuria, which are features of glomerulonephritis, but this patient shows no evidence of kidney involvement or other end-organ damage. The best initial treatment for a mild presentation of mixed cryoglobulinemia arising from chronic HCV infection is to treat and eradicate HCV with sofosbuvir-ledipasvir. Other direct-acting antiviral agents that could be used interchangeably to treat genotype 1 HCV include grazoprevir-elbasvir; paritaprevir-ritonavir, ombitasvir, and dasabuvir; glecaprevir-pibrentasvir; sofosbuvir-daclatasvir; and sofosbuvir-velpatasvir. It is expected that other combinations of direct-acting antivirals will be developed. Treatment of HCV infection with direct-acting antiviral combinations results in a sustained virologic response (cure) in more than 90% of patients, even in those who were previously and unsuccessfully treated with pegylated interferon and ribavirin. In approximately 90% of cases, eradication of HCV leads to resolution of the mixed cryoglobulinemia.

Most of the data pertaining to the treatment of HCV infection in patients with mixed cryoglobulinemia involve treatment with pegylated interferon and ribavirin. However, pegylated interferon and ribavirin are no longer recommended for treatment of HCV infection due to adverse effects and lower efficacy compared to interferon-free, direct-acting antiviral therapy.

For severe end-organ damage from mixed cryoglobulinemia, including kidney failure, gastrointestinal vasculitis, rapidly progressive neuropathy, pulmonary or central nervous system vasculitis, or heart failure, rituximab is a first-line agent and may be used with pulse-dose glucocorticoids. However, this patient has mild manifestations of mixed cryoglobulinemia and, therefore, does not require immunosuppressive therapy with rituximab, cyclophosphamide, or glucocorticoids.

KEY POINT

- Mixed cryoglobulinemia arising from chronic hepatitis C viral infection resolves after treatment and eradication of the virus.

Bibliography

Dammacco F, Sansonno D. Therapy for hepatitis C virus-related cryoglobulinemic vasculitis. N Engl J Med. 2013;369:1035-45. [PMID: 24024840] doi:10.1056/NEJMra1208642

Item 88 Answer: B

Educational Objective: Treat microscopic colitis.

Budesonide is the most appropriate treatment for this patient. Her primary symptom of chronic watery diarrhea, colonoscopy results showing normal-appearing mucosa, and biopsy results revealing lymphocytic infiltration and a subepithelial collagen band are diagnostic for collagenous colitis. Collagenous colitis is a subtype of microscopic colitis. It is a clinicopathologic diagnosis made based on clinical presentation, endoscopy features, and histopathology. The condition occurs more commonly in women than in men and typically presents with abrupt or gradual onset of watery diarrhea that has a relapsing and remitting course over months to years. Mild weight loss may occur. The colonic mucosa is macroscopically normal, and inflammatory changes are only appreciated on histopathologic review of colon biopsy specimens. Several medication classes, including NSAIDs, selective serotonin reuptake inhibitors, and proton pump inhibitors, have been associated with the development of microscopic colitis. The first step in management is to discontinue a potentially causative medication. Supportive treatment with antidiarrheal agents such loperamide can be tried as initial treatment. For patients like this one, whose symptoms do not respond to antidiarrheal medication, the

American Gastroenterological Association (AGA) strongly recommends, based on moderate-quality evidence, the use of budesonide for induction of clinical remission of microscopic colitis because of its favorable harm-benefit profile and convenience of once-daily dosing. The rate of relapse after discontinuation of budesonide is high, and maintenance therapy with the lowest possible dose to maintain remission may be required. Patients treated with budesonide for longer than 6 months should be monitored for corticosteroid-related adverse effects.

Because budesonide is expensive, alternative treatments such as bismuth salicylate may be considered if cost is a determining factor. The AGA conditionally recommends, based on low-quality evidence, bismuth subsalicylate for induction of remission when budesonide therapy is not feasible. Bismuth subsalicylate therapy consists of two to three 262-mg tablets taken orally three to four times daily.

The benefit of mesalamine in achieving clinical remission in microscopic colitis is uncertain, and it is recommended as a potential second-line therapy.

Prednisone should not be used as first-line treatment of microscopic colitis because of its unfavorable side effects, but it may be considered in patients who have microscopic colitis refractory to budesonide.

The AGA conditionally recommends, based on low-quality evidence, against the use of probiotics over no treatment for induction of clinical remission. Various probiotic strains, dosages, and formulations are available, but most have not been evaluated in the treatment of microscopic colitis.

KEY POINT

- The first step in the management of microscopic colitis is to discontinue a potentially causative medication, after which supportive treatment with antidiarrheal agents such loperamide can be tried, with budesonide recommended for patients whose symptoms do not respond.

Bibliography

Pardi DS, Tremaine WJ, Carrasco-Labra A. American Gastroenterological Association Institute technical review on the medical management of microscopic colitis. Gastroenterology. 2016;150:247-274.e11. [PMID: 26584602] doi:10.1053/j.gastro.2015.11.006

Item 89 Answer: A

Educational Objective: Manage hepatic adenoma.

The most appropriate management is to discontinue the oral contraceptive agent. Hepatocellular adenomas are generally seen in women because they can be dependent on estrogen for growth. They may also occur in men, and these adenomas carry a higher risk for malignant transformation. Hepatic adenomas may also be associated with anabolic-steroid use, obesity, and the metabolic syndrome. They are often solitary, ranging in size from 1 to 30 cm. Most patients are asymptomatic, and the adenoma is discovered incidentally during imaging for unrelated problems or because of right-upper-quadrant abdominal pain. The diagnosis is often based on the characteristic imaging findings in a woman of reproductive age. Histology can confirm the diagnosis, but biopsy is not always needed in cases where imaging findings are characteristic; needle biopsy is avoided because it is associated with bleeding.

Hepatic adenomas may increase in size during pregnancy. Women with adenomas greater than 2 cm who are contemplating pregnancy, or who are pregnant, can be treated with radiofrequency ablation but the decision to treat and the treatment modality must be individualized.

The natural history and prognosis of hepatic adenomas is ill-defined. The risk for malignant transformation of hepatic adenomas is approximately 10%. Adenomas larger than 5 cm in size have an increased risk for bleeding that can occasionally cause hemodynamic compromise. In general terms, surgical resection is typically recommended for any symptomatic hepatic adenoma, adenomas 5 cm or larger, or an adenoma found in a male.

Asymptomatic women who are taking estrogen-containing oral contraceptive agents and who have adenomas smaller than 5 cm in size can be managed conservatively, as the risk for hemorrhage or malignant transformation is relatively low. However, liver imaging should be conducted every 6 months for at least 2 years to ensure that the lesion is not growing. Most adenomas tend to regress or even disappear when oral contraceptive agents are discontinued. Failure to regress, continued growth, or an elevation of the α-fetoprotein level may be an indication for surgical resection.

KEY POINT

- For women with asymptomatic hepatic adenomas smaller than 5 cm in size, estrogen-containing oral contraceptive agents should be discontinued, and follow-up liver imaging is recommended every 6 months for at least 2 years.

Bibliography

Marrero JA, Ahn J, Rajender Reddy K; Americal College of Gastroenterology. ACG clinical guideline: the diagnosis and management of focal liver lesions. Am J Gastroenterol. 2014;109:1328-47; quiz 1348. [PMID: 25135008] doi:10.1038/ajg.2014.213

Item 90 Answer: A

Educational Objective: Evaluate the small bowel for a source of gastrointestinal bleeding.

The most appropriate next step in management of this patient is capsule endoscopy. The patient has occult gastrointestinal bleeding, indicated by unexplained iron deficiency anemia with stool testing positive for occult blood and no source of bleeding identified on repeated endoscopy and colonoscopy. The next step is evaluation for potential small-bowel bleeding. Causes of small-bowel bleeding depend on the patient's age. In older patients, vascular lesions such as angiodysplasia account for up to 40% of cases. Capsule endoscopy is noninvasive and is generally able to visualize the

entire small bowel. The main disadvantages are its inability to sample tissue or treat findings. Its overall diagnostic yield ranges from 30% to 70%. Capsule endoscopy is contraindicated in patients with gastroparesis, swallowing difficulty, and partial bowel obstructions, and in any patient who cannot undergo follow-up surgery. Capsule endoscopy has become the first-line test in evaluating the small bowel after a negative endoscopy and colonoscopy in patients with gastrointestinal bleeding of an unknown cause.

CT enterography should be considered for patients presenting with or having a history of small-bowel obstruction where a lesion or mass is suspected. Patients aged 40 years or younger who present with occult small-bowel bleeding are more likely to have tumors (leiomyoma, carcinoid, adenocarcinoma, or lymphoma) as the cause of bleeding.

Push enteroscopy is performed with advancement of the endoscope beyond the ligament of Treitz into the jejunum. The depth of insertion is operator dependent but is also limited because of looping of the scope in the stomach. The diagnostic yield is between 24% and 56%. The primary disadvantage of using push enteroscopy is that the amount of additional small bowel that can be examined is limited compared to capsule endoscopy; however, it does allow for tissue sampling and therapeutic intervention. Studies have shown that sequencing capsule endoscopy followed by push enteroscopy is an effective approach for management of occult small-bowel bleeding.

The diagnostic yield of radiographic imaging with small-bowel follow-through is very low (0%-5%) and, therefore, should not be used in the evaluation of suspected small-bowel bleeding.

KEY POINT

- Capsule endoscopy is the most appropriate test to evaluate patients for causes of small-bowel bleeding after negative upper endoscopy and colonoscopy.

Bibliography

Gerson LB, Fidler JL, Cave DR, Leighton JA. ACG clinical guideline: diagnosis and management of small bowel bleeding. Am J Gastroenterol. 2015;110:1265-87; quiz 1288. [PMID: 26303132] doi:10.1038/ajg.2015.246

Item 91 Answer: D

Educational Objective: Treat chronic hepatitis B viral infection in its immune-active, hepatitis B e antigen–positive phase.

Tenofovir is the most appropriate treatment for this patient. Entecavir would be an equally suitable choice. Chronic hepatitis B virus (HBV) infection is characteristically divided into phases of disease. Not all patients go through each phase. Patients in the hepatitis B e antigen (HBeAg)-positive ("immune-active") or HBeAg-negative ("reactivation") phases have an elevated alanine aminotransferase (ALT) level and an HBV DNA level above 10,000 IU/mL. The patient has chronic HBV infection in the immune-active, HBeAg-positive phase, with ALT and aspartate aminotransferase levels exceeding two times the upper limit of normal and HBV DNA exceeding 20,000 IU/mL. Treatment is necessary to decrease hepatic inflammation, risk for progression to fibrosis, and eventual cirrhosis that will occur without treatment. In approximately 50% of untreated patients with chronic HBV infection in the United States, HBV infection will contribute to the cause of death (from hepatocellular carcinoma or other complications of end-stage liver disease, such as cirrhosis). Patients who respond to treatment have a decreased risk of liver-related complications of HBV infection. Tenofovir or entecavir is first-line treatment for immune-active HBV infection because of low rates of resistance. Treatment goals for HBV infection in the immune-active, HBeAg-positive phase are loss of HBeAg and anti–hepatitis B e antibody seroconversion. For most patients, chronic treatment is necessary because seroconversion of HBeAg or hepatitis B surface antigen is not commonly achieved.

Adefovir and lamivudine are not preferred antiviral agents given the risk for HBV resistance. Resistance rates at 5 years are approximately 30% for adefovir and 70% for lamivudine.

In this patient, oral antiviral regimens are preferred over pegylated interferon because pegylated interferon may exacerbate psoriasis. Pegylated interferon is most appropriate for patients who have higher ALT levels, low HBV DNA levels, and no cirrhosis.

KEY POINT

- Chronic hepatitis B viral infection in the immune-active, hepatitis B e antigen–positive phase should be treated with tenofovir or entecavir to decrease hepatic inflammation and the risk for progression to fibrosis.

Bibliography

Terrault NA, Bzowej NH, Chang KM, Hwang JP, Jonas MM, Murad MH; American Association for the Study of Liver Diseases. AASLD guidelines for treatment of chronic hepatitis B. Hepatology. 2016;63:261-83. [PMID: 26566064] doi:10.1002/hep.28156

Item 92 Answer: C

Educational Objective: Treat irritable bowel syndrome with predominant constipation.

A trial of polyethylene glycol (PEG) 3350 therapy is the most appropriate next step for this patient. She has abdominal discomfort and a change in bowel habits predominated by constipation; these symptoms fulfill the diagnostic criteria for irritable bowel syndrome with predominant constipation (IBS-C). Given her young age and lack of any alarm features, such as blood in the stool, anemia, or a first-degree family member with colon cancer, a diagnosis of IBS-C can be made and treatment can be initiated. The soluble fiber supplement psyllium has demonstrated limited efficacy in IBS, primarily addressing stool frequency and consistency. Insoluble fiber supplements such as bran appear to worsen IBS-C symptoms. Although various surfactant, osmotic, and stimulant laxatives can be used for the constipation symptoms

associated with IBS-C, only the osmotic laxative PEG has been tested in IBS. PEG 3350 has demonstrated efficacy in IBS, and a trial of it is an appropriate first step in management.

A colonoscopy is not warranted, given this patient's age and the nature of her symptoms. The remote family history of colorectal cancer does not increase her risk enough to require a colonoscopy at this time.

This patient has no risk factors for small intestinal bacterial overgrowth, such as small-bowel disease, previous bowel resection, or a primary/secondary gastrointestinal motility disorder; therefore, a glucose breath test is not indicated. Bloating is commonly reported in patients with IBS. If bloating persists after correction of constipation, then testing for small intestinal bacterial overgrowth could be considered.

Although symptoms of bloating, abdominal pain, and constipation can occur in celiac disease, this patient's symptoms do not warrant serum anti-tissue transglutaminase antibody testing for celiac disease. Testing would be indicated if she had a first-degree relative with celiac disease or if she had symptoms of IBS with predominant diarrhea (IBS-D) or IBS with mixed diarrhea and constipation. Furthermore, results of testing for celiac antibodies such as the anti-tissue transglutaminase may be normal in patients on a gluten-free diet. The patient's response to gluten elimination does not necessarily indicate celiac disease because gluten is a FODMAP (Fermentable Oligosaccharides, Disaccharides, Monosaccharides, And Polyols) carbohydrate, which can cause bloating due to FODMAP intolerance.

KEY POINT

- Polyethylene glycol 3350 is a first-line treatment for patients whose symptoms meet the criteria for irritable bowel syndrome with predominant constipation.

Bibliography

Mearin F, Lacy BE, Chang L, Chey WD, Lembo AJ, Simren M, et al. Bowel disorders. Gastroenterology. 2016. [PMID: 27144627] doi:10.1053/j.gastro.2016.02.031

Item 93 Answer: C

Educational Objective: Treat *Helicobacter pylori* infection persisting after treatment.

Bismuth, metronidazole, omeprazole, and tetracycline for 14 days is the most appropriate treatment regimen for this patient. The salvage therapy regimen should consist of different antibiotics from those used in the initial, unsuccessful regimen. This strategy reduces the likelihood of antibiotic resistance, the major reason for treatment failure.

Additional factors in choosing salvage therapy after initial treatment failure include a history of quinolone antibiotic use and penicillin allergy. If the initial unsuccessful treatment was clarithromycin triple therapy and the patient is allergic to penicillin, the best salvage therapy is a bismuth quadruple therapy (bismuth, metronidazole, omeprazole, and tetracycline). In patients with no penicillin allergy, but whose history includes quinolone antibiotic use for any reason, salvage therapies could include bismuth quadruple therapy, rifabutin triple therapy (rifabutin, penicillin, and a proton pump inhibitor [PPI] such as omeprazole) or high-dose dual therapy (amoxicillin and a PPI). Disruption of therapy can cause treatment failure, and the likelihood of treatment success diminishes with each successive treatment attempt. It is essential to counsel the patient carefully on the importance of treatment adherence and potential side effects of the therapy.

Treatment with the same regimen (amoxicillin, clarithromycin, and omeprazole) for a longer period of time will be ineffective because the patient's *Helicobacter pylori* infection is likely resistant to clarithromycin and/or penicillin.

The combination of amoxicillin, metronidazole, and omeprazole is not a recognized treatment regimen for *H. pylori* in any setting. Metronidazole is typically used in patients with penicillin allergy.

Using metronidazole rather than amoxicillin is unlikely to result in *H. pylori* eradication because resistance to clarithromycin is also a likely cause of the initial treatment's failure. Furthermore, the regimen of clarithromycin, metronidazole, and omeprazole could lead to the development of metronidazole resistance in the likely event of treatment failure with this regimen.

KEY POINT

- For *Helicobacter pylori* infection that persists after eradication therapy, the salvage therapy regimen should consist of different antibiotics from those used in the initial, unsuccessful regimen.

Bibliography

Chey WD, Leontiadis GI, Howden CW, Moss SF. ACG clinical guideline: treatment of *Helicobacter pylori* infection. Am J Gastroenterol. 2017;112:212-239. [PMID: 28071659] doi:10.1038/ajg.2016.563

Item 94 Answer: C

H

Educational Objective: Diagnose hepatorenal syndrome.

Hepatorenal syndrome is the most likely diagnosis in this patient. In patients with end-stage liver disease and portal hypertension, hepatorenal syndrome is characterized by the development of oliguric kidney failure, bland urine sediment, and marked sodium retention (edema, ascites, low urinary sodium). Two types of hepatorenal syndrome have been recognized. Type 1 is characterized by acute kidney dysfunction and is usually triggered by a precipitating event such as spontaneous bacterial peritonitis, other infections, gastrointestinal hemorrhage, or a major surgical procedure. Type 2 is more common and is characterized by more slowly progressive kidney failure in patients with refractory ascites. Type 1 hepatorenal syndrome is characterized by a rise in serum creatinine of at least 0.3 mg/dL (26 µmol/L) and/or ≥50% from baseline within 48 hours with a bland urinalysis and normal findings on renal ultrasonography. It is also supported by a lack of

H CONT.

improvement in kidney function after withdrawal of diuretics and two days of volume expansion with intravenous albumin. Often patients with hepatorenal syndrome also have low urine sodium, low fractional excretion of sodium, and oliguria. In addition, patients should have no evidence of shock, no current or recent use of nephrotoxic drugs, and no evidence of renal parenchymal disease (proteinuria less than 0.5 g/day, no microhematuria, and normal renal ultrasound). The main treatment of hepatorenal syndrome is the removal of drugs that may reduce kidney perfusion and volume expansion. Ultimately, hepatorenal syndrome is a condition for which the only cure is liver transplantation.

Acute interstitial nephritis may be associated with drugs, infection, autoimmune diseases, and malignancy. It should be suspected in a patient who presents with an elevated serum creatinine level and urinalysis showing leukocytes, leukocyte casts, and possibly eosinophiluria; urinary sodium level is typically elevated.

Acute tubular necrosis is most commonly caused by ischemia or toxins (including drugs). Urinalysis typically shows pigmented granular (muddy brown) casts and tubular epithelial cells; urinary sodium is typically elevated.

Membranous glomerulonephritis is associated with the nephrotic syndrome (proteinuria, edema, hypertension, microhematuria) and erythrocytes or erythrocyte casts; urinary sodium can be low.

KEY POINT

- In patients with end-stage liver disease and portal hypertension, hepatorenal syndrome is characterized by the development of oliguric kidney failure, bland urine sediment, and marked sodium retention (edema, ascites, low urinary sodium).

Bibliography

Glass L, Sharma P. Evidence-based therapeutic options for hepatorenal syndrome. Gastroenterology. 2016;150:1031-3. [PMID: 26922867] doi:10.1053/j.gastro.2016.02.050

H

Item 95 Answer: D

Educational Objective: Manage walled-off necrosis after acute pancreatitis.

The most appropriate management of the fluid collection is observation. Walled-off necrosis of the pancreas is the most likely diagnosis. The pancreatic fluid collection incidentally found during kidney stone–protocol CT corresponds to the location of pancreatic necrosis during his acute gallstone pancreatitis 6 months earlier. By definition, acute necrotic collections are classified as walled-off necrosis after 4 weeks. The necrotic tissue liquifies with time and develops a mature wall as part of the healing process, as seen on imaging. These fluid collections do not require therapy if they are asymptomatic, and as many as 60% may resolve spontaneously within 1 year; fluid-related complications are rare.

Areas of pancreatic necrosis are frequently identified on imaging during an episode of acute pancreatitis. Patients with uninfected pancreatic necrosis do not benefit from antibiotic use during the acute phase of pancreatitis or later, in the resolving stage. Patients whose condition does not improve or deteriorates 7 to 10 days after presentation of acute pancreatitis may have infected necrosis. CT-guided fine-needle aspiration may help guide treatment decisions regarding antibiotic use, drainage, and continued supportive care. Neither CT-guided fine-needle aspiration nor antibiotic therapy is needed in this asymptomatic patient with walled-off necrosis of the pancreas that is likely to resolve spontaneously. The patient's left flank pain is due to passage of a kidney stone, not the pancreatic fluid collection.

Many walled-off necroses of the pancreas resolve spontaneously, but some persist, enlarge, have a mass effect, and/or cause symptoms. Symptomatic collections may require decompression or debridement. However, this patient is asymptomatic and no intervention is required at this time.

KEY POINT

- Asymptomatic patients with walled-off necrosis of the pancreas require no intervention.

Bibliography

Tyberg A, Karia K, Gabr M, Desai A, Doshi R, Gaidhane M, et al. Management of pancreatic fluid collections: a comprehensive review of the literature. World J Gastroenterol. 2016;22:2256-70. [PMID: 26900288] doi:10.3748/wjg.v22.i7.2256

Item 96 Answer: C

Educational Objective: Screen for hepatocellular carcinoma in a patient with cirrhosis.

The most appropriate management for this patient is ultrasonography screening for hepatocellular carcinoma every 6 months. Liver diseases associated with the highest risk for hepatocellular carcinoma are hepatitis B virus (HBV) and hepatitis C virus (HCV) infections and hemochromatosis. Approximately 80% of hepatocellular carcinoma occurs in patients with cirrhosis, but it can develop in the absence of cirrhosis in patients with HBV infection. All patients with cirrhosis from any cause should undergo liver ultrasonography every 6 months with or without α-fetoprotein measurement. Patients with HCV infection who achieve sustained virologic response (which is synonymous with virologic cure) have a reduced risk for hepatocellular carcinoma. Regardless of virologic response, surveillance is recommended for patients with stage 3 or stage 4 fibrosis (stage 4 fibrosis signifies cirrhosis, as found in this patient).

Liver transplantation evaluation is not indicated for this patient with Child-Turcotte-Pugh Class A cirrhosis and a very low Model for End-Stage Liver Disease (MELD) score. Indications for liver transplantation are a MELD score of at least 15 or decompensated cirrhosis. Virologic cure in patients with compensated cirrhosis prevents decompensation. However, development of hepatocellular carcinoma would be a reason for referral for liver transplantation evaluation.

Measuring HCV RNA again in 12 weeks is not indicated because this patient has achieved virologic cure with undetectable HCV RNA at week 12 after completing treatment for HCV infection. Large studies have demonstrated 98% to 99% concordance between sustained virologic response at 12 and at 24 weeks. Therefore, sustained virologic response at 12 weeks is considered to be consistent with virologic cure, and additional testing is unnecessary.

Upper endoscopy is not necessary because the patient had an upper endoscopy 1 year ago. The standard follow-up interval for small varices in a patient who is not taking a nonselective β-blocker is 2 years.

KEY POINT

- Patients with hepatitis C viral infection who achieve sustained virologic response have a reduced risk for hepatocellular carcinoma; regardless of virologic response, ultrasonographic surveillance is recommended for patients with stage 3 or stage 4 fibrosis.

Bibliography

Morgan RL, Baack B, Smith BD, Yartel A, Pitasi M, Falck-Ytter Y. Eradication of hepatitis C virus infection and the development of hepatocellular carcinoma: a meta-analysis of observational studies. Ann Intern Med. 2013;158:329-37. [PMID: 23460056]

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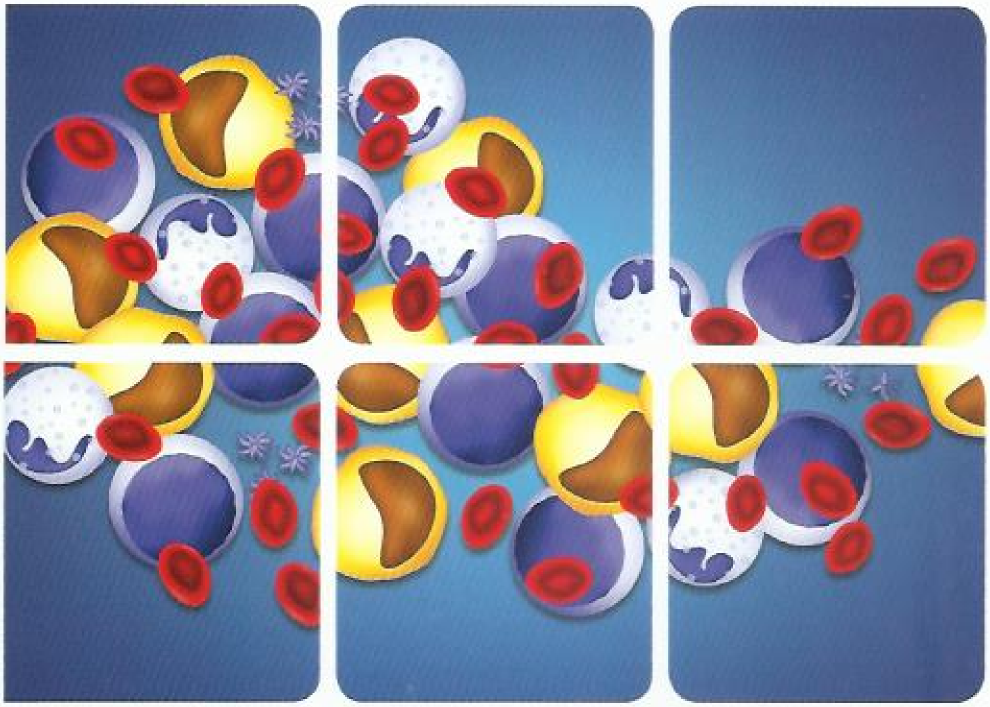

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Absolute neutrophil count–greater than 1500/µL (1.50 × 10^9/L)
Activated partial thromboplastin time–25-35 s
D-dimer–less than 0.5 µg/mL (0.5 mg/L)
Erythrocyte count–4.2-5.9 × 10^6/µL (4.2-5.9 × 10^{12}/L)
Erythrocyte sedimentation rate
  Male–0-15 mm/h
  Female–0-20 mm/h
Erythropoietin–5-36 mU/mL (5-36 U/L)
Haptoglobin, serum–50-150 mg/dL (500-1500 mg/L)
Hematocrit
  Male–41%-51%
  Female–36%-47%
Hemoglobin, blood
  Male–14-17 g/dL (140-170 g/L)
  Female–12-16 g/dL (120-160 g/L)
Leukocyte count–4000-10,000/µL (4.0-10 × 10^9/L)
Mean corpuscular hemoglobin–28-32 pg
Mean corpuscular hemoglobin concentration–32-36 g/dL (320-360 g/L)
Mean corpuscular volume–80-100 fL
Platelet count–150,000-450,000/µL (150-450 × 10^9/L)
Prothrombin time–11-13 s
Reticulocyte count–0.5%-1.5% of erythrocytes; absolute: 23,000-90,000/µL (23-90 × 10^9/L)

Blood, Plasma, and Serum Chemistry Studies

Albumin, serum–3.5-5.5 g/dL (35-55 g/L)
Alkaline phosphatase, serum–36-92 U/L
α Fetoprotein, serum–0.6-6.6 ng/mL (0.6-6.6 µg/L)
Aminotransferase, alanine (ALT)–0-35 U/L
Aminotransferase, aspartate (AST)–0-35 U/L
Ammonia, plasma–40-80 µg/dL (23-47 µmol/L)
Amylase, serum–0-130 U/L
Bilirubin, serum
  Total–0.3-1.2 mg/dL (5.1-20.5 µmol/L)
  Direct–0-0.3 mg/dL (0-5.1 µmol/L)
Blood gases, arterial (ambient air)
  pH–7.38-7.44
  Pco_2–35-45 mm Hg (4.7-6.0 kPa)
  Po_2–80-100 mm Hg (10.6-13.3 kPa)
  Oxygen saturation–95% or greater
Blood urea nitrogen–8-20 mg/dL (2.9-7.1 mmol/L)
B-type natriuretic peptide level
  Heart failure unlikely–less than 100 pg/mL (100 ng/L)
  Heart failure likely–greater than 400 pg/mL (400 ng/L)
Calcium, serum–9-10.5 mg/dL (2.2-2.6 mmol/L)
Carbon dioxide, serum–See Bicarbonate
Chloride, serum–98-106 mEq/L (98-106 mmol/L)
Complement, serum
  C3–55-120 mg/dL (550-1200 mg/L)
  C4–10-40 mg/dL (100-400 mg/L)
C-reactive protein, blood–0-0.8 mg/dL (0-8.0 mg/L)
  Cardiovascular risk prediction
    Low risk–less than 1.0 mg/L
    Average risk–1.0-3.0 mg/L
    High risk–greater than 3.0 mg/L
Creatine kinase, serum–30-170 U/L
Creatinine, serum–0.7-1.3 mg/dL (61.9-115 µmol/L)
Electrolytes, serum
  Sodium–136-145 mEq/L (136-145 mmol/L)
  Potassium–3.5-5.0 mEq/L (3.5-5.0 mmol/L)
  Chloride–98-106 mEq/L (98-106 mmol/L)
  Bicarbonate–23-28 mEq/L (23-28 mmol/L)
Fibrinogen, plasma–150-350 mg/dL (1.5-3.5 g/L)
Folate, serum–4.0-20 ng/mL (9.1-45.3 nmol/L)
Glucose, plasma–fasting, 70-100 mg/dL (3.9-5.6 mmol/L)
γ-Glutamyltransferase, serum–0-30 U/L
Immunoglobulins
  Globulins, total–2.5-3.5 g/dL (25-35 g/L)
    IgG–640-1430 mg/dL (6.4-14.3 g/L)
    IgA–70-300 mg/dL (0.7-3.0 g/L)
    IgM–20-140 mg/dL (0.2-1.4 g/L)
    IgD–less than 8 mg/dL (80 mg/L)
    IgE–0-90 U/mL (0-90 kU/L)
Iron studies
  Ferritin, serum–15-200 ng/mL (15-200 µg/L)
  Iron, serum–60-160 µg/dL (11-29 µmol/L)
  Iron-binding capacity, total (TIBC), serum–250-460 µg/dL (45-82 µmol/L)
  Transferrin saturation–20%-50% (serum iron ÷ TIBC × 100)
Lactate dehydrogenase, serum–60-100 U/L
Lactate, plasma–0.5-2.2 mEq/L (0.5-2.2 mmol/L)
Lipase, serum–13-60 U/L
Magnesium, serum–1.5-2.4 mg/dL (0.62-0.99 mmol/L)
Osmolality, serum–275-295 mOsm/kg H_2O
Phosphatase, alkaline, serum–36-92 U/L
Phosphorus, serum–3.0-4.5 mg/dL (0.97-1.45 mmol/L)
Prostate-specific antigen, serum–less than 4 ng/mL (4 µg/L)
Protein, serum
  Total–6.0-7.8 g/dL (60-78 g/L)
  Albumin–3.5-5.5 g/dL (35-55 g/L)
  Globulins, total–2.5-3.5 g/dL (25-35 g/L)
Rheumatoid factor–less than 40 U/mL (40 kU/L)
Triglycerides–less than 150 mg/dL (1.69 mmol/L), desirable
Troponins, serum
  Troponin I–0-0.1 ng/mL (0-0.1 µg/L)
  Troponin T–0-0.1 ng/mL (0-0.1 µg/L)
Urate, serum
  Male–3.7-8.6 mg/dL (0.22-0.50 mmol/L)
  Female–2.4-5.8 mg/dL (0.14-0.34 mmol/L)
Vitamin B_{12}, serum–200-800 pg/mL (148-590 pmol/L)

Endocrine

Adrenocorticotropic hormone (ACTH), serum–9-52 pg/mL (2-11 pmol/L)
Aldosterone, serum
  Supine–2-5 ng/dL (55-138 pmol/L)
  Standing–7-20 ng/dL (194-554 pmol/L)
Aldosterone, urine–5-19 µg/24 h (13.9-52.6 nmol/24 h)
Catecholamines, fractionated, urine
  Epinephrine–2-24 µg/24 h (10.92-131.04 nmol/24 h)
  Norepinephrine–15-100 µg/24 h (88.65-591 nmol/24 h)
  Dopamine–52-480 µg/24 h (339.56-3134.4 nmol/24 h)

Cortisol, free, urine–less than 50 µg/24 h (138 nmol/24 h)
Cortisol, serum, morning–5-25 µg/dL (138-690 nmol/L)
Dehydroepiandrosterone sulfate (DHEAS), plasma
  Male–1.3-5.5 µg/mL (3.5-14.9 µmol/L)
  Female–0.6-3.3 µg/mL (1.6-8.9 µmol/L)
Epinephrine, plasma (supine)–less than 75 ng/L (410 pmol/L)
Estradiol, serum
  Male–10-30 pg/mL (37-110 pmol/L)
  Female–day 1-10, 14-27 pg/mL (50-100 pmol/L); day 11-20, 14-54 pg/mL (50-200 pmol/L); day 21-30, 19-41 pg/mL (70-150 pmol/L)
Follicle-stimulating hormone, serum
  Male (adult)–5-15 mU/mL (5-15 U/L)
  Female–follicular or luteal phase, 5-20 mU/mL (5-20 U/L); midcycle peak, 30-50 mU/mL (30-50 U/L); postmenopausal, greater than 35 mU/mL (35 U/L)
Growth hormone, plasma–after oral glucose, less than 2 ng/mL (2 µg/L); response to provocative stimuli, greater than 7 ng/mL (7 µg/L)
Hemoglobin A_{1c}, blood–less than 5.7%
Luteinizing hormone, serum
  Male–3-15 mU/mL (3-15 U/L)
  Female–follicular or luteal phase, 5-22 mU/mL (5-22 U/L); midcycle peak, 30-250 mU/mL (30-250 U/L); post-menopausal, greater than 30 mU/mL (30 U/L)
Metanephrines, fractionated, urine
  Metanephrine, unconjugated–90-315 µg/24 h (456-1597 nmol/24 h)
  Normetanephrine–122-676 µg/24 h (666-3691 nmol/24 h)
  Metanephrines, total–224-832 µg/24 h (1136-4218 nmol/24 h)
Metanephrines, fractionated, plasma
  Metanephrine, free–less than or equal to 57 pg/mL (0.2964 nmol/L)
  Normetanephrine, free–less than or equal to 148 pg/mL (0.8288 nmol/L)
  Metanephrines, total–less than or equal to 205 pg/mL (1.066 nmol/L)
Parathyroid hormone, serum–10-65 pg/mL (10-65 ng/L)
Progesterone, blood
  Male (adult)–0.27-0.9 ng/mL (0.9-2.9 nmol/L)
  Female–follicular phase, 0.33-1.20 ng/mL (1.0-3.8 nmol/L); luteal phase, 0.72-17.8 ng/mL (2.3-56.6 nmol/L); postmenopausal, less than 0.2-1 ng/mL (0.6-3.18 nmol/L); oral contraceptives, 0.34-0.92 ng/mL (1.1-2.9 nmol/L)
Prolactin, serum
  Male–less than 15 ng/mL (15 µg/L)
  Female–less than 20 ng/mL (20 µg/L)
Testosterone, total, serum
  Male (adult)–300-1200 ng/dL (10-42 nmol/L)
  Female–20-75 ng/dL (0.7-2.6 nmol/L)
Thyroid iodine (^{131}I) uptake–10%-30% of administered dose at 24 h
Thyroid-stimulating hormone (TSH)–0.5-5.0 µU/mL (0.5-5.0 mU/L)
Thyroxine (T_4)
  Total, serum–5-12 µg/dL (64-155 nmol/L)
  Free–0.9-2.4 ng/dL (12-31 pmol/L)
  Free T_4 index–4-11
Triiodothyronine (T_3)
  Total, serum–70-195 ng/dL (1.1-3.0 nmol/L)
  Free–3.6-5.6 ng/L (5.6-8.6 pmol/L)
Vitamin D
  1,25-dihydroxy, serum–25-65 pg/mL (60-156 pmol/L)
  25-hydroxy, serum–31-80 ng/mL (77-200 nmol/L)

Urine

Albumin-creatinine ratio–less than 30 mg/g
Calcium–100-300 mg/24 h (2.5-7.5 mmol/24 h) on unrestricted diet
Creatinine–15-25 mg/kg per 24 h (133-221 mmol/kg/24 h)
Glomerular filtration rate (GFR)
  Categories of Chronic Kidney Disease (from KDIGO)
    Stage G1–greater than or equal to 90 mL/min/1.73 m^2
    Stage G2–60-89 mL/min/1.73 m^2
    Stage G3a–45-59 mL/min/1.73 m^2
    Stage G3b–30-44 mL/min/1.73 m^2
    Stage G4–15-29 mL/min/1.73 m^2
    Stage G5–less than 15 mL/min/1.73 m^2
    Albuminuria categories
    A1 (Normal)–less than 30 mg/g
    A2 (Moderately increased)–30-300 mg/g
    A3 (Severely increased)–greater than 300 mg/g
Protein-creatinine ratio–less than or equal to 150 mg/g
Uric acid–250-750 mg/24 h (1.48-4.43 mmol/24 h) (varies with diet)

Pulmonary

Forced expiratory volume in 1 second (FEV_1)–greater than 80% of predicted
Forced vital capacity (FVC)–greater than 80% of predicted
FEV_1/FVC–greater than 0.70

Cerebrospinal Fluid

Cell count–0-5/µL (0-5 × 10^6/L)
Glucose–40-80 mg/dL (2.2-4.4 mmol/L); less than 40% of simultaneous plasma concentration is abnormal
Pressure (opening)–70-200 mm H_2O
Protein–15-60 mg/dL (150-600 mg/L)

Hemodynamic Measurements

Cardiac index–2.5-4.2 L/min/m^2
Left ventricular ejection fraction–greater than 55%
Pressures
  Pulmonary artery
    Systolic–20-25 mm Hg
    Diastolic–5-10 mm Hg
    Mean–9-16 mm Hg
  Pulmonary capillary wedge–6-12 mm Hg
  Right atrium–mean 0-5 mm Hg
  Right ventricle
    Systolic–20-25 mm Hg
    Diastolic–0-5 mm Hg

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Part A	Text and Multiple-Choice Questions (MCQs) with Answers, Critiques, and Bibliographies for MCQs
Includes six subspecialty books	Cardiovascular Medicine, Dermatology Gastroenterology and Hepatology, Hematology and Oncology, Neurology, and Rheumatology
Part B	Text and Multiple Choice Questions (MCQs) with Answers, Critiques, and Bibliographies for MCQs
Includes five subspecialty books	Endocrinology and Metabolism, General Internal Medicine, Infectious Disease, Nephrology, Pulmonary and Critical Care Medicine

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- Information on Continuing Medical Education (CME), Maintenance of Certification (MOC), and International Continuing Professional Development (CPD) and MOC
- Errata
- Upcoming CME/MOC submission deadlines
- The MKSAP forum (ACP members only)

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ACP | MKSAP® 18

Medical Knowledge Self-Assessment Program®

Hematology and Oncology

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Welcome to the Hematology and Oncology Section of MKSAP 18!

In these pages, you will find updated information on hematopoietic stem cell disorders, multiple myeloma, bleeding disorders, hematologic issues in pregnancy, and other hematologic topics. Also addressed are issues in oncology; breast, ovarian, and cervical cancers; gastroenterologic malignancies; lung cancer; lymphoid malignancies; melanoma; the effects of cancer therapy and survivorship; and other topics in oncology. All of these topics are uniquely focused on the needs of generalists and subspecialists *outside* of hematology and oncology.

The core content of MKSAP 18 has been developed as in previous editions—all essential information that is newly researched and written in 11 topic areas of internal medicine—created by dozens of leading generalists and subspecialists and guided by certification and recertification requirements, emerging knowledge in the field, and user feedback. MKSAP 18 also contains 1200 all-new peer-reviewed, psychometrically validated, multiple-choice questions (MCQs) for self-assessment and study, including 149 in Hematology and Oncology. MKSAP 18 continues to include *High Value Care* (HVC) recommendations, based on the concept of balancing clinical benefit with costs and harms, with associated MCQs illustrating these principles and HVC Key Points called out in the text. Internists practicing in the hospital setting can easily find comprehensive *Hospitalist*-focused content and MCQs, specially designated in blue and with the **H** symbol.

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On behalf of the many internists who have offered their time and expertise to create the content for MKSAP 18 and the editorial staff who work to bring this material to you in the best possible way, we are honored that you have chosen to use MKSAP 18 and appreciate any feedback about the program you may have. Please feel free to send any comments to mksap_editors@acponline.org.

Sincerely,

Patrick Alguire

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The learning objectives of MKSAP 18 are to

- Close gaps between actual care in your practice and preferred standards of care, based on best evidence
- Diagnose disease states that are less common and sometimes overlooked and confusing
- Improve management of comorbid conditions that can complicate patient care
- Determine when to refer patients for surgery or care by subspecialists
- Pass the ABIM Certification Examination
- Pass the ABIM Maintenance of Certification Examination

Target Audience

- General internists and primary care physicians
- Subspecialists who need to remain up to date in internal medicine
- Residents preparing for the certifying examination in internal medicine
- Physicians preparing for maintenance of certification in internal medicine (recertification)

ABIM Maintenance of Certification

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Errata

Errata for MKSAP 18 will be available through the MKSAP Resource Site at mksap.acponline.org as new information becomes known to the editors.

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Hematology and Oncology High Value Care Recommendations

The American College of Physicians, in collaboration with multiple other organizations, is engaged in a worldwide initiative to promote the practice of High Value Care (HVC). The goals of the HVC initiative are to improve health care outcomes by providing care of proven benefit and reducing costs by avoiding unnecessary and even harmful interventions. The initiative comprises several programs that integrate the important concept of health care value (balancing clinical benefit with costs and harms) for a given intervention into a broad range of educational materials to address the needs of trainees, practicing physicians, and patients.

HVC content has been integrated into MKSAP 18 in several important ways. MKSAP 18 includes HVC-identified key points in the text, HVC-focused multiple choice questions, and, for subscribers to MKSAP Digital, an HVC custom quiz. From the text and questions, we have generated the following list of HVC recommendations that meet the definition below of high value care and bring us closer to our goal of improving patient outcomes while conserving finite resources.

High Value Care Recommendation: A recommendation to choose diagnostic and management strategies for patients in specific clinical situations that balance clinical benefit with cost and harms with the goal of improving patient outcomes.

Below are the High Value Care Recommendations for the Hematology and Oncology section of MKSAP 18.

- Do not obtain a bone marrow evaluation for low-risk monoclonal gammopathy.
- Oral ferrous sulfate is the preferred treatment of iron deficiency because of its tolerability, efficacy, and cost.
- Treatment of inflammatory anemia is seldom necessary and iron replacement is ineffective.
- Avoid erythropoiesis-stimulating agents in patients with chronic kidney disease not undergoing dialysis with a hemoglobin level greater than 10 g/dL (100 g/L).
- Oral cobalamin is preferred to parenteral therapy for cobalamin deficiency.
- Avoid iron supplementation in patients with thalassemia.
- Do not test for glucose-6-phosphate dehydrogenase deficiency during an acute hemolytic episode.
- Avoid transfusions in patients with sickle cell disease and uncomplicated pain crises or chronic anemia.
- Most patients with heparin-associated thrombocytopenia and a low 4T score need no further evaluation.
- Asymptomatic patients with factor XI deficiency do not require intervention before surgery.
- Do not use prothrombin complex concentrates to manage the coagulopathy of liver disease.
- Do not evaluate for thrombophilia in most patients with acute venous thromboembolism.
- Do not perform additional testing in patients with low probability Wells criteria scores and Pulmonary Embolism Rule-Out Criteria scores of zero.
- Do not perform additional testing in patients with low probability scores for deep venous thrombosis or pulmonary embolism and normal D-dimer measurement.
- Most patients with deep venous thrombosis and those with pulmonary embolism and a good prognosis can be managed without hospitalization.
- Withholding warfarin is the preferred treatment for asymptomatic INR elevation between 4.5 and 10 (see Item 44).
- Bridging therapy during warfarin discontinuation before an invasive procedure is not necessary in most patients.
- Treatment is not required for most patients with gestational thrombocytopenia.
- Do not obtain imaging studies for localized tumors that have a low likelihood of distant metastases to certain sites, such as bone or brain.
- Do not obtain PET, CT, or bone scan for staging for newly diagnosed stage 0 to II breast cancer.
- Before administering adjuvant chemotherapy in older women with higher-risk early stage breast cancer, consider life expectancy, functional status, and medical comorbidities.
- Surveillance blood tests and other imaging tests for breast cancer should not be routinely performed and should be guided by a patient's symptoms or findings on examination that raise concern for recurrence.
- Do not offer ovarian cancer screening, even in high-risk women.
- Do not perform surveillance imaging and laboratory studies in asymptomatic cervical cancer survivors.
- Do not obtain PET scans for preoperative staging or postoperative surveillance in colorectal cancer.
- Well-differentiated neuroendocrine tumors require only observation and serial imaging.
- Routine imaging for head and neck cancer after a negative posttreatment scan is not indicated unless there are signs and symptoms suggestive of recurrent disease.

- Do not obtain nonspecific tumor markers, PET scans, and gene expression arrays in the evaluation of cancer of unknown primary.
- Outpatient treatment is reasonable for patients with febrile neutropenia expected to be of short duration, who lack significant comorbidity, and who have reliable home care and follow-up.
- Do not offer aggressive chemotherapy to patients with cancer of unknown primary and several comorbidities and poor performance status (see Item 107).
- Observation is an appropriate management strategy for men with early-stage prostate cancer who have limited life expectancy or significant medical comorbidities (see Item 117).

Hematology and Oncology

Hematopoietic Stem Cells and Their Disorders

Overview

Hematopoietic stem cells nest in the bone marrow and have the capacity to differentiate and self-renew. Hematopoietic stem cells are multipotent and can differentiate into progenitor cells; in turn, these produce leukocytes, erythrocytes, and platelets. This differentiation and proliferation to mature blood cells happens in an orderly manner called hematopoiesis. Hematopoiesis is tightly regulated by multiple factors, including the bone marrow microenvironment and hematopoietic growth factors. This includes erythropoietin, which stimulates erythrocytes; thrombopoietin, which stimulates platelet production; and granulocyte colony-stimulating factor and macrophage colony-stimulating factor, which stimulate granulocyte, monocyte, basophil, and eosinophil production. Disorders of hematopoiesis can occur at the hematopoietic stem cell or progenitor level and can lead to underproduction or overproduction of blood cells.

Bone marrow failure syndromes are characterized by the failure of hematopoiesis to keep up with physiologic demands for blood cell production, leading to peripheral cytopenias. Although rare inherited causes exist, acquired disorders are much more common and can occur secondary to intrinsic bone marrow disorders, such as myelodysplastic syndrome, or extrinsic disorders resulting from toxins or autoimmunity, as in aplastic anemia.

Myeloproliferative neoplasms are clonal myeloid neoplasms with deregulation and excess proliferation of subsets of hematopoietic stem cells. The diagnosis can be made through identification of clonal genetic abnormalities, such as *BCR-ABL* translocation and *JAK2* (*JAK2 V617F*) mutation on peripheral blood testing.

Acute leukemias, either myeloid or lymphoid in origin, are aggressive clonal neoplasms in which cells also lose the capability to differentiate into mature cells. These disorders usually require emergent evaluation and treatment.

Bone Marrow Failure Syndromes

Aplastic Anemia

Aplastic anemia (AA) is an acquired hematopoietic stem cell disorder characterized by severely decreased bone marrow cellularity and pancytopenia. Although the condition is classified as an anemia, patients usually present with a combination of anemia, neutropenia, and thrombocytopenia. Bone marrow cellularity decreases with age while the fat content of the marrow increases. These changes are amplified in AA, which is categorized as severe or very severe based on the degree of bone marrow cellularity and the severity of cytopenias.

AA is caused by a decrease in stem cells as a result of autoimmunity, toxins, and infections. Medications, such as antithyroid medications (methimazole and propylthiouracil), β-lactam antibiotics, sulfonamides, NSAIDs, anticonvulsants, and gold, have also been associated with development of AA. Discontinuing the offending medication usually improves the AA, but it can take many weeks for cell counts to recover.

Most AA is felt to be related to autoimmunity against stem cells. In patients older than 50 years and in younger patients without a suitable stem cell donor, AA is treated by immunosuppression with antithymocyte globulin, cyclosporine, and prednisone. Patients younger than 50 years with a suitable donor are usually treated with allogeneic hematopoietic stem cell transplantation. With advances in immunosuppression, bone marrow transplantation, and supportive care, the overall survival of young patients with a good risk profile has reached greater than 80%. Asymptomatic patients with mild to moderate AA can be closely monitored without immediate treatment.

Patients with AA can develop a clone of paroxysmal nocturnal hemoglobinuria cells, which lack complement-stabilizing CD55 and CD59 proteins. However, identifying the paroxysmal nocturnal hemoglobinuria clone does not routinely change treatment of AA, although it does help explain pathophysiology. AA can be differentiated from a hypoplastic variant of myelodysplastic syndrome (MDS) with decreased bone marrow cellularity by finding dysplastic cells and cytogenetic abnormalities typical for MDS. Hypoplastic MDS is also commonly treated with immunosuppressive treatment.

Pure Red Cell Aplasia

Pure red cell aplasia (PRCA) is characterized by normocytic or macrocytic anemia with decreased reticulocytes and absent or decreased erythrocyte precursors in the bone marrow. Leukocyte and platelet counts are normal. Several conditions have been implicated in the pathogenesis of PRCA, some of which are listed in **Table 1**.

Parvovirus B19 is cytotoxic to the erythrocyte precursors in the bone marrow. Parvovirus infection is usually

TABLE 1. Causes of Acquired Pure Red Cell Aplasia
Parvovirus B19 infection
Thymoma
Autoimmune disease
Lymphoid leukemias and lymphomas
Solid tumors
Drugs (phenytoin, isoniazid)
Pregnancy
Anti-EPO antibodies in patients receiving EPO

EPO = erythropoietin.

transient, lasting 2 to 3 weeks in immunocompetent patients, and does not usually cause clinically significant anemia in healthy patients. However, patients with chronic hemolysis (such as sickle cell anemia) who depend on increased erythrocyte production can have significant anemia with a decreased reticulocyte count. Immunocompromised patients can have sustained viremia leading to prolonged anemia requiring intravenous immune globulin treatment to hasten viral clearance.

A few patients with PRCA have an underlying occult thymoma and can improve with thymectomy. Large granular lymphocyte leukemia is a T-cell lymphoproliferative disorder that can be associated with PRCA. Flow cytometry of the peripheral blood can help identify this disorder.

A bone marrow biopsy specimen showing decreased erythrocyte precursors is required to diagnose PRCA. Idiopathic PRCA is commonly immunologically mediated and treated with immunosuppressive medications, such as prednisone, cyclosporine, and cyclophosphamide.

Neutropenia

Isolated neutropenia is a common finding in internal medicine practice. Most patients with neutropenia have a mild form (1000-1500/µL [$1\text{-}1.5 \times 10^9$/L]), but some have moderate (500-1000/µL [$0.5\text{-}1 \times 10^9$/L]) or severe (500/µL [0.5×10^9/L]) neutropenia. Clinically significant infections do not usually occur unless neutrophil counts are less than 500/µL (0.5×10^9/L). Isolated neutropenia can be secondary to congenital or acquired conditions (**Table 2**).

Benign ethnic neutropenia is a congenital neutropenia seen in black patients and those of Mediterranean descent. These patients have good neutrophil reserve and are not prone to infections. In a healthy black patient with mild neutropenia found on routine testing, no further evaluation is needed.

Cyclical neutropenia is another rare congenital condition in which neutrophil counts decrease every 2 to 5 weeks. The neutrophil count can get low enough that patients develop recurrent infections every 2 to 5 weeks.

Instead of causing leukocytosis, infections can cause neutropenia; this can happen after viral, bacterial, or rickettsial infections. Neutropenia resolves with improvement of the underlying infection. Several drugs have been implicated in causing neutropenia, including chemotherapy, NSAIDs, carbamazepine, phenytoin, propylthiouracil, cephalosporins, trimethoprim-sulfamethoxazole, and psychotropics. Drug-induced neutropenia can be dose dependent or idiosyncratic. In mild, dose-dependent neutropenia, the offending drug may be continued if clinically indicated.

Isolated neutropenia can occur with various autoimmune disorders, such as systemic lupus erythematosus. The neutropenia is usually mild, is rarely clinically significant, and improves with treatment of the underlying autoimmune disorder with immunosuppression. The triad of neutropenia, splenomegaly, and rheumatoid arthritis is called Felty syndrome; the neutropenia can be severe, and patients can have significant infections. Treatment of the underlying rheumatoid arthritis can alleviate the neutropenia, but granulocyte colony stimulating factor is needed in some patients. Large granular lymphocyte leukemia can also be associated with clinical features of Felty syndrome.

TABLE 2. Causes of Neutropenia
Inherited
Cyclic neutropenia
Benign ethnic neutropenia
Severe congenital neutropenia
Neutropenia associated with various congenital syndromes (such as glycogen storage disease type 1b)
Acquired
Autoimmune
Associated with autoimmune conditions (systemic lupus erythematosus, rheumatoid arthritis)
Associated with immunodeficiency
Infection
Viral (HIV, hepatitis, parvovirus, Epstein-Barr virus)
Bacterial (typhoid, tuberculosis, brucellosis)
Fungal (histoplasmosis)
Parasitic (malaria, leishmaniasis)
Rickettsial (ehrlichiosis, Rocky Mountain spotted fever)
Medication (NSAIDs, antibiotics, chemotherapies, diuretics, sulfonylureas, thioamides, quinine, psychotropic drugs, anticonvulsants)
Nutritional (folate or vitamin B_{12} deficiency)
Idiopathic
Sequestration and neutrophil margination (hemodialysis)
Hematologic disorders
Acute leukemia
Aplastic anemia
Myelodysplastic syndrome
Other hematologic disorders

KEY POINTS

- Patients with aplastic anemia who are younger than 50 years and have a suitable donor are usually treated with allogeneic hematopoietic stem cell transplantation, whereas those without a suitable stem cell donor or who are older than 50 years should undergo immunosuppression with antithymocyte globulin, cyclosporine, and prednisone.
- A bone marrow biopsy specimen showing a selective decrease in erythrocyte precursors is required to diagnose idiopathic pure red cell aplasia, which is then treated with immunosuppressive medications.
- The neutropenia associated with various autoimmune diseases, most often systemic lupus erythematosus, is usually mild, is rarely clinically significant, and responds to treatment of the underlying autoimmune disorder.

Myelodysplastic Syndromes

The myelodysplastic syndromes (MDSs) are clonal stem cell disorders with ineffective hematopoiesis leading to dysplastic, hypercellular bone marrow and peripheral blood cytopenias. MDS carries a varied risk of transformation to acute myeloid leukemia (AML) that correlates with prognosis. Most MDS is idiopathic, but secondary MDS can result from chemotherapy, radiation, chemical exposure (benzene), and other factors. Other reversible causes of dysplasia that must be ruled out include vitamin B_{12}, folate, and copper deficiency; alcohol consumption; medications; and infections (such as HIV).

Macrocytic anemia is the most common cytopenia observed in MDS. The peripheral blood smear shows dysplastic cells (such as hypogranular neutrophils and platelets). These blood cells do not function well and increase the risk of infection and bleeding. MDS can have a varied presentation with numerous cell lines involved. The World Health Organization classification of MDS and its features are listed in **Table 3**. MDS is suspected in patients with otherwise unexplained cytopenias, especially with dysplastic findings on peripheral blood smear (**Figure 1**). Bone marrow biopsy is required for diagnosis. The prognosis for patients with MDS depends on bone marrow blasts, degree of cytopenias, and cytogenetics. Patients with few blasts in the bone marrow, reasonable peripheral blood cell counts, and a favorable cytogenetic profile have a median survival of almost 9 years, whereas those with greater than 10% blasts, severe pancytopenia (hemoglobin <8 g/dL [80 g/L], platelet count <50,000/µL [50×10^9/L], absolute neutrophil count <800/µL [0.8×10^9/L]), and adverse cytogenetic mutations survive less than 1 year.

Older adult patients who are asymptomatic and have mild cytopenias and features of MDS can be monitored without detailed evaluation. Allogeneic hematopoietic stem cell transplantation is the only potentially curative option available. Transplantation is not an option for most patients with MDS because most are older and are usually not candidates for intensive treatment.

The two main goals of treatment of MDS are treatment of symptomatic cytopenias and reducing the risk of progression to AML. Symptomatic anemia is treated with transfusions and erythropoiesis-stimulating agents. Patients with MDS who are

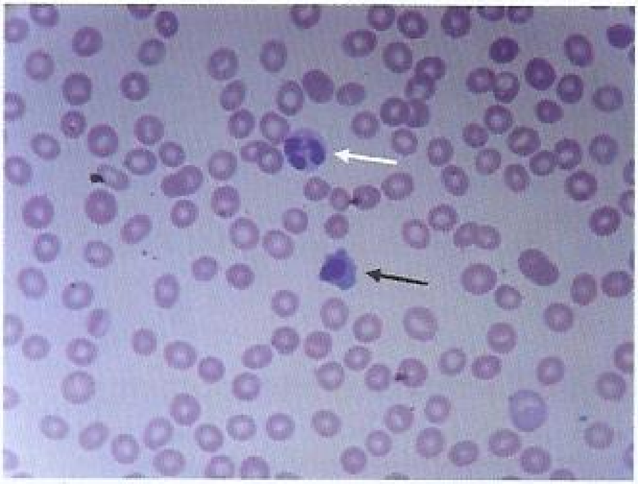

FIGURE 1. Peripheral blood smear from a patient with myelodysplastic syndrome. A dysplastic neutrophil is seen (*solid white arrow*) with hypogranular cytoplasm and a dysplastic nucleus. A nucleated erythrocyte is also seen in this field (*solid black arrow*).

Figure courtesy of Julia Choi, MD; Baylor Scott & White Health.

TABLE 3. World Health Organization Classification of Myelodysplastic Syndrome

Category	Frequency	Marrow Blasts	Other Features
Refractory cytopenia with unilineage dysplasia	20%	<5%	Single cell line dysplasia (usually erythrocytes)
Refractory cytopenia with multilineage dysplasia	30%	<5%	Dysplasia in ≥2 lineages
MDS associated with isolated 5q−	Uncommon	<5%	Increased hypolobated megakaryocytes
Refractory anemia with ring sideroblasts	10%	<5%	Erythroid dysplasia, ≥15% ring sideroblasts
RAEB-1	40%	5%-9%	Unilineage or multilineage dysplasia
RAEB-2	40%	10%-19%	Unilineage or multilineage dysplasia
MDS, unclassified	Uncommon	<5%	Does not fit other categories

MDS = myelodysplastic syndrome; RAEB-1/2 = refractory anemia with excess blasts, type 1 or 2.

at high risk have approximately a 25% risk of conversion to AML in the first year. Treatment of these patients with hypomethylating agents, such as azacytidine and decitabine, has been shown to decrease transfusion dependence and the risk of conversion to AML. A group of patients with low-risk MDS with the -5q cytogenetic abnormality could be treated with the immunomodulatory drug lenalidomide if they are transfusion dependent. Lenalidomide has been approved for this indication and is effective in decreasing transfusion requirements.

Chronic myelomonocytic leukemia has traditionally been considered a subset of MDS but is now classified as a separate entity, sharing some features of MDS with those of myeloproliferative neoplasms. Patients with chronic myelomonocytic leukemia have persistent monocytosis, often with other cytopenias; bone marrow shows dysplastic changes and less than 20% blasts. Prognosis and treatment is analogous to MDS with poor prognosis.

KEY POINTS

- Myelodysplastic syndrome is suspected in patients with cytopenias and with dysplastic findings on peripheral blood smear; bone marrow biopsy is required for diagnosis and to assess prognosis.
- The only cure for myelodysplastic syndrome is allogeneic hematopoietic stem cell transplantation, which is too toxic for most older adult patients in whom this disorder is most prevalent; however, treating patients at high risk of conversion to acute myeloid leukemia with hypomethylating agents has been shown to decrease transfusion dependence and the risk of conversion.

Myeloproliferative Neoplasms

Myeloproliferative neoplasms (MPNs) are clonal stem cell disorders characterized by proliferation of the components of the myeloid, erythroid, or megakaryocyte lineage. They are named based on the dominant cell line affected; for example, erythrocytes are increased in polycythemia, and platelets are increased in essential thrombocythemia. Overlap is considerable among these disorders, and multiple cell lines are usually elevated. A disease-defining genetic chromosomal translocation is seen in chronic myeloid leukemia (CML). Another commonly found mutation involving *JAK2 V617* is associated with polycythemia vera, essential thrombocythemia, myelofibrosis, and other myeloid disorders. Based on the type of MPN, patients are at varied risk of hepatosplenomegaly, thrombosis, and conversion to myelofibrosis or acute myeloid leukemia (AML).

Chronic Myeloid Leukemia

CML is a clonal hematopoietic stem cell disorder characterized by translocation of the long arm of chromosomes 9 and 22 [t(9;22), Philadelphia chromosome] leading to a *BCR-ABL* fusion gene. This gene codes for an abnormal activated tyrosine kinase that promotes dysregulated cell proliferation. At diagnosis, patients with CML can be asymptomatic, with elevated neutrophil counts found on routine laboratory studies, or they can have symptoms such as fatigue, weight loss, abdominal fullness (splenomegaly), and bleeding. CML must be distinguished from a leukemoid reaction, characterized by significant elevation of the neutrophil count with left shift, increased band forms, and, at times, metamyelocytes, seen in acutely ill patients and those with infections such as *Clostridium difficile*. The clinical setting usually allows leukemoid reaction to be distinguished from CML, but in difficult presentations, chromosomal evaluation can help make the diagnosis.

CML has three phases of progression: the chronic phase, the accelerated phase, and blast crisis. The chronic phase is an indolent phase and responds well to therapy. Most patients with CML present in the chronic phase. Accelerated and blast crisis phases denote more aggressive disease that is less responsive to treatment. Blast crisis is considered to be secondary AML.

In CML, peripheral blood neutrophilia along with immature myeloid forms, such as myelocytes and metamyelocytes, are seen (**Figure 2**). In the chronic phase, fewer than 10% of blasts are present in circulation. Peripheral eosinophilia, basophilia, and thrombocytosis can also be seen. CML can be diagnosed by identifying the Philadelphia chromosome (either the fusion gene, t(9;22), or gene transcript, *BCR-ABL*) in a peripheral blood sample using fluorescence in situ hybridization or reverse transcriptase polymerase chain reaction, respectively.

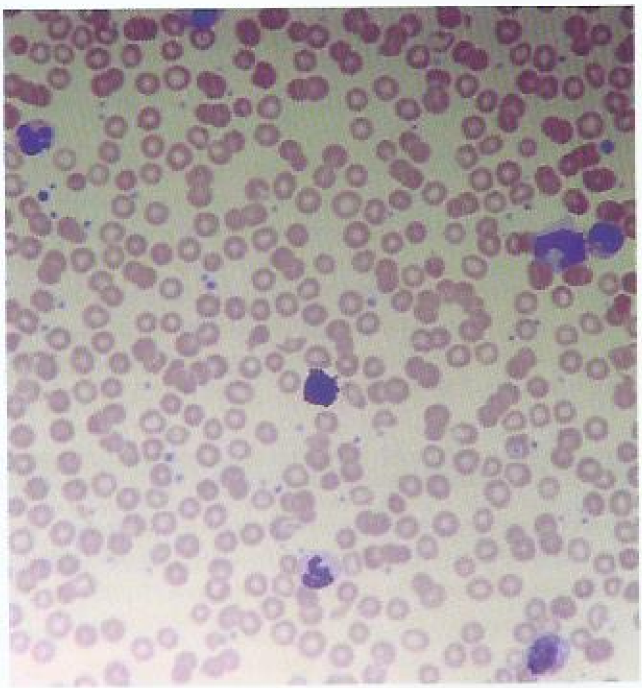

FIGURE 2. Chronic myeloid leukemia is characterized by a preponderance of mature granulocytes (*upper left*) and less mature myeloid cells such as myelocytes (*bottom right*) and metamyelocytes (*top right*). Basophils (*center*) are helpful in differentiating the myeloproliferative neoplasms from leukemoid reactions.

Figure courtesy of Deepty Bhansali, MD; Baylor Scott & White Health.

Therapy is required at diagnosis in all patients to treat symptoms and to prevent progression to blast phase and subsequent AML. Tyrosine kinase inhibitors (TKIs) are highly effective and are the treatment of choice for patients with chronic phase CML. Three TKIs, imatinib, dasatinib, and nilotinib, are FDA approved for the initial treatment of CML. TKIs bind to the BCR-ABL oncoprotein and prevent downstream signaling. Development of these TKIs has revolutionized the treatment of CML, with improved survival, and has significantly decreased the need for stem cell transplantation. Although TKIs are relatively well tolerated, they have unique adverse effects, such as fluid retention and QTc prolongation, requiring close monitoring. They also have significant drug-drug interactions that necessitate caution when starting new medications. TKIs are contraindicated during pregnancy, so either close monitoring of patients off treatment or a switch to interferon is indicated. In patients receiving TKI therapy in whom CML progresses, medication adherence or novel mutation development should be considered. Novel TKIs (bosutinib and ponatinib) are available for refractory CML. For patients with accelerated or blast phase CML, allogeneic hematopoietic stem cell transplantation is considered.

KEY POINT

- Therapy with a tyrosine kinase inhibitor is required at diagnosis in all patients with chronic myeloid leukemia to treat symptoms and to prevent progression to acute myeloid leukemia.

Polycythemia Vera

Polycythemia vera (PV) is a clonal myeloid stem cell neoplasm characterized by excess erythrocyte mass. This increase in erythrocyte mass is independent of erythropoietin level. Thrombocytosis and neutrophilia are commonly seen, justifying the term *polycythemia*, in addition to the increased erythrocyte mass. Activating mutation of the *JAK2* (*JAK2 V617F*) gene is observed in 97% of patients with PV. Most patients with PV are identified by an elevated hemoglobin level (>16.5 g/dL [165 g/L] in men or >16 g/dL [160 g/L] in women) on routine blood testing. Some patients present with symptoms such as fatigue, headache, erythromelalgia (redness and paresthesias of the extremities), pruritus, uncontrolled hypertension, and thrombosis.

Secondary erythrocytosis is much more common than PV. Refer to **Table 4** for common causes of secondary erythrocytosis

TABLE 4. Causes of Secondary Erythrocytosis

Disorders	Symptoms	Physical Examination	Laboratory Studies
Polycythemia vera (primary)	Pruritus after a warm shower Erythromelalgia Transient ischemic attack Deep venous thrombosis/ pulmonary embolism	Splenomegaly Plethora	Low erythropoietin Leukocytosis Basophilia Thrombocytosis *JAK2* positive
Mediated by hypoxemia COPD Sleep apnea Congenital heart disease Intrapulmonary shunting Elevated altitude	Thrombosis Transient ischemic attack Erythromelalgia uncommon Pruritus uncommon	Plethora No splenomegaly Findings consistent with underlying heart or lung disease	Normal leukocyte and platelet counts No basophilia No leukocytosis *JAK2* negative Decreased oxygen saturation
Mediated by ectopic or excessive erythropoietin Renal cell carcinoma Renal artery stenosis/other kidney pathology Hepatocellular carcinoma Uterine fibroids	Thrombosis possible Transient ischemic attack uncommon Erythromelalgia uncommon Pruritus uncommon	Plethora No splenomegaly	High erythropoietin Microscopic hematuria (renal cell carcinoma) Abnormal finding on kidney ultrasonography No basophilia *JAK2* negative
Unusual causes High oxygen affinity hemoglobin	Thrombosis Transient ischemic attack Erythromelalgia uncommon Pruritus uncommon Asymptomatic	Plethora No splenomegaly Age <30 years Family history of erythrocytosis	High erythropoietin No basophilia No leukocytosis *JAK2* negative Abnormal hemoglobin electrophoresis Abnormally low PaO_2 produces 50% hemoglobin saturation

and its clinical features. In most cases of secondary erythrocytosis, the increase in erythrocyte mass depends on the erythropoietin level. Relative polycythemia is seen in patients who have a relative decrease in plasma volume from dehydration with a normal erythrocyte mass leading to elevated hemoglobin levels.

Evaluation of a patient with PV starts with a careful history and physical examination, looking for secondary causes of polycythemia. Smoking history, occupational exposures, and use of medications should be explored. Polycythemia is a common adverse effect of testosterone supplementation, and evaluating the hematocrit level at initiation, 3 to 6 months after testosterone initiation, and annually thereafter is recommended by Endocrine Society guidelines. Guidelines also recommend interrupting the testosterone supplementation if the hematocrit value is greater than 54%. Splenomegaly is a common finding in PV. Patients with PV often have elevated leukocyte and platelet counts along with erythrocytosis. All patients suspected of having PV should undergo a complete blood count, serum erythropoietin level evaluation, and *JAK2* mutation testing. To evaluate for hypoxia, pulse oximetry should be performed. Sleep apnea can be associated with secondary polycythemia but might not be apparent, so careful assessment for signs and symptoms of sleep apnea is important; in patients at high risk, a sleep study may be necessary to evaluate for sleep apnea. Underlying causes of secondary erythrocytosis should be managed; phlebotomy decisions are more complex in these patients because the elevated hemoglobin level may be an appropriate physiologic response.

Finding a low serum erythropoietin level and *JAK2* positivity in a patient with an elevated hemoglobin level is usually diagnostic of PV.

H Thrombosis is a major complication in patients with untreated PV. Whole blood viscosity is increased, with increased risk of arterial thrombosis (stroke and myocardial infarction) and venous thrombosis. *JAK2* mutation has also been implicated in thrombotic risk. Other hematologic complications in PV include progression to post-PV myelofibrosis and transformation to AML. Prognosis after transformation is poor. H

Treatment of PV is required at diagnosis. Phlebotomy with a goal hematocrit level of less than 45% has been shown to decrease the risk of thrombosis and is applied to all patients with PV. Phlebotomy keeps the hematocrit level under control by causing iron deficiency, so iron supplementation should not be given. Low-dose aspirin is considered in all patients with PV to decrease the risk of thrombosis. Hydroxyurea is used in patients with a high risk of thrombosis, such as those older than 60 years and those with a history of thrombosis. The *JAK1/2* inhibitor ruxolitinib is approved for treatment of patients who are intolerant of hydroxyurea or for refractory PV.

KEY POINT

- *JAK2* positivity is found in almost all patients with elevated hemoglobin levels caused by polycythemia vera.

Essential Thrombocythemia

Essential thrombocythemia (ET) is suspected in patients with sustained elevation of platelet counts greater than 450,000/µL (450×10^9/L). Diagnosis of ET requires ruling out other MPNs such as CML, PV, primary myelofibrosis, and myelodysplastic syndromes. *JAK2* mutation is present in about 50% of patients with ET. Other clonal mutations in ET have been identified involving the calreticulin and *MPL* genes. In patients without these clonal mutations, diagnosis of ET requires ruling out reactive thrombocytosis. Iron deficiency anemia is a common cause for reactive thrombocytosis. Other common causes of secondary thrombocytosis are infection, inflammation, and splenectomy.

H Most patients with ET are asymptomatic and present with an elevated platelet count found on routine laboratory testing. Patients can present with vasomotor symptoms such as headache, visual disturbances, dysesthesia of the palms and soles, syncope, and livedo reticularis. Other complications of ET include thrombosis and hemorrhage. Thrombosis can be venous or arterial, manifesting as a cerebrovascular accident, transient ischemic attack, digital ischemia, vision loss, or myocardial infarction. Hemorrhage in ET is commonly seen in patients with a platelet count greater than 1.5 million/µL (1500×10^9/L) or use of high-dose aspirin. Extreme thrombocytosis is thought to increase bleeding risk by causing acquired von Willebrand disease. H

Patients with ET might not require immediate platelet-lowering therapy at diagnosis. The most important factors in defining high risk for thrombosis and the need for preventive therapy are age older than 60 years or history of thrombosis. Patients with platelet counts greater than 1,000,000/µL (1000×10^9/L) are at risk for bleeding and should also be treated with hydroxyurea to lower the platelet count. Other therapies for patients who do not respond to hydroxyurea or who experience significant adverse effects include anagrelide and interferon-α. Low-dose aspirin is considered in all patients at high risk and in patients at low risk who have vasomotor symptoms. Primary care providers should be alert to the value of identifying asymptomatic thrombocytosis that may be discovered incidentally as part of a complete blood count, of ruling out a secondary cause of thrombocytosis, and, in patients with ET who are older than 60 years, of starting hydroxyurea to prevent complications. ET is less likely than other MPNs to progress to AML or myelofibrosis.

KEY POINTS

- The *JAK2* genetic mutation is seen in approximately 50% of patients with essential thrombocythemia and primary myelofibrosis.
- Most patients with essential thrombocythemia present with an elevated platelet count (>450,000/µL [450×10^9/L]) found on routine laboratory testing, and they can also have vasomotor symptoms such as headache, visual disturbances, dysesthesia of the palms and soles, syncope, and livedo reticularis.

(Continued)

KEY POINTS *(continued)*

- Asymptomatic patients with essential thrombocythemia who are older than 60 years with an otherwise unexplained elevated platelet count should be treated with hydroxyurea to lower the platelet count and decrease the risk of thrombotic complications.

Primary Myelofibrosis

Primary myelofibrosis (PMF) carries the worst prognosis of the MPNs. It is a clonal myeloid stem cell disorder with characteristic marrow fibrosis and extramedullary hematopoiesis. This increased fibrosis is thought to be related to proliferation of clonal megakaryocytes, which secrete excess fibroblast growth factor. Hematopoietic progenitors are increased in the circulation, providing a leukoerythroblastic picture seen on peripheral blood smear (**Figure 3**). A leukoerythroblastic smear can also be seen in other myelophthisic disorders, such as bone involvement with carcinoma. As in ET, *JAK2* mutation test results are positive in about 50% of patients with PMF.

Most patients with PMF have significant symptoms at presentation. Cytokine-related hypercatabolic symptoms, such as fatigue, weight loss, fever, and chills, are prominent. Massive splenomegaly is common from extramedullary hematopoiesis and portal hypertension, and it is often accompanied by abdominal discomfort and early satiety. Extramedullary hematopoiesis in the gastrointestinal tract, varices from portal hypertension, and thrombocytopenia can lead to gastrointestinal bleeding. Although patients with PMF present with significant symptoms, some patients can present with more indolent disease.

Diagnosis of PMF requires bone marrow biopsy to document fibrosis in the marrow and to exclude other causes.

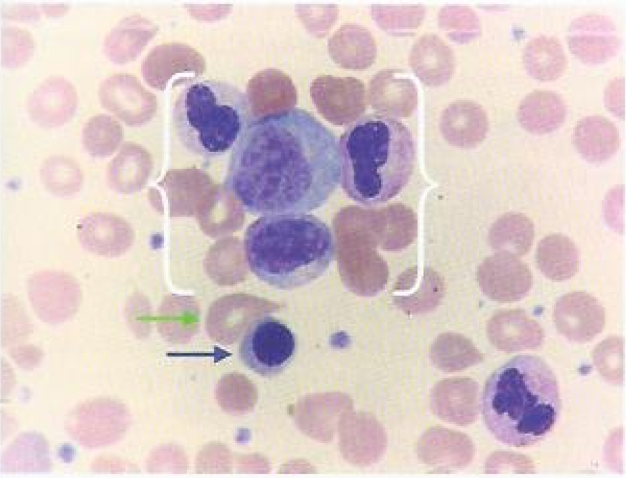

FIGURE 3. A leukoerythroblastic blood smear shows left-shifted granulopoiesis (bands on either side of a large myelocyte above a metamyelocyte in brackets) and nucleated (*blue arrow*) and teardrop-shaped erythrocytes (*green arrow*), which define a crowded myelophthisic marrow such as is seen in primary myelofibrosis or other secondary processes such as metastatic carcinoma. A mature neutrophil is seen in the bottom right.

Biopsy is usually a dry tap with no aspirate because the bone marrow is fibrotic. The Dynamic International Prognostic Scoring System has been developed using various clinical and pathological variables to stratify patients into risk categories. Patients in each risk group have significantly different prognoses; for example, patients in the low-risk group have a median survival of 185 months compared with 16 months in the high-risk group. Treatment of PMF depends on symptoms, risk of disease progression, and survival. The only treatment with potential for cure is allogeneic hematopoietic stem cell transplantation. This type of transplantation is considered in patients who have an HLA-matched donor and who are healthy enough to survive the procedure and have poor prognostic features, including older age, constitutional symptoms, more severe anemia and thrombocytopenia, and increased numbers of blasts in the marrow.

Ruxolitinib has been shown to help improve hypercatabolic symptoms and splenomegaly, with activity independent of *JAK2* mutational status. It does not alter progression to AML. Ruxolitinib is reserved for treatment in patients with debilitating symptoms who are not candidates for hematopoietic stem cell transplantation. Hydroxyurea may be used for patients with low-risk PMF. Splenectomy is only performed in patients with debilitating symptoms related to massive spleen size because it can result in significant morbidity and mortality in PMF.

KEY POINT

- The only treatment with potential for cure for primary myelofibrosis is allogeneic hematopoietic stem cell transplantation.

Eosinophilia and Hypereosinophilic Syndrome

Mild eosinophilia with an eosinophil count of 500 to 1500/µL (0.5-1.5×10^9/L) is not commonly associated with end-organ damage. The causes for eosinophilia, recalled with the mnemonic CHINA (**Table 5**), can be varied. A common cause of eosinophilia, helminth infection should be considered in all patients. Strongyloidiasis can cause eosinophilia and is endemic in the southeastern United States. Eosinophilia may be the only manifestation of this disease, and affected patients can develop disseminated disease if glucocorticoids are mistakenly given to treat hypereosinophilic syndrome (HES).

TABLE 5. Causes of Eosinophilia

C	Collagen vascular disease (eosinophilic granulomatosis with polyangiitis)
H	Helminthic (parasitic worm) infection (*Strongyloides*)
I	Idiopathic hypereosinophilic syndrome (cause unknown after extensive evaluation)
N	Neoplasia (lymphomas most common; myeloproliferative neoplasms)
A	Allergy, atopy, asthma (also drug induced: carbamazepine, sulfonamides)

HES is characterized by sustained eosinophil counts greater than 1500/µL (1.5×10^9/L) and associated end-organ damage attributed to eosinophilia, typically affecting the skin, lungs, heart, gastrointestinal tract, and brain, regardless of causes attributable to eosinophilia. The hypereosinophilic syndrome may be seen in patients with secondary eosinophilia or in those with a primary MPN.

Primary (neoplastic) hypereosinophilic syndrome is an MPN with eosinophilia commonly associated with activation of tyrosine kinase platelet-derived growth factor receptor α or β. Other neoplasms, such as MPNs, AML, lymphomas, and solid tumors, can also manifest with eosinophilia. Treatment of underlying conditions can alleviate eosinophilia. Glucocorticoids are used for treatment of idiopathic HES. In patients with platelet-derived growth factor receptor mutation, imatinib has been shown to be effective.

KEY POINT

- Hypereosinophilic syndrome is characterized by sustained eosinophil counts greater than 1500/µL (1.5×10^9/L) and associated end-organ damage attributable to eosinophilia; it may arise secondary to a variety of underlying causes or from a primary myeloproliferative neoplasm.

Acute Leukemias

H Acute leukemia is a hematologic malignancy characterized by infiltration of the bone marrow, blood, and other tissues by uncontrolled proliferation and abnormal delayed differentiation of clonal myeloid or lymphoid precursor cells, exceeding 20% of the bone marrow or blood. In adults, acute myeloid leukemia (AML) is more common than acute lymphoblastic leukemia (ALL). H

Acute Myeloid Leukemia

H AML typically manifests with anemia, thrombocytopenia, or functional neutropenia secondary to bone marrow replacement with abnormal myeloblasts. Petechiae, epistaxis, and other mucosal hemorrhages occur when the platelet count dips below 20,000/µL (20×10^9/L). Symptoms of anemia vary more with patient's age and comorbidities. Although the leukocyte count is typically elevated, the absolute neutrophil count tends to be low, which confers an increased risk of infection. Myeloblasts are usually seen in the peripheral blood smear but may be absent despite unequivocal bone marrow infiltration. AML is curable in 35% to 40% of adult patients 60 years of age or younger, but the cure rate decreases to just 5% to 15% in adults older than 60 years, when comorbidities, such as cardiopulmonary disease, also preclude the use of intensive chemotherapy. H

Cytogenetic and molecular classification of AML has gained increasing importance in recent years. Acute promyelocytic leukemia, characterized by poorly differentiated leukocytes with distinctive primary granules that contribute to coagulopathy (**Figure 4**) and chromosomal translocation t(15;17), was an earlier prototype for targeted therapy in hematologic malignancies because many patients achieved, and continue to achieve, cure with all-*trans* retinoic acid, which targets the underlying defect in cell differentiation. A growing number of molecular markers are used to guide therapy. *NPM1*-mutated AML is found in about half of patients and appears overtly normal cytogenetically; it is associated with a favorable outcome. In contrast, *FLT3-ITD* identification (found in approximately one third of patients with cytogenetically normal AML) is associated with an unfavorable outcome and merits consideration for allogeneic transplantation in first remission.

H The treatment of AML consists of induction therapy with an anthracycline (such as daunorubicin) and infusional cytarabine. The goal is to ablate the bone marrow, eliminating the blasts, although this transiently destroys the normal hematopoietic cells as well. Cells are expected to recover after a period of aplasia, which extends for 3 to 4 weeks, during which time the patient is supported by transfusions (erythrocytes and platelets) and prompt antibiotic treatment of neutropenic fever. A complete response is achieved in 60% to 85% of patients younger than 60 years. Consolidation therapy for responders consists of additional cycles of conventional chemotherapy in patients at low risk and allogeneic hematopoietic stem cell transplantation for patients at high risk. Treatment for older or frail patients is unsatisfactory; symptom management may include blood and platelet transfusions along with lower dose, often single agent chemotherapy, such as oral hydroxyurea, low-dose cytarabine, and the hypomethylating agents decitabine and azacitidine. These patients are expected to survive only months. Hospice care should also be considered. H

Acute Lymphoblastic Leukemia

H ALL is more common in children and adolescents than in adults. Although ALL in children is often curable, survival in

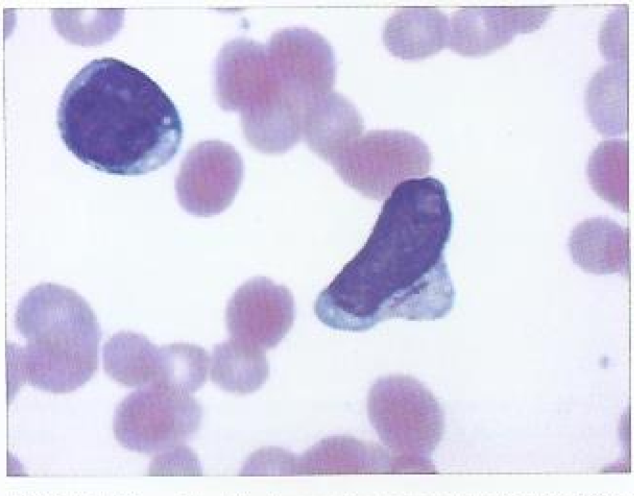

FIGURE 4. This peripheral blood smear shows an immature granulocyte with a rod-shaped inclusion body (Auer rod) characteristic of acute myeloid leukemia.

H CONT.

adult patients (older than 19 years) remains inferior despite the adoption of pediatric ALL regimens. Patients with ALL present with malaise, bleeding, infections, bone pain, or a combination of these symptoms, with a small subset (<10%) having symptomatic central nervous system involvement at diagnosis. In adults, 75% of ALL is of B-cell lineage; mature B-cell ALL can present as extramedullary disease, including gastrointestinal or testicular involvement. A mediastinal mass with wheezing and stridor or skin involvement can be the presenting features of T-cell ALL. Similar to AML, ALL is classified by immunophenotype, cytogenetics, and molecular abnormalities. The most important cytogenetic abnormality in adult ALL is the Philadelphia chromosome, found in 20% to 30% of patients. Historically, Philadelphia chromosome–positive ALL had a poor prognosis. In the modern era, the use of tyrosine kinase inhibitors, such as imatinib and dasatinib, along with more traditional chemotherapy has dramatically improved remission rates. After remission induction, patients with Philadelphia chromosome–positive ALL should receive additional intensive consolidation, such as autologous or allogeneic hematopoietic stem cell transplantation.

Treatment regimens are complex. Regimen backbones include vincristine, anthracycline, corticosteroids, and L-asparaginase. Some of these agents have unique toxicities such as allergic reactions, hypofibrinogenemia and hypertriglyceridemia with L-asparaginase. Induction therapy is followed by intensification and consolidation. Unlike in AML, central nervous system prophylaxis is essential during ALL therapy, and a maintenance phase of oral mercaptopurine (daily) and methotrexate (weekly) can extend up to 2 years. Medication adherence can be problematic during the maintenance phase. H

Adult survivors of childhood leukemia face higher risks of secondary cancer, cardiovascular disease, and the metabolic syndrome (high BMI, truncal obesity, dyslipidemia, insulin resistance, and hypertension) compared with age-matched controls. Primary care physicians encountering such patients should request a treatment summary from the treating facility and encourage patient participation in a local survivor clinic. Screening for lipid profile, diabetes, and hypertension is recommended. Echocardiography to screen for left ventricular dysfunction should be performed at intervals of 3 to 5 years, particularly if anthracycline exposure was high (such as doxorubicin exceeding 300 mg/m^2) or if chest radiation was used. Female survivors have a higher risk of myocardial dysfunction during pregnancy. High-dose glucocorticoids, typical of ALL regimens, pose a risk for osteopenia. The cumulative incidence of secondary cancer after radiation therapy for childhood ALL reaches 11% at 30 years; tumors include skin cancer, thyroid and parotid tumors, sarcomas, and brain tumors. Cranial radiation also increases the risk for stroke and neurocognitive defects. Patients should be counseled about lifestyle risk factors, age-based screening, and early reporting of persistent symptoms.

KEY POINTS

- Acute myeloid leukemia typically manifests with anemia, thrombocytopenia, or functional neutropenia secondary to bone marrow replacement with abnormal myeloblasts, and petechiae and other signs of mucosal bleeding are quite common when the platelet count dips below 20,000/µL (20×10^9/L).
- Treatment of acute myeloid leukemia consists of induction therapy with an anthracycline and infusional cytarabine, followed by consolidation therapy for responders, consisting of additional cycles of conventional chemotherapy for patients at low risk and allogeneic hematopoietic stem cell transplantation for patients at high risk.
- After remission induction with therapy that includes a tyrosine kinase inhibitor, patients with Philadelphia chromosome–positive acute lymphoblastic leukemia should receive additional intensive consolidation such as autologous or allogeneic hematopoietic stem cell transplantation.

Hematopoietic Growth Factors

Erythropoiesis-stimulating agents (which include erythropoietin and darbepoetin) are primarily used in patients with anemia and chronic kidney disease; for patients receiving dialysis, the target hemoglobin level should be no greater than 12 g/dL (120 g/L) to avoid adverse cardiovascular outcomes. Granulocyte colony-stimulating factors (with various formulations) are used to prevent febrile neutropenia in patients receiving myelosuppressive chemotherapy who are at high risk of febrile neutropenia, such as those receiving intensive chemotherapy for high-risk breast cancer and those aged 65 or older with diffuse aggressive lymphoma being treated with curative chemotherapy. Granulocyte colony-stimulating factor is not indicated for most patients with neutropenia who are afebrile, as a routine adjunct to empiric antibiotics for patients presenting with febrile neutropenia, or for patients undergoing induction chemotherapy for acute leukemia.

Hematopoietic Stem Cell Transplantation

H

Autologous hematopoietic stem cell transplantation is performed in select patients who have multiple myeloma or relapsed aggressive lymphoma. Allogeneic transplantation is indicated in patients at high risk with acute leukemia and for the graft-versus-leukemia effect. Allogeneic transplantation is also used to treat patients with aplastic anemia and select patients with hemoglobinopathies such as sickle cell anemia. The allogeneic donor is typically an HLA-matched sibling or

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unrelated adult donor; the risk of graft-versus-host disease, which includes skin, gastrointestinal, and liver manifestations, increases with the degree of donor-recipient HLA disparity. Better supportive measures and reduced-intensity regimens have provided transplant eligibility to older adults. Although hematopoietic stem cell transplantation carries a significant risk of transplant-related mortality, survivors continue to have long-term morbidities unrelated to relapse, such as susceptibility to bacterial or viral infections and delayed pulmonary toxicity. Internists caring for patients who have undergone transplantation should evaluate patients early for symptoms suggesting infection and follow recommended immunization schedules that take into account the prolonged immunosuppressed state of these patients (see MKSAP 18 General Internal Medicine). H

Multiple Myeloma and Related Disorders

Overview

B-cell maturation to plasma cells involves early antigen-independent and antigen-dependent phases. When humoral immunity is stimulated by an infection or inflammation, multiple clones of plasma cells are expanded. These plasma cell clones can produce immunoglobulins of different classes and specificity, giving the characteristic polyclonal spike seen on protein electrophoresis. In contrast, plasma cell dyscrasias (PCDs) or monoclonal gammopathies have clonal expansion of the plasma cell or lymphoplasmacytic cells, which produce the characteristic monoclonal spike (M spike) on protein electrophoresis. This monoclonal (M) protein can be a complete immunoglobulin, with a heavy chain (IgG, IgA, IgD, or IgM) complexed with a light chain (κ or λ), or free light chains (FLCs) without a heavy chain component. Various PCDs have been described (**Table 6**). Note that M spike denotes the presence of M protein, whereas IgM is the immunoglobulin M.

Evaluation for Monoclonal Gammopathies

Monoclonal gammopathy of undetermined significance (MGUS) occurs in approximately 3% of persons older than 50 years, and most remain asymptomatic without progression. It is a clonal premalignant disorder with low risk of conversion to other PCDs. Testing is typically restricted to patients with symptoms and signs of PCD (**Table 7**).

H

The M protein in PCDs can be detected by serum or urine protein electrophoresis (SPEP and UPEP). Occasionally, the M protein is not a full immunoglobulin but rather isolated light chains (κ or λ) that might be missed on protein electrophoresis. SPEP and UPEP can be good initial screening tests to identify and quantify the presence of an M spike, and the serum FLC assay is a sensitive test to identify and quantify FLCs in the serum. Neither SPEP nor UPEP can identify the subtype of immunoglobulin in the M spike, and both may miss small M proteins. Serum and urine immunofixation are more sensitive tests that can subtype the immunoglobulin and differentiate a monoclonal spike from a polyclonal spike. Polyclonal spikes are commonly found in infections, inflammatory processes, and chronic liver disease and do not usually require further hematologic evaluation. Serum FLC testing detects light chains that are not bound to heavy chains and helps quantify them. In inflammatory and infectious processes, κ and λ FLCs are increased, but the ratio remains normal because they increase proportionately. In patients with a PCD, the clonal plasma cells secrete one type of FLC, leading to an increase in the involved light chain and an abnormal FLC ratio. SPEP, serum immunofixation, and serum FLC testing are commonly used for the initial evaluation of PCDs.

Although MGUS and multiple myeloma are common causes of abnormal M proteins, other disorders can also produce an M spike (see Table 6), and patients should be evaluated for the signs and symptoms of these diseases (see Table 7). Tests considered during the evaluation of monoclonal gammopathies include complete blood count with differential; serum chemistries, including creatinine, calcium, and albumin levels; β_2-microglobulin; SPEP; UPEP; serum and urine immunofixation; serum FLC tests; and quantitative immunoglobulins. Plain radiographs of the bones (skeletal surveys) are used to assess for the presence of lytic lesions. Skeletal surveys

TABLE 6. Disorders Associated with Monoclonal Gammopathies

Plasma Cell Disorders
Monoclonal gammopathy of undetermined significance[a]
Multiple myeloma
Immunoglobulin light-chain (AL) amyloidosis
Monoclonal immunoglobulin deposition disease
Proximal tubulopathy (with or without Fanconi syndrome)
Solitary plasmacytoma
Solitary plasmacytoma of bone
Solitary extramedullary plasmacytoma
POEMS syndrome[b]/osteosclerotic myeloma
B-cell Disorders
Waldenström macroglobulinemia/lymphoplasmacytic lymphoma
Marginal zone lymphoma
Chronic lymphocytic leukemia/small lymphocytic lymphoma
Heavy chain disease

[a]Many diseases may be associated with monoclonocal gammopathy of undetermined significance, including but not limited to connective tissue diseases, hepatitis C, HIV, cryoglobulinemia, and cold agglutinin disease.

[b]Polyneuropathy, Organomegaly, Endocrinopathy, presence of M protein, and Skin changes.

TABLE 7. Common Clinical Scenarios for Consideration of Plasma Cell Dyscrasia Testing[a]

Clinical Scenario	Disease Considerations	Disease Characteristics	Additional Investigative Evaluation[b]
Lytic bone lesions or hypercalcemia	MM	Osteolytic bone lesions, PTH-independent hypercalcemia	Standard investigative evaluation
Age-inappropriate bone loss[c]	MGUS, MM	Osteopenia or osteoporosis with or without associated fractures	Standard investigative evaluation
Peripheral neuropathy	AL amyloidosis; MM, WM (rare), MGUS	Sensorimotor axonal polyneuropathy	Tissue aspirate/biopsy for amyloid
	POEMS syndrome; MGUS, MM, solitary plasmacytoma of bone	Sensorimotor inflammatory demyelinating polyneuropathy, hepatosplenomegaly, endocrinopathies (hypogonadism, adrenal insufficiency), hyperpigmentation, hypertrichosis, multicentric Castleman disease, osteosclerotic bone lesions	VEGF, endocrine evaluation (e.g., testosterone level)
	Cryoglobulinemic vasculitis; MGUS, MM, B-cell non-Hodgkin lymphoma (e.g., WM)	Sensory or sensorimotor polyneuropathy, mononeuropathy multiplex	Cryoglobulins, complement levels, hepatitis evaluation
Kidney disease	Cast nephropathy; MM	Acute kidney injury, nonalbumin proteinuria (monoclonal FLCs), bland urine sediment	Kidney biopsy
	AL amyloidosis; MGUS, MM	Nephrotic syndrome	Tissue aspirate/biopsy for amyloid
	Monoclonal gammopathy of renal significance	Varied kidney manifestations in patients who otherwise meet criteria for MGUS with a small plasma clone	Kidney biopsy
	Proximal tubulopathy +/− Fanconi syndrome	Normal anion gap, hyperchloremic metabolic acidosis, hypophosphatemia, hypouricemia, renal glucosuria, amino aciduria	Kidney biopsy, serum phosphorus and uric acid, urinalysis
	Cryoglobulinemic vasculitis	Membranoproliferative glomerulonephritis with proteinuria and active urinary sediment	Cryoglobulins, complement levels, hepatitis evaluation
Anemia	MM	Normocytic (occasionally macrocytic) anemia	Standard investigative evaluation

AL amyloidosis = immunoglobulin light-chain amyloidosis; FLC = free light chain; MGUS = monoclonal gammopathy of undetermined significance; MM = multiple myeloma; POEMS = Polyneuropathy, Organomegaly, Endocrinopathy, M protein, and Skin changes; PTH = parathyroid hormone; VEGF = vascular endothelial growth factor; WM = Waldenström macroglobulinemia.

[a]This is not an all-inclusive list; other less common conditions can be associated with plasma cell dyscrasias.

[b]Evaluation beyond the standard evaluation for a monoclonal gammopathy.

[c]Premenopausal women or men <65 years of age with no additional risk factors for bone loss.

H CONT.

are used to assess for lytic lesions in multiple myeloma. Bone scans, which detect increased osteoblast activity in most bone metastases, may not detect the more purely lytic lesions in multiple myeloma and should not be used. In select patients, PET scans and MRI are required to accurately evaluate bone lesions.

Bone marrow aspirate and biopsy quantifies the percentage of plasma cells in the marrow and help classify the PCD. Cytogenetic evaluation of the bone marrow aspirate helps establish an accurate prognosis. Bone marrow testing can be deferred in patients with low-risk features, such as an IgG gammopathy measuring less than 1.5 g/dL, a normal serum FLC ratio, and no evidence of end organ damage. H

KEY POINTS

- Tests useful in the evaluation of monoclonal gammopathies include complete blood count with differential, serum chemistries, β_2-microglobulin, serum and urine protein electrophoresis, serum and urine immunofixation, serum free light chain testing, and quantitative immunoglobulins.
- HVC Bone marrow evaluation need not be undertaken in patients with a monoclonal gammopathy and low-risk features, such as an IgG gammopathy less than 1.5 g/dL, normal serum free light chain ratio, and no end-organ damage.

Monoclonal Gammopathy of Undetermined Significance

MGUS is characterized by an M protein level less than 3 g/dL (or less than 500 mg/24 h of urinary monoclonal FLCs), clonal plasma cells comprising less than 10% of the bone marrow cellularity, and the absence of related signs and symptoms of end-organ damage (**Table 8**). MGUS is diagnosed incidentally during evaluation for various signs and symptoms such as neuropathy, vasculitis, elevated protein, or end-organ damage.

The prevalence of MGUS increases with age and is noted in approximately 5% of persons older than 70 years. When an asymptomatic condition has a high prevalence rate and low risk of progression to symptomatic disease, it is important to provide an accurate prognosis and appropriate counseling and management. Non-IgM, IgM, and light-chain MGUS are the three types, based on type of M protein. Non-IgM MGUS can progress to multiple myeloma and, although less likely, to other PCDs at a rate of 1% per year. IgM MGUS has the potential to progress to Waldenström macroglobulinemia at a rate of 1.5% per year. Light-chain MGUS can progress to other PCDs at a rate of 0.3%. In addition to the type of M protein, factors that predict the risk of progression include the quantity of M protein and an abnormal serum FLC ratio (**Table 9**).

TABLE 8. Diagnostic Criteria for the Plasma and Lymphoplasmacytic Cell Dyscrasias

Diagnosis	M Protein	Bone Marrow Clonal Plasma Cells or Lymphoid Cells	Disease-Specific Signs/Symptoms
MGUS			
Non-IgM (IgG, IgA)	<3 g/dL	<10%	No
IgM	<3 g/dL	<10%	No
Light chain[a]	Affected serum FLC increased and serum FLC ratio increased Urinary M protein <500 mg/24 h	<10%	No
Smoldering myeloma[b]	IgG or IgA ≥3 g/dL or κ or λ urinary FLC M protein ≥500 mg/24 hr	10%-59%	No
Smoldering WM[b]	IgM ≥3 g/dL	≥10%	No
Multiple myeloma requiring therapy	Present (absent in nonsecretory disease)	≥10% or biopsy evidence of a bony or extramedullary plasmacytoma	Yes
WM requiring therapy	Present	≥10%	Yes
CRAB Criteria for Myeloma-Related Signs and Symptoms			
HyperCalcemia: Serum calcium >11 mg/dL (2.8 mmol/L) or >1 mg/dL (0.3 mmol/L) higher than the upper limit of normal			
Renal failure: Serum creatinine >2 mg/dL (177 µmol/L) or creatinine clearance <40 mL/min			
Anemia: Hemoglobin <10 g/dL (100 g/L) or 2 g/dL (20 g/L) below the lower limit of normal			
Bone disease: ≥1 lytic bone lesions on imaging studies			
Myeloma-Defining Biomarkers for Myeloma-Related Signs and Symptoms			
≥60% clonal plasma cells on bone marrow examination			
Involved: uninvolved serum FLC ratio ≥10[c]			
≥1 focal lesion on MRI			
WM-Related Signs and Symptoms			
Systemic symptoms: Fatigue, B symptoms (fevers, night sweats, weight loss), neuropathy, hyperviscosity			
Physical examination findings: Symptomatic lymphadenopathy or hepatosplenomegaly			
Laboratory findings: Cytopenias (anemia, thrombocytopenia)			

FLC = free light chain; MGUS = monoclonal gammopathy of undetermined significance; WM = Waldenström macroglobulinemia.

[a]Light chain MGUS does not have a heavy chain component.

[b]Smoldering myeloma or WM may have the diagnostic M protein level with or without the percentage of bone marrow clonal plasma or lymphoid cells.

[c]Involved light chain must be greater than 100 mg/dL.

Data from Rajkumar SV, Dimopoulos MA, Palumbo A, Blade J, Merlini G, Mateos MV, et al. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. Lancet Oncol. 2014;15:e538-48. [PMID: 25439696] doi:10.1016/S1470-2045(14)70442-5

TABLE 9. Risk of MGUS Progression to a Clinically Symptomatic Plasma Cell Dyscrasia

Diagnosis	Risk Factors	Progression
Non-light chain MGUS (IgG, IgA, IgM)	M protein ≥1.5 g/dL	At 20 years:
	Non-IgG M protein	3 RFs: 58%
	Abnormal serum FLC ratio	2 RFs: 37%
		1 RF: 21%
		0 RFs: 5%
Smoldering myeloma	M protein ≥3 g/dL	At 5 years:
	Bone marrow plasma cells ≥10%	3 RFs: 76%
		2 RFs: 51%
	Serum FLC ratio <0.125 or >8 mg/dL	1 RF: 25%

FLC = free light chain; MGUS = monoclonal gammopathy of undetermined significance; RF = risk factor.

Data adapted from Rajkumar SV, Kyle RA, Therneau TM, Melton LJ 3rd, Bradwell AR, Clark RJ, et al. Serum free light chain ratio is an independent risk factor for progression in monoclonal gammopathy of undetermined significance. Blood. 2005;106:812-7. [PMID: 15855274]; and Dispenzieri A, Kyle RA, Katzmann JA, Therneau TM, Larson D, Benson J, et al. Immunoglobulin free light chain ratio is an independent risk factor for progression of smoldering (asymptomatic) multiple myeloma. Blood. 2008;111:785-9. [PMID: 17942755]

In addition to the risk of progression, patients with MGUS are at higher risk of osteoporosis and fracture of the axial skeleton, and bone mineral density testing should be considered. Treatment is not required at diagnosis. Patients commonly undergo follow-up for signs and symptoms of progression, initially at 6 months and then yearly, if stable.

Kidney disease in patients with monoclonal gammopathy has traditionally been linked to light chain nephrotoxicity in those with multiple myeloma or amyloid infiltration in those with amyloidosis. More recent data suggest that some patients with features otherwise quite consistent with MGUS may, nonetheless, have significant kidney disease related to the abnormal immunoglobulin. If other, more likely causes of kidney injury are excluded (for example, diabetes or hypertension), these patients should be diagnosed with monoclonal gammopathy of renal significance and require aggressive myeloma-like therapy to prevent progressive and irreversible kidney injury.

KEY POINT

- Monoclonal gammopathy of undetermined significance is characterized by an M protein level less than 3 g/dL, clonal plasma cells comprising less than 10% of the bone marrow cellularity, and the absence of related signs and symptoms of end-organ damage.

Multiple Myeloma

Multiple myeloma (MM) is a clonal plasma cell neoplasm. MM can present as smoldering (asymptomatic) disease with risk of progression or as symptomatic disease, which requires immediate treatment to prevent complications. Smoldering MM has a higher clonal plasma cell burden than MGUS and a higher risk of transformation to MM requiring therapy.

Clinical Manifestations and Findings

MM requiring therapy can manifest with classic symptoms such as hypercalcemia, kidney disease, anemia, and bone disease (see CRAB criteria in Table 8). Other possible symptoms include fatigue, weight loss, neuropathy, and those arising from extramedullary plasmacytoma.

Normocytic anemia is a common finding in MM requiring therapy. Anemia is caused by bone marrow plasma cell infiltration and kidney disease. The peripheral blood smear may show rouleaux formation (**Figure 5**). Patients can also be immunosuppressed from leukopenia, impaired lymphocyte function, and hypogammaglobulinemia. Although patients with MM can have increased total immunoglobulin, normal immunoglobulins are usually reduced. Patients are at increased risk of respiratory infections, and chemotherapy for MM can further increase this risk.

Bone pain is a common symptom of MM. Osteoclast activation and osteoblast inactivation occur, leading to development of lytic lesions (**Figure 6**) and vertebral body compression fracture. This increased bone resorption leads to hypercalcemia. Patients with MM are prone to developing pathologic fractures with minimal or no trauma.

Kidney dysfunction with an elevated creatinine level or occult injury is seen in a significant proportion of patients. The two main causes of kidney disease are elevated FLCs causing cast nephropathy and hypercalcemia. Cast nephropathy, commonly termed myeloma kidney, is caused by deposition of FLCs in the distal tubules, leading to tubulointerstitial damage. Underlying cast nephropathy makes these patients especially vulnerable to additional kidney injury through dehydration, NSAID use, or exposure to radioiodine contrast. Other causes of kidney dysfunction in MM include

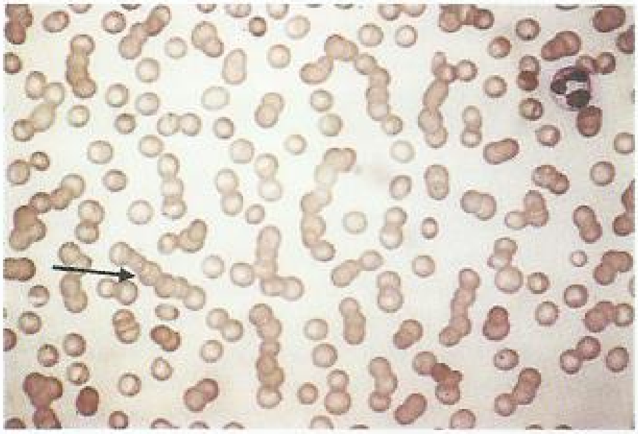

FIGURE 5. Peripheral blood smear showing rouleaux formation. This finding can be seen in patients with multiple myeloma. Rouleaux refers to the appearance of erythrocytes stacked on each other (*arrow*). Various conditions can cause rouleaux formation, including poor preparation of the blood smear.

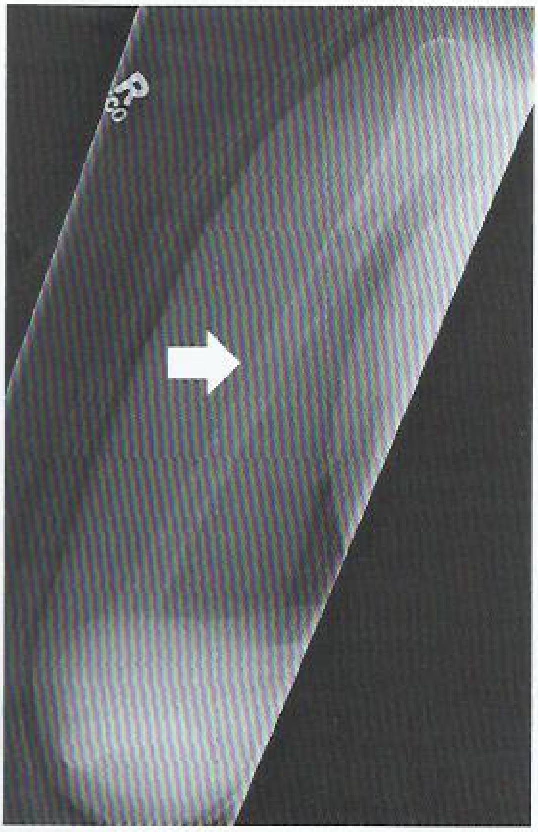

FIGURE 6. Lytic bone lesions in a patient with multiple myeloma. The arrow denotes an oblique pathologic fracture through a mid-humerus lytic lesion. Other lytic lesions can be seen both proximal and distal to the fracture.

H CONT. immunoglobulin light-chain amyloidosis, cryoglobulinemic glomerulonephritis, and proximal tubulopathy. H

Diagnosis and Prognosis

H Diagnostic criteria for MM are listed in Table 8. Evaluating patients with suspected MM includes identification of the M protein, assessment for symptoms of MM, and determination of whether these symptoms are attributable to MM. Identification and quantification of the M protein are accomplished with SPEP, UPEP, and serum FLC testing (see previous section, Evaluation for Monoclonal Gammopathies). Bone marrow biopsy is performed to evaluate the plasma cell burden and to determine cytogenetics for risk stratification. All patients are evaluated for laboratory features of MM with complete blood count, serum creatinine and calcium levels, and skeletal surveys following the CRAB criteria outlined previously. Plain radiography can detect most bone lesions in MM, but in select patients with negative skeletal surveys and with bone symptoms, a CT or MRI is performed (whole-body MRI is preferred). PET-CT is routinely performed during the evaluation of a patient with plasmacytoma to assess the presence of additional occult extramedullary tumors.

Symptoms of organ dysfunction should not necessarily be attributed to the underlying PCD. Kidney biopsy is performed to document myeloma kidney when it is clinically difficult to differentiate kidney injury from another diagnosis, such as diabetic nephropathy. Evaluation for alternative causes of hypercalcemia and anemia should be completed, especially when the patient has low-risk disease. H

Smoldering MM has a risk of conversion to MM requiring therapy of about 10% per year for the first 5 years. The risk of progression decreases after the first 5 years. This risk is not uniform; risk factors for progression include a high M protein level, a large burden of clonal plasma cells, and an abnormal serum FLC ratio (see Table 9). Patients with smoldering MM at imminent risk of progression in the next 2 years and therefore requiring immediate therapy include those with 60% or more plasma cells in the bone marrow, more than one focal bone lesion on MRI, or a serum FLC ratio of 0.01 or less or 100 or greater.

MM is staged based on serum markers such as β2-microglobulin and albumin. However, cytogenetics of the bone marrow more accurately predict prognosis and sometimes guide better treatment decisions.

Treatment

Patients with smoldering MM are usually monitored for progression to MM requiring therapy every 3 to 6 months without beginning treatment. Recent studies have shown improved survival with treatment of high-risk smoldering MM; however, defining these patients at high risk is somewhat controversial, and it is not routine practice to treat them. Bisphosphonates do not decrease the risk of progression in smoldering MM.

Treatment of MM requiring therapy has been revolutionized over the last few years with the advent of new treatment options, which have significantly improved survival (averaging almost 10 years from diagnosis). Patients are initially evaluated for autologous hematopoietic stem cell transplantation (HSCT) eligibility. Autologous HSCT with high-dose melphalan is not curative in MM but does improve progression-free and overall survival. Patients eligible for transplant typically undergo induction therapy with multiagent chemotherapy followed by autologous HSCT and close observation or maintenance therapy. Induction chemotherapy involves various combinations of immunomodulatory drugs (lenalidomide or thalidomide), proteasome inhibitors (bortezomib), glucocorticoids (dexamethasone), and alkylating agents (melphalan or cyclophosphamide).

Treatment for MM is not curative, so all patients eventually present with relapsed or refractory disease. Several new drugs have been approved in this setting, including proteasome inhibitors (carfilzomib and ixazomib), the immunomodulatory drug pomalidomide, histone deacetylase inhibitors (panobinostat), and monoclonal antibodies (daratumumab and elotuzumab). These new agents are effective, and studies are under way evaluating them in the first-line setting.

Agents used to treat MM have unique side effects. Lenalidomide and pomalidomide carry a risk of venous thromboembolism (VTE), and patients are considered for thromboprophylaxis. Bortezomib and thalidomide cause peripheral neuropathy. Bortezomib is associated with a high

risk of herpes zoster reactivation; prophylactic therapy with acyclovir is recommended.

Pain is a dominant symptom in patients with MM requiring therapy, and many patients require treatment with opioids; NSAIDs can worsen kidney disease in these patients. Surgical stabilization of impending fracture is undertaken to prevent morbidity. Bisphosphonates (zoledronic acid and pamidronate) are used to prevent skeletal events. Zoledronic acid has also been shown to improve survival in MM requiring therapy. Patients taking bisphosphonates should be closely monitored for hypocalcemia and osteonecrosis of the jaw.

Nephrotoxic agents and contrast studies should be used judiciously in patients with MM and a risk of worsening kidney disease. Hypercalcemia is treated with hydration and bisphosphonates. Annual influenza vaccination (inactivated) should be administered to all patients with MM. Because of the immunocompromised state of MM, pneumococcal vaccination with the 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine should be administered in accordance with Advisory Committee on Immunization Practices guidelines (see MKSAP 18 General Internal Medicine). Select patients with recurrent infections and hypogammaglobulinemia benefit from intravenous immune globulin infusions.

KEY POINTS

- Hypercalcemia, kidney disease, anemia, and bone disease are classic symptoms of multiple myeloma requiring therapy, which is defined by the presence of an M protein and 10% or more clonal plasma or lymphoid cells in the bone marrow.
- Smoldering multiple myeloma is defined by immunoglobulin levels and the percentage of plasma cells exceeding limits for monoclonal gammopathy of underdetermined significance in patients with no disease-specific symptoms; most of these patients do not require immediate chemotherapy but should be closely monitored to assess disease progression.

(Continued)

KEY POINTS *(continued)*

- Bisphosphonates should be routinely prescribed in patients with myeloma requiring therapy because they prevent skeletal events and improve survival.
- Patients with multiple myeloma eligible for transplant typically receive induction therapy with multiagent chemotherapy followed by autologous hematopoietic stem cell transplantation and close observation or maintenance therapy.

Immunoglobulin Light-Chain Amyloidosis

Amyloidosis refers to a varied group of disorders associated with extracellular deposition of low-molecular-weight proteins in a β-pleated sheet configuration. These are usually abnormal proteins that circulate in the blood and deposit in various organs. Various proteins have been implicated in amyloidosis (**Table 10**). All amyloid deposits have a characteristic apple-green birefringence under polarized light microscopy of the tissue with Congo red staining.

Light-chain amyloidosis (AL) is the most common type. It is a clonal plasma cell dyscrasia characterized by production of amyloidogenic λ or κ free light chains. These light chains can deposit in various organs, resulting in varying clinical presentations of the disease (**Table 11**, **Figure 7**). Diagnosis requires biopsy of the affected tissue that shows the characteristic pathological findings. To avoid invasive biopsy, fat pad or bone marrow biopsy is sometimes performed initially. After confirmation of the amyloid in the tissue, immunohistochemical staining can confirm the light-chain composition of the amyloid deposit or identify alternative components, such as transthyretin or amyloid A protein. Patients with AL amyloidosis should undergo analysis for clonal plasma cell dyscrasias with serum and urine protein electrophoresis, serum FLC testing, and bone marrow biopsy.

All patients are evaluated for extent of organ involvement. Cardiac involvement is common with AL amyloidosis,

TABLE 10. The Amyloidoses

Type	Disease Association	Amyloid Protein
AL amyloidosis	Plasma cell dyscrasias (MGUS, multiple myeloma), Waldenström macroglobulinemia (rare)	Monoclonal free λ or κ light chains
Hereditary amyloidosis	Inherited	Mutated transthyretin (TTR), fibrinogen α chain[a]
AA amyloidosis	Rheumatoid arthritis, inflammatory bowel disease, familial Mediterranean fever, chronic infection	Serum amyloid A protein
Age-related (senile) amyloidosis	Age	Wild-type TTR
Dialysis-related amyloidosis	Dialysis for any reason	β_2-microglobulin

AA = amyloid A (secondary) amyloidosis; AL = immunoglobulin light chain amyloidosis; MGUS = monoclonal gammopathy of undetermined significance.

[a]Not an all-inclusive list.

TABLE 11. Clinical Manifestations of AL Amyloidosis by Organ System

Organ System	Clinical Manifestations	Findings
Kidney	Anasarca, lower extremity edema, foamy urine	Nephrotic range proteinuria with bland urine sediment, hypoalbuminemia, elevated creatinine, nephromegaly on kidney ultrasonography
Gastrointestinal	Gastrointestinal bleeding, dysphagia, early satiety, abdominal distention, steatorrhea	Anemia, iron deficiency, submucosal hematomas on endoscopy, hypoalbuminemia, delayed gastric emptying, intestinal pseudo-obstruction, malabsorption, small bowel bacterial overgrowth
Liver	Weight loss, abdominal pain, features of chronic liver disease and portal hypertension	Cholestatic liver test abnormalities, hepatosplenomegaly, ascites, varices, evidence of portal hypertension
Neurologic	Distal numbness, paresthesias, neuropathic pain, weakness, autonomic nerve dysfunction	Distal sensorimotor polyneuropathy on electromyography/nerve conduction studies, autonomic neuropathy
Cardiac	Chest pain, symptoms from chronic heart failure or arrhythmia	Echocardiographic changes (ventricular hypertrophy with granular appearance, restrictive cardiomyopathy with diastolic heart failure greater than systolic heart failure), electrocardiographic changes (low voltages, pseudoinfarct pattern, conduction system changes, arrhythmias), abnormal cardiac MRI (late gadolinium enhancement)
Coagulation	Bleeding diathesis, periorbital purpura	Factor X deficiency with prolonged PT and aPTT, prolonged PT and aPTT from advanced liver impairment, blood vessel fragility from vascular amyloid deposition
Musculoskeletal	Macroglossia (see Figure 7), muscle pseudohypertrophy, symmetric arthropathy, submandibular gland enlargement, carpal tunnel syndrome	Carpal tunnel syndrome on electromyography/nerve conduction studies, joint space widening on plain radiographs, periarticular soft tissue and muscle infiltration on MRI

aPTT = activated partial thromboplastin time; PT = prothrombin time.

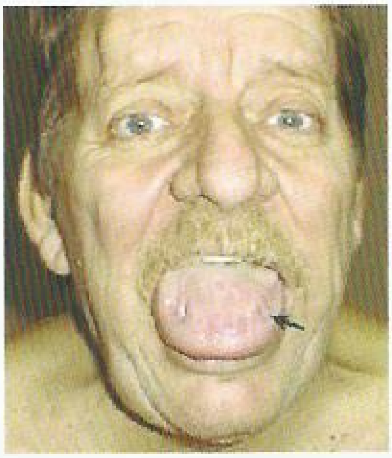

FIGURE 7. Macroglossia is a hallmark feature of light-chain amyloidosis. Heavy infiltration of amyloid restricts mobility of tongue. The tongue cannot be extended, and obstruction of the pharynx causes problems with deglutition and breathing. *Note the indentations from teeth pressing on the enlarged tongue (arrow).*

H CONT. and evaluation with echocardiography, electrocardiography, B-type natriuretic peptide, and serum troponin T is commonly performed. Cardiac MRI is more sensitive than echocardiography and has a distinctive pattern. Kidney involvement usually manifests as nephrotic range proteinuria; 24-hour urine assessment of the protein assists diagnosis. Other organs that can be involved and their clinical features are listed in Table 11. H

Prognosis of AL amyloidosis depends on the presence and extent of cardiac involvement; survival ranges from almost 8 years to only 6 months.

Treatment of AL amyloidosis starts with evaluating the patient for autologous HSCT. Eligibility for transplantation is based on age (younger than 70 years), performance status (independence completing activities of daily living), and the extent of organ involvement. Patients with advanced cardiac disease, stage 4 chronic kidney disease, or large effusions are generally not eligible for transplantation. Autologous HSCT has been shown to improve organ function and survival. Patients ineligible for transplant should receive treatment with melphalan- or bortezomib-based chemotherapy regimens. Supportive care to treat symptoms is necessary.

KEY POINTS

- Diagnosis of immunoglobulin light-chain amyloidosis requires biopsy of the affected tissue showing characteristic pathological findings of apple-green birefringence under polarized light microscopy of the tissue with Congo red staining; immunohistochemical staining then determines the light-chain nature of the amyloid.
- Patients with immunoglobulin light-chain amyloidosis who are ineligible for autologous hematopoietic stem cell transplantation should receive treatment with melphalan- or bortezomib-based chemotherapy regimens.

Waldenström Macroglobulinemia

Waldenström macroglobulinemia (WM) is an indolent B-cell lymphoma with clonal lymphoplasmacytic cells in the bone or lymph nodes that secrete clonal IgM in the blood. WM is differentiated from MGUS by the presence of more than 10% clonal lymphoplasmacytic cells in the bone marrow, greater than 3 g/dL of M protein, symptoms from the disease, or a combination of the three. As in multiple myeloma, patients with smoldering, asymptomatic WM can be observed without therapy.

Patients can present with classic "B symptoms" of drenching night sweats, fever, and weight loss and may have anemia and fatigue. Tissue infiltration leads to hepatosplenomegaly, lymphadenopathy, gastrointestinal dysfunction, and kidney disease. Peripheral sensorimotor neuropathy is seen in 20% of patients and can be associated with antimyelin-associated glycoprotein. Increased serum viscosity from the circulating IgM can lead to hyperviscosity syndrome. Hyperviscosity syndrome can include diverse central nervous system symptoms, including headache, altered mental status, change in vision and hearing, nystagmus, and ataxia. Funduscopic evaluation may reveal dilated retinal veins, papilledema, and flame hemorrhages. Mucosal bleeding is related to platelet dysfunction and dysfibrinogenemia (prolonged thrombin time).

H Symptomatic hyperviscosity requires emergent treatment with plasmapheresis to remove excess IgM. Therapy to decrease IgM production is instituted simultaneously in patients with hyperviscosity symptoms and should be initiated in other patients with symptomatic WM. Rituximab, either as a single agent or in combination with chemotherapy such as cyclophosphamide, bendamustine, and bortezomib, along with glucocorticoids, is commonly used. Recently, ibrutinib (a Bruton's tyrosine kinase inhibitor) has been approved for treatment of WM. H

KEY POINT

- Patients with Waldenström macroglobulinemia can develop a hyperviscosity syndrome, with symptoms including altered mental status and diverse central nervous system symptoms, dilated retinal veins on funduscopic examination, and mucosal bleeding from impaired platelet function and dysfibrinogenemia.

Cryoglobulinemia

Cryoglobulinemia denotes the presence of clonal or polyclonal immunoglobulins that precipitate in the serum at temperatures less than 37 °C (98.6 °F) and dissolve with rewarming. Cold agglutinins, which are often confused with cryoglobulins, are antibodies against erythrocyte antigens that agglutinate erythrocytes in blood at temperatures less than 37 °C (98.6 °F) and can sometimes cause cold agglutinin autoimmune hemolytic anemia.

H Cryoglobulinemias are classified as types I, II, and III based on the composition of the cryoglobulins. Type I cryoglobulinemia involves a monoclonal immunoglobulin, usually IgM, and is associated with plasma cell dyscrasias. Types II and III are called mixed cryoglobulinemias; they are composed of a mixture of polyclonal IgG and monoclonal or polyclonal IgM. Mixed cryoglobulinemias are usually seen in association with infections such as hepatitis C, with connective disorders, and rarely with lymphoproliferative disorders.

Type I cryoglobulinemia is usually asymptomatic but can rarely cause symptoms of hyperviscosity and thrombosis. Patients can present with digital cyanosis, ulcers, Raynaud phenomenon, or gangrene. Patients with neurologic symptoms from the hyperviscosity are treated with emergent plasmapheresis, along with treatment of the underlying plasma cell dyscrasia to prevent production of cryoglobulins. Vasculitic symptoms, such as palpable purpura, glomerulonephritis, and neuropathy, are less common in type I (see MKSAP 18 Rheumatology for further information on mixed cryoglobulinemias). H

KEY POINTS

- Type I cryoglobulinemia involves a monoclonal immunoglobulin, usually IgM, is associated with plasma cell dyscrasias, and is typically asymptomatic.
- Types II and III mixed cryoglobulinemias are composed of a mixture of polyclonal IgG and monoclonal or polyclonal IgM and are usually seen in association with hepatitis C, connective disorders, or lymphoproliferative disorders.

Erythrocyte Disorders

Approach to Anemia

Anemia is a pathologic state resulting in an insufficient number of erythrocytes to deliver oxygen to organs and tissues. Anemia can arise from blood loss, underproduction of erythrocytes, destruction of erythrocytes (hemolysis), or a combination of these factors. Patients with chronic anemia may be entirely asymptomatic or may experience symptoms of dyspnea, decreased exercise tolerance, palpitations, lightheadedness, or fatigue. Symptoms generally reflect the degree of anemia and the rapidity with which anemia develops. Symptoms are also determined by end-organ function and vascular disease. Anemia developing over the same period in a young, otherwise healthy person may be asymptomatic, whereas in someone with critical coronary artery atherosclerosis, it may manifest with severe chest pain.

From a laboratory perspective, the automated complete blood count (CBC) identifies the severity of the anemia. The CBC includes the erythrocyte count, hematocrit level (percentage of total blood volume composed of erythrocytes), hemoglobin concentration in the blood, and erythrocyte

indices such as mean corpuscular volume (MCV) and the red cell distribution width (indication of the range of erythrocyte size). Physiologically, men have a higher hemoglobin concentration than women because of the erythropoietic effects of androgens.

Normal pregnancy is associated with a dilutional anemia resulting from an increase in plasma volume that exceeds the increase in erythrocyte mass to deliver oxygen to the developing fetus at low viscosity. Other pathophysiologic states can affect hemoglobin levels. Because erythrocyte production is controlled by erythropoietin synthesized in the kidney in response to hypoxia, kidney disease can lead to anemia. Similarly, patients deficient in iron, cobalamin, or folate can develop anemia because these vitamins and minerals are required for hemoglobin production. Whether anemia is a normal result of the aging process is a subject of debate, although it is clear that associated pathophysiologic states and, likely, nutritional deficiencies contributing to anemia are more common in older adults.

H In assessing patients with anemia, reviewing the CBC along with the peripheral blood smear can lead to valuable diagnostic clues. Defining the anemia as microcytic, macrocytic, or normocytic can narrow the differential diagnosis. Furthermore, reviewing erythrocyte morphology microscopically can provide a diagnosis. **Table 12** lists common erythrocyte morphologic features and their interpretations. Anemia in adults is commonly caused by iron deficiency, absolute or relative erythropoietin deficiency (kidney disease or the anemia of inflammation, respectively), or acute blood loss. Acquired hemolytic anemia is much less common. Anemia in hospitalized patients most often results from acute blood loss, the anemia of inflammation, or the anemia of kidney disease. H

In addition to the CBC, a reticulocyte count provides information on the marrow response to anemia. A normal marrow will produce reticulocytes in response to anemia or hypoxia. In contrast, patients with vitamin B_{12}, folate, or iron deficiency or those with marrow diseases such as myelodysplasia or aplastic anemia cannot make adequate erythrocytes and therefore have a low reticulocyte count for their degree of anemia. The reticulocyte count may be reported as a percentage of the total erythrocyte count or as the absolute number of reticulocytes as determined by flow cytometry.

An algorithm for the evaluation of anemia can be found in **Figure 8**. In addition to the CBC and review of the peripheral blood smear, a bone marrow aspirate and biopsy can be helpful in the diagnosis of anemia, especially in assessing stem cell disorders such as aplastic anemia, dysmyelopoietic syndrome, and acute leukemia. Anemia combined with other cytopenias increases the likelihood of a primary marrow cause. Prussian blue staining can identify marrow iron stores, although interpretation of serum ferritin levels is often sufficient for that purpose. Anemia should never be considered a final diagnosis;

TABLE 12. Common Erythrocyte Findings on Peripheral Blood Smear

Peripheral Blood Smear Finding	Interpretation
Bite cells (erythrocytes with a nonstaining, clear zone)	Glucose-6-phosphate dehydrogenase deficiency
Burr cells (echinocytes; erythrocytes with a small number of spicules of uniform size and distribution on the cell surface)	Uremia
Elliptocytes (erythrocytes that are elongated, oval, or elliptically shaped)	Hereditary elliptocytosis
Macrocytes or macro-ovalocytes	Cobalamin or folate deficiency, myelodysplasia, use of antimetabolites
Microcytosis, anisopoikilocytosis	Iron deficiency
Nucleated erythrocytes	Marrow stress (hemolysis, hypoxia)
Rouleaux formation ("stacked-coin" appearance of erythrocytes)	Paraproteinemia (myeloma)
Schistocytes (irregularly shaped, jagged fragments of erythrocytes)	Microangiopathy (TTP, HUS, DIC)
Sickle cells (drepanocytes; erythrocytes with spiculated shape)	Sickle cell anemia
Spherocytes (small hyperchromic erythrocytes without central pallor)	Hereditary spherocytosis, warm autoimmune hemolytic anemia
Spur cells (acanthocytes; erythrocytes with a small number of spicules of variable size and distribution on the cell surface)	Severe liver disease
Stomatocytes (erythrocytes with a mouth-shaped area of central pallor)	Artifact, hereditary stomatocytosis
Target cells (codocytes; erythrocytes with an area of central density surrounded by pallor and then a rim of density)	Hemoglobinopathy, liver disease, splenectomy, iron deficiency
Teardrop cells (dacryocytes; cells with round main body part and an elongated end)	Fibrosis, marrow granuloma, marrow infiltration

DIC = disseminated intravascular coagulation; HUS = hemolytic uremic syndrome; TTP = thrombotic thrombocytopenic purpura.

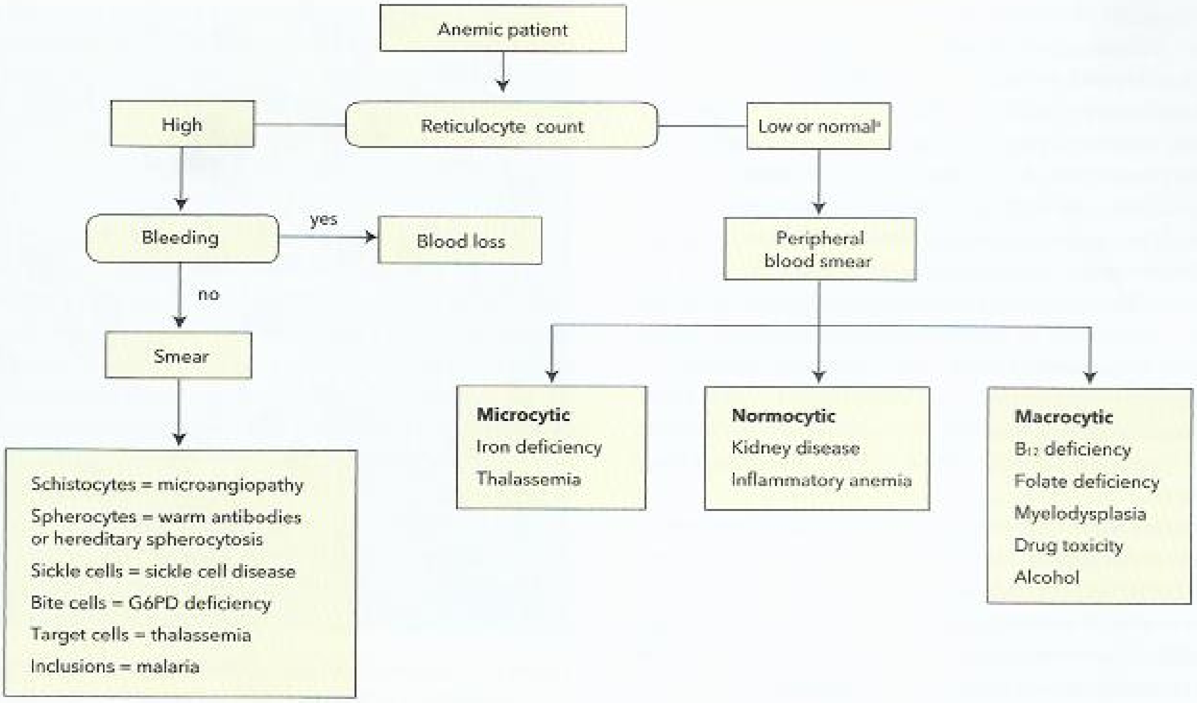

FIGURE 8. Diagnostic algorithm for the evaluation of a patient with anemia.

[a]Reticulocyte count may be low or normal in some patients with bleeding or hemolysis.

the cause must be identified. Recognizing the underlying cause leads to more focused treatment beyond transfusion to correct the anemia, as well as other prevention or therapeutic opportunities linked to the specific cause.

KEY POINTS

- Symptoms from anemia are related to its severity and how rapidly it occurs, as well as to the presence or absence of underlying organ or vascular disease.
- Anemia in hospitalized patients is most likely related to acute blood loss, the anemia of inflammation, or the anemia of kidney disease.

Anemia Due to Erythrocyte Underproduction or Maturation Defects

Iron Deficiency

Iron is an essential component of the hemoglobin molecule. In addition to its critical role in oxygen delivery, iron is also necessary for DNA synthesis and cellular transport. Most of the iron in the body is contained in the erythron; each milliliter of packed red blood cells contains about 1 mg of elemental iron. Hepcidin, the key peptide involved in iron regulation, is produced in the liver and is a negative regulator of iron absorption. Hepcidin production increases with inflammation and decreases in response to hypoxia, anemia, and iron deficiency. Hepcidin production is regulated by several proteins, including human hemochromatosis, hemojuvelin, matriptase-2, and transferrin receptor 1 and 2. These proteins are important in hereditary iron overload states discussed later in this chapter. Hepcidin causes internalization and proteolysis of ferroportin in the enterocyte and macrophage leading to decreased iron absorption from the gut and decreased iron release from macrophages.

Iron is derived from the diet as heme-based iron from red meat, poultry, and fish and non-heme-based iron from green leafy vegetables, lentils, beans, and peas. Vegetable iron has a more limited uptake because of phytates and oxalates that form complexes with iron and limit bioavailability. The typical adult diet contains 5 mg of iron for every 1000 calories. Only 10% to 20% of oral iron is absorbed. Because iron loss cannot efficiently be increased, in a normal physiologic state, iron absorption is about equal to iron loss. The typical adult man loses approximately 1 mg of iron daily from gastrointestinal mucosal turnover, whereas the typical adult woman loses approximately 1.5 mg of iron daily through mucosal turnover and menstrual blood loss.

Iron intake, use, and loss require a fine balance. Iron deficiency is a significant problem because of increased iron requirements during pregnancy and lactation and endemic helminthic infections that increase iron loss. Iron requirements are increased during normal growth and development, making iron deficiency in infants and children a widespread occurrence. Iron deficiency in adults rarely occurs secondary to decreased oral intake but is more commonly secondary to blood loss. For premenopausal women,

this is typically secondary to menstrual blood loss, but for men or postmenopausal women, occult gastrointestinal blood loss should be suspected. Numerous lesions in the upper and lower gastrointestinal tracts may cause such bleeding, but identifying an occult colonic neoplasm may be especially important. Iron is absorbed in the proximal small bowel, and patients with celiac disease, inflammatory bowel disease, or surgical resection can experience iron malabsorption. Importantly, iron malabsorption may occur in the absence of diarrhea, steatorrhea, and weight loss, which are common symptoms of malabsorption. *Helicobacter pylori* infection is associated with iron deficiency because of impaired iron uptake (this mechanism is not well established) and increased iron loss from gastritis or peptic ulcer disease. Common causes of iron deficiency anemia are listed in **Table 13**.

Patients with iron deficiency may be asymptomatic or may experience fatigue, lack of a sense of well-being, irritability, headache, and decreased exercise tolerance. Pica, the tendency to eat or crave starch, clay, paper, ice, or other crunchy foodstuffs, is sometimes seen in severe iron deficiency. The pathophysiology of pica remains poorly understood.

Physical examination findings may be normal in patients with early anemia from iron deficiency. Symptomatic patients can experience tachycardia, conjunctival rim pallor (inferior conjunctival rim same color as palpebral conjunctiva), glossitis, and stomatitis. Severe iron deficiency can cause spooning of the nails (koilonychia).

A low MCV, elevated red-cell distribution width, and peripheral blood smear showing microcytosis and anisopoikilocytosis (**Figure 9**) are virtually diagnostic of iron deficiency, especially in premenopausal women; these findings may obviate the need for additional laboratory testing, provided that a follow-up CBC is performed to assess response to iron therapy.

TABLE 13. Causes of Iron Deficiency Anemia

Loss of iron
Bleeding
Menstruation
Gastrointestinal bleeding (can be microscopic)
Other overt or occult blood loss
Decreased intake
Nutritional deficiency
Decreased absorption
After gastric/duodenal surgery
Celiac disease
Helicobacter pylori infection
Autoimmune atrophic gastritis
Increased iron requirements
Pregnancy
Lactation

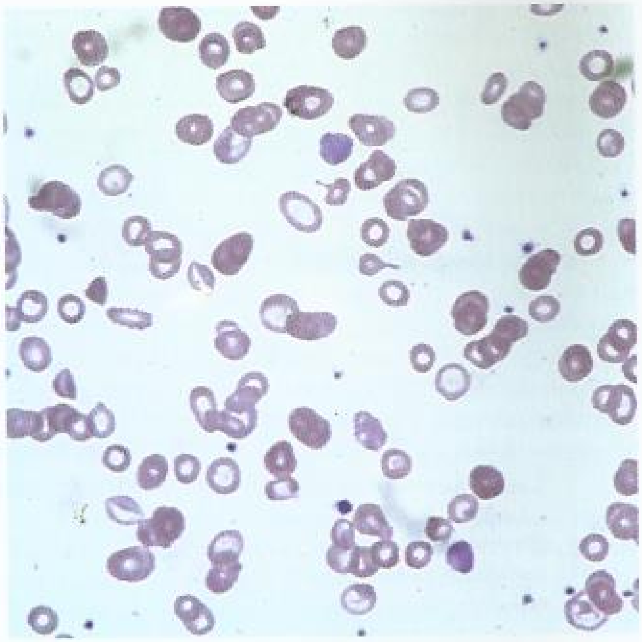

FIGURE 9. Hypochromia and microcytosis with anisopoikilocytosis in a patient with iron deficiency. Note the relatively small erythrocytes compared with the lymphocytes on the smear. Note also the abnormalities in shape and size of the erythrocytes (anisopoikilocytosis).

A low serum iron level, elevated total iron binding capacity, low transferrin saturation (iron/total iron-binding capacity × 100), and serum ferritin level less than 14 ng/mL (14 µg/L) confirm the diagnosis of iron deficiency. Although ferritin is an acute phase reactant that increases with inflammation, a ferritin level greater than 100 ng/mL (100 µg/L) virtually excludes iron deficiency. Measuring serum levels of zinc protoporphyrin and soluble transferrin receptor was previously suggested in the evaluation of iron deficiency, but because of considerable overlap in patients with and without iron deficiency, these measurements are no longer recommended. Thrombocytosis occurs frequently with iron deficiency caused by blood loss. Although a bone marrow stained with Prussian blue can detect iron stores, this test is seldom necessary in the diagnosis of iron deficiency.

Iron deficiency is typically treated with oral iron salts. Oral ferrous sulfate is the least expensive preparation, with each 325-mg tablet containing 65 mg of elemental iron. Oral absorption can be increased with supplemental vitamin C; conversely, medications such as antacids and fiber can reduce absorption. It has become increasingly recognized that frequent dosing (two or three times daily) of oral iron can lead to increased hepcidin production, which actually reduces iron absorption. For this reason, a single daily or every-other-day dose of oral iron sulfate may be the best replacement dose. Although oral ferrous fumarate, ferrous gluconate, and other oral iron salts are available, none have proven superior to ferrous sulfate in tolerability, efficacy, or cost. Delayed-release and slow-release preparations may be better tolerated but are also associated with reduced

iron absorption because these products can bypass the intestinal sites where iron absorption occurs. Although oral iron is typically well tolerated, symptoms can include gastrointestinal upset, constipation, and abdominal pain. Iron replacement typically results in a reticulocytosis within days. Hemoglobin levels typically increase by approximately 1 g per week. Oral iron replacement typically lasts 3 to 6 months after normalization of hemoglobin to replace iron stores.

H For patients undergoing dialysis who have large iron requirements or for patients with celiac disease, inflammatory bowel disease, or those who have undergone resection of the stomach or small bowel, oral iron may not be adequate treatment. These patients typically require parenteral iron. Iron dextran was the principal intravenous iron product used in the past, but with the risk of anaphylaxis and relatively poor bioavailability, newer parenteral iron preparations with a better safety profile and better ferrokinetics are more often used. These include iron sucrose, ferric gluconate, ferumoxytol, and ferric carboxymaltose. Data are inadequate to recommend one newer parenteral agent over another for patients requiring parenteral iron. H

KEY POINTS

- HVC A low mean corpuscular volume, elevated red-cell distribution width, and peripheral blood smear showing microcytosis and anisopoikilocytosis are virtually diagnostic of iron deficiency, especially in premenopausal women; these findings may render additional testing unnecessary, provided the response to iron therapy is monitored.
- HVC Iron deficiency is typically treated with oral iron salts, optimally dosed once daily, with oral ferrous sulfate being the preferred preparation because of its tolerability, efficacy, and cost.

H Inflammatory Anemia

For decades, anemia has been recognized in conjunction with either chronic infections such as tuberculosis or osteomyelitis or in conjunction with malignancy. Because these types of infection and malignancy are "chronic diseases," these anemic states were often referred to as "anemia of chronic disease." From a pathophysiologic standpoint, "inflammatory anemia" is a more appropriate term, because these anemias are related to increased hepcidin production in response to inflammatory mediators such as interleukin-6. Hepcidin causes decreased iron absorption from the enterocyte through internalization and proteolysis of ferroportin. No FDA-approved assays for hepcidin evaluation are available, although several enzyme-linked immunosorbent assays and spectrometry-based assays are in development. Inflammatory cytokines also blunt the erythropoietin response to anemia.

In patients with inflammatory anemia, the peripheral blood smear typically shows a normochromic, normocytic anemia. Over time, as iron absorption decreases, microcytosis can be seen. Typically, patients with inflammatory anemia have a hemoglobin level of 8 to 10 g/dL (80-100 g/L). Because of impaired erythropoiesis, caused by a blunted response to erythropoietin, the reticulocyte count is typically low for the degree of anemia. The characteristic iron study pattern seen in inflammatory anemia is increased serum ferritin level, low serum iron level, and a reduced total iron-binding capacity. **Table 14** lists characteristic laboratory features useful in distinguishing iron deficiency from inflammatory anemia. Although seldom necessary, a bone marrow biopsy specimen would show adequate stainable iron stores.

Patients with diabetes or heart failure can also have an increase in inflammatory cytokines and related inflammatory anemia. In some patients with findings consistent with inflammatory anemia, the inflammatory state is not obvious. Such patients do not require extensive evaluation for the source of inflammation.

Inflammatory anemia seldom requires treatment. Iron replacement is ineffective. Although supplemental erythropoietin can correct anemia in inflammatory states, it can also lead to hypertension and thrombosis and should be used with extreme caution. Patients with cancer who experienced anemia with chemotherapy and who received erythropoietin felt better and had better blood counts, but cancer mortality was increased. H

TABLE 14. Laboratory Characteristics of Inflammatory Anemia, Iron Deficiency Anemia (IDA), and IDA with Inflammation

Finding	Type of Anemia		
	Inflammatory Anemia	Iron Deficiency Anemia	IDA with Inflammation
MCV	72-100 fL	<80 fL	<100 fL
Serum iron	<60 µg/dL (11 µmol/L)	<60 µg/dL (11 µmol/L)	<60 µg/dL (11 µmol/L)
TIBC	<250 µg/dL (45 µmol/L)	>400 µg/dL (72 µmol/L)	<400 µg/dL (72 µmol/L)
TIBC saturation	2%-20%	<15% (usually <10%)	<15%
Ferritin	>35 ng/mL (35 µg/L)	<15 ng/mL (15 µg/L)	<100 ng/mL (100 µg/L)
Serum soluble transferrin receptor concentration	Normal	Increased	Increased
Stainable iron in bone marrow	Present	Absent	Absent

MCV = mean corpuscular volume; TIBC = total iron-binding capacity.

KEY POINTS

- Patients with inflammatory anemia have a hemoglobin level of 8 to 10 g/dL (80-100 g/L) and a peripheral blood smear showing a normochromic, normocytic anemia associated with an elevated serum ferritin level, low serum iron level, and a reduced total iron-binding capacity.
- HVC Treatment is seldom necessary in inflammatory anemia, and iron replacement is ineffective; although supplemental erythropoietin improves anemia, it is associated with worsening hypertension, thrombotic complications, and, in patients with cancer, increased mortality.

Anemia of Kidney Disease

Because erythropoietin is made in the renal cortex in response to anemia and hypoxia, patients with kidney disease can have anemia that is typically normochromic and normocytic. In kidney disease, the reticulocyte count is typically low because of a relative deficiency of erythropoietin. The peripheral blood smear may show burr cells (echinocytes) in patients with features of uremia.

Because kidney disease is also associated with platelet defects and gastrointestinal bleeding from ulcer disease or angiodysplasia, microcytosis in the setting of kidney disease should raise the suspicion for iron deficiency. In some patients, minor elevations in serum creatinine level can be associated with low erythropoietin levels and anemia. Although it is important to first rule out other causes of anemia, measuring the erythropoietin level can be helpful in evaluating anemia in patients with mild kidney disease.

Anemia of kidney disease can be associated with fatigue, depression, dyspnea, and decreased exercise tolerance. Anemia is also associated with increased morbidity and mortality from heart disease and stroke in patients undergoing dialysis. Supplemental use of erythropoiesis-stimulating agents (ESAs) can improve anemia in patients with kidney disease. Guidelines recommend that ESAs be withheld in patients with chronic kidney disease (CKD) not requiring dialysis who have a hemoglobin level greater than 10 g/dL (100 g/L). For patients with CKD with a hemoglobin level less than 10 g/dL (100 g/L), ESA treatment should be individualized based on symptoms, rapidity of hemoglobin decline, and transfusion needs. For patients undergoing dialysis, ESAs should be initiated for hemoglobin levels less than 10 g/dL (100 g/L), but hemoglobin concentrations should not exceed 11.5 g/dL (115 g/L) to avoid adverse effects, including worsening hypertension, volume overload, and thrombotic complications. Patients with CKD require iron replacement because of gastrointestinal blood loss and the need for freely available iron to maintain adequate response to ESAs. Because of high iron requirements in patients taking ESAs, parenteral iron is typically used to maintain a serum ferritin level greater than 100 ng/mL (100 μg/L) with a transferrin saturation of at least 20%. Although more than 95% of patients respond to ESAs, insufficient response can result from iron deficiency, folate deficiency, aluminum toxicity, blood loss, or inflammation.

KEY POINT

- Patients with anemia of kidney disease who are not yet undergoing dialysis and have a hemoglobin level greater than 10 g/dL (100 g/L) should not receive erythropoiesis stimulating agents (ESAs); patients with chronic kidney disease who are not yet undergoing dialysis and have a hemoglobin level less than 10 g/dL (100 g/L) should receive individualized ESA therapy based on symptoms, rapidity of hemoglobin decline, and transfusion needs. HVC

Cobalamin (Vitamin B_{12}) Deficiency

Cobalamin is necessary for DNA synthesis. Humans cannot synthesize cobalamin but must consume it in their diet; it is found in animal meats, liver, shellfish, and dairy products. Dietary deficiency is an uncommon cause of cobalamin deficiency because body stores are typically available for many years. Instead, cobalamin deficiency is nearly always a result of malabsorption. Dietary cobalamin is more available for absorption in an acid environment and requires binding with intrinsic factor to enhance absorption in the terminal ileum.

Cobalamin deficiency may be the result of decreased bioavailability, which may be the result of age-related gastric achlorhydria or the use of proton pump inhibitors, or both. Cobalamin malabsorption can also occur in more generalized malabsorptive states such as inflammatory bowel disease, pancreatic insufficiency, and bacterial overgrowth.

Pernicious anemia, characterized by autoimmune gastritis and intrinsic factor deficiency, is another cause of cobalamin deficiency. Antibodies to parietal cells are found in 90% of patients with pernicious anemia, whereas antibodies to intrinsic factor are detected in about 70% of patients. Although antibody testing is sometimes used in the diagnosis of pernicious anemia, the varied sensitivity and specificity of these tests limits the utility of such testing. The Schilling test is no longer used in the evaluation of cobalamin deficiency because of the limited availability of radioactive intrinsic factor.

Patients with cobalamin deficiency can present with weight loss, glossitis, and "lemon yellow" skin because of pallor and jaundice resulting from ineffective erythropoiesis. Severe cobalamin deficiency can cause neurologic symptoms, including loss of vibratory sense, loss of proprioception, spastic ataxia, and other dorsal column symptoms. Psychiatric symptoms (megaloblastic mania) can manifest as dementia, hallucinations, and frank psychosis.

In patients with cobalamin deficiency, the peripheral blood smear shows oval macrocytes and hypersegmented neutrophils (**Figure 10**). Pancytopenia resulting from ineffective hematopoiesis can also be seen. Other laboratory findings are consistent with intramedullary hemolysis caused by ineffective erythropoiesis, including decreased haptoglobin, elevated lactate dehydrogenase, and elevated indirect bilirubin levels. The reticulocyte count is low in patients with cobalamin deficiency.

Although serum cobalamin levels may be low, serum cobalamin, especially in the low-normal range, may not

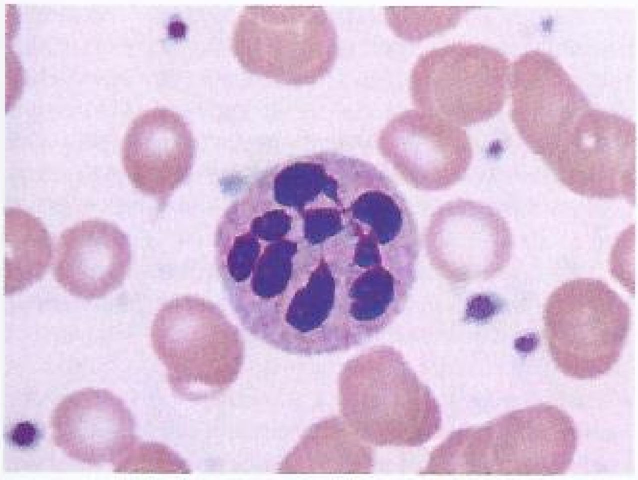

FIGURE 10. Hypersegmented polymorphonuclear (PMN) cell in a patient with pernicious anemia. The presence of hypersegmented PMNs becomes significant when they constitute greater than 5% of PMNs with five or more lobes or 1% with six or more lobes.

adequately represent tissue cobalamin levels. As such, an elevated concentration of methylmalonic acid is a more sensitive indicator of cobalamin deficiency.

Although supplemental folate can improve the anemia found in cobalamin deficiency, folate does not correct or prevent the associated neuropsychiatric complications. An important distinction to make is that folate deficiency leads to an elevation in homocysteine levels with normal levels of methylmalonic acid, whereas cobalamin deficiency has increases in both metabolites.

Patients with cobalamin deficiency can be treated with oral cobalamin, 1000 to 2000 µg daily, regardless of cause; an adequate amount of this dose will be absorbed, even if intrinsic factor is lacking or malabsorption is ongoing. Parenteral cobalamin is more expensive and more cumbersome to administer. Intranasal and oral gel preparations are also available but are not clearly superior to tablet preparations. When cobalamin is replaced, megaloblastic changes in the marrow improve within hours. Reticulocytosis appears in several days, and hemoglobin level increases by approximately 1 g per week. If the response to cobalamin is inadequate, an alternative diagnosis, such as myelodysplasia, should be considered. Neurologic changes may not be reversible with replacement.

KEY POINTS

- An elevated serum methylmalonic acid level accurately reflects tissue cobalamin stores and confirms cobalamin deficiency in patients with borderline or low-normal serum cobalamin levels.
- HVC Treatment for cobalamin deficiency should be instituted with 1000 to 2000 µg/d of oral cobalamin, which is absorbed well even in patients with malabsorption, eliminating the need for parenteral therapy.

Folate Deficiency

Folate is a common component of most diets in the United States; it is found in green leafy vegetables, bananas, lemons, melons, and most other fruits. Supplemental folate has been added to grains in the United States for many years to prevent birth defects. As such, dietary folate deficiency is uncommon except in patients with malnutrition. Persons who consume excess alcohol are apt to ingest inadequate amounts of folate as well as having impaired absorption. Folate is poorly stored and deficiency can develop in weeks to months in patients with insufficient folate ingestion. Patients with disease states characterized by rapid cell turnover, such as pregnancy, hemolysis, or desquamating skin disorders (psoriasis), have increased folate requirements.

Drugs such as triamterene, phenytoin, or methotrexate can lead to folate deficiency by either inhibiting folate absorption or conversion to its active form. Because folate is absorbed in the jejunum, small bowel diseases such as amyloidosis, celiac disease, or inflammatory bowel disease can also inhibit folate absorption.

The peripheral blood smear in folate deficiency is identical to that seen with cobalamin deficiency. Serum folate measurement, if very low, helps establish the diagnosis; however, a normal level may be unreliable because a single meal can normalize levels. Although folate levels in erythrocytes may better reflect chronic folate balance, an elevated serum homocysteine level has a sensitivity and specificity of greater than 90% in diagnosing folate deficiency and is the preferred test when deficiency is suspected despite a normal serum folate level.

After cobalamin deficiency is excluded, patients with folate deficiency should receive oral folate, 1 to 5 mg/d.

KEY POINTS

- A very low serum folate level confirms the diagnosis of folate deficiency; however, a normal level may be seen in patients with clearly reduced tissue stores, so an elevated homocysteine level supports folate deficiency in these patients.
- Cobalamin deficiency should be excluded before patients receive folate therapy; although blood abnormalities may improve with folate supplementation, the neurologic complications of cobalamin deficiency would continue to progress.

Thalassemia

Thalassemia is associated with erythrocyte underproduction and ineffective erythropoiesis and can be considered a disorder of erythrocyte production. Hemoglobin is a tetramer containing two α chains, two β chains ($\alpha_2\beta_2$), and the iron-containing tetrapyrrole heme moiety. Production of α and β chains normally occurs in a balanced fashion from genes located on chromosomes 16 and 11, respectively. Mismatched production of either α or β chains results in impaired production of hemoglobin and

ineffective erythropoiesis. The worldwide incidence of impaired β-chain synthesis is 1% to 5%, with impaired α chain synthesis being even higher. Thalassemia is common in African and Mediterranean countries, the Middle East, and Southeast Asia. Homozygous α-thalassemia leads to intrauterine demise, and homozygous β-thalassemia causes severe symptomatic anemia invariably diagnosed at an early age. Internists are likely to manage patients with heterozygous forms of thalassemia.

The peripheral blood smear typically shows microcytosis, nucleated erythrocytes, and target cells in patients with thalassemia (**Figure 11**). Unlike other underproduction anemias, patients with heterozygous thalassemia typically have a preserved or even an increased erythrocyte count associated with a decreased MCV. Although patients with iron deficiency typically have considerable variation in cell shape and size (anisopoikilocytosis), leading to elevation in red cell distribution width, the microcytic cells in thalassemia are more uniform, and the red cell distribution width is normal. Because of ineffective erythropoiesis, thalassemia is associated with increased lactate dehydrogenase, increased unconjugated bilirubin, and decreased haptoglobin levels.

α-Thalassemia

The α-globin gene is duplicated on chromosome 16 leading to several genotypes. Patients with a single α gene mutation are silent carriers and are clinically healthy. A two-gene mutation results in α-thalassemia trait characterized by a hemoglobin level of approximately 10 g/dL (100 g/L) with microcytosis. Unlike patients with iron deficiency, patients with α-thalassemia trait have normal or elevated iron stores. Diagnosis is usually achieved by excluding other causes of hypochromic microcytic anemia. Select reference laboratories can establish the diagnosis through direct sequencing of the globin genes. Patients with a three-gene mutation have more severe anemia and make a tetramer of β globin called hemoglobin H that can be identified on electrophoresis. In contrast, hemoglobin electrophoresis is normal for α-thalassemia trait.

FIGURE 11. This peripheral blood smear in a patient with β-thalassemia major shows target cells (erythrocytes with an area of central density surrounded by pallor and then a rim of density) and a prominent nucleated erythrocyte.

Patients with α-thalassemia trait should receive supplemental folate and genetic counseling before starting a family. Patients with hemoglobin H disease typically have hemoglobin concentrations of approximately 7 to 8 g/dL (70-80 g/L) and are seldom transfusion dependent. Care should be taken to avoid supplemental iron in patients with thalassemia because these patients absorb iron well; transfusion should also be avoided. In such circumstances, these patients may develop iron overload with resultant heart and liver failure requiring iron chelation therapy with parenteral desferrioxamine or oral iron chelators (deferasirox or deferiprone).

β-Thalassemia

More than 250 mutations have been described in the β-globin gene resulting in a spectrum of diseases from mild reduction in β-chain synthesis (β^+-thalassemia) to complete absence of β chain synthesis (β^0-thalassemia). As such, the clinical spectrum of disease in β-thalassemia includes β-thalassemia minor, β-thalassemia intermedia, and β-thalassemia major. β-Thalassemia minor (trait) is characterized by a microcytic anemia (MCV, 60-70 fL) with a hemoglobin level of 10 to 12 g/dL (100-120 g/L). Unlike α-thalassemia trait, β-thalassemia minor produces an abnormal hemoglobin electrophoresis with an increase in hemoglobin A_2 ($\alpha_2\delta_2$) because of a substitution of δ globin for β globin. Hemoglobin F may also be increased depending on the specific mutation. Patients with β-thalassemia intermedia have hemoglobin levels of 7 g/dL (70 g/L) without need for transfusion.

Patients with β-thalassemia should be treated with folate; as with α-thalassemia, supplemental iron should be avoided.

KEY POINT

- Patients with thalassemia should receive supplemental folate and avoid iron supplementation because they may develop iron overload requiring chelation therapy. HVC

Hemolytic Anemias

Hemolysis occurs when excessive erythrocyte destruction occurs, either through ineffective erythropoiesis; clearance in the reticuloendothelial system of the spleen or liver; immune injury mediated by immunoglobulins or complement; or physical destruction by fibrin, valves, or other intracirculatory devices.

Hemolysis may be accompanied by a bone marrow response (reticulocytosis) and is invariably accompanied by findings consistent with erythrocyte destruction, such as an increase in unconjugated bilirubin, increased lactate dehydrogenase, increased serum free hemoglobin, and hemoglobinuria. Symptoms of hemolysis depend on the degree of anemia and its chronicity. Pigmented gallstones from insoluble calcium bilirubinate are common in chronic hemolytic disorders.

Hemolysis can be broken down into congenital and acquired causes. Congenital disorders segregate into hemoglobinopathies (sickle cell), disorders of the erythrocyte

H CONT.

membrane (hereditary spherocytosis), enzyme defects (glucose-6-phosphate dehydrogenase deficiency), and the thalassemia syndromes.

Acquired hemolysis can occur secondary to medications (fludarabine, bendamustine, quinine, penicillins, α-methyldopa); can be immune in nature; or can occur secondary to micro- or macroangiopathic processes, infections, or physical agents. H

Congenital Hemolytic Anemia

Hereditary Spherocytosis

Hereditary spherocytosis (HS) is typically an autosomal dominant disorder more common in people of Northern European descent. HS is not confined to a single mutation; rather, mutations in α spectrin, β spectrin, ankyrin, band 3, and protein 4.2 have been described in patients with HS. Mutations in these scaffolding proteins adversely affect the interaction between the lipid bilayer and cytoskeleton in the erythrocyte cell wall resulting in a spherocyte (**Figure 12**) characterized by reduced surface-to-volume ratio, osmotic fragility, and splenic sequestration.

Symptoms of HS can be quite variable, and even though HS is a congenital disorder, patients may adapt to mild anemia without symptoms until well into adulthood. An acute episode of bone marrow suppression, typically associated with infection, can lead to new anemia symptoms in patients who were previously able to compensate for hemolysis. In addition to anemia, symptomatic patients typically present with splenomegaly or, more rarely, splenic infarction or rupture, and calcium bilirubinate (pigmented) gallstones are common.

Laboratory findings in HS include spherocytosis on the peripheral blood smear and varying degrees of anemia, reticulocytosis, and hyperbilirubinemia. The mean corpuscular hemoglobin concentration is elevated in patients with HS. Erythrocytes in these patients have increased osmotic fragility when exposed to fluids with high osmolarity. This is the basis of the osmotic fragility test sometimes used to diagnose HS. Flow cytometry can identify characteristic cell surface abnormalities that establish the diagnosis.

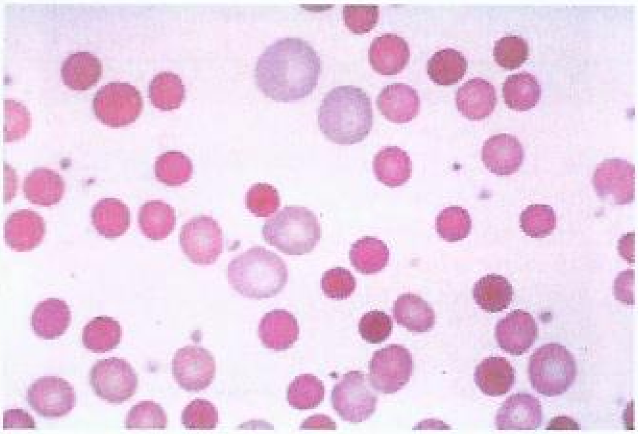

FIGURE 12. This peripheral blood smear in a patient with hereditary spherocytosis shows round cells of uniform density (without central pallor) characteristic of spherocytes.

Patients with HS, as with other hemolytic states, have increased folate requirements and should receive supplemental folate. For severe hemolysis, splenectomy is effective, and partial splenectomy has proven effective in young children whose immune function is improved with a functioning spleen. As with other conditions requiring splenectomy, vaccination for *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Neisseria meningitides* is important before the procedure.

Other congenital disorders of the erythrocyte membrane that can lead to hemolysis include hereditary elliptocytosis and hereditary pyropoikilocytosis. Hereditary elliptocytosis is less commonly associated with anemia.

Glucose-6-Phosphate Dehydrogenase Deficiency

The gene for glucose-6-phosphate dehydrogenase (G6PD) is located on the X chromosome, and as such G6PD deficiency primarily affects men. It can affect women who are homozygous for G6PD disease, through the process of lyonization (inactivation of one of the two X chromosomes) with preference of expression for the defective gene, or who have Turner syndrome (XO karyotype). G6PD deficiency is the most common enzyme deficiency in humans and has been associated with more than 160 gene mutations. G6PD is important in the pentose phosphate pathway, allowing for reduction of nicotinamide adenine dinucleotide phosphate (NADP to NADPH). NADPH is necessary to reduce oxidative stress in response to drugs (chloroquine), infection, or toxins. Two G6PD variants, G6PD A, which produces mild disease that is often asymptomatic, and G6PD Mediterranean are most commonly seen. G6PD Mediterranean is associated with favism, or hemolysis in people who consume fava beans. G6PD variants are thought to provide partial protection for malarial infections. G6PD deficiency occurs most commonly in people of African, Asian, Mediterranean, and Middle Eastern descent and among Kurdish Jews.

H

G6PD deficiency has a varied presentation. It can be associated with neonatal jaundice and, in later life, with acute hemolysis typically occurring within 1 to 3 days after exposure to oxidative stress. Typical triggers include drugs such as chloroquine, sulfonamides, rasburicase, dapsone, and phenazopyridine, and environmental toxins such as naphthalene from mothballs. The peripheral blood smear may show bite cells (**Figure 13**) and Heinz bodies (denatured hemoglobin) visible on supravital stain. Although very uncommon, severe hemolysis can lead to kidney injury and dialysis.

G6PD evaluation involves a fluorescent spot test used to detect NADPH. A positive result shows lack of fluorescence. Evaluation should not be performed during an acute hemolytic episode because, with hemolysis, the older, more enzyme-deficient erythrocytes are preferentially destroyed leaving younger erythrocytes with higher G6PD levels in the circulation; this often leads to a false-negative result. Qualitative G6PD enzyme activity and subtyping can provide a more specific diagnosis.

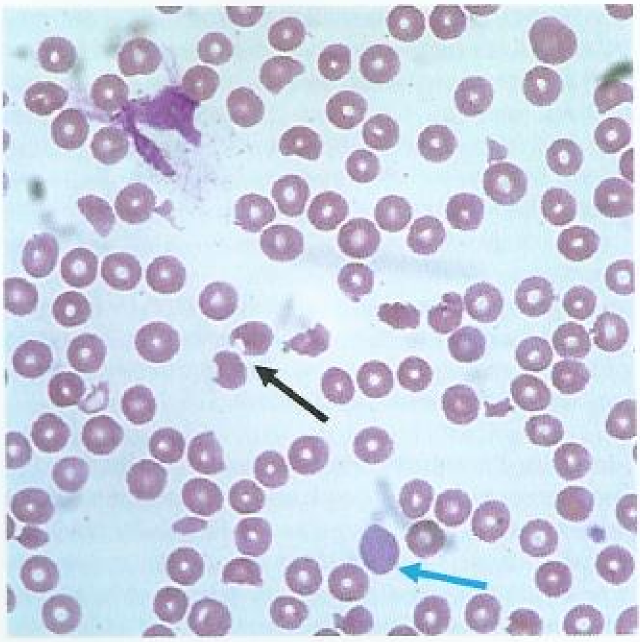

FIGURE 13. Bite cells seen at the center of this slide are typical findings in glucose-6-phosphate dehydrogenase deficiency and are characterized by a membrane defect that appears as though a semicircular bite has been taken out of the erythrocyte. The defect is caused by removal of denatured hemoglobin by macrophages in the spleen. A polychromatophilic macro-ovalocyte can also be seen (bottom), indicating a reticulocyte response.

H CONT.

Typical management of G6PD deficiency includes recognition and diagnosis of the disorder and avoidance of offending agents. During hemolytic episodes, treatment is supportive, with transfusion reserved only for severely symptomatic patients. H

Other less common enzyme defects leading to congenital hemolysis include enzyme deficiencies in the glycolytic pathway, pyruvate kinase deficiency, and aldolase A deficiency.

Sickle Cell Syndromes

H

There is perhaps no hemolytic anemia as clinically dramatic as sickle cell anemia. Affecting nearly every organ system and characterized by extraordinarily painful vaso-occlusive crises, sickle cell disease (SCD) is prevalent among black patients. SCD is characterized by homozygosity for a single point mutation in the sixth position of the β-globin gene resulting in abnormal hemoglobin S (Hb S) that polymerizes under hypoxic conditions, leading to deformed erythrocytes that can adhere to the endothelium of capillaries throughout the circulation. Because of hemolysis, free hemoglobin scavenges nitric oxide, and hemolyzed erythrocytes release arginase, depleting the body of arginine, a necessary precursor to nitric oxide. As a result, patients with SCD experience vasoconstriction and platelet activation, complicating their clinical course.

Hb S is more common in patients of African origin, and most patients homozygous for Hb S (Hb SS) are black, with about 8% of black persons in the United States having sickle cell trait (Hb S). Hb S can be coinherited with hemoglobin C (Hb SC), β-thalassemia (Sβ+-thalassemia), or other hemoglobins, which tends to lead to milder disease than Hb SS. Characteristic electrophoretic patterns for sickling disorders are shown in **Table 15**.

Sickle Cell Disease Complications and Their Management

Chronic hemolysis, vaso-occlusive disease with acute and chronic end-organ damage, nitric oxide depletion, and immune compromise from functional asplenia lead to the myriad of problems faced by patients with SCD. The only potential "cure" for SCD is allogeneic bone marrow transplantation, but the timing and appropriate population for transplantation have not been adequately determined. Hydroxyurea modulates many of the complications of SCD and even prolongs life expectancy because of its ability to increase fetal

TABLE 15. Characteristics of Adult Sickle Cell Syndromes

Disease Type	Hb (g/dL [g/L])	MCV (fL)	Hb S (%)	Hb A (%)	Hb A_2 (%)	Peripheral Blood Smear Findings	Clinical Severity[a] 0 to +++
Sickle trait (AS)	NL	NL	40	60	<3.5	NL	0
Hb SS	6-8 (60-80)	NL	>90	0	<3.5	Sickle cells	+++
Sβ+-thalassemia	9-12 (90-120)	70-75	>60	10-30	>3.5	Rare sickle cells Target cells	+ to ++
Sβ0-thalassemia	7-9 (70-90)	65-70	>80	0	>3.5	Sickle cells Target cells	+++
SCD	10-15 (100-150)	75-NL	50	0	Hb A_2 = 0 Hb C = 50[b]	Sickle cells Target cells	+ to ++

Hb = hemoglobin; Hb SS = homozygous sickle cell anemia; MCV = mean corpuscular volume; NL = normal; Sβ+ = sickle β+; Sβ0 = sickle β0; SCD = hemoglobin SC disease.

[a]Clinical severity is variable within each genotype.

[b]Note that Hb C comigrates with Hb A_2 on standard alkaline cellulose acetate electrophoresis but will separate on citrate agar electrophoresis.

NOTE: Hb percentages may not total 100% because Hb F is not included in this table.

H CONT.

hemoglobin levels and generate nitric oxide. Hydroxyurea is not used often enough and is not always used at the appropriate dose. It should be prescribed for all patients with frequent pain crises, severe symptomatic anemia, or previous acute chest syndrome or stroke. Managing SCD requires a team of providers and must include preventive, acute, and chronic treatment goals (**Table 16**).

Painful vaso-occlusive events are the hallmark of SCD. The frequency and severity of acute painful events varies considerably among patients with SCD, the reasons for which remain poorly understood. In most communities, a few patients with recurrent acute painful events account for most hospitalizations. Research has shown that many practitioners do not properly assess and manage pain in this population, often leaving pain undertreated. Painful events are associated with morbidity and mortality in patients with SCD, and the number of painful crises is inversely related to life expectancy. For these reasons, recognition and treatment of painful events should be immediate. Opiates are the preferred analgesic, with the exception of meperidine, which can cause seizures. Chronic pain is more difficult to treat in SCD, and the pathophysiology is poorly understood. Chronic pain is exacerbated by emotional stress, anxiety, insomnia, and depression and is perhaps best treated with a holistic approach emphasizing nonopioid options such as NSAIDs, relaxation techniques, massage, and biofeedback. A few patients with SCD develop opioid dependence, although the prevalence is no greater than in a comparable age- and illness-matched population.

Two new treatments to prevent painful crisis have recently been approved. Oral L-glutamine, a precursor of nicotinamide adenine dinucleotide (NAD), is necessary to form the antioxidant NADH. It is believed that sickle cell crises are partially related to oxidant stress. A randomized trial in patients receiving L-glutamine showed benefit with reduction in the number

TABLE 16. Common Complications and Treatments in Adults with Sickle Cell Disease

Complications	Treatment
Vaso-occlusive pain episode	**Acute:** rest, relaxation, warmth, NSAIDs, oral and IV hydration, narcotic analgesia
	Recurring: HU for more than 3 episodes/year, pain that interferes with daily activities; avoidance of triggers; nonnarcotic or narcotic analgesia
Acute chest syndrome	**Acute:** oxygen, incentive spirometry, analgesics, empiric antibiotics, IV fluids, simple or erythrocyte exchange transfusions
	Preventive: HU for recurrent acute chest syndrome, incentive spirometry in hospitalized patients
Aplastic crisis	**Acute:** supportive care, blood transfusions as needed
Infection	**Acute:** appropriate and immediate antibiotic management (particular concern for encapsulated bacteria)
	Prevention: influenza, pneumococcal, and meningococcal vaccines
Hyperhemolytic crisis	**Acute:** supportive care, avoid further blood transfusions, immunosuppression might be helpful
	Preventive: avoid blood transfusions if possible, extended antibody screen can lessen but not eliminate recurrence
Multiorgan failure	**Acute:** erythrocyte exchange transfusions
Ischemic stroke	**Acute:** erythrocyte exchange transfusions, aspirin
	Preventive: chronic simple transfusions or erythrocyte exchange transfusions (target Hb S <30%-50%)
Hepatic crisis	**Acute:** supportive, transfusion or exchange transfusion if anemia is symptomatic
Cholelithiasis	**Acute:** if symptomatic, cholecystectomy with preoperative transfusions to hemoglobin of 10 g/dL (100 g/L)
Chronic kidney disease/ proteinuria	**Preventive:** blood pressure control to <130/80 mm Hg
	Secondary preventive: ACE inhibitor or ARB in patients with microalbuminuria
Priapism	**Acute:** relaxation, hydration, narcotic analgesics, aspiration of blood from corpora cavernosa and irrigation with dilute epinephrine, transfusions, shunt procedure
	Preventive: oral α-adrenergic agonists, HU. The role of leuprolide and sildenafil is not clear.
Pulmonary hypertension	No proven therapy established for prevention or treatment
Retinopathy	Annual ophthalmologic examination, laser phototherapy for retinopathy
Osteopenia/osteoporosis	Supplementation with calcium and vitamin D, bone mineral density measurements
Avascular necrosis	Analgesics and physical therapy, arthroplasty
Foot and leg ulcers	**Acute:** early aggressive treatment, debridement, bandage impregnated with zinc oxide
	Preventive: proper footwear to prevent pressure points

ARB = angiotensin receptor blocker; Hb S = hemoglobin S; HU = hydroxyurea; IV = intravenous.

H CONT.

of sickle cell crises. Similarly, the recently approved P-selectin inhibitor, crizanlizumab, has been shown to reduce painful crises by preventing cellular adhesion.

Pulmonary complications are a common source of morbidity and mortality in patients with SCD. Acute chest syndrome (ACS) is a clinical diagnosis based on the constellation of fever (>38.6 °C [101.5 °F]), tachypnea, hypoxia, cough, shortness of breath, and a new pulmonary infiltrate. ACS can be the result of infection, in situ thrombosis, thromboembolism, fat embolism, or a combination of these factors. In addition to supportive measures, including oxygen to treat hypoxia and the use of empiric antibiotics to treat infection, patients with ACS require erythrocyte transfusion, either with packed red blood cells (PRBCs) or as exchange transfusion. In addition to ACS, pulmonary hypertension is a recognized complication of SCD found in up to 30% of patients, typically presenting as worsening right heart failure. Although associated with increased mortality, the appropriate management of pulmonary hypertension in patients with SCD has not been determined. Phosphodiesterase inhibitors, such as sildenafil, have been associated with increased painful crises.

Stroke and other central nervous system disease remain major complications of SCD. Approximately 30% of patients with Hb SS, Hb SC, or $S\beta^{+}$-thalassemia can have silent or symptomatic strokes. Monthly transfusion begun after a stroke can reduce the incidence of subsequent stroke by 50% but carries the risk of iron overload necessitating iron chelation. Hydroxyurea may also help in stroke prevention. In addition to thrombotic stroke, patients with SCD can have moyamoya disease (irregular perforating vascular networks near occluded or stenotic vessels in the region corresponding to lenticulostriate and thalamoperforate arteries) predisposing to cerebral bleeding in the third and fourth decade of life. Adults with SCD have lower cognitive function than healthy adults, perhaps secondary to silent ischemia or chronic anemia. It is unclear whether such cognitive decline can be prevented.

Recently, the National Institutes of Health and the U.S. Department of Health and Human Services published evidence-based guidelines for the treatment of SCD. Strong recommendations from this report are listed in **Table 17**.

Erythrocyte Transfusions in Sickle Cell Disease

Transfusion management in SCD is complicated. Inappropriate transfusion can lead to alloimmunization, iron overload, and infectious complications. Antibody formation can lead to hyperhemolysis, a presumed immune response leading to hemolysis of nearly all transfused blood in addition to native blood. Simple transfusions with PRBCs are used to increase oxygen delivery and should not be used for uncomplicated pain crises or to treat chronic anemia. Patients undergoing surgical procedures requiring general anesthesia should receive PRBC transfusion for a target hemoglobin level of 10 g/dL (100 g/L) to avoid surgical complications. Monthly transfusions (hypertransfusion) in patients with an initial stroke can reduce the incidence of subsequent stroke and reduce stroke occurrence in patients at risk for stroke based on cranial Doppler arterial velocity. Exchange transfusion is often used in the treatment of acute stroke, complicated acute chest syndrome, and acute retinal artery occlusion. With any transfusion, care should be taken to keep hemoglobin concentrations less than 10 g/dL (100 g/L) to avoid problems with blood hyperviscosity. H

TABLE 17. Strong Recommendations from the National Institutes of Health/U.S. Department of Health and Human Services Guidelines for the Management of Sickle Cell Disease

Rapid initiation of opioids for vaso-occlusive crisis
Use of incentive spirometry in hospitalized patients
Use of analgesics and physical therapy for treatment of avascular necrosis
Use of ACE inhibitors in patients with microalbuminuria
Regular ophthalmologic examinations and referral for laser photocoagulation for retinopathy
Use of echocardiography to evaluate signs of pulmonary hypertension
Hydroxyurea for patients with more than 3 vaso-occlusive crises per year, for those with pain or chronic anemia interfering with daily activities, or those with recurrent acute chest syndrome
Preoperative transfusion to serum hemoglobin level of 10 g/dL (100 g/L) for surgeries requiring general anesthesia
Assess for iron overload and begin oral iron chelation if necessary

Other Hemoglobinopathies

More than 1000 mutations have been identified in the α- or β-globin gene, including hemoglobin C, hemoglobin D, and hemoglobin E. Most of these are only clinically relevant if coinherited with Hb S.

KEY POINTS

- Patients with hereditary spherocytosis may remain asymptomatic well into adulthood but may develop acute anemia symptoms when an acute infection suppresses the bone marrow, leading to decompensated hemolysis.
- Evaluation for glucose-6-phosphate dehydrogenase deficiency should not be performed during an acute hemolytic episode, because the older enzyme-deficient erythrocytes are preferentially destroyed during these episodes, which would lead to a false-negative result on testing. HVC
- Painful events are associated with morbidity and mortality in patients with sickle cell disease, and the number of painful crises is inversely related to life expectancy; recognition and treatment of pain should be immediate.
- In patients with frequent acute vaso-occlusive events or other serious complications of sickle cell anemia, hydroxyurea decreases subsequent acute pain events, reduces the risk of acute chest syndrome or stroke, and prolongs survival.

(Continued)

KEY POINTS ***(continued)***

HVC
- In patients with sickle cell disease, simple transfusions with packed red blood cells (PRBCs) should not be used for uncomplicated pain crises or to treat chronic anemia; however, patients undergoing surgical procedures requiring general anesthesia should receive PRBC transfusion for a target hemoglobin level of 10 g/dL (100 g/L) to avoid perioperative complications.

H

Acquired Hemolytic Anemia

Immune-Mediated Hemolysis

Immune-mediated hemolysis is characterized by antibody binding to erythrocytes causing complement-mediated and phagocyte-mediated destruction. Antibodies responsible for immune-mediated hemolysis are divided into warm antibodies, typically IgG, that react at normal body temperature and cold agglutinins, usually IgM, that bind at cooler temperatures. The laboratory hallmark of immune-mediated hemolysis is a positive direct antiglobulin (Coombs) test that detects either IgG or complement (C3) on the erythrocyte surface. Characteristics of immune-mediated hemolysis are shown in **Table 18**.

Warm Autoimmune Hemolytic Anemia

In warm autoimmune hemolytic anemia (WAIHA), pathogenic IgG antibodies are directed against Rh-type antigens on the erythrocyte surface. IgG-coated erythrocytes can be completely phagocytized by splenic macrophages via the Fc receptor and are cleared from the circulation. Warm IgG antibodies can bind and activate complement in a portion of these patients. Partial phagocytosis of the erythrocyte surface area results in spherocytes, which can be viewed on the peripheral blood smear. The direct antiglobulin test result is positive for IgG and is also sometimes positive for C3. Although WAIHA can be a primary disorder, it can also occur secondary to drugs (penicillins or α-methyldopa); lymphoproliferative disorders, such as chronic lymphocytic leukemia; or diseases with disordered immune regulation, such as systemic lupus erythematosus.

Treatment of symptomatic WAIHA involves alleviating immune destruction of erythrocytes using glucocorticoids, intravenous immune globulin, or rituximab. Splenectomy is also effective in nearly 70% of patients. Patients with hemolysis and life-threatening anemia may require blood transfusion (see Transfusion). Although donor blood will also be destroyed at an accelerated rate, improved hemoglobin levels may be sustained while waiting for therapy directed at eliminating the autoantibody to take effect.

Cold Agglutinin Disease

In cold agglutinin disease, pathogenic IgM antibodies are directed against erythrocyte glycoprotein antigens (I or i antigen). Cold agglutinins bind at temperatures lower than normal body temperature (for example, the temperature of distal extremities during cold exposure). Cold agglutinins cause complement fixation, and C3-coated cells are both cleared by hepatic Kupffer cells and destroyed in circulation. The peripheral blood smear shows erythrocyte agglutination leading to a markedly elevated MCV on laboratory testing (**Figure 14**). In cold agglutinin disease, the direct antiglobulin test result is positive for C3. Cold agglutinin disease should always raise suspicion for an underlying lymphoproliferative abnormality, and it can also be seen in *Mycoplasma* and Epstein-Barr virus infections.

Treatment of cold agglutinin disease is primarily directed at avoidance of cold exposure, including warming of all infusates in hospitalized patients. Treatment with glucocorticoids,

TABLE 18. Characteristics of Warm Autoimmune Hemolytic Anemia (WAIHA) and Cold Agglutinin Disease

Characteristic	WAIHA	Cold Agglutinin Disease
Temperature for optimal antibody binding to erythrocytes	37.0 °C (98.6 °F)	<37.0 °C (98.6 °F)
Immunoglobulin class	IgG	IgM
Typical AGT pattern	IgG positive, C3 positive or negative	IgG negative, C3 positive
Peripheral blood smear findings	Spherocytes	Erythrocyte agglutination
Clinical manifestations[a]	Anemia, fatigue, dyspnea, jaundice, splenomegaly	Anemia, fatigue, dyspnea, jaundice, acrocyanosis, splenomegaly
Associated conditions	Autoimmune, lymphoproliferative (chronic lymphocytic leukemia, B-cell non-Hodgkin lymphomas), drug-induced[b]	Infectious (*Mycoplasma* and Epstein-Barr virus), lymphoproliferative (IgM MGUS, Waldenström macroglobulinemia, other B-cell non-Hodgkin lymphomas)
Treatment	Glucocorticoids, splenectomy, immunosuppression, treatment of underlying condition	Cold avoidance, rituximab, plasmapheresis, treatment of underlying condition

AGT = antiglobulin (Coombs) test; MGUS = monoclonal gammopathy of undetermined significance.

[a]Manifestations in cold agglutinin disease are worse upon exposure to the cold. Lymphadenopathy in either entity should raise suspicion of a lymphoproliferative disorder.

[b]Cephalosporins, penicillins, NSAIDs, isoniazid, procainamide, methyldopa, levodopa.

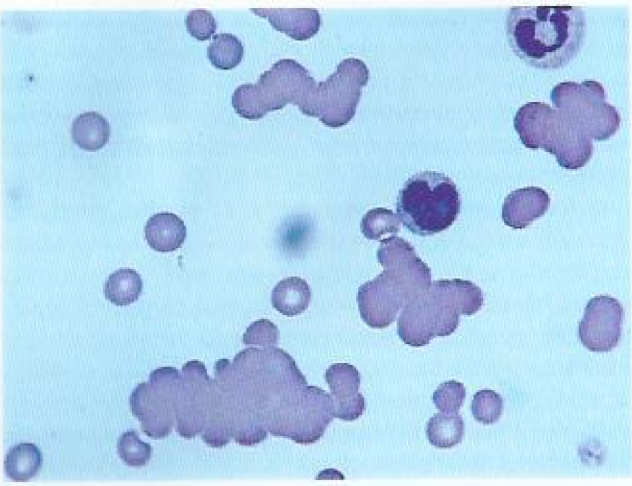

FIGURE 14. Cold agglutinin disease. Notice the erythrocyte agglutination on the slide, which can lead to a spuriously high mean corpuscular volume on automated counters.

FIGURE 15. Peripheral blood smear showing schistocytes, or fragmented erythrocytes.

H CONT. intravenous immune globulin, or splenectomy is seldom effective. Rituximab, fludarabine, or a combination of both has demonstrated activity in case series. H

KEY POINTS

- Treatment of symptomatic warm autoimmune hemolytic anemia involves alleviating immune destruction of erythrocytes using glucocorticoids, intravenous immune globulin, or rituximab; splenectomy is also effective in nearly 70% of patients.
- Treatment of cold agglutinin disease is primarily directed at avoidance of cold exposure, including warming of all infusates in hospitalized patients; the use of glucocorticoids, intravenous immune globulin, or splenectomy is seldom effective.

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Nonimmune Hemolytic Anemia

Microangiopathic Hemolytic Anemia

Microangiopathic hemolytic anemia is characterized by the presence of fragmented erythrocytes (schistocytes) on the peripheral blood smear (**Figure 15**) and is typically caused by erythrocyte destruction resulting from shearing as erythrocytes circulate through fibrin strands. Microangiopathy can be caused by thrombotic thrombocytopenic purpura or the hemolytic uremic syndrome (see Platelet Disorders); malignancy; disseminated intravascular coagulation; hypertensive crisis; drugs such as cyclosporine, mitomycin, or gemcitabine; or eclampsia. Microangiopathy is often accompanied by thrombocytopenia, kidney injury, and central nervous system disturbance. Treatment is directed toward the underlying disease process.

Macroangiopathic Hemolytic Anemia

Patients with artificial valves or those with left ventricular assist devices can develop anemia resulting from erythrocyte fragmentation known as macroangiopathic hemolysis. Similarly, patients with giant hemangiomas, such as those with Kasabach Merritt syndrome, can develop erythrocyte fragmentation from localized intravascular coagulation.

Paroxysmal Nocturnal Hemoglobinuria (PNH)

Patients with PNH lack proteins on the erythrocyte surface that are anchored by glycophosphatidylinositol due to acquired mutations in the *PIGA* gene that persist in bone marrow stem cells. Two of these proteins, CD55 and CD59, protect the erythrocyte from complement mediated destruction. Patients lacking these proteins develop episodic hemolysis, marrow aplasia, and thrombosis. The cause of thrombosis is unclear. Patients with PNH are at higher risk for leukemia or myelodysplasia. Diagnosis involves demonstrating absence of glycophosphatidylinositol linked proteins such as CD55 and CD59 on leukocytes by flow cytometry. PNH therapy includes folate supplementation, glucocorticoids, and a novel monoclonal antibody to C5, eculizumab, which inhibits activation of the terminal complement cascade, decreases hemolysis, reduces thrombotic complications, and improves quality of life. Eculizumab is associated with *Neisseria* infections, so patients should receive meningococcal vaccination before use. H

KEY POINTS

- Treatment of patients with microangiopathic hemolytic anemia is directed toward the underlying disease process, which can include hemolytic uremic syndrome, malignancy, drugs, and thrombotic thrombocytopenic purpura.
- Patients with paroxysmal nocturnal hemoglobinuria develop episodic hemolysis, marrow aplasia, and thrombosis; therapy with eculizumab, a monoclonal antibody to C5 that inhibits terminal complement activation, decreases complications and improves quality of life.

Other Causes of Hemolysis

March Hemoglobinuria

March hemoglobinuria develops after physical erythrocyte destruction in the soles of the feet in response to long distance running or marching. March hemoglobinuria has also been described in hand drummers and karate enthusiasts.

Hemolysis Associated with Chemical and Physical Agents

Arsenic or arsine gas exposure, elevated serum copper levels, the bite of the brown recluse spider, and severe burns are rare causes of hemolysis.

Hemolysis from Infections

Malaria, babesiosis, clostridia, and *Bartonella* (Oroya fever) are all associated with hemolysis.

Iron Overload Syndromes

Primary/Hereditary Hemochromatosis

Hereditary hemochromatosis (HH) is the most common inherited genetic disorder in whites, with a prevalence of 1 in 250 persons of northern European descent. Approximately 85% to 90% of patients with HH are homozygous for the C282Y mutation in the *HFE* gene; the remaining patients are typically compound heterozygotes for C282Y and the H63D or S65C mutations. *HFE* mutations result in hepcidin deficiency and increased ferroportin expression on duodenal enterocytes, which results in increased iron absorption and eventual organ injury because no physiologic mechanism allows for excreting excess iron. Cirrhosis and cardiomyopathy are major causes of morbidity, small joint arthritis is common, and diabetes mellitus and other endocrinopathies may be seen.

Patients may be diagnosed late in the disease course through evaluation of decompensated liver disease or symptomatic cardiomyopathy, although liver and heart damage are largely irreversible at this late stage even if iron stores are actively reduced. The diagnosis may also be made earlier in the disease course through evaluation of abnormal aminotransferase levels that precede cirrhosis, characteristic arthropathy involving the second and third metacarpophalangeal joints (**Figure 16**), or endocrinopathy such as androgen insufficiency arising from pituitary or endocrine organ injury. Skin hyperpigmentation, accounting for the "bronze diabetes" terminology for HH, is likely caused by pituitary infiltration and excess melatonin secretion. The diagnosis is also made through screening family members of patients with known hemochromatosis.

The diagnosis is suspected by finding an elevated transferrin saturation greater than 45% and an elevated serum ferritin level; diagnosis is confirmed through genetic testing.

FIGURE 16. A plain radiograph of the hands shows osteophyte formation involving the distal interphalangeal and proximal interphalangeal joints and the metacarpophalangeal (MCP) joints. These "hook" osteophytes, particularly of the second and third MCP joints, are a characteristic finding in patients with hereditary hemochromatosis.

MRI is used to noninvasively assess the extent of cardiac and liver iron overload and generally obviates the need to perform organ biopsy to quantitate iron deposits. Liver biopsy may still be useful in patients who have hepatitis C infection or alcohol dependence as alternate options for causing liver disease.

First degree relatives of patients with HH should be counseled about their risks and advised to undergo medical evaluation and screening. Asymptomatic family members of patients with hemochromatosis and a serum ferritin level less than 500 ng/mL (500 µg/L) can be safely observed. Symptomatic patients or those with signs of end organ injury should undergo therapeutic phlebotomy, the goal of which is to reduce total body iron stores; each unit (450 500 mL) of blood removed contains 200 to 250 mg iron, which unloads parenchymal deposition over time. Phlebotomy should be performed once or twice per week depending on the patient's hematocrit level. Iron stores in patients with HH may exceed 30 g, requiring phlebotomy over 2 to 3 years. The serum ferritin level should be evaluated every 3 months, with a target goal of 50 to 100 ng/mL (50 100 µg/L). When this goal is reached, maintenance phlebotomy should be instituted; schedules vary from 2 to 6 units of blood per year. Patients with HH without hepatic fibrosis or cardiomyopathy can expect a normal life expectancy with phlebotomy and judicious alcohol intake. Although advanced liver disease is not reversible with phlebotomy, patients benefit from screening for hepatocellular carcinoma and other secondary prevention as indicated for patients with cirrhosis. Similarly, phlebotomy is much less effective in patients who already manifest cardiac toxicity from iron overload.

KEY POINTS

- Hereditary hemochromatosis should be suspected and laboratory testing performed in patients who present with nonspecific aminotransferase elevation, characteristic arthropathy involving the second and third metacarpophalangeal joints, endocrinopathy such as androgen deficiency, or darkening pigmentation of the skin; first-degree relatives of patients with hemochromatosis should be screened.
- Initial laboratory tests to evaluate for hereditary hemochromatosis are transferrin saturation and serum ferritin level; elevated levels are followed by genetic testing to confirm the diagnosis.
- Patients with hereditary hemochromatosis who do not have symptomatic heart disease or liver fibrosis who undergo therapeutic phlebotomy have a normal life expectancy.

Secondary Iron Overload

Secondary iron overload occurs in patients who require chronic transfusion (most commonly in hereditary hemoglobinopathies such as thalassemia major); in subsets of patients with sickle cell anemia; or in acquired bone marrow failure conditions, such as myelodysplastic syndrome. End-organ involvement in secondary iron overload overlaps with that seen in HH, particularly regarding hepatic deposition, although endocrinopathy and cardiac effects are more common and arthropathy is less common. Therapeutic phlebotomy should not be performed, because these patients are anemic. The iron chelator deferoxamine has traditionally been the mainstay of therapy, but it requires continuous infusion, either intravenously or subcutaneously. Several oral iron chelators, including deferasirox and deferiprone, are available and may be more convenient. Monitoring is accomplished by serial serum ferritin measurements.

Porphyria cutanea tarda is a less common cause of secondary iron overload unrelated to chronic transfusion, but it is typically associated with acquired abnormalities in porphyrin metabolism and underlying liver disease, especially hepatitis C infection. Porphyria cutanea tarda is characterized by cutaneous blisters, often on the hands, and hypertrichosis; it responds well to phlebotomy.

KEY POINT

- Therapeutic phlebotomy is contraindicated in most patients with secondary iron overload because they are already anemic and often still transfusion dependent; rather, iron chelation with an oral drug, such as deferasirox or deferiprone, may be more convenient for patients compared with the continuous infusions required to administer deferoxamine.

Platelet Disorders

Normal Platelet Physiology

Platelets are cell fragments released from megakaryocytes that circulate in an inactive state in the blood for 8 to 10 days. One third of the platelets are sequestered in the spleen and released back into the circulation in response to epinephrine.

Platelet activation, the first step in hemostasis, occurs in a three-stage process. Platelets adhere to exposed subendothelial surfaces of injured vessel walls (mediated by von Willebrand factor [vWF]). Platelets then change shape and release adenosine diphosphate and triphosphate, serotonin, fibrinogen, vWF, and factor V. Clopidogrel irreversibly binds to the P2Y12 adenosine diphosphate receptor, blocking platelet activation and aggregation. During shape change, glycoprotein IIb/IIIa receptors are exposed, bind fibrinogen, and initiate reversible platelet-platelet aggregation. The intravenous antiplatelet agents abciximab, eptifibatide, and tirofiban inhibit fibrinogen binding during this stage. In the final stage, arachidonic acid is released and converted to thromboxane A_2, promoting irreversible platelet aggregation and resulting in a platelet plug (aspirin acts by irreversibly acetylating thromboxane A_2). Finally, platelets provide the phospholipid membrane necessary to complete the coagulation cascade (see Bleeding Disorders).

Approach to the Patient with Thrombocytopenia

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Thrombocytopenia must be evaluated according to the platelet count and the clinical setting. Platelet counts greater than 100,000/µL (100×10^9/L) do not increase bleeding risk. Counts between 50,000 and 100,000/µL (50-100×10^9/L) do not require treatment and are adequate for surgical procedures, although 100,000/µL (100×10^9/L) is desirable for neurosurgery. Platelet counts between 30,000 and 50,000/µL (30-50×10^9/L) must be corrected before surgical intervention, and counts less than 10,000/µL (10×10^9/L) are associated with risk of spontaneous bleeding.

The first step of the evaluation is to review the peripheral blood smear and confirm the count. Pseudothrombocytopenia occurs when a patient has antibodies to ethylenediaminetetraacetic acid (EDTA), causing platelets to clump together in vitro. An accurate count can be obtained from blood drawn in citrate or heparin instead of EDTA. Inaccurate platelet counts may also occur if the platelets are exceptionally large (complete blood count machine may count them as erythrocytes) or if erythrocyte fragments (schistocytes) are counted by the machine as if they were platelets (leading to a higher than actual platelet count).

When thrombocytopenia is confirmed, symptoms are assessed, with attention paid to mucocutaneous bleeding (epistaxis, gum bleeding, menorrhagia, hematuria, melena, or hematochezia) and easy bruising. A thorough review of

H CONT medications and supplements is required, especially in relation to the timing of onset of the thrombocytopenia. Drug and alcohol exposure must be documented and quantified, and dietary restrictions noted (for example, vegans may be deficient in vitamin B_{12}). The patient's medical history may show related disorders, such as HIV infection, hepatitis C infection, or thyroid diseases (hyperthyroidism and hypothyroidism may be associated with thrombocytopenia).

The physical examination may reveal blood blisters in the mouth ("wet purpura"), petechiae or ecchymoses on the skin, or splenomegaly. H

Thrombocytopenic Disorders

H Decreased Production

Disorders associated with bone marrow infiltration (myelofibrosis, metastatic tumors, granulomatous diseases) can decrease platelet production, as can nutritional deficiencies (vitamin B_{12} or folate) or abnormalities in stem cell maturation (aplastic anemia and myelodysplasia). Other cytopenias often accompany the low platelet count.

Increased Destruction

Non–Immune-Mediated Thrombocytopenia

Splenomegaly is a common medical problem that causes thrombocytopenia without platelet destruction through increased sequestration. The thrombocytopenia is usually associated with anemia and leukopenia.

Unlike sequestration, non-immune platelet destruction is caused by abnormal platelet aggregation occurring in the setting of disseminated intravascular coagulation or a microangiopathic hemolytic anemia (MAHA) such as thrombotic thrombocytopenic purpura (TTP) or hemolytic uremic syndrome (HUS) (see following sections).

Thrombotic Thrombocytopenic Purpura

Patients with TTP present with MAHA and thrombocytopenia. Acquired TTP is caused by a deficiency in the metalloprotease ADAMTS13, which is responsible for cleaving high-molecular-weight vWF multimers. These multimers accumulate, generating platelet-rich thrombi in small vessels. These thrombi consume platelets and shear erythrocytes, fragmenting them into schistocytes (see Erythrocyte Disorders for figure) and may cause end-organ injury. Autoantibodies to ADAMTS13 are responsible for the deficiency in most patients, but hereditary TTP has been reported in some. Drugs such as ticlopidine, quinine, cyclosporine, gemcitabine, and vascular endothelial growth factor inhibitors (such as bevacizumab) can cause TTP. Drug abuse with oxymorphone, 3,4-methylenedioxymethamphetamine ("ecstasy"), and cocaine has also been reported to cause TTP.

Acquired TTP presents with MAHA (evidenced by elevated lactate dehydrogenase and decreased haptoglobin levels, schistocytes on peripheral blood smear, and a negative direct antiglobulin [Coombs] test result) and thrombocytopenia (with normal coagulation study results). An ADAMTS13 level less than 10% supports the diagnosis; an ADAMTS13 level greater than 50% should suggest an alternate diagnosis. The clinical picture is described in **Table 19**. All patients have MAHA and thrombocytopenia, but only 5% of patients present with all the aforementioned signs. The mortality rate associated with TTP is high, so treatment must begin immediately without waiting for ADAMTS13 test results. Treatment is successful in 85% of patients.

Initial treatment involves therapeutic plasma exchange to remove the high-molecular-weight vWF multimers and replace the deficient ADAMTS13 (plasma infusion, although not a definitive treatment, can be started if therapeutic plasma exchange is delayed). Glucocorticoids are added to decrease autoantibody production. Remission is defined by a normalization of the platelet count and is usually seen after 7 to 10 plasma exchange treatments. Rituximab may be added for patients with refractory disease.

Hemolytic Uremic Syndrome

HUS is characterized by thrombocytopenia, MAHA, and acute kidney injury. Classic HUS presents after an acute diarrheal illness caused by enterotoxin-producing *Escherichia coli* O157:H7 (although other strains have also been implicated). Diagnosis is confirmed by stool culture and polymerase chain reaction for Shiga toxin, free Shiga toxin, or O157:H7 antigen testing. Management is supportive (fluids and transfusions as needed). Antibiotics do not alter the course of the disease. Classic HUS has a 4% associated mortality rate, and long-term sequelae include hypertension and mild kidney disease. Atypical HUS presents without diarrhea and may be caused by complement

TABLE 19. Clinical Characteristics of Thrombotic Thrombocytopenic Purpura

Clinical Features	Laboratory Findings/ Pathologic Explanation
Pallor and fever	Microangiopathic hemolytic anemia in 100% of patients (schistocytes); fever likely from microinfarcts
Bruising, petechiae	Thrombocytopenia in 100% of patients; normal prothrombin time, activated partial thromboplastin time, and fibrinogen level
Kidney injury	Mild kidney disease, proteinuria, hematuria from microthrombi
Fluctuating neurologic findings (confusion, headache, transient numbness, coma)	CT scan may demonstrate cerebrovascular accident; transient microthrombi lead to reversible findings
Nausea, vomiting, diarrhea	Bowel ischemia
Chest pain, arrhythmia	Myocardial injury; abnormal findings on electrocardiogram, troponin elevation

dysregulation or may occur secondary to drugs (see drugs listed in the TTP section previously), systemic lupus erythematosus, or other infection (HIV, *Streptococcus pneumoniae*). In severe cases of HUS or when the distinction from TTP is unclear, treatment with plasma exchange should begin immediately, with eculizumab (a monoclonal antibody that binds to complement C5 and prevents generation of the membrane attack unit, C5b-9) added if atypical HUS is suspected. Drug-induced HUS is managed supportively with drug avoidance.

KEY POINTS

- All patients with acquired thrombotic thrombocytopenic purpura have microangiopathic hemolytic anemia and thrombocytopenia; other clinical features may include fever, kidney disease, and fluctuating neurologic abnormalities.
- The mortality rate associated with thrombotic thrombocytopenic purpura is high, so treatment with therapeutic plasma exchange should be started as soon as a diagnosis is suspected, without awaiting laboratory results confirming ADAMTS13 deficiency.
- Hemolytic uremic syndrome is usually caused by enterotoxin-producing *Escherichia coli*, and management is supportive for most patients; antibiotics do not alter the natural course of disease.

Immune-Mediated Thrombocytopenia

Immune Thrombocytopenic Purpura

Peripheral destruction of platelets with decreased production is a feature of immune thrombocytopenic purpura (ITP) and is caused by autoantibodies directed against glycoproteins on the platelet surface membrane. Because only 6% of patients with platelet counts between 100,000 and 150,000/µL ($100-150 \times 10^9$/L) develop persistent thrombocytopenia, many guidelines suggest the diagnosis of ITP be limited to patients with platelet counts less than 100,000/µL (100×10^9/L). ITP can occur alone, can be triggered by medications, or can be associated with other disorders, such as systemic lupus erythematosus, chronic lymphocytic leukemia, HIV, hepatitis C, or *Helicobacter pylori* infection.

ITP is characterized by the duration of the thrombocytopenia. Acute ITP lasts fewer than 3 months, persistent ITP lasts 3 to 12 months, and chronic ITP lasts longer than 12 months. Many patients are asymptomatic until the platelet count decreases to less than 10,000/µL (10×10^9/L). Petechiae and ecchymoses without lymphadenopathy or splenomegaly are notable physical signs. Laboratory findings are limited to a low platelet count. Antiplatelet antibody testing is not sensitive or specific. Testing for HIV and hepatitis C should be performed. Bone marrow evaluation is not necessary unless clinical findings suggest an alternate diagnosis.

Treatment of acute ITP is instituted when patients become symptomatic or if the platelet count decreases to less than 30,000/µL (30×10^9/L). Asymptomatic patients can be managed with careful observation. Initial therapy involves either glucocorticoids or intravenous immune globulin (IVIG). Glucocorticoids are less expensive and easier to administer, but the response to IVIG is faster. Complications from glucocorticoids may include mood disorders, insomnia, fluid retention, hyperglycemia, and hypertension; complications from IVIG may include infusion reactions (headache, chills, anaphylaxis), kidney disease, and thrombosis. Those patients who relapse or have ITP refractory to these treatments require second-line treatments, which include splenectomy or rituximab.

If ITP remains refractory to second-line treatment, thrombopoietin receptor agonists, such as eltrombopag (given orally daily) and romiplostim (given subcutaneously weekly), may be beneficial (with a target platelet count of 50,000/µL [50×10^9/L]), but they must be taken continuously to prevent relapse.

Because patients with chronic ITP may be asymptomatic, treatment decisions must balance the risk of bleeding against treatment-related toxicities.

Heparin-Induced Thrombocytopenia

Type I heparin-induced thrombocytopenia (HIT) refers to a non-immune-mediated decrease in platelets occurring within the first few days of exposure to heparin. No intervention is needed because type I is clinically benign. Type II HIT is an immune-mediated thrombocytopenia occurring 5 to 10 days after exposure. It is caused by antibodies against platelet factor 4 (complexed to heparin). Associated thrombosis, which includes typical deep venous thrombosis, pulmonary embolism, or more unusual acute arterial occlusions, can be life threatening. The risk is highest with unfractionated heparin compared with low-molecular-weight heparin. Most patients with HIT develop platelet counts less than 150,000/µL (150×10^9/L), but severe thrombocytopenia is unusual. In patients with high baseline platelet counts, a decrease of greater than 50%, even if still within the "normal" range, warrants concern. Skin necrosis at the site of heparin injection or progressive thromboembolic events in patients receiving heparin are signs of possible HIT, even if the platelet count remains normal. The 4T scoring system (**Table 20**) is useful for diagnosis. A low probability score reliably excludes the diagnosis; a high score should prompt empiric therapy pending confirmatory tests.

Testing for heparin-associated antibodies is necessary to confirm the diagnosis. Testing for HIT involves a screening test and a confirmatory test. The enzyme-linked immunosorbent assay for platelet factor 4 antibodies is a very sensitive screening test (a negative test result rules out the diagnosis) but is not specific. The diagnosis must be confirmed with a functional test such as the serotonin release assay or the heparin-induced platelet aggregation assay. Classic platelet aggregation assays provide a more detailed evaluation of platelet function, but they are labor intensive and not used in initial screening.

Heparin must be discontinued immediately. An alternate anticoagulant should then be started (unless the patient is actively bleeding). Argatroban is an intravenous alternative,

TABLE 20. The 4T Scoring System for Predicting Heparin-Induced Thrombocytopenia and Thrombosis

4 Ts	2 Points	1 Point	0 Points
Thrombocytopenia	Platelet count decrease >50% and platelet nadir ≥20,000/µL (20×10^9/L)	Platelet count decrease 30%-50% or platelet nadir 10,000-19,000/µL ($10\text{-}19 \times 10^9$/L)	Platelet count decrease <30% or platelet nadir <10,000/µL (10×10^9/L)
Timing of platelet count decrease	Clear onset between days 5-10 or platelet count decrease ≤1 day (with heparin exposure within 30 days)	Consistent with platelet count decrease between days 5-10, but unclear (e.g., missing platelet counts); onset after day 10; or decrease ≤1 day (heparin exposure 30-100 days ago)	Platelet count decrease <4 days without recent exposure
Thrombosis or other sequelae	New thrombosis (confirmed); skin necrosis; acute systemic reaction after intravenous unfractionated heparin bolus	Progressive or recurrent clot; nonnecrotizing (e.g., erythematous) skin lesions; suspected thrombosis (not proved)	None
Other causes for thrombocytopenia	None apparent	Possible	Definite

High probability: 6-8 points.

Intermediate probability: 4-5 points.

Low probability: 0-3 points.

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but recent reports support the use of non-vitamin K antagonist oral anticoagulants (such as rivaroxaban). Warfarin should not be the initial alternate anticoagulant because antithrombotic efficacy requires 3 to 5 days of therapy, during which time declining levels of protein C increase the thrombotic risk. Transitioning to warfarin is safe after thrombocytopenia resolves. Anticoagulation should be continued for 2 to 3 months in patients with HIT without documented thromboembolic events or 3 to 6 months for patients with HIT with associated thrombosis. Patients should be instructed to avoid heparin for life. H

KEY POINTS

- Antiplatelet antibody testing is not sensitive or specific for immune thrombocytopenic purpura and should not be done.
- Treatment for immune thrombocytopenic purpura is instituted with glucocorticoids or intravenous immune globulin when patients become symptomatic or if the platelet count decreases to less than 30,000/µL (30×10^9/L); asymptomatic patients can be managed with careful observation.
- Heparin-induced thrombocytopenia should be suspected in any patient treated with heparin whose platelet count decreases by greater than 50% from baseline or is less than 150,000/µL (150×10^9/L).
- The 4T scoring algorithm should be used to stratify the likelihood of heparin-induced thrombocytopenia, and heparin should be discontinued and an alternate anticoagulant started for patients with intermediate or high risk for disease while awaiting confirmatory results of heparin-associated antibodies.

(Continued)

KEY POINTS *(continued)*

- Most patients taking heparin who develop thrombocytopenia but have a low 4T score need no further evaluation. HVC
- Diagnosis of heparin-induced thrombocytopenia requires a screening test (enzyme-linked immunosorbent assay for platelet factor 4 antibodies) followed by a confirmatory test (serotonin release assay or heparin-induced platelet aggregation assay).

Qualitative Platelet Disorders

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Acquired Platelet Dysfunction

Patients presenting with mucocutaneous bleeding and normal complete blood count, prothrombin time, and activated partial thromboplastin time should be evaluated for platelet dysfunction, which can result from rare hereditary disorders or acquired disorders (**Table 21**). Von Willebrand disease is a much more common inherited cause of coagulation factor deficiency leading to platelet dysfunction (see Bleeding Disorders). After platelet dysfunction is identified, treatment depends on the clinical situation. Acute bleeding can be managed with platelet transfusions, but complete reversal of antiplatelet agent effects may be detrimental if the therapy is lifesaving (for example, patients with recent cardiac stents). Minor dental procedures or menorrhagia can be managed with antifibrinolytic agents (tranexamic acid or ε-aminocaproic acid).

Platelet Function Testing

Platelet function can be assessed by a variety of laboratory tests. The Platelet Function Analyzer-100 is useful as a screening device, replacing the traditional bleeding time. The test is run on a citrated blood sample exposed to collagen and either epinephrine or adenosine diphosphate. It is a sensitive screen

TABLE 21. Causes of Platelet Dysfunction

	Comments	Severity	Treatment
Congenital Platelet Defects			
Glanzmann thrombasthenia	Defect in glycoprotein IIb-IIIa	Severe	Platelets or recombinant factor VIIa, ε-aminocaproic acid
Bernard-Soulier syndrome	Defect in glycoprotein Ib-IX	Severe	Platelets, ε-aminocaproic acid
Wiskott-Aldrich syndrome	Triad of eczema, thrombocytopenia, immunodeficiency	Moderate	Platelets, ε-aminocaproic acid
Gray platelet syndrome	Patients may develop myelofibrosis	Moderate	Platelets, ε-aminocaproic acid
Storage pool disease	Collection of diseases characterized by defect in platelet granules	Moderate to mild	Platelets, ε-aminocaproic acid; some may respond to desmopressin
Acquired Platelet Defects			
Uremia	Does not correlate with severity of kidney disease	Mild	Dialysis, desmopressin, ε-aminocaproic acid
Liver disease	Also associated with hyperfibrinolysis and coagulopathy	Mild to severe	Platelets, ε-aminocaproic acid
Myeloproliferative neoplasms	If platelet count is >1-1.5 million/µL (1000-1500 × 10^9/L), may be associated with acquired von Willebrand disease	Mild to severe	Before surgical procedures, normalize the platelet count Platelet transfusion may be necessary if bleeding occurs
Post-cardiac bypass	Multifactorial, including interaction with bypass machine	Mild	Platelets, if necessary
Antiplatelet drugs			
IIb-IIIa inhibitors	Antiplatelet effects range from irreversible (abciximab) to reversible (eptifibatide and tirofiban)	Severe	Platelets
Aspirin	Irreversible	Mild	Platelets, if necessary
Clopidogrel	Irreversible	Mild	Platelets, if necessary
NSAIDs	Temporary	Mild	None usually needed
Other drugs and herbs (β-lactams, vitamin E, ginkgo, turmeric, garlic, Chinese tree fungus)		Mild	None usually needed

H CONT.

for von Willebrand disease and will detect abnormalities caused by antiplatelet medications. The Verifynow® test assesses for continued antiplatelet activity of aspirin or clopidogrel, but guidelines do not recommend using it to guide therapy. Thromboelastography and rotational thromboelastometry are bedside devices that analyze platelet function, coagulation, and clot stability and may be useful as screening tests in patients with unexplained bleeding. H

KEY POINTS

- Patients presenting with mucocutaneous bleeding and normal complete blood count, prothrombin time, and activated partial thromboplastin time should be evaluated for von Willebrand disease or acquired platelet dysfunction.
- The Platelet Function Analyzer-100 is a useful screening test for assessing qualitative platelet disorders.

Bleeding Disorders

Normal Hemostasis

Hemostasis is the process by which bleeding is controlled through a complex network of prothrombotic and fibrinolytic activity. Clot generation occurs on phospholipid membranes through the activation of procoagulant factors (**Figure 17**). Traditionally, the process was described as a waterfall coagulation cascade (**Figure 18**), which is still used to understand screening tests and the factors that influence them.

Primary hemostasis describes the interaction between platelets, von Willebrand factor (vWF), and the vessel wall (see Platelet Disorders for platelet activation and vWF activity). Secondary hemostasis refers to the activation of coagulation factors that eventually lead to fibrin clot formation. Clots are then degraded through fibrinolysis.

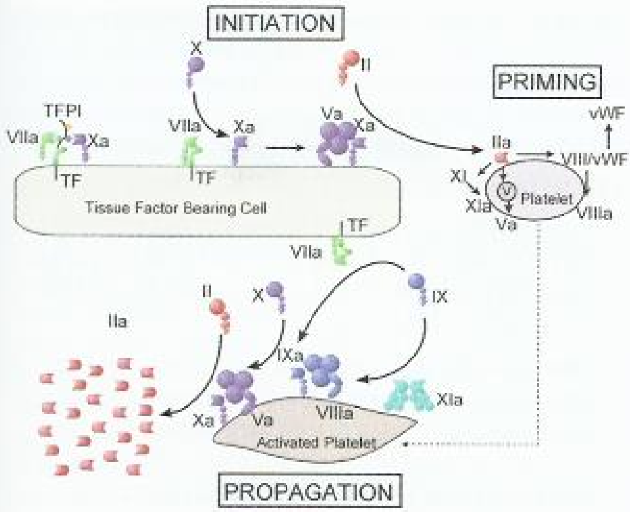

FIGURE 17. The cell-based model of hemostasis is useful for understanding coagulation as it occurs in vivo. The initiation of coagulation takes place on the surface of a tissue factor-bearing cell, such as a macrophage, a tumor cell, or an activated endothelial cell. Tissue factor (TF) and a small amount of factor VIIa generate factor Xa, which joins with factor Va to form a small amount of thrombin (factor II). In the priming step, this small amount of thrombin proceeds to activate platelets and factor VIII, which joins with factor IX to generate factor Xa. On the platelet surface, the prothrombinase complex can generate a large thrombin burst in the propagation step, allowing for cleavage of fibrinogen into fibrin.

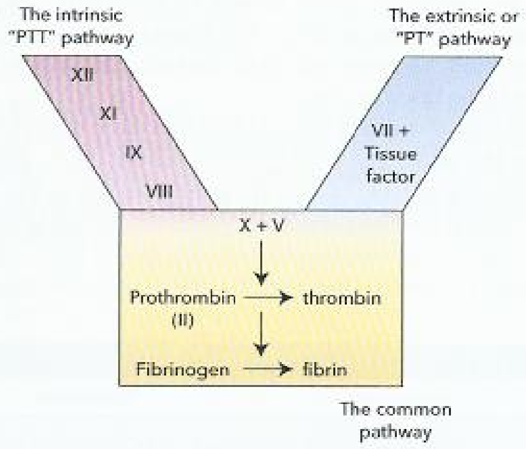

FIGURE 18. The "waterfall" model of hemostasis is useful for teasing out coagulation disorders affecting the prothrombin time (PT) and the activated partial thromboplastin time (aPTT). In this model, factors common to the PT and the aPTT are X, V, II, and fibrinogen. Factor VII is unique to the PT, and factors XII, XI, VIII, and IX are unique to the aPTT.

H Evaluation of Patients with Suspected Bleeding Disorders

Patients with bleeding disorders present with symptoms of easy bruising, bleeding gums, menorrhagia, gastrointestinal bleeding, or postoperative bleeding. The clinical history provides guidance regarding how to proceed in the evaluation, with attention paid to history of tooth extraction, menstrual bleeding, minor and major surgical procedures, and family history of bleeding. Medication use and exposure to alcohol or recreational drugs must be documented. The physical examination focuses on finding evidence of petechiae, ecchymoses, deep tissue hematomas, or joint effusions.

Laboratory tests used to measure hemostasis are the prothrombin time (PT) and the activated partial thromboplastin time (aPTT). The PT, expressed as the INR, is more sensitive to the effects of the vitamin K-dependent factors (II, VII, and X), whereas the aPTT is a more sensitive measurement of factors VIII, IX, XI, and XII. The thrombin time measures fibrinogen convergence to fibrin clot, and the Platelet Function Analyzer-100 (PFA-100®) measures platelet function. Specialized tests include mixing studies to evaluate inhibitors, specific factor level assays, and tests for fibrin degradation products and D-dimers.

Differential diagnoses for patients experiencing bleeding and who have abnormal findings on specific clotting assays are outlined in Table 22. H

KEY POINT

- Basic laboratory tests used to evaluate hemostasis are the prothrombin time, expressed as INR; the activated partial thromboplastin time; the thrombin time, which measures fibrinogen convergence to fibrin; and platelet function as measured by the Platelet Function Analyzer-100.

TABLE 22. Differential Diagnoses for Patients Experiencing Bleeding

Clotting Assay Abnormality	Differential Diagnoses
Prolonged PT, normal aPTT	Factor VII deficiency
	DIC
	Liver disease
	Vitamin K deficiency
	Warfarin ingestion
Normal PT, prolonged aPTT	Deficiency of factors VIII, IX, XI, or XII
	von Willebrand disease (if severe and factor VIII level is quite low)
	Heparin exposure
Prolonged PT and aPTT	Deficiency of factors V, X, II, or fibrinogen
	Severe liver disease, DIC, vitamin K deficiency, warfarin toxicity
	Heparin overdose
Normal PT and aPTT	Platelet dysfunction (acquired and congenital)
	von Willebrand disease (if mild and factor VIII level is not too low)
	Scurvy
	Ehlers-Danlos syndrome
	Hereditary hemorrhagic telangiectasia
	Deficiency of factor XIII

aPTT = activated partial thromboplastin time; DIC = disseminated intravascular coagulation; PT = prothrombin time.

Congenital Bleeding Disorders

Hemophilia A and B and Other Factor Deficiencies

Hemophilia A and B (deficiency of factors VIII and IX, respectively) are X-linked hereditary bleeding disorders primarily found in male patients. Daughters of men with hemophilia are obligate carriers. Hemophilia A is more common than hemophilia B, but both are rare. They present in a similar fashion, with spontaneous hemarthrosis or bleeding into deep muscles or with excessive or delayed bleeding after trauma. Small cuts do not usually bleed excessively, but patients experience mucocutaneous bleeding. The hemophilias are classified as mild, moderate, or severe according to the circulating factor levels (mild, 5%-40%; moderate, 1%-5%; severe, <1%). Patients with mild disease may not present until adulthood.

Diagnosis requires a prolonged aPTT (that corrects in mixing studies) and a normal PT and complete blood count. Assay of individual factors (VIII and IX) confirms the diagnosis. In hemophilia A, vWF must be measured to rule out type 3 von Willebrand disease (see next section).

Arthropathy of the knees, ankles, and elbows occurs as a late sequela in 50% of patients as a result of recurrent hemarthroses. Inhibitors to infused factors (see Management) develop in up to 25% of patients with hemophilia A, and 3% to 5% of patients with hemophilia B.

Managing bleeding in hemophilia A and B requires using virally inactivated factor concentrates (eliminating the historical risk of hepatitis and HIV). Patients with mild hemophilia A can be treated with desmopressin, which stimulates the release of preformed factor VIII from endothelial cells. Antifibrinolytic agents (such as ε-aminocaproic acid and tranexamic acid) are useful in controlling bleeding from dental procedures.

Factor XI deficiency (also known as hemophilia C) is a rare autosomal hereditary disorder seen predominantly in persons of Ashkenazi Jewish heritage. Bleeding symptoms are variable and cannot be predicted by the level of factor XI alone. Asymptomatic patients do not require intervention (for example, before surgery); symptomatic patients require plasma infusions for bleeding episodes and surgical procedures.

KEY POINTS

- Patients with hemophilia A (factor VIII deficiency) or B (factor IX deficiency) have a prolonged activated partial thromboplastin time with a normal prothrombin time and complete blood count.
- Administration of infused factor concentrates can help prevent and control bleeding in patients with hemophilia A or B; some patients with mild hemophilia A may also be treated with desmopressin to stimulate the release of preformed factor VIII from stores in endothelial cells.
- Patients with factor XI deficiency who are asymptomatic do not require prophylactic intervention for surgery. HVC

Von Willebrand Disease

Von Willebrand disease (vWD), the most common hereditary bleeding disorder, is caused by either deficiency or ineffectiveness of vWF. vWF promotes platelet adhesion and functions as a protective carrier protein for factor VIII, so a mild secondary decrease in factor VIII levels occurs. vWF deficiency leads to mucocutaneous bleeding symptoms that mimic thrombocytopenia.

Hereditary vWD is subclassified into three broad groups (**Table 23**), with type 1 being the most common. Patients become symptomatic when vWF levels decrease to less than 30%. Clinical features influence vWF levels, including type O blood (decreased levels) and pregnancy or oral contraceptive use (increased levels). Although the aPTT may be prolonged or

TABLE 23. Types of von Willebrand Disease and Associated Features

Type of vWD	Basic Defect	Diagnostic Test	Symptoms	Treatment
Type 1[a]	Low vWF antigen (<30%) but normal function	RCoF:vWAg 0.6-0.7 PFA-100 prolonged	Mucocutaneous bleeding	Desmopressin
Type 2	Abnormal vWF function	RCoF:vWAg 0.6-0.7	Mucocutaneous bleeding	
Type 2A	From selective deficiency of high-molecular-weight fragments of vWF			Desmopressin vWF concentrates
Type 2B	From increased binding of high-molecular-weight fragments of vWF to platelet receptors			vWF concentrates (desmopressin contraindicated)
Type 3	Severe deficiency	vWAg: unmeasurable RCoF activity: very low Factor VIII activity: 1%-10% of normal	Joint and deep muscle bleeding	vWF concentrates

PFA-100 = Platelet Function Analyzer-100; RCoF = ristocetin cofactor; vWAg = von Willebrand antigen; vWF = von Willebrand factor.

[a]80% of cases.

normal, a prolonged closure time on the PFA-100® would suggest vWD, making this a useful initial evaluation tool. The diagnosis is confirmed by finding a reduction in von Willebrand antigen (quantitative analysis) and reduced vWF ristocetin cofactor activity (a measurement of the functional affect) (see Table 23).

H Management of vWD depends on the severity of bleeding, the type of vWD, and the clinical setting. Desmopressin is effective in type 1 vWD, releasing preformed vWF and factor VIII from endothelial cells. It can be given intravenously before a surgical procedure or intranasally as needed in the outpatient setting. Patients with rare type 2B vWD should not receive desmopressin because it induces platelet aggregation, which can cause secondary thrombocytopenia in these patients. Desmopressin is ineffective in patients with type 3 vWD. vWF concentrates are the preferred treatment for these two subgroups; cryoprecipitate is no longer used because virally inactivated vWF concentrates are safer and more effective. Antifibrinolytic therapy (ε-aminocaproic acid and tranexamic acid) is useful after surgical procedures to protect against delayed bleeding and can be used to treat menorrhagia. H

KEY POINTS

- Von Willebrand factor deficiency in von Willebrand disease leads to mucocutaneous bleeding symptoms that mimic thrombocytopenia, including bleeding gums, epistaxis, menorrhagia, and easy bruising.
- Desmopressin, which stimulates release of preformed von Willebrand factor and factor VIII, is used to treat minor bleeding in most patients with von Willebrand disease and is given prophylactically before surgery or procedures.
- Von Willebrand factor concentrates are used for major bleeding and to treat patients with rare subtypes 2B and 3.

Acquired Bleeding Disorders

H Coagulopathy of Liver Disease

Bleeding in patients with liver disease results from one of many interrelated hemostatic aberrations. The liver is the site of production for procoagulant and fibrinolytic factors. Liver disease is associated with bleeding and thrombosis, but only bleeding manifestations will be discussed here.

Liver disease can result in factor deficiency, hyperfibrinolysis, and mild to moderate thrombocytopenia, leading to PT prolongation, INR elevation, and aPTT prolongation. Distinguishing between liver disease and disseminated intravascular coagulation may be challenging. Measuring factor VIII levels (not affected by liver disease) and factor V levels (not consumed during intravascular coagulation) provides a theoretical means of separating the two disorders. Patients often have components of both liver disease and disseminated intravascular coagulation, and management rarely differs based on distinguishing the two disorders.

Asymptomatic patients do not require treatment, but vitamin K supplementation should be considered if the INR is elevated. Patients experiencing bleeding may require blood product replacement, with cryoprecipitate to increase fibrinogen levels to greater than 100 mg/dL (1 g/L) and platelet transfusions to maintain a platelet count greater than 75,000/µL (75×10^9/L). Fresh frozen plasma may be given for INRs greater than 2, but the short half-life of plasma components and risk of volume overload limit the effectiveness of plasma administration. Prothrombin complex concentrates are costly and associated with thrombotic complications; they should not be routinely used in managing the coagulopathy of liver disease. Accelerated fibrinolysis also contributes to bleeding, but no laboratory tests reliably measure this condition. Viscoelastic testing may be useful, although the predictive value in documenting accelerated fibrinolysis is debated and the test is not widely available. Antifibrinolytic agents are useful in treating hyperfibrinolysis and should be considered when persistent oozing from mucous membranes or delayed bleeding from procedure sites occurs in the absence of or despite correction of overt coagulopathy. H

KEY POINTS

- Although measuring levels of factor VIII (normal in liver disease) and factor V (not consumed during intravascular coagulation) could theoretically distinguish coagulopathy of liver disease from disseminated intravascular coagulation, patients may have components of both disorders, and the management is usually analogous regardless of this distinction.
- Active bleeding in patients with coagulopathy of liver disease should be managed with cryoprecipitate to maintain fibrinogen levels greater than 100 mg/dL (1 g/L) and platelet transfusions to achieve a platelet count greater than 75,000/µL (75×10^9/L).
- Fresh frozen plasma can be administered to patients with coagulopathy of liver disease, active bleeding, and an INR greater than 2, but the short half-life of plasma coagulation factors and risk of volume overload limit its effectiveness.
- Because of their cost and association with prothrombotic complications, prothrombin complex concentrates should not be routinely used to manage the coagulopathy of liver disease. HVC

Vitamin K Deficiency H

Although vitamin K is found in green vegetables, a significant proportion of the daily requirement comes from gut microflora (which may be destroyed by antibiotics); absorption requires biliary and pancreatic function because vitamin K is fat soluble. It acts as a cofactor for carboxylation and activation of certain coagulation factors (see Table 22), as well as for the

H CONT.

endogenous anticoagulants, protein C, and protein S. Patients who cannot take anything by mouth, who have poor oral intake while taking long courses of antibiotics, and who have fat malabsorption are especially at risk for vitamin K deficiency. Vitamin K supplements safely and effectively correct the deficiency, so this diagnosis should always be considered when evaluating a patient with a prolonged PT. The response to supplementation occurs within hours because vitamin K acts by converting precursor proteins synthesized in the liver into active factors. Vitamin K can be administered orally for patients who are able to eat. Critically ill patients or those unable to take anything by mouth should receive vitamin K by slow intravenous infusion. Subcutaneous vitamin K is not reliably absorbed and is unlikely to be safer than intravenous vitamin K.

Acquired von Willebrand Disease

Acquired vWD occurs in conditions of high circulatory shear stress (valvular heart disease, hypertrophic cardiomyopathy, circulatory assist devices, and extracorporeal membrane oxygenation systems) caused by excessive degradation of high-molecular-weight von Willebrand multimers by the proteolytic enzyme ADAMTS13. Affected patients develop bleeding conditions similar to those in hereditary vWD. The prevalence of this disorder is likely to increase as more patients with severe cardiomyopathy are managed with left ventricular assist devices. These patients are routinely managed with warfarin and antiplatelet agents and have a significant incidence of gastrointestinal or other bleeding problems. Desmopressin and vWF concentrates have been used in management.

Acquired Hemophilia

Acquired hemophilia results from an autoantibody directed against factor VIII. Patients present with bleeding symptoms that mimic hereditary hemophilia A. Approximately half of all cases are associated with pregnancy and the postpartum state, malignancy, and other autoimmune disorders, as well as with medications.

Laboratory evaluation shows a normal platelet count and PT with a prolonged aPTT. Mixing studies do not correct the aPTT. Factor analysis shows a low factor VIII level; an inhibitor can be quantified with the Bethesda assay. One Bethesda unit is defined as the reciprocal of the dilution of patient plasma that results in 50% inactivation.

Factor VIII concentrates do not correct the problem. Management of acute bleeding requires activated prothrombin complex concentrates or activated factor VII to overcome the inhibitor. Immunosuppression, using corticosteroids and cyclophosphamide, is required to decrease the formation of inhibitors.

Acquired hemophilia A is just one example of an autoimmune factor deficiency. Acquired inhibitors can occur against any factor and should be considered whenever a patient presents with a new bleeding diathesis and an unexpectedly low factor level. H

KEY POINTS

- An acquired hemophilia from an autoantibody directed against a clotting factor, usually factor VIII, should be expected when a patient presents with a new bleeding diathesis, prolongation of the activated partial thromboplastin or prothrombin time, and a low level of an isolated clotting factor.
- Factor VIII concentrates are ineffective in patients with acquired hemophilia because of the presence of an inhibitor; instead, patients should receive activated prothrombin complex concentrates or activated factor VII for management of acute bleeding.

Disseminated Intravascular Coagulation

H

Disseminated intravascular coagulation results from the simultaneous stimulation of coagulation and fibrinolysis. It is associated with severe sepsis, usually with septic shock; with disseminated malignancy, most classically with mucin-secreting pancreatic adenocarcinoma; and in pregnancy with various severe complications, including sepsis, placental abruption, and eclampsia. Patients with life-threatening illnesses characterized by systemic immune response syndrome with hypotension and multiorgan dysfunction are also at risk. The initial pathogenesis involves widespread endothelial injury and circulating procoagulants that lead to disseminated microvascular thrombi, with consumption of platelets and clotting factors, and erythrocyte shearing injury leading to hemolysis. Fibrinolysis is accelerated, resulting in dissolution of the microvascular thrombus, usually before thrombotic complications are noted. These factors leave the patient vulnerable to bleeding from thrombocytopenia, clotting factor depletion, and fibrinolysis. Classic laboratory findings include thrombocytopenia, prolonged aPTT and PT, elevated INR, hypofibrinogenemia, and elevated D-dimer levels, although laboratory features are unpredictable from patient to patient. Management is directed primarily at the inciting cause of disseminated intravascular coagulation and supported with platelet transfusions, cryoprecipitate, and fresh frozen plasma as needed. H

KEY POINT

- Classic laboratory findings of disseminated intravascular coagulation include thrombocytopenia, prolonged activated partial thromboplastin and prothrombin times, elevated INR, hypofibrinogenemia, and elevated D-dimer levels.

Transfusion Medicine

H

Clinical trials supporting the benefits of a more cautious transfusion strategy have dramatically changed transfusion practice. For elective transfusions, ABO and Rh matching based on a properly labeled blood specimen remains the cornerstone of

H CONT.

safe transfusion. Approximately 5% to 10% of hospitalized patients have evidence of erythrocyte alloimmunization from previous transfusions, pregnancy, or organ transplantation. These antibodies to non-ABO blood group antigens pose a risk for delayed (as opposed to acute) hemolytic transfusion reaction. Other noninfectious risks of transfusion, such as transfusion-associated circulatory overload, are now better recognized. Although the traditionally feared infectious risks of transfusion, hepatitis C virus and HIV, are now quite rare, transfusions are linked to an evolving spectrum of emerging infectious diseases, such as Zika virus.

Blood Donor Screening

Blood donor screening comprises questions to establish the general health of the donor and exclude high-risk behaviors or potential exposures that increase the risk of transfusion-transmitted infection, followed by selected laboratory testing. The hemoglobin level cutoff is 12.5 g/dL (125 g/L) for women, which excludes a small proportion of otherwise healthy women from donating. Most platelets transfused in the United States are collected from donors by apheresis, which increases platelet yield but is a more time-consuming procedure than whole blood donation. Laboratory testing of whole blood and platelet donations includes screening for hepatitis B and C viruses, HIV, human T-cell lymphotropic virus I/II, and West Nile virus; serologic testing for syphilis; and, in select regions of the country, testing for antibodies to *Trypanosoma cruzi* (agent for Chagas disease), *Babesia*, and most recently, Zika virus. Platelet components are also screened for bacterial contamination before being released for transfusion. H

KEY POINT

- Donated whole blood and platelets are screened for hepatitis B and C viruses, HIV, human T-cell lymphotropic virus I/II, and West Nile virus; undergo serologic testing for syphilis; and, in select regions of the country, are tested for antibodies to *Trypanosoma cruzi*, *Babesia*, and most recently, Zika virus.

H

Blood Group Antigens, Pretransfusion Compatibility Testing, and the Direct Antiglobulin Test

A "type and screen" comprises ABO/Rh blood group determination and a screening test for unexpected (non-ABO) antibodies. A "type and cross" uses patient plasma or serum to crossmatch against a representative sample from a donor erythrocyte unit for transfusion. For procedures in which blood transfusion is not invariably needed, a type and screen showing no unexpected antibodies eliminates the need for specific crossmatching; blood can be quickly crossmatched when and if the decision to transfuse is made. Rh-positive persons can receive Rh-positive or Rh-negative blood. Rh-negative persons should receive only Rh-negative blood, except in circumstances of massive transfusion (such as gastrointestinal bleeding or traumatic hemorrhage), when Rh-positive blood can be given to preserve the inventory of scarcer Rh-negative units. Rh-positive blood should never be given to persons already sensitized to Rh antigens or to Rh-negative women of childbearing potential because exposure increases their risk for subsequent pregnancies affected by hemolytic disease of the fetus and newborn. Plasma requires ABO but not Rh matching; platelets, with some exceptions, are not ABO or Rh matched.

A direct antiglobulin (Coombs) test is performed to look for IgG or complement coating a patient's erythrocytes and is part of the investigation for suspected hemolytic transfusion reactions (acute or delayed), autoimmune hemolytic anemia, and hemolytic disease of the newborn. H

KEY POINTS

- Women of childbearing age or younger and patients previously sensitized to Rh antigens should never receive Rh-positive blood.
- For procedures in which blood transfusion is not invariably needed, a type and screen showing no unexpected antibodies eliminates the need for specific crossmatching of individual units.

Blood Components

H

Packed Red Blood Cells

Packed red blood cells (PRBCs), which contain a small amount of residual plasma, are suspended in anticoagulant-preservative solution at a hematocrit level of 55% to 65%. Transfusion of one unit of PRBCs to an average-sized nonbleeding adult raises the hematocrit level by 3% and the hemoglobin level by 1 g/dL (10 g/L). Erythrocyte transfusion to patients with anemia increases oxygen-carrying capacity; the threshold for transfusion varies according to the chronicity of the anemia and the patient's comorbidities.

Plasma

Plasma contains coagulation factors, albumin, immunoglobulins, and other plasma proteins. Plasma transfusion is indicated to restore coagulation factors for which specific factor concentrates are not available or in the setting of multiple acquired deficiencies, as in disseminated intravascular coagulation. If frozen within 6 hours of collection, the product is called "fresh frozen plasma" and has a shelf life of 1 year at −20 °C (−4 °F), or 24 hours after it is thawed at 37 °C (98.6 °F). Thawed fresh frozen plasma can be relabeled as thawed plasma, extending its shelf life to 5 days of storage. Although thawed plasma has lower levels of labile factors, such as factors V and VIII, the difference is not clinically significant in most transfusion situations, particularly because factor VIII is an acute phase reactant.

H CONT.

Cryoprecipitate

Cryoprecipitate is the small fraction of plasma that precipitates when fresh frozen plasma is thawed at 1 to 4 °C (33.8-39.2 °F). It contains mostly fibrinogen and factor VIII and is most often used in conditions associated with hypofibrinogenemia, such as disseminated intravascular coagulation. It is also sometimes used empirically in uremic bleeding, but the mechanism of action is poorly understood. For adult patients who require fibrinogen replacement, multiple (8-10) units of cryoprecipitate (from 8-10 donors) must be pooled together.

Platelets

A unit of platelets is suspended in plasma and has a short shelf life of 5 days at 20 to 24 °C (68-75.2 °F). Platelets can be made from a whole blood donation (a platelet concentrate) or collected by apheresis. A bag of apheresis platelets provides a platelet dose equivalent to 4 to 6 units of platelet concentrate and raises the platelet count of an average-sized adult by 20,000 to 25,000/µL (20-25 × 10^9/L) (for example, from a platelet count of 10,000/µL to 30,000/µL). Platelets are not generally indicated in patients with thrombocytopenia in the absence of trauma, surgery, or bleeding until the platelet count decreases to less than 10,000 to 20,000/µL (10-20 × 10^9/L); the lower platelet count is more applicable to patients with chronic thrombocytopenia who are otherwise stable. The transfusion threshold for patients with bleeding, trauma, or both, is approximately 50,000/µL (50 × 10^9/L).

PRBCs and platelet components can be modified through processes such as leukoreduction, irradiation, and washing, which are indicated in special transfusion circumstances (**Table 24**). H

KEY POINTS

- Transfusion of one unit of packed red blood cells to an average-sized nonbleeding adult raises the hematocrit level by 3% and the hemoglobin level by 1 g/dL (10 g/L); transfusion to patients with anemia increases oxygen-carrying capacity.
- Cryoprecipitate contains a concentrated amount of fibrinogen and is used to treat hypofibrinogenemia seen in disseminated intravascular coagulation.
- Platelets are not generally indicated in otherwise stable patients with chronic thrombocytopenia until the platelet count decreases to less than 10,000 to 20,000/µL (10-20 × 10^9/L).

Plasma Derivatives

H

Plasma pooled together from thousands of donors is fractionated into derivatives such as albumin (used for oncotic pressure in hypotensive patients or after large-volume paracentesis cirrhotic patients), intravenous immune globulin (for patients who have humoral immunodeficiencies), Rh immune globulins (for Rh-negative pregnant women to prevent sensitization from an Rh-positive fetus), or coagulation factor concentrates (such as factor VIII concentrate for von Willebrand disease) (**Table 25**). Plasma derivatives are processed to reduce the risk of infectious disease transmission. Recombinant factor concentrates (not containing any donor plasma) have become the standard of care for younger patients with hemophilia A and B (factor VIII and IX deficiency, respectively).

TABLE 24. Cellular Transfusion Product Modifications

Modification	Notes
Leukoreduction[a]: decreases number of leukocytes present in transfused erythrocytes or platelets	Reduces class I HLA alloantibody production and subsequent platelet transfusion refractoriness. Decreases febrile nonhemolytic transfusion reactions. Decreases transmission of CMV. Leukoreduction cannot be relied on to prevent transfusion-associated GVHD.
Irradiation: prevents replication of lymphocytes and circulating stem cells present in erythrocyte or platelet products	Prevents transfusion-associated GVHD, which is mediated by donor lymphocytes. Indicated in patients with severe immunodeficiency, whether inherited or acquired or following chemotherapy. Indicated in immunocompetent patients receiving HLA-matched platelets or transfusions from relatives.
Washing: removes proteins remaining in the plasma of erythrocyte and platelet products	Used in patients with a history of severe/recurrent allergic reactions, IgA deficiency (when IgA-deficient donors are unavailable). May be indicated for patients with complement-dependent autoimmune hemolytic anemia. Reduces the amount of potassium transfused for patients who are at high risk for hyperkalemia.

CMV = cytomegalovirus; GVHD = graft-versus-host disease.

[a]More than 80% of blood banks in the United States adhere to universal leukoreduction. For those that do not, leukoreduction should be performed for chronically transfused patients, those with a history of a febrile hemolytic transfusion reaction, patients who are potential candidates for or recipients of a solid-organ or hematopoietic stem cell transplant, and immunocompromised recipients who are CMV seronegative.

TABLE 25. Plasma-Derived Therapeutic Products

Product	Indication(s) for Use
Fresh frozen plasma	Replacement fluid for plasma exchange in thrombotic thrombocytopenic purpura
	Prevention and treatment of coagulopathy from massive transfusion
	Treatment of bleeding associated with multiple acquired clotting factor deficiencies (liver disease, disseminated intravascular coagulation, nonemergent warfarin toxicity)
Cryoprecipitate	Congenital or acquired fibrinogen deficiency
	Dysfibrinogenemia
	Factor XIII deficiency
	Treatment of hemophilia A and von Willebrand disease when a specific factor concentrate is not available
Intravenous immune globulin	Acquired or congenital hypogammaglobulinemia
	Autoimmune disorders
Albumin	Replacement fluid for plasma exchange
	Large-volume paracentesis
Prothrombin complex concentrates[a]	Major warfarin-associated hemorrhage
Factor VIII[b]	Hemophilia A, treatment and prevention of bleeding
von Willebrand protein-rich factor VIII[b,c]	von Willebrand disease, treatment and prevention of bleeding
Factor IX[b]	Hemophilia B, treatment and prevention of bleeding
Fibrinogen concentrate	Congenital fibrinogen deficiency, treatment of bleeding
Thrombin[b]	Topical application for small vessel bleeding despite standard surgical techniques or when surgical intervention is not feasible
Protein C concentrate	Severe congenital protein C deficiency (prevention and treatment of venous thrombosis and purpura fulminans)
Antithrombin[b]	Hereditary antithrombin deficiency (perisurgical and obstetric procedure prophylaxis and treatment of established venous thrombosis)
α_1-antitrypsin	Congenital α_1-antitrypsin deficiency (high-risk phenotype, α_1-antitrypsin level <11 µmol/L, ≥18 years of age, and airflow obstruction by spirometry)
C1-esterase inhibitor	Hereditary angioedema, acute attacks

[a]Four-factor prothrombin complex concentrate (containing factors II, VII, IX, and X) is preferred over three-factor prothrombin complex concentrates in which factor VII is missing.

[b]Recombinant product available and preferred as a way of reducing the risk of transmissible infections.

[c]Select plasma-derived factor VIII products are rich in von Willebrand protein.

H CONT.

Prothrombin complex concentrates (PCCs), specifically the newer generation of four factor PCC, which contains factors II, VII, IX, and X, are the preferred product for patients experiencing life-threatening bleeding while taking warfarin anticoagulation. Previously, plasma transfusion with or without vitamin K supplementation was used with the attendant risks of volume overload and allergic reactions. Inappropriate use of PCCs carries a thrombotic risk, so they should not be used in patients who have elevated INRs from warfarin without life-threatening bleeding or before elective invasive procedures in patients receiving anticoagulation or patients with chronic liver disease. A recent multicenter trial demonstrated the safety and efficacy of PCCs compared with plasma transfusion in patients requiring urgent surgical interventions. PCCs contain residual heparin and are contraindicated in patients with heparin-induced thrombocytopenia. H

KEY POINTS

- Recombinant factor concentrates (not containing any donor plasma) are the standard of care for younger patients with hemophilia A and B.
- The newer generation of four-factor prothrombin complex concentrates is the preferred product for patients experiencing life-threatening bleeding while taking warfarin anticoagulation.

Blood Management

H

Patient-centered blood management uses allogeneic blood components to achieve a clinically relevant goal rather than to correct an abnormal laboratory finding; identifies and corrects specific causes of anemia that eliminate the need for transfusion; and reduces iatrogenic blood loss by eliminating unnecessary phlebotomy for routine laboratory testing.

H CONT.

In the previous 2 decades, several large, randomized controlled trials have demonstrated the safety of a restrictive transfusion threshold (hemoglobin level <7-8 g/dL [70-80 g/L]) compared with a more liberal threshold (hemoglobin level <9-10 g/dL [90-100 g/L]) in common clinical settings in which blood is transfused, such as in critically ill patients in the ICU, patients with gastrointestinal bleeding, and older adult patients after hip fracture surgery. With the exception of the "TITRe" trial in cardiac surgery, all the trials found that a restrictive transfusion threshold produced equivalent, and in some cases superior, outcomes, such as in patients with upper gastrointestinal bleeding. Incorporating restrictive transfusion guidelines in computerized physician order entry pathways increases adherence to these thresholds. Although a restrictive transfusion threshold has proven beneficial in many clinical scenarios, emergent transfusion at more liberal transfusion thresholds will remain important in specific instances, such as in patients with anemia and acute coronary syndrome or acute stroke and patients who are actively bleeding and hemodynamically unstable. H

KEY POINT

- A restrictive transfusion threshold (hemoglobin level <7-8 g/dL [70-80 g/L]) provides equivalent outcomes as a more liberal threshold (hemoglobin level <9-10 g/dL [90-100 g/L]) in managing critically ill patients in the ICU, patients with acute gastrointestinal bleeding, and older patients after hip fracture.

H Transfusion Complications

Transfusion reactions occur in approximately 1% of transfusions. They are best classified according to the main presenting symptoms, such as fever and chills, respiratory distress, and allergic manifestations. Although fatal reactions are rare (incidence of 1:200,000-400,000 units), the leading causes are hemolysis, transfusion-related acute lung injury, and transfusion-associated circulatory overload.

Hemolytic Reactions

Acute Hemolytic Transfusion Reactions

Acute hemolytic transfusion reactions result from clerical errors at the time of specimen collection or blood administration. Electronic barcode systems that print a specimen label from the patient's wristband on demand or verify patient-unit compatibility at the time of bedside transfusion reduce such errors but are not yet widely adopted. Patient and specimen identification can be particularly problematic in high-turnover areas such as the emergency department or in mass-casualty incidents. Patients develop fever and flank pain and appear anxious and distressed. Hypotension and diffuse bleeding may be signs that acute hemolysis has triggered disseminated intravascular coagulation. Hemoglobinuria and hemoglobinemia may be noted. Platelets, because of their short shelf life, are administered in adult transfusion practice without regard to ABO compatibility, and, rarely, high-titer ABO antibodies in the plasma of group O platelets may mediate less extensive hemolytic transfusion reactions, which are more subtle and harder to recognize, such as an unexplained drop in hematocrit level or a newly positive direct antiglobulin test result. The most important step in managing signs or symptoms consistent with an acute hemolytic transfusion reaction is to stop the transfusion; outcomes worsen as more incompatible blood is transfused. Clerical review and blood bank notification should follow. Laboratory tests include the direct antiglobulin test, haptoglobin and plasma free hemoglobin measurements, and urinalysis to assess hemoglobinuria. Volume expansion and supportive care for associated complications (disseminated intravascular coagulation, acute kidney injury) are required.

Delayed Hemolytic Transfusion Reaction

Antibodies to non-ABO blood group antigens (so-called "minor" antigens) develop in some persons after transfusion or pregnancy but may be not be detectable when subsequent transfusion is needed years later. When re-exposed to transfused cells with the same antigen, an anamnestic antibody response leads to delayed hemolysis of the transfused antigen-positive erythrocytes, typically 7 to 14 days after the transfusion. The causative association between a hematocrit level decrease, often accompanied by low-grade fever, and a transfusion 1 to 2 weeks beforehand is not always appreciated, particularly in postoperative patients or patients discharged from the hospital. Investigation of a suspected delayed hemolytic transfusion reaction should include a direct antiglobulin test (and blood bank notification) and evaluation of markers of hemolysis, such as lactate dehydrogenase and bilirubin levels and reticulocyte count. Patients should be informed regarding their alloimmunization status so they can communicate this information to other health care providers for subsequent surgery or other care. Some jurisdictions outside the United States have transfusion "antibody registries" for this purpose. H

KEY POINTS

- Acute hemolytic transfusion reactions manifest with fever, flank pain, hypotension, hemoglobinemia, and hemoglobinuria; discontinuing the transfusion is the most important step in treatment.
- A delayed hemolytic transfusion reaction, with low-grade fever and worsening anemia, occurs 1 to 2 weeks after transfusion and should be evaluated measuring direct antiglobulin, haptoglobin, lactate dehydrogenase, bilirubin, and reticulocyte count.

Nonhemolytic Transfusion Reactions H

Transfusion-Associated Circulatory Overload

Transfusion-associated circulatory overload (TACO) is an underrecognized problem and may be the most common serious complication of blood transfusion, affecting 1% to 8% of transfusion recipients. Risk factors include older age, pre-existing

cardiovascular or kidney disease, and rapid administration rate. Signs and symptoms include respiratory distress within 6 hours of transfusion, positive fluid balance, elevated central venous pressure, elevated B-type natriuretic peptide, and compatible radiographic findings of pulmonary edema. Therapy consists of diuretics and a slower rate of blood administration.

Transfusion-Related Acute Lung Injury

Transfusion-related acute lung injury (TRALI) is defined as noncardiogenic pulmonary edema that occurs within 6 hours of transfusion. These patients are more likely to present with fever and hypotension and less likely to have overt signs of volume overload as in patients with TACO. Radiographic findings usually suggest a noncardiac pulmonary edema or adult respiratory distress syndrome but may resemble those seen in TACO. Most cases of TRALI occur because of HLA or neutrophil-specific antibodies in multiparous donors that bind to and activate recipient leukocytes in the pulmonary vasculature. The incidence of this complication has been significantly reduced by screening donors for these antibodies. Management is supportive and includes supplemental oxygen or mechanical ventilatory support as needed. This management is analogous to that used for other causes of adult respiratory distress syndrome, although the prognosis is better and the recovery quicker. TRALI is unlikely to recur in subsequent transfusions for individual patients.

Febrile Nonhemolytic Transfusion Reaction

Febrile nonhemolytic transfusion reaction (FNHTR) is common, occurring in about 1% of transfusion episodes, and is mediated by proinflammatory cytokines elaborated by donor leukocytes during storage. Symptoms encompass a temperature increase of 1 °C (1.8 °F) to greater than 38 °C (100.4 °F) within 4 hours of transfusion or chills and rigors even in the absence of a fever. The differential diagnosis of fever occurring in association with transfusion includes hemolysis and septic transfusion reaction. Investigation consists of a direct antiglobulin test, visual inspection of patient plasma for hemolysis, and a clerical check and, if warranted, obtaining a blood bag culture and blood cultures from the patient. Although antipyretics are appropriate as therapy, no studies have shown that they prevent FNHTR, so routine prophylaxis with antipyretics is not warranted. Prestorage leukocyte reduction of whole blood by filtration at the blood center or at the time of platelet apheresis collection can prevent FNHTR.

KEY POINTS

- Signs and symptoms of transfusion-associated circulatory overload include respiratory distress within 6 hours of transfusion, positive fluid balance, elevated central venous pressure, elevated B-type natriuretic peptide, and compatible radiographic findings of pulmonary edema.

(Continued)

KEY POINTS *(continued)*

- Transfusion-related acute lung injury is defined as noncardiogenic pulmonary edema that occurs within 6 hours of transfusion and is managed similarly to other causes of acute respiratory distress syndrome.

Infectious Complications

Bacterial contamination of blood components occurs from inadequate cleansing of the donor's skin before phlebotomy or from occult (asymptomatic) bacteremia in the blood donor. Platelet components are screened for bacterial contamination before release for transfusion, but residual risk remains, typically for gram-positive organisms that are part of skin flora. Erythrocyte components, when contaminated, tend to contain gram-negative organisms such as *Yersinia*, which thrive in a cold and iron-rich environment. Infectious complications include the transmission of agents not routinely tested for, such as *Babesia*. The clinical features may include fever with or without hypotension.

Allergic Reactions and Anaphylaxis

Mild allergic reactions with pruritus and urticaria occur in 1% to 5% of recipients, during or after the transfusion of plasma-rich components (including platelets). If symptoms resolve after the administration of antihistamines, transfusion can be restarted with the same unit under close observation. The transfusion must be discontinued if symptoms recur or progress beyond urticaria. No evidence supports the routine use of antihistamine or glucocorticoid prophylaxis in patients with previous mild allergic transfusion reactions.

Anaphylactic or anaphylactoid reactions are rare. Manifestations include angioedema, stridor, abdominal symptoms, and hypotension. In addition to antihistamines (H_1 and H_2 blockers), patients may require bronchodilators, fluid resuscitation, and epinephrine. Investigation of possible underlying protein deficiency (IgA or haptoglobin) should be undertaken in a patient with an anaphylactic transfusion reaction. The documentation of severe IgA deficiency with anti-IgA antibodies necessitates the future use of washed cellular blood components or plasma components from IgA-deficient donors.

KEY POINTS

- No evidence supports the routine use of antihistamine or glucocorticoid prophylaxis in patients with a history of mild allergic transfusion reactions.
- Manifestations of anaphylactic or anaphylactoid transfusion reactions include angioedema, stridor, abdominal symptoms, and hypotension and should prompt an investigation for an underlying protein deficiency (IgA or haptoglobin).

Transfusion-Associated Graft-versus-Host Disease

Transfusion-associated graft-versus-host disease is a rare but fatal complication in which donor lymphocytes in a cellular

H CONT. blood product (erythrocytes or platelets) engraft in an immunocompromised recipient and cause toxic effects in the bone marrow, skin, liver, and gastrointestinal tract. Patients at risk include those receiving chemotherapy for autoimmune disorders or malignancy, recipients of blood components from first-degree relatives, and premature infants. Prevention involves γ irradiation of cellular blood components intended for recipients at risk. Patients who have undergone stem cell transplantation typically require irradiated blood components indefinitely; this should be communicated from the transplant center at the time of discharge from the transplant program. H

KEY POINT

- Patients who have undergone stem cell transplantation typically require γ-irradiated blood products to prevent transfusion-associated graft-versus-host disease.

H Transfusion in Special Circumstances

Massive transfusion refers to the transfusion of one total blood volume, which is equivalent to 8 to 10 units of blood, within a 24-hour period. Conditions requiring massive transfusion include trauma, ruptured aortic aneurysm, and severe gastrointestinal bleeding. When whole blood is lost and replaced with crystalloid and PRBCs, a dilutional coagulopathy develops that is often exacerbated by hypothermia, acidosis, and liver injury as well as concomitant disseminated intravascular coagulation. Contemporary practice is to transfuse plasma and platelets concurrently with PRBCs to avert the development of dilutional coagulopathy. During resuscitation, patients must be monitored for electrolyte disturbances such as hypocalcemia (because the citrate in the anticoagulant used for all blood components binds free calcium, which lowers the serum calcium concentration), hyperkalemia or hypokalemia, and metabolic alkalosis (from citrate metabolism).

Autoimmune hemolytic anemia presents a unique transfusion challenge. Warm reactive autoantibodies are usually polyclonal IgG antibodies directed against erythrocytes (the patient's own, reagent, and donor erythrocytes). The clinical significance of warm autoantibodies derives from their hemolytic potential and their interference with routine pretransfusion compatibility testing, specifically the detection of alloantibodies and the provision of crossmatch-compatible blood. The urgency of the transfusion, particularly the presence of acute cardiopulmonary or central nervous system symptoms, must be considered along with the risk for hidden alloantibodies, which are rare in patients without previous pregnancy or transfusion. Transfused units should be matched for ABO and Rh. Care of these patients should be closely coordinated between the hospitalist, hematologist, and blood bank specialist. H

KEY POINTS

- As patients requiring massive transfusion are resuscitated, they must be monitored for electrolyte disturbances such as hypocalcemia, hyperkalemia or hypokalemia, and metabolic alkalosis.
- Patients with warm autoimmune hemolytic anemia have autoantibodies that react against all erythrocytes, including donor erythrocytes, so a completely crossmatch-compatible unit may be impossible to find; these patients should be transfused with ABO and Rh type specific, crossmatch-incompatible blood.

Therapeutic Apheresis H

Apheresis procedures use an automated blood cell separator to collect whole blood, separate it into the plasma and cellular components, remove the component contributing to disease, and return the other blood components to the patient combined with replacement fluids. Plasmapheresis for patients suspected of having Guillain-Barré syndrome is a classic example. Crystalloid and colloid fluids are used for replacement, and plasma components are typically avoided. Therapy for thrombotic thrombocytopenic purpura is more appropriately characterized as plasma exchange because fresh frozen plasma is provided as the replacement fluid. The same cell separators can be used to perform plateletpheresis, erythrocyte exchange transfusion, and other procedures in patients with specific indications (**Table 26**). H

Thrombotic Disorders H

The burden of venous thromboembolic disease continues to increase despite increased awareness of risk factors and prevention options. The incidence of a first episode of venous thromboembolism (VTE) is approximately 1 to 2 per 1000 person/years.

VTE most commonly manifests as lower extremity deep venous thrombosis (DVT) or pulmonary embolism (PE). Many nosocomial VTEs are preventable, although thromboprophylaxis continues to be underused. D-dimer testing and imaging for VTE diagnosis should be used within the context of appropriate clinical algorithms.

Opinions differ regarding the relevance of thrombophilia testing, and results usually do not affect the length of anticoagulation. The landscape of treatment options continues to evolve.

Pathophysiology of Thrombosis

Alterations in three primary mechanisms of thrombosis predispose persons to VTE. Described by the German pathologist Rudolph Virchow more than 150 years ago, reduced or otherwise turbulent blood flow, alterations or injury to the vessel

TABLE 26. Indications for Therapeutic Apheresis[a]

Plasmapheresis/Plasma Exchange
Thrombotic thrombocytopenic purpura
Hyperviscosity syndrome (Waldenström macroglobulinemia and multiple myeloma)
Paraproteinemic polyneuropathies
Guillain-Barré syndrome (acute inflammatory demyelinating polyneuropathy)
Chronic inflammatory demyelinating polyradiculoneuropathy
Myasthenia gravis
ANCA-associated rapidly progressive glomerulonephritis
Anti-glomerular basement membrane disease
Recurrent focal segmental glomerulosclerosis
Severe, symptomatic cryoglobulinemia
Antibody-mediated renal allograft rejection
Fulminant Wilson disease
Erythrocyte Exchange
Severe babesiosis[b]
Sickle cell disease with acute cerebral infarct
Sickle cell disease with severe acute chest syndrome[c]
Leukapheresis
Hyperleukocytosis syndrome
Plateletpheresis
Symptomatic extreme thrombocytosis[d]
Extracorporeal Photopheresis
Cardiac allograft rejection, prophylaxis
Erythrodermic cutaneous T-cell lymphoma/Sézary syndrome
Selective Blood Component Removal
LDL cholesterol for familial hypercholesterolemia

[a]This list includes diseases for which apheresis is an accepted part of front line therapy for a particular indication, either as the sole therapeutic modality or in combination with other therapy. It is not an all-inclusive list.

[b]Erythrocyte exchange for severe malaria is a category II indication (accepted second-line therapy).

[c]Erythrocyte exchange for acute chest syndrome is a category II indication but recommended by many as first line therapy for those severely affected.

[d]The use of plateletpheresis is a category II indication for patients with life-threatening thrombosis or hemorrhage associated with thrombocytosis (for example, in a patient with essential thrombocytosis).

Data from Szczepiorkowski ZM, Winters JL, Bandarenko N, Kim HC, Linenberger ML, Marques MB, et al; Apheresis Applications Committee of the American Society for Apheresis. Guidelines on the use of therapeutic apheresis in clinical practice—evidence-based approach from the Apheresis Applications Committee of the American Society for Apheresis. J Clin Apher. 2010;25:83-177. [PMID: 20568098] doi:10.1002/jca.20240

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wall, and changes in blood components that are prothrombotic or that inhibit fibrinolysis (or both) compose the Virchow triad. VTE usually develops as a result of the synergistic effect of multiple risk factors, which may be inherited, acquired, or a combination of both.

Thrombophilia

Thrombophilia Testing

One aspect of the Virchow triad is blood hypercoagulability, or thrombophilia. Thrombophilia can be inherited or acquired. Thrombophilia testing should not be routinely pursued in all patients presenting with DVT or PE. Although guidelines differ, most experts agree that thrombophilia evaluation should be considered only in certain populations, including patients with thromboses at unusual sites or recurrent idiopathic thrombosis, patients younger than 45 years with unprovoked thrombosis, patients with a clear family history of thrombosis in one or more first degree relatives, and patients with warfarin-induced skin necrosis.

Additionally, many variables can affect outcomes of thrombophilia testing, including acute thrombosis and anticoagulant use, which may lead to false-positive test results. For this reason, and because a known thrombophilia will not change immediate management, testing should not be pursued in the acute setting. Asymptomatic patients with a family history of thrombosis should not undergo thrombophilia testing. H

KEY POINTS

- Thrombophilia evaluation should not be performed in most patients with acute venous thromboembolism. **HVC**
- Thrombophilia testing should be considered in patients with thromboses at unusual sites or recurrent idiopathic thrombosis, patients younger than 45 years with unprovoked thrombosis, patients with a clear family history of thrombosis in one or more first-degree relatives, and patients with warfarin induced skin necrosis.
- Thrombophilia testing is less accurate during episodes of acute venous thromboembolism, and test results would not change immediate management; if indicated, testing should be performed after anticoagulation has been discontinued. **HVC**

Inherited Thrombophilias

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Inherited thrombophilias typically affect components of the coagulation cascade (see Figure 2 in Bleeding Disorders) that keep the hemostatic system in balance, either causing the prothrombotic system to continue unsuppressed or inhibiting clot lysis. All known inherited thrombophilias are autosomal dominant, meaning that most affected patients are heterozygous for the disorder. The two most common inherited causes are factor V Leiden and prothrombin *G20210A* gene mutation. Less common mutations involve antithrombin deficiency and protein C and S deficiency, although these latter disorders seem to be more significant risk factors for VTE.

Failure to identify a thrombophilia does not mean a thrombophilia does not exist. Studies have shown that even when an inherited disorder is not identified, a family history of thrombosis remains an independent risk factor for VTE. It is also possible for two thrombophilic defects to coexist, such as protein S deficiency and factor V Leiden.

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Although identification of the inherited thrombophilias has advanced our understanding of the pathophysiology of VTE, it has had less influence on clinical management. The acute management of patients with VTE does not differ based on the presence of an inherited thrombophilia. Management duration is typically determined by whether the VTE event was provoked by a reversible or self-limited insult and is not often influenced by the presence of an underlying inherited thrombophilia, especially the more common disorders. Even if a patient with VTE is found to have an inherited thrombophilia, no evidence indicates asymptomatic family members should be screened to determine whether they also have the mutation.

Factor V Leiden

Factor V Leiden is the most common inherited thrombophilia. When factor V is activated, it combines with factor X to produce thrombin, which leads to clot formation. This process is regulated by activated protein C, which inactivates factor V to stop the process of ongoing clot formation. Factor V Leiden is resistant to cleavage by activated protein C, leading to predisposition of thrombus formation. Although persons who are heterozygous are at a fourfold to eightfold increased risk for developing a first VTE, most remain asymptomatic. Heterozygous factor V Leiden is found in about 5% of whites, whereas the homozygous form is found in less than 1%. Factor V Leiden is rare in Asian, African, African American, and Native American populations. It does not appear to be associated with arterial thrombosis. Factor V Leiden genetic testing or activated protein C resistance testing can be used to diagnose this condition.

Prothrombin *G20210A* Gene Mutation

The prothrombin *G20210A* gene mutation occurs in approximately 2% of whites and 0.5% of blacks and causes increased production of prothrombin (factor II) through a mutation at nucleotide 20210 from guanine to adenine. Persons with this mutation are at a twofold to fourfold increased risk for developing a first VTE, although, as with factor V Leiden, most patients with this mutation do not experience VTE events. Data are unclear regarding risks with the homozygous state, which is rare.

Antithrombin Deficiency

Antithrombin III (ATIII) and proteins C and S serve as natural anticoagulants in the body. Mutations that lead to loss of function of these components contribute to a tendency to develop VTE.

ATIII deficiency, although rare, with a prevalence of 1 in 3000 to 5000 persons, is a more significant thrombophilic risk factor than factor V Leiden or the prothrombin *G20210A* gene mutation. The main role of ATIII is to inhibit thrombin and activated factors IX and X (IXa and Xa). VTE-related pregnancy loss and pregnancy morbidity is common. Acquired ATIII deficiency is much more common than the congenital version (**Table 27**), and repeat testing is typically required to determine whether the deficiency is persistent.

TABLE 27. Conditions Associated with Acquired Decreased Coagulation Factor Levels

Coagulation Factor	Acquired Condition
Protein C	Acute thrombosis
	Warfarin therapy
	Liver disease
	Protein-losing enteropathy
Protein S	Acute thrombosis
	Warfarin therapy
	Liver disease
	Inflammatory states
	Estrogens (contraceptives, pregnancy, postpartum state, hormone replacement therapy)
	Protein-losing enteropathy
Antithrombin	Acute thrombosis
	Heparin therapy
	Liver disease
	Nephrotic syndrome
	Protein-losing enteropathy

For patients in whom heparin is initiated and titration to a therapeutic range is difficult, ATIII deficiency should be considered because heparin requires ATIII to be effective. ATIII concentrate can be used to treat this condition.

Protein C Deficiency

Protein C is a vitamin K-dependent protein that degrades activated factors V and VIII. Heterozygous protein C deficiency is uncommon, with a prevalence of 2 to 5 per 1000 persons. Many persons with this deficiency will experience a thrombotic event or pregnancy morbidity before 50 years of age, with a strong family history of thrombosis. Patients can also develop warfarin-induced skin necrosis because of further rapid depletion of protein C, which proceeds more rapidly than depletion of the coagulation factors. Homozygous deficiency is rare and causes neonatal purpura fulminans. If protein C deficiency is found, acquired causes should be ruled out (see Table 27). Repeat testing is often necessary to confirm a hereditary deficiency. Patients should not be tested during acute VTE events or while receiving warfarin. Protein C functional testing can be ordered to evaluate for evidence of deficiency.

Protein S Deficiency

Protein S is a cofactor for protein C to degrade activated factors V and VIII. Deficiency is uncommon and bears many similarities to protein C deficiency. Patients who are heterozygous for protein S deficiency typically experience VTE at a younger age

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(<50 years). Protein S is a vitamin K–dependent factor synthesized by the liver; it circulates in a free form and bound to a complement binding protein. Although rare case reports show patients with a functional protein S deficiency, immunoassay of the free form of protein S is usually sufficient to make the diagnosis. Protein S deficiency is likely the most difficult hereditary thrombophilia to confirm because multiple laboratory assays for protein S are available, with cutoffs between normal and deficient that may be imprecise.

Other Inherited Disorders

Methylene tetrahydrofolate reductase (*MTHFR*) gene polymorphisms cause mild elevations in homocysteine levels, which are associated with a mildly increased risk of cardiovascular and thrombotic disease. The heterozygous mutation is found in 20% of whites and 2% of blacks. Vitamin B_6 and B_{12} supplementation can lower homocysteine levels without lowering thrombotic risk, which suggests the mutation may be a marker of thrombotic risk rather than a cause of thrombosis. Testing for the *MTHFR* mutation and measuring homocysteine levels should not be done in the evaluation of thrombophilia.

Factor VIII levels and plasminogen activator inhibitor activity should not be part of the standard thrombophilia evaluation because clinical trials regarding their importance have been inconclusive and results do not influence management. H

KEY POINTS

- Although the risk of venous thromboembolism is increased in patients who are heterozygous for factor V Leiden or prothrombin *G20210A* gene mutation, most patients are asymptomatic.
- HVC Methylene tetrahydrofolate reductase (*MTHFR*) gene mutations are associated with an elevated homocysteine level and a modest increased risk of venous thrombosis; no treatment is available, and *MTHFR* mutation testing and homocysteine level measurement should not be performed.
- HVC Measurement of homocysteine, factor VIII levels, and plasminogen activator inhibitor activity should not be part of the standard thrombophilia evaluation because results do not influence management.

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Acquired Thrombophilias

VTE is more likely to occur in the setting of an acquired rather than an inherited thrombophilia. Many conditions predispose patients to the development of thrombosis.

Surgery, Trauma, Hospitalization, and Immobility

Surgery, trauma, hospitalization, and immobilization are some of the most significant risk factors for VTE. VTE occurs frequently in medical and surgical patients. Approximately half of all new VTEs are diagnosed during or within 3 months of a hospital stay or surgical procedure. If prophylaxis is not used, the risk of DVT in the general surgical patient is 15% to 30%. In the orthopedic patient, the risk of DVT is approximately 60% after hip fracture surgery. Patients with cancer who undergo surgery and those undergoing orthopedic procedures, including knee arthroplasty, hip fracture repair, or hip replacement, are at particularly high risk. Nosocomial VTE risk is also increased for nonsurgical hospitalized patients, more so for immobilized patients, patients with acute neurologic illness, and patients in the medical ICU.

Certain medical conditions, including inflammatory conditions, nephrotic syndrome, and inflammatory bowel disease, have also been associated with increased thrombotic risk. In nephrotic syndrome, this risk is attributed to loss of antithrombin and proteins C and S in the urine. Obesity is also associated with increased thrombotic risk.

Cancer

Thrombosis remains a leading cause of death in patients with cancer and is a significant source of morbidity. Increased thrombotic risk has been associated with numerous malignancies, including prostate and breast cancer.

Cancer is diagnosed in 10% of patients within 1 year of an unprovoked VTE occurrence. Cancer of the ovary, pancreas, and liver are most often found. The only randomized controlled clinical trial that compared routine age- and gender-indicated screening with extensive malignancy screening using CT of the thorax, abdomen, and pelvis showed that extensive malignancy screening provided no survival benefit. Extensive cancer screening should not be performed beyond recommendations for gender and age, independent of the VTE event.

In addition, other factors, such as hormonal therapy, can further increase risk.

Medication

Hormones used in oral contraceptives and in the treatment of menopause increase the risk of VTE. The risk in women using oral contraceptives is increased approximately threefold, but the absolute number of patients affected in this young healthy population remains small. VTE risk correlates with the specific progestin agent and is somewhat higher in oral contraceptives containing desogestrel and gestodene and somewhat lower with levonorgestrel. Injectable progestin agents do not increase the risk. Regardless of the type of contraceptive, VTE risk tends to be greater in obese women and those who are older than 39 years. Women with a previous VTE event and a known inherited thrombophilia should not take oral contraceptives because the thrombotic risk is further increased. However, experts do not recommend routine thrombophilia screening before beginning contraceptive therapy because many women would need to be screened to prevent one adverse event from pulmonary embolism (PE). VTE risk is also increased by approximately twofold in menopausal women taking conjugated estrogen–medroxyprogesterone hormone replacement therapy, but the absolute risk remains small. The VTE risk in

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menopausal women seems lower in those taking estrogen only and in those using transdermal hormone replacement.

The antiestrogen, tamoxifen, also increases VTE risk in women with estrogen receptor-positive breast cancer, and the risk increases further, approximately three times baseline, in women receiving tamoxifen with systemic chemotherapy. The risk for VTE with aromatase inhibitors, such as anastrozole, is lower than that seen with tamoxifen.

Patients with multiple myeloma receiving thalidomide and its analogs as part of combination chemotherapy have a significant risk of VTE that warrants prophylaxis. The vascular endothelial growth factor inhibitor bevacizumab and newer multitargeted tyrosine kinase inhibitors, such as sunitinib and sorafenib, also increase VTE risk.

Glucocorticoid therapy has also been identified to increase the risk for VTE.

Antiphospholipid Antibody Syndrome

The antiphospholipid antibody syndrome is an autoimmune disorder in which thrombosis and fetal demise (in pregnancy) may occur. Patients with antiphospholipid antibody syndrome are at risk for arterial and venous thrombosis.

Antiphospholipid antibodies are the anticardiolipin antibodies and the lupus anticoagulant. The diagnosis of antiphospholipid antibody syndrome is based on the clinical criteria of thromboembolism or pregnancy morbidity and laboratory findings of medium or high titer antiphospholipid antibodies present on two or more occasions at least 12 weeks apart (**Table 28**). A clue to the presence of the lupus anticoagulant is activated partial thromboplastin time prolongation.

Typically, patients who are diagnosed with antiphospholipid antibody syndrome require long term anticoagulation owing to the risk of recurrent thrombosis.

Other Acquired Thrombophilic Conditions

The myeloproliferative neoplasms have been found to carry a particularly increased risk of thrombosis; although these thromboses include PE and DVT, portal vein thrombosis and Budd-Chiari syndrome (hepatic venous outflow obstruction) (see MKSAP 18 Gastroenterology and Hepatology) are often found. Evidence of a myeloproliferative neoplasm is found in approximately 50% of patients with Budd-Chiari syndrome, even when the complete blood count is normal. In the setting of splanchnic vein thrombosis (which includes Budd-Chiari syndrome and portal vein thrombosis), evaluation for evidence of a myeloproliferative neoplasm should be considered, including evaluation for the *JAK2* tyrosine kinase mutation.

Paroxysmal nocturnal hemoglobinuria is another acquired stem cell disorder associated with hemolytic anemia, bone marrow failure, and thrombosis (see Erythrocyte Disorders).

A previous VTE event is one of the most powerful predictors of a subsequent VTE, regardless of whether an additional inherited or acquired thrombophilic risk factor is identified. H

KEY POINTS

- Approximately half of all new VTEs are diagnosed during or within 3 months of a hospital stay or surgical procedure.
- Patients with cancer undergoing extensive surgery and those undergoing knee arthroplasty, hip fracture repair, or hip replacement surgery are at especially high risk for postoperative venous thromboembolism.
- The diagnosis of antiphospholipid antibody syndrome is based on the clinical criteria of thromboembolism or pregnancy morbidity and laboratory findings of medium or high titer antiphospholipid antibodies present on two or more occasions at least 12 weeks apart.
- Evidence of a myeloproliferative neoplasm is found in approximately 50% of patients with Budd-Chiari syndrome, and *JAK2* tyrosine kinase mutation testing should be performed even if blood counts are normal.

TABLE 28. Diagnosis of Antiphospholipid Antibody Syndrome[a]

Vascular Thrombosis	Pregnancy Morbidity	Laboratory Criteria
One or more objectively confirmed episodes of arterial, venous, or small vessel thrombosis occurring in any tissue or organ	One or more unexplained deaths of a morphologically normal fetus at or beyond the 10th week of gestation; or	Lupus anticoagulant, detected according to the guidelines of the International Society on Thrombosis and Haemostasis
	One or more premature births of a morphologically normal neonate before the 34th week of gestation because of eclampsia, pre-eclampsia, or placental insufficiency; or	Anticardiolipin antibody of IgG and/or IgM isotype, present in medium or high titer (greater than 40 GPL or MPL, or greater than the 99th percentile), measured by a standardized ELISA
	Three or more unexplained consecutive spontaneous abortions before the 10th week of gestation	Anti-β_2-glycoprotein-1 antibody of IgG and/or IgM isotype, present in titer greater than the 99th percentile, measured by a standardized ELISA

ELISA = enzyme-linked immunosorbent assay; GPL = specificity for IgG phospholipid antigens; MPL = specificity for IgM phospholipid antigens.

[a]Diagnosis is based on the presence of vascular thrombosis OR pregnancy morbidity PLUS relevant laboratory criteria.

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Deep Venous Thrombosis and Pulmonary Embolism

Prevention

All hospitalized patients should be assessed for the risk of developing a VTE and treated with appropriate prophylaxis (see MKSAP 18 General Internal Medicine) because VTE is a major preventable cause of hospital morbidity and mortality. Generally, unless a clear contraindication to prophylaxis exists, pharmacologic treatment is indicated as opposed to mechanical prophylaxis. In acutely ill patients with risk for thrombosis, low-molecular-weight heparin, low-dose unfractionated heparin, or fondaparinux is advised for prophylaxis. Patients with cancer or stroke and those in the ICU have a particularly high risk for VTE. Despite the well-recognized risks of VTE, the rate of appropriate prophylaxis remains low in general hospitalized patients. Most patients do not require continued pharmacologic VTE prevention after discharge. However, patients with cancer who are undergoing major surgical procedures, patients undergoing knee arthroplasty, and those with hip fracture repair or hip replacement require VTE prophylaxis for as long as 4 weeks after discharge.

Diagnosis

DVT and PE cause significant morbidity and require efficient evaluation and diagnosis. Previous VTE, immobilization, and other thrombophilia risk factors, especially cancer, should be assessed. History pertinent to other potential causes of leg or respiratory symptoms should be elicited. The typical clinical presentation of DVT involves unilateral swelling, pain, warmth, and erythema of the extremity. Patients with PE may present with chest pain, dyspnea, and tachypnea. Less commonly, symptoms may include cough, fever, cyanosis, syncope, or shock.

CT angiography has significantly improved the accuracy of evaluating PE, generally replacing ventilation-perfusion scanning, which lacks specificity, and avoiding the need for more invasive pulmonary arteriography. However, the overuse of CT angiography and D-dimer measurement in patients at low risk for PE has needlessly exposed patients to the additional radiation and expense of these procedures. For patients who present with symptoms suspicious for an acute VTE, validated prediction rules have been developed that use D-dimer testing to help effectively evaluate this condition. The Wells criteria for diagnosis of DVT (**Table 29**) and PE (**Table 30**) and the Geneva Score (**Table 31**) for diagnosis of PE are well-studied tools in this setting. Based on these criteria, patients with low pretest probability and low D-dimer levels do not require imaging because a VTE diagnosis is unlikely. Recent studies suggest that a subset of patients at very low risk can be identified using the Pulmonary Embolism Rule-Out Criteria (PERC) (**Table 32**); these patients do not require D-dimer testing to eliminate the need for additional imaging. American College of Physicians guidelines published in 2015 recommend using the PERC as the initial step in evaluating patients at low risk. If the PERC score is zero, no D-dimer testing is needed, and no CT angiography should be performed. In a recent meta-analysis of 12 studies, it was found that if the PERC were applied, only 0.3% of PEs

TABLE 29. Wells Criteria for Deep Venous Thrombosis

Variables	Points
Leg Symptoms and Findings	
Calf swelling ≥3 cm	+1
Swollen unilateral superficial veins (nonvaricose)	+1
Unilateral pitting edema	+1
Swelling of the entire leg	+1
Localized tenderness along the deep venous system	+1
History	
Previously documented DVT	+1
Active cancer or treatment in previous 6 months	+1
Paralysis, paresis, recent cast immobilization of legs	+1
Recently bedridden for ≥3 days; major surgery	+1
Alternative explanation for leg symptoms at least as likely	−2

DVT = deep venous thrombosis.

0-1 points = DVT unlikely; obtain D-dimer assay. If the result is negative, no further evaluation; if the result is positive, obtain Doppler ultrasonography.

>1 point = DVT likely; obtain Doppler ultrasonography.

From Wells PS, Anderson DR, Rodger M, Forgie M, Kearon C, Dreyer J, et al. Evaluation of D-dimer in the diagnosis of suspected deep-vein thrombosis. N Engl J Med. 2003;349:1227-35. [PMID: 14507948] Reprinted with permission from Massachusetts Medical Society.

TABLE 30. Wells Criteria for Pulmonary Embolism

Variables	Points
Symptoms and Signs	
Hemoptysis	1
Heart rate >100/min	1.5
Clinical signs and symptoms of DVT	3
History	
Previously documented DVT or PE	1.5
Active cancer	1
Bedridden ≥3 days or major surgery in previous 4 weeks	1.5
Other	
PE is most likely diagnosis	3

DVT = deep venous thrombosis; PE = pulmonary embolism.

≤4 points = PE unlikely; obtain D-dimer.

4-6 points = moderate possibility of PE.

>6 points = high probability of PE.

Republished with permission of Schattauer, from Wells PS, Anderson DR, Rodger M, Ginsberg JS, Kearon C, Gent M, et al. Derivation of a simple clinical model to categorize patients probability of pulmonary embolism: increasing the models utility with the SimpliRED D-dimer. Thromb Haemost. 2000;83:416-20. [PMID: 10744147]

TABLE 31. Revised Geneva Score

Clinical Characteristic	Score
Age >65 y	1
Previous PE or DVT	1
Heart rate 75-94/min	1
Heart rate ≥94/min	2
Active cancer	1
Unilateral lower limb pain	1
Hemoptysis	1
Surgery or fracture within last month	1
Pain on lower limb deep venous palpation	1

DVT = deep venous thrombosis; PE = pulmonary embolism.

<2 points: low probability of PE.

2-4 points: intermediate probability.

≥5 points: high probability.

TABLE 32. Pulmonary Embolism Rule-Out Criteria for Predicting Probability of Pulmonary Embolism in Patients with Low Pretest Probability

Clinical Characteristic	Meets Criterion	Does Not Meet Criterion
Age <50 y	0	1
Initial heart rate <100 beats/min	0	1
Initial oxygen saturation >94% on room air	0	1
No unilateral leg swelling	0	1
No hemoptysis	0	1
No surgery or trauma within 4 wk	0	1
No history of venous thromboembolism	0	1
No estrogen use	0	1

Pretest probability with score of 0 is <1%.

Reprinted with permission from Raja AS, Greenberg JO, Qaseem A, Denberg TD, Fitterman N, Schuur JD; Clinical Guidelines Committee of the American College of Physicians. Evaluation of patients with suspected acute pulmonary embolism: best practice advice from the clinical guidelines committee of the American College of Physicians. Ann Intern Med. 2015;163:701-11. [PMID: 26414967] doi:10.7326/M14-1772. Copyright 2015 American College of Physicians.

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would have been missed, and 22% of D-dimer testing would have been safely avoided. PERC will help eliminate unnecessary D-dimer testing in patients at low risk.

In patients at low risk but who have a PERC score greater than zero, D-dimer testing should be pursued. If the result is negative, no imaging is warranted. If the result is positive, further evaluation is merited. If a patient has a moderate or high pretest probability, imaging studies are indicated. D-dimer testing should not be pursued in patients with moderate or high pretest probability because results would not change the need for imaging.

Duplex ultrasonography is the imaging modality of choice for suspected DVT. Lower extremity DVT is considered proximal if the popliteal veins are involved and is considered distal if only the calf veins are involved. CT angiography is the study of choice for suspected PE.

In patients with kidney disease or in whom intravenous contrast is contraindicated, a ventilation-perfusion lung scan can be pursued. A normal ventilation-perfusion scan result effectively rules out PE, and a high probability study result in a patient with a high likelihood of disease has a strong positive predictive value. The sensitivity and specificity of low probability or intermediate probability study results may not be accurate enough to establish or rule out the diagnosis. MRI can visualize intraluminal filling defects in the pulmonary vasculature, but not as well as CT, and avoids the ionizing radiation of CT. New MRI techniques are being evaluated that may enhance its role in diagnosis. CT is still considered standard of care for evaluation of PE.

Patients with study results that establish the diagnosis of PE do not require routine duplex imaging of the lower extremities, and patients with acute DVT in the absence of respiratory symptoms do not require CT angiography. Patients with established PE should undergo cardiac ultrasonography to evaluate acute pulmonary artery hypertension and right ventricular strain that may signify a more massive PE. Serum troponin and B-type natriuretic peptide measurements also help stratify risk in patients with PE. An elevated serum troponin level is associated with increased mortality. H

KEY POINTS

- Patients with a Pulmonary Embolism Rule-Out Criteria score of zero do not require further testing with D-dimer or imaging. HVC
- Patients with a low probability Wells criteria score for DVT or PE should undergo D-dimer testing; if the results are normal, no further imaging is necessary. HVC
- Patients with moderate or high probability Wells criteria do not require D-dimer testing but should undergo duplex imaging of the lower extremities for symptoms suggesting deep venous thrombosis or CT angiography for symptoms suggesting pulmonary embolism.

Treatment

H

Most patients with DVT can be efficiently and safely diagnosed and treated without hospitalization. More recent literature has shown a subset of patients with PE with an excellent prognosis who can also avoid inpatient care. Clinical predication models have been developed to help determine the outcome of patients with acute PE, such as the Pulmonary Embolism Severity Index (PESI), which predicts clinical severity and outcome of patients with PE using 11 clinical criteria. In a multicenter, prospective, open-label, randomized trial of patients with low-risk PE as determined by the PESI score, no difference was found between outpatient and inpatient management

H CONT.

in recurrent VTE, major bleeding, or 90-day mortality. A simplified version of the PESI defines patients who are younger than 80 years, who are without significant comorbidity, and who have a pulse rate less than 110/min, systolic blood pressure greater than 100 mm Hg, and oxygen saturation greater than 90% breathing ambient air as low risk for adverse outcomes.

For most patients, anticoagulation is the primary treatment for VTE. Anticoagulant options for acute VTE include unfractionated heparin, which usually requires hospitalization, low-molecular-weight heparin (LMWH), fondaparinux, or one of the non–vitamin K oral anticoagulants, all of which are safe and effective for immediate outpatient management, although patients must learn injection technique for LMWH and fondaparinux. Traditional vitamin K antagonists are not effective without at least 5 days of concomitant parenteral heparin therapy, and dabigatran and edoxaban have not been evaluated in acute VTE without previous parenteral heparin therapy. Apixaban and rivaroxaban are safe and effective as monotherapy. Patients who require hospitalization should avoid initial treatment with unfractionated heparin because of its unpredictable bioavailability compared with LMWH; however, unfractionated heparin, with a short half-life of residual anticoagulation after the infusion is stopped, may be preferred in patients who are not stable and who may need emergent surgery or transition to thrombolytic therapy.

Duration of therapy varies based on the clinical scenario surrounding the event (**Table 33**). In provoked thrombosis with reversible risk factors, 3 months of anticoagulation is adequate. Extended therapy should be considered in patients at low bleeding risk with unprovoked VTE or with irreversible risk factors for recurrent VTE, such as underlying heart failure or stroke with long-term ambulatory dysfunction. If extended therapy is chosen, the risks, benefits, and choice of anticoagulant should be re-evaluated yearly.

In patients with unprovoked VTE in whom anticoagulation is discontinued, initiating aspirin is associated with approximately a 30% to 40% risk reduction in recurrent VTE. The American College of Chest Physicians (ACCP) guidelines published in 2016 recommend aspirin if a patient with unprovoked VTE does not continue long-term anticoagulation.

In patients with malignancy, LMWH remains preferable to warfarin; the CLOT trial, in which patients were randomly assigned to LMWH or warfarin, found that 15% of patients treated with warfarin developed recurrent VTE compared with 7.9% of patients treated with LMWH. Anticoagulation should be continued as long as the cancer is active.

The role of non–vitamin K antagonist oral anticoagulants compared with LMWH has not been studied in patients with cancer. Although 6 months of anticoagulation was studied in clinical trials, anticoagulation is recommended for the duration of cancer activity.

Thrombolytic therapy is necessary to treat patients with massive PE and shock from low cardiac output. Growing data, including meta-analyses, support thrombolytic therapy as superior to traditional anticoagulation in select patients with submassive PE who remain normotensive but have poor prognostic features on cardiac ultrasonography and elevated serum troponin and B-type natriuretic peptide levels. For acute DVT, thrombolysis is indicated for massive thrombus leading to impaired venous drainage, severe edema, and acute limb

TABLE 33. Duration of Anticoagulant Therapy for Venous Thromboembolism[a]

Type of Thrombotic Event	Duration of Anticoagulant Therapy
Distal leg DVT	
Provoked or unprovoked, mild symptoms	No anticoagulation suggested, but monitor with serial duplex ultrasonography for 2 weeks
Provoked or unprovoked, moderate-severe symptoms	3 months
Proximal leg DVT or PE	
Provoked (by surgery, trauma, immobility)	3 months
Unprovoked	Extended[b]
Recurrent	Duration of therapy depends on whether VTE events were provoked or unprovoked
Upper extremity DVT, proximal	At least 3 months
Cancer-associated DVT or PE	As long as the cancer is active or being treated
	LMWH is the preferred anticoagulant
Chronic thromboembolic pulmonary hypertension	Extended[b]

DVT = deep venous thrombosis; LMWH = low-molecular-weight heparin; PE = pulmonary embolism; VTE = venous thromboembolism.

[a]Decisions regarding duration of anticoagulation must always weigh the risk of VTE recurrence, risk of bleeding, and patient preference.

[b]Indicates long-term anticoagulation therapy with periodic (such as once per year) re-evaluation of the risks, benefits, and burdens of long-term therapy and discussion of new clinical study results and new anticoagulant drugs.

Data from Kearon C, Akl EA, Ornelas J, Blaivas A, Jimenez D, Bounameaux H, et al. Antithrombotic therapy for VTE disease: CHEST Guideline and Expert Panel Report. Chest. 2016;149:315-52. [PMID: 26867832] doi:10.1016/j.chest.2015.11.026

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ischemia. The main function of an inferior vena cava (IVC) filter is to prevent death from PE. In 2012, the ACCP recommended IVC filters for those with a contraindication to anticoagulation who either have acute PE or acute proximal (above the knee) DVT. If an IVC filter is placed, a temporary filter should be used.

Distal DVT does not usually require anticoagulation. Isolated distal DVT can be monitored with serial Doppler ultrasonography performed 5 to 7 days after the initial event in otherwise healthy, asymptomatic patients. According to ACCP guidelines, anticoagulation similar to that for proximal DVT is suggested in patients with certain risk factors for extension, including a positive D-dimer test result, extensive thrombosis or proximity to proximal veins, no reversible provoking factor for DVT, active cancer, history of VTE, and inpatient status. H

KEY POINTS

HVC

- Most patients with deep venous thrombosis and those with pulmonary embolism who have a good prognosis (defined as age <80 years, no significant comorbidity, and stable vital signs) can be safely managed without hospitalization.
- If patients with deep venous thrombosis or pulmonary embolism require hospitalization, they should be treated initially with low-molecular-weight heparin, fondaparinux, or the non–vitamin K antagonist oral anticoagulants (apixaban or rivaroxaban) instead of unfractionated heparin, unless they are unstable and at risk for requiring emergent surgery or thrombolytic therapy.
- In patients with a provoked thrombosis with reversible risk factors, 3 months of anticoagulation is adequate, but in patients at low bleeding risk with unprovoked VTE or with irreversible risk factors, extended therapy should be considered.

H

Long-term Complications

Patients with DVT or PE can develop long-term complications affecting function and quality of life. Approximately 25% to 40% of patients with symptomatic DVT can develop aspects of postthrombotic syndrome (PTS) and chronic venous insufficiency, which often develop within 2 years of diagnosis. Symptoms of postthrombotic syndrome include pain in the affected limb, heaviness, swelling, stasis dermatitis, and ulceration. It often leads to poor quality of life and contributes to work disability. Treatment includes leg exercises, avoiding dependent positions for lengthy periods, and using compression stockings. Skin moisturizers and a low-moderate potency topical glucocorticoid may be used for stasis dermatitis (see MKSAP 18 Dermatology).

Patients with PE can also develop chronic thromboembolic pulmonary hypertension (see Pulmonary and Critical Care Medicine), cardiopulmonary dysfunction, or decreased exercise tolerance.

Other Sites of Thrombosis

Superficial Vein Thrombosis and Thrombophlebitis

Superficial thrombophlebitis describes thrombus in a vein located near the skin's surface; it is a common inflammatory-thrombotic disorder that does not usually cause significant morbidity or progress to PE. It typically is treated with supportive care, analgesia, warm compresses, and NSAIDs. Imaging is indicated if symptoms progress or swelling occurs. Cannulated veins of the hands and arms often thrombose after infusions and intravenous catheter placement; this condition does not require anticoagulant therapy.

Superficial vein thrombosis (SVT) often affects the lower extremities and is thought to account for 10% of lower extremity thromboses. When affecting the great saphenous vein (also referred to as the greater or long saphenous vein), SVT may progress into the deep venous system. In a randomized trial of fondaparinux versus placebo for lower extremity SVT, it was found that fondaparinux was safe and effective in preventing PE. In patients with lower extremity SVT of at least 5 cm in length or close to the deep venous system, fondaparinux or an alternate anticoagulant is recommended. Anticoagulation may also be indicated for patients with SVT and other thrombophilic risk factors, including cancer or previous DVT. Patients with lower extremity SVT who are not treated initially with anticoagulants should undergo follow-up evaluation in 1 week to assess signs of thrombus progression. Imaging is necessary for persistent or worsening symptoms. H

KEY POINTS

- Patients with lower extremity superficial vein thrombosis managed conservatively with warm compresses, analgesics, and NSAIDs require follow-up evaluation after 1 week to determine whether symptoms have resolved; duplex imaging is indicated for symptoms that persist or worsen.
- In patients with lower extremity superficial vein thrombosis of at least 5 cm in length or close to the deep venous system, or in patients with other thrombophilic risk factors, including cancer or previous venous thromboembolism, therapy with fondaparinux or an alternate anticoagulant is recommended.

Unexplained Arterial Thrombosis

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Thrombophilias do not play a significant role in arterial thrombosis. The primary causes of arterial thrombosis are arteriosclerosis and atrial fibrillation with systemic arterial embolism. Patients with arterial thrombosis due to arteriosclerosis are typically treated with antiplatelet therapy. It is unknown whether patients with arterial clots in whom a strong thrombophilia is found are more effectively treated with antiplatelet therapy or anticoagulants. H

KEY POINT

- Patients with arterial thrombosis due to arteriosclerosis are typically treated with antiplatelet therapy.

Upper Extremity Deep Venous Thrombosis

Upper extremity DVT accounts for 10% all DVT occurrences. Secondary DVT of the upper extremity is much more common than primary (two thirds versus one third). Secondary upper extremity DVT usually occurs with central venous catheter use or malignancy; treatment consists of 3 months of anticoagulation. However, if the catheter will not be removed in the setting of a proximal DVT, anticoagulation should continue as long as the catheter remains in place.

Primary upper extremity DVT is uncommon and usually caused by anatomic abnormalities of the thoracic outlet system leading to axillosubclavian compression and thrombosis (venous thoracic outlet syndrome). Patients are usually young, and thrombus occurs with strenuous upper extremity activity. Expert recommendations vary regarding the use of thrombolysis or thoracic outlet decompression surgery in addition to anticoagulation. ACCP guidelines recommend that treatment of primary and secondary upper extremity DVT follow similar guidelines as lower extremity DVT. Provoked upper extremity DVT should be treated for 3 months.

KEY POINT

- Provoked upper extremity deep venous thrombosis (DVT) should be managed with 3 months of anticoagulation; however, in patients with catheter-associated DVT in whom the catheter will not be removed, anticoagulation should continue for as long as the catheter remains in place.

Anticoagulants

Unfractionated Heparin

Unfractionated heparin works by binding to antithrombin, which leads to activation and potentiation of its action, resulting in inactivation of thrombin and factor Xa.

The activated partial thromboplastin time (aPTT) is used in monitoring patients receiving heparin therapy. In the setting of lupus anticoagulant (which prolongs the aPTT), heparin resistance, or markedly elevated factor VIII, antifactor Xa monitoring can be used. Although ideal dosing has been controversial, a weight-based nomogram is usually used, and most hospitals follow a specific heparin dosing algorithm. Typically, an initial bolus dose of 80 to 100 U/kg is given.

Heparin is available in intravenous and subcutaneous preparations for the treatment of VTE, although the intravenous form is typically used. A parenteral agent should be overlapped with warfarin for 5 days and until the INR is 2 or greater for at least 24 hours.

The rate of heparin-associated major bleeding is approximately 3%. Failure to follow a dosage adjustment algorithm is associated with increased bleeding risk. When major bleeding occurs, protamine sulfate can be administered to reverse anticoagulation. A dose of 1 mg of protamine per 100 units of heparin is recommended. Protamine has its own significant adverse effects, which include allergic reactions, hypotension, bradycardia, and respiratory toxicity.

Although weight-based nomograms for instituting heparin therapy and specific algorithms for adjusting dose based on aPTT results have enhanced the safety and efficacy of unfractionated heparin, variations in bioavailability and potential delay in arriving at a therapeutic dose are still more likely than in patients treated with LMWH. Unfractionated heparin should generally be reserved for patients for whom LMWH is contraindicated or in those who require anticoagulation that can be stopped quickly, generally in anticipation of an invasive procedure or surgery.

Heparin-induced thrombocytopenia is a paradoxical adverse effect of heparin that can result in life-threatening thrombosis (see Platelet Disorders).

KEY POINTS

- A weight-based nomogram is usually used to determine the initial dose of unfractionated heparin, and algorithms are used to calculate subsequent dose modifications based on the activated partial thromboplastin time.
- Protamine sulfate can be administered to reverse the anticoagulant effects of unfractionated heparin.
- Variations in bioavailability of unfractionated heparin lead to an increased likelihood of delay in achieving a steady-state therapeutic dose compared with treatment with low-molecular-weight heparin.

Low-Molecular-Weight Heparin

LMWH is derived from unfractionated heparin through a chemical depolymerization producing smaller fragments that are one third the size of heparin.

LMWH does not affect the aPTT because the smaller fragment size does not bind as readily to thrombin but retains the ability to inactivate factor Xa. Dosing is more predictable and laboratory testing is generally unnecessary. LMWH is cleared through the kidney, and the biological half-life is increased in patients with kidney disease. In obese patients, twice daily dosing is suggested. Although laboratory monitoring is typically unnecessary, it is required when treating patients with stage V chronic kidney disease or severe obesity; anti-Xa levels should be obtained 3 to 4 hours after dosing.

LMWH is preferred to unfractionated heparin. In a meta-analysis of DVT treatment comparing LMWH with unfractionated heparin, LMWH was associated with less major bleeding, decreased mortality, and decreased thrombotic recurrence.

Protamine does not fully reverse the anti-Xa effect of LMWH but provides some benefit in restoring hemostasis; it should be given at a dose of 0.5 to 1 mg of protamine per 1 mg of enoxaparin.

KEY POINTS

- Low-molecular-weight heparin typically does not require laboratory monitoring and is associated with less bleeding, decreased recurrent thrombosis, and improved mortality compared with unfractionated heparin.
- Patients with severe obesity or stage V chronic kidney disease who are treated with low-molecular-weight heparin should have factor Xa levels measured 3 to 4 hours after a dose is administered to assess the adequacy of anticoagulation.

H Fondaparinux

In a clinical trial, fondaparinux, dose adjusted based on patients' weights, was noninferior to enoxaparin with respect to the primary endpoint of recurrent VTE at 3 months (3.9% vs. 4.1%). Fondaparinux is also cleared through the kidney and should be avoided in patients with creatinine clearance less than 30 mL/min. As with LMWH or unfractionated heparin, treatment with fondaparinux and warfarin should overlap for 5 days.

Fondaparinux has no reversal agent. Caution should be used in patients at risk for bleeding because the half-life is 17 hours. Prothrombin complex concentrates (PCCs) and fresh frozen plasma (FFP) have been administered with positive outcomes in patients experiencing bleeding. H

KEY POINT

- Because fondaparinux is cleared through the kidney, it should be avoided in patients with a creatinine clearance less than 30 mL/min.

H Warfarin

Warfarin is a vitamin K antagonist. It inhibits vitamin K epoxide reductase, which leads to inhibition of γ carboxylation of precursor coagulation factors II, VII, IX, and X and proteins C and S. Laboratory monitoring involves the prothrombin time and INR.

Because warfarin lowers protein C levels before inducing its anticoagulant effect, it can initially cause a prothrombotic state. For this reason, for the treatment of acute VTE, it must be administered initially with a parenteral anticoagulant. Warfarin should be initiated as soon as possible after diagnosis of VTE. Typically, unfractionated heparin or LMWH is used with warfarin. As noted previously, the parenteral agent should be given for at least 5 days, and the INR can be measured on day 3; heparin is continued until the INR is 2 or greater for at least 24 hours.

Although non-vitamin K antagonist oral anticoagulants have changed the landscape of treatment for patients with VTE, warfarin remains a reasonable anticoagulant for some patients. This may include patients with known kidney disease and obesity or patients with a mechanical heart valve, for whom alternate oral anticoagulants have not been approved.

Patients must have access to continued outpatient INR monitoring. Studies evaluating the use of cytochrome 2C9 and vitamin K epoxide reductase (VKORC1) pharmacogenetics to guide warfarin therapy have not shown benefit. Common reasons for fluctuations in INR include changes in vitamin K intake, medications, and nonadherence. Studies attempting to decrease INR variability with low-dose daily vitamin K supplementation were unsuccessful, so this supplementation is not indicated.

Bleeding is the most significant complication in patients treated with warfarin, occurring in 1% to 3% of patients per year. The risk is higher when warfarin therapy is initiated and during episodes of concurrent acute illness. Bleeding risk increases further in patients with an INR greater than 5. Independent of INR, bleeding risk is increased in patients older than 75 years or in those with previous stroke, gastrointestinal bleeding, or most other chronic comorbidities. Concomitant aspirin, clopidogrel, and NSAID use increases the bleeding risk. The indication for antiplatelet agents for patients taking warfarin should be carefully reviewed, and dual antiplatelet therapy avoided if possible. Acetaminophen should be used instead of NSAIDs when feasible.

Concern is often expressed when older adults begin oral anticoagulation, often for atrial fibrillation, because age is an important risk factor for stroke and bleeding complications associated with warfarin. Oral anticoagulation may be prematurely excluded as a therapeutic option in these patients because of concerns regarding a "falls risk." The true risk of serious bleeding related to a fall while taking an anticoagulant is unclear, although small studies have not shown an increased risk of major bleeding in patients taking oral anticoagulants who were considered at high risk for falls. Risk factors for falls should be thoroughly evaluated and appropriate steps employed for prevention (see MKSAP 18 General Internal Medicine). Recommendations suggest that neither age nor a risk of falls is reason to withhold warfarin anticoagulation from a patient who has clinical criteria warranting such therapy for VTE or stroke prevention.

Patients with asymptomatic INR elevation between 4.5 and 10 can often be managed by simply withholding warfarin. For INRs greater than 10 in patients without bleeding, oral vitamin K, 2.5 mg, should be given. In patients experiencing bleeding, in addition to vitamin K, three- or four-factor PCCs should be given rather than FFP. Although FFP contains the appropriate clotting factors, it requires thawing and large volumes to correct the INR. Three- and four-factor PCCs contain proteins C and S and factors II, IX, and X; four-factor PCC also contains factor VII. In a clinical trial of vitamin K antagonist-related bleeding, four-factor PCC was found to be noninferior to FFP for hemostatic efficacy. Four-factor PCC is preferred because of its rapid reversal of INR, rapid infusion and administration, and lack of volume overload. Recombinant factor VIIa is not recommended for warfarin reversal.

Bridging therapy, which uses heparin or LMWH for patients in whom warfarin has been stopped for an invasive

H CONT procedure and will be resumed, is not necessary for most patients and is associated with more bleeding complications without additional anticoagulant benefit. The exception to this may be patients with recent VTE (within the past 4 weeks), history of VTE during anticoagulant interruption for surgery, or a procedure with very high VTE risk, such as orthopedic surgery. Bridging is also indicated in patients with atrial fibrillation who have had a stroke or transient ischemic attack in the preceding year, in patients who have multiple risk factors for stroke ($CHADS_2$ score of 5-6), and in most patients with a mechanical heart valve. H

KEY POINTS

- Warfarin must be administered initially with at least 5 days of a parenteral anticoagulant (usually unfractionated or low-molecular-weight heparin) for the treatment of venous thromboembolism.
- HVC Bridging therapy, which uses unfractionated heparin or low-molecular-weight heparin during warfarin discontinuation before an invasive procedure, is not indicated for most patients because it is associated with more bleeding complications without any reduction in thrombotic events.

H Non-Vitamin K Antagonist Oral Anticoagulants

The non-vitamin K antagonist oral anticoagulants (NOACs) have emerged as a safe and effective treatment for certain patients with VTE. In the 2016 CHEST guidelines for DVT and PE treatment, NOACs are suggested as the treatment of choice for anticoagulation in patients without cancer. The NOACs available for use in the United States are dabigatran, rivaroxaban, apixaban, edoxaban, and betrixaban. In clinical trials of patients with VTE, patients were initially treated with a parenteral agent and transitioned to dabigatran or edoxaban. Rivaroxaban and apixaban were studied without concomitant parenteral therapy and were approved as monotherapy for DVT and PE. Dabigatran functions as a direct thrombin inhibitor, whereas the other agents are factor Xa inhibitors. Betrixaban is only approved for DVT prophylaxis (**Table 34**).

Routine coagulation studies do not reliably measure the degree of coagulation activity. However, the thrombin time is quite sensitive to the presence of dabigatran and, if normal, indicates that the anticoagulant effect of dabigatran is no longer significant.

Advantages of the NOACs include no need for routine monitoring, rapid onset of action and short half-life, fixed dosing, and fewer drug-drug interactions. These drugs are as effective as warfarin in the prevention of VTE; although the overall bleeding risk was comparable, less central nervous system bleeding, fatal bleeding, and use of blood product support among patients taking NOACs was seen than with warfarin. The bleeding risk is higher in patients taking aspirin or clopidogrel with a NOAC and is further increased in patients taking dual antiplatelet drugs plus NOACs. These qualities must be considered when choosing the appropriate patient for these therapies. No head-to-head trials have been performed comparing the various NOACs. It must be noted that certain patient groups were excluded from the major trials of the NOACs, including patients with severe obesity (BMI >40), pregnant patients, and those with mechanical heart valves. Nonadherent patients should not be treated with NOACs, and the additional cost of these drugs compared with warfarin may be a barrier for some patients. Few patients with cancer were included in clinical trials, and LMWH is still considered standard of care for VTE in these patients. In patients with antiphospholipid antibody syndrome, the role of NOACs remains unclear, although clinical trials are ongoing. Treatment failures with the use of NOACs in patients with antiphospholipid antibody syndrome have been reported. Dyspepsia and gastrointestinal bleeding were seen more frequently with dabigatran compared with warfarin in clinical trials. In patients with concern for gastrointestinal bleeding, dabigatran may not be the preferred option.

All of the NOACs are at least partially eliminated through the kidney (see Table 34), and the dose must be reduced in patients with advanced chronic kidney disease. Apixaban has the lowest renal elimination, so it is approved for patients undergoing dialysis; however, many physicians still prefer warfarin in patients with kidney disease, and caution should be used.

Bridging therapy is typically unnecessary in patients taking NOACs. Discontinuation of the NOAC depends on the half-life of the drug, the type of procedure, and the patient's kidney function. NOACs should be stopped 24 to 48 hours before surgery with moderate bleeding risk and 72 hours before surgery with higher bleeding risk. In patients with impaired kidney function, NOACs should be stopped earlier. For procedures with low bleeding risk, NOACs can be resumed promptly when effective hemostasis is secured. For procedures with higher rates of bleeding, reinstitution is usually delayed 2 to 3 days.

The standard approach to patients experiencing bleeding involves hemodynamic monitoring and resuscitation with fluid and blood products. Activated charcoal can be considered if the NOAC was ingested recently (<6 hours). Hemodialysis can be considered with dabigatran therapy if new kidney disease is found. No specific antidote is available for bleeding associated with rivaroxaban, apixaban, or edoxaban. For patients experiencing major bleeding while taking these agents, fibrinolytic agents such as tranexamic acid or ε-aminocaproic acid may be used. Although three- and four-factor PCCs and recombinant factor VIIa have been used in NOAC-associated bleeding, their benefit has not been confirmed in randomized trials, and the data remain unclear. Idarucizumab, a monoclonal antibody fragment, binds free and thrombin-bound dabigatran and neutralizes its activity. In a phase 3, multicenter, prospective, cohort trial, idarucizumab was found to be safe and effective in reversing the anticoagulant effects of dabigatran in patients who either experienced serious, overt, life-threatening bleeding determined to require

TABLE 34. Key Features of the Non-Vitamin K Antagonist Oral Anticoagulants	Dabigatran	Rivaroxaban	Apixaban	Edoxaban	Betrixaban
Class of anticoagulant	Direct factor IIa inhibitor	Direct factor Xa inhibitor	Direct factor Xa inhibitor	Direct factor Xa inhibitor	Direct factor Xa inhibitor
T_{max} (h)	2	3	3	1-2	3-4
Half-life (h)	12-17	7-11	9-14	9-11	20
Protein binding	35%	95%	87%	54%	60%
Renal elimination	80%	66% (33% as active metabolite)	25%	35%	5%
FDA-approved indications	Atrial fibrillation VTE treatment	Atrial fibrillation VTE treatment[a] VTE prevention	Atrial fibrillation VTE treatment[a] VTE prevention	Atrial fibrillation VTE treatment	Extended VTE prophylaxis
Reversal agent	Idarucizumab	No	No	No	No
Dosing					
Atrial fibrillation	CrCl >30 mL/min: 150 mg twice daily CrCl 15-30 mL/min: 75 mg twice daily CrCl ≤15 mL/min: do not use	CrCl >50 mL/min: 20 mg once daily CrCl 15-50 mL/min: 15 mg once daily CrCl ≤15 mL/min: do not use	5 mg twice daily 2.5 mg twice daily if ≥2 criteria present: (a) ≥80 years of age (b) Weight ≤60 kg (132 lb) (c) Creatinine ≥1.5 mg/dL (133 µmol/L)	60 mg once daily CrCl 15-50 mL/min: 30 mg once daily CrCl >95 mL/min: do not use	NA
VTE prevention	NA	10 mg once daily	2.5 mg twice daily	NA	160 mg day 1; 80 mg/d for 35-42 days
VTE treatment	CrCl >30 mL/min: 150 mg twice daily CrCl <30 mL/min: do not use	CrCl >30 mL/min: 15 mg twice daily × 3 wk, then 20 mg once daily CrCl ≤30 mL/min: do not use	VTE treatment: 10 mg twice daily × 1 wk, then 5 mg twice daily Reduction in VTE recurrence: 2.5 mg twice daily	60 mg once daily 30 mg once daily with the following criteria: CrCl 30-50 mL/min Weight ≤60 kg (132 lb) Concomitant p-glycoprotein inhibitor use	NA

CrCl = creatinine clearance; h = hour; NA = not applicable; T_{max} = time to maximum concentration; VTE = venous thromboembolism.

[a]Approved as monotherapy for VTE.

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a reversal agent or who required an urgent invasive procedure that could not be delayed. Idarucizumab was FDA approved for this indication in October 2015. Specific antidotes for this class of agents continue to be developed. H

KEY POINTS

- The non–vitamin K antagonist oral anticoagulants dabigatran, rivaroxaban, apixaban, edoxaban, and betrixaban have a rapid onset of activity, no need for laboratory monitoring, and therapeutic effect that is less likely than warfarin to be influenced by changes in diet or medications.

(Continued)

KEY POINTS *(continued)*

- Non–vitamin K antagonist oral anticoagulants (NOACs) are as effective as warfarin in preventing and treating venous thromboembolism; although the overall rate of bleeding is comparable, patients taking a NOAC have less central nervous system bleeding and less fatal bleeding.
- The non–vitamin K antagonist oral anticoagulants should not be used in patients with valvular heart disease or severe obesity, or in those who are pregnant or nonadherent; patients with active cancer are better treated with low-molecular-weight or unfractionated heparin.

Hematologic Issues in Pregnancy

Gestational Anemia

During pregnancy, an increase in plasma volume occurs that is greater than the increase in erythrocyte mass, resulting in a physiologic decrease in measured hemoglobin level, although it typically remains greater than 10.5 g/dL (105 g/L). If the hemoglobin level decreases further, additional evaluation of the anemia is warranted. Iron, vitamin B_{12}, and folate levels should be tested.

Sickle Cell Disease

The physiologic stresses of pregnancy are especially challenging for women with sickle cell disease (SCD). Patients are unable to produce the expected increase in erythrocyte mass, and folate requirements increase because of the rapid turnover of erythrocytes, requiring additional folate supplementation. Iron and vitamin B_{12} stores must also be monitored. Although expert opinion is not uniform, recent guidelines from the National Institutes of Health did not recommend prophylactic transfusions in pregnancy for women with sickle cell anemia. Other experts disagree, suggesting prophylactic transfusion in pregnant women during the third trimester to achieve a hemoglobin level of 9 g/dL (90 g/L) or reserving such transfusions for women with previous fetal loss, more severe anemia, frequent acute painful events, or history of acute chest syndrome. However, frequent transfusions may lead to alloimmunization, increasing the risk of hemolytic disease of the newborn. Although routine use of prophylactic transfusion is debatable, pregnant women with more severe and symptomatic anemia should be transfused as should any woman with acute chest syndrome or stroke. Pregnant women with SCD should be monitored closely with monthly complete blood counts in collaboration with a hematologist.

H In women with SCD, pregnancy affects multiple organ systems in addition to causing anemia. The risk of venous thromboembolism is increased, and prophylactic anticoagulation should be administered in hospitalized patients. The increased cardiopulmonary demands of pregnancy increase the risk of pulmonary hypertension, with an associated 16% mortality risk. Suggestive clinical features should be evaluated by echocardiography.

Medications used to control SCD, such as hydroxyurea and chelating agents, must be discontinued during pregnancy. Painful vaso-occlusive crises increase during pregnancy; pain should be managed with narcotic analgesics, and NSAIDs should be avoided after the 30th week of gestation.

Pregnant patients with SCD are also at increased risk for complications of the pregnancy itself, including intrauterine growth restriction, eclampsia, preterm labor, placental abruption, and stillbirth. H

KEY POINTS

- Although the use of routine prophylactic transfusion in pregnant women with sickle cell anemia remains controversial, transfusions should be given to those patients with more severe and symptomatic anemia or those who develop additional complications such as acute chest syndrome or stroke.
- Medications used to control sickle cell disease, such as hydroxyurea and chelating agents, must be discontinued during pregnancy.

Thrombocytopenia in Pregnancy

Gestational Thrombocytopenia

Gestational thrombocytopenia affects approximately 5% of pregnant women. The cause is uncertain, but it may be a milder form of immune thrombocytopenic purpura. Most patients are asymptomatic, with platelet counts greater than 100,000/µL (100×10^9/L), although platelet counts may reach a nadir of 70,000/µL (70×10^9/L). Patients with gestational thrombocytopenia have no history of thrombocytopenia, and the platelet count does not decrease until late in gestation. The fetus is unaffected, intervention is unnecessary, and platelet counts spontaneously return to normal after delivery.

KEY POINT

- HVC Patients with gestational thrombocytopenia have no history of thrombocytopenia, and because the thrombocytopenia is not severe, without predisposition to bleeding, and platelet counts resolve spontaneously, no treatment is necessary.

Immune Thrombocytopenic Purpura

Immune thrombocytopenic purpura (ITP) (see Platelet Disorders) can occur in women of childbearing age and may present during pregnancy. Differentiating ITP from gestational thrombocytopenia may be difficult, but features suggesting ITP include earlier presentation (first trimester), lower platelet count nadir (<70,000/µL [70×10^9/L]), and history of thrombocytopenia before pregnancy (even if it was only mild). If the platelet count remains greater than 30,000/µL (30×10^9/L), the pregnancy is not at risk. Patients should receive intravenous immune globulin or glucocorticoids at any time during pregnancy if the platelet count decreases below 30,000/µL (30×10^9/L). The target platelet count for delivery (vaginal or cesarean section) is 50,000/µL (50×10^9/L), and therapy should begin approximately 1 week before the expected delivery date to achieve that goal. Neuraxial anesthesia requires a platelet count greater than approximately 80,000/µL (80×10^9/L).

ITP autoantibodies can cross the placenta and affect the fetus; 20% to 30% of neonates are reported to have platelet counts less than 50,000/µL (50×10^9/L) (especially if an older sibling was born with thrombocytopenia). Fetal platelet counts can continue to decrease for 2 to 5 days after delivery. Fetal

thrombocytopenia is not influenced by maternal treatment with either glucocorticoids or intravenous immune globulin. Despite the increased likelihood of neonatal thrombocytopenia, the risk of intracerebral hemorrhage is less than 1% and is unaffected by delivery by cesarean section.

KEY POINTS

- Differentiating immune thrombocytopenic purpura from gestational thrombocytopenia may be difficult, but suggestive features include earlier presentation (first trimester), lower platelet count nadir (<70,000/µL [70×10^9/L]), and history of thrombocytopenia before pregnancy.
- Women should receive intravenous immune globulin or glucocorticoids to treat immune thrombocytopenic purpura if the platelet count decreases below 30,000/µL (30×10^9/L) at any time during the pregnancy as well as 1 week before delivery to achieve a platelet count of at least 50,000/µL (50×10^9/L) for delivery or 80,000/µL (80×10^9/L) if neuraxial anesthesia is anticipated.

H Microangiopathy of Pregnancy

The thrombotic microangiopathies of pregnancy encompass a spectrum of disorders presenting with clinical features of microangiopathic hemolytic anemia and thrombocytopenia. The differentiating features of these disorders are noted in Table 35.

The distinction between HELLP (Hemolysis, Elevated Liver enzymes, Low Platelets) syndrome, pre-eclampsia, and acute fatty liver of pregnancy may be difficult but is not crucial because management for all of these is supportive and focused on early delivery. Thrombotic thrombocytopenic purpura and hemolytic uremic syndrome (see Platelet Disorders) can also occur during pregnancy (see Table 35) and may require additional therapy, including plasma exchange or the anticomplement agent eculizumab. H

KEY POINTS

- HELLP (Hemolysis, Elevated Liver enzymes, Low Platelets) syndrome, pre-eclampsia, and acute fatty liver of pregnancy present with microangiopathic hemolysis and, usually, thrombocytopenia; although distinguishing among these disorders may be difficult, the management of each is supportive and involves early delivery.
- Thrombotic thrombocytopenic purpura and hemolytic uremic syndrome may present during pregnancy and are important to distinguish from other causes of microangiopathic hemolysis and thrombocytopenia because more specific therapy, such as plasma exchange, may be indicated.

Thrombophilia and Venous Thromboembolism in Pregnancy

Epidemiology, Pathophysiology, and Risk Factors

The risk of venous thromboembolism (VTE) in pregnancy is higher than in the general population, but the absolute risk is still low (<1%). Nevertheless, pulmonary emboli account for about 9% of maternal deaths. The increased risk is a result of venous stasis caused by uterine compression and increased venous capacitance, increased circulating procoagulant factors,

TABLE 35. Clinical and Laboratory Features of the Thrombotic Microangiopathies of Pregnancy

Feature	Pre-eclampsia	HELLP	AFLP	TTP	HUS
Hypertension	+++	+++	+	+/−	+
Proteinuria	+++	++	+/−	+	+
Abdominal pain	+/−	++	++	+/−	+/−
Jaundice	+/−	+/−	++	+/−	+/−
Neurologic findings	+/−	+/−	+/−	++	+/−
Thrombocytopenia	+	+++	+	+++	++
Hemolysis	+/−	+++	+	+++	++
Kidney disease	+	+	+/−	+	+++
Disseminated intravascular coagulation	+/−	++	+++	+/−	+/−
Elevated liver chemistry test results	+	+++	+++	+/−	+/−
Hypoglycemia	+/−	+/−	+++	+/−	+/−

AFLP = acute fatty liver of pregnancy; HELLP = Hemolysis, Elevated Liver enzymes, and Low Platelets; HUS = hemolytic uremic syndrome; TTP = thrombotic thrombocytopenic purpura.

+++ = always present.

++ = usually present.

+ = likely to be present.

+/− = may or may not be present.

and decreased circulating protein S. VTE risk increases further in the postpartum period after endothelial injury during delivery and an additional increase in the procoagulant factors. Factors that further increase VTE risk include multiple births, advanced maternal age, obesity, smoking, cesarean section, and varicose veins.

The possibility of VTE is increased in patients with inherited thrombophilias. However, testing for these disorders in pregnancy is complicated and is not routinely recommended. Deep venous thrombosis most often occurs in the left lower extremity.

Prevention

Patients with a history of an idiopathic VTE, VTE associated with pregnancy or oral contraceptives, or a hereditary thrombophilia require antenatal and postpartum anticoagulation continuing for 6 weeks following delivery. Low-molecular-weight heparin (LMWH) should be used in the antenatal setting because warfarin is teratogenic and the non–vitamin K antagonist oral anticoagulants have not been studied in pregnancy. LMWH can be transitioned to unfractionated heparin (for its shorter duration of action) around the time of delivery.

Diagnosis

Diagnosing a deep venous thrombosis requires evaluation by Doppler ultrasonography. Pulmonary embolism diagnosis in pregnancy presents a challenge because concerns about fetal radiation exposure may limit use of CT angiography, which is the definitive diagnostic test. Although D-dimer levels rise during pregnancy, patients at low risk (Wells score ≤4) who have a normal D-dimer level do not require further evaluation (see Thrombotic Disorders). In women for whom the risk remains moderate or high, a ventilation-perfusion lung scan should be performed. If the ventilation-perfusion scan result is normal, pulmonary embolism is ruled out, and if marked perfusion defects unmatched by ventilation abnormalities are noted, the diagnosis is likely. If the ventilation-perfusion scan result remains indeterminate, the patient should undergo CT angiographic imaging.

Treatment

LMWH is the treatment of choice for pregnant women with VTE. Therapy should begin with the standard recommended dose and then be titrated to the anti-Xa level because weight-based dosing algorithms that customarily eliminate the need for anti-Xa monitoring may not be reliable during pregnancy. Warfarin is teratogenic and must be avoided in the first trimester, but it is safe to resume after delivery and with breastfeeding. The non–vitamin K antagonist oral anticoagulants have not been evaluated in this setting, so they cannot be recommended. Thrombolytic therapy raises the risk of maternal hemorrhage and should be reserved for life-threatening situations. LMWH must be interrupted at least 24 hours before delivery; unfractionated heparin can be used instead and discontinued as labor progresses or several hours before cesarean section. Postpartum treatment is begun as soon as hemostasis is achieved. Postpartum anticoagulation should continue for at least 6 weeks. The goal is for a total anticoagulation period of 3 to 6 months.

KEY POINTS

- Patients with a history of idiopathic venous thromboembolism (VTE), VTE associated with pregnancy or oral contraceptives, or a hereditary thrombophilia require antenatal and postpartum anticoagulation continuing for 6 weeks after delivery.
- Unfractionated or low-molecular-weight heparin should be used for anticoagulation during pregnancy in patients with venous thromboembolism because warfarin is teratogenic and the non–vitamin K antagonist oral anticoagulants have not been studied in pregnancy; warfarin is safe to resume postpartum and while breastfeeding.

Issues in Oncology

Introduction

Technological advances are changing the field of medical oncology at a rapid rate. The successful incorporation of immune checkpoint inhibitors and other immunologic strategies to facilitate activation of the patient's own immune system as part of the standard treatment of many malignancies has been a major advance. Other changes include expanded routine use of molecular profiling in several tumor types and the resultant application of precision therapeutics, which are selected on the basis of specific mutations within a person's tumor. "Precision medicine," or "precision therapeutics," is a term often used interchangeably with "personalized medicine," but rather than denoting therapeutic approaches tailored to individual patients, precision medicine focuses on identifying effective approaches for patients based on genetic, environmental, and lifestyle factors. However, many aspects of oncology, including the use of traditional histologic diagnosis and clinical staging, as well as extensive use of cytotoxic chemotherapy, radiation therapy, and surgery, remain central to current oncologic practice.

Despite the many technological advances, careful clinical evaluation and staging, understanding and communicating realistic goals of care, and recognizing and promoting patient preferences remain central to the practice of oncology. Meaningful progress has been made in many cancers. However, most cancers, once metastasized, are treatable but still incurable. Oncology has also become the focus of concerns regarding unsustainable costs in care, specifically in terms of the costs of new drugs, and the impact of financial toxicity has become an important consideration in oncologic care.

Staging

In order to plan a proper treatment strategy, a clinician must first determine the stage, or extent, of the cancer. Early-stage cancers often can be cured by local therapy, such as surgery or radiation, whereas more advanced-stage cancers require a more systemic approach. With the use of the TNM cancer staging system, most solid tumors are staged on a scale of 1 to 4. In the TNM system, *T* (T1-T4) refers to the size or extent of local invasion of the primary tumor, *N* (N0-N3) indicates locoregional lymph node involvement, and *M* indicates the absence (M0) or presence (M1) of distant metastases. If the main tumor, cancer in nearby lymph nodes, or metastasis cannot be measured, this is denoted with X (for example, TXNXMX). Some hematologic tumors have unique tumor-specific staging systems.

The required studies and imaging techniques will be dependent on the expected behavior pattern of each cancer type and will differ from one tumor to the next. Therefore, a proper cancer evaluation requires knowledge of the specific disease entity so that the necessary tests can be done. Tests with a very low yield should not be ordered in the absence of specific directing symptoms. For example, bone and brain imaging is appropriate in the staging of patients with lung cancer because bone and brain metastases are common in the early course of this disease. However, patients with presumed locoregional colorectal cancer rarely present with bone or brain metastases; consequently, routine imaging of these sites as part of staging in the absence of specific symptoms is not necessary. Thoughtfully performed staging is generally the most accurate prognostic indicator and largely dictates the therapeutic strategy for patients with cancer.

KEY POINTS

- Most solid tumors are staged using the TNM cancer staging system, in which *T* represents the size or extent of local invasion of the primary tumor (T1-T4), *N* indicates locoregional lymph node involvement (N0-N3), and *M* indicates the absence (M0) or presence (M1) of distant metastases.
- HVC Diagnostic imaging may be crucial in determining the accurate stage of a tumor, but patients with localized tumors that have a low likelihood of distant metastases to certain sites, such as bone or brain, should not have routine imaging of those sites.
- Thoughtfully performed staging is generally the most accurate prognostic indicator and largely dictates the therapeutic strategy for patients with cancer.

Performance Status

Performance status is a means of quantifying how medically fit a patient is overall. A good performance status predicts favorable tolerance and response to treatment. Patients with a poor performance status are much more likely to experience serious or life-threatening toxicity and much less likely to benefit from treatment.

It is important to differentiate patients with a poor performance status who are debilitated due to chronic comorbidities from patients who would otherwise be medically fit but are acutely debilitated by their disease. The latter situation may warrant an attempt at aggressive treatment, because reversing the cancer process is the only thing that will improve the patient's overall condition, whereas the former may need to be treated with less aggressive treatment or possibly no specific anticancer treatment. Cancer drug approvals are based on clinical trials, virtually all of which limit participants to patients with good performance status, so the degree to which the results of these trials are relevant to patients with poor performance status is questionable.

In addition, age alone should not be regarded as a reason to avoid aggressive treatment. Elderly patients who are otherwise medically fit and healthy and hence have a good performance status may tolerate aggressive therapy well, whereas younger patients with several medical comorbidities resulting in a poor performance status may be unable to tolerate aggressive treatment.

The two most commonly used performance status scales are the Karnofsky score and the Eastern Cooperative Oncology Group/World Health Organization system (also called the Zubrod score). These are outlined and contrasted in **Table 36**.

KEY POINTS

- Patients with poor performance status may be conceptualized as composing two groups: patients who are debilitated by chronic comorbidities and may need less aggressive treatment and patients who are debilitated by the cancer but are otherwise medically fit and might benefit from aggressive treatment.
- Most clinical trials used to determine treatment efficacy are based on patients with good performance status.

Goals of Therapy

Clear and candid communication between clinician and patient is essential for good oncologic care. When communicating treatment options and recommendations, clinicians must work to establish realistic treatment goals. When cure is not realistically possible, goals such as lengthening survival, shrinking a tumor, controlling disease growth, palliation or prevention of disease-related symptoms, and maintaining quality of life at a level acceptable to the patient should be considered. The potential benefits of treatment have to be weighed and discussed along with their risks and toxicities. Patients with incurable cancer face choices of more aggressive therapy associated with more unpleasant and potentially dangerous side effects that are designed to prolong their life. The gravity of those side effects is weighed against the duration of prolonged survival, but all patients have a unique perspective on how they interpret this equation. Similarly, more aggressive initial therapy may result in prolonged remission or disease-free survival but no change in overall survival. Some patients would gladly accept the increased

TABLE 36. Oncology Performance Status Systems

ECOG/WHO Performance Status[a]
0 - Fully active; no restrictions on activities
1 - Unable to do strenuous activities, but able to carry out office work, light housework, or sedentary activities
2 - Able to walk and manage self-care, but unable to work; out of bed or chair >50% of waking hours
3 - Confined to bed or chair >50% of waking hours; capable of limited self-care
4 - Moribund. Fully confined to a bed or chair; unable to do any self-care
5 - Death
Karnofsky Performance Status
100 - Normal; no symptoms or evidence of disease
90 - Minor symptoms, but able to carry on normal activities
80 - Some symptoms; normal activity requires effort
70 - Unable to carry on normal activities, but able to care for self
60 - Needs frequent care for most needs; some occasional assistance with self-care
50 - Needs considerable assistance with self-care and frequent medical care
40 - Disabled; needs special care and assistance
30 - Severely disabled; hospitalized
20 - Very ill; significant supportive care is needed
10 - Actively dying
0 - Death

ECOG = Eastern Cooperative Oncology Group; WHO = World Health Organization.

[a]Also called the Zubrod score.

toxicity of such therapy for a prolonged period without cancer, whereas others would not.

More recently, as costs of anticancer treatments have increased astronomically, the concept of financial toxicity—the impact that the cancer diagnosis will have on the patient's financial stability and overall well-being—has received greater attention. A diagnosis of cancer has been shown to be a leading cause of personal bankruptcy, and studies show financial worries contribute to the anxiety of many patients with cancer. Inability to meet copays or coinsurance requirements, especially for expensive oral anticancer medications, is a leading cause of failure to properly receive therapy. A clear understanding of the goals of care and the toxicities, including financial toxicity, is necessary for patients and physicians to make informed choices in treatment options. This concept of financial toxicity goes beyond individual patients in affecting the overall health care economy. Quantifying the overall benefit of extending a patient's life by relatively short periods (less than 2 months' median benefit) and contrasting that benefit by the financial cost of care require complex ethical, economic, and public health decisions.

Early-stage cancers often have a high chance of cure. With increasing cancer stage, however, the possibility of cure diminishes. Most metastatic cancers are treatable but not curable. This is especially true for patients with poor performance status due to chronic medical comorbidities or those who have not been able to tolerate initial treatment attempts. For such patients or for those who have exhausted standard treatment options, supportive, comfort-oriented care may be most appropriate. Use of adequate analgesia, as well as support from palliative medicine specialists, is important throughout the continuum of care but particularly so in patients with pain or with symptoms from either disease or therapy. Recent studies suggest that such palliative care, when instituted as part of early aggressive therapy, helps patients better tolerate their cancer care and should not be delayed to the point at which no more active cancer therapy is considered.

KEY POINTS

- The potential benefits of treatment must be weighed and discussed along with their risks and toxicities, including financial toxicity, as the costs of anticancer treatments have increased significantly.
- Palliative care should be instituted early on in the management of patients with cancer and not reserved for the time when they are no longer receiving cancer therapy.

Understanding Cancer Terminology

The field of oncology has its own language and terminology that is often misunderstood. A clear understanding of this terminology is necessary to facilitate informed discussions and develop realistic treatment goals.

The one pure and simple term is *cure*. *Cure* means, as one would expect, that the cancer is gone, no further treatment is required, and the patient will live out his or her life without seeing that type of cancer again. This should not be confused with *overall survival*, which is defined as the amount of time from initiation of a treatment until death. Overall survival is often misunderstood by patients to be synonymous with *cure*. Median survival benefits that are reported in studies are typically offered to patients as indicators of how long they will live, but it must be understood that medians of studies are meaningful for populations but not for individual patients. This can be further compounded by the frequent use of the phrase *significant improvement in survival*, in which *significant* refers to the statistical certainty of the finding but is often misinterpreted as a *substantial* improvement in survival. Many drugs have been approved with *significant* improvements in survival that are limited to less than 2 or 3 months, a quantity that most would agree is not substantial. Furthermore, one must be cautious about interpreting nonrandomized comparisons of older versus newer survival data, because screening and surveillance techniques are leading to more accurate staging and earlier recognition of smaller volumes of cancer recurrence, creating a lead-time bias that may appear to amplify the benefits of a newer treatment compared with an older one. Thus, randomized controlled trials are the optimal means of comparing one treatment with another.

One of the most misrepresented and misunderstood terms is *progression-free survival*. It is the time from when a treatment is started until that treatment is no longer controlling the tumor. Because the duration of progression-free survival is defined by cancer progression or death, whichever occurs first, the word *survival* is maintained in the term; however it has little to do with overall survival and is often, and sometimes deliberately, confused with it. *Progression-free interval* would more accurately describe what is referred to as progression-free survival.

Response rate is the percentage of patients in a clinical trial whose tumor shrinks to a prespecified degree with treatment as indicated on imaging studies, such as CT or MRI. Response rate has not been shown to correlate with other metrics, such as overall survival, but there is a strong emotional benefit to patients when the tumor is regressing, and in symptomatic patients, such shrinkage is likely to alleviate, prevent, or delay symptoms.

KEY POINT

- The terminology used in oncology is often misunderstood and can affect patients' understanding of their disease; an increase in overall survival is not synonymous with cure, median survival is only relevant to populations (not individuals), and significant improvements seen in clinical trials do not necessarily mean substantial improvements.

Treatment Approaches

The classic cancer treatment modalities are surgery, radiation, and chemotherapy. As current technology has advanced, chemotherapy is best subdivided into the more classic cytotoxic chemotherapies, targeted or precision therapies, and immunotherapies.

Traditional Cancer Therapies

For tumors that are localized, surgical resection remains at the center of treatment. Following resection, the patient is never at risk for harm from the tumor that has been removed but rather from microscopic tumors that may still remain in the patient. Neoadjuvant (preoperative) or adjuvant (postoperative) treatment with radiation, chemotherapy, or both, may be used to eradicate residual microscopic disease and increase the chance for cure. The nature of the treatment, in terms of chemotherapy, radiation, or both, will depend on the type of tumor and its characteristic pattern of spread. Neoadjuvant and adjuvant therapy acknowledge the fact that some patients being treated would be cured with surgery alone and are therefore exposed to needless additional toxicity. Randomized trials are crucial in determining whether, for any given population of patients, neoadjuvant or adjuvant therapy improves some important outcome, such as cure, overall survival, or disease-free survival, without unacceptable toxicity. Conversion therapy seeks to convert an unresectable tumor to a resectable one by shrinking it away from critical structures and creating a plane for resection that previously was lacking; this differs from neoadjuvant chemotherapy, which is used for micrometastases of an already resectable tumor.

Balancing therapy efficacy and toxicity—in particular, the need for adjuvant or neoadjuvant therapy or the desired aggressiveness of the primary chemotherapy, radiation therapy, or surgical therapy for populations of patients—has traditionally been based on stage, pathology, and understanding of the overall behavior of that tumor. Currently available imaging and laboratory studies are somewhat limited in terms of their ability to identify which patients will or will not be at risk for recurrence of cancer after definitive surgery. Numerous tumor markers, gene panels, and other technologies are available, but few are definitive. The preferred assay would be predictive, meaning that it could identify the subset of those patients who are at risk for recurrence and who will benefit from an intervention such as adjuvant chemotherapy to delay or prevent such recurrence. An example of this is a commercially available 21-gene assay for breast cancer that identifies a patient population who is at risk for recurrence and will have that risk lowered by chemotherapy. Such predictive tools are highly useful because they provide actionable information in terms of who to treat and who not to treat. Unfortunately, attempts to develop such predictive assays have rarely been successful. A similar multigene assay in colorectal cancer is prognostic in that it can quantitate a patient's risk of recurrence, but fails to identify which patients, if any, will have their risk lowered by

chemotherapy. Therefore, it does not provide information that is definitive for decision making. Such prognostic tests are of much less value than risk factors that can be used to define better therapy, but these tests still may be of value to individual patients who may rely on that statistical information to better plan their lives.

Cancer Treatment During Pregnancy

According to the International Network on Cancer, Infertility, and Pregnancy (INCIP), prenatal exposure of children to maternal cancer with or without treatment has not been shown to impair physical or mental development in early childhood.

KEY POINTS

- Treatment with radiation, chemotherapy, or both, in addition to definitive surgery is called neoadjuvant if administered preoperatively or adjuvant if administered postoperatively.
- Predictive assays can identify the subset of patients who will or will not benefit from an intervention, whereas prognostic assays can identify the subset of patients at higher or lower risk but not those who will or will not benefit from an intervention.

Precision Medicine

Current developments in chemotherapy are centered on creating agents that target specific aspects of a tumor cell. Although in theory these agents should be more selective and have fewer toxicities than older, conventional chemotherapies, this has not always turned out to be the case. Many of the signaling pathways that are hyperactive in tumor cells remain at least somewhat active in normal cells, and so disruption of these pathways can produce considerable side effects.

The goal of precision medicine is to identify specific aspects of the tumor that can guide clinicians in deciding which therapies are or are not appropriate for a particular patient. Markers can be either inclusionary, in that they include a patient in a therapy that otherwise might not be considered, or exclusionary, in that they exclude a patient from a treatment that otherwise might have been used.

An example of an inclusionary marker is the V600 *BRAF* mutation in melanoma. Specific *BRAF* inhibitors, such as vemurafenib and dabrafenib, would only be appropriate for use in melanomas that harbor this specific mutation. Melanomas lacking this mutation would not be treated with these agents. Trastuzumab, a monoclonal antibody against the human epidermal growth factor receptor 2 (*HER2*) on the cell surface, is only active in those breast or gastroesophageal tumors that overexpress *HER2*. In short, targeted therapy only works if the target is both present and clinically relevant.

Examples of exclusionary markers are *RAS* mutations. The anti–epidermal growth factor receptor (EGFR) monoclonal antibodies cetuximab and panitumumab were initially thought to be appropriate for treatment of all colorectal cancers. Subsequently, it was determined that any tumors harboring mutations in either the *KRAS* or *NRAS* gene were not only highly resistant to responding to these agents, but in fact the growth of the *RAS*-mutated tumors may even be accelerated by these agents. All metastatic colorectal cancers now require tumor genotyping for *KRAS* and *NRAS* mutations, and only those tumors lacking the mutations are appropriate for treatment with cetuximab or panitumumab.

KEY POINT

- Precision medicine refers to agents that target specific aspects of a tumor cell; inclusionary markers include patients in a therapy that otherwise might not be considered, and exclusionary markers exclude patients from a treatment that might otherwise be used.

Immunotherapy

Immunotherapy agents are drugs that do not attack the cancer directly but rather mobilize the patient's own immune system to do so. This has become possible through the identification of "immune checkpoints," which serve as "brakes" on the immune system in order to prevent the immune system from attacking itself and causing autoimmune diseases. Antibodies that block these checkpoints release the brakes on the immune system and allow it to aggressively attack the tumor. Side effects are related to resultant autoimmunity from the less-regulated immune system. The first immune checkpoint identified was the antigen-4 (A-4) molecule on the surface of the cytotoxic lymphocyte (T cell), hence its designation cytotoxic T-lymphocyte antigen-4 (CTLA-4). Antibodies that block CTLA-4, such as ipilimumab, have been successful in mobilizing the immune system against melanoma, renal cell carcinoma, and other malignancies. The other immune checkpoint that has been successfully exploited is the programmed death 1 (PD-1) receptor. Anti–PD-1 agents, such as nivolumab or pembrolizumab, have shown substantial and durable activity against melanoma and non–small cell lung cancers, as well as other tumors. Agents against the ligand of PD-1 have also shown important clinical activity. Combinations of these agents are showing further effectiveness but with increased toxicity and also considerable expense. Many other checkpoints in the immune system are now being exploited by numerous drugs in development, and it is possible that immunotherapy will substantially change the outlook for patients with many different types of cancer in the foreseeable future.

KEY POINT

- Immune checkpoints prevent the immune system from attacking normal tissues (self), but immunotherapy can take advantage of this by inhibiting the checkpoints and allowing the immune system to be more aggressive and so attack cancer cells.

Breast Cancer

Introduction

Breast cancer is the most common type of cancer in women in the United States, excluding skin cancers. In 2015, there were an estimated 231,840 new invasive breast cancer cases and 60,290 in situ cases diagnosed. The lifetime risk of developing invasive breast cancer is 12.4% (about 1 in 8) for U.S. women. There were an estimated 40,290 deaths from breast cancer in the United States in 2015: it remains the second leading cause of cancer death in women. The lifetime risk of dying from breast cancer for U.S. women is 2.76%. Breast cancer is rare in men.

Epidemiology and Risk Factors

Breast cancer incidence increases with age. The incidence per decade of life is listed in **Table 37**. The median age of diagnosis in women is 61 years. Incidence rates are highest in non-Hispanic white and black women. Other risk factors for breast cancer are listed in **Table 38**.

Patients with deleterious *BRCA1* or *BRCA2* gene mutations have a 50% to 85% lifetime risk of breast cancer. Patients who received chest wall irradiation between ages 10 and 30 years for treatment of Hodgkin lymphoma have a 30% to 50% risk of breast cancer. Atypical breast lesions, such as atypical hyperplasia or lobular carcinoma in situ, result in a cumulative 30-year breast cancer risk of up to 35%.

Patients with possible hereditary breast cancer syndromes should be referred to a genetic counselor for assessment and possible genetic testing. The criteria for genetic testing are outlined in **Table 39**.

TABLE 37. Breast Cancer Risk per Decade of Life for U.S. Women[a]

Decade of Life	Fractional Risk for Being Diagnosed with Breast Cancer in the Next 10 Years
20s	1 in 1674
30s	1 in 225
40s	1 in 68
50s	1 in 42
60s	1 in 28
70s	1 in 26
80s	1 in 33

[a]All Races.

Data from Howlader N, Noone AM, Krapcho M, Garshell J, Miller D, Altekruse SF, et al. SEER Cancer Statistics Review, 1975-2012, National Cancer Institute. Bethesda, MD. http://seer.cancer.gov/csr/1975_2012/. Based on November 2014 SEER data submission. The Surveillance, Epidemiology, and End Results Program (SEER) Website. Updated November 18, 2015. Accessed February 7, 2018.

KEY POINTS

- Breast cancer incidence increases with age, with the highest incidence in non-Hispanic white women and second highest in black women.
- Women with possible hereditary breast cancer syndromes should be referred to a genetic counselor for possible genetic testing for breast cancer susceptibility genes, such as *BRCA1* and *BRCA2*.

Chemoprevention and Other Risk Reduction Strategies

Breast cancer screening for average-risk women is discussed in MKSAP 18 General Internal Medicine. The American Cancer Society recommends screening certain women at high risk using annual mammography and breast MRI (**Table 40**).

Women with a 5-year risk of breast cancer of 1.67% or greater are candidates for breast cancer chemoprevention with antiestrogens. A recommended tool for estimating 5-year and lifetime risks of breast cancer is the Gail Model Risk Assessment Tool (www.cancer.gov/bcrisktool/). All patients with atypical hyperplasia or lobular carcinoma in situ (LCIS) are candidates for chemoprophylaxis. At present, there is insufficient evidence to recommend for or against screening with breast MRI in patients with atypical hyperplasia or LCIS.

Tamoxifen and raloxifene are selective estrogen receptor modifiers (SERMs) that block estrogen uptake in breast tissue. Exemestane and anastrozole are aromatase inhibitors that prevent the conversion of androgens into estrogens. These agents proportionally decrease the risk of breast cancer by 28% to 65% and are given for 5 years. **Table 41** summarizes these chemoprophylaxis options.

For women with *BRCA1* or *BRCA2* mutations, breast cancer screening with breast MRI should start at age 25 years and with mammography at age 30 years. The benefit of tamoxifen prophylaxis in *BRCA1* and *BRCA2* mutation carriers is not clear, although limited retrospective data suggest a benefit. Surgical prophylaxis options for *BRCA1* and *BRCA2* mutation carriers include prophylactic bilateral mastectomies, which decrease the risk of breast cancer by greater than 90%, and prophylactic bilateral salpingo-oophorectomy (BSO), which decreases the risk of ovarian, fallopian tube, and primary peritoneal cancers by greater than 80% and all-cause mortality to age 70 years by 77%. If done while a woman is premenopausal, prophylactic bilateral salpingo-oophorectomy also decreases the risk of breast cancer by 50% and is recommended between ages 35 and 40 years, after completion of childbearing. Because *BRCA2* mutation carriers on average develop ovarian cancer 8 to 10 years later than *BRCA1* carriers, bilateral salpingo-oophorectomy can be delayed until age 40 to 45 years in women who have had prophylactic mastectomies.

TABLE 38. Breast Cancer Risk Factors

Breast Cancer Risk Factor Category	Breast Cancer Risk Factors	Increase in Breast Cancer Risk or Lifetime Breast Cancer Risk
Reproductive factors	Early menarche, late menopause, first full-term pregnancy after age 30 years, or nulliparous	RR 1.2-3.5
Lifestyle	Obesity (BMI ≥30), lack of regular exercise, vitamin D deficiency, alcohol intake	RR 1.2-1.6 Obesity: RR, 1.6 for BMI >30.7 versus BMI <22.9 in postmenopausal women[a] Regular exercise: RR decreased by 25% in physically active women compared with the least active women[b] Vitamin D deficiency: Postmenopausal breast cancer risk decreased by 12% for each 5 ng/mL (12.5 nmol/L) increase in 25(OH)D levels between 27 and 35 ng/mL[c] (67.4 and 87.4 nmol/L) Alcohol intake: mildly increased risk (RR 1.05) with 2 to 3 drinks per week. RR 1.41 for women consuming 2 to 5 drinks per day[d]
Treatment related: radiation	Prior chest wall radiation in patients younger than age 30 years (e.g., mantle radiation for Hodgkin lymphoma)	RR 5.0, with highest risk for younger age at radiation therapy; risk remains increased for at least 40 years after radiation therapy, with 30% to 50% lifetime risk of breast cancer[e]
Treatment related: HRT	Combination estrogen and progesterone HRT after menopause	RR 1.2-1.4; increased risk begins after 3 years of therapy[a]
Breast density[f]	Increased breast density	Risk increases with each category of breast density; for ≥75% density, RR is 4.7 compared with <10% density[g]
Atypical breast lesions	Atypical ductal or lobular hyperplasia, LCIS	RR 3.8-5.3 for atypical hyperplasia[h] and RR 5.4-8.0 for LCIS[i]; 30% to 35% lifetime risk of breast cancer (bilateral risk)[h,i]
Family history of breast cancer and familial breast cancer syndromes	*BRCA1/2* mutation represents the most common familial breast cancer syndrome (5% to 10% of all breast cancer tumors); others are rare	*BRCA1/2* mutations (RR 3.0 to 7.0) confer a 50% to 87% lifetime risk of breast cancer and a 20% to 45% lifetime risk of ovarian cancer

25(OH)D = 25-hydroxyvitamin D; *BRCA1/2* = breast cancer susceptibility 1 or breast cancer susceptibility 2 genes; HRT = hormone replacement therapy; LCIS = lobular carcinoma in situ; RR = relative risk.

[a]Data from Clemons M, Goss P. Estrogen and the risk of breast cancer. N Engl J Med. 2001 Jan 25;344 (4):276-85. Erratum in: N Engl J Med. 2001 Jun 7;344(23):1804. [PMID: 11172156]

[b]Data from Lynch BM, Neilson HK, Friedenreich CM. Physical activity and breast cancer prevention. Recent Results Cancer Res. 2011;186:13-42. [PMID: 21113759]

[c]Data from Bauer SR, Hankinson SE, Bertone-Johnson ER, Ding EL. Plasma vitamin D levels, menopause, and risk of breast cancer: dose-response meta-analysis of prospective studies. Medicine (Baltimore). 2013 May;92(3):123-31. [PMID: 23625163]

[d]Data from Bagnardi V, Rota M, Botteri E, et al. Light alcohol drinking and cancer: a meta-analysis. Ann Oncol. 2013 Feb;24(2):301-8. [PMID: 22910838] and Smith-Warner SA, Spiegelman D, Yaun SS, et al. Alcohol and breast cancer in women: a pooled analysis of cohor studies. JAMA. 1998 Feb 18;279(7):535-40. [PMID: 9480365]

[e]Data from Swerdlow AJ, Cooke R, Bates A, et al. Breast cancer risk after supradiaphragmatic radiotherapy for Hodgkin's lymphoma in England and Wales: a National Cohort Study. J Clin Oncol. 2012 Aug 1;30(22):2745-52. [PMID: 22734026]

[f]Breast density refers to the amount of radiologically dense breast tissue appearing on a mammogram.

[g]Data from Boyd NF, Guo H, Martin LJ, et al. Mammographic density and the risk and detection of breast cancer. N Engl J Med. 2007 Jan 18;356(3):227-36. [PMID: 17229950]

[h]Data from Degnim AC, Cisscher DW, Berman HK, et al. Stratifications of breast cancer risk in women with atypia: a Mayo cohort study. J Clin Oncol. 2007 Jul 1;25(19):2671-7. [PMID: 17563394] and Marshall LM, Hunter DJ, Connolly JL, et al. Risk of breast cancer associated with atypical hyperplasia of lobular and ductal types. Cancer Epidemiol Biomarkers Prev. 1997 May;6(5):297-301. [PMID: 9149887]

[i]Data from Bodian CA, Perzin KH, Lattes R. Lobular neoplasia. Long term risk of breast cancer and relation to other factors. Cancer. 1996 Sep 1;78(5):1024-34. [PMID: 8780540]

KEY POINTS

- Women at high risk for breast cancer should be screened with annual mammography and breast MRI; this includes women with a *BRCA1* or *BRCA2* gene mutation or with a first-degree relative with a *BRCA1* or *BRCA2* mutation, women with a strong family history of breast cancer, those with a history of chest radiation at a young age, and those with a rare hereditary breast cancer syndrome.

(Continued)

KEY POINTS ***(continued)***

- Women with a 5-year risk of breast cancer of 1.67% or greater or with lobular carcinoma in situ or atypical hyperplasia are candidates for breast cancer chemoprophylaxis.
- Surgical prophylaxis options for *BRCA1* and *BRCA2* mutation carriers include prophylactic bilateral mastectomy and prophylactic bilateral salpingo-oophorectomy.

TABLE 39. Highlights of NCCN[a] and USPSTF[b] Recommendations for Breast and Ovarian Cancer Syndrome Genetic Testing

Individuals with a Personal History of Breast or Ovarian Cancer
Breast cancer diagnosed at or before age 45 years
Breast cancer diagnosed at or before age 50 years with one or more relatives[c] with breast cancer, pancreatic cancer, or prostate cancer with Gleason score ≥7 at any age
Women with two primary breast cancers, with the first diagnosed at or before age 50
Breast cancer diagnosed at any age with one or more relatives[c] diagnosed with ovarian cancer
Triple negative breast cancer[d] diagnosed at or before age 60 years
Breast cancer in women of Ashkenazi (Eastern European) Jewish ancestry
Men with breast cancer diagnosed at any age
Ovarian cancer diagnosed at any age
Individuals without a Personal History of Breast or Ovarian Cancer
Family history of a known deleterious *BRCA1/2* mutation
Two first-degree relatives with breast cancer, one of whom received the diagnosis at age 50 years or younger
Three or more first- or second-degree relatives with breast cancer regardless of age at diagnosis
More than three family members[c] with breast cancer, ovarian cancer, pancreatic cancer, and/or aggressive prostate cancer
A combination of both breast and ovarian cancer among first- and second-degree relatives
A first-degree relative with bilateral breast cancer
A combination of two or more first- or second-degree relatives with ovarian cancer regardless of age at diagnosis
A first- or second-degree relative with both breast and ovarian cancer at any age
A history of breast cancer in a male relative
Women of Ashkenazi (Eastern European) Jewish ancestry with a first-degree relative (or two second-degree relatives on the same side of the family) with breast or ovarian cancer

BRCA1/2 = breast cancer susceptibility 1 or breast cancer susceptibility 2 genes; NCCN = National Comprehensive Cancer Network; USPSTF = U.S. Preventive Services Task Force.

[a]Full testing guidelines can be accessed at www.nccn.org/professionals/physician_gls/f_guidelines.asp.

[b]Full testing guidelines can be accessed at www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementFinal/brca-related-cancer-risk-assessment-genetic-counseling-and-genetic-testing.

[c]First-degree, second-degree, or third-degree relatives on the same side of the family.

[d]Negative for estrogen and progesterone receptors and *HER2* amplification.

TABLE 40. American Cancer Society Recommendations for MRI Breast Cancer Screening

Women with *BRCA1/2* mutations
Women who are a first-degree relative of a *BRCA1/2* carrier but are untested[a]
Women with a strong family history of breast cancer with a lifetime breast cancer risk of ≥20% to 25% as calculated by models[b] largely dependent on family history
Women who had radiation to the chest wall between ages 10 and 30 years (e.g., mantle radiation therapy for Hodgkin lymphoma)
Women with a history of other rare familial breast cancer syndromes

BRCA1/2 = breast cancer susceptibility 1 or breast cancer susceptibility 2 genes.

[a]Testing for the *BRCA1* or *BRCA2* mutation that is present in the family is strongly recommended, but some patients decide to defer testing. In this situation where their carrier status is unknown, breast MRI screening is recommended. If they are later tested and do not carry the mutation, MRI screening should be stopped.

[b]Models that can be used to estimate lifetime risk of breast cancer to determine if MRI screening is appropriate (please note that the Gail Model is not recommended for this use):

- BRCAPRO: www4.utsouthwestern.edu/breasthealth/cagene/default.asp
- Claus model: Claus EB, Risch N, Thompson WD. The calculation of breast cancer risk for women with a first degree family history of ovarian cancer. Breast Cancer Res Treat. 1993 Nov;28(2):115-20. [PMID: 8173064]
- Tyrer-Cuzik (also called IBIS Breast Cancer Risk Evaluation Tool): www.ems-trials.org/riskevaluator/

TABLE 41. Primary Chemoprevention for Breast Cancer

Considerations	Tamoxifen	Raloxifene	Exemestane	Anastrozole
Mechanism of action	SERM	SERM	Aromatase inhibitor	Aromatase inhibitor
Breast cancer risk reduction	43% at 7 years[a] 28% at 10 years[b]	As effective as tamoxifen at reducing the risk of invasive cancers, but less effective at reducing noninvasive cancers[c]	65% at 3 years[d]	53% at 5 years[e]
Important toxicities	Vasomotor symptoms, cataracts, vascular events (stroke, TIA, DVT/PE), and endometrial cancer and uterine sarcoma in postmenopausal women	Vasomotor symptoms, cataracts, vascular events (25% lower risk of vascular events than with tamoxifen)	Vasomotor symptoms, arthralgia, headaches, and insomnia	Vasomotor symptoms, arthralgia, carpal tunnel syndrome, dry eyes, and hypertension
Indicated for use in premenopausal women	Yes	Not studied; should not be used unless part of a clinical trial	Not effective in premenopausal women	Not effective in premenopausal women
Other	Contraindicated in women with prior thromboembolic events; 32% reduction in osteoporotic fractures[a]	Contraindicated in women with prior thromboembolic events	At 3-year follow-up, no increase in osteoporosis, fractures, endometrial cancer, vascular events, or cardiac disease	At 5-year follow-up, no increase in thromboembolic events, fractures, cerebrovascular events, or myocardial infarction

DVT = deep venous thrombosis; PE = pulmonary embolism; SERM = selective estrogen receptor modulator; TIA = transient ischemic attack.

[a]Fisher B, Constantino JP, Wickerham DL, et al. Tamoxifen for the prevention of breast cancer: current status of the National Surgical Adjuvant Breast and Bowel Project P-1 study. J Natl Cancer Inst. 2005 Nov 16;97(22):1652-62. [PMID: 16288118]

[b]Cuzick J, Sestak I, Cawthorn S, et al; IBIS-I Investigators. Tamoxifen for prevention of breast cancer: extended long-term follow-up of the IBIS-I breast cancer prevention trial. Lancet Oncol. 2015 Jan;16(1):67-75. [PMID: 25497694]

[c]Vogel VG, Costantino JP, Wickerham DL, et al; National Surgical Adjuvant Breast and Bowel Project (NSABP). Effects of tamoxifen vs raloxifene on the risk of developing invasive breast cancer and other disease outcomes: the NSABP study of tamoxifen and raloxifene (STAR) P-2 trial. JAMA. 2006 Jun 21;295(23):2727-41. Erratum in: JAMA. 2006 Dec 27;296(24):2926. [PMID: 16754727]

[d]Goss PE, Ingle JN, Alés-Martinez JE, et al; NCIC CTG MAP.3 Study Investigators. Exemestane for breast cancer prevention in postmenopausal women. N Engl J Med. 2011 Jun 23;364(25):2381-91. Erratum in: N Engl J Med. 2011 Oct 6;365(14):1361. [PMID: 21639806]

[e]Cuzick J, Sestak I, Forbes JF, et al; IBIS-II Investigators. Anastrozole for prevention of breast cancer in high risk postmenopausal women (IBIS-II): an international, double-blind, randomised placebo-controlled trial. Lancet. 2014 Mar 22;383(9922):1041-8. Erratum in: Lancet. 2014 Mar 22;383(9922):1040. [PMID: 24333009]

Staging and Prognosis of Early-Stage Breast Cancer

Breast cancer is most commonly staged by the TNM system. Breast cancer staging and prognosis are presented in **Table 42**. In addition to the excellent prognosis for small tumors with neither lymph node involvement nor distant metastases, the presence of hormone receptors, absence of human epidermal growth factor 2 (*HER2*) overexpression, and absence of lymphovascular invasion also favorably affect prognosis. Estrogen receptors, when detected, imply a better differentiated tumor and suggest response to hormone antagonist therapy. Tumors with a genetic mutation that leads to *HER2* overexpression imply an unfavorable prognosis, although monoclonal antibodies such as trastuzumab that block those receptors are effective therapy and have markedly improved the prognosis for these women.

For asymptomatic patients with newly diagnosed stage 0 to II (early-stage) breast cancer, current guidelines recommend against using imaging studies such as PET, CT, or bone scan, or measuring serum markers such as CA15-3 or CA27-29, for staging. These studies have little diagnostic yield for patients with stage I to II breast cancer who do not have symptoms, findings on examination, or laboratory evidence of metastases. One large series showed that the incidence of bone metastases in stage I to III breast cancer was 5% to 6% for stage I to II and 14% for stage III; for liver metastases, the incidence was 0% in stage I to II and 0.7% in stage III; and for lung metastases, incidence was 0% in stage I to II and 7% in stage III. Imaging studies for staging are recommended in patients with stage III disease or in patients with earlier-stage disease who have signs or symptoms suggestive of metastatic disease.

Advances in breast cancer diagnosis and treatment have led to markedly improved survival rates during the past 40 years. Surveillance, Epidemiology, and End Results (SEER) data from 1975 to 2013 show a 34% decrease in deaths from breast cancer. The 5-year relative survival for all invasive breast cancer stages in patients diagnosed from 2006 to 2012 is 90.8%.

KEY POINTS

- Clinical features associated with a more favorable prognosis of early-stage breast cancer include hormone receptor–positive cancer, absence of *HER2* overexpression, small tumor size, low tumor grade, and negative lymph nodes.

(Continued)

TABLE 42. Staging and Prognosis of Invasive Breast Cancer

Stage	Definition	5-Year Relative Survival[a] Rates
0	Ductal carcinoma in situ (negative lymph nodes)	99%
I	IA: Tumor ≤2 cm and negative lymph nodes	95%
	IB: Tumor ≤2 cm and 1 to 3 micrometastatic positive lymph nodes (0.2-2 mm)	
IIA	Tumor ≤2 cm with 1 to 3 positive lymph nodes (>2 mm) *OR*	85%
	Tumor 2-5 cm with negative lymph nodes	
IIB	Tumor 2-5 cm with 1 to 3 positive lymph nodes *OR*	70%
	Tumor >5 cm with negative lymph nodes	
IIIA	Tumor ≤5 cm with 4 to 9 positive lymph nodes *OR*	52%
	Tumor >5 cm with 1 to 9 positive lymph nodes	
IIIB	Tumors with skin or chest wall involvement with 0 to 9 positive lymph nodes	48%
IIIC	Tumors with 10 or more positive lymph nodes	Not stated
IV	Distant metastatic disease	22%

[a]Relative survival is an estimate of the percentage of patients who would be expected to survive the effects of their cancer.

Data from Howlader N, Noone AM, Krapcho M, Garshell J, Miller D, Altekruse SF, et al. SEER Cancer Statistics Review, 1975-2012, National Cancer Institute. Bethesda, MD. http://seer.cancer.gov/csr/1975_2012/. Based on November 2014 SEER data submission. The Surveillance, Epidemiology, and End Results Program (SEER) Website. Updated November 18, 2015. Accessed February 7, 2018.

KEY POINTS ***(continued)***

HVC • Imaging studies such as PET, CT, or bone scan for staging are not recommended in asymptomatic patients with newly diagnosed stage 0 to II breast cancer.

Primary Breast Cancer Therapy

Ductal Carcinoma in Situ

Ductal carcinoma in situ (DCIS), classified as stage 0 breast cancer, is a noninvasive breast cancer that usually presents as calcifications on mammography (see **Figure 19**). Its incidence has increased greatly, from 3% of breast cancers before the era of mammographic screening to 20% to 25% of breast cancers today. Infrequently, DCIS presents as a palpable mass.

Because more than half of local recurrences of DCIS are invasive cancers, the goal of treatment has been to eradicate the area of DCIS and decrease the risks of local recurrence and deaths from breast cancer. Surgical treatment has traditionally been either wide excision (lumpectomy), often followed by breast radiation or mastectomy. Radiation may be omitted in some cases of low grade or intermediate grade DCIS. Mastectomy is usually recommended if the DCIS is more extensive and cannot be fully removed by a wide excision.

Recent studies have questioned the benefit of these approaches. An observational study of more than 100,000 women with DCIS showed that although adding radiation to wide excision decreased the risk of local recurrence from 4.9% to 2.5%, it did not decrease the 10-year breast cancer–specific mortality of 0.9%. Similarly, patients who had mastectomies had a lower risk of local recurrence than patients who had lumpectomies but no decrease in the risk of death from breast cancer. Women younger than 35 years, black women, women younger than 40 years presenting with a palpable mass, and women with DCIS that is either estrogen receptor negative or *HER2* positive have a worse prognosis.

In women with estrogen receptor–positive DCIS, tamoxifen and aromatase inhibitors decrease the risks of local recurrence and contralateral breast cancers. Tamoxifen is the

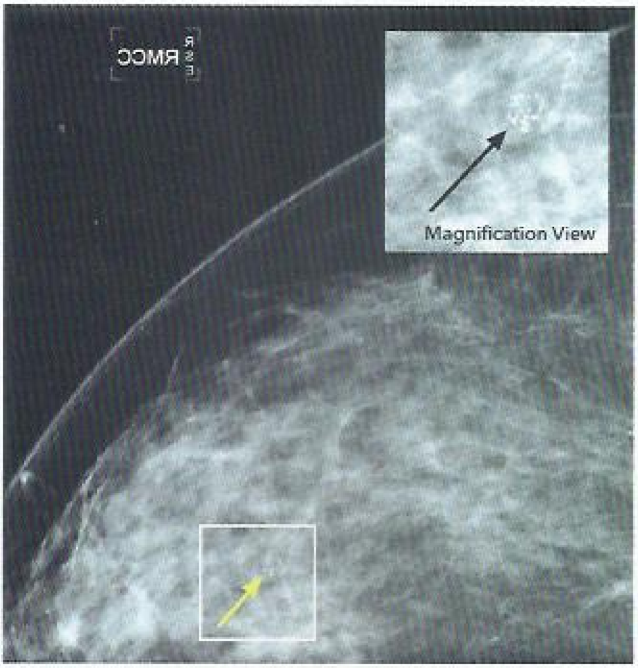

FIGURE 19. Ductal carcinoma in situ presenting as calcifications on mammography.

appropriate treatment in premenopausal women. For postmenopausal women, both tamoxifen and anastrozole are effective options, with anastrozole being superior in women younger than age 60 years. Both hormonal therapies are equally effective in women age 60 years or older. Unlike with hormone receptor–positive invasive cancers, antiestrogen treatment of DCIS does not have a survival benefit.

Patients with DCIS should have annual mammography starting 6 to 12 months after radiation therapy, if given, and follow-up visits every 6 to 12 months for 5 years after diagnosis.

KEY POINTS

- Although mastectomy or postlumpectomy radiation decreases the risk for local recurrence when compared to wide excision in women with ductal carcinoma in situ, neither improves overall 10-year survival.
- In estrogen receptor–positive DCIS, tamoxifen and aromatase inhibitors further decrease the risks of local recurrence and contralateral breast cancer but do not improve overall survival.

Invasive Breast Cancer

Most early-stage invasive breast cancers are treated with initial excision, followed by radiation and systemic adjuvant therapy. There are two surgical options for invasive breast cancer. Breast conservation therapy involves wide excision followed by breast radiation and is typically used in patients with cancers 5 cm or less in size, without skin involvement, and with clear margins after excision. Mastectomy is recommended for larger cancers, cancers with skin involvement, and inflammatory breast cancers. Mastectomy may also be chosen in situations where radiation is contraindicated, or in women with *BRCA1* or *BRCA2* mutations or strong family histories of breast cancer where there is a high risk of subsequent breast cancers. For some patients with large tumors, neoadjuvant chemotherapy or endocrine therapy can be given before surgery to decrease the cancer to a size that allows for breast conservation.

In patients with clinically negative axillary lymph nodes, a sentinel node biopsy is done at the time of breast surgery. In patients having breast conservation surgery who will receive chemotherapy or antiestrogen therapy as well as whole breast radiation, axillary dissection is not required if no more than two sentinel nodes are involved. For patients with clinically involved axillary nodes or three or more positive sentinel nodes, an axillary dissection is recommended. The sentinel node procedure has a lower risk of lymphedema, sensory loss, and shoulder abduction defects than axillary dissection.

Primary breast radiation usually consists of radiation to the whole breast, although partial breast radiation is an option in some patients. Postmastectomy radiation is recommended for cancers greater than 5 cm in size, inadequate or positive margins or skin involvement, inflammatory breast cancers, or four or more positive axillary nodes. Depending on other risk factors, it may be recommended in women with one to three positive axillary nodes. Postmastectomy radiation decreases both the risk of local recurrence and the risk of distant metastases and increases overall survival.

For women older than age 70 years with cancers less than 2 cm in size, no clinically involved lymph nodes, and estrogen receptor–positive breast cancer, wide excision followed by antiestrogen therapy alone is an acceptable treatment option. Whole breast radiation in this situation decreases the risk of local recurrence from 9% to 2% at 12 years, but has no impact on the risk of distant metastases, breast cancer–specific survival, or overall survival.

KEY POINTS

- Breast conserving therapy is effective for patients with tumors 5 cm or less in size, without skin involvement, and with clear margins after excision in women who do not have hereditary syndromes that place them at high risk for subsequent breast cancer.
- For patients undergoing breast conservation surgery followed by chemotherapy or antiestrogen therapy and whole breast radiation, axillary node dissection is not required if no more than two sentinel nodes are involved. HVC
- Postmastectomy radiation is recommended for cancers greater than 5 cm in size, positive margins or skin involvement, inflammatory breast cancers, and many patients with positive axillary lymph nodes.

Adjuvant Systemic Therapy for Nonmetastatic Breast Cancer

Patients with stage I to III (potentially curable) breast cancer receive adjuvant systemic therapy to eradicate occult microscopic foci of breast cancer and decrease the risk of local and distant recurrence. The type of adjuvant therapy used depends on the biology and stage of the breast cancer. Antiestrogen therapy has the additional benefit of decreasing the risk of contralateral breast cancer.

Adjuvant Endocrine Therapy

Approximately 75% of breast cancers are hormone receptor positive (positive for the estrogen receptor, progesterone receptor, or both). Patients with hormone receptor–positive breast cancers are recommended to receive adjuvant antiestrogen therapy for at least 5 years. The Early Breast Cancer Trialists Collaborative Group meta-analysis of adjuvant tamoxifen showed a 39% proportional reduction in breast cancer recurrence at 15 years and a 30% proportional reduction in breast cancer mortality. In postmenopausal women, aromatase inhibitors compared to tamoxifen resulted in a further 29% proportional decrease in breast cancer recurrence. Both tamoxifen and aromatase inhibitors also decrease the risk of contralateral breast cancer.

Tamoxifen is a selective estrogen receptor modulator that blocks estrogen uptake by breast cancer cells. It is effective in

both premenopausal and postmenopausal women. The aromatase inhibitors letrozole, anastrozole, and exemestane have similar efficacy and prevent conversion of adrenal androgens to estrogen but do not inhibit ovarian estrogen production. They are thus not effective in premenopausal women unless ovarian suppression is given concomitantly.

For postmenopausal women, aromatase inhibitor therapy provides superior results to using tamoxifen alone. Patients may take tamoxifen for 2 years and then change to an aromatase inhibitor for at least 3 to 5 years, or they can take 5 years of an aromatase inhibitor. A 2016 study showed the benefit of extending aromatase inhibitor use to a total of 10 years, whether or not tamoxifen was given initially, with an improvement in disease-free survival at 5 years from 91% to 95% but no difference in overall survival. Recommending extended aromatase inhibitor treatment will depend on a patient's quality of life, the toxic effects of treatment, and the risk of recurrence.

For premenopausal women with low-risk breast cancer who do not require adjuvant chemotherapy, tamoxifen for at least 5 years and preferably 10 years is recommended. Extending tamoxifen use to 10 years decreased the absolute risk of recurrences between 5 and 14 years after diagnosis from 25% to 21.4% and reduced the risk of breast cancer mortality from 15% to 12.5%. Patients who become postmenopausal while taking tamoxifen may be changed to an aromatase inhibitor.

For premenopausal women who receive adjuvant chemotherapy for higher risk hormone-positive breast cancer and who remain premenopausal, ovarian suppression achieved by surgical oophorectomy or pelvic irradiation in addition to either tamoxifen or an aromatase inhibitor is superior to tamoxifen alone. In the Suppression of Ovarian Function Trial (SOFT), adding ovarian suppression to tamoxifen improved absolute 5-year breast cancer–free survival by 4.5%. Breast cancer–free survival was improved by 7.7% with the use of ovarian suppression and exemestane compared to tamoxifen alone. The benefit was particularly dramatic in patients younger than age 35 years. Patients treated with ovarian suppression had more hot flushes, vaginal dryness, decreased libido, insomnia, depression, arthralgia, hypertension, glucose intolerance, and osteoporosis.

Tamoxifen side effects include endometrial cancer in women older than age 55 years, hot flushes, vaginal discharge, sexual dysfunction, venous thromboembolic events, and stroke.

Aromatase inhibitor side effects include arthralgia; vaginal dryness; sexual dysfunction; and higher risks of osteoporosis, fractures, cardiovascular events, and hyperlipidemia. Compared to tamoxifen, they have a lower risk of venous thrombosis and endometrial cancer. Up to one third of women develop aromatase inhibitor–associated symmetric arthralgia, joint stiffness, and bone pain. This musculoskeletal syndrome is managed with NSAIDs, a treatment break and change to an alternate aromatase inhibitor, or a change to tamoxifen.

KEY POINTS

- Premenopausal women with low-risk breast cancer who do not require adjuvant chemotherapy should receive tamoxifen for at least 5 years and preferably 10 years.
- Premenopausal women with higher-risk hormone-positive breast cancer who receive adjuvant chemotherapy should also receive ovarian suppression in addition to either tamoxifen or an aromatase inhibitor.
- Postmenopausal women should receive an aromatase inhibitor for 5 years and preferably 10 years, whether or not tamoxifen was given initially.

Adjuvant Chemotherapy

Increasingly, the use of adjuvant chemotherapy for early breast cancer is based more on tumor biology rather than on stage. The behavior of hormone receptor–negative and of *HER2*-positive cancers is more aggressive and there is benefit to adjuvant chemotherapy for cancers that are greater than 5 mm in size, lymph node positive, or both.

For hormone receptor–positive, *HER2*-negative breast cancers with zero to three positive axillary nodes, the use of multigene assays that predict the risk of recurrence with antiestrogen therapy alone has significantly decreased the use of adjuvant chemotherapy. The most commonly used molecular prognostic profile in the United States is the 21-gene recurrence score. Tumors with low-risk scores have a favorable prognosis with antiestrogen therapy alone and do not benefit from the addition of chemotherapy.

Clinicopathologic factors that suggest benefit to adjuvant chemotherapy include high tumor grade, extensive lymphatic invasion, very large primary tumor size, skin or chest wall involvement, and involvement of more than four axillary nodes.

Women with hormone receptor–negative, *HER2*-negative cancers (triple-negative breast cancer) have a 50% proportional reduction in the risk of recurrence and of breast cancer mortality with adjuvant chemotherapy. Adjuvant chemotherapy is recommended for triple-negative cancers larger than 5 mm in size or with positive lymph nodes.

When adjuvant chemotherapy is given for high-risk hormone receptor–positive cancers or triple-negative cancers, typically two or three agents are given for four to eight cycles. The most common chemotherapies used for adjuvant treatment are anthracyclines (doxorubicin or epirubicin), cyclophosphamide, and the taxanes (paclitaxel or docetaxel).

Adjuvant chemotherapy combined with *HER2*-targeted treatment such as the monoclonal antibody trastuzumab or the combination of trastuzumab and pertuzumab is recommended for *HER2*-positive cancers that are greater than 5 mm in size, node positive, or both. Chemotherapy with trastuzumab decreases the risk of cancer recurrence by 53% and the risk of death by 34%. The main toxicities of trastuzumab are infusion reactions such as fever, chills, and cardiomyopathy. The addition of pertuzumab in treatment of cancers that are greater than 2 cm in size, node positive, or both, improves 5-year

disease-free survival from 81% to 86%. For *HER2*-positive breast cancers that are smaller than 3 cm in size and node negative, treatment with paclitaxel and trastuzumab is a less toxic option, with a 3-year disease-free survival rate of 98.5%.

Acute side effects of adjuvant chemotherapy include bone marrow suppression with anemia and neutropenia, alopecia, allergic reactions, neuropathy, nausea, and premature menopause and infertility in premenopausal women (see Effects of Cancer Therapy and Survivorship). Women of childbearing age who wish to preserve fertility should meet with a fertility specialist before chemotherapy. Serious long-term toxicities include cardiomyopathy, neuropathy, myelodysplasia, and acute myelocytic leukemia. The risk of cardiomyopathy after four cycles of an anthracycline is 1.5%. The risk of acute leukemia after regimens containing an anthracycline or cyclophosphamide is 0.5%.

For women of advanced age with higher-risk early breast cancer, it is important to consider estimated life expectancy, functional status, and medical comorbidities before administering adjuvant chemotherapy. There is a higher risk of cardiotoxicity in older women.

KEY POINTS

- Patients with hormone receptor-positive tumors, zero to three positive axillary lymph nodes, and low-risk scores on the 21-gene recurrence assay have a favorable prognosis with antiestrogen therapy alone and do not benefit from the addition of chemotherapy.
- Adjuvant chemotherapy is most appropriate for patients with triple-negative tumors greater than 5 mm in size, skin involvement, or positive axillary lymph nodes.
- HVC For women of advanced age with higher-risk early stage breast cancer, consider life expectancy, functional status, and medical comorbidities before administering adjuvant chemotherapy.

Locally Advanced and Inflammatory Breast Cancer

Locally advanced breast cancer includes a subset of clinical stage IIB cancers (T3N0M0), as well as stages IIIA to IIIC cancers. These cancers have high-risk characteristics such as skin involvement, chest wall involvement, extensive lymph node involvement, or inflammatory changes.

Inflammatory breast cancer is a type of locally advanced breast cancer that presents with swelling, thickening, and erythema of the skin overlying the breast, classically with a peau d'orange (orange peel) appearance (**Figure 20**). Patients often present with breast enlargement or swelling developed during a few weeks or months and may have been treated for presumed mastitis. It is important to consider that inflammatory breast cancer may be the underlying cause in patients who do not respond to antibiotics for an apparent mastitis. A palpable breast mass may be present. The skin changes are due to the obstruction of dermal lymphatic vessels by cancer cells, although demonstrating dermal lymphatic invasion on biopsy is not necessary for the diagnosis. One third of patients have distant metastases at diagnosis, and nearly all have lymph node involvement. For this reason, these patients should have routine CT and bone scan imaging, even in the absence of symptoms of metastatic disease.

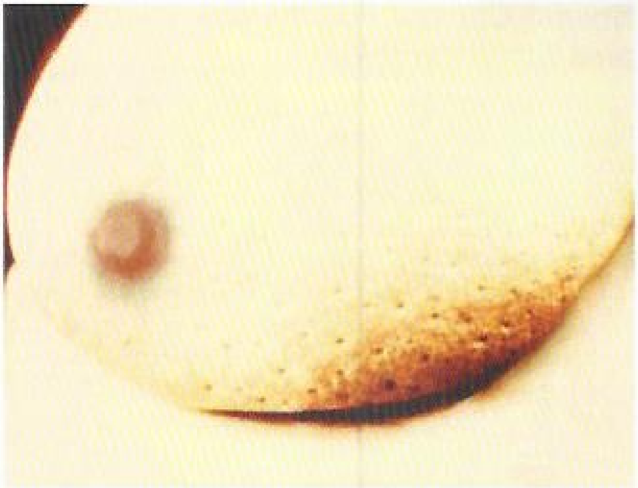

FIGURE 20. Inflammatory breast cancer often has a characteristic "p'eau d'orange" (orange peel) appearance of the skin, due to tumor emboli in the dermal lymphatics. Erythema is often present as well.

Locally advanced cancers are usually treated initially with neoadjuvant chemotherapy, followed by surgery, and then radiation. In some situations, neoadjuvant antiestrogen therapy can be used instead of chemotherapy, although this is typically limited to postmenopausal women who are not candidates for chemotherapy. Tumors with skin involvement or inflammatory cancers require mastectomy, but in other cases, neoadjuvant therapy will often decrease the size of the primary breast cancer to allow for breast conserving lumpectomy. All patients should have an axillary dissection at the time of mastectomy or lumpectomy and should receive radiation therapy afterward. The amount of residual cancer after neoadjuvant chemotherapy has prognostic significance, particularly in triple-negative or hormone-negative, *HER2*-positive cancers. Patients with complete pathologic responses have the lowest risk of recurrence.

Patients with hormone receptor–positive cancers should receive at least 5 years and ideally 10 years of antiestrogen therapy. Patients with *HER2*-positive cancers should complete one year of trastuzumab therapy.

KEY POINTS

- Inflammatory breast cancer, characterized by swelling, thickening, and erythema of the skin overlying the breast, classically with a peau d'orange (orange peel) appearance, may be mistaken for infectious mastitis and delay evaluation and treatment of the underlying malignancy.
- Locally advanced cancers are usually treated with neoadjuvant chemotherapy, surgery, and radiation.

Breast Cancer Follow-up and Survivorship

In 2016, there were more than 2.8 million women alive in the United States with a previous or current diagnosis of breast cancer. Once patients with nonmetastatic breast cancer complete surgery, radiation, and chemotherapy, they are monitored for local recurrence, distant recurrence, second primary cancers, and physical and psychosocial long-term effects of breast cancer and treatment. Patients with hormone receptor–positive breast cancer remain on antiestrogen treatment for at least 5 years and up to 10 years and require management of menopausal symptoms and other toxicities during that time. Guidelines recommend that patients be evaluated for a detailed cancer-related history and physical examination every 3 to 6 months for the first 3 years, every 6 to 12 months for the next 2 years, and then annually.

Patients should have annual mammograms of remaining breast tissue. Screening breast MRIs are needed only if patients meet criteria for screening MRIs (see Chemoprevention and other Risk Reduction Strategies). Patients should not have routine blood tests at follow-up visits or other routine imaging studies as these are not helpful for diagnosing recurrences earlier. Laboratory and imaging studies other than breast imaging should be guided by a patient's symptoms or findings on examination that raise concern for recurrence.

Patients should be evaluated at each visit for changes in family history of cancers and referred for genetic counseling as appropriate. Patients on tamoxifen should have annual gynecologic examinations and be evaluated by a gynecologist for any abnormal vaginal bleeding. Patients on aromatase inhibitors should have bone density studies every 2 years and should receive treatment of osteoporosis, ideally with a bisphosphonate, if their T score is −2.5 or lower.

For patients with breast asymmetry, reconstruction options can be offered and are often fully covered by insurance. Patients should receive physical therapy for lymphedema or decreased arm mobility after surgery or radiation to axillary nodes. Menopausal symptoms should be managed with nonhormonal options, such as gabapentin for nocturnal hot flushes. Depression, anxiety, and sexual dysfunction are not uncommon in this population and should be appropriately assessed and managed. For patients taking tamoxifen, it is important to avoid medications with strong CYP2D6 inhibition, such as bupropion or fluoxetine, as these may decrease tamoxifen activation.

KEY POINTS

- After completion of treatment, follow-up monitoring should be every 3 to 6 months for the first 3 years, every 6 to 12 months for the next 2 years, and then annually, with annual mammography for all survivors, and breast MRI for those at high risk of recurrence.

(Continued)

KEY POINTS *(continued)*

- Patients with hormone receptor–positive breast cancer remain on antiestrogen treatment for at least 5 years and up to 10 years.
- Surveillance blood tests and other imaging tests for breast cancer should not be routinely performed and should be guided by a patient's symptoms or findings on examination that raise concern for recurrence. **HVC**
- Breast cancer survivors should be monitored and treated for the side effects of treatment.

Metastatic Breast Cancer

Approximately 5% of patients with breast cancer present with initial stage IV disease and up to 30% with early-stage disease develop metastases. Metastatic breast cancer is not curable, but systemic therapy can improve survival, relieve symptoms, and maintain quality of life. Treatment and prognosis are related to whether visceral metastases are present, the number of sites involved, the interval between initial diagnosis and metastases (intervals of less than 2 years have a poorer prognosis), the patient's performance status, and tumor biology. The median overall survival for patients with metastatic breast cancer is 2 years but is longer for women with hormone receptor–positive cancer or *HER2*-positive cancer some of whom may have prolonged survival, in part related to more treatment options.

It is important to biopsy a site of initial metastasis both to confirm the diagnosis and to assess hormone receptor and *HER2* status. Because there may be discordance in the receptors in the metastatic lesion compared to the primary breast cancer in 10% to 15% of patients, the selection of systemic therapy might be altered.

In postmenopausal women with hormone receptor–positive, *HER2*-negative breast cancer, initial treatment is usually hormonal therapy; aromatase inhibitors are superior to other agents as first-line treatment. Fulvestrant, which inhibits estrogen receptor function, and tamoxifen are other options. Premenopausal women can receive tamoxifen, ovarian suppression alone, or ovarian suppression combined with either tamoxifen or aromatase inhibitors as initial treatment. Patients who respond are usually treated with sequential hormonal therapies. In patients with rapidly progressive disease or extensive visceral metastases, initial chemotherapy may be used because of its higher response rate.

Combining targeted agents such as the CDK4/6 inhibitor palbociclib or the mammalian target of rapamycin (mTOR) inhibitor everolimus with antiestrogens improves the response rate and duration of response to hormonal therapy. In patients who develop metastatic breast cancer during adjuvant therapy with an aromatase inhibitor, palbociclib plus fulvestrant is usually the recommended first-line therapy. For women who develop metastatic breast cancer after having completed adjuvant therapy with an aromatase inhibitor, palbociclib plus an aromatase inhibitor is usually given as the initial systemic therapy.

In *HER2*-positive advanced breast cancer, treatment should include *HER2*-directed therapy such as trastuzumab given with either chemotherapy or antiestrogen therapy, depending on the hormone receptor status of the cancer and the sites of disease. First-line treatment with dual *HER2*-targeted therapy with trastuzumab and pertuzumab added to the taxane docetaxel has been shown to improve overall survival, with median overall survival of 56 months in a phase 3 clinical trial. Ado-trastuzumab emtansine is an innovative antibody-drug conjugate that links trastuzumab to the microtubule inhibitor emtansine, delivering chemotherapy more specifically to *HER2*-overexpressing cells.

Triple-negative breast cancers have a higher relapse rate than hormone receptor–positive cancers; recur earlier, with a peak at 3 years after diagnosis and a very low risk of relapse after 5 years; and have a higher risk of locoregional recurrence and brain and lung metastases. Advanced triple-negative breast cancer is treated with chemotherapy. These cancers may be particularly responsive to platinum agents, particularly in *BRCA1* mutation carriers.

Chemotherapy agents used in patients with advanced breast cancer include taxanes, capecitabine, eribulin, gemcitabine, ixabepilone, and liposomal doxorubicin. Single-agent chemotherapy is usually given, with combination chemotherapy reserved for patients with extensive visceral metastases where a higher response rate is important.

In patients with *BRCA1* or *BRCA2* mutations, poly (ADP-ribose) polymerase (PARP) inhibitors have shown encouraging results. These agents cause "synthetic lethality" by producing an increase in double-strand DNA breaks that would usually be repaired by the *BRCA* pathway.

For all subtypes of metastatic breast cancer, bone-modifying agents such as zoledronic acid or denosumab are recommended for patients with bone metastases to decrease skeletal-related events (fractures, pain, and need for radiation). Palliative radiation can be used to treat painful bone metastases as well as other sites of tumor-related pain or obstruction. Triple-negative breast cancers and *HER2*-positive cancers have a higher risk of brain metastases, which are treated with whole brain radiation, stereotactic radiation, or surgery. Palliative care teams can be helpful for managing symptoms of pain, nausea, anorexia, and fatigue. Throughout the course of advanced breast cancer, discussions with patients about their goals of care should take place, focusing on their values and preferences as they are treated for an incurable illness.

KEY POINTS

- Metastatic breast cancer is not curable, but it can be treated with systemic therapy with the goals of improved survival, palliation of symptoms, and maintaining quality of life.
- The site of initial metastasis should be biopsied to confirm the diagnosis and to assess hormone receptor and *HER2* status, which can be discordant from the primary breast cancer.

Ovarian Cancer

Epidemiology and Risk Factors

Ovarian cancer, the leading cause of gynecologic cancer deaths, will be newly diagnosed in approximately 22,000 women in 2016 in the United States, with an estimated 14,000 deaths. This chapter will focus on the 95% of ovarian cancers that are of epithelial origin.

Risk factors for ovarian epithelial cancer include inheritance of ovarian cancer susceptibility genes, increasing age, infertility, nulliparity, endometriosis, polycystic ovary syndrome, use of an intrauterine device, and cigarette smoking.

The most common ovarian cancer susceptibility genes are *BRCA1*, *BRCA2*, and the mismatch repair (MMR) genes associated with hereditary nonpolyposis colon cancer (HNPCC), also known as Lynch syndrome. Approximately 10% to 15% of women with ovarian cancer carry a mutation in one of these genes, and all women with epithelial ovarian cancer should be offered genetic testing for *BRCA1* and *BRCA2* mutations. In patients with a personal or family history of other HNPCC-related cancers (colorectal, small bowel or endometrial cancers or transitional cell cancers of the renal pelvis or ureter), HNPCC testing is recommended as well. There are different criteria for HNPCC genetic testing, including criteria and prediction models based on the number of affected relatives and age of onset, as well as tumor-based strategies often used in colorectal and endometrial cancers involving testing for microsatellite instability (MSI) or immunohistochemistry staining for mismatch repair proteins. The cumulative lifetime risk of ovarian cancer is 1.4% in patients without a susceptibility gene, 45% in *BRCA1* carriers, 12% in *BRCA2* carriers, and 3% to 13.5% in MMR gene mutation carriers.

KEY POINT

- Genetic testing for *BRCA1*, *BRCA2*, and mismatch repair gene mutations is recommended for all women with ovarian cancer.

Screening and Risk-Reduction Strategies

Ovarian cancer screening with transvaginal ultrasonography or serum CA-125 testing is not effective and is not recommended for patients of average, or even high, risk.

For women with *BRCA1*, *BRCA2*, or MMR gene mutations, prophylactic bilateral salpingo-oophorectomy (BSO) is recommended after completion of childbearing. Prophylactic BSO is recommended by age 35 to 40 years for *BRCA1* carriers and by age 45 years for *BRCA2* carriers. For *BRCA1* or *BRCA2* carriers, prophylactic BSO decreases the risk of ovarian, fallopian tube, and primary peritoneal cancers by greater than 80% and decreases all-cause mortality to age 70 years by 77%. Recommendations for genetic testing for breast and ovarian cancer syndromes are discussed in Breast Cancer. In women

with Lynch syndrome, BSO and hysterectomy are recommended because of the increased risk of endometrial cancer.

Oral contraceptives reduce the risk of ovarian cancer by 40% to 50%, with the greatest benefit seen after 15 years of use.

KEY POINTS

HVC • Ovarian cancer screening is not recommended, even for women at high risk for ovarian cancer.

- Prophylactic bilateral salpingo-oophorectomy is recommended by age 35 to 40 years for *BRCA1* carriers and by age 45 years for *BRCA2* carriers.

Diagnosis

Ovarian cancer usually presents with advanced disease, either acutely with such symptoms as pleural effusions or bowel obstruction or subacutely with such symptoms as bloating, abdominal or pelvic pain, urinary frequency, or early satiety. An incidental ovarian mass may be found on routine examination. Initial studies for suspected ovarian cancer should include a pelvic examination, general physical examination, serum CA-125 level, complete blood count, liver chemistry tests, and transvaginal and transabdominal ultrasonography. Additional imaging with abdominal and pelvic CT or MRI and chest imaging with CT or chest radiography are added as clinically indicated. Patients with a high suspicion of ovarian cancer should be referred to a gynecologic oncologist.

For early ovarian cancer, surgical exploration is recommended for diagnosis because removing the ovarian cancer intact without rupture improves survival. For advanced ovarian cancers with peritoneal masses, ascites, or pleural effusions, fluid cytology or imaging-guided biopsy can be done, particularly in cases where the disease is not initially resectable and neoadjuvant chemotherapy may be used.

Staging and prognosis are shown in **Table 43**. Early stage, low grade, serous histology, extent of disease after surgical debulking, and young age are associated with improved survival. A recent analysis showed that 31% of patients diagnosed with ovarian cancer survived 10 years, with one third of these long-term survivors having stage III or IV cancer.

KEY POINTS

- Most women with ovarian cancer present with symptoms of advanced disease, either with acute symptoms such as pleural effusions or bowel obstruction, or with subacute symptoms such as bloating, abdominal or pelvic pain, urinary frequency, or early satiety.
- Diagnostic surgical exploration is most appropriate for early ovarian cancer because intact cancer removal improves survival, and fluid cytology or imaging-guided biopsy is more appropriate for advanced cancers, particularly those that are not initially resectable.

TABLE 43. International Federation of Gynecology and Obstetrics Ovarian Cancer Staging, Treatment, and Survival

Stage	Definition	Treatment	5-Year Survival
Stage I disease (favorable)[a]	Cancer in one or both ovaries, not high grade or clear cell, negative peritoneal washings, no rupture	Surgery alone	94% overall survival
Stage I disease (unfavorable); stage II disease	Unfavorable stage I disease: Confined to ovaries but with high-grade or clear cell histology, rupture, or positive peritoneal washings Stage II disease: spread beyond ovaries but confined to pelvis	Surgery followed by 3 to 6 cycles of chemotherapy (usually carboplatin and paclitaxel)	Stage I: 85% relative survival[b] Stage II: 70%-78% relative survival
Optimally debulked stage III disease	Spread to abdomen, with residual tumor masses <1 cm after debulking surgery	Surgery followed by IV or IV/IP chemotherapy	IV chemotherapy: 40% overall survival IV/IP chemotherapy: 50% overall survival (23% decreased risk of death with IP/IV versus IV chemotherapy)
Suboptimally debulked stage III disease or stage IV disease[c]	Stage III (suboptimal) disease: spread to abdomen with residual masses >1 cm after debulking surgery Stage IV disease: spread beyond abdomen	Surgery (usually done even for stage IV disease as it improves survival) and chemotherapy; preoperative (neoadjuvant) chemotherapy given for initially unresectable cancer	Stage III: 39% relative survival Stage IV: 17% relative survival

IP = intraperitoneal; IV = intravenous.

[a]Careful staging is critical: almost one third of patients with apparent early disease will have more advanced disease when thorough staging is completed.

[b]Relative survival is an estimate of the percentage of patients who would be expected to survive the effects of their cancer.

[c]According to recent guidelines by the American Society of Clinical Oncology (ASCO) and Society of Gynecologic Oncology (SGO), patients with stage IIIC or IV ovarian cancer who are at high perioperative risk or who have a low likelihood of optimal tumor debulking should receive neoadjuvant chemotherapy followed by reevaluation for cytoreductive surgery.

Treatment

Surgical staging includes total hysterectomy, BSO, peritoneal washings, omentectomy, and pelvic and para-aortic lymph node sampling. In advanced ovarian cancer, surgical debulking, including the resection of metastatic disease, improves prognosis. The volume of residual disease after surgery correlates inversely with survival. Neoadjuvant chemotherapy is usually recommended for patients with initially unresectable disease.

Patients with early-stage ovarian cancer who have favorable histology may be treated with surgical resection alone. All other patients should receive adjuvant chemotherapy. Patients with stage III disease have improved survival, albeit with increased toxicity, from intraperitoneal along with intravenous chemotherapy; nevertheless, intraperitoneal therapy remains underused. Platinum-taxane chemotherapy is generally used for all stages. According to recent guidelines by the American Society of Clinical Oncology (ASCO) and Society of Gynecologic Oncology (SGO), patients with stage IIIC or IV ovarian cancer who are at high perioperative risk or who have a low likelihood of optimal tumor debulking should receive neoadjuvant chemotherapy followed by reevaluation for cytoreductive surgery.

For patients who achieve a clinical remission after chemotherapy, maintenance therapy has not been shown to improve survival. Similarly, second-look laparotomy to determine if a patient is in a pathologic response has not been shown to be beneficial.

KEY POINTS

- Patients with early-stage ovarian cancer with favorable histology may be treated with surgery alone; all other patients should receive platinum-taxane chemotherapy.
- Intraperitoneal chemotherapy, when added to intravenous chemotherapy, leads to improved survival in patients with stage III ovarian cancer.
- HVC Maintenance chemotherapy and second-look laparotomy do not improve survival in patients with ovarian cancer who achieve clinical remission.

Monitoring and Follow-up

Posttreatment surveillance consists of physical and pelvic examinations every 3 to 6 months for 5 years, then annually. The need to monitor serum CA-125 at each visit if initially elevated is controversial, as such monitoring does not improve survival. Other laboratory tests and imaging tests are recommended only as indicated for symptoms or findings suggesting recurrence.

Management of Recurrent Ovarian Cancer

Despite optimal treatment, 80% to 85% of women with stage III or IV ovarian cancer will relapse. Patients who relapse 6 months or more after initial chemotherapy are considered to have platinum-sensitive disease, have a better prognosis, and are usually treated with platinum-containing combination chemotherapy. Adding the angiogenesis inhibitor bevacizumab improves disease-free survival but not overall survival, and increases the risk of serious gastrointestinal toxicities including perforation. For patients with platinum-resistant disease, various single agents can be used palliatively, as can bevacizumab alone or with chemotherapy. For *BRCA1* or *BRCA2* carriers with recurrent ovarian cancer, the poly (ADP-ribose) polymerase (PARP) inhibitor olaparib can be given after progression on chemotherapy.

KEY POINT

- Patients who relapse more than 6 months after discontinuing platinum-based chemotherapy are considered to have platinum-sensitive disease and should be treated with platinum-based combination chemotherapy.

Cervical Cancer

Epidemiology and Risk Factors

In 2018, there will be an estimated 13,240 new patients diagnosed with invasive cervical cancer and 4170 deaths from cervical cancer in the United States. The mean age of diagnosis in the United States is 48 years. During the last 30 years, cervical cancer incidence and deaths in developed countries have decreased by more than 50%, primarily because of screening and preventive treatment. It remains the second most common cause of mortality from cancer in women worldwide, with more than 260,000 women dying each year of cervical cancer. More than 85% of deaths are in less developed countries.

Human papillomavirus (HPV) is the causative agent in most patients and can be detected in 99.7% of cervical cancers. Risk factors include sexual habits associated with a higher risk of acquiring HPV, such as earlier onset of sexual activity and several partners. Immunosuppression, including HIV infection, low socioeconomic status, and oral contraceptive use are additional risk factors. Cigarette smoking increases the risk of squamous cell carcinoma of the cervix. Squamous cell carcinoma is the histologic type in 69% of cervical cancers, with adenocarcinoma accounting for 25%. HPV vaccination decreases the incidence of cervical dysplasia and cervical cancer. Cervical cancer screening and HPV vaccination are covered in MKSAP 18 General Internal Medicine.

KEY POINT

- Human papillomavirus (HPV) is the causative agent in most patients with cervical cancer, and HPV vaccination significantly reduces the risk.

Diagnosis, Staging, and Treatment

Early cervical cancer is frequently asymptomatic. The most common symptoms are abnormal or heavy vaginal bleeding or vaginal discharge. Pelvic or back pain and bowel or bladder symptoms are presentations of advanced disease. Diagnosis is made by direct biopsy of a visible lesion, colposcopy, or cone biopsy (conization). Current guidelines for staging studies recommend a complete blood count, liver chemistry tests, kidney function studies, and imaging studies for moderate-risk and high-risk stage cancers. Chest radiography, CT or PET-CT scan, and MRI can be added as indicated. Cystoscopy and proctoscopy are optional. HIV testing should be considered. Cervical cancer staging and treatment are described in **Table 44.** For patients with tumors 2 cm in size or smaller that are confined to the cervix and with no lymph node involvement, fertility-sparing surgeries such as conization (only for stage IA) or radical trachelectomy are options. Vaginal radical trachelectomy involves removal of the cervix with conservation of the uterus. A permanent cerclage is placed in the uterine isthmus.

Patients with disease confined to the cervix who have tumors 2 cm or less in size and no node involvement can be treated by limited surgery that preserves fertility such as radical trachelectomy, which removes the cervix with conservation of the uterus. For high-risk disease, adding weekly cisplatin-based chemotherapy to radiation decreases the risk of recurrence by 34% and improves overall survival. Adding the anti-vascular endothelial growth factor monoclonal antibody bevacizumab to chemotherapy improves overall survival in patients with distant metastases.

KEY POINTS

- Early cervical cancer is frequently asymptomatic, but the most common symptoms are abnormal or heavy vaginal bleeding or vaginal discharge; advanced cervical cancer symptoms include pelvic or back pain and bowel or bladder symptoms.
- Select patients with cervical cancer confined to the cervix can be treated with surgery that preserves fertility.
- Patients with bulky or locally advanced cervical cancer are treated with cisplatin-based chemotherapy and radiation instead of surgery.

Prognosis and Surveillance

The 5-year relative survival for all stages of cervical cancer is 67.5%. The anatomic stage is the most important predictor of prognosis. Ninety percent of patients with localized disease survive 5 years. The 5-year survival rate drops to 58% for patients with regional disease and 17% for patients with disease extending outside of the true pelvis or involving the bladder or rectum.

Surveillance is recommended to monitor for recurrences that are potentially curable. Guidelines recommend doing a history and physical examination every 3 to 6 months for 2 years, every 6 to 12 months during years 3 to 5, and then annually based on the risk of recurrence. Annual vaginal cytology, cervical cytology, or both is recommended. Imaging and laboratory studies are recommended only if indicated based on symptoms or findings on examination that are suspicious for recurrence.

TABLE 44. International Federation of Gynecology and Obstetrics Cervical Cancer Staging and Treatment

Stage	Treatment
I: Carcinoma is strictly confined to the cervix IA: Microscopic disease only, up to 5 mm in depth and up to 7 mm in horizontal spread IB: Clinically visible disease, or microscopic disease larger than IA criteria	IA and IB: Modified radical (for lesions <2 cm) or radical hysterectomy with pelvic lymph-node dissection is preferred; if poor functional status, radiation can be used instead. If treated with surgery, adjuvant radiation or chemoradiation is added if indicated based on final pathologic findings. Fertility preservation surgery is an option for cancers ≤2 cm with no lymph node metastases. IA: Simple hysterectomy, cone biopsy (conization), or removal of cervix (trachelectomy) are options.
IIA and IIB: Cervical carcinoma invades beyond the uterus, but not to the pelvic wall or lower third of the vagina. IIB has parametrial invasion.	IIA: Same as for stage I IIB: Same as for stage III
III: The tumor extends to the pelvic wall and/or involves the lower third of the vagina and/or causes hydronephrosis or nonfunctioning kidney	III: Radiation with concurrent platinum-based chemotherapy
IV: The carcinoma extends beyond the true pelvis or involves (biopsy proven) the mucosa of the bladder or rectum IVA: Spread to adjacent organs IVB: Distant metastases	IVA: Same as for stage III IVB: Palliative cisplatin-based chemotherapy, with radiation for local symptoms, such as bleeding or pain

KEY POINT

HVC • Surveillance imaging and laboratory studies for cervical cancer survivors are recommended only if there are signs or symptoms suggestive of recurrence.

Gastroenterological Malignancies

Colorectal Cancer

Colorectal cancer (CRC) is the fourth most common cancer and the second leading cause of cancer death in North America, yet it is largely preventable through screening. CRC screening of average-risk patients is discussed in MKSAP 18 General Internal Medicine. Most colon cancers are adenocarcinomas that begin in the inner lining and progress to involve or spread beyond the full thickness of the bowel wall, then to regional lymph nodes, and subsequently to distant organ metastases. Epidemiology, pathophysiology, risk factors (and screening high-risk patients), and clinical manifestations will be discussed in MKSAP 18 Gastroenterology and Hepatology.

Recent evidence suggests tumors on the right side of the large intestine (cecum, ascending colon, and proximal two thirds of transverse colon) have a completely different biology, likely related to embryologic origin, and a substantially worse prognosis than tumors on the left side (distal one third of transverse colon, descending colon, sigmoid colon, and rectum). Symptoms may also differ based on tumor location, with left-side tumors more likely to cause a change in bowel habits. Cancer in the cecum, with a larger lumen and less formed stool, does not generally cause a change in bowel habits until the tumor is advanced in size, but may present with iron-deficiency anemia with occult, chronic blood loss. Colon cancer at any location may also present with hematochezia, pain, or acute clinical signs from perforation or obstruction.

Approximately 15% of CRCs lack one or more mismatch repair enzymes and are known as mismatch repair deficient (dMMR) CRC. This manifests itself as increased microsatellite instability (MSI) in the cancer cell's DNA; the terms *dMMR* and *MSI* are essentially synonymous. Most guidelines now recommend that all CRCs should be screened for dMMR or MSI. Approximately 25% of patients with dMMR tumors will have Lynch syndrome, which is associated with a high lifetime risk of CRC as well as endometrial and other cancers. Patients and family members with Lynch syndrome require formal genetic counseling and more intense cancer surveillance. Mismatch repair status or the tumor can affect treatment choices in patients with stage II or stage IV cancer as discussed below.

KEY POINTS

- Recent evidence suggests tumors on the right side of the large intestine have a different biology and substantially worse prognosis than tumors on the left side.

(Continued)

KEY POINTS ***(continued)***

- Tumors in all colorectal cancer patients should be screened for mismatch repair enzyme deficiency or microsatellite instability, which increases the risk of Lynch syndrome and other cancers.

Staging

Staging with the TNM cancer staging system is the first step in treatment planning (**Table 45**). Evaluation includes serum carcinoembryonic antigen (CEA) in addition to routine laboratory studies; a full colonoscopy (if possible); and contrast-enhanced CT scans of the chest, abdomen, and pelvis. Rectal cancers also require a rectal MRI or endorectal ultrasonography, both of which offer more precision in assessing tumor penetration and lymph node involvement. PET scans have not been demonstrated to provide greater accuracy in staging and should not be routinely used for preoperative staging or postoperative surveillance.

Treatment

Rectal Cancer

Rectal cancers without full thickness penetration of the bowel wall or enlarged lymph nodes are stage I and are treated with surgical resection. Small tumors may be resected by a transanal approach, decreasing postoperative morbidity. Unless more extensive disease is found at operation, no further treatment is warranted.

Full-thickness tumors (stage II) and involved lymph nodes (stage III) require radiation, chemotherapy, and surgery. The optimal sequencing and combining of the three treatment modalities is being studied. Attempts are made to preserve anal sphincter function, but distal rectal lesions may require an abdominal-perineal resection and permanent colostomy.

Intravenous 5-fluorouracil (5-FU) or oral capecitabine, a prodrug that is converted into 5-FU, is given concurrently with radiation therapy. The chemotherapy may be associated

TABLE 45. Staging of Colorectal Cancer

Stage	Description	Approximate 5-Year Disease-Free Survival
I	Tumor does not invade the full thickness of bowel wall (T1, T2); lymph nodes not involved (N0)	90%-95%
II	Tumor invades full thickness of the bowel and may invade into pericolonic or perirectal fat (T3, T4); lymph nodes not involved (N0)	70%-85%
III	One or more lymph nodes involved with cancer (N1, N2); any T stage	25%-70%
IV	Metastatic tumor spread to distant site (M1); any T stage; any N stage	0%-10%

with edema and erythema of the palms and soles that may progress to blistering and necrosis (hand-foot syndrome), mucositis, diarrhea, and neutropenia. Leucovorin, 5-FU, and oxaliplatin (FOLFOX) or capecitabine plus oxaliplatin (CAPOX) regimens are typically used for the chemotherapy-only portion of the treatment. Oxaliplatin often causes a peripheral neuropathy that does not resolve fully in some patients.

Following therapy, patients with rectal cancer should be evaluated at approximately 6-month intervals for up to 5 years with a history, physical examination, and serum CEA level assessment. Contrast-enhanced CT scans of the chest, abdomen, and pelvis are typically obtained annually for 5 years.

Colon Cancer

Nonmetastatic colon cancers are managed with initial surgery. Pathologic evaluation determines further treatment.

Patients with stage II cancer lacking high-risk features, such as poorly differentiated histology, T4 primary tumor, lymphovascular invasion, inadequate lymph node sampling, poorly differentiated histology, elevated postoperative CEA, or perforation or obstruction, are unlikely to benefit from adjuvant treatment. Patients with one or more of these risk factors may be considered for adjuvant 5-FU or capecitabine. All stage II colon tumors should be assessed for MSI or dMMR, because such tumors, when stage II, are at low risk for recurrence, do not benefit from adjuvant chemotherapy, and should not be treated regardless of the presence of other potential risk factors.

FOLFOX and CAPOX, given for approximately 6 months, are equally acceptable adjuvant chemotherapy regimens and reduce the risk of cancer recurrence and death in patients with stage III cancer.

As with rectal cancer, routine evaluation and serum CEA assessment should be done at approximately 6-month intervals, with annual CT scans for up to 5 years after therapy.

Postoperative surveillance following curative resection is used to identify oligometastatic disease in the liver or lung that may be resectable. Patients with metastatic foci confined to liver or lung should be referred for surgical evaluation. Complete resection of metastatic foci may lead to cure in 25% of these patients. Contrast-enhanced CT scans of the chest, abdomen, and pelvis are recommended annually for up to 5 years postoperatively. PET scanning should not be used for routine surveillance. Colonoscopy is recommended one year after resection (or 3 to 6 months after resection if a complete colonoscopy was not done preoperatively), and then in 3 years, followed by every 5 years, unless abnormalities are found. In 2016, the United States Multi-Society Task Force on Colorectal Cancer recommended that flexible sigmoidoscopy or endoscopic ultrasound be performed every 3 to 6 months for the first 2 to 3 years after surgery in patients with rectal cancer who are at increased risk for local recurrence.

KEY POINTS

- Pretreatment evaluation of rectal cancer requires a rectal MRI or endorectal ultrasonography.
- PET scans should not be used for preoperative staging or postoperative surveillance in colorectal cancer. **HVC**
- Standard treatment of stages II and III rectal cancer is either chemoradiotherapy (with 5-fluorouracil or capecitabine), followed by surgery and adjuvant chemotherapy, or neoadjuvant chemotherapy followed by chemoradiotherapy, followed by surgery.
- Patients with stage II colon cancer that lacks high-risk features are unlikely to benefit from adjuvant chemotherapy. **HVC**
- Posttreatment surveillance for patients with colon cancer includes periodic history; physical examination; serum carcinoembryonic antigen level testing; and CT of the chest, abdomen, and pelvis, as early detection and resection of isolated metastatic disease can still result in cure; repeat colonoscopy should be done at 1 year, then in 3 years, followed by every 5 years.

Metastatic Disease

All metastatic CRC requires molecular analysis for *KRAS*, *NRAS*, and *BRAF* gene mutation status as well as dMMR determination. This rarely affects the choice of first-line therapy but will define subsequent treatment options, discussed later. These tests can be done on either the primary tumor or a metastasis; rebiopsy of metastases for the purpose of these studies is rarely needed.

Patients with metastatic disease limited to the liver should be evaluated for surgical resection with curative intent. Unresectable metastatic CRC is treatable but not curable. Although chemotherapy may be palliative and even extend survival, patients who have a poor performance status may not benefit or may have unacceptable toxicity. A careful discussion should be undertaken with the patient to establish goals of care and expectations.

5-FU is at the center of most treatment regimens, with longer infusions preferable to bolus administration. Newer drugs have failed to replace 5-FU, but leucovorin is often combined with 5-FU, or capecitabine can be an alternative to 5-FU. Other cytotoxic agents used in metastatic CRC include irinotecan and oxaliplatin. The anti-vascular endothelial growth factor (VEGF) monoclonal antibody bevacizumab is often given concurrently with first-line cytotoxic chemotherapy regimens. This agent has essentially no antitumor activity in CRC on its own, but it does potentiate other chemotherapies, resulting in a modestly increased duration of progression-free survival, and in some studies, in increased duration of overall survival. Studies have shown that continuing an anti-VEGF agent with second-line chemotherapy also modestly improves overall survival. Bevacizumab commonly causes hypertension,

sometimes requiring antihypertensive medication. It also interferes with wound healing and needs to be discontinued 6 to 8 weeks before elective surgery and withheld for at least a month after surgery. Very rare but potentially life-threatening side effects include arterial thrombotic events such as myocardial infarction, cerebrovascular accidents, and gastrointestinal perforations.

Panitumumab and cetuximab are monoclonal antibodies that bind to and block activation of the epidermal growth factor receptor (EGFR). They are potentially active only in tumors that are nonmutated (wild-type) *KRAS*, *NRAS*, and *BRAF* genes. In addition, more recent data suggest that these agents may only have activity in tumors derived from the left side of the large intestine. The major side effect of these agents is an acneiform rash, which can be painful, pruritic, and socially debilitating. There is a tight correlation between rash and antitumor activity, and patients who have only a mild skin rash are unlikely to benefit from these agents. Anti-EGFR agents should not be used concurrently with anti-VEGF agents; two large randomized trials found an unexpected detriment with concurrent use.

Thus far, immune checkpoint inhibitors have been inactive in metastatic CRC, with the exception of those rare tumors that are metastatic and dMMR. The programmed death 1 (PD-1) receptor inhibitors pembrolizumab and nivolumab have both shown activity in such patients; however, dMMR tumors make up only 1% or 2% of metastatic CRC.

Multigene sequencing may open some experimental options, but it does not yield actionable information in terms of standard management options at this time. Thus the expense is not warranted outside of a potential research setting.

KEY POINTS

- All metastatic colorectal cancers require molecular analysis for *KRAS*, *NRAS*, and *BRAF* gene mutation status as well as mismatch repair gene deficiency, which will determine treatment after first-line therapy.
- The anti-vascular endothelial growth factor antibody bevacizumab potentiates the efficacy of 5-fluorouracil combined with either leucovorin or capecitabine in treating metastatic colon cancer, but is associated with worsening hypertension, arterial thrombosis, poor wound healing, and gastrointestinal perforation and fistula formation.

Anal Cancer

Anal cancer is a human papillomavirus (HPV)-associated malignancy. Unlike rectal cancer, which is an adenocarcinoma, anal cancer is a squamous cell carcinoma. Anal cancer is often curable with combined radiation and chemotherapy; surgery is typically not indicated. Mitomycin plus 5-FU or capecitabine is the standard chemotherapy regimen. Although complete regression may be observed as soon as 8 weeks after radiation, responding tumors may continue to regress for up to 6 months after radiation. If tumor growth is seen after radiation, then salvage surgery with a permanent colostomy is indicated. Distant metastases are rare. When they do develop, chemotherapy with oxaliplatin, cisplatin, or carboplatin is often active.

Although HPV vaccination would be expected to be as effective at cancer prevention as it is with other HPV-related malignancies, there is no evidence that HPV vaccination plays a role in treatment or post-treatment management of patients with anal cancer. See MKSAP 18 General Internal Medicine for further discussion of HPV vaccination.

KEY POINT

- Anal cancer, a squamous cell carcinoma linked to human papillomavirus, is often cured by combination radiation and chemotherapy, sparing the need for surgical resection and subsequent colostomy.

Pancreatic Cancer

There are approximately 53,000 patients diagnosed with exocrine pancreatic cancer per year in the United States. Mortality is high, with 42,000 deaths expected annually. Only patients who can undergo a complete resection have a chance of cure. When disease is unresectable because of invasion into critical vascular structures, median survival is approximately 1 year. For those with metastatic disease, median survival is typically less than half that.

Most pancreatic cancers lack a genetic predisposition, although 5% to 10% of patients have either a strong family history of pancreatic cancer, an identifiable mutation that confers increased risk, or both. Some rare familial pancreatic cancer syndromes have been recognized, including patients with *BRCA* gene mutations, but *BRCA* screening is not recommended for those without a strong family history. Chronic pancreatitis, obesity, type 2 diabetes mellitus, high red meat consumption, alcohol abuse, and tobacco use are implicated risk factors.

H Painless jaundice, abdominal pain, weight loss, persistent fevers, or protracted nausea and vomiting may be presenting symptoms. Manifestations of hypercoagulability, including Trousseau syndrome (a migratory superficial thrombophlebitis of the lower extremities), chronic disseminated intravascular coagulation, deep venous thrombosis, or pulmonary embolism, may be the initial manifestations of underlying pancreatic cancer. H

A contrast-enhanced CT of the chest and abdomen (or noncontrast chest CT and abdominal MRI) are appropriate for staging and treatment planning. PET scans have not been shown to add value in pancreatic cancer and are not part of standard management. For patients whose disease is confined to the pancreas with or without involved local regional lymph nodes, resectability is the most important question. Endoscopic ultrasonography may help in staging and is used to more precisely guide diagnostic needle biopsy. Some patients with clinical features that strongly suggest malignancy may not require such preoperative biopsy, as false-negative results

would not obviate the need for surgical resection. Magnetic resonance cholangiopancreatography may also be useful in delineating resectability in borderline patients. Conversion therapy—using radiation or chemotherapy to convert locally unresectable disease to resectable—has garnered interest, but evidence defining how successful this approach actually is remains limited and preliminary.

Patients without evidence of metastatic disease who appear to have technically resectable disease should undergo resection.

Patients who are medically well enough to receive chemotherapy after resection should do so. A trial that compared single-agent gemcitabine to observation showed improved survival for patients who received gemcitabine, and a more recent trial comparing single-agent gemcitabine to gemcitabine plus capecitabine showed improved survival for the combination arm. The data for use of adjuvant radiation therapy are controversial.

Patients experience considerable morbidity following resection of pancreatic cancer, with most requiring pancreatic enzyme replacement therapy and those with the most extensive pancreatic resection needing lifelong insulin therapy.

For metastatic disease, the combination regimen of oxaliplatin, irinotecan, 5-FU, and leucovorin (FOLFIRINOX) or the combination of nab-paclitaxel and gemcitabine has each shown better antitumor activity and modest survival benefits over single-agent gemcitabine in randomized trials, but the combination regimens have higher toxicity. In second-line therapy, liposome-encapsulated irinotecan added to 5-FU has shown activity. Clinical trials are needed to define second-line therapy for metastatic pancreatic cancer.

KEY POINTS

- Patients without metastatic disease who have clinical staging suggesting resectable or borderline resectable pancreatic cancer should undergo resection as it is the only option for cure.
- PET scans have not been shown to add value in the staging of pancreatic cancer and are not part of standard management.
- The use of adjuvant chemotherapy with gemcitabine and capecitabine following successful pancreatic resection will prolong survival.

Gastroesophageal Cancer

Epidemiology, risk factors, and clinical manifestations of esophageal and gastric cancer are discussed in MKSAP 18 Gastroenterology and Hepatology.

Upper gastrointestinal tract cancers are a major cause of cancer deaths worldwide, particularly in Asia and Africa. The incidence has been increasing significantly in the United States and Western countries, albeit with changing pathology. With the dramatic rise in the incidence of adenocarcinoma of the distal esophagus and proximal stomach, gastroesophageal cancer is now considered a single entity.

Smoking and alcohol use remain the major risk factors for the traditional squamous cell carcinoma of the esophagus. Risk factors for adenocarcinoma also include smoking along with gastroesophageal reflux disease (GERD) and obesity. The development of Barrett esophagus as a result of GERD, especially with dysplastic features, is a further risk for developing adenocarcinoma of the esophagus, and regular surveillance is indicated. See MKSAP 18 Gastroenterology and Hepatology for more detailed information on Barrett esophagus and GERD.

Pain or difficulty on swallowing, weight loss, nausea, vomiting, or persistent dyspepsia may be presenting symptoms. Upper endoscopy and biopsy establishes the diagnosis. Endoscopic ultrasonography is routinely used to assess the depth of tumor penetration and presence of involved lymph nodes. In contrast to the evaluation of other gastrointestinal tumors, PET-CT is widely used as part of standard preoperative staging.

Surgery is the primary treatment of locoregional disease, found in approximately one third of patients. Data have shown a survival benefit for preoperative therapy with either neoadjuvant chemotherapy or the combination of neoadjuvant chemotherapy and radiation therapy. For those patients with cancer who undergo surgery first and whose cancer is more advanced than stage I, adjuvant chemotherapy is warranted. A recently reported trial of adjuvant chemotherapy with or without adjuvant radiation therapy showed no difference in outcome, raising questions as to the utility of radiation in this setting. Unfortunately, recurrence rates following surgical resection remain high, even with the use of adjuvant therapy.

Treatment of recurrent or metastatic disease is only modestly effective and is not curative.

Approximately 25% of gastroesophageal cancers overexpress the human epidermal growth factor receptor 2 (*HER2*), and it is now standard practice to evaluate gastroesophageal tumors for *HER2* overexpression. For these patients only, the addition of the anti-*HER2* monoclonal antibody trastuzumab to chemotherapy provides a modest but statistically significant survival benefit. More recently, the anti-VEGF receptor monoclonal antibody ramucirumab has shown modest activity as a non-first-line treatment, either alone or in combination with a taxane.

KEY POINTS

- Smoking, obesity, and gastroesophageal reflux disease, especially with the development of Barrett esophagus, are risk factors for adenocarcinoma of the esophagus, gastroesophageal junction, and proximal stomach.
- In contrast to other gastrointestinal tumors, PET-CT is widely used as part of standard preoperative staging of gastroesophageal cancer.
- Upper gastrointestinal tumors should be evaluated for human epidermal growth factor 2 (*HER2*) overexpression; adding trastuzumab to chemotherapy regimens for patients with *HER2* overexpression provides a modest survival benefit.

Gastric Lymphoma

The stomach may be the primary site for extranodal lymphoma, a heterogeneous group of B-cell and T-cell neoplasms, generally treated with combination chemotherapy. A specific variant, mucosa-associated lymphoid tissue (MALT) lymphomas, are indolent tumors that often present with localized disease and concomitant *Helicobacter pylori* infection. In that setting, standard treatment to eradicate the *H. pylori* infection results in sustained complete remission in the majority of patients without the need for additional chemotherapy or radiation therapy. MALT is discussed further in Lymphoid Malignancies.

Neuroendocrine Tumors

Gastrointestinal neuroendocrine tumors (NETs) (formerly called carcinoid tumors) arise from the endocrine cells of the digestive tract. Pancreatic NETs arise from the islets of Langerhans cells and were previously called islet cell tumors. Although histologically similar, gastrointestinal and pancreatic NETs behave differently, with several drugs showing activity against pancreatic NETs but not gastrointestinal NETs. The clinical features of pancreatic NETs are discussed in MKSAP 18 Gastroenterology & Hepatology. NETs are rare in incidence but are typically indolent, and patients frequently survive many years, resulting in a high prevalence relative to the incidence.

Well-differentiated NETs exhibit indolent growth. These range from low grade (low proliferative index) to intermediate grade (somewhat higher proliferative index). As would be expected, intermediate-grade tumors are generally, but not always, more aggressive than low-grade tumors. Poorly differentiated, high-grade NETs are highly aggressive tumors that are treated with etoposide plus cisplatin regimens used for small cell lung cancer.

Most NETs do not produce hormones and are termed "nonfunctional," but approximately 25% do produce a hormone, in which case the hormone-related symptoms are often both the source of presentation and morbidity. Gastrointestinal NETs can produce serotonin, which can cause the classic carcinoid syndrome of diarrhea and facial flushing.

Nonfunctional NETs are often discovered incidentally. The liver is the most common site of metastases, and metastatic disease may be present asymptomatically for years before it is identified.

Given the indolent nature of NETs, observation and serial imaging are appropriate initially; asymptomatic patients may do well, with minimal growth and no symptoms for years, even with metastatic disease. Follow-up examination and imaging at approximately 3 months is appropriate. In patients whose disease appears stable at the 3-month CT scan, further monitoring with serial imaging at 3-month to 6-month intervals is appropriate.

In tumors with somatostatin receptors, the somatostatin analogs octreotide or lanreotide may be used for hormonal control or for stabilization of progressing disease. Hepatic arterial embolization, radiofrequency ablation, or surgical debulking are sometimes used to decrease hormone production or to relieve symptoms of tumor bulk.

When treatment is needed, pancreatic NETs can be treated with temozolamide plus capecitabine, or sunitinib (an anti-VEGF tyrosine kinase inhibitor), or everolimus (a mammalian target of rapamycin [mTOR] inhibitor). Everolimus has more modest activity in gastrointestinal NETs, but the other agents used for pancreatic NETs are inactive in gastrointestinal NETs.

KEY POINTS

- Gastrointestinal neuroendocrine tumors (NETs) arise from the endocrine cells of the digestive tract, whereas pancreatic NETs arise from the islets of Langerhans cells; although histologically similar, gastrointestinal and pancreatic NETs behave differently, with several drugs showing activity against pancreatic NETs but not gastrointestinal NETs.
- Gastrointestinal neuroendocrine tumors can produce serotonin, which can cause the carcinoid syndrome characterized by diarrhea and facial flushing.
- Well-differentiated neuroendocrine tumors are indolent and only require observation and serial imaging. HVC

Gastrointestinal Stromal Tumors

Gastrointestinal stromal tumors (GISTs), derived from the precursors of the interstitial cells of Cajal, are sarcomas characterized by an activating mutation in the c-*kit* proto-oncogene, which leads to constitutive activation of the receptor tyrosine kinase. Histologically, GISTs are identified by overexpression of the *KIT* gene, the immunohistochemical marker for KIT protein. Although these tumors may be asymptomatic or discovered during an endoscopic or imaging procedure done for another purpose, most are associated with nonspecific gastrointestinal symptoms, and some may cause overt bleeding, pain, or signs of obstruction. They are most commonly located in the stomach, which confers a better prognosis, and in the proximal intestine. Other prognostic factors include tumor size and mitotic rate.

For patients undergoing a potentially curative resection of a localized GIST, low-risk tumors do not benefit from further treatment. Higher-risk tumors are treated with adjuvant tyrosine kinase inhibitor imatinib; 3 years of imatinib yields outcomes superior to 1 year of treatment. Imatinib is also used to treat patients who present with unresectable or metastatic disease.

KEY POINT

- High-risk gastrointestinal stromal tumors should be treated with surgery and 3 years of adjuvant imatinib.

Lung Cancer

This section will focus on treatment and follow-up of patients with lung cancer. See MKSAP 18 Pulmonary and Critical Care Medicine for discussion of epidemiology, screening, clinical manifestations, diagnosis, and staging of patients with lung cancer. Initial biopsy can distinguish tumors as either non-small cell lung cancer (NSCLC) or small cell lung cancer (SCLC). NSCLC can be divided into pathologic subtypes, including large cell, adenocarcinoma, and squamous cell cancer. Although these subtypes have characteristic clinical features, the diagnosis, staging, and therapy for all forms of NSCLC are similar. The staging criteria and treatment of SCLC differ from NSCLC.

Non-Small Cell Lung Cancer

Treatment of NSCLC, like that of most other solid malignancies, is based largely on disease stage. For the purposes of this discussion, it is best to divide NSCLC into early stage, locally advanced, and metastatic categories.

Early-Stage Disease

Early-stage disease refers to lung cancer that is amenable to surgical resection at the time of diagnosis. This typically encompasses stage I and II cancers, though some patients with stage II cancer are not amenable to resection based on location or extent of the primary tumor. Stages I and II are differentiated by hilar nodal metastatic disease (present in some patients with stage II cancer, but not present in stage I) and also by the size and invasiveness of the primary tumor into adjacent structures. As in many other cancers, multidisciplinary evaluation is of vital importance to these patients in order to make the most accurate determination regarding optimal treatment.

Patients deemed potential surgical candidates based on imaging need to have a rigorous functional evaluation to help predict their anticipated pulmonary reserve after surgery. The initial evaluation consists of FEV_1 and DLCO measurement. If both test variables are favorable, then no further evaluation is needed. However, if one or the other variable falls in a range suggesting impaired lung function, then calculation of the predicted postoperative FEV_1 and DLCO should be performed, which is determined by baseline values and assessment of the fractional contribution of the lung to be resected. If the predictive postoperative lung function values indicate mild to moderate impairment, then exercise testing is often used. Based on the results of these assessments, a decision can be made regarding suitability for resection. Patients with pathologic stage I cancer who are undergoing surgical resection have a 60% to 70% survival rate at 5 years and patients with stage II cancer have approximately a 40% survival rate.

For patients who are not surgical candidates, other options are available, including stereotactic body radiation and other ablative treatments that can be used to treat the primary tumor. Such treatments have been shown to have excellent rates of local control, but they are only suitable for patients with relatively small tumors. For larger tumors, conventional radiation is used. There are no data supporting the use of chemotherapy combined with radiation in patients with stage I or II disease. Despite the adverse effect of their comorbid lung disease, patients with localized tumors treated with radiation have a mean survival of greater than 3 years.

Lobectomy is the preferred surgical procedure in early-stage disease. Proximal tumors may be less amenable to lobectomy. In those patients, sleeve resection (resection of the involved lobe and a portion of the main stem bronchus) has fewer postoperative complications and is preferable to pneumonectomy. Sublobar resection is not recommended but can be considered in selected patient populations (such as elderly patients and those with stage I cancer).

Patients treated surgically for stage I or II disease who have positive margins benefit from postoperative radiation therapy and show an improvement in overall survival. This is not the case for patients with negative surgical margins.

Cisplatin-based adjuvant chemotherapy has been shown to improve survival after resection in patients with resected stage II or III lung cancer. The LACE meta-analysis, which used patient data from five different cisplatin-based adjuvant chemotherapy trials, found a 5.4% decrease in the risk of death at 5 years in patients with resected stage II or III disease. Another meta-analysis identified a 4% improvement in survival at 5 years in patients treated with cisplatin-based chemotherapy after surgery and radiation. Approximately 50% of patients who had surgically resected stage I, II, or IIIA cancer survived 5 years. Chemotherapy consists of cisplatin with a second agent and is typically given for four cycles. The most commonly used chemotherapy partners are vinorelbine, pemetrexed, gemcitabine, and docetaxel.

After completion of treatment, patients with early-stage disease remain at risk for both distant and local recurrence. Many patients with smoking histories are also at risk for developing a second primary lung cancer and cancers of the head, neck, and other sites. Current accepted recommendations for surveillance include history, physical examination, and chest CT at least every 6 months for the first 2 years and then annually. Smoking cessation decreases the risk of new primary lung cancers, although the magnitude of benefit is uncertain, ranging from 20% to 90%; the risk steadily declines beginning 5 years after quitting, but it never quite reaches the incidence found in nonsmokers.

KEY POINTS

- Lobectomy is the preferred surgical procedure in early-stage disease.
- Potential surgical candidates with early-stage lung cancer must have FEV_1 and DLCO measurement to predict their anticipated postoperative pulmonary reserve and suitability for resection.

(Continued)

KEY POINTS *(continued)*

- Patients with early-stage lung cancer who are not surgical candidates can be treated with radiation therapy; stereotactic body radiation is appropriate for small tumors, but conventional radiation is used for large tumors.
- Postoperative radiation therapy is used to treat patients with resected localized lung cancer and positive tumor margins; cisplatin-based adjuvant chemotherapy is standard treatment of all resected stage II and III lung cancer.

Locally Advanced Disease

Locally advanced lung cancer is most commonly defined by the presence of clinically detectable lymphadenopathy in the mediastinum or by a primary tumor that invades into local structures, such as the mediastinum, heart, trachea, esophagus, or great vessels.

Safer, more refined surgical technique, along with more precise preoperative staging that more accurately defines the primary tumor, has expanded the number of patients eligible for surgical resection, although it is unclear whether this has resulted in improved survival outcomes. For example, some patients with T4 tumors showing invasion into adjacent vital structures, with no evidence of mediastinal node involvement, can have surgical resection and their disease treated as stage III disease. Patients with satellite nodules in the same lobe (T3) or in another ipsilateral lobe (T4) were previously considered to have metastatic disease, but can be resected with curative intent. Even patients with an isolated tumor nodule in the contralateral lung, traditionally considered incurable metastatic disease, can now undergo resection to remove all sites of cancer under the assumption that the nodule could represent a second localized primary lung cancer. Finally, patients with limited ipsilateral mediastinal node involvement, a single node station, and nonbulky disease can undergo surgical resection. These patients will all generally receive neoadjuvant or adjuvant chemotherapy or radiation treatment.

Patients who present with bulky or multistation (widespread mediastinal or hilar lymph node involvement) mediastinal lymphadenopathy are treated with combined platinum-based chemotherapy and radiation, which has been found to be superior to sequential treatment. Unfortunately, the risk of recurrence, both locoregional and distant, is very high after chemoradiation treatment (approaching 70% to 90%).

KEY POINT

- Surgical techniques have improved substantially and, along with better preoperative staging, allow surgical therapy with curative intent for various patients who were traditionally considered to have unresectable disease.

Metastatic Disease

Metastatic lung cancer is defined as the spread of disease to distant sites such as liver, bone, or brain. The presence of one or more tumor nodules in the contralateral lung also qualifies as metastatic disease, but as the prognosis for that pattern of metastatic disease is notably better than that of patients with distant disease, it has been reclassified as M1a, with other distant sites given the designation of M1b.

In the past, all patients with metastatic NSCLC were treated with the same chemotherapy regimens. With the recent development of precision medicine, specific molecular and genetic targets have been discovered, resulting in more tailored treatments. Furthermore, it is now understood that patients with different histologic types of lung cancer respond differently to various chemotherapy agents. Immunotherapy has now been shown to have an impact on the treatment of advanced lung cancer. Despite these advances, however, metastatic NSCLC remains incurable. Level 1 evidence supports early palliative care interventions in this patient population. Their quality of life will be improved even as they continue to receive aggressive chemotherapy.

Before deciding the optimal treatment for any given patient, it is essential to define histology, assess for molecular alterations, and determine performance status. For patients with non-squamous histology (particularly adenocarcinoma), testing for molecular alterations is mandatory. At present, it is considered standard care to test for mutation in the epidermal growth factor receptor (*EGFR*) gene and for translocations involving *ALK* or *ROS1*. If an *EGFR* mutation is identified, initial treatment with erlotinib is recommended. If an *ALK* or *ROS1* translocation is identified, initial treatment with crizotinib is recommended. Erlotinib and crizotinib are both small molecule tyrosine kinase inhibitors that are specific for those genetic alterations. Although many other molecular and genetic alterations have been identified in patients with NSCLC, further investigation is required before changes in treatment become evidence-based care.

If a patient has negative findings for the alterations noted above, treatment with chemotherapy is indicated only if the patient has a good performance status. Patients with poor performance status do not benefit from chemotherapy treatment. Front-line chemotherapy is given with a platinum-based doublet regimen. Either cisplatin or carboplatin can be used; cisplatin is slightly more active, but carboplatin is more commonly used because of its more favorable side-effect profile. Histologic assessment can help guide choice of the second agent, as patients with adenocarcinoma have been shown to respond well to pemetrexed, whereas those with squamous cell carcinoma respond better to gemcitabine, based on the results of a phase III clinical trial comparing these two agents. Other commonly used second agents in this setting include paclitaxel, docetaxel, and vinorelbine. Chemotherapy is administered for four to six cycles and can be given in combination with bevacizumab. Bevacizumab is a monoclonal

antibody directed against vascular endothelial growth factor and when given in combination with platinum-based chemotherapy for patients with non–squamous cell forms of NSCLC in the first-line setting, it has been shown to improve both progression-free survival and overall survival, though the degree of benefit is modest. In addition, bevacizumab carries the risk of thrombosis, stroke, myocardial infarction, and hemoptysis in some patients. For patients who respond to front-line chemotherapy, maintenance treatment with docetaxel, pemetrexed, or gemcitabine has been shown to improve progression-free survival, and pemetrexed has also been shown to improve overall survival.

Immunotherapy with agents that act on the programmed cell death ligand 1 (PD-L1) have shown impressive activity in metastatic NSCLC. Pembrolizumab is superior to chemotherapy in the first-line treatment of patients with NSCLC who have PD-L1 expression greater than 50% with a higher response rate, progression-free survival, and overall survival when compared to standard chemotherapy. Pembrolizumab and nivolumab are also both more active than chemotherapy in the second-line setting.

KEY POINTS

- Metastatic non–small cell lung cancer that demonstrates an epidermal growth factor receptor gene mutation should be treated initially with erlotinib; if an *ALK* or *ROS1* translocation is identified, initial treatment should be with crizotinib.
- If metastatic non–small cell lung cancer is negative for gene mutations or translocations, platinum-based doublet chemotherapy in combination with bevacizumab is appropriate for patients with good performance status.

Small Cell Lung Cancer

SCLC, a neuroendocrine neoplasm, has been decreasing in incidence during the past several years, and currently it accounts for approximately 10% of lung cancer cases. SCLC is almost exclusively caused by smoking. In unfortunate contrast to the advances made in the treatment of NSCLC, little has changed in the prognosis or treatment of SCLC patients. Most patients initially present with distant metastatic disease. SCLC is known to be associated with paraneoplastic syndromes, most prominently syndrome of inappropriate antidiuretic hormone secretion and Eaton-Lambert myasthenia. The staging of SCLC is straightforward and defines patients with "limited disease" that can be encompassed by a hemithoracic radiation portal; all others, including those with distant metastases, have "extensive disease." Patients should undergo routine CT scan of the thorax, abdomen, and pelvis, but even those who have no bone or central nervous system symptoms should undergo whole body bone scintigraphy and an MRI of the brain.

Typically, primary SCLC presents with proximal and often large tumors, but occasionally it presents as a solitary pulmonary nodule (see Lung Tumors: Pulmonary Nodule Evaluation) and is often not diagnosed until after surgical resection. After resection, these rare patients can be treated with adjuvant chemotherapy, but radiation therapy can be avoided if surgical margins are negative. Surgery can also be performed for small primary tumors without lymph node spread, although preoperative evaluation in those patients should include endobronchial ultrasonography or, if that procedure is not available, mediastinoscopy to rule out occult nodal involvement. Those patients should also receive adjuvant chemotherapy.

Most patients with SCLC will not meet the criteria for primary surgery. Treatment of limited disease consists of combined cisplatin-based chemotherapy, typically cisplatin plus etoposide, and radiation. Chemotherapy is continued after radiation for up to six cycles; prophylactic cranial irradiation should be used in patients with responsive disease because this treatment decreases the rate of subsequent brain metastases and improves overall survival.

For patients who present with extensive disease, treatment consists of platinum-based chemotherapy without radiation, again for up to six cycles. Patients with limited disease that is responsive to treatment and no evidence of brain metastases should be treated with prophylactic cranial irradiation. Patients with extensive disease who have a favorable response to chemotherapy but persistent involvement in the lung can be treated with additional radiation therapy.

Despite treatment response, recurrences are very common, even in patients with limited disease at the time of diagnosis. For patients who had a disease-free interval of more than 3 months, treatment with the initial platinum-based doublet regimen can be used because the likelihood of response is good. However, for patients who relapsed earlier, treatment options and outcomes are generally poor. As in NSCLC, addressing goals of care and aggressive symptom management are of significant importance in this setting.

KEY POINTS

- Routine staging of patients with small cell lung cancer includes whole body bone scintigraphy and MRI of the brain, even if they have no bone or central nervous system symptoms, along with routine CT scan of the thorax, abdomen, and pelvis.
- Although patients with SCLC typically present at an advanced stage, those with early-stage disease can be considered for resection and adjuvant chemotherapy without radiation if surgical margins are negative.
- Treatment of limited-disease SCLC consists of combined cisplatin-based chemotherapy and radiation to the area of lung involvement; treatment of extensive disease consists of analogous chemotherapy, but additional radiation treatment is not indicated.
- Patients with both limited- and extensive-stage SCLC who respond to chemotherapy should receive prophylactic radiation to the central nervous system.

Head and Neck Cancer

Head and neck cancers include primary tumors of the oral cavity, oropharynx, nasopharynx, hypopharynx, larynx, paranasal sinuses, thyroid, and salivary glands. Squamous cell carcinoma is the most common form of head and neck cancer and is therefore the focus of this chapter. Thyroid cancer is discussed in MKSAP 18 Endocrinology and Metabolism.

Risk Factors

The most important risk factor for head and neck cancer is tobacco use, which includes smoked and smokeless tobacco. Alcohol use is also a known risk factor, and the combination of alcohol and tobacco has been found to synergistically increase risk.

Human papillomavirus (HPV), more likely to be found in men and women with behavioral risk for other sexually transmitted diseases, is a recently recognized and increasingly important cause of head and neck cancer, with most HPV-associated cancers arising in the oropharynx (tonsil and base of tongue most commonly). The prognosis of HPV-associated cancer is significantly better than that for non-HPV-related cancer, but smoking can mitigate this improvement. Treatment of head and neck cancer is not altered based on HPV status, although several ongoing studies are addressing this issue.

KEY POINTS

- Tobacco and alcohol use are important risk factors for head and neck cancer, and their combined use synergistically increases risk.
- Human papillomavirus infection is an important cause of oropharyngeal cancer; it does not affect therapy, but the prognosis is better than that for non-HPV-related cancer.

Clinical Manifestations

Presenting symptoms vary with the location of the cancer, but concerning signs and symptoms that generally should raise suspicion of head and neck cancer include persistent or progressive lymph node enlargement or other neck mass, unilateral hearing loss, unilateral ear pain, nasal obstruction, oral pain, nonhealing oral ulcers, dysphagia, odynophagia, and hoarseness.

Evaluation and Staging

Initial evaluation of patients suspected of having head and neck cancer includes history, physical examination, and direct laryngoscopy. Fine-needle aspiration of suspicious lesions will generally establish the diagnosis. Assessment of HPV status using tumor staining for p16, which is overexpressed in HPV-positive cancers, is standard. Although HPV positivity significantly improves prognosis, this finding is not currently used to make treatment decisions.

Once a diagnosis has been established, imaging studies are indicated for accurate assessment of the extent of local disease and evaluation of nodal and distant metastatic disease. MRI is generally superior to CT for anatomic assessment of the primary tumor. PET CT is useful to identify primary tumors and for evaluating regional lymph nodes, tumor invasion, and distant metastatic disease, although it is not accurate in nodes 5 mm or smaller.

The staging of head and neck cancers is complex, as each subsite uses a different staging system. In general, however, staging of primary tumors is based on both size and extent of invasion into adjacent structures, with higher stage tumors exhibiting greater degrees of invasiveness. Nodal staging is predicated on the number of nodes involved, size, and presence or absence of bilateral lymphadenopathy. The stage of head and neck cancer, as with many other malignancies, is the single most important determinant of prognosis. Patients with localized disease have 70% to 90% long-term survival. Given the complexity of head and neck cancer treatment, multimodality tumor board discussion is valuable for determining the proper course of treatment.

KEY POINT

- In patients suspected of having head and neck cancer, fine-needle aspiration should be performed to establish the diagnosis.

Treatment

Approximately one third of patients present with localized or early stage head and neck cancer, generally small tumors that have no lymph node metastases. Although surgery is preferred for early-stage oral cancer and radiation for early laryngeal disease, early-stage head and neck cancer can be effectively treated with either surgery or radiation therapy. Treatment decisions weigh the accessibility of the lesion and complications expected with surgical resection, including quality-of-life issues such as appearance and preservation of speech, with the expected morbidity of radiation therapy, including acute mucositis and fatigue, along with more long-lasting alterations in taste, xerostomia, dental disease, and an increased risk of second malignancies. The need for and extent of additional dissection of lymph nodes in the neck is determined by the site and stage of the primary tumor, anatomy of lymphatic drainage, presence or absence of enlarged nodes, and the results of diagnostic imaging.

The need for adjuvant radiation for patients with primary surgical resection is based on tumor pathology and is recommended for patients with one or more high-risk features (**Table 46**). Combined chemotherapy and radiation can be used for patients felt to be at very high risk for recurrence, most commonly in the setting of extracapsular extension or positive or close margins. Adjuvant chemoradiation is typically given with single-agent cisplatin and concomitant radiation.

TABLE 46. High-Risk Pathologic Features in Head and Neck Cancer
T3 or T4 tumor
Positive or close resection margins
Lymph node extracapsular extension
≥2 positive lymph nodes (N2 or N3)
Perineural invasion
Lymphovascular invasion

Data from Adelstein D, Gillison ML, Pfister DG, Spencer S, Adkins D, Brizel DM, et al. NCCN guidelines insights: head and neck cancers, version 2.2017. J Natl Compr Canc Netw. 2017;15:761-770. [PMID: 28596256] doi:10.6004/jnccn.2017.0101

For patients with more advanced disease at the time of diagnosis, based on either having an unresectable primary tumor or extensive nodal disease, initial treatment with combined chemotherapy and radiation is recommended. Surgery is reserved for treatment of persistent disease or in the setting of inadequate response to treatment. In patients treated with definitive chemoradiotherapy, systemic therapy can be given with cisplatin, a platinum agent, or with cetuximab, a monoclonal antibody directed against the epidermal growth factor receptor.

Treatment of nasopharyngeal carcinoma differs somewhat from that of other sites. Nasopharyngeal carcinoma is rarely resectable at the time of diagnosis, and therefore surgery plays little role in the treatment of this disease. For very early-stage disease, radiation alone can be used with excellent control rates. However, for all other patients, initial treatment with chemoradiotherapy is used. The role of additional adjuvant chemotherapy in more advanced disease is uncertain.

KEY POINTS

- Early-stage oral head and neck cancers are generally treated with surgery, although radiation therapy is preferred for localized tumors of the larynx.
- Adjuvant therapy for locally advanced head and neck cancer includes radiation alone or in combination with single-agent cisplatin chemotherapy.
- Advanced head and neck cancer includes patients with unresectable tumors or extensive nodal disease and should be treated with combined chemotherapy (cisplatin or cetuximab) and radiation; surgery is reserved for treatment of persistent disease or inadequate response to treatment.

Posttreatment Surveillance

After treatment of localized disease, a history and physical examination, including direct laryngoscopy, nasopharyngoscopy, or both, to evaluate for local recurrence and second primary cancers should be conducted every 1 to 3 months for the first year after primary treatment, decreasing in frequency thereafter, with annual evaluation at 5 years. Patients treated with radiotherapy that includes the thyroid bed are at risk for hypothyroidism and thyroid carcinoma. Periodic assessment of thyroid function and a physical examination of the thyroid are indicated, although thyroid ultrasonography should not be performed. Similarly, PET-CT or other imaging surveillance following a negative posttreatment scan is not indicated. Imaging should be performed as needed based on signs and symptoms suggestive of recurrent disease. Patients should be offered lung cancer screening if they meet high-risk criteria.

KEY POINTS

- Posttreatment surveillance for head and neck cancer consisting of history and physical examinations should be performed every 1 to 3 months for the first year, decreasing in frequency through year 5, and then annually.
- Routine imaging for head and neck cancer after a negative posttreatment scan is not indicated unless there are signs and symptoms suggestive of recurrent disease. HVC

Management of Recurrent Head and Neck Cancer

For patients with recurrent head and neck cancer, it is important to decide whether potentially curative therapy is still possible or if treatment instead should be palliative. Cure is most likely in patients whose recurrence is with small localized disease, who have a longer time to recurrence (also termed longer disease-free survival), and who have a site of recurrence in the larynx or nasopharynx. Patients with limited recurrence are treated with surgery and adjuvant therapy as needed. For patients with unresectable local recurrence, treatment with radiation or chemoradiation is appropriate. Reirradiation can be associated with long-term survival, but it is also associated with a potentially significant risk of toxicity including pain, tissue necrosis, infection, and fatal bleeding.

For patients with distant metastatic disease or unresectable persistent local disease not amenable to surgery or radiation, systemic chemotherapy is the mainstay of treatment. The current standard front-line treatment of patients with good performance status is the combination of a platinum agent (cisplatin or carboplatin) with 5-fluorouracil and cetuximab. If progression occurs after front-line therapy, single-agent therapy is indicated, using drugs not previously used. The programmed cell death 1 (PD-1) inhibitors pembrolizumab and nivolumab are FDA approved for treatment following progression after platinum-containing chemotherapy. Patients with distant metastases and unresectable local disease have a poor prognosis, especially if their performance status is declining; treatment decisions should include options for palliative and hospice care.

KEY POINTS

- Favorable factors of recurrent head and neck cancer include small, localized disease; longer time to recurrence; and site of recurrence in the larynx or nasopharynx.
- Patients with good performance status and advanced disease not amenable to surgery or radiation should first receive a combination of a platinum agent (cisplatin or carboplatin) with 5-fluorouracil and cetuximab.

Genitourinary Cancer

Prostate Cancer

Epidemiology and Risk Factors

Adenocarcinoma of the prostate remains one of the most commonly diagnosed types of cancer among men in the United States, with an estimated lifetime risk of one in seven. Age is a very important risk factor; prostate cancer is rarely diagnosed before age 40 years, but after that point, the incidence increases significantly. Ethnicity is also an important risk factor, with the incidence significantly greater for black men than for white or Hispanic men. Further, black men are more likely to be diagnosed at a younger age with higher-risk disease. Genetics and family history also play an important role in risk. Men with a first-degree relative diagnosed with prostate cancer are twice as likely to be diagnosed. Prostate cancer is also linked with germline mutations in different genes, such as *BRCA2*, *HOXB13*, and the Lynch syndrome genes.

Diagnosis and Staging

Prostate cancer is most commonly diagnosed after identification of an elevated serum prostate-specific antigen (PSA) level during screening and in the absence of symptoms. See MKSAP 18 General Internal Medicine for a discussion of current issues relating to prostate cancer screening.

Although urinary symptoms might be present in patients with prostate cancer, they are usually related to benign prostatic hyperplasia and not to the cancer. In some men diagnosed with metastatic disease at the time of initial presentation, bone pain or back pain can be the presenting symptom. If the diagnosis is suspected on the basis of an elevated serum PSA level, the elevation should first be confirmed by a second measurement at least 1 month later. Persistent serum PSA elevation should prompt urology referral, as should a palpable abnormal finding in the prostate on digital rectal examination.

Prostate biopsy is performed using transrectal ultrasonography for guidance, and several cores should be taken from different regions of the gland. Studies have found that increasing the number of cores improves diagnostic accuracy without causing a significant increase in complications. Most commonly, at least five to seven cores are taken per side to provide a sufficient diagnostic yield. Atypical small acinar proliferation and multifocal high-grade prostatic intraepithelial neoplasia are both associated with a high risk of underlying cancer and should prompt rebiopsy.

Risk stratification using serum PSA, Gleason score, and TNM cancer staging based on biopsy results and digital rectal examination is essential for determining prognosis and treatment options (**Table 47**). Imaging studies need not be done in patients whose risk is very low or low but should be obtained in others to evaluate regional lymph node involvement and metastatic disease.

KEY POINT

- Prostate cancer is most commonly diagnosed after identification of an elevated serum prostate-specific antigen level during screening and in the absence of symptoms.

Treatment

Treatment options for men with newly diagnosed localized prostate cancer include active surveillance, radiation, and radical prostatectomy. For men with limited life expectancy or significant medical comorbidities, observation is most appropriate.

Active surveillance is deferral of curative-intent therapy in lieu of regular monitoring for evidence of disease progression. It is an option for men with very-low-risk or low-risk prostate cancer who have a life expectancy of at least 10 years. Active surveillance should consist of digital rectal examination (not more than every 12 months), serial measurement of

TABLE 47. Prostate Cancer Risk Stratification

Risk Category	Definition[a]
Very low	Stage T1c, serum PSA <10 ng/mL (10 µg/L), Gleason score ≤6, fewer than 3 biopsy cores positive, ≤50% cancer in each core, PSA density <0.15 ng/mL/g
Low	T1-T2a, Gleason score ≤6, PSA <10 ng/mL (10 µg/L)
Intermediate	T2b-T2c OR Gleason score 7 OR PSA 10-20 ng/mL (10-20 µg/L)
High	T3a OR Gleason score 8-10 OR PSA >20 ng/mL (20 µg/L)
Very high	T3b-T4, primary Gleason pattern 5, >4 cores with Gleason score 8-10

PSA = prostate-specific antigen.

[a]T1 = tumors that are not palpable or seen on imaging; T1a (<5% of specimen) and T1b (>5% of specimen) are discovered incidentally in a pathologic specimen resected for benign disease; T1c discovered in prostate biopsy for elevated serum PSA.

T2 = palpable tumors; T2a involves <50% of one lobe; T2b involves >50% of one lobe; T2c are in both lobes of the prostate.

T3a extends through the prostate capsule; T3b involves the seminal vesicles.

T4 tumors are fixed to adjacent structures.

Data from NCCN Clinical Guidelines in Oncology. Prostate Cancer. Version 2.2017. NCCN.org. https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf. Accessed February 17, 2018.

serum PSA (assessing level changes and calculating PSA doubling time), and repeat biopsy. A PSA doubling time of less than 3 years is considered an indication for treatment. Repeat biopsy is typically done at 1 year, and if no high-grade disease is identified, it can be done less often after that. Fifteen-year metastasis-free survival is as high as 97% in appropriately selected patients.

Active treatment of low-risk localized prostate cancer is typically a choice between external beam radiation and radical prostatectomy. Brachytherapy, in which radioactive implants are inserted into the prostate, is also an option for men with low-risk cancer or selected men with low-volume intermediate-risk cancer.

Radiation is associated with short-term risks of enteritis (approximately 20% of men) and cystitis (approximately 50% of men). These conditions become long-term complications in a very small percentage of men. Erectile dysfunction typically increases over time after radiation, such that by 2 years, approximately 60% to 70% of men have at least moderate erectile dysfunction.

With radical prostatectomy, the main risks are urinary incontinence and erectile dysfunction. Urinary incontinence is relatively common immediately after surgery. The rate of chronic moderate to severe incontinence is approximately 5% to 10%. Erectile dysfunction is relatively common after surgery and can persist for several years. Approximately 40% of men reported erectile dysfunction 2 years after surgery.

A recent study showed no difference in survival after 10 years for patients with localized prostate cancer detected through serum PSA screening who were randomized to receive active surveillance, surgery, or radiation therapy. There was a trend toward improved survival for patients older than 65 years of age who received either of the active interventions. Patients receiving surgery or radiation had decreased disease progression and decreased metastatic disease.

For men with intermediate-risk or higher-risk localized disease who are treated with radiation therapy, the addition of a gonadotropin-releasing hormone (GnRH) agonist will delay disease progression. It has also been shown to improve overall survival in men with high-risk and very-high-risk prostate cancer. For those men with high-risk or very-high-risk localized prostate cancer, six cycles of adjuvant docetaxel given after radiation therapy in addition to androgen deprivation therapy improves disease-free survival and overall survival.

After definitive local treatment, men are monitored for evidence of recurrence with serial serum PSA measurements every 3 to 4 months and digital rectal examination yearly unless PSA is undetectable. After radical prostatectomy, the PSA should rapidly become undetectable, but after radiation treatment, the PSA will fall gradually, will reach a nadir, and will not necessarily become undetectable. PSA recurrence after surgery is defined as a detectable PSA level that increases on at least two measurements; after radiation, PSA recurrence is defined as an increase in the PSA level by at least 2 ng/mL (2 µg/L) above the nadir PSA.

For men with PSA-only recurrence, an evaluation to look for evidence of clinical local or metastatic disease with imaging studies is indicated. If men were treated with initial surgery and metastatic disease has not been identified, salvage radiation with or without androgen deprivation therapy (ADT) can be offered. Likewise, if men were treated initially with radiation, salvage surgery can be offered, but it is only indicated if a transrectal ultrasound-guided biopsy specimen is positive and no metastatic disease is identified; if the specimen is negative, then ADT can be considered.

It is important to note that for men with PSA-only recurrence, with or without clinical metastatic disease, observation is a reasonable consideration depending on patient and disease-specific factors, such as symptoms and PSA doubling time. This is especially true for men with PSA-only recurrence, as it can take several years for clinical metastatic disease to develop in that setting.

KEY POINTS

- Active surveillance, including serial serum prostate-specific antigen (PSA) and repeat biopsy, is appropriate for men with very-low-risk or low-risk prostate cancer.
- Treatment of localized low-risk prostate cancer is typically either external beam radiation or radical prostatectomy, in which both have equal efficacy; brachytherapy is also an option.
- Gonadotropin deprivation is typically administered after radiation therapy for localized intermediate-risk or high-risk prostate cancer.
- Patients with PSA-only recurrence may be treated with androgen deprivation therapy, although observation is a reasonable choice because it may take several years for overt metastatic disease to develop. **HVC**

Metastatic Prostate Cancer

Once distant metastatic disease is diagnosed, the mainstay of therapy is ADT. Options for providing ADT include orchiectomy, GnRH-agonist therapy (with or without antiandrogen) and GnRH-antagonist therapy (**Table 48**). Psychological aversion to orchiectomy by both patients and physicians has limited its use in the United States, although it is a rapidly acting and cost-effective way to achieve androgen depletion and remains the mainstay of ADT in other parts of the world.

At present, there is no clear advantage to combined androgen blockade using a GnRH agonist or antagonist plus an antiandrogen. In patients who have clinical metastatic disease, antiandrogen therapy should precede or be started at the same time as a GnRH agonist, and the combination should be continued for at least 7 days because of the risk of a transient worsening of disease-related symptoms, termed a flare reaction. Continuation is not necessary if a GnRH antagonist is used. Intermittent ADT is not typically recommended in men with clinical metastatic disease, although it can be offered to

TABLE 48. Treatments for Metastatic Prostate Cancer

Class	Agents	Mechanism of Action	Indications
GnRH agonist	Leuprolide, goserelin, triptorelin, buserelin, histrelin	Binds to GnRH receptor, causes initial release of FSH/LH (and also testosterone) followed by suppression	Metastatic prostate cancer; neoadjuvant/adjuvant ADT in combination with radiation
GnRH antagonist	Degarelix	Binds to GnRH receptor and suppresses activity without initial increase in activity seen with GnRH agonists	Metastatic prostate cancer; neoadjuvant/adjuvant ADT in combination with radiation
Antiandrogen	Bicalutamide, flutamide	Binds to androgen receptor with competitive inhibition of testosterone binding	Metastatic castrate-sensitive prostate cancer (not indicated as monotherapy, only in combination with GnRH agonist or antagonist)
CYP17 inhibitor	Abiraterone plus prednisone	Blocks androgen synthesis in tumor tissue, testes, and adrenal glands	Metastatic castrate-resistant prostate cancer; used in combination with prednisone as it can cause adrenal insufficiency
Androgen receptor blockade	Enzalutamide	Binds to the androgen binding site of the androgen receptor in a non-competitive fashion	Metastatic castrate-resistant prostate cancer
Tumor vaccine	Sipuleucel-T	Autologous dendritic cell therapeutic vaccine Aims to increase T cell response to prostatic acid phosphatase	Asymptomatic or minimally symptomatic metastatic castrate-resistant prostate cancer with no visceral metastatic disease Not indicated for PSA-only relapse; does not result in PSA response
Bone-seeking isotope	Radium-223	Alpha particle-emitting isotope that concentrates in bone	Metastatic castrate-resistant prostate cancer with symptomatic bone metastases and no known visceral metastatic disease
Chemotherapeutic	Docetaxel plus prednisone	Antimicrotubule agent	Metastatic castrate-resistant prostate cancer with clinical metastatic disease Metastatic castrate-sensitive prostate cancer in combination with ADT in men with clinical metastatic disease Adjuvant therapy after radiation in men with high-risk or very-high-risk prostate cancer, in combination with ADT
Chemotherapeutic	Cabazitaxel plus prednisone	Antimicrotubule agent	Metastatic castrate-resistant prostate cancer following disease progression after docetaxel treatment

ADT = androgen-deprivation therapy; CYP17 = 17α hydroxy/17,20-lyase; FSH = follicle-stimulating hormone; GnRH = gonadotropin releasing hormone; LH = luteinizing hormone; PSA = prostate specific antigen.

mitigate side effects. Response can be assessed most easily by serial serum PSA measurement, but imaging also plays a role. The serum testosterone level should be less than 50 ng/dL (1.7 nmol/L) in men treated with ADT.

Men with clinical metastatic disease who respond to ADT are considered to have castrate sensitive prostate cancer. In this population, evidence from two recently reported phase III randomized clinical trials indicates that treatment with docetaxel for six cycles with ADT results in improved disease free survival and overall survival.

ADT results in many short-term and long-term side effects. Short-term effects include loss of lean body mass, fatigue, gynecomastia, hair loss, decreased libido, erectile dysfunction, and vasomotor symptoms. Long-term risks include a possible increase in cardiovascular disease, increased risk of venous thromboembolism, and reduction in bone density. Osteoporosis is a prevalent and underappreciated complication of ADT. All men being treated with ADT should take supplemental calcium and vitamin D, and baseline fracture risk should be assessed using a dual-energy x-ray absorptiometry (or "DEXA") scan. Osteoclast inhibitors will reduce bone pain and lower fracture risk in men with ADT-resistant, metastatic prostate cancer.

After identification of progressive disease in men being treated with ADT (castrate-resistant prostate cancer), many treatment options exist (see Table 48). There is no optimal sequence of therapies. Initial treatment options for castrate-resistant prostate cancer include docetaxel with prednisone, abiraterone with prednisone, enzalutamide, radium-223 (for symptomatic bone metastases), and secondary hormone

therapy. Secondary hormone therapies are older treatments that are generally not as effective as newer treatments. Secondary hormone therapies include the addition of an antiandrogen in men not previously exposed to one, addition of ketoconazole (with or without hydrocortisone), antiandrogen withdrawal and use of diethylstilbestrol, or another form of estrogen. For patients who develop progressive disease after treatment with docetaxel, cabazitaxel with prednisone can be used.

KEY POINTS

- Continuous androgen deprivation therapy (ADT), including orchiectomy, gonadotropin-releasing hormone–agonist therapy, and gonadotropin-releasing hormone–antagonist therapy is most appropriate for metastatic prostate cancer.
- Men who respond to ADT and then receive docetaxel chemotherapy will have prolonged survival without disease progression and prolonged overall survival.
- All men who are treated with ADT should take supplemental calcium and vitamin D and have measurement of baseline bone mineral density because osteoporosis is a prevalent and underappreciated complication of ADT.

Testicular Cancer

Testicular cancer is the most common solid tumor diagnosed in men aged 15 to 35 years, although it accounts for only about 1% of all cancers diagnosed in the United States. It is also one of the most curable forms of cancer, due in large part to its sensitivity to chemotherapy. It most commonly presents as a unilateral testicular swelling or mass. However, other presentations are also possible in men with more advanced disease at diagnosis.

Patients with localized symptoms should have a scrotal ultrasound to rule out benign cystic or infectious causes of scrotal enlargement and baseline tumor markers, including α-fetoprotein and β-human chorionic gonadotropin. Diagnosis is made most commonly through inguinal orchiectomy. Needle biopsy of a testicular mass is contraindicated because of concern regarding tumor seeding to the scrotum and inguinal nodes. When the diagnosis is confirmed, evaluation with chest radiography, CT of the abdomen and pelvis, and tumor marker levels after orchiectomy are used for staging. It is important to realize that marker levels fall at predictable rates after surgery, with serum α-fetoprotein the slowest to fall because of its longer serum half-life. Therefore, sufficient time is needed before concluding that markers remain elevated after orchiectomy.

The most common site of spread is to retroperitoneal nodes. Histologically, testicular cancers are either pure seminomas or nonseminomatous germ cell tumors. Management depends on histology, the results of staging studies, and the presence or absence of serum tumor marker elevation after orchiectomy. It is essential to discuss and offer cryopreservation of sperm before initiating additional treatment.

For pure seminoma, active surveillance can be offered after surgery for early-stage disease; adjuvant radiation or chemotherapy with one to two cycles of carboplatin is also appropriate options. Stage II seminoma is defined by retroperitoneal lymph node metastases. For patients with low-volume lymph node metastatic disease, either adjuvant radiation or cisplatin-based combination chemotherapy can be used. In general, as the size of the largest lymph node metastasis increases to more than 2 cm, chemotherapy is preferred over radiation. For stage III seminoma disease, which signifies distant metastatic disease, cisplatin-based chemotherapy is used. PET-CT can be used to determine whether residual masses after chemotherapy require resection. Residual masses that show negative results on PET scan may be benign and can be followed, with resection based on any further increase in size. Residual masses that show positive results on PET scan should be promptly resected, as cure remains possible.

Patients with early-stage nonseminomatous germ cell tumors can be managed with active surveillance (in selected patients), retroperitoneal lymph node dissection (RPLND), or limited chemotherapy. Adjuvant chemotherapy can be considered in patients with positive findings on RPLND. Persistence of tumor marker elevation after orchiectomy without abnormal imaging findings is an indication for chemotherapy. Patients with clinically metastatic retroperitoneal nodes can be managed with RPLND or primary chemotherapy if markers are negative and nodal metastases are limited and small. For patients with several positive nodes, large nodes (>5 cm), or elevated markers, chemotherapy is recommended. Any residual masses after chemotherapy should be resected.

For the first year after treatment, patients should be seen for interview and examination every 2 to 3 months and should have tumor marker measurement and imaging studies periodically, with specific intervals determined by histology, stage, and previous treatment. After the first year, evaluations can be performed less often.

Patients with recurrent disease are treated with combination chemotherapy and can also be treated with high-dose chemotherapy and autologous hematopoietic stem cell transplantation.

Men treated with chemotherapy for testicular cancer are at risk for many different long-term complications, including cardiovascular disease, metabolic syndrome, pulmonary toxicity, hypogonadism, infertility, chronic kidney disease, and neurotoxicity. Further, there is a well-described risk of a second malignancy among men treated for testicular cancer. The risk of a second solid tumor is approximately twofold higher than in men without a history of testicular cancer.

KEY POINTS

- Measurement of serum tumor markers (α-fetoprotein, lactate dehydrogenase, β-human chorionic gonadotropin) are important before and after inguinal orchiectomy for staging and prognosis of testicular cancer.
- Patients with stage II seminoma, defined by retroperitoneal lymph node metastasis, can be treated with adjuvant radiation or cisplatin-based chemotherapy, although chemotherapy is preferred if the largest metastasis increases above 2 cm.
- Patients with seminoma and residual masses after chemotherapy should receive PET-CT; masses with negative findings on PET-CT can be observed with follow-up imaging to assess progression, and masses with positive findings should be resected.
- Patients with nonseminoma and clinically metastatic nodes can be treated with retroperitoneal lymph node dissection or primary chemotherapy; chemotherapy is preferred if there are several positive nodes, large nodes (>5 cm), or elevated serum tumor markers.

Renal Cell Carcinoma

Renal cancers typically arise in the cortex of the kidney. The most common histology is clear cell carcinoma, which is also the most responsive to medical treatment. In the past, the most common presenting symptoms of renal cell carcinoma were hematuria, abdominal mass, and weight loss, but most patients are currently diagnosed incidentally based on imaging studies done for other reasons. Ultrasonography can be used to differentiate benign cysts from complex cysts or solid masses. If a lesion is not clearly a benign cyst, CT is indicated for further evaluation. Biopsy is only indicated if CT does not clearly indicate renal cell carcinoma.

Many different paraneoplastic syndromes can be seen in patients with renal cell carcinoma, including anemia, hepatic dysfunction in the absence of liver metastases (known as Stauffer syndrome), fever, hypercalcemia, erythrocytosis, AA amyloidosis, thrombocytosis, and polymyalgia rheumatica. Many of these conditions can improve with resection of the primary tumor, metastatic sites, or both.

For localized disease, surgery is indicated. This consists of either radical nephrectomy or partial nephrectomy, depending on the size and location of the primary tumor. In most patients no adjuvant therapy is indicated. Sunitinib has recently been approved by the US Food and Drug Administration (FDA) for use as adjuvant treatment in patients with high-risk clear cell carcinoma of the kidney following definitive surgery. In a phase III trial it improved disease-free survival by 1.2 years compared with no treatment. Postoperative surveillance to identify recurrent disease is indicated, with the frequency of interventions depending on the extent of local disease. This typically consists of a history and physical examination, basic laboratory studies, and imaging of the chest and abdomen. Cryoablation, radiofrequency ablation, or even active surveillance may be indicated for managing small tumors in frail patients who have a high risk of postoperative complications.

Resection of the primary renal cell cancer improves survival for select patients with metastatic disease. Debulking nephrectomy can be considered because there is evidence indicating that this procedure is associated with improved survival. Surgery also has a possible role in the treatment of isolated or several easily resected areas of metastatic disease.

No specific front-line therapy has been shown superior for patients who present with metastatic clear cell or non-clear cell histology. Various novel agents, including the programmed death 1 (PD-1) receptor antibody nivolumab and the vascular endothelial growth factor (VEGF) inhibitors lenvatinib and axitinib, have shown activity for patients with disease recurrence.

KEY POINT

- Many different paraneoplastic syndromes can be seen in patients with renal cell carcinoma, including anemia, hepatic dysfunction in the absence of liver metastases, fever, hypercalcemia, erythrocytosis, AA amyloidosis, thrombocytosis, and polymyalgia rheumatica. Resecting a primary renal cell cancer may improve the response to chemotherapy in patients with metastatic disease.

Bladder Cancer

Bladder cancer is the most common cancer of the genitourinary tract. Most patients have transitional cell carcinoma, which is the focus of this section. The most common presenting symptom is hematuria, which is often gross hematuria and may be intermittent. It is typically painless, although irritative urinary symptoms can be present with or without hematuria. It is important to assess for gross hematuria in review of systems questioning for all patients and confirm with a urinalysis if a patient does note hematuria. Any patient with gross hematuria should be referred for urologic evaluation, as should any patient confirmed to have persistent microscopic hematuria after evaluating benign causes, such as urinary tract infection, nephrolithiasis, or underlying kidney disease with a glomerular source of erythrocytes. Notably, use of anticoagulants does not alter these recommendations.

The primary modality of initial evaluation is cystoscopy combined with urine cytology, with biopsy of any visible tumor or mucosal abnormality. Random biopsy is performed if no abnormality is seen. If cancer is confirmed, then transurethral resection of the bladder tumor (TURBT) and examination under anesthesia is performed to determine histology and also depth of invasion.

Most patients are found to have non-muscle invasive disease. This can include exophytic lesion (Ta, which can be low grade or high grade), carcinoma in situ (Tis, always high grade), or early-stage invasive cancer (T1). Small low-grade Ta tumors are treated with TURBT followed by a single dose of

intravesical chemotherapy. All other noninvasive disease (including recurrent low-grade Ta disease) is treated with TURBT followed by six treatments of intravesical chemotherapy, most commonly bacillus Calmette-Guérin or mitomycin, although other compounds are used. After primary treatment, cystoscopic surveillance is indicated because of the risk for recurrent disease. There is a higher risk for muscle invasive recurrence for patients with larger tumors, less differentiated tumors, tumors that invade into the lamina propria, and tumors with multifocal or noninvasive recurrence. Most patients require cystoscopy 3 months after initial therapy, with subsequent cystoscopy at 3-month to 1-year intervals based on risk of recurrence. Cystectomy can be considered for patients at high risk for developing muscle-invasive disease.

If muscle-invasive disease is diagnosed, cystectomy is indicated, with or without neoadjuvant cisplatin-based chemotherapy. Partial cystectomy can be considered in very carefully selected patients. If bladder preservation is desired, maximal TURBT can be combined with concurrent chemoradiotherapy. Adjuvant chemotherapy after surgical resection is appropriate to consider in patients with poor-risk features, such as positive nodes and extension beyond the bladder.

Treatment of metastatic disease requires systemic therapy, and treatment outcomes remain poor. Cisplatin-based combination chemotherapy remains the evidence-based choice in patients eligible to receive cisplatin. After further progression, single-agent therapy is recommended. Immunotherapy plays a role here with the recent FDA approval of atezolizumab, a monoclonal antibody directed against the programmed death ligand 1 (PD-L1) receptor.

KEY POINTS

- Any patient with gross hematuria should be referred for urologic evaluation, as should any patient confirmed to have microscopic hematuria in the absence of an apparent benign cause; use of anticoagulants does not alter these recommendations.
- Bladder cancer typically does not invade the muscle, and treatment includes transurethral resection of the bladder tumor (TURBT) plus intravesical chemotherapy, usually bacillus Calmette-Guérin or mitomycin.
- Muscle-invasive bladder cancer is treated with cystectomy with or without neoadjuvant cisplatin-based chemotherapy; partial cystectomy with bladder preservation through maximal TURBT and concurrent chemoradiotherapy can be performed in select patients.

Lymphoid Malignancies

Epidemiology and Risk Factors

The American Cancer Society estimates that in 2018 83,180 new cases of lymphoma will be diagnosed in the United States. The lifetime risk of developing non-Hodgkin lymphoma is 2.1%, whereas the lifetime risk of developing Hodgkin lymphoma is considerably less. Although incidence has only slightly declined recently, death rates have decreased significantly owing to improvements in treatment. The incidence of non-Hodgkin lymphoma rises with increased age, whereas the incidence of Hodgkin lymphoma shows a bimodal age distribution, with an early peak in the second and third decades of life, then a decline, followed by a sustained increase with older age.

Although most of these cases seem sporadic, familial clustering can be seen, with an increased relative risk in first-degree relatives. Patients with both congenital and acquired immunosuppression (such as HIV infection, organ transplantation, or an inherited immunodeficiency) are at greater risk.

Various viral infections are also associated with increased risk. Epstein-Barr virus is associated with Burkitt lymphoma, seen in African pediatric patients, as well as some cases of Hodgkin lymphoma. Human T-cell lymphotropic virus type 1 (HTLV-1) is associated with T-cell leukemias and lymphomas, endemic in Japan, West Africa, Central America, the southeastern United States, and the Caribbean. Hepatitis C virus is associated with an increased risk of lymphoma, particularly splenic marginal zone lymphoma. HIV infection is associated with an increased risk of principally B-cell lymphomas, typically with aggressive histology, more advanced stage, more B symptoms, and a higher risk of extranodal and central nervous system involvement. Kaposi sarcoma herpesvirus (human herpesvirus 8) is associated not only with Kaposi sarcoma but also with primary effusion lymphoma.

Patients with autoimmune rheumatic disorders, such as Sjögren syndrome, systemic lupus erythematosus, and rheumatoid arthritis, have an increased risk of non-Hodgkin lymphoma. The strongest association is with Sjögren syndrome and extranodal marginal zone lymphomas.

Evaluation and Diagnosis

Enlarged lymph nodes are the most common sign of lymphoma. There are many causes of lymphadenopathy, and in most patients, it is of benign origin (infectious or inflammatory). Palpable small and modest-sized cervical and inguinal lymph nodes may be noted in otherwise healthy adults and need not be evaluated further. This finding in young adults and of brief (less than 3 to 4 weeks) duration is likely to be benign. CT scan of the chest, abdomen, and pelvis can assess palpable lymph nodes not amenable to physical examination but generally should not be done in asymptomatic patients. When the size, distribution, or persistence of enlarged lymph nodes or systemic symptoms raises concern for lymphoma, a diagnosis is generally established based on lymph node biopsy. An excisional biopsy is often preferable to a core needle biopsy as it may better determine nodal architecture. Fine-needle aspiration cytology is generally inadequate to make a specific diagnosis, but it may show features suspicious for lymphoma, requiring a more definitive excisional biopsy or, conversely,

may reveal findings consistent with inflammation that make lymphoma less likely. Flow cytometry on cytology can demonstrate B-cell or T-cell markers, as well as features consistent with monoclonality.

Although most patients with lymphoma present with lymph node involvement, presentation in extranodal sites is not uncommon.

KEY POINTS

- Lymphadenopathy is the most common sign of lymphoma; increase in size, distribution, and persistence, along with systemic symptoms, raises the concern for lymphoma.
- Diagnosis of lymphoma is generally established by excision or core needle biopsy.

Classifications, Staging, and Prognosis of Malignant Lymphoma

Malignant lymphoma represents a spectrum of disorders. Diagnosis and classification are established not just on standard histopathologic staining looking at cell type and nodal architecture but also on flow cytometry, various immunohistochemical stains, and cytogenetic and molecular genetic features. The classification systems are complex and have continued to evolve during the past decades. The most commonly recognized system is the World Health Organization update on the Revised European-American Lymphoma classification. Experienced hematopathologists are essential to obtaining proper classification. However, there can be significant discordance among experts and some overlap among tumor types.

Staging the anatomical extent of spread can be simplified through the Ann Arbor staging criteria (**Figure 21**).

Lymphomas are staged I to IV based on the number of sites of disease and the presence of extranodal involvement. Staging involves physical examination, CT scans, and PET scans in most patients. However, PET scans tend not to be sensitive for some very indolent lymphomas (such as small lymphocytic lymphoma and marginal zone lymphomas). Bone marrow aspiration and biopsy have typically been part of staging for many lymphomas, but the use of PET scans may obviate the need for bone marrow biopsies in many patients with Hodgkin lymphoma and large cell lymphoma as marrow involvement is rarely found if it is not suggested by PET.

Lymphoma stages are also designated A or B: A indicates no systemic symptoms are present, and B indicates the presence of one or more of the following: fever, drenching night sweats, or unexplained weight loss.

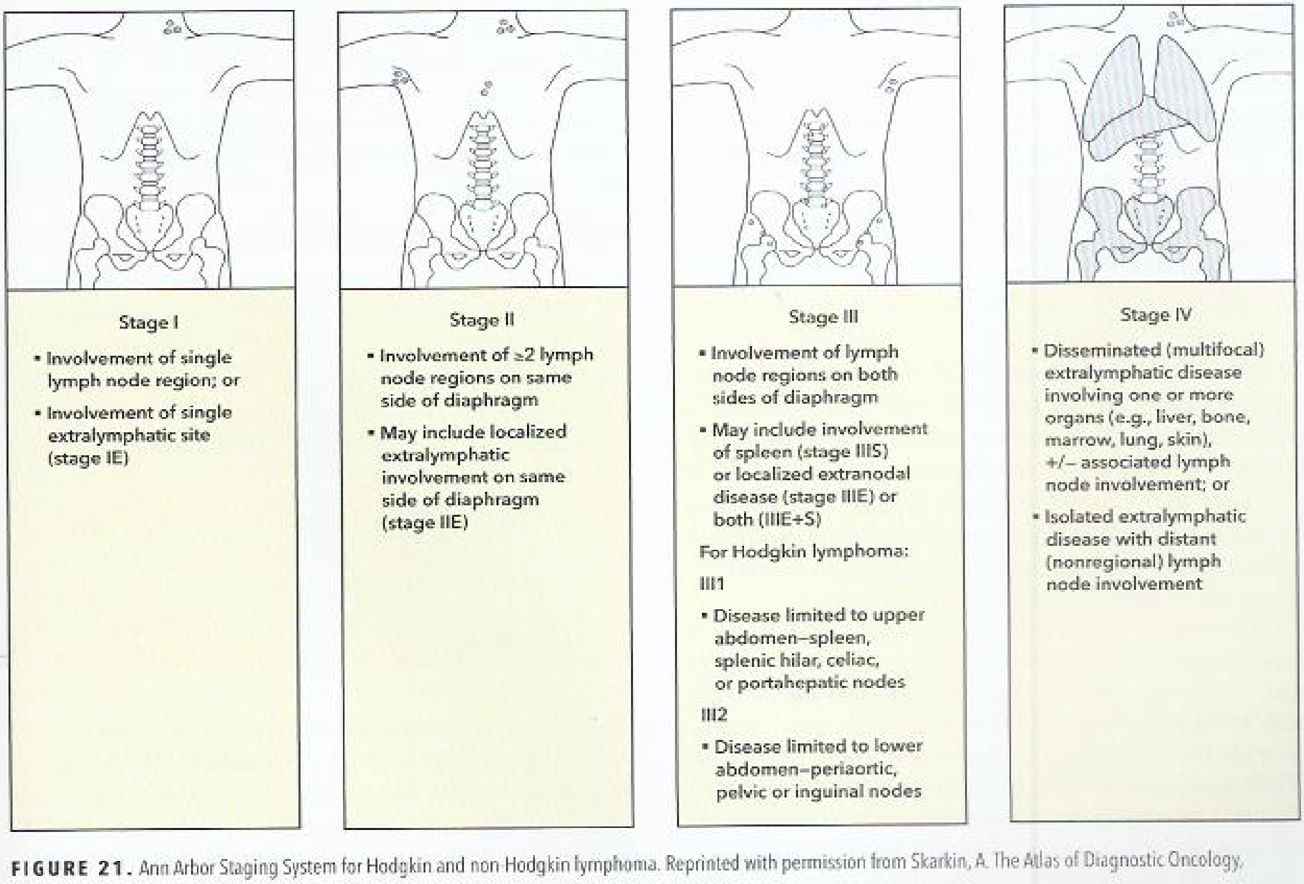

FIGURE 21. Ann Arbor Staging System for Hodgkin and non-Hodgkin lymphoma. Reprinted with permission from Skarkin, A. The Atlas of Diagnostic Oncology, 3rd Edition. Philadelphia, PA: Mosby. Copyright Elsevier, 2002.

The prognosis of the lymphoma varies greatly depending on the subtype, stage, and comorbidities. Immunophenotypic, cytogenetic, and molecular genetic classifications also commonly inform the prognosis. Prognostic indices have been reported and validated for most common types, including the International Prognostic Index for large cell lymphoma, the Follicular Lymphoma International Prognostic Index, and the Mantle cell lymphoma Prognostic Index.

KEY POINTS

- Staging of lymphoma involves physical examination, CT scans, and PET scans in most patients.
- HVC A negative PET scan may obviate the need for bone marrow biopsies in many patients with Hodgkin and large cell lymphoma, but PET scans are not sensitive to very indolent lymphomas.

Non-Hodgkin Lymphomas

Approximately 85% of non Hodgkin lymphomas are B cell derived and express surface immunoglobulin and B-cell markers, whereas 15% are T-cell derived.

Indolent B-Cell Lymphomas

The indolent lymphomas may be present for many years without symptoms and typically have a favorable response to various sequential therapies when needed, but all have a tendency for continued relapse.

Follicular Lymphoma

Follicular lymphomas demonstrate lymph node architecture with a follicular morphology. They arise from the germinal center B cells of the lymph node and are characterized by the presence of a t(14;18) translocation that causes an overexpression of the *BCL2* oncogene. Follicular lymphomas are classified based on their dominant cell type: predominantly smaller cells (grade 1), a mixture of smaller and larger cells (grade 2), and predominantly large cells (grade 3). Grades 1 and 2 are commonly combined as the distinction between them is somewhat subjective. Grade 3 follicular lymphoma can be divided into 3A and 3B, with the latter composed of sheets of more uniform poorly differentiated cells. Grade 3A follicular lymphoma is more akin in behavior and treatment to grades 1 and 2, whereas 3B is treated more like diffuse large B cell lymphoma, although this is somewhat controversial.

Follicular lymphoma is the most common indolent B-cell lymphoma and accounts for approximately 30% of non Hodgkin lymphomas. Many patients are not symptomatic at diagnosis and in some cases do not require therapy for many years. There is no clear evidence that early treatment leads to improved outcomes, so asymptomatic patients without bulky disease are usually observed. Some patients may undergo spontaneous, although generally transient, regression of disease.

Most patients with follicular lymphoma will present with stage III or IV disease. Single agent rituximab is associated with high response rates and durable remissions. Combining rituximab with chemotherapy (such as the alkylating agent bendamustine) leads to remission in more than 90% of patients. The use of maintenance rituximab after induction of an initial remission is associated with prolonged duration of remission or relapse free survival, but no clear improvement in overall survival. Patients with relapsing or refractory cases can be treated with various other approaches, including alternate chemotherapy regimens (such as rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone [R-CHOP]), the anti CD20 antibody obinutuzumab, the phosphoinositide 3-kinase inhibitor idelalisib, radioimmunotherapy with ibritumomab tiuxetan, as well as autologous or allogeneic hematopoietic stem cell transplantation (HSCT).

A minority of patients present with localized disease and can be approached with radiation therapy with curative intent rather than with systemic therapy. Whether systemic therapy, such as rituximab, with or without chemotherapy should be used in addition to or as an alternative to radiotherapy in patients with localized follicular (and other low grade) lymphomas is controversial.

Histologic transformation, most typically to a diffuse large B cell lymphoma, occurs in approximately 30% of patients with follicular lymphomas and is associated with an aggressive course and poor prognosis. Transformation may be suggested by a change in the clinical pattern of disease with new systemic symptoms or rapid progression of a localized area of disease, a rise in serum lactate dehydrogenase, or markedly higher areas of standardized uptake values on PET scans. A new biopsy is required to establish that transformation has occurred.

KEY POINTS

- Many patients with follicular lymphoma are not symptomatic at diagnosis and may not require therapy for many years. HVC
- In advanced-stage follicular lymphoma, rituximab plus chemotherapy leads to remission in more than 90% of patients, although the disease will recur in most patients.
- Histologic transformation of follicular lymphoma to a diffuse large B cell lymphoma, which should be confirmed by obtaining another lymph node biopsy, occurs in approximately 30% of patients and is associated with a poor prognosis.

Mucosa-associated Lymphoid Tissue Lymphoma

Mucosa associated lymphoid tissue (MALT) lymphoma is an extranodal marginal zone lymphoma. Gastric MALT lymphoma may be the best known, particularly given its common association with *Helicobacter pylori* infection. However, MALT lymphomas can arise in other sites such as the gastrointestinal

tract, thyroid, orbits, skin, and lung and generally demonstrate indolent behavior and a low propensity for transformation. Repetitive immune stimulation, from underlying chronic infection or an autoimmune process, is likely to play a role in the pathogenesis of this tumor.

H. pylori–associated gastric MALT lymphoma should be treated with antibiotics and proton pump inhibitors initially. Other localized MALT lymphomas may be treated with radiation, to which they are quite sensitive. When systemic therapy is required, rituximab alone or in combination with chemotherapy is associated with high response rates.

KEY POINT

- *Helicobacter pylori*–associated gastric MALT lymphoma should be treated with antibiotics and proton pump inhibitors initially; other localized MALT lymphomas may be treated with radiation.

Chronic Lymphocytic Leukemia

Chronic lymphocytic leukemia (CLL) is generally easy to diagnose because it manifests as an increase in absolute lymphocytes on complete blood count. The lymphocytes are predominantly small and mature appearing, although they may be fragile and form "smudge cells" on the peripheral smear. Flow cytometry using peripheral blood is essential in establishing the diagnosis and will reveal B-cell antigens (CD19, 20, and 23), coexpression of CD5 (normally a T-cell marker), and low levels of a monoclonal surface immunoglobulin. Bone marrow aspiration and biopsy are no longer necessary to diagnose and stage most patients with CLL.

Although less common, other lymphomas may present similarly to CLL in peripheral blood smears and must be distinguished by morphology, flow cytometry, and genetic studies. These other disorders include hairy cell leukemia, marginal and mantle zone lymphomas, T-cell lymphoma, and prolymphocytic leukemia.

CLL and small lymphocytic lymphoma represent the same disease, with the designation as leukemia or lymphoma based on the dominant clinical manifestation in either peripheral blood and marrow or nodal involvement, respectively. Both CLL and small lymphocytic lymphoma are treated the same. CLL is now grouped more with the lymphomas than with the leukemias in treatment centers.

CLL is typically an indolent disease, and many patients require no therapy for many years and sometimes decades. Prognosis can relate to clinical staging (Rai and Binet staging systems are based on the extent of cytopenias, organomegaly, and degree of nodal involvement) but also on cytogenetic and molecular genetic characteristics. The specific nature of the mutation can help indicate the prognosis.

The past decade has seen a rapid advance in the number and efficacy of active agents for CLL. Although these therapies are not curative, most patients can now achieve durable remissions once treatment is required. Treatment options available include alkylating agents (chlorambucil, cyclophosphamide, bendamustine), purine nucleoside analogues (fludarabine, cladribine, pentostatin), monoclonal antibodies (rituximab, alemtuzumab, ofatumumab, obinutuzumab), and the phosphoinositide-3 kinase inhibitor idelalisib. There has been an increase in use of the Bruton kinase inhibitor ibrutinib, which is now approved for first-line therapy and active in a broad spectrum of patients, including those with 17p deletion. Venetoclax, a *BCL2* inhibitor, is active in refractory cases, induces brisk apoptosis, and occasionally induces tumor lysis syndrome. Lenalidomide, an immune modulator approved for myeloma and myelodysplasia, is also active. Allogeneic HSCT is rarely performed in CLL but has been used in refractory cases in appropriate patients. Anti-CD19 chimeric antigen receptor (CAR) T-cell therapy has also been shown to be active in refractory cases. Older chemoimmunotherapy regimens, although quite active, may increasingly give way to targeted therapies.

Patients with CLL are prone to infection, in part related to commonly associated hypogammaglobulinemia. In patients with repeated infections and hypogammaglobulinemia, regular treatment with intravenous gamma globulin reduces infectious events. The infection risk increases in more advanced disease, a result of both impaired T-cell-mediated and B-cell–mediated immune response along with treatment-induced immunosuppression. Patients with CLL and small lymphocytic lymphoma may also develop autoimmune cytopenias such as immune thrombocytopenic purpura and autoimmune hemolytic anemias. Transformation to a large cell lymphoma (known as Richter transformation) occurs in about 5% of patients with CLL and small lymphocytic lymphoma and is generally associated with a poor prognosis and refractory disease.

KEY POINTS

- Chronic lymphocytic leukemia and small lymphocytic lymphoma are the same disease, but the former predominates in peripheral blood and bone marrow, whereas the latter predominates in lymph nodes.
- The diagnosis of chronic lymphocytic leukemia manifests as an increase in absolute lymphocytes on complete blood count; the lymphocytes are predominantly small and mature appearing and may form "smudge cells" on the peripheral smear.
- Patients with low-stage, asymptomatic chronic lymphocytic leukemia can be observed without therapy for decades.

Hairy Cell Leukemia

Like CLL, hairy cell leukemia is a low-grade B-cell disorder but with characteristic clinical, pathologic, immunophenotypic, and genetic changes. Patients typically present with cytopenias and splenomegaly; lymphadenopathy is typically absent. Circulating "hairy cells," characterized by cytoplasmic projections, are often identified in the peripheral blood smear (**Figure 22**); when seen

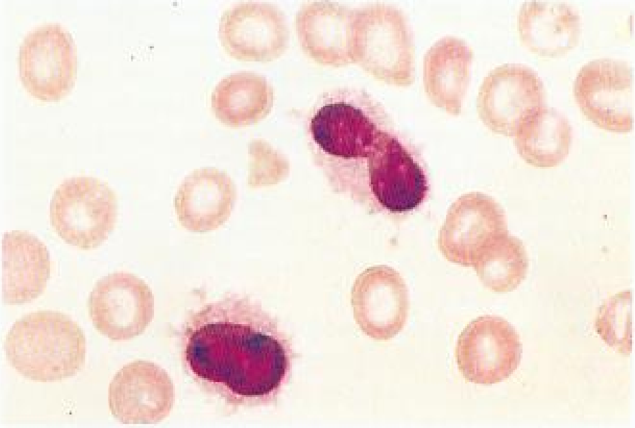

FIGURE 22. Hairy cell leukemia depicted by a peripheral blood smear showing atypical lymphocytes with thread-like cytoplasmic projections from the cell surface.

on bone marrow biopsy, these cells have a lacunar appearance. Classically, the bone marrow aspirate is a dry tap due to some degree of marrow fibrosis. Flow cytometry shows hairy cells positive for characteristic surface markers. In addition, the presence of a *BRAF* V600E mutation has been associated with hairy cell leukemia in most patients and represents not only a diagnostic marker but also a therapeutic target.

As with CLL and other low-grade lymphomas, some patients with hairy cell leukemia do not require immediate treatment if not symptomatic. However, the front-line therapy remains purine nucleoside agents, typically pentostatin or cladribine. These agents are highly active, and almost all patients respond, many with durable responses, with only one course of treatment. Relapses can be treated with the alternate purine nucleoside agent. Rituximab is also active in relapse. The selective *BRAF* inhibitor vemurafenib has also shown activity in relapsed patients.

Hairy cell leukemia variant is a distinct entity that typically presents with a high circulating leukocyte count, as opposed to the leukopenia seen in the classic form. These patients respond less well to cladribine and have shorter durations of response.

KEY POINTS

- Patients with hairy cell leukemia typically present with circulating "hairy cells," cytopenias, and splenomegaly but no lymphadenopathy.
- Durable remissions of hairy cell leukemia can often be achieved with one course of a purine nucleoside agent such as pentostatin or cladribine.

Aggressive B-Cell Lymphomas

The more aggressive lymphomas, such as diffuse large B-cell and Burkitt lymphoma, are more likely to present with systemic symptoms or signs of rapid tumor progression. Diagnosis should be promptly pursued because these patients have a greater potential for cure with therapy.

Diffuse Large B-Cell Lymphoma

Diffuse large B-cell lymphoma represents approximately 30% of non Hodgkin lymphomas. Although diffuse large B-cell lymphoma can be subdivided based on gene expression profiling (activated B cell versus germinal center type), and although this subtyping may be associated with prognostic differences, there is no clear indication yet that the initial treatment approach should be altered based on the subtype. These patients often present with symptomatic enlarging lymphadenopathy in the neck or abdomen. Approximately 40% may have symptoms or signs of extranodal disease, and one third have systemic symptoms. Biopsy specimens show diffuse effacement of normal nodal architecture by large, atypical lymphoid cells with prominent nucleoli and basophilic cytoplasm. Flow cytometry reveals B-cell antigens, and most patients have monoclonal surface immunoglobulin. The B-cell lymphoma 6 (*BCL6*) gene shows rearrangement or other mutations that lead to overexpression in most patients.

Sixty percent of patients have advanced (stage III or IV) disease at diagnosis, and standard therapy is R-CHOP. Consolidative radiation therapy may be given to sites of bulky disease. Residual masses, which are often benign, may remain after treatment. PET may help determine if these represent active disease or just scarring.

Patients with poor prognostic features, such as elevated serum lactate dehydrogenase level, extensive tumor burden, and poor performance status, may receive more aggressive initial therapy. Those patients who present with localized disease can be treated with a shorter course of chemotherapy with consolidative radiation therapy. In addition to further standard chemotherapy, autologous HSCT and anti-CD19 chimeric antigen receptor (CAR) T-cell therapy may be used as salvage therapy in patients who relapse.

Primary mediastinal large cell lymphoma is a distinct clinical, morphologic, and genetic lymphoma, often presenting in younger patients. It putatively arises from thymic B cells. It has a female predilection, a tendency to present with bulky but localized disease, and a relatively high cure rate. It may have significant overlap histologically and genetically with nodular sclerosing Hodgkin lymphoma, and some cases may be difficult to classify as one or the other; these are called mediastinal gray-zone lymphomas.

KEY POINTS

- Aggressive B-cell lymphomas, such as diffuse large B-cell and Burkitt lymphoma, progress more quickly than indolent lymphomas but have a greater potential for cure.
- Standard therapy for most patients with advanced-stage diffuse large B-cell lymphoma is rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone.

Mantle Cell Lymphoma

Mantle cell lymphomas represent approximately 3% to 6% of non-Hodgkin lymphomas. Median age at diagnosis is 68 years, and there is a 3-to-1 male predominance. It is defined and presumably initiated by a t(11;14) translocation, which leads to constitutive overexpression of cyclin D1, a cell-cycle gene regulator. Patients can present with nodal or extranodal disease, and the disease is usually widely disseminated at diagnosis. Gastrointestinal involvement with several polyps (lymphomatoid polyposis) is well described, as is involvement of the peripheral blood and bone marrow.

Although mantle cell lymphoma is responsive to various conventional chemotherapy regimens and newer agents, it is associated with a predilection for continued relapse. There is no clear consensus on the optimal therapeutic approach, with treatments spanning a spectrum of least aggressive (lenalidomide or bendamustine plus rituximab) to more aggressive (R-CHOP with or without HSCT). A subset of patients with indolent disease may not require therapy for many years.

Burkitt Lymphoma

A relatively rare lymphoma, Burkitt lymphoma, is remarkable for its extremely rapid growth. The endemic form occurs primarily in Africa, is a common cause of childhood cancer, and is associated with Epstein-Barr virus infection. Patients may present with a large jaw mass (**Figure 23**). The sporadic form is more typically seen in the United States, occurs at a somewhat later age, and is more likely to present with abdominal or pelvic involvement. A third variety of Burkitt lymphoma is the immunodeficiency-associated form and occurs in HIV-infected patients. *MYC* gene activation is characteristic of this lymphoma. The serum lactate dehydrogenase level is typically high.

Early signs of the tumor lysis syndrome are often present in patients with Burkitt lymphoma even before treatment is initiated and should be anticipated because the tumor is quite chemosensitive. Various aggressive multiagent chemotherapy regimens with rituximab have been associated with high cure rates. These regimens are more intensive than standard lymphoma therapy and are associated with some risk of treatment-related mortality (for a more complete discussion, see Oncologic Emergencies and Urgencies). Treatment of occult central nervous system involvement is included in initial treatment regimens because of the risk for leptomeningeal involvement.

KEY POINT

- Prophylaxis to manage tumor lysis syndrome should be instituted before initiation of chemotherapy for patients with Burkitt lymphoma.

T-Cell Lymphomas

T-cell lymphomas represent approximately 10% to 15% of lymphomas in Western countries but are more common in Asia. They include various subtypes and are a heterogeneous group

FIGURE 23. A large jaw mass associated with Burkitt lymphoma.

of disorders characterized by distinct presentations and morphology. Diagnosis can be made on routine pathology and supplemented by flow cytometry and immunohistochemistry. Monoclonality can be confirmed by findings of clonal rearrangements of the T-cell receptor genes detected by polymerase chain reaction. In general, T-cell lymphomas are more refractory to therapy than B-cell lymphomas. Although various new agents are available for treatment, studies are small and many responses are transient.

Cutaneous T-Cell Lymphoma

Mycosis fungoides and Sézary syndrome are the two major subtypes of cutaneous T-cell lymphoma. The skin findings in mycosis fungoides are quite heterogeneous, ranging from nonspecific macular-papular eruptions or plaques, to more defined skin tumors with ulceration, to diffuse erythroderma. There is often a preceding prodromal illness, or "premycotic" period, with milder skin disease that waxes and wanes or that may progress for months or even years without a definitive diagnosis; skin biopsies done during that interval are nonspecific. Pruritus is common and can be debilitating. Ultimately, as skin involvement becomes more extensive, the disease progresses to involve extracutaneous sites, including lymph nodes and organs, such as the lung, liver, and gastrointestinal tract. Infections are more common as a function of underlying

immunodeficiency and disruption of the protective barrier provided by healthy skin. The Sézary syndrome is a more aggressive form of cutaneous T-cell lymphoma in which diffuse erythroderma characterizes the skin involvement and malignant T cells circulate in the blood.

The staging of cutaneous T cell lymphoma is dependent on the extent of skin disease and involvement of lymph nodes and extranodal sites. Early stages of cutaneous T-cell lymphoma are confined to the skin and managed with topical therapy, such as glucocorticoids, retinoids, or ultraviolet light therapy, that may be combined with interferon. Survival is greater than 10 years. More advanced disease is associated with a survival of less than 4 years and requires more aggressive skin treatment with electron beam radiation along with systemic chemotherapy. Patients with Sézary syndrome require systemic chemotherapy. Extracorporeal photopheresis uses psoralens, compounds that enter cells and sensitize them to injury after activation with ultraviolet light; this technique is also used in Sézary syndrome.

Peripheral T-Cell Lymphoma, Not Otherwise Specified

Peripheral T-cell lymphoma, not otherwise specified, is the most commonly diagnosed subtype of peripheral T-cell lymphoma. It typically presents in older adults at an advanced stage, has a male predominance, and has a generally poor clinical outcome compared to B-cell lymphomas.

Various combination chemotherapy regimens have been used. The addition of etoposide to standard combination chemotherapy may provide some benefit as part of initial therapy. The use of chemotherapy designed for acute lymphoblastic leukemia or management with HSCT, both autologous and allogeneic, may benefit some patients, although there is controversy as to when and in whom these are best used. As with other T-cell lymphomas, newer chemotherapy agents such as pralatrexate and romidepsin yield responses in some patients with relapsed disease.

Anaplastic Large Cell Lymphoma

Anaplastic large cell lymphoma can present with nodal as well as extranodal disease, including skin, bone marrow, and bone. Patients commonly have B symptoms. Tumor cells are typically CD30 positive. An important prognostic and potentially therapeutic distinction is the presence or absence of a t(2;5) or variant *ALK* gene translocation and protein expression.

ALK-positive patients are younger (mean age at diagnosis is approximately 35 years) and have a much more favorable prognosis with conventional chemotherapy and may also respond to treatment with crizotinib, an oral targeted agent also active in lung cancer with *ALK* gene translocations.

Angioimmunoblastic T-Cell Lymphoma

Angioimmunoblastic T-cell lymphoma, initially termed angioimmunoblastic lymphadenopathy, was thought to be a disease of impaired immune regulation rather than a true malignancy; however, patients with this disease are now recognized to have clonal rearrangement of T-cell receptors consistent with a T-cell neoplasm. Patients with angioimmunoblastic T cell lymphoma often present with systemic B symptoms, generalized lymphadenopathy, hepatosplenomegaly, and a skin rash. They commonly show polyclonal hypergammaglobulinemia and elevated erythrocyte sedimentation rate and C-reactive protein level. Autoimmune manifestations (such as a Coombs-positive autoimmune hemolytic anemia) may be present. Although the lymphoma in some patients is responsive to glucocorticoids and conventional chemotherapy, it typically has a moderately aggressive clinical course and median survival of less than 2 years.

KEY POINTS

- The skin findings in mycosis fungoides, a subtype of cutaneous T-cell lymphoma, range from nonspecific macular papular eruptions or plaques, to more defined skin tumors with ulceration, to diffuse erythroderma.
- The Sézary syndrome is a more aggressive subtype of cutaneous T-cell lymphoma in which diffuse erythroderma characterizes the skin involvement and malignant T cells circulate in the blood.
- Peripheral T-cell lymphoma, not otherwise specified, is treated with combination chemotherapy.

Lymphoblastic Lymphoma

Lymphoblastic lymphoma is an aggressive lymphoma that can be of T- or B-cell origin. It is akin to and treated with protocols for acute lymphoblastic leukemia. Presentation with a mediastinal mass, blood or bone marrow, and central nervous system involvement is typical.

Hodgkin Lymphoma

Hodgkin lymphoma represents approximately 10% of lymphomas and is curable in most, but not all, patients. It has a bimodal incidence, although it most commonly presents in young adults. Presentation with mediastinal, cervical, and supraclavicular involvement is particularly common for the nodular sclerosing subtype (**Figure 24**). Patients may also present with B symptoms, although that is more commonly seen in elderly patients with more advanced disease. Pruritus may also be a presenting symptom.

The diagnosis is established with a lymph node biopsy specimen showing Reed-Sternberg cells (**Figure 25**), malignant cells that originate from germinal center B cells and are seen in an inflammatory infiltrate. The number of Reed-Sternberg cells and variability in the composition of the infiltrate lead to pathologic subtypes, including nodular sclerosis, mixed cellularity, lymphocyte predominant, and lymphocyte depleted. Patients are staged by physical examination and PET-CT scan. Staging laparotomies, including diagnostic splenectomy, are no longer done. Routine bone marrow biopsy, in the absence of unexplained blood abnormalities, is not indicated.

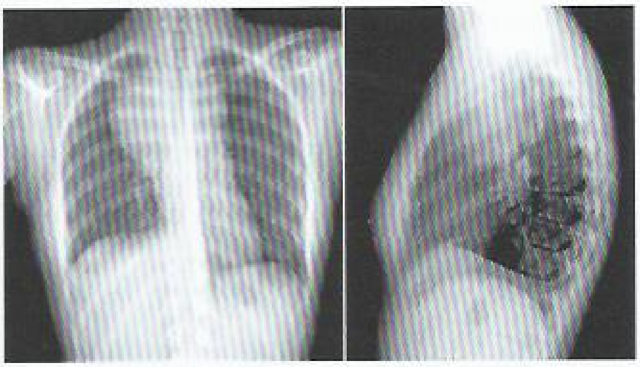

FIGURE 24. Hodgkin lymphoma is the most common lymphoma to involve the mediastinum, shown in this chest radiograph (left) as a mass that originates from the mediastinum, given the convex angles resulting from the mass impinging on the pleura. The lateral film (right) localizes the mass to the anterior mediastinum. Hodgkin lymphoma is the most common cause of anterior mediastinal masses in patients aged 20 to 30 years.

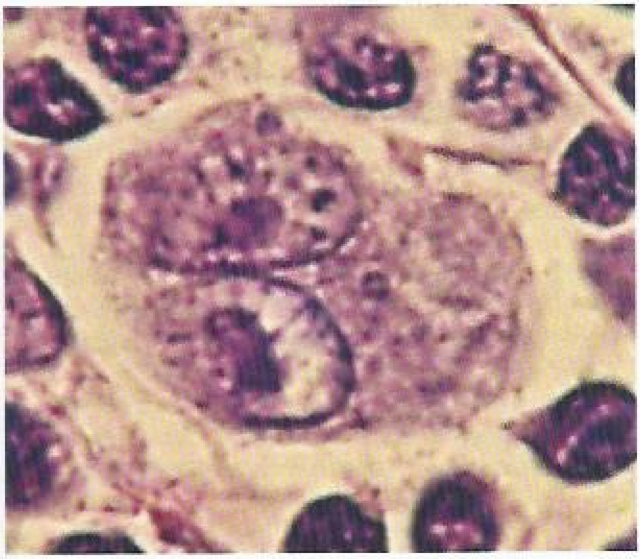

FIGURE 25. Reed-Sternberg cells are large and either are multinucleated or have a bilobed nucleus ("owls eye" appearance) with prominent eosinophilic inclusion-like nucleoli. They can be seen with light microscopy in biopsies from individuals with Hodgkin lymphoma. They are usually derived from B lymphocytes. When seen against a sea of B cells, they give the tissue a "starry sky" or "moth-eaten" appearance. The absence of Reed-Sternberg cells has very high negative predictive value for Hodgkin disease.

More than 90% of patients present with "classic" Hodgkin lymphoma pathology and, even with early-stage disease, receive chemotherapy because this has been shown to result in higher cure rates. The doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) regimen is most commonly used in the United States. ABVD has replaced alkylating agent-based regimens such as mechlorethamine, vincristine, procarbazine, and prednisone, in part because of higher rates of fertility preservation and a lower risk of secondary acute leukemia. For patients with early-stage, favorable disease, treatment can consist of short-course chemotherapy (as short as two cycles of ABVD) and involved field radiation. Chemotherapy alone (ABVD for four to six cycles) in patients with good response is also an option. For more advanced disease, chemotherapy alone is used. Although the regimen is usually well tolerated, up to 25% of patients may develop bleomycin-induced lung injury during treatment or within 6 months of its conclusion. A portion of those patients will have sustained exertional dyspnea associated with a decline in pulmonary function.

Complete response indicated by PET scan after two to three cycles of chemotherapy is a reliable prognostic indicator. Early repeat PET scan is an appropriate response adapted strategy in Hodgkin lymphoma and may allow some patients with early-stage disease to forgo radiation therapy and thereby reduce the risks of late radiation side effects.

For patients with relapsed or refractory disease, salvage chemotherapy and autologous or allogeneic HSCT may provide curative options. Brentuximab vedotin (an anti-CD30 monoclonal antibody conjugated with a peptide link to monomethyl auristatin E [MMAE]) is active in refractory disease and has also been used for consolidation after autologous HSCT. The programmed death 1 (PD-1) antibodies (pembrolizumab and nivolumab) are highly active in relapsed or refractory disease. The incorporation of these drugs in earlier treatment regimens is being studied.

Nodular lymphocyte-predominant Hodgkin lymphoma is distinct clinically and pathologically from classic Hodgkin lymphoma (nodular sclerosis, mixed cellularity, and lymphocyte depleted). It represents approximately 10% of Hodgkin lymphomas and is more likely to present with localized disease but is associated with a high rate of late relapse. Early-stage disease may be treated with radiation therapy alone. Single-agent rituximab or combined with chemotherapy may be used for more advanced or relapsed disease.

KEY POINTS

- All patients with classic Hodgkin lymphoma, regardless of stage, receive chemotherapy. Patients with early-stage nodular lymphocyte-predominant Hodgkin lymphoma may be treated with radiation alone, but in the more advanced stages, they should be treated with rituximab with or without chemotherapy.
- Complete response indicated by PET scan after two to three cycles of chemotherapy can allow some patients with early-stage classical Hodgkin lymphoma to forgo radiation therapy.

Cancer of Unknown Primary Site

Introduction

Despite steady improvements in diagnostic and imaging techniques during the past decades, a reasonable evaluation will not identify the source of cancer in a small number (less

than 5%) of all patients presenting with metastatic cancer. This heterogeneous group of patients is classified as having cancer of unknown primary (CUP). As diagnostic imaging continues to improve, the frequency of CUP diagnoses is decreasing.

Diagnosis and Evaluation

On identification of metastatic cancer, a full medical history and physical examination should be obtained, as well as contrast-enhanced CT of the chest, abdomen, and pelvis. Histologic evaluation of the most accessible tumor mass should include a limited number of immunohistochemical stains to assess the nature of the tumor and to identify or exclude treatable histologies (such as lymphoma or germ cell tumor). Patterns of clinical presentation, or subgroups (discussed later), that also suggest a potential for better outcome should be sought. In addition, specific symptom or presentation-related evaluations may be pursued, such as upper endoscopy and colonoscopy in patients with symptoms or evidence of gastrointestinal bleeding. Patients with regional lymphadenopathy require focused evaluation, such as pan-endoscopic evaluation of the head and neck for patients with isolated or dominant cervical lymphadenopathy or anoscopy for those with isolated inguinal lymphadenopathy. In female patients, breast examination and mammography should be done to search for a breast primary cancer, and a gynecologic evaluation should be performed to look for an ovarian primary. Male patients require a testicular examination and, in those with bone metastases, a prostate examination and serum prostate-specific antigen to evaluate for prostate cancer. Nonspecific tumor markers, such as serum carcinoembryonic antigen, CA-19-9, CA 15-3, or CA 125, are not definitive for identifying a specific site of origin and are not routinely recommended. PET may in some patients suggest the possible primary location, but false-positive results are significant and PET scan findings are not apt to change the treatment plan. The use of gene expression arrays has been commercially promoted, but the clinical utility of these tests to identify more effective therapy is unknown. As these add expense without clear benefit, their routine use in the evaluation of CUP is not recommended.

Ultimately, CUP is a diagnosis of exclusion after evaluation has failed to identify the primary tumor, which either may be too small to be detected or may have been destroyed immunologically and is no longer present. Both patients and clinicians tend to overemphasize the importance of identifying the primary site. Such efforts often deflect focus from the major issue, which is the presence of metastatic cancer. Once the more treatable possibilities have been excluded, specific identification of the site of origin is very unlikely to improve treatment options or clinical outcome. At that point, it should be determined if the metastatic cancer has a favorable or unfavorable prognosis and if there is a specific, efficacious therapy for that patient.

KEY POINTS

- In patients with a metastatic cancer of unknown primary site, CT scans and histologic, endoscopic, and gender-specific cancer evaluations are reasonable; however, nonspecific tumor markers, PET scans, and gene expression arrays are not definitive and have not been shown to be beneficial and should not be done. **HVC**
- After reasonable attempts to identify primary cancer have failed, management should shift focus, treating the metastasis based on histology and prognostic factors as finding the primary site is unlikely to improve treatment options or clinical outcome.

Favorable Prognostic Subgroups of Cancer of Unknown Primary Site

For patients with CUP, the identification of a favorable prognostic subgroup allows selection of specific surgical, radiation, or chemotherapy to which patients are more likely to respond and on occasion achieves long-term remission and cure.

Poorly Differentiated Cancer of Unknown Primary Site

Poorly differentiated cancers are usually more aggressive than well-differentiated cancers, and metastatic poorly differentiated adenocarcinoma has a poor prognosis; however, some patients with poorly differentiated CUP that is not definitively an adenocarcinoma may have specific treatment options as a result of their histology. In particular, young men with poorly differentiated carcinoma that is predominantly in the midline, such as those with large retroperitoneal or mediastinal lymphadenopathy, or both, should be carefully evaluated for the possibility of a germ cell tumor. Serum α-fetoprotein and β-human chorionic gonadotropin levels should be measured, and a testicular examination and ultrasonography should be performed. Even if these evaluations have negative findings, an unrecognized germ cell tumor may still exist, and these patients should be treated for this possibility with a platinum-based chemotherapy regimen.

Patients with poorly differentiated neuroendocrine tumors also warrant careful consideration. These tumors frequently both metastasize like small cell lung cancers and respond similarly to platinum-based chemotherapy.

Isolated Regional Lymphadenopathy

A group of patients with CUP who may have a more favorable prognosis is women found to have adenocarcinoma in isolated axillary lymphadenopathy. These patients should be presumptively considered to have locoregional breast cancer. If mammography is unrevealing, a breast MRI should be performed. If the MRI scan is negative, the patient is still assumed to have a presumptive stage II breast cancer. Given the inability to identify the primary, a mastectomy or whole breast radiation therapy is recommended. These patients should all receive adjuvant treatment consistent with a stage II breast cancer

diagnosis. Patients with isolated or dominant cervical lymphadenopathy should undergo full endoscopic examination of the upper aero-digestive tract to evaluate for a head and neck primary. Even if a primary is not identified, treatment along a head and neck paradigm with chemotherapy and radiation therapy is often appropriate. In particular, patients with high cervical lymphadenopathy with squamous cell cancer occasionally achieve cure. Supraclavicular lymphadenopathy or adenocarcinoma makes a head and neck primary far less likely, and therapy is less efficacious.

Isolated inguinal lymphadenopathy should prompt a careful examination of the anal, perineal, and genital regions that includes anoscopy. Even in the absence of a defined primary tumor, definitive resection or radiation to inguinal or other isolated solitary or regional lymph nodes may provide long-term tumor control and cures in rare circumstances.

Peritoneal Carcinomatosis in Women

Women who have adenocarcinoma with abdominal carcinomatosis and ascites should be presumptively treated for ovarian cancer. Ovarian cancer paradigms, including initial cytoreductive surgery and ovarian cancer chemotherapy regimens, should be used.

KEY POINTS

- Patients with cancer of unknown primary who have poorly differentiated carcinoma predominantly in the midline, such as those with large retroperitoneal or mediastinal lymphadenopathy, are likely to have a germ cell tumor and should be treated for that possibility with platinum-based chemotherapy.
- Women with a cancer of unknown primary who have axillary lymphadenopathy and a negative breast MRI scan should be treated for presumptive stage II breast cancer.
- Women with adenocarcinoma with abdominal carcinomatosis and ascites should be treated for presumptive ovarian cancer.
- Patients with isolated or dominant cervical lymphadenopathy and cancer of unknown primary should be treated along a head and neck cancer paradigm with chemotherapy and radiation therapy.

Nonfavorable Subgroups of Cancer of Unknown Primary Site

Therapy for CUP that does not fall into one of the favorable subgroups is empirically directed with chemotherapy and radiation therapy based on the pattern of presentation. CUP presenting above the diaphragm should be evaluated and managed as metastatic lung cancer. CUP that is predominantly below the diaphragm should be managed as gastrointestinal cancer.

Chronic medical comorbidities and performance status of the patient greatly influences the range of treatment options. As with other solid tumors, patients with several comorbidities and poor performance status are far less likely to benefit from aggressive chemotherapy and are far more likely to experience serious or life-threatening toxicity. Palliative and hospice care should be considered in such patients. Clinical trials that may demonstrate tumor response are typically restricted to patients with normal organ function and good performance status. The results of those trials are unlikely to be informative regarding the response to therapy or prognosis for patients who are not well enough to have qualified for entry into those trials.

KEY POINTS

- Therapy for cancer of unknown primary that does not fall into one of the favorable subgroups should be managed based on pattern of presentation; cancer presenting above the diaphragm should be treated as metastatic lung cancer and cancer presenting below the diaphragm should be treated as gastrointestinal cancer.
- Palliative or hospice care is appropriate for patients with an unfavorable subtype of cancer of unknown primary site who have comorbidities and poor performance status. HVC

Melanoma

Melanoma has been steadily increasing in incidence worldwide, with risk related to sun exposure. Most melanomas begin in and present with cutaneous disease, but they can also begin in mucosal sites. About half arise in preexisting nevi, but many begin in apparently normal skin. Melanoma can also present in nodal or visceral sites without a known cutaneous or mucosal primary. About 10% of patients with melanoma have a familial history, and mutations in certain genes, such as *CDKN2A*, have been identified in some families. Ocular melanoma is the most common cancer of the eye, and uveal melanomas have a distinct biology and behavior. Epidemiology, diagnosis, and staging of melanoma are discussed in MKSAP 18 Dermatology.

Advances in systemic therapy during the past decade have resulted in significant improvements in survival for metastatic melanoma patients. These advances include the use of molecular therapy targeted at specific gene mutations and immunotherapy, including the use of immune checkpoint inhibitors.

Treatment of Melanoma

Melanoma has the potential to behave quite aggressively, but it is a highly curable disease when detected and treated early with simple excision. For localized melanomas, prognosis is related to the depth of invasion, either by Clark level (I to V) or by Breslow's depth. A high mitotic rate, lymphovascular invasion, and the presence of bleeding or ulceration are poor prognostic signs. Surgical resection margins for melanomas do not

have to be excessive: 1-cm margins are acceptable for lesions that are less than 1 mm in thickness. Patients with melanomas between 1 mm and 2 mm in thickness should be resected with a 2-cm margin provided that a skin graft is not required for closure. Patients with lesions that are greater than 2 mm in thickness should be resected with 2 cm margins. Early stage patients can be assessed clinically and do not need radiographic staging (for example, CT and PET) and surveillance.

As the depth of invasion increases, the risk of nodal and ultimately distant metastasis increases. Nodal metastases are uncommon and need not be assessed if the patient has thin lesions with a Breslow depth of less than 1 mm. Assessing for lymph node metastasis with lymphatic mapping and sentinel lymph node biopsy is often recommended for intermediate and thicker melanomas. If the sentinel node is positive, a lymph node dissection commonly yields other positive nodes. Although prophylactic lymphadenectomies or completion node dissections for those with positive sentinel nodes have not definitively shown an overall survival benefit, node dissections can be curative in 20% to 50% of patients who present with or who develop regional nodal disease. The use of interferon as adjuvant therapy for resected high-risk disease has been extensively studied and is FDA approved. Although there is some demonstrated improvement in disease free survival, the overall survival benefit is uncertain, and this therapy is associated with considerable side effects. Adjuvant ipilimumab (see below) also has shown modest benefit in disease free survival, but as of yet, no overall survival benefit has been shown. Adjuvant nivolumab has been recently shown to be more effective than ipilimumab in node-positive disease.

For distant metastatic disease, surgery may still play a significant role. Melanoma can present with solitary or oligometastatic disease amenable to resection that is curable in some patients. Standard cytotoxic chemotherapy is associated with low response rates and no longer plays a large role in the treatment of metastatic melanoma. The biologic agents interferon-alfa and interleukin-2 can induce responses in some patients, but they cause considerable toxicity and are generally used only in specialized referral centers. The current focus is on targeted therapy for patients with specific gene mutations and on the use of checkpoint inhibitors of programmed cell death transmembrane proteins.

Approximately one half of melanomas harbor a *BRAF* gene mutation (most commonly V600E), and another 20% have a *MEK* or *NRAS* mutation; all of these mutations activate the mitogen-activated protein kinase pathway. Melanomas with these mutations may respond to oral therapy with the *BRAF* inhibitors vemurafenib and dabrafenib. Combining *BRAF* inhibitors with MEK inhibitors trametinib and cobimetinib improves the rate and duration of response. These are available as combined oral agents.

In addition to the efficacy of *BRAF* inhibitors, the use of immune checkpoint inhibitors has revolutionized the therapy and prognosis of patients with metastatic melanoma. Cellular immunity is based on T cells recognizing peptide fragments expressed on the surface of antigen-presenting cells when bound to histocompatibility complex molecules. Cytotoxic T-lymphocyte associated protein 4 (*CTLA4*) is a potent down-regulator of this process. *CTLA4* is stimulated by T-cell activation and various cytokines, serving as an inhibitory factor or braking "checkpoint" on immune activation. The antibody against *CTLA4*, ipilimumab, can result in dramatic tumor response, albeit in a small percentage of patients. Tumor response is independent of *BRAF* status.

The programmed cell death-1 (PD-1) receptor is another transmembrane protein that acts as an inhibitory molecule when bound to the PD-ligand 1 and stops tumor cell apoptosis while down-regulating other aspects of T-cell immune response. Nivolumab and pembrolizumab are both anti-PD-1 antibodies that can result in significant melanoma response rates with sometimes durable response and dramatic survival improvement. Ipilimumab alone has a relatively low response rate and is associated with considerable toxicity, with various immune related adverse events that can include colitis, hepatitis, pneumonitis, and endocrine insufficiency syndromes. Similar side effects can occur with nivolumab and pembrolizumab but are less frequent, and these antibodies are associated with a higher response rate (30% to 40%). Combining ipilimumab with nivolumab improves results compared with ipilimumab or nivolumab alone. The best dosage, schedule, and sequence for these newer agents continue to be explored.

KEY POINTS

- Surgical resection can be curative in many patients with melanoma, including those with solitary or oligometastatic disease.
- Nodal metastases are uncommon and need not be assessed in patients with thin melanoma lesions (Breslow depth less than 1 mm). **HVC**
- More than one half of patients have melanoma that harbors a V600E *BRAF* or *MEK* gene mutation, which may respond to the *BRAF* inhibitors vemurafenib and dabrafenib combined with MEK inhibitors trametinib and cobimetinib.
- The combination of ipilimumab, a checkpoint inhibitor targeting cytotoxic T-lymphocyte associated protein 4 (*CTLA4*), and nivolumab, an antibody against programmed cell death-1 receptor, has shown significant improvements in survival for patients with metastatic melanoma.

Follow-up

All patients should be encouraged to perform skin self-examinations as well as receive annual skin evaluations by a dermatologist for life. Patients with early-stage melanoma need not undergo routine blood testing or imaging studies in the absence of signs or symptoms.

Oncologic Urgencies and Emergencies

Structural Urgencies and Emergencies

Superior Vena Cava Syndrome

Obstruction of the superior vena cava (SVC), or SVC syndrome, occurs in approximately 15,000 persons in the United States each year. Most cases are caused by malignancies with large mediastinal masses. Patients typically present with edema of the head, neck, and arms, often with cyanosis, plethora, and distended cutaneous collateral vessels. They may have headache, cough, dyspnea, hoarseness, or syncope. The severity of symptoms depends on the degree of narrowing of the SVC and the speed of onset, with slower development allowing venous collaterals to develop. Most patients do not require emergency intervention, and deaths due to SVC syndrome are rare, although tumors in that region may cause other emergencies, such as bronchial obstruction or cardiac tamponade. A chest CT scan with intravenous contrast usually confirms the diagnosis (**Figure 26**). Lung cancer accounts for almost 75% of cases of SVC syndrome, with lymphoma and metastatic disease each causing approximately 10%; rarer tumors, such as germ cell tumor, thymoma, or mesothelioma, account for the remainder.

Management is based on the severity of symptoms and the underlying malignancy. In patients requiring immediate treatment of respiratory distress, an SVC stent can be placed without tissue diagnosis and results in prompt improvement in symptoms. For most patients, a tissue diagnosis is obtained, with treatment directed by the type of cancer. Options for obtaining diagnostic tissue include mediastinoscopy, bronchoscopy, thoracentesis (if a pleural effusion is present), or biopsy of a peripheral area of lymphadenopathy. Complication rates are usually low.

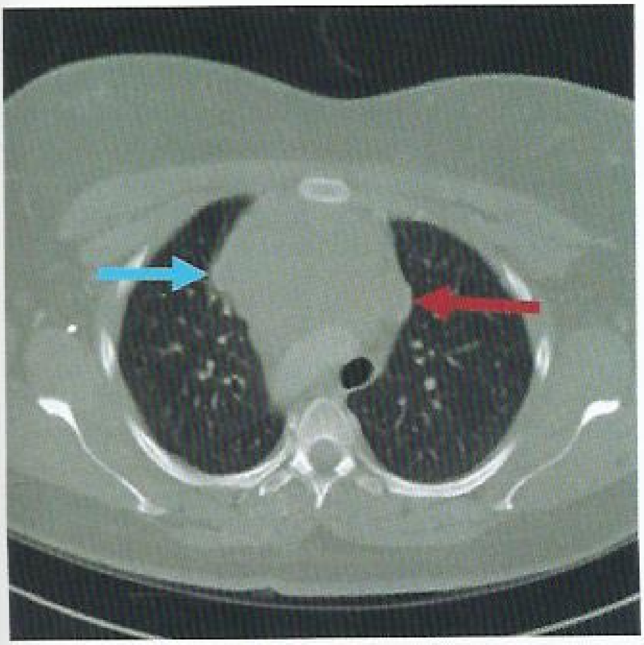

FIGURE 26. Superior vena cava (SVC) syndrome often presents on chest CT scan with bronchial obstruction due to mediastinal mass (*blue arrow*) and SVC compression (*red arrow*).

Types of cancer that are highly responsive to chemotherapy, such as small cell lung cancer, lymphoma, and germ cell cancers, are treated with initial chemotherapy. Non–small cell lung cancer may be treated with initial chemotherapy, radiation therapy, or both. Initial surgery may be required in thymoma and mesothelioma. Although glucocorticoids and loop diuretics are often used, there is no clear evidence of their effectiveness. If thrombosis is present, anticoagulation should be added unless contraindicated.

Treatment of curable malignancies should not be compromised by the presence of SVC syndrome. The survival is the same as in patients with the same malignancies without this presentation.

KEY POINTS

- Most patients with superior vena cava syndrome do not require emergency intervention; a tissue diagnosis should be obtained first with treatment directed by the type of cancer.
- Presentation with superior vena cava syndrome does not worsen prognosis in patients who present with otherwise curable malignancies.

Central Nervous System Emergencies

Increased Intracranial Pressure

Elevated intracranial pressure can result from primary brain malignancies or from brain metastases, which occur in 10% to 20% of adults cancer patients. The most common types of primary cancer that cause brain metastases are lung cancer, breast cancer, and melanoma. Median survival after diagnosis of brain metastases varies from less than 3 months to more than 25 months.

Symptoms of increased intracranial pressure include headache, depressed global consciousness, vomiting, and even signs and symptoms of herniation. Emergent CT or MRI imaging will confirm the diagnosis. Glucocorticoids relieve symptoms in 75% of patients by decreasing tumor-related vasogenic edema. Patients with severe symptoms are treated with a loading dose of dexamethasone of 10 to 20 mg followed by 4 to 6 mg every 6 hours. The most critically ill patients may require other measures, including osmotic diuresis with mannitol, head elevation, hyperventilation, and possibly decompressive surgery. Antiepileptic drugs should be used in the 25% of patients who present with seizures. See MKSAP 18 Neurology for further discussion of antiepileptic drugs. Anticoagulation can be safely used when indicated. Lumbar puncture is contraindicated in patients with an increased intracranial pressure because of the risk of herniation.

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Spinal Cord Compression

Neoplastic epidural spinal cord compression (ESCC) develops in approximately 2.5% of patients with metastatic cancer. The most common types of cancer that cause ESCC in adults are lung, breast, and prostate cancer; myeloma; and lymphoma. Approximately 85% of ESCC cases are due to epidural extension from vertebral body metastases. Lymphomas are more likely to involve a paraspinal mass that extends through the neural foramina to cause cord compression. Pain, often worse with recumbency, is present in more than 80% of patients and usually precedes neurologic symptoms by several weeks. The absence of neurologic signs should not delay evaluation of such pain. At times, ESCC may be the first sign of cancer, although patients with such a presentation often have other systemic signs, such as anorexia and weight loss. Pain can be radicular. Weakness is present in more than 60% of patients at presentation. If a sensory level is present, it is typically one to five levels below the actual level of cord compression. Bowel and bladder dysfunction is a late finding that is present in up to half of patients. MRI of the entire thecal sac is the preferred imaging test when ESCC is suspected.

The patient's neurologic status at diagnosis is the most important predictor of outcome. Of patients who are able to walk when starting treatment, 80% remain ambulatory; however, less than 20% of nonambulatory patients regain the ability to walk. Patients are initially treated with glucocorticoids at either a moderate or high dose if paraparesis or paraplegia is present. Definitive treatment with surgery, radiation, or both depends on whether the patient has a known cancer diagnosis, as well as the stability of the spine, the sensitivity of the cancer to radiation, and the patient's overall prognosis. For patients who are acceptable surgical candidates with an expected survival of at least 3 months, initial decompressive surgery followed by radiation increases the likelihood of ambulation compared with radiation alone. See MKSAP 18 Neurology for further discussion of spinal cord compression. H

KEY POINTS

- Neoplastic spinal cord compression is initially treated with glucocorticoids; definitive treatment with surgery, radiation, or both depends on the whether the patient has a known cancer diagnosis, stability of the spine, the sensitivity of the cancer to radiation, and the patient's overall prognosis.
- Neurologic status is the most important predictor of outcome for patients with neoplastic spinal cord compression; ambulatory patients tend to remain ambulatory with treatment, but nonambulatory patients typically do not regain the ability to walk.

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Malignant Pleural and Pericardial Effusions

Types of cancer that most commonly cause malignant pleural effusions include lymphomas; mesotheliomas; and carcinomas of the breast, lung, gastrointestinal tract, and ovaries. Patients present with progressive dyspnea and may or may not have concomitant chest pain. See MKSAP 18 Pulmonary and Critical Care Medicine for further discussion of pleural effusions. Chest radiography is the initial diagnostic study, often followed by CT imaging, which provides more precise anatomic detail. Therapeutic thoracentesis is used as the initial treatment of symptomatic effusions. Further management depends on the rate of reaccumulation, the severity of symptoms, and the patient's prognosis. Recurrent effusion is common, unless the tumor is responsive to systemic therapy. Repeat thoracentesis is appropriate for slowly recurring effusions. For effusions with more rapid reaccumulation, the best options for management are placement of an indwelling pleural catheter with intermittent outpatient drainage or pleurodesis, with similar palliation obtained by either method. Less frequently, pleurectomy can be done to control malignant pleural effusions.

Malignancy accounts for 13% to 23% of pericardial effusions and may be the first presentation of the disease. Lung, breast, and esophageal cancers; melanoma; lymphoma; and leukemia are the most common malignancies that cause pericardial effusions. Cardiac tamponade results when the pericardial fluid pressure impairs filling of one or both ventricles, leading to decreased cardiac output. Patients present with dyspnea, chest discomfort, or fatigue. They usually have elevated jugular venous distention and may have hypotension and peripheral edema. Pulsus paradoxus, a greater than 10 mm decrease in systolic pressure with inspiration, is also typically present. Echocardiography usually establishes the diagnosis. Symptoms from progressive cardiac tamponade may be inappropriately attributed to nonspecific systemic signs of cancer or heart failure until cardiac filling and cardiac output is emergently compromised. See MKSAP 18 Cardiovascular Medicine for further discussion of cardiac tamponade.

Treatment of symptomatic pericardial effusion involves percutaneous pericardiocentesis or drainage during surgical placement of a pericardial window. The most common treatments to prevent recurrence are prolonged catheter drainage or surgical decompression with a pericardial window. H

KEY POINT

- For slowly recurring malignant pleural effusions, repeat thoracentesis is appropriate; for more rapidly recurring pleural effusions, either an indwelling pleural catheter with intermittent outpatient drainage or pleurodesis is used.

H

Metabolic Urgencies and Emergencies

Tumor Lysis Syndrome

Tumor lysis syndrome (TLS) is caused when tumor cells release their contents into the bloodstream, either spontaneously or as a result of treatment, leading to hyperuricemia, hyperkalemia,

H CONT.

hyperphosphatemia, and hypocalcemia. These electrolyte abnormalities can lead to acute kidney injury, cardiac arrhythmias, seizures, and death. TLS is seen most often in highly proliferative hematologic malignancies such as acute leukemia and high-grade lymphomas, but can develop in many other cancers.

The risk of TLS can be categorized based on the volume of cancer mass present; the cell-lysis potential of the cancer; and patient characteristics of preexisting kidney failure, dehydration, acidosis, hypotension, or nephrotoxin exposure. Patients at intermediate risk for TLS can be managed with monitoring of laboratory values, hydration, and allopurinol, and those at high risk should receive intravenous hydration and rasburicase, a urate oxidase enzyme that metabolizes uric acid, before receiving chemotherapy. There is no clear benefit of alkalinization to increase uric acid excretion, particularly given the availability of rasburicase. Alkalinization increases the risk of hyperphosphatemia.

Patients who develop TLS require continuous cardiac monitoring; serum measurement of electrolytes, creatinine, and uric acid every 4 to 6 hours; and correction of electrolyte abnormalities. Rasburicase should be given and patients should receive aggressive hydration if kidney function allows, with the use of a loop diuretic if needed to improve urinary output. Patients may require renal replacement therapy for severe oliguria or anuria, persistent hyperkalemia, symptomatic hypocalcemia, or a calcium phosphate product greater than or equal to 70 mg^2/dL^2. H

KEY POINT

- Tumor lysis syndrome should be treated with rasburicase and aggressive hydration if kidney function allows; patients require continuous cardiac monitoring and measurement of electrolyte, creatinine, and uric acid levels every 4 to 6 hours.

H Hypercalcemia of Malignancy

Hypercalcemia of malignancy (HCM) occurs in 20% to 30% of patients with advanced cancer. It is most frequent in patients with myeloma and cancer of the lung, breast, kidney, and head and neck. Osteolytic bone metastases are usually the cause of HCM in breast cancer and myeloma, although the incidence of hypercalcemia in these patients may be decreasing with the prophylactic use of bisphosphonates. Paraneoplastic production of parathyroid hormone–related protein may occur in localized tumors without widespread bone metastases. Lymphomas can cause hypercalcemia by overproduction of 1,25-dihydroxyvitamin D. Malignancies such as ovarian cancer can produce ectopic parathyroid hormone.

Patients may present with nausea, vomiting, constipation, fatigue, polyuria, polydipsia, altered mental status, or muscle weakness. Symptoms depend on both the serum calcium level and the rate of rise. Rapidly rising levels and levels greater than 14 mg/dL (3.5 mmol/L) are most likely to cause severe symptoms. Hypercalcemia can result in dehydration, nephrogenic diabetes insipidus, and acute kidney injury.

Patients with severe or symptomatic hypercalcemia should receive isotonic saline volume expansion. Loop diuretics are not recommended unless kidney failure or heart failure is present, in which case volume expansion should precede the administration of loop diuretics to avoid hypotension and further kidney injury. Calcitonin increases kidney excretion of calcium and decreases bone resorption; it can decrease calcium within several hours in responsive patients. The most effective agents are bisphosphonates, such as zoledronic acid, which inhibit bone resorption and can lower calcium levels to normal in 50% of patients in 4 days and in 88% of patients in 10 days. The receptor activator of nuclear factor κB ligand denosumab can be considered for patients who do not respond to zoledronic acid. It can be safely used in patients with kidney failure where bisphosphonates may be contraindicated. Effective treatment of the underlying malignancy remains the most appropriate means of controlling hypercalcemia. H

KEY POINT

- Patients with severe or symptomatic hypercalcemia should receive isotonic saline volume expansion, calcitonin, and bisphosphonates; loop diuretics are not recommended unless kidney failure or heart failure is present.

Effects of Cancer Therapy and Survivorship

Effects of Cancer Therapy

Hematologic Toxicity

The major toxicity of many traditional chemotherapeutic agents remains myelosuppression, leading to anemia, neutropenia, and thrombocytopenia.

Neutropenia and Fever

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The risk of infection increases with the magnitude and the duration of neutropenia, which typically occurs 5 to 15 days after chemotherapy administration. Serious infectious complications are more likely when the absolute neutrophil count is below 500/µL ($0.5 \times 10^9/L$) and the expected duration is more than 7 days. Fever in a patient with neutropenia is an emergency, as patients can become septic quickly. Prompt evaluation, including blood count and other appropriate cultures, and administration of empiric, broad-spectrum antibiotics, typically a third-generation cephalosporin alone or in combination (even in the absence of a documented or suspected site of infection), is critical. Selected patients without significant comorbidities who are medically stable and adherent, and in whom a short duration of neutropenia is anticipated, can be treated on an outpatient basis with intravenous or oral antibiotics. H

The prophylactic use of granulocyte colony-stimulating factor or granulocyte-macrophage colony-stimulating factor reduces the risk of febrile neutropenia. These medications may

be given to patients receiving regimens associated with a high risk of this complication or as secondary prophylaxis in patients with a previous episode of neutropenic fever. Growth factors are not used in the treatment of patients with neutropenic fever unless the patient has either persistent fever despite antibiotic treatment or severe neutropenia (absolute neutrophil count less than 100/µL [0.1×10^9/L]) expected to last more than 7 days.

KEY POINT

HVC
- Growth factors are not used in the treatment of patients with neutropenic fever unless the patient has either persistent fever despite antibiotic treatment or severe neutropenia (absolute neutrophil count less than 100/µL [0.1×10^9/L]) expected to last more than 7 days.

Anemia and Thrombocytopenia

Anemia in patients with cancer may be multifactorial, related to chronic inflammation, bone marrow suppression, blood loss, and chemotherapy. Anemia contributes significantly but not solely to the fatigue patients with cancer endure. Erythrocyte transfusions and erythropoietin administration are sometimes required. The enthusiasm for erythropoietin has been tempered by studies suggesting that symptom improvement is achieved at a cost of more rapid cancer progression and increased risk of venous thromboembolism. This concern has prompted increased regulation and a significant decrease in the use of erythropoietin therapy in patients with cancer, particularly for those receiving curative or adjuvant treatments.

Thrombocytopenia is generally managed with platelet transfusions, when needed, and appropriate dose reductions and delays.

Nausea and Vomiting

Although nausea and vomiting are still common side effects of chemotherapy, their incidence and severity have been markedly reduced by antiemetic medications. Delayed nausea (more than 1 day after treatment), especially with cisplatin regimens, has not been as effectively prevented. Chemotherapy agents can be separated into mild, moderate, and severe emetogenic effect categories. For patients receiving moderate to severely emetogenic drugs, administration of serotonin receptor antagonists (such as ondansetron or the longer-acting palonosetron) in combination with high-dose glucocorticoid therapy is standard. Improvement in both acute and delayed nausea and vomiting is seen with the addition of neurokinin 1 receptor blockers (such as aprepitant and netupitant). Further benefit has been reported with the antipsychotic agent olanzapine.

Dermatologic Effects

Cutaneous toxicities vary in frequency, severity, and type. Alopecia is the most common but does not occur with all chemotherapy agents. Almost all drugs have the potential to cause allergic reactions; examples of severe reactions include toxic epidermal necrolysis and Stevens Johnson syndrome. Fluoropyrimidines (5-fluorouracil and capecitabine) are associated with palmar plantar erythrodysesthesia ("hand-foot syndrome"), described as redness, peeling, and tenderness of the palms and soles. Small-molecule epidermal growth factor receptor (EGFR) inhibitors, such as erlotinib and gefitinib, used to treat *EGFR*-mutated lung cancer, are associated with pustular acneiform eruptions and other skin changes, including dryness. Monoclonal antibodies against EGFR (cetuximab and panitumumab) are associated with a similar and often more severe acneiform eruption. See MKSAP 18 Dermatology for further discussion of dermatologic chemotherapy reactions.

Disorders of Pulmonary Function

A wide variety of chemotherapy agents can be associated with pulmonary injury, likely from various mechanisms. Bleomycin, nitrosoureas, and gemcitabine may have the strongest associations with pulmonary toxicity, but many others have toxicity potential. In addition, various monoclonal antibodies and targeted therapies can be associated with pulmonary toxicities, including rituximab, trastuzumab, cetuximab, and erlotinib.

Radiation therapy can be associated with a pneumonitis, typically occurring within 1 to 3 months of treatment, and may lead to the development of radiation fibrosis. See MKSAP 18 Pulmonary and Critical Care Medicine for further discussion of disorders of pulmonary function related to chemotherapy.

Disorders of Genitourinary and Kidney Function

Several chemotherapy agents can affect kidney function. Cisplatin is the most common agent and is associated with acute tubular necrosis. The risk is reduced with the use of aggressive hydration. Ifosfamide can be associated with kidney disease and significant tubular toxicity, with long-term potassium, magnesium, and bicarbonate wasting. Both ifosfamide and cyclophosphamide, in high doses, may cause a hemorrhagic cystitis. Hemolytic uremic syndrome is associated with various chemotherapy agents, most commonly with mitomycin and gemcitabine. Kidney failure can occur with tumor lysis syndrome.

Neurologic Toxicity

Peripheral neuropathy is a common toxicity of several chemotherapy agents, most commonly occurring with platinums, taxanes, and vinca alkaloids, as well as with newer agents, such as bortezomib. Oxaliplatin causes a transient hypersensitivity to cold—patients must avoid eating, drinking, or even touching cold items for several days after infusions—as well as a non–temperature-dependent persistent peripheral neuropathy that may be more problematic in the long term. Therapies are sometimes continued with appropriate dose reductions if there are only mild sensory symptoms. However, when patients develop significant symptoms with dysfunction, pain, and motor weakness, therapies are discontinued. Although symptoms may alleviate over time, some patients are left with significant deficits. Medications such as gabapentin and

duloxetine may help alleviate discomfort but no definitive neuroprotective agents or strategies have proved to reliably prevent or resolve these symptoms.

Rituximab, along with other immunosuppressive agents, rarely has been associated with progressive multifocal leukoencephalopathy. 5-Fluorouracil and high-dose cytosine arabinoside are associated with cerebellar toxicity. The reversible posterior encephalopathy syndrome, consisting of headache, visual disturbances, delirium, and seizures associated with characteristic white matter edema in the posterior brain, has been linked to chemotherapy that targets vascular endothelial growth factor, such as bevacizumab or sunitinib.

Whole brain radiation can cause impairment of cognitive function. In some situations, this toxicity can be reduced by the use of focused high-dose radiation (gamma knife or stereotactic radiosurgery) to identified lesions. See MKSAP 18 Neurology for further discussion of disorders of peripheral neuropathy related to chemotherapy.

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Toxicities Related to Immune Dysregulation

With the increasing use of checkpoint inhibitors for various tumors, patients with cancer are at risk for toxicities associated with the induction of autoimmunity. Antibodies such as ipilimumab (anti-cytotoxic T-lymphocyte associated protein 4 [CTLA4]), pembrolizumab and nivolumab (anti-programmed death receptor-1 [PD-1]), and atezolizumab (anti-programmed death ligand-1 [PDL1]), are associated with immune-related toxicities, including colitis, pneumonitis, hepatitis, dermatitis, hypophysitis, thyroiditis, and adrenalitis. These toxicities occur in a small but significant minority of patients and require prompt recognition and often glucocorticoid therapy as well as hormone replacement, if indicated. H

KEY POINTS

- Fever in a neutropenic patient with cancer is an emergency requiring prompt evaluation and administration of empiric broad-spectrum antibiotics.
- HVC Patients with febrile neutropenia expected to be of short duration, who lack significant comorbidity and who have reliable home care and follow-up, can be treated with oral antibiotics on an outpatient basis.
- Standard antiemetic treatment of patients taking moderate to severe emetogenic chemotherapy drugs is a serotonin receptor antagonist (ondansetron or palonosetron) and a high-dose glucocorticoid.

Survivorship Issues

As patients with cancer live longer, being either cured or surviving for more extended periods, survivorship issues have assumed greater importance. Survivorship embodies the care that follows patients on completion of their treatments, including screening for recurrence and secondary malignancies; monitoring for late organ dysfunction; and helping patients cope with the psychological, sexual, vocational, and other effects of treatment. An initial treatment plan for cancer may be based not only on providing the highest probability of cure but also on a strategy to reduce the risk of long-term complications.

Late Effects of Cancer Therapy

Effects on Bone Health

Bone loss occurs at an increased rate in female cancer survivors who have taken long-term glucocorticoids; those who have undergone surgical, radiation, or chemotherapy-induced premature menopause; and those taking aromatase inhibitors for breast cancer. Men treated for prostate cancer with androgen deprivation therapy may also develop osteoporosis. Multiple myeloma, in addition to causing lytic bone disease, can be associated with generalized bone loss. Assessment of bone density and treatment or prophylaxis should be considered to reduce the risk of fracture. Treatment commonly includes routine supplements of vitamin D and calcium (while monitoring serum calcium levels) and bisphosphonates or denosumab (a receptor activator of nuclear factor κB ligand monoclonal antibody). Vigilance for complications with these agents, which can include osteonecrosis of the jaw and atypical subtrochanteric spiral fractures of the femur, is required for patients on these agents.

Disorders of Cardiac Function

Radiation therapy to the heart can lead to valvular disease, myocardial and pericardial disease, and coronary disease. These risks have been reduced owing to advances in dosing, treatment planning, and modern radiation techniques. Doxorubicin and other anthracyclines can cause irreversible cardiomyopathy; the risk for this increases with cumulative dosing. Trastuzumab can also induce non-dose-dependent cardiomyopathy; the risk increases when trastuzumab is combined with anthracyclines. Fluoropyrimidines (5-fluorouracil and capecitabine) have been associated with a risk of coronary spasm and ischemia during administration.

Newer generation tyrosine kinase inhibitors for treatment of chronic myeloid leukemia have been associated with cardiovascular morbidity; nilotinib and ponatinib are associated with coronary insufficiency, and dasatinib is associated with pulmonary hypertension. The anti-vascular endothelial growth factor antibody bevacizumab is associated with an increased risk of coronary and other vascular events, both arterial and venous.

Monitoring for and management of cardiac complications in cancer survivors is discussed in MKSAP 18 Cardiovascular Medicine.

Sexual Function and Fertility

Surgery, radiation, and chemotherapy all have the potential to affect sexual function and fertility of both men and women. Altered body image after breast surgery or other radical resection and the generalized fatigue associated with most radiation or chemotherapy may reduce libido. Anxiety and depression

further diminish interest in sex. Individual counseling and support groups may be helpful.

In women, premature menopause and infertility can result from both pelvic radiotherapy and chemotherapy, particularly with alkylating agents. Risk factors for infertility relate to the dose and duration of chemotherapy as well as patient age, with older women being at greater risk for premature menopause. Consultation with experts in fertility should be considered in younger women who desire future childbearing; egg and embryo harvests may be options. Fertility evaluations can often be done on an emergency basis so delay in the initiation of definitive cancer treatment is minimized. Men may be offered the option of semen cryopreservation.

Hormonal therapy for women with breast cancer, including tamoxifen, aromatase inhibitors, and ovarian suppression, may cause menopausal symptoms, decreased libido, and vaginal dryness. Men with prostate cancer commonly suffer from erectile dysfunction after surgery, radiation, and androgen suppression therapy.

Cognitive Decline

Short-term and long-term declines in cognitive function are now recognized as a complication after cancer therapy. It remains unclear whether cancer and its treatment unmasks preexisting cognitive impairment that was not yet manifest, whether the decline represents a sign of more rapid aging, or whether there is a more specific neurotoxic effect. Symptoms may include impairment of multitasking and executive function, memory, and verbal ability. Behavioral therapy may be beneficial. Patients with cancer who complain of a decline in cognitive function should have their experience acknowledged and validated, and behavioral therapy should be offered.

KEY POINTS

- Fertility preservation options before cancer treatment include egg and embryo harvests for women and semen cryopreservation for men.
- Patients with cancer who complain of a decline in cognitive function should have their experience acknowledged and validated, and behavioral therapy should be offered.

Survivorship Care Plan

Patients with cancer go through distinct phases of management, beginning with the initial therapy and any maintenance or adjuvant treatment needed to achieve and prolong remission. Once in remission, these patients go through a phase of surveillance for disease recurrence. Whereas the duration of the surveillance phase and the extent of active assessment through physician examination and diagnostic imaging differs based on the underlying cancer, patients eventually reach the "survivor" phase, wherein disease recurrence becomes unlikely.

Providing patients with a prescription for survivorship is an important responsibility of oncologists. Patients are given a formal document summarizing their diagnosis, stage, and treatment details, along with recommended follow-up by the oncologist as they return to their internist. Recommendations can include surveillance for cancer recurrence; lifestyle modifications, such as diet, exercise, and avoiding tobacco and alcohol to reduce the risk of a second malignancy; and a discussion of the late effects of cancer treatment that may occur and any strategies for preventing or reducing them.

Cancer survivors should, at a minimum, have age- and gender-appropriate cancer screening. Secondary malignancies may develop in cancer survivors owing to a preexisting genetic predisposition, a "field" effect from previous carcinogen exposure, or late effects of previous cancer treatments. Patients with *BRCA* gene mutations have an increased risk of breast and ovarian cancer. Patients with smoking-related head and neck cancer are prone to second head and neck cancers, as well as lung and esophageal cancers. Patients exposed to chemotherapy with alkylating agents have an increased risk of myelodysplastic syndromes and acute leukemia. Radiation to the neck can be associated with the development not just of hypothyroidism but also of thyroid cancer years later. Women receiving radiation to the mediastinum for Hodgkin lymphoma and other cancers have a marked increase of breast cancer, particularly if they were treated in adolescence and early adulthood, with the increased risk beginning within 8 years of treatment. Screening MRI, mammography, or a combination of both modalities is recommended for these patients beginning at age 25 years or 8 years after completion of radiation therapy, whichever occurs last.

KEY POINTS

- A "prescription for survivorship" provides the patient with recommendations regarding surveillance for cancer recurrence, lifestyle modifications to reduce the risk of a second malignancy, and strategies to prevent or reduce the late effects of cancer treatment.
- Various factors, including genetic predisposition, "field" effect, and the carcinogenic effects of cancer therapies, all increase the risk of secondary malignancies in patients in remission after therapy for their primary cancer.
- Mediastinal radiation is associated with a marked increase of breast cancer beginning within 8 years of treatment; screening MRI, mammography, or a combination of both modalities is recommended for women beginning at age 25 years or 8 years after completion of radiation therapy, whichever occurs last.

Bibliography

Hematopoietic Stem Cells and Their Disorders

Al Ustwani O, Gupta N, Bakhribah H, Griffiths E, Wang E, Wetzler M. Clinical updates in adult acute lymphoblastic leukemia. Crit Rev Oncol Hematol. 2016;99:189-99. [PMID: 26777876] doi:10.1016/j.critrevonc.2015.12.007

Diller L. Clinical practice. Adult primary care after childhood acute lymphoblastic leukemia. N Engl J Med. 2011;365:1417-24. [PMID: 21995389] doi:10.1056/NEJMcp1103645

Döhner H, Weisdorf DJ, Bloomfield CD. Acute myeloid leukemia. N Engl J Med. 2015;373:1136-52. [PMID: 26376137] doi:10.1056/NEJMra1406184

Fenaux P, Haase D, Sanz GF, Santini V, Buske C; ESMO Guidelines Working Group. Myelodysplastic syndromes: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2014;25 Suppl 3:iii57-69. [PMID: 25185242] doi:10.1093/annonc/mdu180

Greenberg PL, Stone RM, Bejar R, Bennett JM, Bloomfield CD, Borate U, et al; National comprehensive cancer network. Myelodysplastic syndromes, version 2.2015. J Natl Compr Canc Netw. 2015;13:261-72. [PMID: 25736003]

Killick SB, Bown N, Cavenagh J, Dokal I, Foukaneli T, Hill A, et al; British Society for Standards in Haematology. Guidelines for the diagnosis and management of adult aplastic anaemia. Br J Haematol. 2016;172:187-207. [PMID: 26568159] doi:10.1111/bjh.13853

Smith TJ, Bohlke K, Lyman GH, Carson KR, Crawford J, Cross SJ, et al; American Society of Clinical Oncology. recommendations for the use of WBC growth factors: American Society of Clinical Oncology Clinical Practice Guideline Update. J Clin Oncol. 2015;33:3199-212. [PMID: 26169616] doi:10.1200/JCO.2015.62.3488

Spivak JL. Myeloproliferative neoplasms. N Engl J Med. 2017;376:2168-2181. [PMID: 28564565] doi:10.1056/NEJMra1406186

Vannucchi AM, Barbui T, Cervantes F, Harrison C, Kiladjian JJ, Kröger N, et al; ESMO Guidelines Committee. Philadelphia chromosome-negative chronic myeloproliferative neoplasms: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2015;26 Suppl 5:v85-99. [PMID: 26242182] doi:10.1093/annonc/mdv203

Vannucchi AM, Kiladjian JJ, Griesshammer M, Masszi T, Durrant S, Passamonti F, et al. Ruxolitinib versus standard therapy for the treatment of polycythemia vera. N Engl J Med. 2015;372:426-35. [PMID: 25629741] doi:10.1056/NEJMoa1409002

Multiple Myeloma and Related Disorders

Chng WJ, Dispenzieri A, Chim CS, Fonseca R, Goldschmidt H, Lentzsch S, et al; International Myeloma Working Group. IMWG consensus on risk stratification in multiple myeloma. Leukemia. 2014;28:269-77. [PMID: 23974982] doi:10.1038/leu.2013.247

Gillmore JD, Wechalekar A, Bird J, Cavenagh J, Hawkins S, Kazmi M, et al; BCSH Committee. Guidelines on the diagnosis and investigation of AL amyloidosis. Br J Haematol. 2015;168:207-18. [PMID: 25312307] doi:10.1111/bjh.13156

Kumar S, Dispenzieri A, Lacy MQ, Hayman SR, Buadi FK, Colby C, et al. Revised prognostic staging system for light chain amyloidosis incorporating cardiac biomarkers and serum free light chain measurements. J Clin Oncol. 2012;30:989-95. [PMID: 22331953] doi:10.1200/JCO.2011.38.5724

Leblond V, Kastritis E, Advani R, Ansell SM, Buske C, Castillo JJ, et al. Treatment recommendations from the Eighth International Workshop on Waldenström's Macroglobulinemia. Blood. 2016;128:1321-8. [PMID: 27432877] doi:10.1182/blood-2016-04-711234

Lokhorst HM, Plesner T, Laubach JP, Nahi H, Gimsing P, Hansson M, et al. Targeting CD38 with daratumumab monotherapy in multiple myeloma. N Engl J Med. 2015;373:1207-19. [PMID: 26308596] doi:10.1056/NEJMoa1506348

Palumbo A, Rajkumar SV, San Miguel JF, Larocca A, Niesvizky R, Morgan G, et al. International Myeloma Working Group consensus statement for the management, treatment, and supportive care of patients with myeloma not eligible for standard autologous stem-cell transplantation. J Clin Oncol. 2014;32:587-600. [PMID: 24419113] doi:10.1200/JCO.2013.48.7934

Rajkumar SV, Dimopoulos MA, Palumbo A, Blade J, Merlini G, Mateos MV, et al. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. Lancet Oncol. 2014;15:e538-48. [PMID: 25439696] doi:10.1016/S1470-2045(14)70442-5

van de Donk NW, Palumbo A, Johnsen HE, Engelhardt M, Gay F, Gregersen H, et al; European Myeloma Network. The clinical relevance and management of monoclonal gammopathy of undetermined significance and related disorders: recommendations from the European Myeloma Network. Haematologica. 2014;99:984-96. [PMID: 24658815] doi:10.3324/haematol.2013.100552

Erythrocyte Disorders

Barcellini W. Immune hemolysis: diagnosis and treatment recommendations. Semin Hematol. 2015;52:304-12. [PMID: 26404442] doi:10.1053/j.seminhematol.2015.05.001

Brodsky RA. Complement in hemolytic anemia. Blood. 2015;126:2459-65. [PMID: 26582375] doi:10.1182/blood-2015-06-640995

Da Costa L, Galimand J, Fenneteau O, Mohandas N. Hereditary spherocytosis, elliptocytosis, and other red cell membrane disorders. Blood Rev. 2013;27:167-78. [PMID: 23664421] doi:10.1016/j.blre.2013.04.003

Finberg KE. Regulation of systemic iron homeostasis. Curr Opin Hematol. 2013;20:208-14. [PMID: 23426198] doi:10.1097/MOH.0b013e32835f5a47

Chapter 1: Diagnosis and evaluation of anemia in CKD. Kidney Int Suppl (2011). 2012;2:288-291. [PMID: 25018948]

Lopez A, Cacoub P, Macdougall IC, Peyrin-Biroulet L. Iron deficiency anaemia. Lancet. 2016;387:907-16. [PMID: 26314490] doi:10.1016/S0140-6736(15)60865-0

Luzzatto L, Nannelli C, Notaro R. Glucose-6-phosphate dehydrogenase deficiency. Hematol Oncol Clin North Am. 2016;30:373-93. [PMID: 27040960] doi:10.1016/j.hoc.2015.11.006

Moretti D, Goede JS, Zeder C, Jiskra M, Chatzinakou V, Tjalsma H, et al. Oral iron supplements increase hepcidin and decrease iron absorption from daily or twice-daily doses in iron-depleted young women. Blood. 2015;126:1981-9. [PMID: 26289639] doi:10.1182/blood-2015-05-642223

Piel FB, Steinberg MH, Rees DC. Sickle cell disease. N Engl J Med. 2017;376:1561-1573. [PMID: 28423290] doi:10.1056/NEJMra1510865

Rund D. Thalassemia 2016: Modern medicine battles an ancient disease. Am J Hematol. 2016;91:15-21. [PMID: 26537527] doi:10.1002/ajh.24231

Shipton MJ, Thachil J. Vitamin B12 deficiency - a 21st century perspective. Clin Med (Lond). 2015;15:145-50. [PMID: 25824066] doi:10.7861/clinmedicine.15-2-145

Vichinsky E. Non-transfusion-dependent thalassemia and thalassemia intermedia: epidemiology, complications, and management. Curr Med Res Opin. 2016;32:191-204. [PMID: 26479125] doi:10.1185/03007995.2015.1110128

Iron Overload Syndromes

Bacon BR, Adams PC, Kowdley KV, Powell LW, Tavill AS; American Association for the Study of Liver Diseases. Diagnosis and management of hemochromatosis: 2011 practice guideline by the American Association for the Study of Liver Diseases. Hepatology. 2011;54:328-43. [PMID: 21452290] doi:10.1002/hep.24330

Brittenham GM. Iron-chelating therapy for transfusional iron overload. N Engl J Med. 2011;364:146-56. [PMID: 21226580] doi:10.1056/NEJMct1004810

Platelet Disorders

Fakhouri F, Zuber J, Frémeaux-Bacchi V, Loirat C. Haemolytic uraemic syndrome. Lancet. 2017;390:681-696. [PMID: 28242109] doi:10.1016/S0140-6736(17)30062-4

George JN. Measuring ADAMTS13 activity in patients with suspected thrombotic thrombocytopenic purpura: when, how, and why? [Editorial]. Transfusion. 2015;55:11-3. [PMID: 25582234] doi:10.1111/trf.12885

Greinacher A. CLINICAL PRACTICE. Heparin-induced thrombocytopenia. N Engl J Med. 2015;373:252-61. [PMID: 26176382] doi:10.1056/NEJMcp1411910

McGowan KE, Makari J, Diamantouros A, Bucci C, Rempel P, Selby R, et al. Reducing the hospital burden of heparin-induced thrombocytopenia: impact of an avoid-heparin program. Blood. 2016;127:1954-9. [PMID: 26817956] doi:10.1182/blood-2015-07-660001

Neunert C, Noroozi N, Norman G, Buchanan GR, Goy J, Nazi I, et al. Severe bleeding events in adults and children with primary immune thrombocytopenia: a systematic review. J Thromb Haemost. 2015;13:457-64. [PMID: 25495497] doi:10.1111/jth.12813

Paniccia R, Priora R, Liotta AA, Abbate R. Platelet function tests: a comparative review. Vasc Health Risk Manag. 2015;11:133-48. [PMID: 25733843] doi:10.2147/VHRM.S44469

Tarantino MD, Fogarty PF, Shah P, Brainsky A. Dental procedures in 24 patients with chronic immune thrombocytopenia in prospective clinical studies of eltrombopag. Platelets. 2015;26:93-6. [PMID: 24433306] doi:10.3109/09537104.2013.870333

Warkentin TE, Pai M, Linkins LA. Direct oral anticoagulants for treatment of HIT: update of Hamilton experience and literature review. Blood. 2017;130:1104-1113. [PMID: 28646118] doi:10.1182/blood-2017-04-778993

Wei Y, Ji XB, Wang YW, Wang JX, Yang EQ, Wang ZC, et al. High-dose dexamethasone vs prednisone for treatment of adult immune thrombocytopenia: a prospective multicenter randomized trial. Blood. 2016;127:296-302; quiz 370. [PMID: 26480931] doi:10.1182/blood-2015-07-659656

Bleeding Disorders

Blackshear JL, Wysokinska EM, Safford RE, Thomas CS, Shapiro BP, Ung S, et al. Shear stress-associated acquired von Willebrand syndrome in patients with mitral regurgitation. J Thromb Haemost. 2014;12:1966-74. [PMID: 25251907] doi:10.1111/jth.12734

Donohoe K, Levine R. Acquired factor V inhibitor after exposure to topical human thrombin related to an otorhinolaryngological procedure. J Thromb Haemost. 2015;13:1787-9. [PMID: 26270511] doi:10.1111/jth.13114

Ferraris VA, Boral LI, Cohen AJ, Smyth SS, White GC 2nd. Consensus review of the treatment of cardiovascular disease in people with hemophilia A and B. Cardiol Rev. 2015;23:53-68. [PMID: 25436468] doi:10.1097/CRD.0000000000000045

Franchini M, Mannucci PM. Acquired haemophilia A: a 2013 update. Thromb Haemost. 2013;110:1114–20. [PMID: 24008306] doi:10.1160/TH13-05-0363

Marks PW. Hematologic manifestations of liver disease. Semin Hematol. 2013;50:216–21. [PMID: 23953338] doi:10.1053/j.seminhematol.2013.06.003

Ng C, Motto DG, Di Paola J. Diagnostic approach to von Willebrand disease. Blood. 2015;125:2029–37. [PMID: 25712990] doi:10.1182/blood-2014-08-528398

Roberts JC, Morateck PA, Christopherson PA, Yan K, Hoffmann RG, Gill JC, et al; Zimmerman Program Investigators. Rapid discrimination of the phenotypic variants of von Willebrand disease. Blood. 2016;127:2472–80. [PMID: 26917779] doi:10.1182/blood-2015-11-664680

Yates SG, Gavva C, Agrawal D, Sarode R. How do we transfuse blood components in cirrhotic patients undergoing gastrointestinal procedures? Transfusion. 2016;56:791–8. [PMID: 26876945] doi:10.1111/trf.13495

Transfusion Medicine

Carson JL, Grossman BJ, Kleinman S, Tinmouth AT, Marques MB, Fung MK, et al; Clinical Transfusion Medicine Committee of the AABB. Red blood cell transfusion: a clinical practice guideline from the AABB*. Ann Intern Med. 2012;157:49–58. [PMID: 22751760]

Delaney M, Wendel S, Bercovitz RS, Cid J, Cohn C, Dunbar NM, et al; Biomedical Excellence for Safer Transfusion (BEST) Collaborative. Transfusion reactions: prevention, diagnosis, and treatment. Lancet. 2016;388:2825–2836. [PMID: 27083327] doi:10.1016/S0140-6736(15)01313-6

Goldstein JN, Refaai MA, Milling TJ Jr, Lewis B, Goldberg-Alberts R, Hug BA, et al. Four-factor prothrombin complex concentrate versus plasma for rapid vitamin K antagonist reversal in patients needing urgent surgical or invasive interventions: a phase 3b, open-label, non-inferiority, randomised trial. Lancet. 2015;385:2077–87. [PMID: 25728933] doi:10.1016/S0140-6736(14)61685-8

Goodnough LT, Levy JH, Murphy MF. Concepts of blood transfusion in adults. Lancet. 2013;381:1845–54. [PMID: 23706801] doi:10.1016/S0140-6736(13)60650-9

Murphy GJ, Pike K, Rogers CA, Wordsworth S, Stokes EA, Angelini GD, et al; TITRe2 Investigators. Liberal or restrictive transfusion after cardiac surgery. N Engl J Med. 2015;372:997–1008. [PMID: 25760354] doi:10.1056/NEJMoa1403612

Schwartz J, Winters JL, Padmanabhan A, Balogun RA, Delaney M, Linenberger ML, et al. Guidelines on the use of therapeutic apheresis in clinical practice-evidence-based approach from the Writing Committee of the American Society for Apheresis: the sixth special issue. J Clin Apher. 2013;28:145–284. [PMID: 23868759] doi:10.1002/jca.21276

Villanueva C, Colomo A, Bosch A, Concepción M, Hernandez-Gea V, Aracil C, et al. Transfusion strategies for acute upper gastrointestinal bleeding. N Engl J Med. 2013;368:11–21. [PMID: 23281973] doi:10.1056/NEJMoa1211801

Thrombotic Disorders

Kearon C, Akl EA, Ornelas J, Blaivas A, Jimenez D, Bounameaux H, et al. Antithrombotic therapy for VTE disease: CHEST Guideline and Expert Panel Report. Chest. 2016;149:315–52. [PMID: 26867832] doi:10.1016/j.chest.2015.11.026

Pollack CV Jr, Reilly PA, Eikelboom J, Glund S, Verhamme P, Bernstein RA, et al. Idarucizumab for dabigatran reversal. N Engl J Med. 2015;373:511–20. [PMID: 26095746] doi:10.1056/NEJMoa1502000

Raja AS, Greenberg JO, Qaseem A, Denberg TD, Fitterman N, Schuur JD; Clinical Guidelines Committee of the American College of Physicians. Evaluation of patients with suspected acute pulmonary embolism: best practice advice from the Clinical Guidelines Committee of the American College of Physicians. Ann Intern Med. 2015;163:701–11. [PMID: 26414967]

van Dongen CJ, van den Belt AG, Prins MH, Lensing AW. Fixed dose subcutaneous low molecular weight heparins versus adjusted dose unfractionated heparin for venous thromboembolism. Cochrane Database Syst Rev. 2004:CD001100. [PMID: 15495007]

Hematologic Issues in Pregnancy

Kamel H, Navi BB, Sriram N, Hovsepian DA, Devereux RB, Elkind MS. Risk of a thrombotic event after the 6-week postpartum period. N Engl J Med. 2014;370:1307–15. [PMID: 24524551] doi:10.1056/NEJMoa1311485

Klings ES, Machado RF, Barst RJ, Morris CR, Mubarak KK, Gordeuk VR, et al; American Thoracic Society Ad Hoc Committee on Pulmonary Hypertension of Sickle Cell Disease. An official American Thoracic Society clinical practice guideline: diagnosis, risk stratification, and management of pulmonary hypertension of sickle cell disease. Am J Respir Crit Care Med. 2014;189:727–40. [PMID: 24628312] doi:10.1164/rccm.201401-0065ST

Malinowski AK, Shehata N, D'Souza R, Kuo KH, Ward R, Shah PS, et al. Prophylactic transfusion for pregnant women with sickle cell disease: a systematic review and meta-analysis. Blood. 2015;126:2424–35; quiz 2437. [PMID: 26302758] doi:10.1182/blood-2015-06-649319

Scully M, Thomas M, Underwood M, Watson H, Langley K, Camilleri RS, et al; collaborators of the UK TTP Registry. Thrombotic thrombocytopenic purpura and pregnancy: presentation, management, and subsequent pregnancy outcomes. Blood. 2014;124:211–9. [PMID: 24859360] doi:10.1182/blood-2014-02-553131

Yawn BP, Buchanan GR, Afenyi-Annan AN, Ballas SK, Hassell KL, James AH, et al. Management of sickle cell disease: summary of the 2014 evidence-based report by expert panel members. JAMA. 2014;312:1033–48. [PMID: 25203083] doi:10.1001/jama.2014.10517

Issues in Oncology

Kesselheim AS, Avorn J, Sarpatwari A. The high cost of prescription drugs in the united states: origins and prospects for reform. JAMA. 2016;316:858–71. [PMID: 27552619] doi:10.1001/jama.2016.11237

Khalil DN, Smith EL, Brentjens RJ, Wolchok JD. The future of cancer treatment: immunomodulation, CARs and combination immunotherapy. Nat Rev Clin Oncol. 2016;13:273–90. [PMID: 26977780] doi:10.1038/nrclinonc.2016.25

Saltz LB. Perspectives on cost and value in cancer care [Editorial]. JAMA Oncol. 2016;2:19–21. [PMID: 26501848] doi:10.1001/jamaoncol.2015.4191

Breast Cancer

Finch AP, Lubinski J, Møller P, Singer CF, Karlan B, Senter L, et al. Impact of oophorectomy on cancer incidence and mortality in women with a BRCA1 or BRCA2 mutation. J Clin Oncol. 2014;32:1547–53. [PMID: 24567435] doi:10.1200/JCO.2013.53.2820

Finn RS, Crown JP, Lang I, Boer K, Bondarenko IM, Kulyk SO, et al. The cyclin-dependent kinase 4/6 inhibitor palbociclib in combination with letrozole versus letrozole alone as first-line treatment of oestrogen receptor-positive, HER2-negative, advanced breast cancer (PALOMA-1/TRIO-18): a randomised phase 2 study. Lancet Oncol. 2015;16:25–35. [PMID: 25524798] doi:10.1016/S1470-2045(14)71159-3

Francis PA, Regan MM, Fleming GF, Láng I, Ciruelos E, Bellet M, et al; SOFT Investigators. Adjuvant ovarian suppression in premenopausal breast cancer. N Engl J Med. 2015;372:436–46. [PMID: 25495490] doi:10.1056/NEJMoa1412379

Goss PE, Ingle JN, Pritchard KI, Robert NJ, Muss H, Gralow J, et al. Extending aromatase-inhibitor adjuvant therapy to 10 years. N Engl J Med. 2016;375:209–19. [PMID: 27264120] doi:10.1056/NEJMoa1604700

Hartmann LC, Degnim AC, Santen RJ, Dupont WD, Ghosh K. Atypical hyperplasia of the breast-risk assessment and management options. N Engl J Med. 2015;372:78–89. [PMID: 25551530] doi:10.1056/NEJMsr1407164

Hartmann LC, Lindor NM. The role of risk-reducing surgery in hereditary breast and ovarian cancer. N Engl J Med. 2016;374:454–68. [PMID: 26840135] doi:10.1056/NEJMra1503523

Hughes KS, Schnaper LA, Bellon JR, Cirrincione CT, Berry DA, McCormick B, et al. Lumpectomy plus tamoxifen with or without irradiation in women age 70 years or older with early breast cancer: long-term follow-up of CALGB 9343. J Clin Oncol. 2013;31:2382–7. [PMID: 23690420] doi:10.1200/JCO.2012.45.2615

McLornan DP, List A, Mufti GJ. Applying synthetic lethality for the selective targeting of cancer. N Engl J Med. 2014;371:1725–35. [PMID: 25354106] doi:10.1056/NEJMra1407390

Narod SA, Iqbal J, Giannakeas V, Sopik V, Sun P. Breast cancer mortality after a diagnosis of ductal carcinoma in situ. JAMA Oncol. 2015;1:888–96. [PMID: 26291673] doi:10.1001/jamaoncol.2015.2510

Rugo HS, Rumble RB, Macrae E, Barton DL, Connolly HK, Dickler MN, et al. Endocrine therapy for hormone receptor-positive metastatic breast cancer: American Society of Clinical Oncology Guideline. J Clin Oncol. 2016;34:3069–103. [PMID: 27217461] doi:10.1200/JCO.2016.67.1487

Solin LJ, Gray R, Hughes LL, et al. Surgical excision without radiation for ductal carcinoma in situ of the breast: 12-year results from the ECOG-ACRIN E5194 study. J Clin Oncol. 2015 Nov 20;33(33):3938–44. [PMID: 26371148]

Sparano JA, Gray RJ, Makower DF, Pritchard KI, Albain KS, Hayes DF, et al. Prospective validation of a 21-gene expression assay in breast cancer. N Engl J Med. 2015;373:2005–14. [PMID: 26412349] doi:10.1056/NEJMoa1510764

Swain SM, Baselga J, Kim SB, Ro J, Semiglazov V, Campone M, et al; CLEOPATRA Study Group. Pertuzumab, trastuzumab, and docetaxel in HER2-positive metastatic breast cancer. N Engl J Med. 2015;372:724–34. [PMID: 25693012] doi:10.1056/NEJMoa1413513

Ovarian Cancer

Beral V, Gaitskell K, Hermon C, Moser K, Reeves G, Peto R; Collaborative Group On Epidemiological Studies Of Ovarian Cancer. Menopausal hormone use

and ovarian cancer risk: individual participant meta-analysis of 52 epidemiological studies. Lancet. 2015;385:1835-42. [PMID: 25684585] doi:10.1016/S0140-6736(14)61687-1

Cress RD, Chen YS, Morris CR, Petersen M, Leiserowitz GS. Characteristics of long-term survivors of epithelial ovarian cancer. Obstet Gynecol. 2015;126:491-7. [PMID: 26244529] doi:10.1097/AOG.0000000000000981

Finch AP, Lubinski J, Møller P, Singer CF, Karlan B, Senter L, et al. Impact of oophorectomy on cancer incidence and mortality in women with a BRCA1 or BRCA2 mutation. J Clin Oncol. 2014;32:1547-53. [PMID: 24567435] doi:10.1200/JCO.2013.53.2820

Hartmann LC, Lindor NM. The role of risk reducing surgery in hereditary breast and ovarian cancer. N Engl J Med. 2016;374:454-68. [PMID: 26840135] doi:10.1056/NEJMra1503523

Jacobs IJ, Menon U, Ryan A, Gentry-Maharaj A, Burnell M, Kalsi JK, et al. Ovarian cancer screening and mortality in the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS): a randomised controlled trial. Lancet. 2016;387:945-956. [PMID: 26707054] doi:10.1016/S0140-6736(15)01224-6

Jelovac D, Armstrong DK. Recent progress in the diagnosis and treatment of ovarian cancer. CA Cancer J Clin. 2011;61:183-203. [PMID: 21521830] doi:10.3322/caac.20113

Kaufman B, Shapira-Frommer R, Schmutzler RK, Audeh MW, Friedlander M, Balmaña J, et al. Olaparib monotherapy in patients with advanced cancer and a germline BRCA1/2 mutation. J Clin Oncol. 2015;33:244-50. [PMID: 25366685] doi:10.1200/JCO.2014.56.2728

Menon U, Ryan A, Kalsi J, Gentry-Maharaj A, Dawnay A, Habib M, et al. Risk algorithm using serial biomarker measurements doubles the number of screen-detected cancers compared with a single-threshold rule in the United Kingdom Collaborative Trial of Ovarian Cancer Screening. J Clin Oncol. 2015;33:2062-71. [PMID: 25964255] doi:10.1200/JCO.2014.59.4945

Pujade-Lauraine E, Hilpert F, Weber B, Reuss A, Poveda A, Kristensen G, et al. Bevacizumab combined with chemotherapy for platinum-resistant recurrent ovarian cancer: The AURELIA open-label randomized phase III trial. J Clin Oncol. 2014;32:1302-8. [PMID: 24637997] doi:10.1200/JCO.2013.51.4489

Tewari D, Java JJ, Salani R, Armstrong DK, Markman M, Herzog T, et al. Long-term survival advantage and prognostic factors associated with intraperitoneal chemotherapy treatment in advanced ovarian cancer: a gynecologic oncology group study. J Clin Oncol. 2015;33:1460-6. [PMID: 25800756] doi:10.1200/JCO.2014.55.9898

Wright AA, Bohlke K, Armstrong DK, Bookman MA, Cliby WA, Coleman RL, et al. Neoadjuvant Chemotherapy for Newly Diagnosed, Advanced Ovarian Cancer: Society of Gynecologic Oncology and American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol. 2016;34:3460-73. [PMID: 27502591] doi:10.1200/JCO.2016.68.6907

Cervical Cancer

Monk BJ, Tewari KS, Koh WJ. Multimodality therapy for locally advanced cervical carcinoma: state of the art and future directions. J Clin Oncol. 2007;25:2952-65. [PMID: 17617527]

Tewari KS, Sill MW, Long HJ 3rd, Penson RT, Huang H, Ramondetta LM, et al. Improved survival with bevacizumab in advanced cervical cancer. N Engl J Med. 2014;370:734-43. [PMID: 24552320] doi:10.1056/NEJMoa1309748

Tsu V, Jerónimo J. Saving the world's women from cervical cancer. N Engl J Med. 2016;374:2509-11. [PMID: 27355529] doi:10.1056/NEJMp1604113

Gastroenterological Malignancies

Ahn DH, Williams TM, Goldstein DA, El-Rayes B, Bekaii-Saab T. Adjuvant therapy for pancreas cancer in an era of value based cancer care. Cancer Treat Rev. 2016;42:10-7. [PMID: 26620819] doi:10.1016/j.ctrv.2015.11.004

Allegra CJ, Rumble RB, Hamilton SR, Mangu PB, Roach N, Hantel A, et al. Extended ras gene mutation testing in metastatic colorectal carcinoma to predict response to anti-epidermal growth factor receptor monoclonal antibody therapy: American Society of Clinical Oncology Provisional Clinical Opinion Update 2015. J Clin Oncol. 2016;34:179-85. [PMID: 26438111] doi:10.1200/JCO.2015.63.9674

André T, de Gramont A, Vernerey D, Chibaudel B, Bonnetain F, Tijeras-Raballand A, et al. Adjuvant fluorouracil, leucovorin, and oxaliplatin in stage II to III colon cancer: updated 10-year survival and outcomes according to BRAF mutation and mismatch repair status of the MOSAIC study. J Clin Oncol. 2015;33:4176-87. [PMID: 26527776] doi:10.1200/JCO.2015.63.4238

Benjamin RS, Casali PG. Adjuvant imatinib for GI stromal tumors: when and for how long? J Clin Oncol. 2016;34:215-8. [PMID: 26644523] doi:10.1200/JCO.2015.64.0102

Brenner H, Kloor M, Pox CP. Colorectal cancer. Lancet. 2014;383:1490-1502. [PMID: 24225001] doi:10.1016/S0140-6736(13)61649-9

Julie DR, Goodman KA. Advances in the management of anal cancer. Curr Oncol Rep. 2016;18:20. [PMID: 26905274] doi:10.1007/s11912-016-0503-3

Kahi CJ, Boland CR, Dominitz JA, Giardiello FM, Johnson DA, Kaltenbach T, et al; United States Multi-Society Task Force on Colorectal Cancer. Colonoscopy Surveillance After Colorectal Cancer Resection: Recommendations of the US Multi-Society Task Force on Colorectal Cancer. Gastroenterology. 2016;150:758-768.e11. [PMID: 26892199] doi:10.1053/j.gastro.2016.01.001

Patel SA, Ryan DP, Hong TS. Combined modality therapy for rectal cancer. Cancer J. 2016;22:211-7. [PMID: 27341601] doi:10.1097/PPO.0000000000000193

Primrose JN, Perera R, Gray A, Rose P, Fuller A, Corkhill A, et al; FACS Trial Investigators. Effect of 3 to 5 years of scheduled CEA and CT follow-up to detect recurrence of colorectal cancer: the FACS randomized clinical trial. JAMA. 2014;311:263-70. [PMID: 24430319] doi:10.1001/jama.2013.285718

Raj N, Reidy-Lagunes D. Systemic therapies for advanced pancreatic neuroendocrine tumors. Hematol Oncol Clin North Am. 2016;30:119-33. [PMID: 26614372] doi:10.1016/j.hoc.2015.09.005

Rustgi AK, El-Serag HB. Esophageal carcinoma. N Engl J Med. 2014;371:2499-509. [PMID: 25539106] doi:10.1056/NEJMra1314530

Smith JJ, D'Angelica MI. Surgical management of hepatic metastases of colorectal cancer. Hematol Oncol Clin North Am. 2015;29:61-84. [PMID: 25475573] doi:10.1016/j.hoc.2014.09.003

Lung Cancer

Brunelli A, Kim AW, Berger KI, Addrizzo-Harris DJ. Physiologic evaluation of the patient with lung cancer being considered for resectional surgery: diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2013;143:e166S-e190S. [PMID: 23649437] doi:10.1378/chest.12-2395Burdett S, Pignon JP, Tierney J, et al; Non-Small Cell Lung Cancer Collaborative Group. Adjuvant chemotherapy for resected early-stage non-small cell lung cancer. Cochrane Database Syst Rev. 2015 Mar 2;(3):CD011430. [PMID: 25730344]

Curran WJ Jr, Paulus R, Langer CJ, Komaki R, Lee JS, Hauser S, et al. Sequential vs. concurrent chemoradiation for stage III non-small cell lung cancer: randomized phase III trial RTOG 9410. J Natl Cancer Inst. 2011;103:1452-60. [PMID: 21903745] doi:10.1093/jnci/djr325

Ettinger DS, Wood DE, Akerley W, Bazhenova LA, Borghaei H, Camidge DR, et al. NCCN guidelines insights: non-small cell lung cancer, version 4.2016. J Natl Compr Canc Netw. 2016;14:255-64. [PMID: 26957612]

Khullar OV, Liu Y, Gillespie T, et al. Survival after sublobar resection versus lobectomy for clinical stage IA lung cancer: an analysis from the National Cancer Data Base. J Thorac Oncol. 2015 Nov;10(11):1625-33. [PMID: 26352534]

Pignon JP, Tribodet H, Scagliotti GV, Douillard JY, Shepherd FA, Stephens RJ, et al; LACE Collaborative Group. Lung adjuvant cisplatin evaluation: a pooled analysis by the LACE Collaborative Group. J Clin Oncol. 2008;26:3552-9. [PMID: 18506026] doi:10.1200/JCO.2007.13.9030

Scagliotti GV, Parikh P, von Pawel J, Biesma B, Vansteenkiste J, Manegold C, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer. J Clin Oncol. 2008;26:3543-51. [PMID: 18506025] doi:10.1200/JCO.2007.15.0375

Soria JC, Mauguen A, Reck M, Sandler AB, Saijo N, Johnson DH, et al; meta-analysis of bevacizumab in advanced NSCLC collaborative group. Systematic review and meta-analysis of randomised, phase II/III trials adding bevacizumab to platinum-based chemotherapy as first-line treatment in patients with advanced non-small-cell lung cancer. Ann Oncol. 2013;24:20-30. [PMID: 23180113] doi:10.1093/annonc/mds590

Wang EH, Corso CD, Rutter CE, Park HS, Chen AB, Kim AW, et al. Postoperative radiation therapy is associated with improved overall survival in incompletely resected stage II and III non-small-cell lung cancer. J Clin Oncol. 2015;33:2727-34. [PMID: 26101240] doi:10.1200/JCO.2015.61.1517

Head and Neck Cancer

Adelstein D, Gillison ML, Pfister DG, Spencer S, Adkins D, Brizel DM, et al. NCCN guidelines insights: head and neck cancers, version 2.2017. J Natl Compr Canc Netw. 2017;15:761-770. [PMID: 28596256] doi:10.6004/jnccn.2017.0101

Bonner JA, Harari PM, Giralt J, Cohen RB, Jones CU, Sur RK, et al. Radiotherapy plus cetuximab for locoregionally advanced head and neck cancer: 5-year survival data from a phase 3 randomised trial, and relation between cetuximab-induced rash and survival. Lancet Oncol. 2010;11:21-8. [PMID: 19897418] doi:10.1016/S1470-2045(09)70311-0

Chen QY, Wen YF, Guo L, Liu H, Huang PY, Mo HY, et al. Concurrent chemoradiotherapy vs radiotherapy alone in stage II nasopharyngeal carcinoma:

phase III randomized trial. J Natl Cancer Inst. 2011;103:1761-70. [PMID: 22056739] doi:10.1093/jnci/djr432

Cohen EE, Karrison TG, Kocherginsky M, Mueller J, Egan R, Huang CH, et al. Phase III randomized trial of induction chemotherapy in patients with N2 or N3 locally advanced head and neck cancer. J Clin Oncol. 2014;32:2735-43. [PMID: 25049329] doi:10.1200/JCO.2013.54.6309

Goodwin WJ Jr. Salvage surgery for patients with recurrent squamous cell carcinoma of the upper aerodigestive tract: when do the ends justify the means? Laryngoscope. 2000;110:1-18. [PMID: 10714711]

Hitt R, Grau JJ, López-Pousa A, Berrocal A, García-Girón C, Irigoyen A, et al; Spanish Head and Neck Cancer Cooperative Group (TTCC). A randomized phase III trial comparing induction chemotherapy followed by chemoradiotherapy versus chemoradiotherapy alone as treatment of unresectable head and neck cancer. Ann Oncol. 2014;25:216-25. [PMID: 24256848] doi:10.1093/annonc/mdt461

Ho AS, Kraus DH, Ganly I, Lee NY, Shah JP, Morris LG. Decision making in the management of recurrent head and neck cancer. Head Neck. 2014;36:144-51. [PMID: 23471843] doi:10.1002/hed.23227

Schwartz DL, Ford E, Rajendran J, Yueh B, Coltrera MD, Virgin J, et al. FDG-PET/CT imaging for preradiotherapy staging of head-and-neck squamous cell carcinoma. Int J Radiat Oncol Biol Phys. 2005;61:129-36. [PMID: 15629603]

Tandon S, Shahab R, Benton JI, Ghosh SK, Sheard J, Jones TM. Fine-needle aspiration cytology in a regional head and neck cancer center: comparison with a systematic review and meta-analysis. Head Neck. 2008;30:1246-52. [PMID: 18528906] doi:10.1002/hed.20849

Vermorken JB, Mesia R, Rivera F, Remenar E, Kawecki A, Rottey S, et al. Platinum-based chemotherapy plus cetuximab in head and neck cancer. N Engl J Med. 2008;359:1116-27. [PMID: 18784101] doi:10.1056/NEJMoa0802656

Genitourinary Cancer

Bolla M, Van Tienhoven G, Warde P, Dubois JB, Mirimanoff RO, Storme G, et al. External irradiation with or without long-term androgen suppression for prostate cancer with high metastatic risk: 10-year results of an EORTC randomised study. Lancet Oncol. 2010;11:1066-73. [PMID: 20933466] doi:10.1016/S1470-2045(10)70223-0

Chen RC, Rumble RB, Loblaw DA, Finelli A, Ehdaie B, Cooperberg MR, et al. Active surveillance for the management of localized prostate cancer (Cancer Care Ontario Guideline): American Society of Clinical Oncology clinical practice guideline endorsement. J Clin Oncol. 2016;34:2182-90. [PMID: 26884580] doi:10.1200/JCO.2015.65.7759

Hall MC, Chang SS, Dalbagni G, Pruthi RS, Seigne JD, Skinner EC, et al. Guideline for the management of nonmuscle invasive bladder cancer (stages Ta, T1, and Tis): 2007 update. J Urol. 2007;178:2314-30. [PMID: 17993339]

James ND, Sydes MR, Clarke NW, Mason MD, Dearnaley DP, Spears MR, et al; STAMPEDE investigators. Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multiarm, multistage, platform randomised controlled trial. Lancet. 2016;387:1163-77. [PMID: 26719232] doi:10.1016/S0140-6736(15)01037-5

Motzer RJ, Escudier B, McDermott DF, George S, Hammers HJ, Srinivas S, et al; CheckMate 025 Investigators. Nivolumab versus everolimus in advanced renal-cell carcinoma. N Engl J Med. 2015;373:1803-13. [PMID: 26406148] doi:10.1056/NEJMoa1510665

NCCN Clinical Guidelines in Oncology. Prostate Cancer. Version 2.2017. NCCN.org. https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf. Accessed February 17, 2018.

Nielsen M, Qaseem A; High Value Care Task Force of the American College of Physicians. Hematuria as a marker of occult urinary tract cancer: advice for high-value care from the American College of Physicians. Ann Intern Med. 2016;164:488-97. [PMID: 26810935]

Ravaud A, Motzer RJ, Pandha HS, George DJ, Pantuck AJ, Patel A, et al; S-TRAC Investigators. Adjuvant Sunitinib in High-Risk Renal-Cell Carcinoma after Nephrectomy. N Engl J Med. 2016;375:2246-2254. [PMID: 27718781]

Sweeney CJ, Chen YH, Carducci M, Liu G, Jarrard DF, Eisenberger M, et al. Chemohormonal therapy in metastatic hormone-sensitive prostate cancer. N Engl J Med. 2015;373:737-46. [PMID: 26244877] doi:10.1056/NEJMoa1503747

Travis LB, Fosså SD, Schonfeld SJ, McMaster ML, Lynch CF, Storm H, et al. Second cancers among 40,576 testicular cancer patients: focus on long-term survivors. J Natl Cancer Inst. 2005;97:1354-65. [PMID: 16174857]

Lymphoid Malignancies

Ansell SM. Hodgkin lymphoma: diagnosis and treatment. Mayo Clin Proc. 2015;90:1574-83. [PMID: 26541251] doi:10.1016/j.mayocp.2015.07.005

Burger JA, Tedeschi A, Barr PM, Robak T, Owen C, Ghia P, et al; RESONATE-2 Investigators. Ibrutinib as initial therapy for patients with chronic lymphocytic leukemia. N Engl J Med. 2015;373:2425-37. [PMID: 26639149] doi:10.1056/NEJMoa1509388

Casulo C, Friedberg J. Treating Burkitt lymphoma in adults. Curr Hematol Malig Rep. 2015;10:266-71. [PMID: 26013028] doi:10.1007/s11899-015-0263-4

Cheah CY, Seymour JF, Wang ML. Mantle cell lymphoma. J Clin Oncol. 2016;34:1256-69. [PMID: 26755518] doi:10.1200/JCO.2015.63.5904

Getta BM, Park JH, Tallman MS. Hairy cell leukemia: past, present and future. Best Pract Res Clin Haematol. 2015;28:269-72. [PMID: 26614906] doi:10.1016/j.beha.2015.10.015

Kahl BS, Yang DT. Follicular lymphoma: evolving therapeutic strategies. Blood. 2016;127:2055-63. [PMID: 26989204] doi:10.1182/blood-2015-11-624288

Lunning MA, Horwitz S. Treatment of peripheral T-cell lymphoma: are we data driven or driving the data? Curr Treat Options Oncol. 2013;14:212-23. [PMID: 23568456] doi:10.1007/s11864-013-0232-x

Matsuki E, Younes A. Checkpoint inhibitors and other immune therapies for Hodgkin and non-Hodgkin lymphoma. Curr Treat Options Oncol. 2016;17:31. [PMID: 27193488] doi:10.1007/s11864-016-0401-9

Roberts AW, Davids MS, Pagel JM, Kahl BS, Puvvada SD, Gerecitano JF, et al. Targeting BCL2 with venetoclax in relapsed chronic lymphocytic leukemia. N Engl J Med. 2016;374:311-22. [PMID: 26639348] doi:10.1056/NEJMoa1513257

Routledge DJ, Bloor AJ. Recent advances in therapy of chronic lymphocytic leukaemia. Br J Haematol. 2016;174:351-67. [PMID: 27291144] doi:10.1111/bjh.14184

Thanarajasingam G, Bennani-Baiti N, Thompson CA. PET-CT in staging, response evaluation, and surveillance of lymphoma. Curr Treat Options Oncol. 2016;17:24. [PMID: 27032646] doi:10.1007/s11864-016-0399-z

Zucca E, Bertoni F. The spectrum of MALT lymphoma at different sites: biological and therapeutic relevance. Blood. 2016;127:2082-92. [PMID: 26989205] doi:10.1182/blood-2015-12-624304

Cancer of Unknown Primary Site

Fizazi K, Greco FA, Pavlidis N, Daugaard G, Oien K, Pentheroudakis G; ESMO Guidelines Committee. Cancers of unknown primary site: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2015;26 Suppl 5:v133-8. [PMID: 26314775] doi:10.1093/annonc/mdv305

Samadder NJ, Smith KR, Hanson H, Pimentel R, Wong J, Boucher K, et al. Familial risk in patients with carcinoma of unknown primary. JAMA Oncol. 2016;2:340-6. [PMID: 26863281] doi:10.1001/jamaoncol.2015.4265

Varadhachary GR, Raber MN. Cancer of unknown primary site. N Engl J Med. 2014;371:757-65. [PMID: 25140961] doi:10.1056/NEJMra1303917

Melanoma

Larkin J, Chiarion-Sileni V, Gonzalez R, Grob JJ, Cowey CL, Lao CD, et al. Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. N Engl J Med. 2015;373:23-34. [PMID: 26027431] doi:10.1056/NEJMoa1504030

Lee DY, Lau BJ, Huynh KT, Flaherty DC, Lee JH, Stern SL, et al. Impact of completion lymph node dissection on patients with positive sentinel lymph node biopsy in melanoma. J Am Coll Surg. 2016;223:9-18. [PMID: 27236435] doi:10.1016/j.jamcollsurg.2016.01.045

Long GV, Weber JS, Infante JR, Kim KB, Daud A, Gonzalez R, et al. Overall survival and durable responses in patients with BRAF V600-mutant metastatic melanoma receiving dabrafenib combined with trametinib. J Clin Oncol. 2016;34:871-8. [PMID: 26811525] doi:10.1200/JCO.2015.62.9345

Morton DL, Thompson JF, Cochran AJ, Mozzillo N, Nieweg OE, Roses DF, et al; MSLT Group. Final trial report of sentinel-node biopsy versus nodal observation in melanoma. N Engl J Med. 2014;370:599-609. [PMID: 24521106] doi:10.1056/NEJMoa1310460

Weber J, Mandala M, Del Vecchio M, Gogas HJ, Arance AM, Cowey CL, et al; CheckMate 238 Collaborators. Adjuvant nivolumab versus ipilimumab in resected stage III or IV melanoma. N Engl J Med. 2017. [PMID: 28891423] doi:10.1056/NEJMoa1709030

Oncologic Urgencies and Emergencies

Howard SC, Jones DP, Pui CH. The tumor lysis syndrome. N Engl J Med. 2011;364:1844-54. [PMID: 21561350] doi:10.1056/NEJMra0904569

Lin X, DeAngelis LM. Treatment of brain metastases. J Clin Oncol. 2015;33:3475-84. [PMID: 26282648] doi:10.1200/JCO.2015.60.9503

Patchell RA, Tibbs PA, Regine WF, Payne R, Saris S, Kryscio RJ, et al. Direct decompressive surgical resection in the treatment of spinal cord compression caused by metastatic cancer: a randomised trial. Lancet. 2005;366:643-8. [PMID: 16112300]

Wilson LD, Detterbeck FC, Yahalom J. Clinical practice. Superior vena cava syndrome with malignant causes. N Engl J Med. 2007;356:1862–9. [PMID: 17476012]

Effects of Cancer Therapy and Survivorship

Ganz PA, Earle CC, Goodwin PJ. Journal of Clinical Oncology update on progress in cancer survivorship care and research. J Clin Oncol. 2012;30:3655–6. [PMID: 23008327] doi:10.1200/JCO.2012.45.3886

Glaspy J. Current status of use of erythropoietic agents in cancer patients. Semin Thromb Hemost. 2014;40:306–12. [PMID: 24676903] doi:10.1055/s-0034-1370768

Hesketh PJ, Bohlke K, Lyman GH, Basch E, Chesney M, Clark-Snow RA, et al; American Society of Clinical Oncology. Antiemetics: American Society of Clinical Oncology focused guideline update. J Clin Oncol. 2016;34:381–6. [PMID: 26527784] doi:10.1200/JCO.2015.64.3635

Mulder RL, Kremer LC, Hudson MM, Bhatia S, Landier W, Levitt G, et al; International Late Effects of Childhood Cancer Guideline Harmonization Group. Recommendations for breast cancer surveillance for female survivors of childhood, adolescent, and young adult cancer given chest radiation: a report from the International Late Effects of Childhood Cancer Guideline Harmonization Group. Lancet Oncol. 2013;14:e621–9. [PMID: 24275135] doi:10.1016/S1470-2045(13)70303-6

Navari RM, Qin R, Ruddy KJ, Liu H, Powell SF, Bajaj M, et al. Olanzapine for the prevention of chemotherapy-induced nausea and vomiting. N Engl J Med. 2016;375:134–42. [PMID: 27410922] doi:10.1056/NEJMoa1515725

Nolan CP, DeAngelis LM. Neurologic complications of chemotherapy and radiation therapy. Continuum (Minneap Minn). 2015;21:429–51. [PMID: 25837905] doi:10.1212/01.CON.0000464179.81957.51

Rowland JH, Bellizzi KM. Cancer survivorship issues: life after treatment and implications for an aging population. J Clin Oncol. 2014;32:2662–8. [PMID: 25071099] doi:10.1200/JCO.2014.55.8361

Runowicz CD, Leach CR, Henry NL, Henry KS, Mackey HT, Cowens-Alvarado RL, et al. American Cancer Society/American Society of Clinical Oncology Breast Cancer Survivorship Care Guideline. J Clin Oncol. 2016;34:611–35. [PMID: 26644543] doi:10.1200/JCO.2015.64.3809

Smith TJ, Bohlke K, Lyman GH, Carson KR, Crawford J, Cross SJ, et al; American Society of Clinical Oncology. Recommendations for the use of WBC growth factors: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol. 2015;33:3199–212. [PMID: 26169616] doi:10.1200/JCO.2015.62.3488

White L, Ybarra M. Neutropenic fever. Emerg Med Clin North Am. 2014;32:549–61. [PMID: 25060249] doi:10.1016/j.emc.2014.04.002

Hematology and Oncology Self-Assessment Test

This self assessment test contains one-best-answer multiple-choice questions. Please read these directions carefully before answering the questions. Answers, critiques, and bibliographies immediately follow these multiple-choice questions. The American College of Physicians (ACP) is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

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Directions

*Each of the numbered items is followed by lettered answers. Select the **ONE** lettered answer that is **BEST** in each case.*

Hematology Questions

Item 1

A 34-year-old woman is evaluated for a rash on her lower extremities that appeared 3 days ago. She also reports easy bruising for the past week and bleeding when she brushes her teeth. Her medical history is otherwise unremarkable, and she takes no medications.

On physical examination, vital signs are normal. Petechiae are noted on the lower extremities, and ecchymoses are present on her right thigh and on her abdomen. No hepatomegaly, splenomegaly, or lymphadenopathy is noted.

Laboratory studies:

Hemoglobin	12.8 g/dL (128 g/L)
Leukocyte count	6600/μL (6.6 × 10^9/L) with a normal differential
Mean corpuscular volume	82 fL
Platelet count	28,000/μL (28 × 10^9/L)
Hepatitis C antibody	Negative

Large and giant platelets are seen on the peripheral blood smear, but no schistocytes or platelet clumping is noted.

Which of the following laboratory tests should be performed?

(A) Antiplatelet antibodies
(B) HIV testing
(C) Lupus anticoagulant
(D) Vitamin B_{12} level

Item 2

A 68-year-old man is evaluated for epistaxis, gum bleeding, and easy bruising of 3 months' duration. Medical history is notable for anxiety, depression, and hyperlipidemia. Medications are atorvastatin, citalopram, a multivitamin, and ginkgo biloba.

On physical examination, vital signs are normal; BMI is 21. Scattered petechiae and several small ecchymoses are visible on the anterior thigh. The examination is otherwise normal.

Laboratory studies:

Activated partial thromboplastin time (aPTT)	Normal
Hemoglobin	14.8 g/dL (148 g/L)
Leukocyte count	4200/μL (4.2 × 10^9/L)
Platelet count	245,000/μL (245 × 10^9/L)
Prothrombin time (PT)	Normal
Thrombin time	Normal

Which of the following is the most appropriate diagnostic test to perform next?

(A) Fibrinogen level
(B) Mixing studies for PT and aPTT
(C) Peripheral blood smear review
(D) Platelet Function Analyzer-100
(E) Serum protein electrophoresis

Item 3

A 59-year-old woman arrives at the emergency department with left lower leg swelling of 2 weeks' duration and shortness of breath of 1 week's duration that has worsened during the past 6 hours. She reports no chest pain or hemoptysis. She has no history of recent travel, surgery, malignancy, or immobilization. She takes no medications.

On physical examination, temperature is 37.7 °C (99.9 °F), blood pressure is 140/85 mm Hg, pulse rate is 102/min, and respiration rate is 19/min. Oxygen saturation is 95% breathing ambient air. Edema of the left lower extremity is noted.

Laboratory studies show an elevated D-dimer level.

CT angiography shows a right subsegmental pulmonary embolism.

The patient's Pulmonary Embolism Severity Index score is 59.

It is determined the patient can be safely treated as an outpatient.

Which of the following is the most appropriate treatment?

(A) Apixaban
(B) Dabigatran
(C) Edoxaban
(D) Low-molecular-weight heparin

Item 4

A 52-year-old woman with a recent diagnosis of adenocarcinoma is seen for follow-up to discuss management plans. Medical history is notable for an 80-pack-year history of smoking. She takes no medications.

On physical examination, temperature is 37.2 °C (99.0 °F), blood pressure is 110/75 mm Hg, pulse rate is 99/min, and respiration rate is 20/min. Oxygen saturation is 95% breathing ambient air. Temporal wasting is noted. Pulmonary examination reveals decreased breath sounds in the right upper lobe. The remainder of the examination is unremarkable.

Laboratory studies:

Hemoglobin	10.6 g/dL (106 g/L)
Leukocyte count	9700/μL (9.7 × 10^9/L)
Mean corpuscular volume	87 fL
Iron studies	
Ferritin	430 ng/mL (430 μg/L)
Iron	30 μg/dL (5 μmol/L)
Total iron-binding capacity	200 μg/dL (36 μmol/L)
Transferrin saturation	15%

A peripheral blood smear is normal. A chest radiograph shows a right upper lung mass and bilateral hilar and mediastinal lymphadenopathy. She will begin chemotherapy for the non–small cell lung cancer.

Which of the following is the most appropriate treatment for this patient's anemia?

(A) Erythropoietin
(B) Oral ferrous sulfate
(C) Parenteral iron sucrose
(D) No treatment

Item 5

A 74-year-old man is evaluated in follow-up for myelodysplastic syndrome diagnosed 3 months ago. Cytogenetic studies and fluorescence in situ hybridization showed deletion of 5q. It was determined he has low-risk MDS by the Revised International Prognostic Scoring System. He requires erythrocyte transfusions every 2 weeks to prevent symptomatic anemia. He takes no medications.

On physical examination, pulse rate is 120/min, and respiration rate is 24/min; other vital signs are normal. Skin pallor is noted. Cardiac examination reveals tachycardia.

Laboratory studies show a hemoglobin level of 6.5 g/dL (65 g/L), leukocyte count of 2500/µL (2.5×10^9/L), and platelet count of 220,000/µL (220×10^9/L).

Which of the following is the most appropriate treatment?

(A) Allogeneic hematopoietic stem cell transplantation
(B) Antithymocyte globulin and cyclosporine
(C) Imatinib
(D) Lenalidomide

Item 6

A 45-year-old man is evaluated for shortness of breath with exertion and lower extremity edema of 6 months' duration. He reports no chest pain, fever, or cough. He takes no medications.

On physical examination, vital signs are normal. Jugular venous distention is noted. Cardiopulmonary examination reveals crackles at the base of the lungs. He also has 1+ lower extremity edema.

Laboratory studies are remarkable for eosinophilia, with an absolute eosinophil count of 2500/µL (2.5×10^9/L). A review of the medical record shows an eosinophil count of 2900/µL (2.9×10^9/L) 1 year ago.

An electrocardiogram shows sinus rhythm with low-voltage QRS and nonspecific ST changes. An echocardiogram shows findings compatible with a restrictive cardiomyopathy.

Which of the following is the most appropriate initial management?

(A) Evaluation for helminth infection
(B) Fat pad biopsy
(C) Prednisone
(D) Repeat laboratory evaluation in 3 months

Item 7

A 30-year-old man is evaluated for worsening exertional dyspnea. One week ago, he developed fever, sore throat, and cough. Those symptoms have resolved, but he has become more easily fatigued and short of breath. He had cholecystectomy 2 years ago because of symptomatic cholelithiasis; at that time, he was noted to be anemic and was diagnosed with hereditary spherocytosis. His only medication is a folate supplement.

On physical examination, he is pale but in no distress. Temperature is 37.0 °C (98.7 °F), blood pressure is 100/60 mm Hg, pulse rate is 116/min, and respiratory rate is 16/min. Oxygen saturation is 98% breathing ambient air. The spleen is palpable 3 cm below the left costal margin. Other examination findings are normal.

Laboratory studies:

Hemoglobin	7 g/dL (70 g/L)
Leukocyte count	5600/µL (5.6×10^9/L), with a normal differential
Mean corpuscular hemoglobin concentration	40 g/dL (400 g/L)
Platelet count	213,000/µL (213×10^9/L)
Reticulocyte count	1% of erythrocytes
Bilirubin	
Total	6.2 mg/dL (106 µmol/L)
Indirect	5.6 mg/dL (95.8 µmol/L)

Spherocytes are seen on the peripheral blood smear. A direct antiglobulin test is negative.

Which of the following is the most appropriate management?

(A) Erythropoiesis-stimulating agent
(B) Prednisone
(C) Splenectomy
(D) Observation

Item 8

H

A 64-year-old man is evaluated in the hospital for progressive shortness of breath and hypoxia 18 hours after undergoing surgery for an obstructing colonic adenocarcinoma with known liver metastases. Medical history is also notable for hypertension treated with hydrochlorothiazide.

On physical examination, vital signs are normal. Oxygen saturation is 92% breathing ambient air. The abdominal dressing is clean and dry. The examination is otherwise unremarkable.

CT angiography shows a left lower lobe pulmonary embolism.

Which of the following is the most appropriate treatment?

(A) Dabigatran
(B) Enoxaparin
(C) Fondaparinux
(D) Rivaroxaban
(E) Warfarin

Item 9

A 39-year-old woman is evaluated for new-onset nonproductive cough and dyspnea on exertion. She is pregnant at 32 weeks' gestation. Medical history is unremarkable. Her only medication is a prenatal vitamin.

On physical examination, temperature is 37.0 °C (98.6 °F), blood pressure is 105/62 mm Hg, pulse rate is 100/min, and respiration rate is 22/min. Oxygen saturation is 86% breathing ambient air. Cardiopulmonary examination is normal. She has a gravid uterus and 1+ edema of the lower extremities without calf tenderness.

Laboratory studies:

Hemoglobin	12.1 g/dL (121 g/L)
Leukocyte count	4800/µL (4.8×10^9/L)
Platelet count	189,000/µL (189×10^9/L)
Urinalysis	Normal

Doppler ultrasonography of both legs is negative for deep venous thrombosis.

Which of the following is the most appropriate diagnostic test to perform next?

(A) CT angiography
(B) D-dimer assay
(C) Magnetic resonance pulmonary angiography
(D) Pulmonary function testing
(E) Ventilation-perfusion lung scan

Item 10

A 52-year-old woman undergoes perioperative evaluation. She has osteoarthritis of the right hip since sustaining injuries in a motor vehicle accident 15 years ago and is scheduled for elective hip arthroplasty in the next few months. Medical history is otherwise notable for type 2 diabetes mellitus. She is up to date on routine health care. Her last menstrual period was 5 weeks ago. Medications are ibuprofen and metformin.

On physical examination, vital signs are normal. She has painful and limited range of motion in the right hip.

Laboratory studies:

Hemoglobin	10 g/dL (100 g/L)
Mean corpuscular volume	81 fL
Platelet count	223,000/µL (223×10^9/L)
Creatinine	1 mg/dL (88.4 µmol/L)
Hemoglobin A_{1c}	7.5%

Which of the following is the most appropriate test to perform next?

(A) Hemoglobin electrophoresis
(B) Iron studies
(C) Vitamin B_{12} level
(D) No further evaluation

H

Item 11

A 55-year-old man is evaluated in the emergency department for abrupt loss of consciousness after a fall. Medical history is notable for atrial fibrillation. He has otherwise been well without additional medical problems. Medications are warfarin and metoprolol.

On physical examination, temperature is 37 °C (98.6 °F), blood pressure is 135/85 mm Hg, pulse rate is 83/min and irregular, and respiration rate is 16/min. The patient is obtunded without localizing neurologic findings. Cardiac examination reveals an irregularly irregular rhythm. The remainder of the examination is unremarkable.

Head CT scan shows a large subdural hematoma.

Laboratory studies show a hemoglobin level of 13 g/dL (130 g/L), platelet count of 183,000/µL (183×10^9/L), and INR of 3.0.

Intravenous vitamin K is administered, and plans are made for emergent neurosurgery.

Which of the following is the most appropriate treatment?

(A) Cryoprecipitate
(B) Four-factor prothrombin complex concentrate
(C) Fresh frozen plasma
(D) Idarucizumab

Item 12

A 50-year-old woman undergoes follow-up evaluation for a right iliofemoral deep venous thrombosis diagnosed 6 weeks ago by Doppler ultrasonography. She reports no new symptoms and notes her right leg edema is improving. She has no history of travel, surgery, or immobility. She indicates feeling well before her diagnosis, with no shortness of breath. She had a normal screening colonoscopy 3 months ago and a normal mammogram and Pap smear 6 months ago. Medical history is otherwise unremarkable. Her only medication is rivaroxaban.

On physical examination, vital signs are normal. She has mild edema of the right lower extremity. The examination is otherwise unremarkable.

Which of the following is the most appropriate diagnostic test to perform next?

(A) Abdominal and pelvic CT
(B) Chest CT
(C) Repeat lower extremity Doppler ultrasonography
(D) No additional testing

Item 13

H

A 35-year-old man is evaluated in the emergency department for fever and epistaxis. He has been experiencing malaise for several weeks and fever, chills, and anorexia for the past 3 days. Today he developed epistaxis. He takes no medications.

On physical examination, temperature is 38.8 °C (100.4 °F), blood pressure is 105/70 mm Hg, pulse rate is 110/min, and respiration rate is 24/min. He is diaphoretic. Dried blood is noted in the nares, and gingival bleeding is present. No lymphadenopathy or hepatosplenomegaly is noted. He has petechiae bilaterally on the lower extremities.

Laboratory studies:

Activated partial thromboplastin time	60 s
Hemoglobin	9.8 g/dL (98 g/L)
Leukocyte count	3600/µL (3.6×10^9/L) with 20% neutrophils, 3% bands, 35% lymphocytes, 23% monocytes, and 18% "atypical" cells
Platelet count	17,000/µL (17×10^9/L)
Prothrombin time	24 s
Fibrinogen	93 mg/dL (0.93 g/L)

The peripheral blood smear shows immature leukocytes with prominent granules in the cytoplasm.

Which of the following is the most likely diagnosis?

(A) Acute promyelocytic leukemia
(B) Aplastic anemia
(C) Chronic granulocytic leukemia
(D) Immune thrombocytopenic purpura

Item 14

A 67-year-old woman undergoes follow-up evaluation for an elevated globulin fraction of total serum protein level. She has no symptoms. Medical history is notable for hypertension treated with hydrochlorothiazide and atorvastatin.

On physical examination, vital signs are normal. No lymphadenopathy or hepatosplenomegaly is noted.

Laboratory studies:

Hemoglobin	14.5 g/dL (145 g/L)
Leukocyte count	7000/μL (7×10^9/L)
Platelet count	300,000/μL (300×10^9/L)
Calcium	9.1 mg/dL (2.3 mmol/L)
Creatinine	0.8 mg/dL (70.7 μmol/L)

Serum protein electrophoresis and immunofixation show an IgG monoclonal spike of 0.7 g/dL. Serum free light chain assay and 24-hour urine protein electrophoresis are normal.

Skeletal survey shows no lytic lesions.

Which of the following is the most appropriate management?

(A) Kidney biopsy
(B) MRI of the cervical, thoracic, and lumbar spine
(C) Repeat laboratory studies in 6 months
(D) Serum β_2 microglobulin I measurement

Item 15

A 65-year-old woman is evaluated for recurrent sinusitis. She has felt unwell for the past year, experiencing six episodes of sinusitis requiring antibiotic treatment and two courses of oral glucocorticoids. The most recent culture of the sinus drainage grew *Haemophilus influenzae*. Laboratory studies obtained 6 months ago showed mild anemia but were otherwise unremarkable. CT imaging revealed changes consistent with chronic sinusitis.

On physical examination, temperature is 38.0 °C (100.4 °F), and all other vital signs are normal. Nasal examination reveals left sinus ostia purulent drainage. She has no nasal polyps. Palpation of the maxillary sinuses elicits tenderness.

Laboratory studies:

Hemoglobin	9 g/dL (90 g/L)
Leukocyte count	4500/μL (4.5×10^9/L) with lymphocyte count of 400/μL (normal 1000-3000/μL)
Absolute neutrophil count	1500/μL (1.5×10^9/L)
Platelet count	100,000/μL (100×10^9/L)
Calcium	9.1 mg/dL (2.3 mmol/L)
Creatinine	0.8 mg/dL (70.7 μmol/L)
Immunoglobulins	
IgG	300 mg/dL (3 g/L)
IgA	Undetectable
IgM	Undetectable

Serum protein electrophoresis shows a monoclonal spike. Skeletal survey shows multiple lytic bone lesions. A bone marrow biopsy specimen shows 25% plasma cells. Plans are made to begin therapy for her plasma cell malignancy.

Which of the following is the most appropriate immediate management to prevent recurrent infection?

(A) Acyclovir
(B) Granulocyte colony-stimulating factor
(C) Fluconazole
(D) Intravenous immune globulin

Item 16

A 53-year-old man is evaluated for tea-colored urine. He reports no other symptoms. He was hospitalized 2 weeks ago with melena. Upper gastrointestinal endoscopy and colonoscopy at the time did not show a bleeding source, but he stabilized after the transfusion of one unit of blood. He was discharged 10 days ago and has returned to work. Medical history is otherwise significant for trauma sustained in a motor vehicle accident 5 years ago, requiring multiple surgeries. He takes no medications.

On physical examination, temperature is 37.8 °C (100.1 °F), and other vital signs are normal, with no postural blood pressure or pulse changes. Scleral icterus is noted. The stool guaiac test result is negative. The remainder of the examination is unremarkable.

Laboratory studies:

	Current	10 Days Ago
Hemoglobin	6.9 g/dL (69 g/L)	8 g/dL (80 g/L)
Bilirubin		
Total	5 mg/dL (34.2 μmol/L)	1.1 mg/dL (18.8 μmol/L)
Direct	0.7 mg/dL (12 μmol/L)	–
Urinalysis	4+ blood, 2-3 erythrocytes/hpf, 1 leukocyte/hpf	–

Which of the following is the most appropriate next step in the management of this patient?

(A) Direct antiglobulin (Coombs) test
(B) Flow cytometry
(C) Repeat upper and lower endoscopy
(D) Transfusion of one unit of blood

Item 17

H

A 31-year-old woman arrives at the hospital in labor at 39 weeks' gestation of an otherwise uncomplicated first pregnancy. Her labor fails to progress after 20 hours; a cesarean section delivers a healthy female infant. A few minutes after the procedure, the patient begins to have heavy vaginal bleeding. Placental abruption is diagnosed and appropriately managed with fluid resuscitation and transfusion of 3 units of blood.

On physical examination, temperature is 36.7 °C (98.0 °F), blood pressure is 98/63 mm Hg, pulse rate is 102/min, and respiration rate is 22/min. Moderate bleeding persists.

H CONT.

Laboratory studies:

Activated partial thromboplastin time	38 s
D-dimer	Elevated
Hemoglobin	7.1 g/dL (71 g/L)
Platelet count	83,000/µL (83×10^9/L)
Prothrombin time	17.9 s
Fibrinogen	75 mg/dL (0.75 g/L)

Infusion of which of the following is the most appropriate management?

(A) Albumin
(B) Cryo-poor plasma
(C) Cryoprecipitate
(D) Platelets

Item 18

H

A 22-year-old woman is evaluated in the emergency department for a 2-day history of progressive fatigue and shortness of breath. Medical history is significant for sickle cell disease diagnosed at age 6 years. Her sickle cell disease is under good control with rare crisis. Medications are hydroxyurea and folic acid.

On physical examination, temperature and blood pressure are normal, pulse rate is 125/min, and respiration rate is 25/min. Oxygen saturation is 93% breathing ambient air. Lungs are clear without wheezing. Other examination findings are unremarkable.

Laboratory studies:

Hemoglobin	4 g/dL (40 g/L)
Leukocyte count	13,000/µL (13×10^9/L)
Platelet count	500,000/µL (500×10^9/L)
Reticulocyte count	0.1% of erythrocytes

Chest radiograph is normal.

Which of the following is the most likely diagnosis?

(A) Aplastic anemia
(B) Hyperhemolysis syndrome
(C) Myelodysplastic syndrome
(D) Parvovirus B19 infection

Item 19

A 76-year-old woman arrives for follow-up consultation regarding a recent diagnosis of essential thrombocythemia. She was hospitalized 5 days ago for a cerebrovascular accident. Evaluation at the time showed a platelet count of 660,000/µL (660×10^9/L). Results of iron studies, *JAK2 V617F* mutation testing, and polymerase chain reaction for *BCR-ABL* were normal. No secondary cause of thrombocythemia was found. Medical history is also notable for type 2 diabetes mellitus and dyslipidemia. Medications are low-dose aspirin, metformin, and atorvastatin.

On physical examination, vital signs are normal. She displays slight left hemiparesis. The spleen tip is palpable.

A bone marrow biopsy specimen showed hypercellularity with increased numbers of enlarged megakaryocytes.

Which of the following is the most appropriate management?

(A) Add clopidogrel
(B) Add hydroxyurea
(C) Change aspirin to clopidogrel
(D) Perform plateletpheresis

Item 20

A 28-year-old woman undergoes follow-up consultation regarding a pre-employment physical examination. She reports feeling well, with no recent illness. Medical history is notable for gastroesophageal reflux disease. Her only medication is omeprazole. She is black.

On physical examination, vital signs and other examination findings are normal.

Laboratory studies:

Hemoglobin	13.2 g/dL (132 g/L)
Leukocyte count	1867/µL (1.87×10^9/L) with 75% neutrophils, 20% lymphocytes, and 5% monocytes
Absolute neutrophil count	1400/µL (1.4×10^9/L)
Platelet count	258,000/µL (258×10^9/L)

A peripheral blood smear shows decreased neutrophils, normal lymphocytes, normochromic erythrocytes, and normal platelets.

Which of the following is the most likely diagnosis?

(A) Autoimmune neutropenia
(B) Benign ethnic neutropenia
(C) Cyclical neutropenia
(D) Drug-induced neutropenia

Item 21

H

A 52-year-old man is evaluated in the emergency department for decreased exercise tolerance and yellowing of the eyes for the past 3 days. He was diagnosed with leprosy 6 days ago and began antibacterial therapy 4 days ago. His complete blood count at that time was normal. He is a Haitian immigrant. Medications are dapsone, rifampicin, and clofazimine.

On physical examination, temperature is 36.7 °C (98.0 °F), blood pressure is 125/75 mm Hg, pulse rate is 100/min, and respiration rate is 18/min. He has icteric sclerae. Cardiac examination reveals a grade 2/6 systolic flow murmur. Multiple raised erythematous papules with decreased sensation are noted on the back and hands. No organomegaly is observed.

Laboratory studies:

Haptoglobin	Undetectable
Hemoglobin	5.6 g/dL (56 g/L)
Leukocyte count	5600/µL (5.6×10^9/L)
Platelet count	223,000/µL (223×10^9/L)
Reticulocyte count	12% of erythrocytes

H CONT.

Examination of the peripheral blood smear shows bite cells. The direct antiglobulin (Coombs) test is negative.

Which of the following is the most appropriate immediate management?

(A) Administer prednisone
(B) Administer rituximab
(C) Discontinue dapsone
(D) Measure ADAMTS13 activity
(E) Measure glucose-6-phosphate dehydrogenase level

Item 22

An 80-year-old woman is evaluated for fatigue and exertional dyspnea developing over several months. Medical history is significant for longstanding hypertension, but she has not been adherent with her medications.

On physical examination, vital signs are normal except for blood pressure of 180/110 mm Hg. She is frail, with pallor of mucous membranes and nail beds. The remainder of the examination is normal.

Laboratory studies:

Hemoglobin	9 g/dL (90 g/L)
Leukocyte count	8700/µL (8.7 × 10^9/L), with a normal differential
Mean corpuscular volume	85 fL
Platelet count	380,000 (380 × 10^9/L)
Reticulocyte count	1% of erythrocytes
Creatinine	1.8 mg/dL (159 µmol/L)
Folate	8 ng/mL (18.1 nmol/L)
Iron studies	
Ferritin	120 ng/mL (120 µg/L)
Iron	70 µg/dL (13 µmol/L)
Total iron-binding capacity	250 µg/dL (44.8 µmol/L)
Vitamin B_{12}	540 pg/mL (399 pmol/L)

Peripheral blood smear shows normal erythrocyte morphology.

On kidney ultrasonography, kidneys are small bilaterally, with echographic features suggesting chronic kidney disease.

Which of the following is the most likely cause of this patient's anemia?

(A) Erythropoietin deficiency
(B) Inflammation
(C) Iron deficiency
(D) Myelodysplastic syndrome

H

Item 23

A 61-year-old man is evaluated for worsening symptoms of edema and dizziness with standing over the past 6 months. His only medication is as-needed acetaminophen.

On physical examination, temperature is 37.0 °C (98.6 °F), blood pressure is 105/60 mm Hg sitting and 80/50 mm Hg standing, pulse rate is 105/min, and respiration rate is 18/min. Indentations are noted on the sides of the tongue, which appears enlarged. Jugular venous distention is noted. Cardiopulmonary examination reveals decreased breath sounds at the lung bases and an S_3 gallop. Dependent edema is present.

On laboratory evaluation, the serum creatinine level is 1.5 mg/dL (132.6 µmol/L); 24-hour urine collection shows 3.5 g of albumin. Serum protein electrophoresis shows an IgG λ spike of 1.2 g/dL (0.012 g/L).

Echocardiography shows increased thickening of the left ventricular wall and significant diastolic dysfunction. Left ventricular ejection fraction is 51%.

Which of the following is the most appropriate diagnostic test to perform next?

(A) Abdominal fat pad biopsy
(B) Cardiac catheterization
(C) Kidney biopsy
(D) Tilt table test

Item 24

A 28-year-old woman is evaluated for decreased exercise tolerance and ice cravings for the past several weeks. Medical history is notable for Crohn colitis diagnosed 6 years ago. Her symptoms flared 3 months ago with increased abdominal pain and diarrhea, and she began therapy with azathioprine and infliximab. Her only other medication is ferrous sulfate tablets, 325 mg once daily, which she has been taking for 6 weeks after being diagnosed with iron deficiency anemia; her hemoglobin level at that time was 8.2 g/dL (82 g/L).

On physical examination, vital signs are normal. She is thin, with pale conjunctivae and nail beds. Cardiac examination reveals a grade 2/6 systolic flow murmur. The remainder of the examination is unremarkable.

Laboratory studies show a hemoglobin level of 7.5 g/dL (75 g/L) and a serum ferritin level of 1 ng/mL (1 µg/L).

Which of the following is the most appropriate treatment?

(A) Intravenous iron preparation
(B) Oral iron in a liquid preparation
(C) Oral iron tablets three times daily
(D) Sustained-release iron preparation

Item 25

A 74-year-old man undergoes follow-up evaluation for anemia found on preoperative assessment. He reports a 3-month history of night sweats but no headaches, vision changes, or shortness of breath. He is scheduled to have hip replacement surgery. Medical history is significant for hypertension. His only medication is hydrochlorothiazide.

On physical examination, vital signs are normal. Funduscopic examination is normal. No lymphadenopathy is present in the cervical, axillary, or inguinal regions. Hepatosplenomegaly is noted on abdominal examination.

Laboratory studies:

Hemoglobin	8.4 g/dL (84 g/L)
Leukocyte count	7000/µL (7×10^9/L) with normal differential
Mean corpuscular volume	102 fL
Platelet count	300,000/µL (300×10^9/L)
Reticulocyte count	1.9% of erythrocytes
Calcium	9.4 mg/dL (2.4 mmol/L)
Creatinine	1.1 mg/dL (97.2 µmol/L)

Serum protein electrophoresis with immunofixation shows an IgM spike of 330 mg/dL (3.3 g/L).

CT scan of the chest and abdomen shows hepatomegaly and splenomegaly. Prominent lymph nodes are seen in the para-aortic and celiac regions, the largest of which is 2.1 cm.

Which of the following is the most appropriate diagnostic test to perform next?

(A) Bone marrow biopsy
(B) CT imaging-guided needle biopsy of a para-aortic lymph node
(C) Excisional biopsy of a para-aortic lymph node
(D) Serum viscosity testing

Item 26

A 53-year-old man is evaluated for fatigue and arthralgia for the past 2 years. He indicates multiple joints in the hands and lower extremities are involved, but the pain is not exacerbated by joint use and is partially relieved with ibuprofen. He typically consumes two beers per day. His only medication is ibuprofen.

On physical examination, vital signs are normal. The right second and third metacarpophalangeal (MCP) joints are swollen. The examination is otherwise unremarkable.

Hand radiographs show hook-like osteophytes in the MCP joints.

Which of the following is the most appropriate test to perform next?

(A) *HFE* genotyping
(B) Liver biopsy
(C) Rheumatoid factor and anti–cyclic citrullinated peptide antibodies
(D) Transferrin saturation and serum ferritin level

H

Item 27

A 45-year-old man is evaluated in the hospital for worsening pain and progressive swelling of the left lower extremity that began abruptly approximately 12 hours ago. Medical history is otherwise noncontributory, and he takes no other medications.

On physical examination, pulse rate is 112/min; other vital signs are normal. He has erythema and marked edema of the entire left lower extremity. The left foot appears cyanotic, with decreased sensation, absent arterial pulses, and delayed capillary refill. The physical examination is otherwise unremarkable.

Doppler ultrasonography of the left lower extremity shows extensive ileofemoral deep venous thrombosis.

Which of the following is the most appropriate management?

(A) Alteplase
(B) Argatroban
(C) Rivaroxaban
(D) Unfractionated heparin
(E) Unfractionated heparin plus inferior vena cava filter insertion

Item 28

H

A 68-year-old man is evaluated in the emergency department for fatigue and exertional dyspnea. He has a 5-year history of chronic lymphocytic leukemia, which has not required therapy. He takes no medications.

On physical examination, temperature is 37 °C (98.6 °F), blood pressure is 123/82 mm Hg, pulse rate is 108/min, and respiration rate is 18/min. Oxygen saturation is 95% breathing ambient air. Cervical, axillary, and inguinal lymphadenopathy and splenomegaly are present.

Laboratory studies:

Hemoglobin	5 g/dL (50 g/L)
Leukocyte count	35,000/µL (35×10^9/L) with 85% lymphocytes, 15% neutrophils
Platelet count	180,000/µL (180×10^9/L)
Reticulocyte count	10% of erythrocytes

A direct antiglobulin test result is positive for IgG and C3. The patient is group A-positive and crossmatch incompatible with 5 units of group A-positive blood.

Glucocorticoid therapy is started.

Which of the following is the most appropriate management?

(A) Avoid transfusion until a compatible unit can be found
(B) Begin plasma exchange therapy
(C) Transfuse crossmatch-incompatible blood
(D) Transfuse O-negative uncrossmatched blood

Item 29

A 73-year-old man undergoes follow-up evaluation after autologous hematopoietic stem cell transplantation (HSCT) 3 weeks ago for multiple myeloma. He had induction chemotherapy 1 year ago. He is doing well, without fever, chills, cough, or localizing symptoms of infection. Medications are acyclovir and omeprazole.

On physical examination, vital signs are normal; BMI is 20. He weighs 2.5 kg (6 lb) less than he did 2 months ago before HSCT. Alopecia is noted.

In the next 30 days, this patient is at increased risk for which of the following treatment-related complications?

(A) Acute graft-versus-host disease
(B) Infection
(C) Lymphoma
(D) Myelodysplastic syndrome

Item 30

A 60-year-old man is evaluated for an asymptomatic elevation of serum protein. Medical history is unremarkable, and he takes no medications.

On physical examination, vital signs are normal. Neurologic examination reveals no deficits.

Laboratory studies:

Hemoglobin	14 g/dL (140 g/L)
Leukocyte count	7000/µL (7×10^9/L)
Platelet count	300,000/µL (300×10^9/L)
Calcium	9.4 mg/dL (2.4 mmol/L)
Creatinine	1.1 mg/dL (97.2 µmol/L)

Serum protein electrophoresis and immunofixation show an IgA spike of 3.5 g/dL. Skeletal survey findings are negative.

Which of the following is the most appropriate next test?

(A) Bone scan
(B) CT of the chest, abdomen, and pelvis
(C) Whole body MRI
(D) No further testing

H

Item 31

A 70-year-old man is evaluated in the emergency department for headache, confusion, and weakness. Medical history is significant for ischemic cardiomyopathy with heart failure and mural thrombus. Medications are lisinopril, carvedilol, spironolactone, furosemide, and warfarin.

On physical examination, the patient is disoriented. Temperature and respiration rate are normal, blood pressure is 160/90 mm Hg, and pulse rate is 88/min. The examination is otherwise unremarkable.

Laboratory studies show an INR of 7.5.

CT scan of the head shows left intraparenchymal hemorrhage.

In addition to vitamin K administration, which of the following is the most appropriate treatment?

(A) Fresh frozen plasma
(B) Idarucizumab
(C) Prothrombin complex concentrate
(D) Recombinant activated factor VII

Item 32

A 76-year-old woman is evaluated for worsening fatigue. She reports no additional symptoms. Medical history is significant for myelodysplastic syndrome diagnosed 3 years ago, which has required the transfusion of 1 to 2 units of blood every 5 to 6 weeks to maintain a hemoglobin level of approximately 8 g/dL (80 g/L); she has exertional dyspnea when the hemoglobin level drops below 7 g/dL (70 g/L).

On physical examination, vital signs are normal. The abdomen is soft. Conjunctival pallor is noted. The examination is otherwise noncontributory.

Laboratory studies show a hemoglobin level of 7.5 g/dL (75 g/L) and a serum ferritin level of 1638 ng/mL (1638 µg/L).

Which of the following is the most appropriate management?

(A) Begin deferasirox
(B) Begin succimer
(C) Perform therapeutic phlebotomy
(D) Withhold transfusion until hemoglobin level is 6 g/dL (60 g/L)

Item 33

A 63-year-old man is evaluated for increasing fatigue and exertional dyspnea over the past 5 months. Medical history is notable for diabetes mellitus, hypertension, and chronic kidney disease. Medications are insulin glargine, metformin, enalapril, aspirin, and atorvastatin.

On physical examination, vital signs are normal. Pallor is noted. Examination findings are otherwise normal.

Laboratory studies show a hemoglobin level of 9.5 g/dL (90 g/L) (11 g/dL [110 g/L] 1 year ago), reticulocyte count of 1% of erythrocytes, and serum creatinine level of 2.0 mg/dL (176.8 µmol/L) (1.6 mg/dL [141.4 µmol/L] 1 year ago). Serum haptoglobin, iron, ferritin, and folate levels; total iron-binding capacity; vitamin B_{12} level; and liver chemistry studies are normal.

The stool guaiac test result is negative for occult blood.

Which of the following is the most appropriate next step in management?

(A) Darbepoetin administration for a target hemoglobin level of 11 g/dL (110 g/L)
(B) Darbepoetin administration for a target hemoglobin level of 14 g/dL (140 g/L)
(C) Oral iron supplementation and repeat hemoglobin level in 1 month
(D) Parenteral iron supplementation and repeat hemoglobin level in 1 month

Item 34

H

A 67-year-old woman arrives at the emergency department with hematuria of 3 days' duration. She has no other sites of bleeding. Medical history is significant for recently diagnosed nonvalvular paroxysmal atrial fibrillation and hypertension. Medications are hydrochlorothiazide and dabigatran.

On physical examination, vital signs are normal and other examination findings are unremarkable.

A urine sample is grossly bloody.

Laboratory studies:

Activated partial thromboplastin time	58 s
Hemoglobin	12.8 g/dL (128 g/L)
Prothrombin time	12 s
Creatinine	1.1 mg/dL (97.2 µmol/L)
Urinalysis	pH 5.0; 4+ blood; no protein. On microscopic examination, erythrocytes were too numerous to count. No casts or dysmorphic erythrocytes observed.

H

CONT.

In addition to discontinuing dabigatran, which of the following is the most appropriate immediate management?

(A) Four-factor prothrombin complex concentrate
(B) Fresh frozen plasma
(C) Idarucizumab
(D) Vitamin K
(E) Observation

Item 35

A 32-year-old man undergoes preoperative consultation for a hip replacement. He has an 18-month history of hip pain secondary to avascular necrosis of the left hip. He also has sickle cell disease, requiring three to four hospitalizations per year for vaso-occlusive crisis. Medications are ibuprofen, hydroxyurea, and folic acid.

On physical examination, vital signs are normal. Cardiac examination reveals a grade 2/6 systolic flow murmur. He has left hip pain with abduction.

Laboratory studies show a hemoglobin level of 5.8 g/dL (58 g/L; baseline, 5-6.5 g/dL [50-65 g/L]).

Which of the following is the most appropriate preoperative transfusion management for this patient?

(A) Exchange transfusion to 30% hemoglobin S
(B) Exchange transfusion to 50% hemoglobin S
(C) Simple transfusion to a target hemoglobin level of 10 g/dL (100 g/L)
(D) Simple transfusion to a target hemoglobin level of 12 g/dL (120 g/L)
(E) No transfusion

H

Item 36

A 32-year-old woman is evaluated for a painful rash occurring bilaterally on her lower extremities, which began 2 days ago. She was admitted to the hospital 5 days ago for diagnosis and treatment of pulmonary embolism with heparin and warfarin. Her father had a pulmonary embolism after a long airplane ride. Her medical history is otherwise unremarkable, and she takes no other medications.

On physical examination, vital signs are normal. She has nonblanchable macules and papules and areas of cutaneous necrosis in an angulated reticular pattern on the lower legs; findings on the feet are shown (see top of next column). The examination is otherwise unremarkable.

Laboratory studies show a normal complete blood count, a normal peripheral blood smear, and an INR of 4.

Which of the following is the most likely diagnosis?

(A) Factor V Leiden mutation
(B) Plasminogen activator inhibitor 1 deficiency
(C) Protein C deficiency
(D) Prothrombin gene mutation

ITEM 36

Item 37

A 25-year-old woman is evaluated in the emergency department for mild shortness of breath and right lateral chest pain of 2 days' duration. She reports no orthopnea or lower extremity edema. Medical history is unremarkable other than anxiety related to meeting the demands of her new job as an engineer. She takes no medications.

On physical examination, she is in no apparent distress. Vital signs are normal. Oxygen saturation is 99% breathing ambient air. The lungs are clear to auscultation. No peripheral edema is noted.

Her Wells Criteria for Pulmonary Embolism score is 0.

A complete blood count, electrocardiogram, and chest radiograph are normal.

Which of the following tests should be performed next to rule out pulmonary embolism?

(A) CT angiography of the chest
(B) D-dimer
(C) Echocardiography
(D) No further testing

Item 38

A 35-year-old man is evaluated for a 6-month history of night sweats, malaise, and weight loss of 11.3 kg (25 lb). He reports no fevers or other localizing symptoms. His only medication is acetaminophen.

On physical examination, vital signs are normal. Abdominal examination reveals splenomegaly. The remainder of the examination is noncontributory.

Laboratory studies show a hemoglobin level of 12.5 g/dL (125 g/L); a leukocyte count of 55,000/µL (55×10^9/L), with 87% neutrophils, 2% myelocytes, 1% metamyelocytes, 0.5% basophils, 7% lymphocytes, and 2.5% monocytes; and a platelet count of 450,000/µL (450×10^9/L).

Polymerase chain reaction for *BCR-ABL* fusion gene is positive. A bone marrow biopsy specimen shows hypercellular marrow with myeloid hyperplasia and 1% myeloid blasts.

Which of the following is the most appropriate treatment?

(A) Bone marrow transplantation
(B) Idarubicin and cytarabine
(C) Imatinib
(D) Vancomycin and levofloxacin

Item 39

A 24-year-old man with progressive fatigue and intermittent dark urine over several months is evaluated in the emergency department for exertional dyspnea, abdominal pain, and red urine.

On physical examination, he is pale. Temperature is 37.0 °C (98.6 °F), blood pressure is 110/70 mm Hg, pulse rate is 112/min, and respiration rate is 16/min. Oxygen saturation is 98% breathing ambient air. Scattered petechiae are visible on the skin. The abdomen is not distended and is diffusely tender to palpation without guarding. Bowel sounds are normal. The remainder of the examination is normal.

Laboratory studies:

Haptoglobin	Undetectable
Hemoglobin	7.2 g/dL (72 g/L)
Leukocyte count	1200/µL (1.2×10^9/L) with 70% neutrophils and 30% lymphocytes
Mean corpuscular volume	84 fL
Platelet count	23,000/µL (23×10^9/L)
Reticulocyte count	8% of erythrocytes
Lactate dehydrogenase	500 U/L
Urinalysis	4+ blood; 0-1 erythrocytes/hpf; 0 leukocytes/hpf

The peripheral blood smear shows normal-appearing erythrocytes without spherocytes, schistocytes, agglutinated erythrocytes, or immature-appearing leukocytes.

Which of the following is the most appropriate next test?

(A) Direct antiglobulin test
(B) Flow cytometry
(C) Methylmalonic acid measurement
(D) Quantitative and functional levels of C1 esterase inhibitor

Item 40

H

A 43-year-old man with chronic alcoholic liver disease is hospitalized after massive vomiting of blood. Medical history is notable for alcohol dependence. He takes no medications.

On physical examination, temperature is normal, blood pressure is 102/68 mm Hg, pulse rate is 118/min, and respiration rate is 22/min. He is jaundiced and has spider angiomata on the anterior chest. The liver is palpable but not tender.

Laboratory studies:

Activated partial thromboplastin time	45 s
Prothrombin time	17.8 s
Hemoglobin	9.8 g/dL (98 g/L)
Platelet count	42,000/µL (42×10^9/L)
D-dimer	5800 µg/mL (5800 mg/L)
Fibrinogen	66 mg/dL (0.6 g/L)

He receives volume resuscitation with fluids, erythrocyte and platelet transfusions, and vitamin K.

Which of the following should also be provided to manage this patient's coagulopathy?

(A) Activated factor VII concentrate
(B) ε-Aminocaproic acid
(C) Cryoprecipitate
(D) Four-factor prothrombin concentrate

Item 41

H

A 73-year-old man is admitted to the hospital with right lower lobe pneumonia. He has stage III colonic adenocarcinoma and underwent colonic resection 2 months ago. He has begun combination chemotherapy.

On physical examination, temperature is 38.5 °C (101.3 °F), blood pressure is 110/50 mm Hg, pulse rate is 103/min, and respiration rate is 24/min. Oxygen saturation is 98% breathing ambient air. Crackles are heard in the right lower lobe. The examination is otherwise noncontributory.

Which of the following is the most appropriate venous thromboembolism prophylaxis intervention?

(A) Aspirin
(B) Enoxaparin
(C) Graduated compression stockings
(D) Intermittent pneumatic compression
(E) Warfarin

Item 42

A 22-year-old woman is seen for a routine prenatal evaluation; she is 10 weeks pregnant. This is her second pregnancy; the first pregnancy was uncomplicated. Medical history is notable for sickle cell disease requiring one to two hospitalizations per year for painful events. She has no history of stroke or acute chest syndrome. Her only medication is a folic acid supplement.

On physical examination, vital signs are normal. Cardiac examination reveals a grade 2/6 systolic flow murmur. She has a gravid uterus.

Laboratory studies show a hemoglobin level of 6.4 g/dL (64 g/L; baseline, 5-7 g/dL [50-70 g/L]), leukocyte count of 11,500/µL (11.5×10^9/L), and platelet count of 279,000/µL (279×10^9/L).

Which of the following is the most appropriate treatment?

(A) Clopidogrel
(B) Exchange transfusion throughout pregnancy
(C) Hydroxyurea
(D) Simple transfusion throughout pregnancy
(E) Expectant care

Item 43

A 22-year-old woman undergoes routine evaluation for chronic anemia, which was diagnosed 6 years ago. Medical history is otherwise unremarkable, but a maternal aunt

also has anemia. Her only medication is a combination oral contraceptive pill. On physical examination, vital signs are normal. No hepatosplenomegaly is noted.

Laboratory studies:

Hemoglobin	10 g/dL (100 g/L)
Mean corpuscular volume	67 fL
Iron studies	
Ferritin	200 ng/mL (200 µg/L)
Iron	150 µg/dL (27 µmol/L)
Total iron binding capacity	340 µg/dL (61 µmol/L)

Hemoglobin electrophoresis reveals a normal pattern of migration of hemoglobin A and normal levels of hemoglobin A_2 and hemoglobin F.

Which of the following is the most likely diagnosis?

(A) Inflammatory anemia
(B) Iron deficiency
(C) α-Thalassemia silent carrier
(D) α-Thalassemia trait
(E) β-Thalassemia minor

Item 44

A 61-year-old woman undergoes routine evaluation. She reports no recent changes in her medications. She has a history of idiopathic deep venous thrombosis. Her only medication is warfarin, initiated 2 months ago.

On physical examination, vital signs are normal, and the examination is unremarkable.

She has an INR of 7.2.

In addition to withholding warfarin, which of the following is the most appropriate management?

(A) Administer fresh frozen plasma
(B) Administer prothrombin complex concentrate
(C) Administer vitamin K
(D) Remeasure INR in 2 days

Item 45

A 36-year-old woman is evaluated for a severe headache. She is at 36 weeks' gestation with her first pregnancy. Her only medication is a prenatal vitamin.

On physical examination, temperature is 37.0 °C (98.7 °F), blood pressure is 160/100 mm Hg, pulse rate is 100/min, and respiration rate is 16/min. Oxygen saturation is 98% breathing ambient air. Neurologic examination is nonfocal. Cardiopulmonary examination is normal. She has a gravid uterus and 2+ edema of the lower extremities. No petechiae or ecchymoses are seen.

Laboratory studies:

Hemoglobin	11.9 g/dL (119 g/L)
Leukocyte count	12,700/µL (12.7×10^9/L)
Platelet count	52,000/µL (52×10^9/L)
Alanine aminotransferase	50 U/L
Aspartate aminotransferase	52 U/L
Creatinine	1.2 mg/dL (106 µmol/L)
Urinalysis	3+ proteinuria

The peripheral smear shows occasional fragmented erythrocytes without platelet clumping.

Which of the following is the most appropriate management?

(A) Eculizumab
(B) Emergent delivery
(C) High-dose dexamethasone
(D) Plasma exchange

Item 46

A 28-year-old woman is evaluated preoperatively; she is scheduled for elective repair of an umbilical hernia. Medical history is notable for heavy menstrual periods and 5 days of bleeding after extraction of wisdom teeth. Her only medication is an oral contraceptive.

On physical examination, vital signs and other findings are normal.

Laboratory studies show a normal complete blood count. The activated partial thromboplastin time and prothrombin time are normal. The Platelet Function Analyzer-100 result is prolonged.

Which of the following is the most likely diagnosis?

(A) Congenital hemophilia A
(B) Factor XI deficiency
(C) Lupus anticoagulant
(D) von Willebrand disease

Item 47

A 24-year-old woman is evaluated for severe pain in her arms and legs of 5 hours' duration. Medical history is notable for lifelong mild anemia and four episodes of similar pain without precipitating factors, each episode resolving in 3 to 4 days. She has a cousin with sickle cell disease. She takes no medications.

On physical examination, vital signs are normal. She has normal range of motion in all joints with no skeletal deformities.

Laboratory studies:

Hemoglobin	11.2 g/dL (112 g/L)
Mean corpuscular volume	76 fL
Hemoglobin electrophoresis	
Hemoglobin A	33%
Hemoglobin A_2	4%
Hemoglobin S	63%
Hemoglobin F	0%

Which of the following is the most likely diagnosis?

(A) Hemoglobin E disease
(B) Hemoglobin S β-thalassemia
(C) Hemoglobin SS disease
(D) Sickle cell trait

Item 48

H

A 55-year-old man is evaluated in the emergency department for hematemesis. He has had intermittent epigastric

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discomfort for the past few weeks that does not vary with meals. He does not smoke cigarettes, drink alcohol, or take any medications.

On physical examination, temperature is 37 °C (98.6 °F), blood pressure is 118/68 mm Hg without postural changes, pulse rate is 110/min, and respiration rate is 18/min. Physical examination findings are unrevealing.

Laboratory studies show a hemoglobin level of 8.0 g/dL (80 g/L), platelet count of 130,000/µL (130 × 10⁹/L), and prothrombin time of 10 s.

Crystalloid resuscitation is initiated, and the patient undergoes upper endoscopy, which reveals an 8-mm duodenal ulcer with a clean ulcer base without active arterial bleeding.

Which of the following is the most appropriate management?

(A) Continue crystalloid resuscitation
(B) Packed red blood cell transfusion
(C) Plasma transfusion
(D) Platelet transfusion

Item 49

A 22-year-old man with sickle cell anemia (SCA) is seen 1 week after hospitalization for acute chest syndrome that required critical care and treatment with exchange transfusion and noninvasive assisted ventilation. He has not had any previous pulmonary or any other major complications from his SCA and typically has two to three episodes of acute pain events yearly. He reports he has returned to his usual level of activity and has no pulmonary symptoms and no pain. His only medication is folate, 1 mg/d.

On physical examination, vital signs are normal. He appears pale. Cardiac examination reveals a grade 3/4 systolic flow murmur. The remainder of the examination, including pulmonary examination, is unremarkable.

Laboratory studies:

Hemoglobin	8.4 g/dL (84 g/L)
Leukocyte count	14,000/µL (14 × 10⁹/L)
Mean corpuscular volume	86 fL
Platelet count	325,000 (325 × 10⁹/L)
Reticulocyte count	8% of erythrocytes

Which of the following is the most appropriate management?

(A) Folate supplementation of 4 mg/d
(B) Hydroxyurea
(C) Incentive spirometry
(D) Monthly exchange transfusions
(E) Monthly simple transfusions

Item 50

An 81-year-old woman is evaluated for a 1-year history of headaches, redness of the face, and itching. She indicates being otherwise capable of performing her daily activities on her farm. She reports no shortness of breath, chest pain, or difficulty sleeping. Medical history is significant for hypertension; she has never smoked and does not drink alcohol. Her only medication is hydrochlorothiazide.

On physical examination, vital signs are normal except for a blood pressure of 160/90 mm Hg; BMI is 19. Abdominal examination shows splenomegaly.

Laboratory studies:

Erythropoietin	Undetectable
Hemoglobin	17.5 g/dL (175 g/L)
Leukocyte count	11,000/µL (11 × 10⁹/L)
Platelet count	400,000/µL (400 × 10⁹/L)

Which of the following is the most appropriate diagnostic test to perform next?

(A) Calreticulin mutation testing
(B) *JAK2 V617F* mutation testing
(C) Polymerase chain reaction for *BCR-ABL*
(D) Sleep study

Item 51

H

A 42-year-old man is admitted to the hospital with an acute change in mental status and fever of 2 days' duration. Medical history is noncontributory, and he takes no medications.

On physical examination, temperature is 38.2 °C (100.8 °F), blood pressure is 108/70 mm Hg, pulse rate is 104/min, and respiration rate is 18/min. Oxygen saturation is 96% breathing ambient air. He is agitated and disoriented to place and time. Petechiae are noted on his shins. The remainder of the examination is normal.

Laboratory studies:

Haptoglobin	20 mg/dL (200 mg/L)
Hemoglobin	10.2 g/dL (102 g/L)
Leukocyte count	9800/µL (9.8 × 10⁹/L)
Platelet count	44,000/µL (44 × 10⁹/L)
Reticulocytes	6.8% of erythrocytes
Creatinine	1.4 mg/dL (123.8 µmol/L)
Lactate dehydrogenase	1600 U/L

The direct antiglobulin (Coombs) test is negative.

Therapy should be immediately initiated pending results of which of the following studies?

(A) ADAMTS13 activity
(B) Coagulation studies
(C) Peripheral blood smear
(D) Stool culture and testing for Shiga toxin

Item 52

A 27-year-old woman arrives to establish primary care. She feels well. Her last menstrual period was 2 weeks ago, and menses are regular. Medical history is significant for acute lymphoblastic leukemia diagnosed at 5 years of age. She received treatment for 2 years and has been leukemia free since the completion of therapy. She takes no medications.

On physical examination, vital signs are normal; BMI is 27. Other examination findings are unremarkable.

Complete blood counts performed within the past year were normal.

The patient will arrange a treatment summary to be transferred to the office.

Which of the following is the most appropriate test to obtain next in this patient?

(A) Bone marrow biopsy
(B) Estrogen and progesterone levels
(C) Exercise stress test
(D) Lipid profile and fasting blood glucose
(E) Whole genome sequencing

H

Item 53

A 78-year-old woman is hospitalized from an outpatient infusion clinic for progressive shortness of breath. She was receiving a transfusion of one unit of blood. She reports no chest pain, cough, dizziness, or palpitations. Medical history is notable for heart failure, hypertension, and myelodysplastic syndrome with symptomatic anemia requiring transfusion approximately every 3 weeks. Medications are low-dose aspirin, metoprolol, lisinopril, hydrochlorothiazide, and azacytidine.

On physical examination, temperature is 36.7 °C (98.0 °F), blood pressure is 153/76 mm Hg (pretransfusion, 123/71 mm Hg), pulse rate is 94/min (pretransfusion, 65/min), and respiration rate is 32/min (pretransfusion, 20/min). Oxygen saturation is 85% breathing ambient air. Jugular venous pressure is 10 cm H_2O. An S_3 is present on cardiac examination. Bilateral crackles are heard on pulmonary examination.

A chest radiograph shows moderate pulmonary vascular congestion with a small left pleural effusion.

Which of the following is the most likely diagnosis?

(A) Acute hemolytic transfusion reaction
(B) Anaphylactic reaction
(C) Transfusion-associated circulatory overload
(D) Transfusion-related acute lung injury

H

Item 54

A 24-year-old man is admitted to the hospital for fever, chest pain, shortness of breath, and cough of 3 days' duration. He is homozygous for hemoglobin S (Hb SS). Medications are folate and hydroxyurea.

On physical examination, temperature is 38.9 °C (102 °F), blood pressure is 100/70 mm Hg, pulse rate is 110/min, and respiration rate is 22/min. Oxygen saturation is 90% breathing 40% oxygen. He appears ill. Cardiopulmonary examination reveals a grade 2/6 systolic flow murmur and crackles in the lower lung fields bilaterally. The remainder of the examination is unremarkable.

Laboratory studies show a hemoglobin level of 7.8 g/dL (78 g/L) and a leukocyte count of 22,000/µL (22×10^9/L).

Bilateral lower lobe infiltrates are seen on a chest radiograph. The patient receives intravenous saline, prophylactic doses of low-molecular-weight heparin, and ceftriaxone and levofloxacin. Incentive spirometry is begun. Six hours later, he has worsening hypoxia and respiratory distress requiring intubation and mechanical ventilation. A repeat chest radiograph shows worsening infiltrates.

Which of the following is the most appropriate management?

(A) CT pulmonary angiography
(B) Exchange transfusion
(C) Intravenous amphotericin
(D) Intravenous full-dose unfractionated heparin
(E) Lower extremity Doppler ultrasonography

Item 55

H

A 77-year-old woman is evaluated in the emergency department with a 3-day history of progressive abdominal pain and fever. Medical history is notable for atrial fibrillation. Her only medication is dabigatran; she took her last dose 16 hours ago.

On physical examination, temperature is 39.1 °C (102.3 °F), blood pressure is 90/55 mm Hg, pulse rate is 115/min, and respiration rate is normal. She has abdominal guarding with rebound tenderness. The examination is otherwise unremarkable.

Laboratory studies show an activated partial thromboplastin time of greater than 100 seconds and a serum creatinine level of 1.7 mg/dL (150 µmol/L).

CT scan of the abdomen shows a complete large bowel obstruction.

Emergency surgery is planned.

Which of the following is the most appropriate management of the patient's anticoagulation?

(A) Dialysis
(B) Fresh frozen plasma
(C) Idarucizumab
(D) Prothrombin complex concentrate

Item 56

H

A 56-year-old man is brought to the emergency department after being found lying unresponsive in the local train station. Medical history is significant for chronic alcohol dependence. He is homeless. The patient is a frequent visitor to the emergency department for minor trauma and ailments; his last visit was 6 months ago. Until that time, the patient lived in various shelters and received at least one nutritious meal per day. His whereabouts and living circumstances since that time are unknown. His medical history is otherwise not significant, and at his last visit to the emergency department, he was taking no medications.

On physical examination, vital signs are normal. The patient is disheveled, cachectic, and malodorous. He moans in response to painful stimuli and moves all extremities. He has poor dentition. Hepatomegaly is noted.

H CONT.

Laboratory studies:

Hemoglobin	7.4 g/dL (74 g/L)
Leukocyte count	4200/µL (4.2 × 10⁹/L)
Mean corpuscular volume	110 fL
Platelet count	97,000/µL (97 × 10⁹/L)
Reticulocyte count	1% of erythrocytes
Blood alcohol level	500 mg/dL (108 mmol/L)

Hypersegmented neutrophils are seen on the peripheral blood smear.

Which of the following is the most likely cause of this patient's anemia?

(A) Cobalamin deficiency
(B) Folate deficiency
(C) Inflammatory anemia
(D) Iron deficiency

Item 57

A 59-year-old man is evaluated for progressive fatigue of 3 months' duration and recent worsening of his chronic back pain. He also reports swelling of his lower extremities. He does not indicate problems with urination. Medical history is notable for chronic low back pain. His only medication is acetaminophen as needed.

On physical examination, vital signs are normal. Deep palpation of the lower back elicits pain. He has 1+ edema of the lower extremities.

Laboratory studies:

Hemoglobin	8 g/dL (80 g/L)
Leukocyte count	4000/µL (4 × 10⁹/L)
Platelet count	300,000/µL (300 × 10⁹/L)
Albumin	2.7 g/dL (27 g/L)
Calcium	13.4 mg/dL (3.4 mmol/L)
Creatinine	2.1 mg/dL (186 µmol/L)
Protein, total	9.2 g/dL (92 g/L)

A radiograph of the lumbar spine shows compression fracture of the L1 vertebral body.

Which of the following is the most appropriate diagnostic test to perform next?

(A) Bone scan
(B) Prostate-specific antigen measurement
(C) Serum parathyroid hormone measurement
(D) Serum protein electrophoresis and free light chain analysis

Item 58

A 67-year-old woman is evaluated for slowly worsening fatigue and exertional dyspnea of several months' duration, with more recent yellowing of the skin. Medical history is notable for Hashimoto thyroiditis diagnosed 30 years ago. Her only medication is levothyroxine.

On physical examination, temperature is 36.7 °C (98.0 °F), blood pressure is 125/75 mm Hg, pulse rate is 100/min, and respiration rate is 18/min. Jaundice is noted. The remainder of the examination is noncontributory.

Laboratory studies:

Hemoglobin	6.2 g/dL (62 g/L)
Leukocyte count	3100/µL (3.1 × 10⁹/L), with a normal differential
Mean corpuscular volume	110 fL
Platelet count	94,000 (94 × 10⁹/L)
Bilirubin	
Total	6.2 mg/dL (106 µmol/L)
Direct	1.0 mg/dL (17.1 µmol/L)
Lactate dehydrogenase	400 U/L

A peripheral blood smear shows macrocytic erythrocytes with rare nucleated erythrocytes and scattered, six-lobed neutrophils. A direct antiglobulin (Coombs) test is negative.

Which of the following should be obtained next?

(A) Bone marrow biopsy
(B) Cobalamin and folate levels
(C) Flow cytometry
(D) Glucose-6-phosphate dehydrogenase level

Item 59

A 68-year-old man notes 3 days of melena and the recent onset of epistaxis and easy bruising. He had no bleeding problems until the past week. He has advanced ischemic cardiomyopathy and had a left ventricular assist device (LVAD) placed 3 months ago. He had no bleeding history before LVAD implantation surgery, and his preoperative coagulation studies were normal. Medications are atorvastatin, carvedilol, lisinopril, spironolactone, and warfarin initiated after LVAD placement.

On physical examination, other than a pulse rate of 112/min, vital signs are normal. Oxygen saturation is 94% breathing ambient air. He has crusted blood in the left nares, scattered ecchymoses, and multiple petechiae. The surgical scar on the anterior chest appears well healed. Stool for fecal occult blood is strongly positive. The remainder of the examination is normal.

Laboratory studies:

Activated partial thromboplastin time	40 s
Hemoglobin	8.0 mg/dL (80 g/L)
Platelet count	130,000/µL (130 × 10⁹/L)
Prothrombin time	19 s
INR	2.0
Platelet Function Analyzer-100	Prolonged
Aminotransferases	Normal
Fibrinogen	350 mg/dL (3.5 g/L)

Which of the following is the most likely cause of this patient's new bleeding symptoms?

(A) Acquired von Willebrand disease
(B) Coagulopathy of liver disease
(C) Dysfibrinogenemia
(D) Immune thrombocytopenic purpura

Item 60

An 81-year-old man is evaluated for increasing fatigue. He has no other symptoms to report. Medical history is

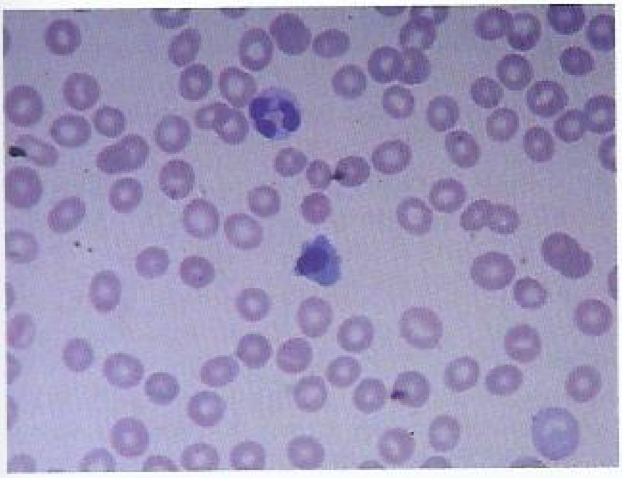
significant for diabetes mellitus and hypertension. He does not drink alcohol or smoke. Medications are metformin and lisinopril.

On physical examination, vital signs are normal. The examination is unremarkable.

Laboratory studies:

Hemoglobin	8.5 g/dL (85 g/L)
Leukocyte count	3100/μL (3.1×10^9/L) with 35% neutrophils, 45% lymphocytes, 20% monocytes
Mean corpuscular volume	105 fL
Platelet count	120,000/μL (120×10^9/L)

Serum levels of vitamin B_{12} and folate are normal. Peripheral blood smear is shown.



Which of the following is the most appropriate diagnostic test to perform next to evaluate this patient's anemia?

(A) *BCR-ABL* testing
(B) Bone marrow biopsy
(C) Immunoelectrophoresis
(D) *JAK2* mutation testing

Item 61

A 24-year-old woman is evaluated for an episode of syncope. She is in her sixth month of pregnancy. She reports exertional dyspnea and occasional chest pain. She has sickle cell disease characterized by acute pain events occurring four to five times per year, typically not requiring hospitalization. She had an episode of acute chest syndrome 1 year ago, at which time she received exchange transfusion. Medications are a prenatal multivitamin and folic acid supplement.

On physical examination, temperature is 37 °C (98.7 °F), blood pressure is 90/60 mm Hg, pulse rate is 110/min, and respiration rate is 20/min. Oxygen saturation is 98% breathing ambient air. Cardiac examination reveals a parasternal heave. The pulmonic component of the S_2 is accentuated, and a holosystolic murmur that increases with inspiration is heard at the apex. Other examination findings are normal.

Electrocardiography reveals right axis deviation, a tall R wave in lead V1, and inverted T waves in V1 to V3.

Laboratory studies:

Hemoglobin	8.2 g/dL (82 g/L)
Leukocyte count	13,600/μL (13.6×10^9/L)
Platelet count	385,000/μL (385×10^9/L)
Reticulocytes	7% of erythrocytes

Which of the following is the most appropriate diagnostic test to perform next?

(A) Cardiac MRI
(B) Echocardiography
(C) Exercise stress test
(D) Thoracic aortography

Item 62

A 71-year-old man is evaluated for headaches of 2 months' duration. He reports no shortness of breath and has a good energy level. Medical history is significant for hypertension, hypothyroidism, and hypogonadism; he has never smoked. Medications are lisinopril, levothyroxine, and testosterone injections.

On physical examination, vital signs are normal except for a blood pressure of 160/92 mm Hg; BMI is 19. He has facial plethora. Cardiopulmonary examination is normal. No hepatosplenomegaly is noted.

Laboratory studies:

Erythropoietin	40 mU/mL (40 U/L)
Hematocrit	56%
Hemoglobin	18.9 g/dL (189 g/L)
Leukocyte count	7000/μL (7×10^9/L) with normal differential
Platelet count	300,000/μL (300×10^9/L)

Which of the following is the most likely cause of this patient's findings?

(A) Levothyroxine
(B) Lisinopril
(C) Polycythemia vera
(D) Testosterone

Item 63

H

A 59-year-old man is evaluated in the hospital for swelling of his left leg. He was admitted 5 days ago with deep venous thrombosis of the right lower extremity and bilateral pulmonary emboli. Therapy with low-molecular-weight heparin (LMWH) was initiated on hospital day 1. Medical history is significant for chronic heart failure, with a hospitalization 1 month ago for pulmonary edema. Other medications are lisinopril, furosemide, and metoprolol.

On physical examination, temperature is 38.1 °C (100.6 °F), blood pressure is 132/84 mm Hg, pulse rate is 104/min, and respiration rate is 24/min. Oxygen saturation is 91% breathing ambient air. The right and left legs are swollen to midthigh.

Laboratory studies show a hemoglobin level of 12.8 g/dL (128 g/L), leukocyte count of 11,200/μL (11.2×10^9/L), and

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platelet count of 78,000/µL (78×10^9/L) (at admission, 168,000/µL [168×10^9/L]).

Doppler ultrasonography discloses a new left femoral vein thrombosis.

Which of the following is the most appropriate management?

(A) Discontinue LMWH and begin argatroban
(B) Discontinue LMWH and begin unfractionated heparin
(C) Insert an inferior vena cava retrievable filter
(D) Overlap LMWH and warfarin for 5 days

Item 64

An 18-year-old man is evaluated in the emergency department for abdominal cramping and bloody diarrhea of 6 days' duration. Medical history is unremarkable, and he takes no medications.

On physical examination, temperature is 37.0 °C (98.6 °F), blood pressure is 98/60 mm Hg, pulse rate is 100/min, and respiration rate is 16/min. Oxygen saturation is normal breathing ambient air. His abdomen is tender, without guarding or organomegaly. The examination is otherwise unremarkable.

Laboratory studies:

Haptoglobin	Undetectable
Hemoglobin	6.1 g/dL (61 g/L)
Leukocyte count	6800/µL (6.8×10^9/L)
Platelet count	37,000/µL (37×10^9/L)
Reticulocytes	9.8% of erythrocytes
Creatinine	3.6 mg/dL (318 µmol/L)
Urinalysis	3+ blood; 3+ protein; 0-2 erythrocytes/hpf; 0-2 leukocytes/hpf; several granular casts

The peripheral blood smear shows schistocytes and scant platelets without clumps. The direct antiglobulin (Coombs) test is negative.

What is the most likely diagnosis?

(A) Atypical hemolytic uremic syndrome
(B) Hemolytic uremic syndrome
(C) Immune hemolytic anemia and thrombocytopenia
(D) Rapidly progressive glomerulonephritis

Item 65

A 62-year-old woman is evaluated for mild anemia noted on routine complete blood counts over the past 6 months. Medical history is notable for a mechanical bileaflet mitral valve placed 14 years ago and essential hypertension diagnosed 15 years ago. Medications are warfarin, atenolol, and lisinopril.

On physical examination, vital signs are normal. Cardiac examination reveals crisp mechanical valve sounds without murmur. The remainder of the examination is noncontributory.

Laboratory studies:

Haptoglobin	Undetectable
Hemoglobin	10.6 g/dL (106 g/L)
Mean corpuscular volume	86 fL
Reticulocyte count	9% of erythrocytes
Lactate dehydrogenase	400 U/L

The peripheral blood smear shows normochromic normocytic erythrocytes with rare schistocytes. Leukocyte and platelet counts are normal.

Echocardiography reveals normal valve function.

Which of the following is the most likely diagnosis?

(A) Drug-induced hemolysis
(B) Gastrointestinal blood loss
(C) Glucose-6-phosphate dehydrogenase deficiency
(D) Valve hemolysis

Item 66

A 54-year-old man undergoes follow-up evaluation for deep venous thrombosis after a left hip replacement 2 months ago. He is feeling well, his swelling has improved, and he reports no pain. His only medication is rivaroxaban.

On physical examination, vital signs are normal. The examination is otherwise unremarkable.

Which of the following is the most appropriate management?

(A) Completion of 3-month course of anticoagulation
(B) D-dimer measurement
(C) Extended anticoagulation
(D) Thrombophilia evaluation

Item 67

A 32-year-old woman is evaluated in the emergency department for extremely heavy menstrual bleeding. She reports she is on the third day of her menstrual cycle and is changing her pad or tampon every 2 hours with "clots." Medications are a daily multivitamin and ibuprofen as needed for cramps.

On physical examination, vital signs are normal. She has no ecchymoses, petechiae, or splenomegaly.

Laboratory studies:

Hemoglobin	10.5 g/dL (105 g/L)
Leukocyte count	Normal
Mean corpuscular volume	72 fL
Platelet count	68,000/µL (68×10^9/L)

Review of the peripheral blood smear shows platelet clumps. A repeat platelet count performed on blood obtained in a heparinized container is normal.

In addition to iron deficiency anemia, which of the following is the most likely diagnosis?

(A) Essential thrombocythemia
(B) Immune thrombocytopenic purpura
(C) Myelodysplastic syndrome
(D) Pseudothrombocytopenia

Item 68

A 62-year-old man arrives for follow-up consultation for multiple myeloma diagnosed 3 weeks ago. A skeletal survey showed multiple lytic lesions in the spine and pelvis, but the patient's vertebral height was maintained. MRI showed abnormalities in the vertebral bodies but no evidence of spinal

cord compression. Myeloma therapy was begun with bortezomib, lenalidomide, and dexamethasone. Medical history is otherwise unremarkable. He takes no other medications.

On physical examination, vital signs are normal. The lower spine is nontender to palpation. The remainder of the physical examination is unremarkable.

Laboratory studies show a serum calcium level of 9.1 mg/dL (2.3 mmol/L) and a serum creatinine level of 0.8 mg/dL (70.7 µmol/L); a complete blood count and serum electrolyte levels are normal.

Which of the following is the most appropriate management of this patient's lytic bone lesions?

(A) Dual-energy x-ray absorptiometry
(B) Radiation therapy
(C) Zoledronic acid
(D) Current myeloma treatment

Item 69

A 32-year-old woman is hospitalized with progressive exertional dyspnea. She has noted dark urine for the last week and yellowing of her skin for several days. Medical history is unremarkable, and she takes no medications.

On physical examination, temperature is 36.7 °C (98.0 °F), blood pressure is 100/70 mm Hg, pulse rate is 100/min, and respiration rate is 18/min. Icteric sclera and skin are noted. Cardiac examination reveals a grade 2/6 systolic flow murmur. No lymphadenopathy or hepatosplenomegaly is present. The remainder of the examination is noncontributory.

Laboratory studies:

Haptoglobin	Undetectable
Hemoglobin	4.8 g/dL (48 g/L)
Leukocyte count	8200/µL (8.2×10^9/L)
Mean corpuscular volume	134 fL
Platelet count	230,000 (230×10^9/L)
Reticulocyte count	12% of erythrocytes
Bilirubin	
Total	6.7 mg/dL (114.6 µmol/L)
Direct	1.2 mg/dL (20.5 µmol/L)
Lactate dehydrogenase	660 U/L
Urinalysis	Dipstick positive for 4+ blood; 0-1 leukocytes/hpf, and 0 erythrocytes/hpf

A peripheral blood smear shows erythrocyte agglutination. A direct antiglobulin (Coombs) test is positive for C3. Diagnostic testing for *Mycoplasma* and Epstein-Barr virus is negative.

Which of the following is the most appropriate treatment?

(A) Intravenous immune globulin
(B) Prednisone
(C) Rituximab
(D) Splenectomy

Item 70

A 24-year-old woman is admitted to the hospital with a right lower lobe pulmonary embolism. Her mother experienced a deep venous thrombosis 25 years ago. Weight-based intravenous heparin is initiated.

On physical examination, temperature and blood pressure are normal, pulse rate is 120/min, and respiration rate is 19/min. Oxygen saturation is 91% breathing ambient air. The examination is otherwise unremarkable.

Despite appropriately increasing doses of heparin, her activated partial thromboplastin time remains in the normal range.

Which of the following is the most likely diagnosis?

(A) Antiphospholipid antibody syndrome
(B) Antithrombin deficiency
(C) Factor V Leiden
(D) Protein C deficiency

Item 71

A 64-year-old woman is evaluated in the emergency department for large ecchymoses, bleeding gums, and a hematoma extending from her upper thigh to her knee. Medical history is significant for chronic lymphocytic leukemia, which has been asymptomatic and managed expectantly. She has experienced no previous bleeding symptoms and has no family history of bleeding disorders. She takes no medications.

On physical examination, other than a pulse rate of 104/min, vital signs are normal. Ecchymoses are present on her arms and legs. Small cervical and axillary lymph nodes are palpable. Other examination findings are normal.

Laboratory studies:

Activated partial thromboplastin time (aPTT)	88 s
aPTT with mixing study	64 s
Hemoglobin	10.8 g/dL (108 g/L)
Leukocyte count	65,000/µL (65×10^9/L)
Platelet count	215,000/µL (215×10^9/L)
Prothrombin time	11.5 s
Factor VIII	1%

Administration of which of the following is the most appropriate management?

(A) Activated factor VII
(B) Cryoprecipitate
(C) Desmopressin
(D) Fresh frozen plasma

Item 72

A 74-year-old man is noted to have prolonged bleeding from venipuncture sites and new ecchymoses. He was admitted to the hospital 2 weeks ago for antibiotic treatment of a lung abscess. He developed *Clostridium difficile*-related diarrhea 1 week ago. His oral intake has been poor. Medical history is notable for hyperlipidemia. Medications are ampicillin-sulbactam, oral vancomycin, atorvastatin, and low-dose subcutaneous low-molecular-weight heparin.

H CONT.

On physical examination, temperature is 38.2 °C (100.8 °F), blood pressure is 115/68 mm Hg, pulse rate is 96/min, and respiration rate is 24/min. He is thin and chronically ill appearing. On pulmonary examination, crackles are heard at the right lung base. The remainder of the examination is normal.

Laboratory studies:

Activated partial thromboplastin time	30 s
Hemoglobin	11.8 g/dL (118 g/L)
Prothrombin time	22 s
Alanine aminotransferase	54 U/L
Aspartate aminotransferase	56 U/L
Factor V	100%
Factor VIII	100%
Factor X	24%

Which of the following is the most appropriate management?

(A) Administer vitamin K
(B) Discontinue atorvastatin
(C) Discontinue heparin and repeat tests in 24 hours
(D) Transfuse fresh frozen plasma

Item 73

A 26-year-old man undergoes follow-up evaluation after hospitalization for deep venous thrombosis last week. He reports no recent travel, surgery, or immobilization. He has a sister who was diagnosed with an unprovoked deep venous thrombosis 1 year ago at 35 years of age. Medical history is otherwise unremarkable. His only medication is rivaroxaban.

On physical examination, vital signs are normal. The examination is otherwise unremarkable.

The possibility of an inherited thrombophilia is discussed with the patient. After reviewing the risks and benefits of additional testing, he would like to be further evaluated for a possible thrombophilia.

Which of the following is the ideal testing strategy?

(A) Test now
(B) Test in 2 months
(C) Test a saved blood sample obtained during hospitalization but before anticoagulation
(D) Temporarily stop rivaroxaban in 1 year and test 2 weeks later

H Item 74

A 35-year-old woman arrives at the emergency department with epigastric abdominal pain of 3 months' duration, which has worsened during the past week. She also reports fatigue. Medical history is significant for a deep venous thrombosis that occurred 4 years ago, which was treated with 6 months of anticoagulation. She takes no medications.

On physical examination, vital signs are normal, except for a pulse rate of 105/min. She has mildly diffuse abdominal tenderness. The physical examination is otherwise noncontributory.

Laboratory studies:

Haptoglobin	110 mg/dL (1100 mg/L)
Hemoglobin	11 g/dL (110 g/L)
Leukocyte count	3800/µL (3.8×10^9/L)
Mean corpuscular volume	80 fL
Platelet count	252,000/µL (252×10^9/L)
Alkaline phosphatase	158 U/L
Bilirubin	
Total	3.5 mg/dL (59.9 µmol/L)
Direct	3.0 mg/dL (51.3 µmol/L)
γ-Glutamyltransferase	120 U/L

Prothrombin and activated partial thromboplastin times are normal. Testing for hepatitis B and C are negative.

A triphasic CT scan of the abdomen shows occlusion of the hepatic veins, ascites, splenomegaly, and abdominal varices; no cirrhosis is seen.

Which of the following is the most appropriate diagnostic test to perform next?

(A) α-Fetoprotein
(B) Factor VIII level
(C) Flow cytometry for CD 55/59
(D) *JAK2 V617F* mutation

Item 75 H

A 28-year-old woman is evaluated for severe anemia. She was admitted to the hospital 5 days ago for Lyme-related meningoencephalitis. Her only medication is intravenous ceftriaxone.

On physical examination, temperature is 36.7 °C (98.0 °F), blood pressure is 110/70 mm Hg, pulse rate is 100/min, and respiration rate is 15/min. She is alert and oriented. She has icteric sclera. Cardiac examination is normal, and no lymphadenopathy or organomegaly is noted.

Laboratory studies:

Hemoglobin	6.5 g/dL (65 g/L)
Leukocyte count	11,000/µL (11×10^9/L)
Platelet count	145,000 (145×10^9/L)
Reticulocyte count	10% of erythrocytes
Lactate dehydrogenase	400 U/L

The peripheral blood smear shows occasional spherocytes. A direct antiglobulin (Coombs) test is positive for IgG.

Which of the following is the most likely diagnosis?

(A) Cold agglutinin disease
(B) Drug-induced hemolysis
(C) Glucose-6-phosphate dehydrogenase deficiency
(D) Lyme-induced hemolysis

Item 76 H

A 68-year-old woman is hospitalized with fatigue, anorexia, and myalgia worsening over the last week. She underwent laparotomy 4 weeks ago for trauma sustained in a motor vehicle accident, which necessitated a splenectomy.

H CONT.

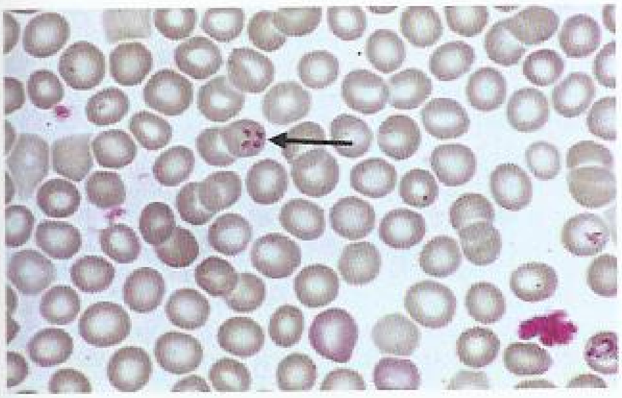
She received 3 units of blood as well as pneumococcal, haemophilus, and meningococcal vaccination; she was discharged on postoperative day 8. Hemoglobin level at discharge was 11 mg/dL (110 g/L). Her only medication is acetaminophen as needed for pain.

On physical examination, temperature is 38.6 °C (101.5 °F), blood pressure is 138/63 mm Hg, pulse rate is 92/min, and respiration rate is 18/min. The examination is otherwise noncontributory.

Laboratory studies:

Hemoglobin	9.9 g/dL (99 g/L)
Leukocyte count	10,100/µL (10.1×10^9/L) with 82% neutrophils, 2% bands, 11% lymphocytes, 3% monocytes, and 2% atypical lymphocytes
Platelet count	92,000/µL (92×10^9/L)
Reticulocyte count	8% of erythrocytes
Alkaline phosphatase	833 U/L
Alanine aminotransferase	140 U/L
Aspartate aminotransferase	134 U/L

Blood cultures are obtained. Peripheral blood smear is shown.



Which of the following transfusion-transmitted diseases is the most likely diagnosis?

(A) Babesiosis
(B) Bacterial infection
(C) Cytomegalovirus
(D) West Nile virus
(E) Zika virus

Item 77

A 32-year-old woman is evaluated for urinary frequency and dysuria. She is at 10 weeks' gestation with her first pregnancy. Medical history is notable for chronic immune thrombocytopenic purpura diagnosed 6 years ago. Her only medication is a prenatal vitamin.

On physical examination, blood pressure is 110/60 mm Hg; vital signs are otherwise normal. She has a gravid uterus. No petechiae or ecchymoses are noted.

Laboratory studies:

Hemoglobin	12.2 g/dL (122 g/L)
Leukocyte count	9800/µL (9.8×10^9/L)
Platelet count	40,000/µL (40×10^9/L); normally 60,000-80,000/µL (60-80×10^9/L)
Aminotransferase levels	Normal
Urinalysis	Nitrite +, leukocyte esterase +, small blood; no protein

A peripheral blood smear shows large and giant platelets but no clumps or schistocytes.

In addition to treating this patient's urinary tract infection, which of the following is the most appropriate management?

(A) Begin intravenous immune globulin
(B) Begin prednisone
(C) Transfuse platelets
(D) Monitor platelet count

Oncology Questions

Item 78

A 65-year-old woman is evaluated for new-onset hemoptysis. Her medical history is significant for a 40-pack-year smoking history. She takes no medications.

On physical examination, vital signs are normal. BMI is 29. Oxygen saturation is normal breathing ambient air. Digital clubbing is present.

CT scan of the chest, abdomen, and pelvis shows a large left hilar mass; there are no other pulmonary lesions, and there is no evidence of metastatic disease. Bronchoscopy with biopsy reveals small cell lung cancer. Brain MRI shows no metastatic disease.

Which of the following is the most appropriate treatment?

(A) Chemotherapy alone
(B) Chemotherapy followed by radiation
(C) Combined chemotherapy and radiation
(D) Radiation alone

Item 79

A 77-year-old man is evaluated for a 6-month history of worsening urinary frequency and nocturia. He takes no medications.

On physical examination, vital signs are normal. BMI is 22. Digital rectal examination reveals a firm, enlarged prostate.

Laboratory studies reveal a serum prostate-specific antigen level of 18.5 ng/mL (18.5 µg/L). Biopsy of the prostate reveals adenocarcinoma with bilateral gland involvement; the Gleason score is 8.

MRI of the pelvis shows evidence of focal extension beyond the prostate capsule. Bone and CT scans are negative for metastatic disease.

Which of the following is the most appropriate management?

(A) Brachytherapy
(B) Gonadotropin-releasing hormone agonist
(C) Gonadotropin-releasing hormone agonist plus radiation
(D) Radiation

H

Item 80

A 59-year-old woman is hospitalized with a biopsy-confirmed poorly differentiated squamous cell carcinoma of the base of tongue. Her medical history is significant for a 30-pack-year smoking history and moderate to heavy alcohol use. She takes no medications.

On physical examination, vital signs are normal. BMI is 24. Right-sided lymphadenopathy is present on palpation. There is a large mass on the right base of the tongue extending across the midline, nearly obstructing the airway.

Laboratory studies are notable for a serum creatinine level of 1.8 mg/dL (159.12 µmol/L).

CT scan of the neck shows a very large mass on the right base of the tongue that crosses the midline, extending into the extrinsic muscles of the tongue and adjacent to the carotid artery. Multiple enlarged right-sided cervical lymph nodes are noted, with the largest being 3.5 cm. Enlarged nodes are also noted on the left side. CT scan of the chest is negative.

Which of the following is the most appropriate treatment?

(A) Bevacizumab
(B) Cetuximab plus radiation
(C) Cisplatin plus radiation
(D) Radiation alone

Item 81

A 29-year-old woman diagnosed with stage IA cervical cancer is evaluated during a follow-up visit. The patient would like to preserve fertility. She has no other medical problems and takes no medications.

On physical examination, vital signs are normal. The general physical examination is normal.

Which of the following is the most appropriate management?

(A) Conization
(B) Neoadjuvant chemotherapy
(C) Radiation therapy
(D) Radical hysterectomy

Item 82

A 48-year-old woman is evaluated during a follow-up visit for breast cancer. At age 43 years, she was diagnosed with low-risk, stage IIA invasive ductal cancer. The cancer was estrogen receptor positive, progesterone receptor positive, and *HER2* negative. She has completed 5 years of tamoxifen and has tolerated it well. She continues to have menstrual periods. She takes no other medications.

On physical examination, vital signs are normal. There are well-healed incisions of the right breast and axilla. There are no breast masses.

Which of the following is the most appropriate management?

(A) Continue tamoxifen for 5 more years
(B) Stop tamoxifen
(C) Stop tamoxifen; begin anastrozole
(D) Stop tamoxifen; begin leuprolide and anastrozole

Item 83

A 22-year-old man is evaluated for a mass on the left side of his neck. He has not experienced fevers, night sweats, or weight loss. He takes no medications.

On physical examination, all vital signs are normal. A left supraclavicular lymph node is enlarged to 4 cm, and axillary lymphadenopathy is noted bilaterally. There is no hepatosplenomegaly.

A biopsy specimen of the supraclavicular lymph node reveals Hodgkin lymphoma, nodular sclerosis subtype.

Laboratory results, including complete blood count, biochemical profile, and serum lactate dehydrogenase, are normal.

CT scan and PET scan show mediastinal lymphadenopathy, with nodes up to 4 cm in size, and left supraclavicular and bilateral axillary lymphadenopathy. No infradiaphragmatic disease is observed.

Which of the following is the most appropriate initial management?

(A) Bone marrow biopsy
(B) Chemotherapy
(C) Radiation therapy
(D) Staging laparotomy and splenectomy

Item 84

A 42-year-old woman is evaluated during a follow-up visit. She was diagnosed 4 years ago with stage IIIA high-grade serous ovarian cancer, with a deleterious *BRCA1* germline mutation found on genetic testing. She was treated with total abdominal hysterectomy, bilateral salpingo-oophorectomy, and chemotherapy with intravenous and intraperitoneal cisplatin and paclitaxel. Her cancer recurred 18 months after she completed chemotherapy, and she underwent two additional sequential chemotherapies, including carboplatin and paclitaxel, cisplatin and gemcitabine, and bevacizumab. The cancer is progressing on her current treatment. Her performance status is good (Eastern Cooperative Oncology Group = 1). The patient is still taking chemotherapy medications.

On physical examination, vital signs are normal. Abdominal distention with lateral dullness is present. The remainder of the examination is normal.

Laboratory studies reveal a serum CA-125 value of 145 U/mL (145 kU/L) (1 month ago, 82 U/mL [82 kU/L]).

CT scans of the chest, abdomen, and pelvis show increased size and number of peritoneal masses and increasing ascites. There are no pleural effusions.

In addition to stopping the current chemotherapy regimen, which of the following is the most appropriate treatment?

(A) High-dose chemotherapy with hematopoietic stem cell transplantation
(B) Oral (poly adenosine diphosphate-ribose) polymerase inhibitor
(C) Repeat intraperitoneal cisplatin chemotherapy
(D) Supportive care

Item 85

A 38-year-old woman is evaluated. She has just been diagnosed with hormone receptor–negative, *HER2*-positive stage II infiltrating ductal breast cancer. She takes no medications. Neoadjuvant chemotherapy with docetaxel, trastuzumab, and pertuzumab is planned; a port has been placed, and treatment is to start next week. The patient has a 2-year-old daughter and has very recently decided that she wishes to conceive again.

On physical examination, vital signs are normal. A 2.5-cm left breast mass is noted, with no regional lymph adenopathy.

Which of the following is the most appropriate management?

(A) Advise against any further pregnancies
(B) Cancel chemotherapy and proceed with mastectomy and radiation therapy
(C) Delay chemotherapy until counseled by a fertility specialist
(D) Proceed with chemotherapy

Item 86

A 62-year-old woman is evaluated during a follow-up visit for recently diagnosed stage IIIA high-grade serous ovarian cancer. She underwent total abdominal hysterectomy and bilateral salpingo-oophorectomy and completed six cycles of chemotherapy with cisplatin and paclitaxel. The patient's paternal aunt was diagnosed with breast cancer at age 52 years. There is no personal or family history of any other cancers. She takes no medications.

On physical examination, vital signs and the remainder of the examination are normal.

Laboratory studies reveal a serum CA-125 value of 14 U/mL (14 kU/L) after chemotherapy (383 U/mL [383 kU/L] at diagnosis).

Which of the following is the most appropriate test to perform next?

(A) Chest radiography annually
(B) CT of the abdomen and pelvis in 3 months
(C) Genetic testing for *BRCA1* and *BRCA2* mutations
(D) Genetic testing for Lynch mutations

Item 87

A 65-year-old man is evaluated for persistent dyspepsia despite treatment with antacid therapy. He also has recent weight loss of 3 kg (6.6 lb) and development of epigastric abdominal pain. He does not smoke or drink alcohol. He takes no medications other than antacids.

On physical examination, vital signs are normal. There is epigastric tenderness but no abdominal masses, no hepatosplenomegaly, and no lymphadenopathy.

The endoscopic biopsy specimen shows evidence of mucosa-associated lymphoid tissue (MALT) lymphoma involving the stomach. Immunohistochemical stains for *Helicobacter pylori* are positive.

A CT scan shows thickening of the gastric wall but no abdominal or other lymphadenopathy.

Which of the following is the most appropriate management?

(A) Combination therapy with rituximab and chemotherapy
(B) Gastrectomy
(C) PET
(D) Proton pump inhibitor and antibiotic therapy
(E) Radiation therapy

Item 88

A 55-year-old woman is evaluated in the office for a recent diagnosis of lobular carcinoma in situ and atypical lobular hyperplasia. She wishes to discuss options to decrease her risk of breast cancer. The patient is postmenopausal. Her medical history is significant for a left calf deep venous thrombosis at 25 years of age concurrent with oral contraceptive use. She takes no medications.

On physical examination, vital signs are normal. There is a healed left upper breast incision. The remainder of the examination is normal.

Which of the following is the most appropriate preventive measure for this patient?

(A) Exemestane
(B) High-dose vitamin D
(C) Low-fat diet
(D) Raloxifene
(E) Tamoxifen

Item 89

A 74-year-old man is evaluated for a 4-month history of increasing fatigue. He also reports increased dyspnea climbing stairs. He takes no medications.

On physical examination, vital signs are normal. The remainder of the physical examination is unremarkable.

Laboratory studies reveal a hemoglobin level of 8.8 g/dL (88 g/L) and a mean corpuscular volume of 70 fL.

A colonoscopy, performed to the ileocecal valve, identifies a fungating mass at the hepatic flexure. A biopsy specimen shows moderately differentiated invasive adenocarcinoma.

Which of the following is the most appropriate test to perform next?

(A) Contrast-enhanced CT scan of the chest, abdomen, and pelvis
(B) CT colonography
(C) Liver MRI scan
(D) Whole body PET/CT scan

Item 90

A 57-year-old postmenopausal woman is evaluated following the diagnosis of right breast ductal carcinoma

in situ after lumpectomy. Pathologic findings showed a grade 3 ductal carcinoma in situ spanning 2.5 cm with negative margins that is estrogen receptor–positive; lymph nodes were not sampled. She has received primary breast radiation therapy. She takes no medications.

On physical examination, vital signs are normal. There is a healed right breast incision. There are no breast masses or lymphadenopathy.

Which of the following is the most appropriate management to decrease the risk of ipsilateral and contralateral breast cancer?

(A) Initiate anastrozole
(B) Initiate raloxifene
(C) Initiate tamoxifen plus docetaxel
(D) Obtain 21-gene recurrence score testing

Item 91

A 62-year-old woman is evaluated for a 3-month history of worsening cough and a 2-week history of shortness of breath. She has lost 9.1 kg (20.0 lb). She quit smoking 25 years ago. She takes no medications.

On physical examination, vital signs are normal. Oxygen saturation is 94% breathing ambient air. Pulmonary examination reveals decreased breath sounds in the left lower lung field.

CT scan of the chest shows a large left pleural effusion, multiple right-sided lung nodules, and hypodense lesions in the upper portion of the liver. Bone scan reveals metastatic lesions involving the ribs and thoracic spine. Brain MRI shows no metastatic disease.

Thoracentesis is performed and cytologic findings confirm adenocarcinoma.

Which of the following is the most appropriate management?

(A) Erlotinib
(B) Prophylactic cranial irradiation
(C) Radiation to the metastatic lesion on the thoracic spine
(D) Systemic chemotherapy
(E) Test for activating mutations

Item 92

A 60-year-old man is seen for a routine evaluation. His family history is notable for prostate cancer in his father. He takes no medications.

On physical examination, vital signs are normal. The remainder of the examination is normal.

After discussion of the benefits and harms of prostate cancer screening, the patient wishes to proceed with screening.

Laboratory studies reveal a serum prostate-specific antigen level of 5.1 ng/mL (5.1 µg/L).

Biopsy of the prostate reveals cancer in two cores of the right lobe (Gleason score, 6), with less than 10% cancer in each core.

Which of the following is the most appropriate management?

(A) Active surveillance
(B) Bone scan
(C) Leuprolide
(D) Observation

Item 93

A 61-year-old woman is evaluated for follow-up of stage IVA hypopharyngeal squamous cell carcinoma, which was treated with combined cisplatin and radiation therapy 1 year ago. She has xerostomia and some dysphagia since completing therapy. She has a 30-pack-year smoking history and quit smoking 1 year ago. She takes no medications.

On physical examination, vital signs are normal. BMI is 21. There is chronic induration of the right neck and limitation in neck range of motion, findings that have been noted on previous examinations. There is no palpable lymphadenopathy.

Laboratory studies reveal a normal thyroid-stimulating hormone level.

Recent laryngoscopy identified no evidence of recurrent cancer or new primary cancer.

Which of the following is the most appropriate screening or surveillance test to perform next?

(A) Head and neck CT scan
(B) Low-dose chest CT scan
(C) PET/CT scan
(D) Thyroid ultrasonography

Item 94

A 23-year-old woman is evaluated for swollen glands on the left side of her neck, which have persisted for 6 weeks. She has not had fevers, night sweats, or weight loss. Fine-needle aspiration of a cervical lymph node performed 1 week ago yielded no evidence of malignancy on either cytologic evaluation or flow cytometry. She takes no medications.

On physical examination, all vital signs are normal. There are multiple left cervical and supraclavicular nodes measuring up to 3 cm in size, which are firm and rubbery. The chest is clear to auscultation. There is no hepatosplenomegaly.

Laboratory results, including complete blood count with differential, are normal.

Which of the following is the most appropriate management?

(A) Core lymph node biopsy
(B) PET/CT scan
(C) Surgical lymph node biopsy
(D) Observation

Item 95

H

A 61-year-old man is hospitalized after several days of productive cough, fatigue, and fever. He quit smoking 10 years ago. He takes no medications.

H CONT

On physical examination, temperature is 39.2 °C (102.6 °F), blood pressure is 110/75 mm Hg, pulse rate is 110/min, and respiration rate is 24/min. Oxygen saturation is 90% breathing 2 L/min of oxygen through nasal cannula. Pulmonary examination reveals crackles in the right lower lung field. He has good performance status.

Chest radiograph shows right lower lobe pneumonia and a right hilar mass. CT scan of the chest and abdomen confirms an endobronchial lesion and right hilar mass, multiple lytic bone lesions, and a right adrenal mass. Bronchoscopy with biopsy confirms squamous cell carcinoma. Bone scan confirms multiple osseous metastatic lesions. Brain MRI shows no metastatic disease.

In addition to platinum-based chemotherapy, which of the following is most likely to improve outcome in this patient?

(A) Palliative care consultation
(B) PET/CT scan
(C) Prophylactic cranial irradiation
(D) Test for epidermal growth factor receptor mutation

Item 96

A 42-year-old woman has follow-up evaluation for stage II colon cancer that was diagnosed 3 years ago. Her tumor was found to be deficient in the mismatch repair protein MLH1. Genetic evaluation showed that she had Lynch syndrome, a germline mutation of one of the DNA mismatch repair genes. Nine months later, she developed recurrent disease with liver and lung metastases. Analysis of her tumor at that time revealed a *KRAS* mutation. She was treated initially with 5-fluorouracil, leucovorin, and oxaliplatin (FOLFOX) and then with irinotecan, each with only a short duration of tumor control and subsequent progression of disease. She reports that she has been able to maintain her full-time job and has been walking more than a mile daily. She takes no medications.

On physical examination, vital signs and the remainder of the examination are normal.

Which of the following is the most appropriate treatment?

(A) An epidermal growth factor receptor inhibitor
(B) An immune checkpoint inhibitor
(C) Dual antibody therapy targeting vascular endothelial growth factor and endothelial growth factor receptor
(D) No further chemotherapy; palliation care only

Item 97

A 69-year-old man with previously untreated chronic lymphocytic leukemia returns to the office after his third hospitalization this year for pneumonia. He received the pneumococcal conjugate vaccine at age 65 years and the polysaccharide vaccine at age 66 years. He is taking no medications.

On physical examination, vital signs are normal. He has diffuse lymphadenopathy with nodes up to 2.5 cm in size and a palpable spleen below his left costal margin. The chest is clear to auscultation.

Laboratory studies:

Leukocyte count	34,000/µL (34×10^9/L) with 91% lymphocytes, 5% neutrophils, 3% monocytes, and 1% bands
Platelet count	118,000/µL (118×10^9/L)
Hemoglobin	12.2 g/dL (122 g/L)

Which of the following is the most appropriate management?

(A) Assess immunoglobulin levels
(B) Start bendamustine and rituximab
(C) Start granulocyte colony-stimulating factor (G-CSF) injections
(D) Start ibrutinib

Item 98

A 69-year-old man is evaluated on routine follow-up. He has a history of stage IIIC sigmoid colon cancer that was resected 18 months ago. He received postoperative chemotherapy and has been followed expectantly since that time. He takes no medications.

On physical examination, vital signs are normal. Examination is notable for a liver edge palpable 2 cm below the right costal margin.

He is now found to have a new elevation in serum carcinoembryonic antigen level.

A contrast-enhanced CT scan of the chest, abdomen and pelvis shows numerous hypodense lesions up to 4 cm in diameter in the liver and lungs. Previous postoperative CT scan results were normal.

Which of the following is the most appropriate diagnostic test to perform next?

(A) Multi-gene sequencing of tumor
(B) Needle biopsy of most accessible lesion
(C) PET/CT scan
(D) *RAS* mutation status of primary tumor

Item 99

A 70-year-old woman is evaluated for a 1-month history of worsening productive cough with 1 week of blood-tinged sputum. Her appetite is decreased, and she has lost 10 lb (4.5 kg); but her performance status is otherwise normal, and she takes no medications.

On physical examination, vital signs are normal. The remainder of the physical examination, including the pulmonary examination, is normal. BMI is 27. Oxygen saturation is normal on ambient air.

CT scan of the chest, abdomen, and pelvis reveals a 4-cm left upper lobe mass, ipsilateral mediastinal lymphadenopathy, and a 4-cm adrenal mass. CT-guided biopsy of the lung mass confirms adenocarcinoma; mutation testing results are negative. Brain MRI shows no metastatic disease.

Repeat CT scan after six cycles of carboplatin and pemetrexed chemotherapy reveals a reduction in size of

the lung mass, stable lymphadenopathy, and significant reduction in size of the adrenal mass. Her appetite remains diminished, but her weight is stable. The cough and sputum production have resolved.

Which of the following is the most appropriate treatment?

(A) Carboplatin and gemcitabine for four more cycles
(B) Erlotinib maintenance chemotherapy
(C) Pemetrexed maintenance chemotherapy
(D) Radiation

Item 100

A 70-year-old man is evaluated for a 2 month history of persistent hoarse voice. He has a 50-pack-year smoking history. His medical history is otherwise normal, and he takes no medications.

On physical examination, vital signs and other findings are normal.

Laryngoscopy shows a small mass on the right vocal cord without fixation or limitation in mobility. CT scan of the neck shows a small lesion on the right vocal cord with no evidence of left-sided involvement, cartilage involvement, or lymphadenopathy.

Which of the following is the most appropriate treatment?

(A) Chemotherapy plus radiation
(B) Partial laryngectomy
(C) Radiation therapy
(D) Total laryngectomy, chemotherapy, and radiation

Item 101

A 55-year-old woman is evaluated for rectal bleeding and pain with defecation that had increased during the past 3 months. She takes no medications.

On physical examination, vital signs are normal. BMI is 19. The rectal examination reveals a brown stool sample that is guaiac positive. The remainder of the physical examination is unremarkable.

Hemoglobin level is 12.5 g/dL (125 g/L). Leukocyte count, platelet count, and liver chemistry test results are normal.

A colonoscopy to the ileocecal valve identifies a fungating mass 8 cm from the anal verge, and a biopsy specimen shows adenocarcinoma. An MRI of the pelvis shows a nonobstructing tumor invading into the muscularis but not through the full thickness of the rectal wall (T2). No abnormal lymph nodes are seen. Contrast-enhanced CT scans of the chest and abdomen are normal.

Which of the following is the most appropriate treatment?

(A) Chemotherapy
(B) Radiation therapy
(C) Radiation therapy plus chemotherapy
(D) Radiation therapy plus chemotherapy followed by surgery
(E) Surgery

Item 102

H

A 26-year-old woman is hospitalized with a temperature of 38 °C (101.5 °F) 10 days after her first cycle of chemotherapy with rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP) for diffuse large B-cell lymphoma. Other than fever, she has no symptoms of infection.

On physical examination, temperature is 38.6 °C (101.5 °F). The remainder of the vital signs and physical examination are normal.

Pertinent laboratory results are a leukocyte count of 1100/µL (1.1×10^9/L) with 10% neutrophils, platelet count of 144,000/µL (144×10^9/L), and hemoglobin level of 11.2 g/dL (112 g/L). Blood and urine culture results are pending. Chest radiographic findings are negative.

Empiric broad-spectrum antibiotics are initiated.

Which of the following is the most appropriate additional management?

(A) Reduce the doses of cyclophosphamide and doxorubicin
(B) Start granulocyte colony-stimulating factor (G-CSF) now
(C) Start G-CSF on day 2 of her subsequent cycles of therapy
(D) Start levofloxacin prophylaxis before next cycles of therapy

Item 103

A 50-year-old woman is evaluated for nausea and abdominal discomfort that have been present and increasing for the past 3 to 4 months. She takes no medications.

On physical examination, vital signs are normal. BMI is 24. The abdominal examination reveals no masses, tenderness, or organomegaly.

An esophagogastroscopy identifies a discrete 8-cm mass in the pylorus. The biopsy specimen shows a gastrointestinal stromal tumor (GIST). Immunohistochemical stain for the *KIT* gene is strongly positive.

Contrast-enhanced CT scans of the chest, abdomen, and pelvis confirm the mass and do not identify any other abnormal findings.

The patient undergoes a distal gastrectomy. Pathologic findings confirm a GIST and further note a high mitotic rate (10 mitoses per 50 high-power fields). Margins of resection and all lymph nodes examined are free of tumor.

Which of the following is the most appropriate management?

(A) Intravenous rituximab
(B) Oral imatinib
(C) Radiation therapy
(D) Observation without further therapy

Item 104

H

A 36-year-old woman is hospitalized with a 2-week history of gradually worsening dyspnea on exertion, facial swelling, and a sensation of head fullness. She has had fatigue, night sweats, and a 4.5-kg (10-lb) weight loss over the past

2 months. Her medical history is otherwise unremarkable, and she takes no medications.

On physical examination, vital signs are normal. She is not in respiratory distress and has no stridor. She has facial and neck edema, and her face appears flushed. There is no lymphadenopathy. Lungs are clear on auscultation. Cardiac and abdominal examinations are normal.

A CT scan of the chest done in the emergency department shows an 8.5-cm right mediastinal mass with compression of the superior vena cava. There is no evidence of thrombosis. There are no other areas of lymphadenopathy and no lung masses.

Which of the following is the most appropriate next step in management?

(A) Dexamethasone
(B) Mediastinoscopy
(C) Percutaneous intravascular stent placement
(D) Urgent radiation therapy

Item 105

A 49-year-old man is evaluated for a 1-month history of a painless enlarging left neck mass. His medical history is unremarkable, and he takes no medications.

On physical examination, vital signs are normal. BMI is 26. On palpation, there is a 2-cm left anterior cervical lymph node near the angle of the mandible.

Laryngoscopy shows a left-sided tonsil cancer. Biopsy of the tonsil reveals moderately differentiated squamous cell carcinoma that is positive for p16 (human papillomavirus). CT scan of the neck reveals a cystic left-sided cervical lymph node; a left tonsil mass is noted. CT scan of the chest is negative.

Postoperative pathology reveals a 2.5-cm tonsil cancer with negative margins and 3/26 positive cervical nodes, one with extracapsular extension.

Which of the following is the most appropriate treatment?

(A) Cisplatin alone
(B) Cisplatin plus human papillomavirus vaccine
(C) Cisplatin plus radiation
(D) Radiation alone

Item 106

A 65-year-old man is evaluated for an episode of hemoptysis. His medical history is significant for a 30-pack-year smoking history; he quit smoking 1 year ago. He takes no medications.

On physical examination, vital signs are normal. BMI is 28. Oxygen saturation is 96% breathing ambient air.

CT scan of the chest identifies a 3.5-cm spiculated mass in the right lower lobe and an enlarged hilar lymph node. PET/CT scans and brain MRI scans show no evidence of metastatic disease.

Surgery is performed and reveals a 3.2-cm, poorly differentiated adenocarcinoma with negative margins, two hilar lymph nodes positive for metastatic adenocarcinoma, and negative mediastinal lymph nodes.

Which of the following is the most appropriate management?

(A) Adjuvant chemoradiation
(B) Adjuvant chemotherapy
(C) Adjuvant radiation
(D) Observation

Item 107

A 77-year old man is evaluated in the office for weight loss and failure to thrive. He reports that he spends most of the day in a bed or chair and rarely leaves the house, and then only for short times and with considerable assistance. His appetite has been poor, and his abdominal girth has expanded. He estimates that his weight has dropped about 9 kg (20 lb) from his baseline. He takes no medications.

On physical examination, vital signs are normal. BMI is 17. He is frail, fatigued, and cachectic. Marked bitemporal wasting is noted. The sclerae are icteric. Breath sounds are diminished at bases bilaterally. The liver edge is palpable below the rib cage in the midcostal line. The abdomen is distended. There is 2+ dependent edema. The remainder of the examination is normal.

Laboratory studies:

Albumin	1.9 g/dL (19 g/L)
Alkaline phosphatase	353 U/L
Bilirubin	3.1 mg/dL (17.1 µmol/L)
Complete blood count	Hemoglobin 10 g/dL (100 g/L), with normochromic normocytic indices, normal leukocyte and platelet counts
Creatinine	0.5 mg/dL (44.2 µmol/L)

A contrast-enhanced CT scan of the chest, abdomen, and pelvis shows extensive hypodense lesions replacing more than 50% of the liver, and ascites and abdominal carcinomatosis. A diagnostic paracentesis is performed and cytologic findings show moderately differentiated adenocarcinoma.

Which of the following is the most appropriate management?

(A) Combination chemotherapy targeted at a gastrointestinal primary tumor
(B) Combination chemotherapy targeted at a germ cell tumor
(C) Hepatic arterial embolization
(D) Supportive management and hospice care

Item 108

A 58-year-old woman is evaluated for a 6-month history of headache and facial redness. Her medical history is unremarkable, and she takes no medications.

On physical examination, she is afebrile. Blood pressure is 160/95 mm Hg, pulse rate is 96/min, and respiration rate is 20/min. BMI is 28. Oxygen saturation is normal. Facial plethora and palmar erythema are present. There is no hepatomegaly or splenomegaly on palpation.

Laboratory studies:

Erythropoietin	Markedly elevated
Hemoglobin	18.1 g/dL (181 g/L)
Leukocyte count	5400/µL (5.4×10^9/L) with a normal differential
Liver chemistry tests	Normal
Platelet count	250,000/µL (250×10^9/L)
Urinalysis	Normal

Which of the following is the most appropriate diagnostic test to perform next?

(A) Bone marrow biopsy

(B) Chest radiography

(C) CT scan of the abdomen

(D) *JAK2* mutation testing

Item 109

A 71-year-old man is evaluated during a follow-up appointment for stage II rectal cancer that was resected 3 years ago. He takes no medications.

On physical examination, vital signs are normal. BMI is 23. The liver edge is palpable 3 cm below the xiphisternum.

A surveillance CT scan shows three new hypodense lesions in the left lobe of the liver consistent with metastatic disease. The largest lesion is 4 cm. No other abnormal findings are found on a contrast-enhanced CT scan of the chest, abdomen, and pelvis.

Which of the following is the most appropriate management?

(A) Hepatic arterial embolization

(B) Needle biopsy of the most accessible liver lesion

(C) Palliative chemotherapy

(D) Resection of all lesions

Item 110

A 66-year-old woman is evaluated for a lump in her left axilla. She is otherwise feeling well and takes no medications. On physical examination, vital signs are normal. A firm, 2-cm mass is palpable in the left axilla. The right axilla is normal. Bilateral breast examination results are normal. The remainder of the physical examination is unremarkable.

Mammography and an MRI scan of the breasts show the enlarged left axillary node but no other abnormal findings.

An excisional biopsy of the axillary node reveals a moderately differentiated adenocarcinoma that is estrogen receptor negative, progesterone receptor negative, and *HER2* negative (1+).

A CT scan of the chest, abdomen, and pelvis shows no abnormal findings. A bone scan is normal.

Which of the following is the most appropriate management?

(A) Left axillary dissection and management as primary breast cancer

(B) Letrozole

(C) Radiation therapy to the left axilla

(D) Observation with no further therapy at this time

Item 111

H

A 37-year-old man is evaluated in the hospital for rapidly enlarging axillary and supraclavicular lymphadenopathy. He is HIV positive. His only medication is efavirenz-emtricitabine-tenofovir.

On physical examination, vital signs are normal. A left supraclavicular lymph node is enlarged to 5 cm, and a left axillary node is enlarged to 6 cm. The remainder of the physical examination is normal.

Laboratory studies:

Creatinine	1.7 mg/dL (150.3 mmol/L)
Hemoglobin	8.6 g/dL (86 g/L)
Lactate dehydrogenase	2459 U/L
Leukocyte count	2600/µL (2.6×10^9/L)
Platelet count	110,000/µL (110×10^9/L)
Urate	13.3 mg/dL (0.78 mmol/L)

Biopsy of the node shows CD20-positive Burkitt lymphoma.

A CT scan of the chest, abdomen, and pelvis without contrast identifies mesenteric and retroperitoneal lymphadenopathy and splenomegaly. There is no hydronephrosis.

Before starting chemotherapy, which of the following is the most appropriate treatment?

(A) Allopurinol and intravenous hydration

(B) High-dose glucocorticoid therapy

(C) Radiation therapy

(D) Rasburicase and intravenous hydration

Item 112

A 32-year-old woman is evaluated during a follow-up visit for management of stage IIIA left breast cancer (3.5 cm, grade 3 invasive ductal carcinoma; estrogen receptor positive, progesterone receptor positive, and *HER2* negative; four positive axillary lymph nodes). She has completed neoadjuvant chemotherapy, lumpectomy, and axillary dissection as well as primary breast radiation. She resumed menstruation after completing chemotherapy, and her estradiol levels are in the premenopausal range. She takes no medications.

On physical examination, vital signs are normal. There are healed incisions on the left breast and axilla. There are no breast masses.

Which of the following is the most appropriate treatment?

(A) An aromatase inhibitor

(B) Leuprolide

(C) Leuprolide and an aromatase inhibitor

(D) Tamoxifen

Item 113

A 55-year-old woman is evaluated during a follow-up examination. She completed six cycles of chemotherapy with rituximab plus cyclophosphamide, doxorubicin,

vincristine, and prednisone (R-CHOP) for stage III diffuse large B cell lymphoma with bulky retroperitoneal lymphadenopathy. She takes no medications.

The results of the physical examination are unremarkable, with no findings of lymphadenopathy or abdominal masses.

CT scan shows a decrease in the confluent retroperitoneal nodal mass, from 15 cm × 17 cm before chemotherapy to 5 cm × 4 cm. PET scan shows no metabolic activity of the mass. No other areas of disease are noted.

Which of the following is the most appropriate management?

(A) Autologous stem cell transplant
(B) CT-guided biopsy of the residual mass
(C) Radiation therapy to the site of residual disease
(D) Surgical biopsy of the residual mass
(E) Observation by serial CT scanning

Item 114

A 55-year-old woman is evaluated to discuss additional cancer therapy. She was recently diagnosed with stage IIIB ovarian high-grade serous carcinoma. She underwent surgical staging, total abdominal hysterectomy, salpingo-oophorectomy, and debulking, with residual tumor size less than 1 cm. Genetic testing was negative for *BRCA1* and *BRCA2* mutations. She takes no medications.

On physical examination, vital signs are normal. There is a healing midline abdominal incision. The remainder of the examination is normal.

Her performance status is excellent (Eastern Cooperative Oncology Group performance status = 0.

Which of the following is the most appropriate treatment?

(A) High-dose chemotherapy with hematopoietic stem cell transplantation
(B) Intravenous and intraperitoneal cisplatin and paclitaxel chemotherapy
(C) Intravenous cisplatin and paclitaxel chemotherapy
(D) Olaparib

Item 115

A 61-year-old woman has a follow-up evaluation for the incidental discovery of several hypodense lesions in both lobes of her liver and a 2.5-cm mesenteric mass during CT imaging for nephrolithiasis. She has fully recovered from the nephrolithiasis and now feels entirely well. She does not have abdominal pain, a change in either appetite or bowel habits, hot flushes, or facial flushing. She takes no medications.

On physical examination, vital signs and the remainder of the examination are normal.

Complete blood count and liver chemistry test results are normal.

A needle biopsy of an accessible liver lesion shows a well-differentiated low-grade neuroendocrine tumor, with a low rate of mitotic figures.

Which of the following is the most appropriate management?

(A) Begin hormonal therapy with a somatostatin analogue
(B) Hepatic artery embolization
(C) No immediate intervention; repeat CT scan in 3 months
(D) Surgery to remove primary tumor
(E) Systemic chemotherapy

Item 116

A 40-year-old woman is evaluated in the office following a recent diagnosis of stage IIA breast cancer. Pathologic findings showed a 2.5 cm, grade 2 invasive ductal carcinoma with no lymphatic or vascular invasion and negative margins. The cancer was estrogen receptor positive, progesterone receptor positive, and *HER2* negative. Two sentinel nodes were negative. The 21-gene recurrence score is 8 (low risk of recurrence). She takes no medications.

She is seeking advice about adjuvant systemic therapy. The patient is premenopausal and has no family history of breast or ovarian cancer.

On physical examination, vital signs are normal. There is a healed right upper outer breast incision and healed right axillary incision. The remainder of the examination is normal.

Laboratory studies show normal findings on complete blood count, basic metabolic panel, and liver chemistry tests.

In addition to primary breast radiation, which of the following is the most appropriate treatment?

(A) Adjuvant chemotherapy
(B) Adjuvant chemotherapy followed by tamoxifen
(C) Ovarian suppression and anastrozole
(D) Tamoxifen

Item 117

A 75-year-old man is evaluated for a 3-month history of worsening urinary hesitancy, decreased stream, and a sense of incompletely emptying his bladder. His medical history is significant for COPD, hypertension, and stroke. He has dyspnea with minimal exertion. His medications are ipratropium bromide, salmeterol, fluticasone, amlodipine, atorvastatin, and aspirin.

On physical examination, there is evidence of mild muscle wasting. His respiration rate is 18/min; other vital signs are normal. Oxygen saturation is 92% breathing ambient air. Pulmonary examination reveals decreased breath sounds throughout both lung fields. Digital rectal examination reveals an enlarged prostate without any palpable nodules.

Laboratory studies reveal a serum prostate-specific antigen level of 6 ng/mL (6 µg/L).

Biopsy of the prostate confirms prostate cancer with a Gleason score of 6. The patient begins therapy with tamsulosin, and his voiding symptoms improve.

Which of the following is the most appropriate management of his prostate cancer?

(A) Active surveillance
(B) Androgen deprivation therapy
(C) Bone scan
(D) Radiation
(E) Observation

Item 118

A 40-year-old woman is evaluated during a follow-up visit after a recent diagnosis of stage IIB left breast cancer. She has postoperative left breast pain but no other symptoms. She takes no medications.

On physical examination, vital signs are normal. There is a healed left breast incision and a healed left axillary incision. The remainder of the examination is normal.

Results from a complete blood count and chemistry panel, including liver chemistry tests and serum alkaline phosphatase levels, are normal.

Which of the following is the most appropriate imaging study to perform next?

(A) Bone scan
(B) CT of the chest, abdomen, and pelvis
(C) PET scan
(D) No imaging studies

Item 119

A 67-year-old man is evaluated for fatigue and anemia of approximately 2 month's duration. He has no other symptoms and takes no medications.

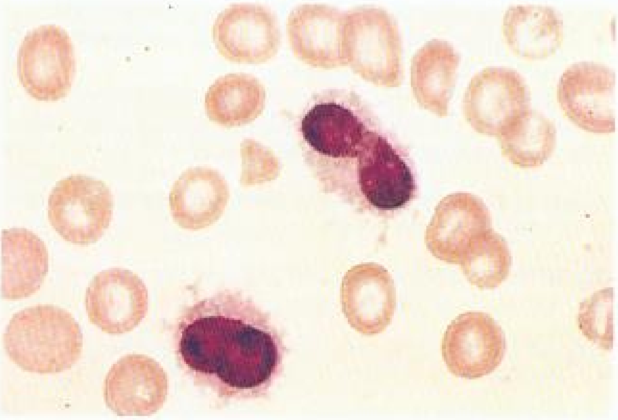
On physical examination, vital signs are normal. Petechiae are noted on the lower extremities, and there is conjunctival pallor. The spleen is palpable 4 cm below the costal margin. There is no lymphadenopathy and no hepatomegaly.

Laboratory studies:

Hemoglobin	10.4 g/dL (104 g/L)
Leukocyte count	2200/µL (2.2×10^9/L) with 63% lymphocytes, 34% segmented neutrophils, 3% monocytes
Platelet count	73,000/µL (73×10^9/L)

Flow cytometry of peripheral blood confirms kappa-restricted CD20+ B cells expressing CD11c, CD25, and CD103.

Peripheral blood smear is shown below:



Which of the following is the most appropriate treatment?

(A) Cladribine
(B) Interferon alfa
(C) Rituximab
(D) Splenectomy
(E) Observation

Item 120

A 43-year-old woman with a 7-year history of relapsing follicular lymphoma is evaluated for fevers, night sweats, and a rapidly enlarging right inguinal nodal mass. Her lymphoma has been treated on multiple occasions. Her current relapse began 1 year ago with diffuse lymphadenopathy; however, the onset of her symptoms and the right inguinal node enlargement is recent. She takes no medications.

On physical examination, all vital signs are normal. There is diffuse cervical and axillary lymphadenopathy bilaterally. The left inguinal node is enlarged to 2 cm; the right inguinal node is enlarged to 5 cm. There is no splenomegaly.

Laboratory results are significant only for a serum lactate dehydrogenase level of 6420 U/L.

Which of the following is the most appropriate management?

(A) Biopsy of the right inguinal lymph node
(B) Oral idelalisib
(C) Radiation therapy to the right inguinal node
(D) Repeat a course of chemotherapy

Item 121

A 58-year-old woman is evaluated for a palpable mass in her right groin. She takes no medications.

On physical examination, vital signs are normal. A hard, fixed, 3-cm lymph node is palpated in the right inguinal region. Careful inspection of the perianal skin, vulva, vagina, and cervix shows no findings. The remainder of the physical examination is normal.

A biopsy of the enlarged node demonstrates poorly differentiated carcinoma.

A contrast-enhanced CT scan of the chest, abdomen, and pelvis shows the enlarged inguinal node and no other abnormal findings.

Which of the following is the most appropriate diagnostic test to perform next?

(A) Anoscopy
(B) Bone scan
(C) Colonoscopy and upper endoscopy
(D) PET scan
(E) Serum CEA, CA-15-3, and CA-125

Item 122

A 53-year-old man is evaluated after a hemicolectomy for a well-differentiated adenocarcinoma of the descending colon. Final pathologic findings showed a well-differentiated

adenocarcinoma penetrating into the serosa (T3). Margins of resection were free of tumor. No lymphovascular or perineural invasion was seen. Twenty-seven lymph nodes were identified, and all were free of cancer. He takes no medications.

CT scans of the chest, abdomen, and pelvis showed no evidence of metastatic disease.

On physical examination, vital signs are normal. All other examination findings are normal.

The postoperative carcinoembryonic antigen (CEA) level is normal.

Which of the following is the most appropriate management?

(A) FOLFOX (parenteral 5-fluorouracil, leucovorin, and oxaliplatin)
(B) Oral capecitabine
(C) Radiation therapy
(D) No further treatment

Item 123

A 42-year-old woman is evaluated in the office after care in the emergency department for a new-onset seizure. She has a history of malignant melanoma resected 7 years ago. It had a 3.2-mm depth of invasion by Breslow microstaging. Her only medications are dexamethasone and levetiracetam.

On physical examination, vital signs are normal. There is no lymphadenopathy. Results of the neurologic examination are normal.

Brain MRI shows a 3.5-cm left frontal lesion consistent with metastatic disease. CT scan of the chest, abdomen, and pelvis is negative.

Which of the following is the most appropriate treatment?

(A) Ipilimumab and nivolumab
(B) Stereotactic radiosurgery to the brain lesion
(C) Surgical resection of the brain lesion
(D) Vemurafenib plus cobimetinib
(E) Whole brain radiation therapy

Item 124

A 56-year-old man is evaluated for a 3-month history of anorectal pain with bleeding. Medical history is significant for a long-standing HIV infection for which he is taking appropriate antiretroviral therapy. Viral load is undetectable, with a CD4 T-cell count of 650/µL.

On physical examination, vital signs are normal. The examination is notable for a hard, tender mass palpable in the anal canal. There is no inguinal lymphadenopathy.

Pelvic MRI shows a 3-cm mass in the anal canal and one enlarged 11-mm local-regional lymph node. Contrast-enhanced CT of chest and abdomen are normal.

Which of the following is the most appropriate treatment?

(A) Human papillomavirus (HPV) vaccination
(B) Pelvic radiation therapy
(C) Pelvic radiation therapy and concurrent chemotherapy
(D) Surgery

Item 125

A 65-year-old woman is evaluated during a follow-up visit for breast cancer management. She was diagnosed 6 years ago with stage IIB left breast cancer. Pathologic findings showed a 2.5-cm, grade 3 infiltrating ductal cancer that was estrogen receptor positive, progesterone receptor positive, and *HER2* negative. Three axillary lymph nodes were positive. She received adjuvant chemotherapy followed by 5 years of anastrozole. She takes no other medications. She has had no side effects from the anastrozole, and her bone density has remained normal.

On physical examination, vital signs are normal. There are well-healed incisions of the left breast and axilla. There are no breast masses.

Which of the following is the most appropriate management?

(A) Continue anastrozole; add tamoxifen for an additional 5 years
(B) Continue anastrozole alone for an additional 5 years
(C) Stop anastrozole
(D) Stop anastrozole; begin tamoxifen for an additional 5 years

Item 126

H

A 55-year-old man is hospitalized for a 6-month history of progressive shortness of breath and cough. He has lost 18.1 kg (40.0 lb). He has been experiencing generalized weakness and has become more inactive. Although he is independent with self-care, he no longer leaves home and spends most of his time in bed because he is too weak to do any household chores and becomes dyspneic with minimal exertion. His medical history is significant for diabetes mellitus, chronic kidney disease, and a 40-pack-year smoking history. He takes basal and prandial insulin and acetaminophen as needed for pain.

On physical examination, he is cachectic and frail. He is afebrile. Blood pressure is 105/60 mm Hg, pulse rate is 92/min, and respiration rate is 24/min. BMI is 20. Oxygen saturation is 93% breathing 2 L/min of oxygen through nasal cannula. Breath sounds are normal. Hepatomegaly is present on palpation.

Laboratory studies reveal a hemoglobin level of 9.2 g/dL (92 g/L), an albumin level of 2.9 g/dL (29 g/L), and a creatinine level of 2.1 mg/dL (185.6 µmol/L).

CT scan of the chest, abdomen, and pelvis shows a large right upper lung mass with associated hilar and mediastinal lymphadenopathy, multiple osseous metastatic lesions, and multiple hepatic lesions. Brain MRI shows no metastatic disease. Liver biopsy findings confirm metastatic adenocarcinoma.

Which of the following is the most appropriate management?

(A) Ablation of liver metastases
(B) Palliative care consultation
(C) Platinum-based chemotherapy
(D) Radiation to the right upper lobe

Item 127

A 60-year-old woman is evaluated in the emergency department for a 4-week history of worsening midthoracic back pain and a 1-week history of leg weakness and numbness in her lower abdomen and legs. She does not have any bowel or bladder incontinence. She has hormone receptor-positive, *HER2*-negative breast cancer that has metastasized to the spine, ribs, and pelvis. Current medications are letrozole and palbociclib. Until this recent deterioration, she has had excellent functional status.

On physical examination, vital signs are normal. She has tenderness to percussion on the T6 vertebra. There is a sensory level at the T8 vertebral body; bilateral, proximal, and distal lower-extremity weakness; hyperactive knee and ankle reflexes; and bilateral plantar extension responses. The remainder of the physical examination is normal.

MRI scans show a large lytic lesion in the T6 vertebral body, with an epidural mass causing compression of the spinal canal.

In addition to intravenous dexamethasone, which of the following is the most appropriate treatment?

(A) Elective radiation therapy
(B) Immediate decompressive surgery
(C) Palliative care only
(D) Urgent radiation therapy

Item 128

A 38-year-old woman seeks advice about decreasing her risk for ovarian cancer. Her mother and maternal grandmother were diagnosed with breast cancer at 40 years of age and 38 years of age, respectively. The patient tested positive for a deleterious *BRCA2* gene mutation and had bilateral prophylactic mastectomies done at age 35 years. She has a 2-year-old son and would like to have at least one other child. She is premenopausal and takes no medications. There is no family history of ovarian cancer.

On physical examination, vital signs are normal. Chest wall and gynecologic examination are normal. The remainder of the examination is normal.

Which of the following is the most appropriate recommendation?

(A) Annual pelvic examination and serum CA-125 screening studies
(B) Bilateral salpingo-oophorectomy by age 40 to 45 years
(C) Bilateral salpingo-oophorectomy now
(D) Long-term oral contraceptive use

Item 129

An 82-year-old woman is evaluated for persistent swellings in her neck, armpit, and groin. She describes no additional symptoms. She has long-standing systolic hypertension for which she takes chlorthalidone.

On physical examination, blood pressure is 154/82 mm Hg. The other vital signs are normal. There are bilateral enlargements of cervical, supraclavicular, axillary, and inguinal lymph nodes. The remainder of the examination is unremarkable.

Laboratory studies:

Hemoglobin	12.5 g/dL (125 g/L)
Leukocyte count	14,000/µL (14×10^9/L) with 66% lymphocytes, 23% segmented neutrophils, 6% monocytes, 1% eosinophils, and 4% bands
Platelet count	174,000/µL (174×10^9/L)

Smudge cells are noted on a peripheral blood smear.

Which of the following is the most appropriate diagnostic test to perform next?

(A) Bone marrow aspiration and biopsy
(B) CT scan of the chest, abdomen, and pelvis
(C) Cytogenetic studies on peripheral blood
(D) Flow cytometry on peripheral blood

Item 130

A 50-year-old woman is evaluated for a 4-month history of left flank pain, worsening despite NSAIDs and now requiring opioid analgesics, and 4-kg (8.8 lb) weight loss. Her medical history is otherwise unremarkable.

On physical examination, the skin and mucous membranes are pale. Vital signs are normal. There is left flank tenderness on palpation. The remainder of the physical examination is unremarkable.

Laboratory studies reveal a hemoglobin level of 10.1 g/dL (101 g/L).

CT scan of the chest, abdomen, and pelvis reveals a 10-cm left kidney mass with radiographic features suggesting renal cell carcinoma and a 1.2-cm single pulmonary nodule.

Which of the following is the most appropriate management?

(A) Left radical nephrectomy
(B) Nivolumab
(C) PET/CT scan
(D) Radiation to the kidney mass

Item 131

A 75-year-old man is evaluated for generalized lymphadenopathy. He is otherwise asymptomatic and takes no medications.

On physical examination, all vital signs are normal. There is generalized lymphadenopathy with nodes 1 cm to 2.5 cm in size in his cervical, supraclavicular, axillary, and inguinal areas bilaterally. There is no hepatosplenomegaly. The remainder of the physical examination is normal.

CT scan of the chest, abdomen, and pelvis shows mediastinal and retroperitoneal nodes that are 1.5 cm to 2.0 cm in size.

Laboratory results, including complete blood count, biochemistry profile, and lactate dehydrogenase level, are normal. Serum urate level is 9.5 mg/dL (0.56 mmol/L).

Left inguinal node biopsy shows follicular lymphoma.

Which of the following is the most appropriate management?

(A) Allopurinol
(B) Radiation therapy

(C) Rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP)
(D) Observation

Item 132

A 27-year-old woman seeks advice on breast cancer screening recommendations. Medical history is significant for stage IIB Hodgkin lymphoma diagnosed at age 19 years, treated with mantle and para-aortic radiation; there has been no evidence of recurrence. The patient is premenopausal and has no family history of breast or ovarian cancer. She takes no medications.

On physical examination, vital signs are normal. BMI is 28. There is a healed right supraclavicular incision from a previous lymph node biopsy. Breast examination findings are normal.

When should this patient begin breast cancer screening?

(A) At age 30 years
(B) At age 40 years
(C) At age 50 years
(D) Now

Item 133

A 32-year-old woman is evaluated after a recent diagnosis of stage IIB right breast cancer. She will be starting neoadjuvant chemotherapy with cyclophosphamide, doxorubicin, and paclitaxel, along with *HER2*-targeted therapy. She has a 1-year-old son and is interested in having more children.

Which of the following is the most appropriate management?

(A) Fertility specialist consultation after chemotherapy
(B) Fertility specialist consultation before chemotherapy
(C) Goserelin during chemotherapy
(D) Recommend against future childbearing

Item 134

A 69-year-old woman is evaluated for 6 months of progressive dysphagia. She has been previously healthy and takes no medications.

On physical examination, vital signs and the remainder of the physical examination are normal.

Results of upper endoscopy and biopsy indicate adenocarcinoma of the gastroesophageal junction. The staging evaluation reveals a T3 tumor on ultrasound and no evidence of distant metastatic disease. The patient's tumor is technically resectable.

Which of the following is the most reasonable treatment strategy?

(A) Adjuvant radiation therapy
(B) Neoadjuvant chemotherapy plus radiation therapy
(C) Palliative chemotherapy
(D) Surgery alone

Item 135

An 81-year-old man is evaluated for a 2-week history of gross hematuria. He is a former cigarette smoker, having quit 15 years ago. He is otherwise healthy and takes no medications.

On physical examination, vital signs and other findings are normal.

An ultrasound of the kidneys, ureters, and bladder is unremarkable.

Cystoscopy reveals a lesion along the bladder wall. Transurethral resection of the bladder tumor reveals high-grade, stage T1 transitional cell carcinoma.

Which of the following is the most appropriate treatment?

(A) Cisplatin-based systemic chemotherapy
(B) Intravesicular bacillus Calmette-Guérin
(C) Intravesicular bacillus Calmette-Guérin followed by partial cystectomy
(D) Partial cystectomy

Item 136

A 70-year-old man is seen for treatment recommendations for newly diagnosed colon cancer metastatic to the liver. He also has a long-standing history of diabetes and heart failure for which he takes metformin and lisinopril. The patient spends most of the day on the couch and is unable to walk across the room, dress himself, or do other basic activities of daily living without becoming dyspneic and fatigued. His appetite is poor.

On physical examination, vital signs are normal. The patient is thin and has obvious muscle wasting. The liver edge is palpable. The examination is otherwise normal.

The patient has read about an ongoing clinical trial of a chemotherapy regimen for metastatic colon cancer that resulted in a response rate of 40% and a progression-free survival of 11 months.

Which of the following would this patient be likely to experience with the treatment given relative to the results reported in this clinical trial?

(A) Comparable efficacy and comparable toxicity
(B) Comparable efficacy but increased toxicity
(C) Decreased efficacy and comparable toxicity
(D) Decreased efficacy and increased toxicity

Item 137

A 62-year-old woman is evaluated for recurrent breast cancer with bone and liver metastases. She was diagnosed with stage IA estrogen receptor–positive, progesterone receptor–positive, *HER2*-negative right breast cancer 8 years ago. She underwent lumpectomy and sentinel lymph-node biopsy and primary breast radiation, and completed 5 years of anastrozole therapy 2 years ago. She presented with right hip pain, with lesions on a bone scan consistent with metastases. Biopsy of a bone lesion shows metastatic adenocarcinoma that is estrogen receptor positive, progesterone receptor positive, and *HER2* negative, consistent with metastatic breast cancer. She takes no medications.

On physical examination, vital signs are normal. Healed incisions of the right breast and axilla are present. Tenderness to palpation of the right lateral hip is noted. The remainder of the examination is normal.

Which of the following is the most appropriate treatment?

(A) Exemestane
(B) Letrozole plus palbociclib
(C) Raloxifene
(D) Tamoxifen

Item 138

A 65-year-old woman is evaluated 3 weeks postoperatively following right hemicolectomy for colon cancer. Pathology of the surgical specimen revealed a 3-cm adenocarcinoma invading into but not through the colonic wall. Four of 17 local-regional lymph nodes examined contained metastatic cancer. All margins of resection were free of tumor. Contrast-enhanced CT scans of the chest, abdomen, and pelvis were unremarkable. She takes no medications.

On physical examination, vital signs are normal. Surgical incisions are fully healed. The remainder of the examination is normal.

Carcinoembryonic antigen (CEA) is 1.7 µg/L (normal is less than 5.0 µg/L).

Which of the following is the most appropriate treatment?

(A) 5-Fluorouracil, leucovorin, and oxaliplatin (FOLFOX)
(B) Radiation therapy
(C) Radiation therapy plus FOLFOX
(D) No further therapy

Item 139

A 78-year-old woman is evaluated for increasing fatigue during the past 2 weeks. She has a 7-year history of chronic lymphocytic leukemia previously treated with bendamustine and rituximab with excellent results. One month ago, after presenting with persistent night sweats, she was diagnosed with relapsed chronic lymphocytic leukemia based on lymphocytosis on a complete blood count and results of peripheral blood flow cytometry. Her hemoglobin level at that time was 12.1 g/dL (121 g/L). She was started on oral ibrutinib.

On physical examination, vital signs are normal. Scleral icterus is noted. The spleen is palpable 3 cm below the costal margin. There is no peripheral lymphadenopathy.

Laboratory studies:	
Hemoglobin	7.4 g/dL (74 g/L)
Leukocyte count	22,000/µL (22×10^9/L) with 79% lymphocytes
Platelet count	122,000/µL (122×10^9/L)
Reticulocyte count	11% of erythrocytes

Which of the following is the most appropriate management?

(A) Anti-parvovirus IgM antibody assay
(B) Bone marrow aspiration and biopsy
(C) Direct antiglobulin (Coombs) test
(D) Discontinue ibrutinib
(E) Splenectomy

Item 140

A 65-year-old man is evaluated for cough and shortness of breath with exertion for the past 2 months, accompanied by 10 pounds of weight loss. He takes no medications.

On physical examination, vital signs are normal. Examination reveals decreased breath sounds in the lower right lung field.

Chest radiograph reveals right lower lobe opacity, and CT scan of the chest reveals a large right lower lobe mass, liver masses, and a right adrenal mass. These findings are consistent with metastases.

A biopsy of a right lung mass reveals adenocarcinoma. Testing for driver mutations is negative.

Which of the following is the most appropriate diagnostic or screening test to perform next?

(A) Liver biopsy
(B) Programmed cell death ligand 1 expression
(C) PET/CT scan
(D) Pulmonary function testing

Item 141

A 29-year-old man is evaluated for a 2-month history of night sweats, fevers, a sense of abdominal fullness, and fatigue. He takes no medications.

On physical examination, vital signs are normal. The abdomen is distended with diffuse tenderness without rebound or guarding. Bowel sounds are normal. Other examination findings are normal.

Laboratory results, including complete blood count and serum bilirubin, creatinine, alkaline phosphatase, aminotransferase, α-fetoprotein, and β-human chorionic gonadotropin levels, are normal. A contrast-enhanced CT scan of the chest, abdomen, and pelvis shows bulky retroperitoneal lymphadenopathy (the largest mass is 10 cm in diameter) with somewhat smaller but still enlarged mediastinal lymphadenopathy. A biopsy specimen of the most accessible enlarged node shows poorly differentiated carcinoma. A testicular ultrasound is unremarkable.

Which of the following is the most appropriate treatment?

(A) A gastrointestinal cancer chemotherapy regimen
(B) A germ cell chemotherapy regimen
(C) Radiation therapy to the lymphadenopathy
(D) Surgical debulking of the lymphadenopathy

Item 142

A 71-year-old man has a follow-up evaluation. He was recently diagnosed with metastatic melanoma characterized by a *BRAF* V600E mutation for which he was treated with a *BRAF* inhibitor. After treatment, he was found to

have major tumor regression at all disease sites. He takes no medications.

On physical examination, vital signs and other findings are normal.

Which of the following best describes the type of tumor marker present in this patient?

(A) Exclusionary predictive marker
(B) Exclusionary prognostic marker
(C) Inclusionary predictive marker
(D) Inclusionary prognostic marker

Item 143

A 26-year-old woman is interested in genetic testing for *BRCA1* and *BRCA2* gene mutations based on her family history. Her mother was diagnosed with triple-negative breast cancer at age 53 years and died at age 55 years. Her maternal aunt was diagnosed with ovarian cancer at age 48 years and is still alive but is not interested in genetic testing. Her maternal and paternal relatives are of Ashkenazi Jewish descent. The patient is premenopausal and takes no medications.

On physical examination, vital signs are normal. Breast and gynecologic examination findings are normal.

Which of the following is the most appropriate management?

(A) Recommend a direct-to-consumer genetic test
(B) Recommend against genetic testing
(C) Recommend genetic testing for the three *BRCA1* and *BRCA2* mutations most common in patients of Ashkenazi Jewish ethnicity
(D) Refer to a genetic counselor

Item 144

A 28-year-old man is evaluated for a 1-month history of right testicular swelling. His medical history is unremarkable, and he takes no medications.

On physical examination, vital signs are normal. Palpation reveals an enlarged right testicle that is firm and mildly tender.

Scrotal ultrasonography shows a 5-cm right testicular mass.

Which of the following is the most appropriate management?

(A) Measurement of β-human chorionic gonadotropin and α-fetoprotein levels
(B) Needle biopsy
(C) PET-CT scan
(D) Radical inguinal orchiectomy

Item 145

A 40-year-old woman is evaluated in the emergency department for a 2-week history of worsening headache and imbalance. She has metastatic hormone receptor–negative, *HER2*-positive breast cancer with bone metastases and is being treated with paclitaxel, trastuzumab, and pertuzumab with good control of her systemic disease.

On physical examination, the patient is afebrile. Blood pressure is 168/88 mm Hg, pulse rate is 104/min, and respiration rate is normal. She is awake and alert. She has past-pointing on finger-to-nose testing and truncal ataxia. The remainder of the examination is normal.

Head CT scan without contrast in the emergency department shows a 1.5-cm mass in the left cerebellum with surrounding edema and a 1-cm left frontal mass with edema. No midline shift is present.

Which of the following is the most appropriate initial management?

(A) Dexamethasone
(B) Levetiracetam
(C) Mannitol
(D) Urgent neurosurgery
(E) Whole brain radiation

Item 146

A 42-year-old woman is evaluated during a follow-up visit for stage IIA cervical squamous cell cancer. She has completed therapy with pelvic external beam radiation and concomitant weekly cisplatin chemotherapy, with cervical brachytherapy added during the fourth week of therapy. She has had an excellent response to treatment. She is otherwise well and takes no medications.

On physical examination, vital signs are normal. Pelvic examination reveals no evidence of tumor, and the remainder of the examination is normal.

Which of the following is the most appropriate posttreatment surveillance for this patient?

(A) CT of the pelvis every 6 months
(B) Complete blood count, serum creatinine, and liver chemistry tests every 3 months
(C) History, physical, and gynecologic examination every 3 months
(D) Pelvic ultrasonography every 6 months

Item 147

A 59-year-old woman is evaluated for a 2-month history of shortness of breath and cough. She has a 55-pack-year smoking history. She takes no medications.

On physical examination, vital signs are normal. BMI is 23. Oxygen saturation is normal. Pulmonary examination reveals decreased breath sounds and crackles in the right base posteriorly. Her performance status is good.

CT scan of the chest shows a large, centrally located right lower lobe mass, evidence of mediastinal invasion, bulky mediastinal lymph nodes, and hilar lymphadenopathy.

Bronchoscopy with biopsy of an endobronchial lesion confirms non–small cell lung cancer.

Brain MRI, CT scans of the abdomen and pelvis, and bone scan show no metastatic disease.

Which of the following is the most appropriate management?

(A) Chemotherapy
(B) Combined chemotherapy and radiation
(C) Pembrolizumab
(D) Radiation
(E) Surgical resection of the right lower lobe mass

Item 148

A 48-year-old man is evaluated for increasing dysphagia during the past 2 months. He reports that he first noticed difficulty swallowing solid foods, such as steak, but that this symptom has advanced to occasional difficulty with liquids. He is, however, maintaining adequate hydration and nutrition. He is not currently taking medications.

On physical examination, vital signs are normal. There is a 1.5-cm left supraclavicular node and a liver edge that is palpable below the right costal margin.

A CT scan of the chest and abdomen shows a mass in the lower third of the esophagus just proximal to the gastroesophageal junction. The liver has multiple hypodense lesions consistent with metastases. Endoscopic evaluation reveals a near-obstructing lesion in the distal esophagus. Biopsy shows adenocarcinoma.

Which of the following is the most appropriate diagnostic test to perform next?

(A) Assess tumor tissue for *BRAF* mutation status
(B) Assess tumor tissue for *HER2* amplification
(C) Assess tumor tissue for *RAS* mutation status
(D) Obtain PET/CT scan
(E) Obtain upper gastrointestinal imaging (barium swallow)

Item 149

A 65-year-old man is evaluated after a recent diagnosis of prostate cancer with multiple painful metastases to the lumbar spine. He was treated initially with both bicalutamide and leuprolide for 4 weeks, after which he continued on leuprolide alone with excellent symptomatic relief of bone pain. He started treatment 2 months ago.

On physical examination, vital signs and the remainder of the examination are normal.

Laboratory studies reveal a serum prostate-specific antigen level of 20 ng/mL (20 µg/L), down from 122 ng/mL (122 µg/L) at the time of diagnosis 2 months ago. Complete blood count and liver chemistry test results are normal.

Which of the following is the most appropriate management?

(A) Continue leuprolide alone
(B) Leuprolide plus docetaxel
(C) Radiation to the lumbar spine
(D) Stop leuprolide and start docetaxel

Answers and Critiques

Hematology Answers

Item 1 Answer: B

Educational Objective: Evaluate HIV as a cause of immune thrombocytopenic purpura.

Testing should be performed for HIV. Immune thrombocytopenic purpura (ITP) is caused by autoantibodies directed against glycoproteins on the platelet surface. ITP is diagnosed when thrombocytopenia is found with no alternate cause. ITP can be idiopathic, triggered by medications, or associated with other disorders, such as systemic lupus erythematosus (SLE), chronic lymphocytic leukemia, lymphoma, HIV, hepatitis C, or *Helicobacter pylori* infection. Unless additional cytopenias are discovered or other findings suggest an alternate diagnosis, a bone marrow biopsy in these patients is not necessary. ITP is not uncommon among patients with HIV infection, even early in the disease and in the absence of any other symptoms of immunosuppression or opportunistic infection. ITP is also associated with chronic hepatitis C that may also be asymptomatic. This patient's hepatitis C test was negative, so no further evaluation is needed; however, routine testing for HIV is recommended before starting any immunosuppressive treatment.

Unlike autoimmune hemolytic anemia, no diagnostic test is available for immune-mediated thrombocytopenia. Antiplatelet antibody testing is not recommended because of low sensitivity and specificity, and this test should not be performed in the evaluation of thrombocytopenia.

ITP may be associated with other autoimmune diseases, such as Hashimoto thyroiditis, or with SLE. This patient lacks any history of venous thromboembolism or fetal loss that would suggest an underlying anticardiolipin antibody syndrome and has no other clinical features to suggest SLE; testing for the lupus anticoagulant is unnecessary.

Although vitamin B_{12} and folate deficiency can result in thrombocytopenia, the patient's mean corpuscular volume is normal, so no evidence indicates cobalamin deficiency.

KEY POINT

- Immune thrombocytopenic purpura can be idiopathic, triggered by medications, or associated with other disorders, such as systemic lupus erythematosus, chronic lymphocytic leukemia, lymphoma, HIV, hepatitis C, or *Helicobacter pylori* infection.

Bibliography

Neunert C, Lim W, Crowther M, Cohen A, Solberg L Jr, Crowther MA; American Society of Hematology. The American Society of Hematology 2011 evidence-based practice guideline for immune thrombocytopenia. Blood. 2011;117:4190-207. [PMID: 21325604] doi:10.1182/blood-2010-08-302984

Item 2 Answer: D

Educational Objective: Evaluate for acquired platelet dysfunction.

Patients who present with symptoms of mucocutaneous bleeding and a normal platelet count should be evaluated for acquired platelet dysfunction using the Platelet Function Analyzer-100 (PFA-100). Selective serotonin reuptake inhibitors (SSRIs) such as citalopram decrease serotonin uptake from platelets and have a reported association with gastrointestinal bleeding, especially in older adults. Herbal supplements like ginkgo biloba have been reported to increase platelet dysfunction in patients taking antiplatelet agents and may interact with this patient's SSRI. The PFA-100 provides a rapid screening test of platelet function and has replaced the bleeding time test. Anticoagulated whole blood is passed through small membranes coated with collagen and epinephrine or collagen and adenosine diphosphate. Platelets adhere to the membrane and close a small aperture. A prolonged closure time implies abnormal platelet activity.

Patients with hypofibrinogenemia may have significant bleeding, but it is uncommon as an isolated finding and is much more likely to be seen in patients with liver disease or disseminated intravascular coagulation who also have abnormalities of the prothrombin time (PT), activated partial thromboplastin time (aPTT), and platelet count. Furthermore, the normal thrombin time excludes hypofibrinogenemia.

Rarely, older patients without a personal or family history of bleeding may present with acute new-onset bleeding caused by acquired hemophilia. Such bleeding can be mucocutaneous or intramuscular. The PT is normal, but the aPTT is significantly prolonged, and a 1:1 mixing study of the patient's plasma with normal plasma is unsuccessful at completely correcting the aPTT. This patient's PT and aPTT are normal, and mixing studies will not provide further information.

Although a peripheral blood smear is the first step in evaluating a patient with abnormal platelet counts, all of this patient's cell counts are normal, and a peripheral blood smear review will not help determine the cause of his bleeding.

Serum protein electrophoresis will detect paraprotein, which might cause bleeding by interfering with coagulation factors and prolonging the prothrombin or thrombin times. Because all of this patient's coagulation parameters are normal, looking for a paraprotein is unnecessary at this time.

KEY POINT

- Patients who present with symptoms of mucocutaneous bleeding and a normal platelet count should be evaluated for acquired platelet dysfunction using the Platelet Function Analyzer-100.

Bibliography

Konkle BA. Acquired disorders of platelet function. Hematology Am Soc Hematol Educ Program. 2011;2011:391-6. [PMID: 22160063] doi:10.1182/asheducation-2011.1.391

Item 3 Answer: A

Educational Objective: Treat pulmonary embolism with non–vitamin K antagonist oral anticoagulant monotherapy.

This patient should be treated with apixaban. Patients with pulmonary embolism (PE) were previously hospitalized for anticoagulant therapy. However, admission rates are decreasing because of the recognition that appropriate patients can be safely managed in the outpatient setting. The Outpatient Treatment for Pulmonary Embolism (OTPE) trial was an open-label, randomized, noninferiority trial. A total of 344 patients with acute, symptomatic, objectively confirmed PE were randomly assigned to inpatient or outpatient management. Patients were classified as low risk or high risk of death using the Pulmonary Embolism Severity Index (PESI). Among patients with low-risk PESI scores who were randomly assigned to outpatient or inpatient care, recurrent venous thromboembolism (VTE) occurred within 90 days in 1 of 171 (0.6%) outpatients and zero inpatients, a finding that met the criteria for noninferiority. The PESI stratifies patients into five risk categories for all-cause 30-day mortality based on 11 clinical **parameters**.

TABLE. Pulmonary Embolism Severity Index

Clinical Parameter	Score
Age (in years)	(enter age)
Male sex	10
Current cancer	30
Chronic heart failure	10
Chronic lung disease	10
Pulse rate >110/min	20
Systolic BP <100 mm Hg	30
Respiration rate >30/min	20
Temperature <36 °C (96.8 °F)	20
Disorientation, lethargy, stupor, or coma	60
Oxygen saturation <90%	20

In the appropriate clinical setting, patients with a PESI score less than 65 are very low risk for 30-day mortality (0%), and those with a score less than 85 are low risk for 30-day mortality (1%); patients in these categories can be considered for outpatient management. This patient's PESI score is 59. Therefore, outpatient management can be considered, but the appropriate agent must be selected. The 2016 American College of Chest Physicians guidelines recommend non–vitamin K antagonist oral anticoagulants as first line for patients without cancer with VTE. Dabigatran and edoxaban require bridging with parenteral anticoagulation, whereas apixaban and rivaroxaban can be used as monotherapy in the treatment of VTE.

Long-term low-molecular-weight heparin is only considered first-line treatment in patients with malignancy. This patient does not have cancer; therefore, apixaban is a more appropriate choice.

KEY POINT

- Patients with a Pulmonary Embolism Severity Index score of less than 65 are at low risk of death and may be managed in the outpatient setting with a non-vitamin K antagonist oral anticoagulant, such as apixaban or rivaroxaban.

Bibliography

Aujesky D, Roy PM, Verschuren F, Righini M, Osterwalder J, Egloff M, et al. Outpatient versus inpatient treatment for patients with acute pulmonary embolism: an international, open-label, randomised, non-inferiority trial. Lancet. 2011;378:41-8. [PMID: 21703676] doi:10.1016/S0140-6736(11)60824-6

Item 4 Answer: D

Educational Objective: Manage inflammatory anemia.

No treatment for anemia is necessary at this time. The patient has findings typical of inflammatory anemia. Inflammatory anemia occurs in response to the inflammatory cytokine IL-6 that leads to hepatic synthesis of hepcidin, which in turn causes proteolysis of the membrane protein ferroportin. As a result, iron absorption from the gut is diminished, as is iron release from macrophages. Patients with chronic infections, such as tuberculosis or osteomyelitis; patients with malignancy; or patients with other chronic inflammatory conditions, such as rheumatologic diseases, can develop inflammatory anemia. Inflammatory anemia is characterized by a hemoglobin level of approximately 10 g/dL (100 g/L) with normocytic or slightly microcytic indices. Characteristically, the serum iron level is low, and the total iron-binding capacity (TIBC) is often low, as well. The serum ferritin level is elevated. In contrast, patients with iron deficiency have a low serum ferritin level and an elevated TIBC. Patients with inflammatory anemia do not require specific therapy.

The use of erythropoiesis-stimulating agents, such as erythropoietin or longer-acting darbepoetin, should not be used to treat inflammatory anemia in most patients with cancer because of the lack of benefit and accompanying risks, including hypertension, stroke, and tumor progression. Patients with inflammatory anemia do not respond to oral or parenteral iron supplementation.

KEY POINT

- Inflammatory anemia is usually mild to moderate in severity, characterized by low serum iron levels and total iron-binding capacity and elevated serum ferritin level, and usually requires no specific therapy.

Bibliography

Wang CY, Babitt JL. Hepcidin regulation in the anemia of inflammation. Curr Opin Hematol. 2016:23:189-97. [PMID: 26886082] doi:10.1097/MOH.0000000000000236

Item 5 Answer: D

Educational Objective: Treat a patient with low-risk myelodysplastic syndrome.

This patient with transfusion dependent myelodysplastic syndrome (MDS) should be treated with lenalidomide. Treatment of MDS has two goals. The first goal is to relieve transfusion dependence; the second is to prevent transformation to acute myeloid leukemia (AML). He has low risk MDS with chromosome 5q deletion (−5q), and lenalidomide will help with his transfusion-dependent anemia. Patients with infrequent transfusion requirements can be supported with periodic transfusions alone, but in patients requiring frequent transfusions, supplemental treatments to help decrease transfusion requirements should be used to improve quality of life and decrease transfusion associated iron overload and alloimmunization. In more than 50% of patients with −5q MDS, treatment with low dose lenalidomide has been shown to achieve transfusion independence and is recommended as first-line therapy. Other second-line treatments for low-risk MDS with −5q include recombinant erythropoietin and the hypomethylating agents azacitidine and decitabine. Hypomethylating agents can reduce transfusion requirements and delay transformation to AML. However, both also worsen blood counts initially and may take up to 6 months to show an effect. Finally, this patient is not at high risk for AML transformation.

Allogeneic hematopoietic stem cell transplantation is usually performed in young patients with high risk MDS. In patients with low risk disease, early transplantation is not recommended and can be associated with worse survival.

Immunosuppression with antithymocyte globulin and cyclosporine, similar to that used for aplastic anemia, has been shown to decrease transfusion requirements in younger patients (age <65 years) and those with hypoplastic bone marrow. However, in this 74-year-old patient with −5q mutation, immunosuppression is not effective and has significant adverse effects.

Imatinib is a tyrosine kinase inhibitor that is effective in treating patients with chronic myeloid leukemia and dysregulated tyrosine kinase as a result of the *BCR ABL* fusion gene. It is not effective in MDS.

KEY POINT

- In patients with myelodysplastic syndrome requiring frequent transfusions, supplemental treatments to help decrease transfusion requirements, such as lenalidomide, should be used to improve quality of life and decrease transfusion associated iron overload and alloimmunization.

Bibliography

Giagounidis A, Mufti GJ, Mittelman M, Sanz G, Platzbecker U, Muus P, et al. Outcomes in RBC transfusion-dependent patients with low-/intermediate-1-risk myelodysplastic syndromes with isolated deletion 5q treated with lenalidomide: a subset analysis from the MDS-004 study. Eur J Haematol. 2014;93:429-38. [PMID: 24813620] doi:10.1111/ejh.12380

Item 6 Answer: A

Educational Objective: Evaluate eosinophilia.

This patient should be evaluated for hypereosinophilic syndrome (HES), beginning with an evaluation for helminth infection. He has sustained moderate eosinophilia and end-organ damage (restrictive cardiomyopathy), which are characteristic of HES. Organ involvement is more common when the peripheral eosinophil count is greater than 1500/µL (1.5×10^9/L) as in this patient. The numerous neoplastic and nonneoplastic causes of eosinophilia can be recalled using the mnemonic CHINA (Collagen vascular disease, Helminthic infection, Idiopathic, Neoplasia, Allergy/Atopy/Asthma). Helminth infection is a common cause of eosinophilia and should be evaluated and ruled out in all patients. Eosinophilia of any cause can be associated with end organ damage, and evaluation for organ involvement is indicated. Organs commonly involved are the skin (eczema, erythroderma, urticaria, and angioedema), lungs (parenchymal infiltrates, pleural effusion, lymphadenopathy, and pulmonary emboli), gastrointestinal tract (eosinophilic gastritis, enteritis, colitis, chronic active hepatitis, focal hepatic lesions, eosinophilic cholangitis, Budd-Chiari syndrome), and heart (mitral or tricuspid regurgitation, cardiomegaly, restrictive cardiomyopathy).

Fat pad biopsy is performed during evaluation for systemic amyloidosis. Amyloidosis involving the heart can cause restrictive heart disease. However, in this patient with sustained elevation of the eosinophil count, HES is more likely the underlying condition.

Prednisone initiation in clinically stable patients with HES without evaluation for the underlying cause of the illness is not recommended because patients with infectious causes of eosinophilia (such as *Strongyloides*) can experience significant symptom flare. In unstable patients, empiric treatment with glucocorticoids must be initiated emergently with ivermectin if risk factors for exposure to strongyloides are present. Patients with negative infectious evaluations should be evaluated for allergic, immunologic, and neoplastic causes of hypereosinophilia, including myeloproliferative disorders, lymphomas, and solid tumors.

Although repeat testing of the eosinophil count is recommended in all patients, at least 1 month apart to confirm sustained elevation, this patient already has two measurements showing sustained hypereosinophilia as well as symptoms of cardiac involvement. Therefore, repeat testing of the eosinophil count in 3 months is not appropriate.

KEY POINT

- Hypereosinophilic syndrome is characterized by moderate eosinophilia and end-organ damage commonly involving the skin, lungs, gastrointestinal tract, and heart; secondary causes of eosinophilia should be excluded.

Bibliography

Klion AD. How I treat hypereosinophilic syndromes. Blood. 2015;126:1069-77. [PMID: 25964669] doi:10.1182/blood-2014-11-551614

Item 7 Answer: D

Educational Objective: Manage hereditary spherocytosis during an acute aplastic crisis.

The most appropriate management for this patient is clinical observation. He has hereditary spherocytosis (HS) characterized by a mild lifelong anemia in association with symptomatic cholelithiasis at an early age. The presence of spherocytes is supported by an elevated mean corpuscular hemoglobin concentration frequently seen in this disorder. HS is caused by mutations in several scaffolding proteins that make these cells less distensible and more susceptible to osmotic stress and hemolysis. Patients with this disorder may have mild anemia, an elevated reticulocyte response, and few or no symptoms. The development of pigmented gallstones resulting from excess bilirubin production may result in symptomatic cholelithiasis. Symptoms of anemia may arise when the bone marrow is suppressed, most commonly by an acute infection. In this situation, the reticulocyte count falls, and the patient rapidly develops symptomatic anemia. Parvovirus is most classically linked with bone marrow suppression, but many other viral and infectious agents can have a similar effect. The bone marrow suppression following acute infections is self-limited, but some patients may become symptomatic to the point of requiring blood transfusion.

A subset of patients with HS has chronic hemolytic anemia that is much more severe. These patients will benefit from splenectomy. The spleen is the major site of erythrocyte destruction; after splenectomy, the membrane defect remains unchanged, but erythrocyte survival will be significantly prolonged. Splenectomy is not needed in managing an acute, self-limited aplastic crisis.

Prednisone would be indicated to treat warm antibody autoimmune hemolytic anemia (WAIHA). Spherocytes are also seen in patients with WAIHA, but the direct antiglobulin test result would be positive. WAIHA would not explain the lifelong anemia in this patient.

Erythropoietin deficiency plays no role in the pathogenesis of HS. Endogenous erythropoietin levels are apt to be markedly elevated in this patient, and no evidence indicates that therapy with exogenous erythropoiesis-stimulating agents has any beneficial role.

KEY POINT

- Acute viral infections may trigger a transient aplastic crisis in patients with hereditary spherocytosis.

Bibliography

Perrotta S, Gallagher PG, Mohandas N. Hereditary spherocytosis. Lancet. 2008;372:1411-26. [PMID: 18940465] doi:10.1016/S0140-6736(08)61588-3

Item 8 Answer: B

H

Educational Objective: Treat a patient with malignancy-associated pulmonary embolism.

The most appropriate treatment for this patient is enoxaparin. Approximately 20% of all venous thromboembolisms (VTEs) occur in patients with cancer. The risk for VTE is determined by general risk factors (age, obesity, personal or family history of VTE, coexisting medical conditions, inherited and acquired thrombophilias) and cancer-specific risk factors (cancer type, cancer stage, chemotherapy type, hormonal therapy, surgery, central venous catheters). Active cancer or cancer actively being treated with chemotherapy or radiation therapy increases the VTE risk approximately five- to sixfold, but a history of cancer, or cancer that has undergone curative therapy without evidence of residual disease, does not. He has been diagnosed with metastatic colon cancer and developed a pulmonary embolism. In patients with active malignancy, studies such as the CLOT trial have shown that low-molecular-weight heparin (LMWH), such as enoxaparin, is the anticoagulant of choice. In the CLOT trial, LMWH was compared with warfarin in patients with malignancy and thrombosis. LMWH was associated with a statistically significant reduction in the rate of recurrent VTE, making it a preferable choice to warfarin. Extended therapy with LMWH is recommended while the cancer remains active. Extended anticoagulation should be weighed against the risk of bleeding, cost of therapy, quality of life, life expectancy, and patient preference. The decision to continue extended therapy requires frequent reassessments of risk and benefit.

Efficacy and safety data are insufficient to recommend either fondaparinux or the non-vitamin K antagonist oral anticoagulants (NOACs) for the treatment of malignancy-associated VTE. Although clinical trials are under way to assess the role of NOACs in patients with cancer, guidelines do not exist at this time, and their use has not been standardized in these patients. Few patients with cancer were included in the original clinical trials of these anticoagulants, and LMWH is still considered standard of care for VTE in these patients.

KEY POINT

- Low-molecular-weight heparin is the anticoagulant of choice for patients with active cancer and a venous thromboembolism.

Bibliography

Lee AY, Levine MN, Baker RI, Bowden C, Kakkar AK, Prins M, et al; Randomized Comparison of Low-Molecular-Weight Heparin versus Oral Anticoagulant Therapy for the Prevention of Recurrent Venous Thromboembolism in Patients with Cancer (CLOT) Investigators.

Low-molecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. N Engl J Med. 2003;349:146-53. [PMID: 12853587]

Item 9 Answer: E

Educational Objective: Diagnose pulmonary embolism in a pregnant patient.

A ventilation-perfusion (V/Q) lung scan should be performed next. Pregnant patients with pulmonary embolism (PE) present with symptoms (like dyspnea) that may overlap with symptoms of pregnancy, so a high index of suspicion is needed. New-onset cough is the presenting finding in 24% of pregnant women with PE. Doppler studies may be negative if the primary clot is in the pelvic veins; if results are negative, evaluation for venous thromboembolism requires imaging of the lung. V/Q scanning should be the initial study in pregnant patients. If the V/Q scan is normal, PE can be reliably excluded. If the V/Q scan is strongly positive, showing perfusion defects without matched ventilation abnormalities in this patient with no asthma or underlying lung disease, PE can be reliably diagnosed and therapy initiated.

CT angiography, the gold standard in the diagnosis of PE in most patients, should not be the initial study in pregnant patients because of radiation exposure to both the mother and the fetus. CT angiography should be reserved for instances when the V/Q scan is equivocal.

D-dimer assays are used to guide venous thromboembolism diagnosis in nonpregnant patients with low probability of disease, but D-dimer levels are elevated during pregnancy, with assays only 73% sensitive and 15% specific in this population. Additionally, D-dimer level should be determined only in patients with a low theoretical suspicion for PE. This patient has a moderate or high presumed likelihood.

Magnetic resonance pulmonary angiography has not been evaluated in pregnant patients, but in nonpregnant patients, the sensitivity for PE is only 85% (although the specificity is 98%). In addition, the long-term effects of gadolinium on the fetus are unknown.

Pulmonary function testing would be helpful to rule out bronchospastic disease as a cause for the patient's cough, but it should be done only after the more life-threatening diagnosis of PE is ruled out.

KEY POINT

- In the presence of normal Doppler studies of the lower extremities, ventilation-perfusion lung scanning is the initial lung imaging study to evaluate for pulmonary embolism in pregnant patients; D-dimer testing has no diagnostic role.

Bibliography

Leung AN, Bull TM, Jaeschke R, Lockwood CJ, Boiselle PM, Hurwitz LM, et al; ATS/STR Committee on Pulmonary Embolism in Pregnancy. An official American Thoracic Society/Society of Thoracic Radiology clinical practice guideline: evaluation of suspected pulmonary embolism in pregnancy. Am J Respir Crit Care Med. 2011;184:1200-8. [PMID: 22086989] doi:10.1164/rccm.201108-1575ST

Item 10 Answer: B

Educational Objective: Evaluate preoperative anemia.

Iron studies should be performed next. Preoperative anemia is associated with increased perioperative mortality in patients with cardiovascular disease; it is also a significant predictor for perioperative blood transfusion, which itself is associated with postoperative morbidity. The common causes for preoperative anemia are iron deficiency, vitamin B_{12} deficiency, chronic inflammatory disease, and chronic kidney disease. The hemoglobin level should be measured in the setting of signs or symptoms of anemia or surgery with a large expected blood loss at least 4 weeks before the surgery date. If anemia is identified, laboratory testing should begin with an assessment of iron status. Transferrin saturation less than 15% (or serum ferritin level less than 15 ng/mL [15 μg/L]) is consistent with iron deficiency anemia and should be treated with oral iron. If the response to oral iron is suboptimal because of patient adherence and surgical scheduling, intravenous iron should be used. Iron deficiency in this patient could be attributable to menstrual blood loss, occult gastrointestinal blood loss from NSAID-induced gastritis, or colon cancer. Evaluation and correction of the cause of iron deficiency anemia should take place before elective surgery.

Hemoglobin electrophoresis is useful to detect genetic hemoglobinopathies such as sickle cell disease or thalassemia, which are associated with lifelong anemia unlikely to present for the first time at this patient's age. These conditions could be suspected with examination of a peripheral blood smear.

Vitamin B_{12} deficiency is less common than iron deficiency in most patients scheduled to undergo orthopedic surgery, and it is typically associated with macrocytic anemia, which is not present in this patient.

Ignoring this patient's anemia is not appropriate, considering the increased risk of perioperative allogeneic transfusion, which carries its own risks and is avoidable if the anemia is treated beforehand.

KEY POINT

- Patients scheduled for elective surgery who have anemia should be evaluated for iron deficiency; preoperative management of iron deficiency anemia includes oral iron replacement and evaluation to determine the source of blood loss.

Bibliography

Goodnough LT, Maniatis A, Earnshaw P, Benoni G, Beris P, Bisbe E, et al. Detection, evaluation, and management of preoperative anaemia in the elective orthopaedic surgical patient: NATA guidelines. Br J Anaesth. 2011;106:13-22. [PMID: 21148637] doi:10.1093/bja/aeq361

Item 11 Answer: B

H

Educational Objective: Reverse warfarin anticoagulation with four-factor prothrombin complex concentrate.

This patient should be given four-factor prothrombin complex concentrate (4F-PCC). Patients who receive anticoagulation

H CONT.

with a vitamin K antagonist have an increased risk for major gastrointestinal and central nervous system bleeding and an increased risk for periprocedural bleeding. Although vitamin K alone can be effective in reversing the effect of warfarin, its hemostatic effect can take several hours, and, in urgent situations, simultaneous replacement of the vitamin K-dependent coagulation factors is necessary. 4F-PCC contains factors II, VII, IX, and X as a lyophilized powder and can be administered quickly in a small reconstituted volume. It provides effective hemostasis 90% of the time and is the preferred option for most patients who require urgent warfarin reversal. Thromboembolism is a potential adverse effect. 4F-PCC should be avoided in patients with a history of heparin-induced thrombocytopenia because it contains residual heparin.

Cryoprecipitate would be indicated to treat severe hypofibrinogenemia, usually arising as a consequence of disseminated intravascular coagulation (DIC) or severe liver disease. There is no reason to anticipate DIC in this patient, and he has no history of liver disease.

Plasma transfusion is more time consuming (preparation and administration) and is associated with a much higher risk of fluid overload from the volume needed to replace the coagulation factors. It is no longer the best option to reverse warfarin with the availability of 4F-PCC.

Idarucizumab is a monoclonal antibody that binds the non-vitamin K antagonist oral anticoagulant dabigatran and causes a rapid reduction in available dabigatran in the body for up to 24 hours. Idarucizumab will not reverse warfarin anticoagulation.

KEY POINT

- Four-factor prothrombin complex concentrate should be used to reverse the effects of warfarin anticoagulation in patients experiencing severe bleeding and those requiring urgent surgery.

Bibliography

Goldstein JN, Refaai MA, Milling TJ Jr, Lewis B, Goldberg-Alberts R, Hug BA, et al. Four-factor prothrombin complex concentrate versus plasma for rapid vitamin K antagonist reversal in patients needing urgent surgical or invasive interventions: a phase 3b, open-label, non-inferiority, randomised trial. Lancet. 2015;385:2077-87. [PMID: 25728933] doi:10.1016/S0140-6736(14)61685-8

Item 12 Answer: D

Educational Objective: Evaluate a patient with deep venous thrombosis for occult malignancy.

This patient requires no additional testing. Cancer is eventually found in approximately 10% of patients with an unprovoked venous thromboembolism (VTE) within 1 year of VTE occurrence. Cancers of the ovary, pancreas, and liver are most often found. Testing for cancer in patients with idiopathic VTE leads to diagnosis of cancer at an earlier stage of the disease. However, a recent systematic review concluded that evidence is insufficient to draw definitive conclusions about the effectiveness of extensive testing for undiagnosed cancer in patients with a first episode of unprovoked VTE in reducing cancer and VTE related morbidity and mortality. The results are imprecise and could be consistent with either harm or benefit. The authors concluded that further good quality, large-scale, randomized controlled trials are required before firm conclusions can be made. Furthermore, extensive cancer screening can cause significant economic and psychological burden. A recent economic analysis concluded that addition of a comprehensive CT of the abdomen-pelvis for the screening of occult cancer in patients with unprovoked VTE is not cost effective; it is both more costly and not more effective in detecting occult cancer. Therefore, age-appropriate malignancy screening is advised along with symptom-based assessment. Based on this patient's age and sex, she is up to date on her cancer screening tests, and no further testing is required.

Because the patient has no pulmonary symptoms and has no history of smoking, CT of the chest or abdomen is not necessary at this time.

Although the patient has some persistent lower extremity edema, this can occur during treatment and may persist despite thrombosis resolution. Because the edema seems to be slowly improving and her course of treatment was initiated only 6 weeks ago, repeat Doppler ultrasonography would not be necessary at this time.

KEY POINT

- In approximately 10% of patients in whom an unprovoked venous thromboembolism is diagnosed, cancer will be found within 1 year, so an age-appropriate screening test should be performed.

Bibliography

Carrier M, Lazo-Langner A, Shivakumar S, Tagalakis V, Zarychanski R, Solymoss S, et al; SOME Investigators. Screening for occult cancer in unprovoked venous thromboembolism. N Engl J Med. 2015;373:697-704. [PMID: 26095467] doi:10.1056/NEJMoa1506623

Item 13 Answer: A

H

Educational Objective: Diagnose acute promyelocytic leukemia.

This patient has pancytopenia, immature leukocytes with morphologic features consistent with promyelocytes, and laboratory features of disseminated intravascular coagulation (DIC), all of which are consistent with acute promyelocytic leukemia (APML). Acute leukemia can present with a leukocyte count within or below the normal range. It can include bleeding, as in this patient, from thrombocytopenia that may be accompanied by coagulopathy. APML is a subset of acute myeloid leukemia that often presents with bleeding and coagulopathy; this coagulopathy contributes to early mortality and morbidity. Features of DIC should prompt transfusion with fresh frozen plasma and cryoprecipitate (for hypofibrinogenemia) in addition to platelet transfusion for thrombocytopenia. A bone marrow aspirate and biopsy should be performed urgently to confirm the diagnosis because the coagulopathy of APML responds to therapy

H CONT

with all-*trans* retinoic acid, which targets the underlying defect in cellular differentiation.

Pancytopenia is expected in patients with aplastic anemia, but those patients would not have the atypical cells seen in the peripheral blood of this patient and would not present with DIC.

Although immature leukocytes, including myelocytes and promyelocytes, may be seen in the peripheral blood in patients with chronic granulocytic leukemia, these patients have leukocytosis, not leukopenia, and most of the increase comes from mature polymorphonuclear leukocytes.

Although severe thrombocytopenia and bleeding are typical of the acute presentation of immune thrombocytopenic purpura, this patient's pancytopenia, coagulopathy, and abnormal leukocytes are inconsistent with this diagnosis.

KEY POINT

- Acute promyelocytic leukemia may present with a reduced total leukocyte count and features of disseminated intravascular coagulation.

Bibliography

Döhner H, Weisdorf DJ, Bloomfield CD. Acute myeloid leukemia. N Engl J Med. 2015;373:1136-52. [PMID: 26376137] doi:10.1056/NEJMra1406184

Item 14 Answer: C

Educational Objective: **Evaluate monoclonal gammopathy of undetermined significance.**

This patient should have laboratory studies repeated in 6 months. She has incidentally found low-risk monoclonal gammopathy of undetermined significance (MGUS); follow-up in 6 months to 1 year with repeat serum protein electrophoresis, hemoglobin and calcium levels, and kidney function is appropriate. At that time, if the MGUS is stable, the interval for follow-up could be extended further. The risk of progression of MGUS to multiple myeloma or other lymphoproliferative disorders is determined by various risk factors. In this patient with IgG MGUS, an M spike of less than 1.5 g/dL, and normal serum free light chain assay findings, the risk of progression is low at 5% over 20 years. Patients with low-risk MGUS with no other concerning clinical features do not require bone marrow biopsy to evaluate the plasma cell burden. MGUS is seen in 3% of the population older than 50 years, and most of them do not progress, so extensive evaluation is not recommended unless other concerning features are present.

Although kidney injury attributed to multiple myeloma has long been recognized, recent evidence suggests that a portion of patients with MGUS who do not meet criteria for myeloma will, nonetheless, have kidney disease without any other contributing cause beyond the monoclonal protein. These patients have monoclonal gammopathy of renal significance and have characteristic findings on a kidney biopsy specimen. But in this patient with normal kidney function and no proteinuria, kidney biopsy is not indicated.

In this patient with low-risk MGUS and no symptoms, MRI of the spine is not appropriate. An MRI or CT is more sensitive at detecting bone lesions than plain radiography and should be considered when used to risk stratify patients with smoldering multiple myeloma. MRI or CT may be important to assess spinal cord compression in patients with multiple myeloma and back pain. A skeletal survey is adequate in this low-risk patient.

Measurement of the β_2-microglobulin I level is a part of the risk stratification strategy for patients with multiple myeloma but not for those with MGUS.

KEY POINT

- In patients with IgG monoclonal gammopathy of undetermined significance, an M spike of less than 1.5 g/dL, and normal findings on serum free light chain assay and urine protein electrophoresis, the risk of progression is low, so extensive evaluation is not recommended.

Bibliography

van de Donk NW, Palumbo A, Johnsen HE, Engelhardt M, Gay F, Gregersen H, et al; European Myeloma Network. The clinical relevance and management of monoclonal gammopathy of undetermined significance and related disorders: recommendations from the European Myeloma Network. Haematologica. 2014;99:984-96. [PMID: 24658815] doi:10.3324/haematol.2013.100552

Item 15 Answer: D

Educational Objective: **Treat symptomatic secondary hypogammaglobulinemia.**

This patient should be given intravenous immune globulin (IVIG). She has acquired hypogammaglobulinemia with recurrent sinus infections. Patients with multiple myeloma are at risk for acquired hypogammaglobulinemia from a decrease in normal plasma cells and the effects of treatment. Patients with acquired hypogammaglobulinemia without recurrent infections should not be offered IVIG replacement. Prophylactic antibiotics are also an option in some patients who have recurrent infections with susceptible organisms. In addition to the cost of infusion, IVIG has numerous adverse effects, including anaphylaxis, serum sickness, kidney failure, hypertension, and headache. In patients with recurrent infections, IVIG provides protection from infection by providing passive immunity; the product is collected from healthy donors who likely have antibodies against the causative organisms. In this patient with recurrent sinus infections, a trial of IVIG should be given. Although efficacy is uncertain, vaccination against influenza, pneumococcus, and *Haemophilus influenzae* is also recommended.

Prophylactic acyclovir is often recommended for patients receiving bortezomib therapy (increased risk for herpes zoster) after autologous stem cell transplantation and for patients with recurrent herpetic infections. It is

not provided routinely to patients with multiple myeloma to prevent infection and is unlikely to be of benefit in this patient with recurrent bacterial sinusitis.

Granulocyte colony-stimulating factor is used in conjunction with certain myelotoxic chemotherapies as infection prophylaxis and in some patients with severe neutropenia, such as severe congenital neutropenia. It is not appropriate in this patient with mild neutropenia.

Patients with myeloma are at increased risk for bacterial infection owing to impaired lymphocyte and plasma cell function and hypogammaglobulinemia. The most commonly encountered organisms are *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Escherichia coli* presenting as sinusitis, pneumonia, and urinary tract infections. Routine prophylaxis against fungal infection with fluconazole is not beneficial.

KEY POINT

- In patients with multiple myeloma, hypogammaglobulinemia, and recurrent infections, intravenous immune globulin should be given to provide passive immunity against causative organisms.

Bibliography

Friman V, Winqvist O, Blimark C, Langerbeins P, Chapel H, Dhalla F. Secondary immunodeficiency in lymphoproliferative malignancies. Hematol Oncol. 2016;34:121-32. [PMID: 27402426] doi:10.1002/hon.2323

Item 16 Answer: A

Educational Objective: Diagnose a delayed hemolytic transfusion reaction.

A direct antiglobulin (Coombs) test (DAT) should be ordered for this patient who is likely experiencing a delayed hemolytic transfusion reaction (DHTR), which is an anamnestic antibody response to previous erythrocyte antigen (non-ABO) sensitization that typically occurs 7 to 14 days after the index transfusion. The primary alloimmunization event is usually a remote transfusion or pregnancy. At the time of the index transfusion, the antibody level is usually lower than the detectable threshold determined by routine blood bank screening. A DHTR is associated with jaundice, low-grade fever, and an otherwise unexplained decrease in the hemoglobin concentration; it is sometimes accompanied by hemoglobinuria, which is confirmed by urinalysis and this patient's presenting symptom of tea-colored urine. Laboratory testing in these patients shows indirect hyperbilirubinemia. The DAT will be positive, whereas the indirect antiglobulin test, which is invariably negative before transfusion, may remain negative or show an unexpected alloantibody. For patients known to have received a recent transfusion, obtaining a transfusion history from the outside blood bank may be helpful.

Flow cytometry will assist in the diagnosis of paroxysmal nocturnal hemoglobinuria (PNH), an acquired clonal stem cell disorder that should be considered in patients presenting with hemolytic anemia, pancytopenia, or unprovoked atypical thrombosis. Hemolytic anemia occurring within days of a transfusion in a previously sensitized individual is more likely to represent DHTR than PNH.

Patients thought to have obscure gastrointestinal bleeding should be considered for repeat upper endoscopy, colonoscopy, or both. Up to 50% of lesions can be identified using this strategy. However, this patient's decrease in hemoglobin level, hemoglobinuria, and elevated total bilirubin level suggest hemolysis, not gastrointestinal bleeding.

Patients who are well compensated for their degree of anemia do not require immediate transfusion.

KEY POINT

- A positive direct antiglobulin (Coombs) test will confirm a delayed hemolytic transfusion reaction, a diagnosis that should be considered in a patient with low-grade fever and features of hemolytic anemia after recent transfusion.

Bibliography

Delaney M, Wendel S, Bercovitz RS, Cid J, Cohn C, Dunbar NM, et al; Biomedical Excellence for Safer Transfusion (BEST) Collaborative. Transfusion reactions: prevention, diagnosis, and treatment. Lancet. 2016;388:2825-2836. [PMID: 27083327] doi:10.1016/S0140-6736(15)01313-6

Item 17 Answer: C

H

Educational Objective: Treat disseminated intravascular coagulation with cryoprecipitate transfusion.

The most appropriate management for this patient is to transfuse 10 units of pooled cryoprecipitate. Cryoprecipitate is appropriate as adjunctive therapy if bleeding and hypofibrinogenemia persist in disseminated intravascular coagulation (DIC). This patient's clinical presentation of thrombocytopenia, abnormally prolonged clotting times, and low fibrinogen level are consistent with DIC, which is associated with placental abruption and other obstetric emergencies and severe inflammatory immune response syndrome with multiorgan dysfunction. The hemostatic defect in DIC is multifactorial, ultimately involving the consumption of coagulation factors and platelets. Bleeding in DIC typically responds to treatment of the underlying cause and should resolve in this patient with appropriate obstetric management of the placental abruption. However, transfusion support may still be required to address the coagulopathy. Cryoprecipitate is manufactured from fresh frozen plasma and contains fibrinogen in a more concentrated form. The appropriate amount requires pooling 8 to 10 units of cryoprecipitate, each unit being derived from 1 pint of whole blood.

Twenty-five percent albumin is fractionated from large pools of donated plasma and does not contain any coagulation proteins. It is hyperoncotic and used to treat hypotension, commonly in the postoperative setting and after large-volume paracentesis. This patient's blood pressure has stabilized, so she needs definitive management of the coagulopathy. Twenty-five percent albumin would not be appropriate therapy.

Cryo-poor plasma is derived from fresh frozen plasma in which the cryoprecipitate has been separated. Its use is limited to refractory thrombotic thrombocytopenic purpura,

H CONT.

although any advantage over fresh frozen plasma in this disorder has not been proven. It is not appropriate for treatment of most coagulopathies.

Although the patient does have thrombocytopenia, a platelet count exceeding 50,000/µL (50×10^9/L) is generally acceptable to manage postsurgical bleeding (with a count of approximately 100,000/µL [100×10^9/L] preferred for intracranial bleeding); therefore, a platelet transfusion is not the most immediate need.

KEY POINT

- Cryoprecipitate is the treatment of choice for patients with bleeding and hypofibrinogenemia secondary to disseminated intravascular coagulation.

Bibliography

Levy JH, Goodnough LT. How I use fibrinogen replacement therapy in acquired bleeding. Blood. 2015;125:1387-93. [PMID: 25519751] doi:10.1182/blood-2014-08-552000

H

Item 18 Answer: D

Educational Objective: Diagnose parvovirus B19 infection in a patient with sickle cell disease.

This patient has parvovirus B19 infection presenting with pure red cell aplasia (PRCA). Patients with sickle cell anemia have chronic hemolysis and depend on increased erythrocyte production to maintain the hemoglobin level. Parvovirus B19 infection preferentially affects erythrocyte precursors in the bone marrow, causing transient PRCA. This patient's very low reticulocyte count is consistent with the decreased erythrocyte production seen in PRCA. Infection with parvovirus B19 in children can present as erythema infectiosum with fever and rash. Although adults can have flu-like illness and arthralgia, most are asymptomatic. However, in patients with hemolytic anemia, it can present with transient aplastic crisis. Supportive transfusions are usually required to treat symptoms from severe anemia.

Aplastic anemia (AA) is a condition characterized by pancytopenia with associated neutropenia, anemia, and thrombocytopenia and a severely hypocellular bone marrow. Isolated cytopenias are uncommon despite the designation of anemia. AA is usually acquired and is caused by toxic, viral, or autoimmune mechanisms. The lack of other cytopenias makes AA an unlikely diagnosis.

In some patients with sickle cell disease, a rare condition known as hyperhemolysis is thought to be responsible for an acute hemolytic anemia and reticulocytosis. Episodes have sometimes been associated with delayed transfusion reactions and acute vasoocclusive events. Hyperhemolysis syndrome would be associated with an elevated reticulocyte count, not a reduced count.

Myelodysplastic syndrome (MDS) ranges in severity from an asymptomatic disease characterized by mild normocytic or macrocytic anemia to a transfusion-dependent anemia. The incidence of MDS increases with age. Abnormal erythrocyte forms with basophilic stippling or Howell-Jolly bodies and dysplastic neutrophils with decreased nuclear segmentation and granulation may be present. MDS is unlikely to cause a symptomatic anemia developing over a few days in a young patient with sickle cell disease.

KEY POINT

- Parvovirus B19 infection preferentially affects erythrocyte precursors in the bone marrow, causing transient pure red cell aplasia in patients with sickle cell anemia.

Bibliography

Yawn BP, Buchanan GR, Afenyi-Annan AN, Ballas SK, Hassell KL, James AH, et al. Management of sickle cell disease: summary of the 2014 evidence-based report by expert panel members. JAMA. 2014;312:1033-48. [PMID: 25203083] doi:10.1001/jama.2014.10517

Item 19 Answer: B

Educational Objective: Treat essential thrombocythemia.

The patient has essential thrombocythemia (ET) and should be treated with hydroxyurea. The first step in evaluating thrombocytosis is to rule out a secondary elevation. Chronic infection, collagen vascular disease, malignancy, ongoing bleeding, and iron deficiency can all cause a reactive thrombocytosis. *JAK2* mutation testing is positive in only about 60% of patients with ET, but other clonal mutations involving calreticulin and *MPL* genes have been identified in some patients with *JAK2*-negative ET. Approximately 10% to 15% of patients with ET have negative results for all three mutations (termed triple-negative patients). A bone marrow biopsy specimen showing hypercellularity with increased numbers of enlarged megakaryocytes is required to make the diagnosis in the few patients with ET who do not have any of the three mutations listed previously.

The most significant complications that may occur during follow-up of ET are thrombosis (10%-15% 15-year cumulative risk; arterial is more common than venous), hemorrhage (8.6% 15-year cumulative risk), progression to myelofibrosis (10% 15-year cumulative risk), and transformation to acute leukemia (3% 15-year cumulative risk). The patient's age (older than 60 years) and previous thromboembolic event place her at particularly high risk for subsequent thromboembolic complications. Platelet-lowering therapy is indicated for any patient at high risk. Hydroxyurea is well tolerated in older adult patients and is considered first-line therapy for nonpregnant patients. For that reason, she should be treated with aspirin and hydroxyurea.

Patients with high-risk ET, such as this patient who has a history of stroke, require antiplatelet therapy and platelet-lowering therapy with agents such as hydroxyurea. Changing antiplatelet therapy from aspirin to clopidogrel would not address this patient's need for platelet-lowering therapy nor would adding a second antiplatelet medication, such as clopidogrel, to the aspirin.

Plateletpheresis may be indicated in the emergent management of patients with ET who have markedly elevated platelet counts, usually greater than 1,000,000/µL (1000 × 10^9/L), and acute hemorrhage. Plateletpheresis would not be indicated in this patient.

KEY POINT

- Patients with essential thrombocythemia who are older than 60 years or who have had previous thromboembolic complications should be treated with aspirin and hydroxyurea.

Bibliography

Nangalia J, Massie CE, Baxter EJ, Nice FL, Gundem G, Wedge DC, et al. Somatic CALR mutations in myeloproliferative neoplasms with nonmutated JAK2. N Engl J Med. 2013;369:2391-405. [PMID: 24325359] doi:10.1056/NEJMoa1312542

Item 20 Answer: B

Educational Objective: Diagnose benign ethnic neutropenia.

This patient most likely has benign ethnic neutropenia. Isolated neutropenia usually has a hereditary, toxic, or immune cause. Isolated mild neutropenia (1000-1500/µL [1-1.5 × 10^9/L]) found on routine testing in asymptomatic black patients, or occasionally in other ethnic groups (Sephardic Jews, West Indians, Arabs of the Middle East), likely has a benign ethnic cause. An absolute neutrophil count less than 500/µL (0.5 × 10^9/L) is less likely to be a normal variant and more likely to be associated with increased risk for bacterial and fungal infections. Patients with benign ethnic neutropenia usually have good bone marrow reserve and are not prone to developing infections. A detailed evaluation for other causes of neutropenia is usually not required in these patients. Having a previous history of mild neutropenia supports the diagnosis but is not required.

Autoimmune neutropenia is caused by destruction of the neutrophils by autoantibodies. It is more commonly seen in conjunction with other autoimmune disorders, such as systemic lupus erythematosus or Felty syndrome. Felty syndrome is a triad of rheumatoid arthritis, splenomegaly, and neutropenia. This patient has no signs or symptoms of an autoimmune disorder. Although idiopathic autoimmune neutropenia without an underlying systemic disorder can occur, benign ethnic neutropenia would be a much more likely diagnosis in this asymptomatic black patient with mild neutropenia.

Cyclical neutropenia is a rare congenital disorder in which the neutrophil count nadirs every 2 to 5 weeks with recurrent infections. Diagnosis requires twice-weekly complete blood counts for 6 to 8 weeks. This patient's clinical history does not indicate recurrent infections or other typical findings of cyclical neutropenia.

Drug-induced neutropenia occurs in patients taking medications such as chemotherapy, NSAIDs, carbamazepine, phenytoin, propylthiouracil, cephalosporins, trimethoprim-sulfamethoxazole, or psychotropic drugs. Omeprazole has not been commonly implicated in causing neutropenia. Drug-induced neutropenia is diagnosed by temporal relationship of the neutropenia with starting the medication and improvement with stopping the offending medication. It is important to note that improvement in neutropenia may lag behind by many weeks after stopping the medication.

KEY POINT

- Benign ethnic neutropenia typically appears as an isolated, mild neutropenia (1000-1500/µL [1-1.5 × 10^9/L]) found on routine testing in asymptomatic black persons or certain other ethnic groups.

Bibliography

Gibson C, Berliner N. How we evaluate and treat neutropenia in adults. Blood. 2014;124:1251-8; quiz 1378. [PMID: 24869938] doi:10.1182/blood-2014-02-482612

Item 21 Answer: C

H

Educational Objective: Manage glucose-6-phosphate dehydrogenase deficiency.

The most appropriate management for this patient is to discontinue dapsone. He most likely has glucose-6-phosphate dehydrogenase (G6PD) deficiency as a result of his dapsone therapy. He developed an acute hemolytic anemia, indicated by an acute reduction in the hemoglobin and haptoglobin levels and reticulocytosis, and the bite cells seen on the peripheral blood smear also suggest G6PD deficiency. A drug reaction should always be suspected in such settings. Dapsone is one of the most commonly encountered drugs leading to G6PD-mediated hemolysis, so this drug should be promptly discontinued. G6PD deficiency is X linked, so it is much more common in men, especially in those of African descent. G6PD levels should not be checked during an acute hemolytic event because they are normal in newly produced erythrocytes but decrease up to 75% as the cells age. As a result, during an acute hemolytic event, the older, more deficient erythrocytes are preferentially destroyed, leaving the newer less deficient cells to circulate. This leads to falsely normal G6PD levels, so G6PD measurement should be delayed for several weeks after a hemolytic event.

Warm antibody autoimmune hemolytic anemia would be appropriately treated with glucocorticoids, such as prednisone, but this disease is unlikely with the negative direct antiglobulin test result and the absence of spherocytes in the peripheral blood.

Rituximab would be indicated to treat cold agglutinin autoimmune hemolytic anemia. However, no agglutinated cells are seen on the peripheral blood smear, and the direct antiglobulin test result would be positive, indicating complement on the erythrocyte surface in this disease.

This patient's platelet count is normal, and no fragmented erythrocytes or schistocytes are seen on the peripheral blood smear, so thrombotic thrombocytopenia purpura, which would be confirmed by a reduction in ADAMTS13 activity, is not likely.

KEY POINT

- Testing for glucose-6-phosphate dehydrogenase activity is reliable in men who are not experiencing an acute hemolytic episode but is less useful during acute episodes because reticulocytes produce higher levels of enzyme, resulting in a falsely normal test result.

Bibliography

Luzzatto L, Seneca E. G6PD deficiency: a classic example of pharmacogenetics with on-going clinical implications. Br J Haematol. 2014;164:469-80. [PMID: 24372186] doi:10.1111/bjh.12665

Item 22 Answer: A

Educational Objective: Diagnose the anemia of kidney disease.

This patient most likely has anemia resulting from erythropoietin deficiency. Normocytic anemia with unremarkable erythrocyte morphology and a low reticulocyte count in a patient with underlying chronic kidney disease is usually caused by erythropoietin deficiency. Measuring erythropoietin levels may be useful in making the diagnosis of the anemia of kidney disease, and low erythropoietin measurements can distinguish these patients from those with other causes of anemia. The modest absolute increase in serum creatinine level underestimates the severity of kidney injury in this frail, older adult patient with reduced muscle mass. Administration of erythropoiesis-stimulating agents will correct the anemia of kidney disease.

The anemia of inflammation is caused by inhibition of iron transport and suppression of erythropoietin by hepcidin and other inflammatory cytokines. Although it is classically seen in patients with chronic infection, cancer, or autoimmune-inflammatory disease, the anemia of inflammation may also occur in patients with diabetes and heart failure and, on occasion, in patients without any overt underlying disease. This patient lacks characteristic laboratory features, including a low total iron-binding capacity and serum iron level and normal or elevated ferritin level.

Iron deficiency is not uncommon in patients with chronic kidney disease because they are at risk for gastrointestinal bleeding from angiodysplasia or ulcer disease, but these patients typically have microcytic erythrocytes, low serum iron and ferritin levels, and elevated total iron-binding capacity.

Patients with myelodysplastic syndrome often have pancytopenia; although early stages and forms of this syndrome with a better prognosis may have isolated anemia, the presence of macrocytosis, which is absent in this patient, is characteristic.

KEY POINT

- Normocytic anemia with a low reticulocyte count and normal erythrocyte morphology in a patient with underlying chronic kidney disease is usually caused by erythropoietin deficiency and will respond to therapy with an erythropoiesis-stimulating agent; however, normalization of the blood count is not advised.

Bibliography

Chapter 1: Diagnosis and evaluation of anemia in CKD. Kidney Int Suppl (2011). 2012;2:288-291. [PMID: 25018948]

Item 23 Answer: A

H

Educational Objective: Diagnose amyloidosis.

The most appropriate test to perform next is an abdominal fat pad biopsy. This patient has cardiomyopathy, nephrotic syndrome, autonomic dysfunction, and macroglossia, which are likely caused by amyloidosis. Amyloid deposition can occur in one or more organs and cause symptoms related to the sites of deposition. Sites commonly involved are the kidneys, the gastrointestinal tract, and the cardiac, neurologic, coagulation, and musculoskeletal systems. In this patient, nephrotic-range proteinuria, cardiomyopathy, orthostatic hypotension, and macroglossia all suggest amyloidosis. The finding of an IgG λ monoclonal gammopathy can also be associated with amyloidosis. Diagnosis requires biopsy of the affected organ and demonstration of characteristic apple-green birefringence with Congo red staining. Fat pad biopsy is sometimes performed when multiorgan involvement is suspected because it is less invasive; however, if findings are unrevealing, biopsy of the organ(s) involved, such as the kidney, may be required. Because different proteins can be involved in amyloid deposition, protein typing with tests such as mass spectrometry is done after amyloidosis is diagnosed. Proper identification of the amyloid type is critical and guides appropriate therapy.

Cardiac catheterization to evaluate for coronary artery disease is not the best test to perform in this patient with multisystem involvement and no symptoms or signs of acute ischemia. However, cardiac biopsy is sometimes required in patients with suspected isolated cardiac involvement with amyloidosis.

Tilt table testing may be helpful in patients with reflex syncope triggered by standing, patients in high-risk settings with a single unexplained episode of syncope, or patients with recurrent episodes in the absence of organic heart disease. This patient does not have syncope but rather a multiplicity of findings suggesting a systemic disease not likely to be elucidated with tilt table testing.

KEY POINT

- Diagnosis of amyloidosis requires biopsy of the affected organ and demonstration of characteristic apple-green birefringence with Congo red staining; fat pad biopsy is sometimes performed because it is less invasive.

Bibliography

Gillmore JD, Wechalekar A, Bird J, Cavenagh J, Hawkins S, Kazmi M, et al; BCSH Committee. Guidelines on the diagnosis and investigation of AL amyloidosis. Br J Haematol. 2015;168:207-18. [PMID: 25312307] doi:10.1111/bjh.13156

Item 24 Answer: A

Educational Objective: Treat iron deficiency due to malabsorption.

The most appropriate treatment is parenteral iron therapy. This patient has severe iron deficiency and inflammatory

bowel disease, which impairs iron absorption in the duodenum and proximal jejunum and commonly leads to increased gastrointestinal blood loss. Several parenteral iron preparations are available, including iron sucrose, ferric gluconate, ferumoxytol, and iron carboxymaltose. These preparations are better absorbed and have a better side effect profile than previous parenteral preparations, such as iron dextran.

Liquid preparations of iron are useful in pediatric populations or to provide an even lower dose of iron than would be present in a single tablet, but no evidence suggests that the liquid form is better absorbed.

Increasing the frequency of oral iron therapy will not address the basic problem of this patient's malabsorption. Additionally, recent information indicates that patients with iron deficiency with normal intestinal function have a paradoxical decrease in iron absorption when supplements are administered multiple times per day compared with once daily, perhaps owing to hepcidin stimulation. Hepcidin, a peptide hormone produced in the liver, is a main regulator of iron homeostasis. It decreases intestinal iron absorption and release of iron stores by down-regulating the ferroportin-mediated release of iron from enterocytes, hepatocytes, and macrophages. Hepcidin is produced by hepatocytes when iron is abundant and in inflammatory anemia; it is suppressed in iron deficiency anemia.

Sustained-release iron preparations should never be used because much of the iron in these preparations is released distal to the jejunal site of absorption.

KEY POINT

- Patients with inflammatory bowel disease have difficulty absorbing oral iron to balance their increased iron loss from bleeding, so parenteral iron is an appropriate alternative for restoring iron stores.

Bibliography

Auerbach M, Adamson JW. How we diagnose and treat iron deficiency anemia. Am J Hematol. 2016;91:31-8. [PMID: 26408108] doi:10.1002/ajh.24201

Item 25 Answer: A

Educational Objective: Diagnose Waldenström macroglobulinemia.

A bone marrow biopsy is the most appropriate diagnostic test to perform in this patient. He has hepatosplenomegaly, anemia, and night sweats along with an IgM spike on laboratory testing, indicating he most likely has Waldenström macroglobulinemia (WM). WM is an indolent B-cell lymphoma with clonal lymphoplasmacytic infiltration of the bone marrow that secretes IgM in the blood. Patients with WM can present with classic "B symptoms" of drenching night sweats, fever, weight loss, and anemia. Tissue infiltration of the lymphoma can cause hepatosplenomegaly and lymphadenopathy. Bone marrow biopsy to document lymphoplasmacytic infiltrate will confirm the diagnosis.

For patients suspected of having a lymphoma, excisional biopsy of a lymph node is preferred to needle biopsy because it provides better architectural detail for distinguishing malignant from benign causes and for classifying the nature of the malignancy. In patients with WM, bone marrow biopsy is predictably diagnostic and a much less invasive option than is para-aortic lymph node excision.

Increased IgM protein in the blood can cause hyperviscosity, with symptoms such as altered vision, headache, hearing loss, tinnitus, dizziness, nystagmus, altered mental status, and nasal and oropharyngeal bleeding. Funduscopic evaluation may show hyperviscosity-related findings, including dilated retinal veins, papilledema, and flame hemorrhages. This patient has no signs or symptoms of hyperviscosity and has an M protein level of less than 400 mg/dL (4 g/L), so serum viscosity testing is not indicated.

KEY POINT

- Waldenström macroglobulinemia is an indolent B-cell lymphoma with clonal lymphoplasmacytic infiltration of the bone marrow that secretes IgM in the blood, and a bone marrow biopsy will confirm the diagnosis.

Bibliography

Castillo JJ, Garcia-Sanz R, Hatjiharissi E, Kyle RA, Leleu X, McMaster M, et al. Recommendations for the diagnosis and initial evaluation of patients with Waldenström Macroglobulinaemia: a task force from the 8th International Workshop on Waldenström Macroglobulinaemia. Br J Haematol. 2016;175:77-86. [PMID: 27378193] doi:10.1111/bjh.14196

Item 26 Answer: D

Educational Objective: Diagnose hereditary hemochromatosis.

The most appropriate test to perform next is transferrin saturation and serum ferritin level. Historically, patients with hereditary hemochromatosis presented with signs of cirrhosis, diabetes mellitus, and skin pigmentation. Because of earlier recognition, fatigue, arthralgias, and loss of libido are more common presenting symptoms. Patients with hemochromatosis have rheumatic symptoms that typically involve the small joints of the hand, especially the second and third metacarpophalangeal (MCP) joints associated with characteristic radiographic findings, including hook-like osteophytes. Guidelines support initial testing with transferrin saturation to diagnosis iron overload. A transferrin saturation greater than 45% is often chosen as the cutoff to warrant additional testing, although this threshold has lower specificity and positive predictive value compared with higher cutoff values. A normal serum ferritin level and transferrin saturation less than 45% have a negative predictive value of 97% to exclude iron overload.

Symmetrical involvement of MCP joints suggests the possibility of rheumatoid arthritis (RA), but hook-like osteophytes on the metacarpal heads is a disease-specific finding for hemochromatosis. For these reasons, RA is an unlikely

diagnosis, and it is unnecessary to perform rheumatoid factor and anti-cyclic citrullinated peptide antibody testing. The MCP involvement and radiographic changes also make primary osteoarthritis an unlikely diagnosis.

HFE genotyping is reserved for patients in whom the serum ferritin level is elevated, a high transferrin saturation is noted, or both. It would not be the appropriate initial test to perform in this patient who has had no other testing. C282Y homozygosity accounts for 80% to 85% of typical patients with hereditary hemochromatosis; C282Y/H63D and C282Y/S65C compound heterozygosity are the next most prevalent genotypes.

Since the advent of *HFE* mutational analysis, the role of liver biopsy has diminished. Liver biopsy is generally reserved to stage liver disease in patients known to be C282Y homozygous or compound heterozygous when the serum ferritin level is greater than 1000 ng/mL (1000 µg/L) with or without elevated liver enzyme levels. Liver biopsy may also be useful when other pathogens, including alcohol and chronic hepatitis, might be causing liver injury.

KEY POINT

- Atypical presentations of rheumatoid arthritis and osteoarthritis, particularly with hook-like osteophytes of the second and third metacarpophalangeal joints, suggest the possibility of hemochromatosis; evaluating the transferrin saturation and serum ferritin level should be considered.

Bibliography

Bacon BR, Adams PC, Kowdley KV, Powell LW, Tavill AS; American Association for the Study of Liver Diseases. Diagnosis and management of hemochromatosis: 2011 practice guideline by the American Association for the Study of Liver Diseases. Hepatology. 2011;54:328-43. [PMID: 21452290] doi:10.1002/hep.24330

H

Item 27 Answer: A

Educational Objective: Treat massive lower extremity deep venous thrombosis.

Thrombolytic therapy with alteplase is the most appropriate management for this patient. He has signs and symptoms of extensive proximal deep venous thrombosis (DVT) leading to progressive edema of the leg, compromising arterial blood flow and causing acute ischemic injury. He is at risk for amputation of the leg and increased risk of death. Results of a systematic review of thrombolytic therapy showed greater improvement in venous patency, increased complete clot lysis, and reduced postthrombotic syndrome compared with anticoagulant therapy alone. Thrombolytic therapy was not associated with significant differences in mortality, stroke or intracerebral hemorrhage, pulmonary embolism, or leg ulceration; however, there were few events overall and with wide confidence intervals, and the review could not rule out clinically relevant differences. Bleeding risk with thrombolytic therapy is slightly greater than that associated with anticoagulant therapy, and strict eligibility criteria to reduce the risk of bleeding complications limit the applicability of this treatment. Thrombolytic agents include tissue plasminogen activator, streptokinase, and urokinase. Derivatives of tissue plasminogen activator, such as alteplase, are most commonly used in the setting of thrombosis because they more selectively activate fibrin-bound plasminogen.

The parenteral direct thrombin inhibitors argatroban and lepirudin are reserved for the treatment of heparin-induced thrombocytopenia. Argatroban and lepirudin are not thrombolytic.

Rivaroxaban, a non-vitamin K antagonist oral anticoagulant, is an accepted monotherapy for DVT (heparin not required). However, rivaroxaban has no immediate effect on thrombus dissolution.

Unfractionated heparin potentiates the natural anticoagulant activity of antithrombin and acts as a nonspecific anticoagulant, mostly against thrombin and activated factor X. Heparin will prevent propagation of the thrombus but does not provide an immediate decrease in the size of an existing thrombus; therefore, it will not reverse tissue ischemia.

The role of an inferior vena cava filter in a patient with massive proximal DVT is uncertain. Although it might decrease the short-term risk of pulmonary embolism, it will predispose to subsequent DVT and increase the risk of postphlebitic syndrome. If a filter were used, it should be inserted after thrombolytic therapy.

KEY POINT

- Thrombolysis should be considered as the initial therapy for patients with iliofemoral deep venous thrombosis with acute limb ischemia.

Bibliography

Watson L, Broderick C, Armon MP. Thrombolysis for acute deep vein thrombosis. Cochrane Database Syst Rev. 2014 Jan 23;(1):CD002783. doi:n10.1002/14651858.CD002783.pub3. Review. Update in: Cochrane Database Syst Rev. 2016 Nov 10;11:CD002783. [PMID: 24452314]

Item 28 Answer: C

H

Educational Objective: Treat autoimmune hemolytic anemia with transfusion of crossmatch-incompatible blood.

The most appropriate management is to transfuse with crossmatch-incompatible blood. Although the goal of pretransfusion testing is to ensure the provision of ABO and Rh crossmatch-compatible blood, compatibility might not be achievable in autoimmune hemolytic anemia. Autoimmune hemolytic anemia is caused by the production of autoreactive antibodies against the patient's own erythrocytes. The direct antiglobulin test detects the presence of IgG or complement coating the patient's erythrocytes. In many patients who have IgG autoantibodies, the autoantibodies are of sufficient concentration in the serum or plasma to cause an incompatible crossmatch with donor erythrocytes because the autoantibody is directed against a core antigen on erythrocytes that is present not only on the patient's erythrocytes but also on all donor cells. Although the autoantibody will shorten the

H CONT.

survival of transfused cells, they will still survive for days or even weeks and should provide effective therapy for problems related to acute anemia until immunosuppressive therapy becomes effective. A response to immunosuppressive therapy takes 1 to 2 weeks. The major risk in these patients is the failure to identify any additional alloantibody that may be present and could lead to more fulminant acute hemolytic transfusion reactions. In the absence of pregnancy or previous transfusion, the likelihood of non-ABO erythrocyte alloantibody development is extremely low. Therefore, a unit that is ABO and Rh matched is appropriate, even if crossmatch incompatible.

It is not appropriate to withhold transfusion when a patient has severe anemia-related symptoms.

Plasma exchange therapy is not effective for removing IgG antibodies because of a large extravascular space for IgG distribution that equilibrates back into the vascular pool as plasma is removed.

Using "universal" group O-negative or group O-positive blood provides no advantage. It would still be crossmatch incompatible because of the underlying autoantibody. Uncrossmatched blood is reserved for situations of exsanguination in which blood transfusion is urgently required before "type and cross" can be completed.

KEY POINT

- In patients with severe symptomatic autoimmune hemolytic anemia, the autoantibody typically reacts against all erythrocytes, and a completely crossmatch-compatible unit may be impossible to find; these patients should receive ABO and Rh-matched blood even if it is not crossmatch compatible.

Bibliography

Lechner K, Jäger U. How I treat autoimmune hemolytic anemias in adults. Blood. 2010;116:1831-8. [PMID: 20548093] doi:10.1182/blood-2010-03-259325

Item 29 Answer: B

Educational Objective: Identify an increased risk of infection after autologous hematopoietic stem cell transplantation.

This patient is at increased risk of infection. The most common indications for autologous hematopoietic stem cell transplantation (HSCT) are multiple myeloma and relapsed non-Hodgkin lymphoma. With appropriate supportive care, many older patients are eligible for autologous HSCT. Fatigue, altered taste, diminished appetite, and persistent mild diarrhea are common adverse effects of high-dose chemotherapy, an integral part of HSCT. The most common concern in patients who have undergone HSCT is the increased risk of infection, which persists for 6 to 12 months after HSCT. This risk is attributed to compromised function of neutrophils and lymphocytes and is sometimes associated with mild neutropenia and lymphopenia. For this reason, patients should be counseled to report warning symptoms, such as fever and respiratory or other localizing symptoms of infection, early in the course.

Graft-versus-host disease (GVHD) is a major risk of allogeneic HSCT. Acute GVHD occurs when graft T cells recognize the patient's normal gut, skin, and liver sinusoids as foreign. Severe GVHD is life threatening and is treated with high-dose glucocorticoids. Anti-T-lymphocyte immune globulin as part of the myeloablative conditioning regimen can markedly reduce the prevalence of chronic GVHD 2 years after allogeneic HSCT in HLA-matched siblings. GVHD is not a complication of autologous HSCT.

Hematopoietic clonal disorders, including myelodysplasia, leukemia, and lymphoma, can occur decades after completion of therapy. Typical agents associated with therapy-related myelodysplasia include alkylators, anthracyclines, and topoisomerase II inhibitors. Likewise, leukemia and lymphoma can develop as a late consequence of exposure to chemotherapy and radiation. But these disorders would not occur in the months immediately following uncomplicated autologous HSCT.

KEY POINT

- Immediately following hematopoietic stem cell transplantation, patients are at increased risk of infection because of compromised function of lymphocytes and neutrophils.

Bibliography

Hashmi SK. Basics of hematopoietic cell transplantation for primary care physicians and internists. Prim Care. 2016;43:693-701. [PMID: 27866586] doi:10.1016/j.pop.2016.07.003

Item 30 Answer: C

Educational Objective: Evaluate smoldering multiple myeloma with whole body MRI.

Whole body MRI is the most appropriate next diagnostic test for this patient. Smoldering multiple myeloma (MM) is characterized by a serum M protein level of 3 g/dL or greater (or ≥500 mg/24 hr of urinary monoclonal free light chains) or bone marrow plasma clonal cells of 10% or greater and no evidence of myeloma-related signs or symptoms requiring therapy. All patients with MM should be assessed for skeletal lesions at diagnosis, periodically thereafter, and when any new symptoms occur. Skeletal survey with plain radiography is commonly used to assess for lytic lesions in patients with monoclonal gammopathy. However, MRI has recently been found to be more sensitive at identifying myeloma bone lesions and soft tissue lesions from plasmacytoma. The International Myeloma Working Group recommends that all patients with smoldering MM undergo whole body MRI (or spine and pelvic MRI if whole body MRI is not available). Whole body MRI is considered the gold standard for imaging of the axial skeleton, for the evaluation of painful lesions, and for distinguishing benign versus malignant osteoporotic vertebral fractures. If a patient is discovered to have more than one lesion greater than 5 mm, the patient

should be considered symptomatic and requires consideration for treatment. With equivocal small lesions, a second MRI should be performed after 3 to 6 months; if the MRI shows progression, the patient should be treated as having symptomatic myeloma. In this patient with smoldering MM, negative findings on plain radiographs do not reliably rule out a skeletal lesion, and MRI is needed for further evaluation.

Although bone scans are useful in detecting bone metastases from underlying cancer, the bone lesions in MM are often purely lytic and lack the enhanced osteoblastic activity that is shown by bone scan imaging. Bone scans should not be used to assess bone involvement in myeloma.

CT is more sensitive than plain radiography in detecting bone lesions but is less sensitive than MRI in detecting small lesions. Additionally, patients with MM are at high risk for contrast nephropathy from CT contrast.

No further testing is inappropriate because the detection of asymptomatic focal lesions on whole body MRI determines the plan of care for patients with smoldering MM.

KEY POINT

- The International Myeloma Working Group recommends that all patients with smoldering multiple myeloma undergo whole body MRI to assess for lytic lesions.

Bibliography

Dimopoulos MA, Hillengass J, Usmani S, Zamagni E, Lentzsch S, Davies FE, et al. Role of magnetic resonance imaging in the management of patients with multiple myeloma: a consensus statement. J Clin Oncol. 2015; 33:657-64. [PMID: 25605835] doi:10.1200/JCO.2014.57.9961

H

Item 31 Answer: C

Educational Objective: Treat warfarin-associated bleeding.

The most appropriate treatment for this patient is vitamin K and prothrombin complex concentrates (PCCs), specifically, four-factor PCC. Four-factor PCC is a combination of inactivated factors II, VII, IX, and X. Treatment recommendations for over-anticoagulation with warfarin are based on the degree of over-anticoagulation as measured by the INR and clinical manifestations of bleeding. The first step in all cases of over-anticoagulation is withholding warfarin. For patients with an INR of 4.5 to 10 and with no evidence of bleeding, routine use of vitamin K is not recommended. For patients with an INR greater than 10 and with no evidence of bleeding, oral vitamin K is recommended. For patients with major bleeding, such as this patient with an intracerebral hemorrhage, rapid reversal of anticoagulation is recommended with four-factor PCC rather than fresh frozen plasma (FFP). These patients are also likely to benefit from the addition of vitamin K by slow intravenous injection rather than using coagulation factors alone. Clinical trials have shown four-factor PCC to be noninferior to FFP in reversing warfarin anticoagulation. However, four-factor PCC is preferred because of its rapid reversal of the INR, rapid infusion and administration, and no risk of volume overload as is sometimes seen with plasma infusions. Additionally, four-factor PCC does not require thawing or typing.

Although FFP contains the appropriate clotting factors, it requires thawing and large volumes to correct the INR. This patient also has heart failure, making infusion of FFP problematic because of the volume needed.

Idarucizumab is a monoclonal antibody approved for reversal of the anticoagulant effects of dabigatran. It is not used to reverse the effects of vitamin K antagonist anticoagulants.

Recombinant activated factor VII has been found to reduce the INR in warfarin-associated bleeding, but its overall effect on outcome has been unclear, with a varied rate of thromboembolic events. It is not recommended for acute warfarin reversal.

KEY POINT

- In patients with INR elevation and bleeding associated with warfarin administration, urgent reversal of anticoagulation should be accomplished using vitamin K and prothrombin complex concentrates.

Bibliography

Sarode R, Milling TJ Jr, Refaai MA, Mangione A, Schneider A, Durn BL, et al. Efficacy and safety of a 4-factor prothrombin complex concentrate in patients on vitamin K antagonists presenting with major bleeding: a randomized, plasma-controlled, phase IIIb study. Circulation. 2013;128:1234-43. [PMID: 23935011] doi:10.1161/CIRCULATIONAHA.113.002283

Item 32 Answer: A

Educational Objective: Treat secondary iron overload.

This patient should begin deferasirox for treatment of secondary iron overload. In most cases, secondary iron overload occurs in patients with severe anemia who require chronic transfusion therapy. Because iron excretion has no regulated mechanism, multiple transfusions (for anemias not stemming from blood loss or iron deficiency) lead to iron overload, with subsequent secondary organ damage. If these anemias resolve (either from hematopoietic stem cell transplantation or remission of leukemias), phlebotomy should be initiated. When anemia is ongoing, such as in this patient, iron chelation is required, for which deferoxamine or deferasirox may be used. These agents are relatively toxic, leading to potential kidney and liver damage, agranulocytosis, or ocular and ophthalmic disorders; therefore, careful monitoring is required. Serum ferritin level correlates with iron burden in patients receiving chronic transfusion, and levels greater than 1000 ng/mL (1000 µg/L) are generally considered an indication for therapy. Deferoxamine is only available for parenteral administration, which is much less convenient in the long-term outpatient setting than oral iron chelation. The availability of oral iron chelation with deferasirox has increased medication adherence for patients who develop secondary iron overload from chronic transfusions for hemoglobinopathies or myelodysplastic syndrome. Deferasirox

commonly causes gastrointestinal side effects. The medication is often better tolerated in the evening, before the evening meal.

Succimer is used to chelate lead and enhance excretion in patients with chronic lead intoxication. It would not be used to treat iron overload.

Therapeutic phlebotomy is the management of choice for hereditary (primary) hemochromatosis. It effectively removes 200 mg of iron with each pint of blood removed. However, therapeutic phlebotomy is not suitable for patients with symptomatic anemia who require chronic transfusion, as is the case with this patient.

Withholding transfusion is not appropriate because of this patient's age and her symptomatic anemia.

KEY POINT

- Secondary iron overload from chronic transfusions can be effectively treated with oral chelation agents, such as deferasirox.

Bibliography

Nolte F, Angelucci E, Breccia M, Gattermann N, Santini V, Vey N, et al. Updated recommendations on the management of gastrointestinal disturbances during iron chelation therapy with deferasirox in transfusion dependent patients with myelodysplastic syndrome - emphasis on optimized dosing schedules and new formulations. Leuk Res. 2015;39:1028-33. [PMID: 26293555] doi:10.1016/j.leukres.2015.06.008

Item 33 Answer: A

Educational Objective: Treat the anemia of chronic kidney disease with an erythropoiesis-stimulating agent.

Darbepoetin should be administered to achieve a hemoglobin level of 11 to 12 g/dL (110-120 g/L). Erythropoiesis-stimulating agents (ESAs) such as erythropoietin and darbepoetin have dramatically reduced the need for transfusion in patients with the anemia of chronic kidney disease (CKD) but have little impact on quality of life or mortality. This patient has symptomatic anemia of CKD, which is determined by ruling out other causes of anemia in patients with reduced kidney function. Although symptomatic anemia occurs commonly in patients with advanced CKD who are receiving hemodialysis, it may also occur in patients with stages III and IV CKD. Regardless of stage, patients with symptomatic anemia of CKD will benefit from ESAs by reducing their transfusion requirements. However, a "normal" hemoglobin threshold is not the preferred target level for patients taking ESAs. Numerous studies have shown that ESAs increase adverse cardiovascular outcomes when the hemoglobin level exceeds 11 to 12 g/dL (110-120 g/L). Additionally, ESAs can cause hypertension and thrombosis.

Iron stores must be normal for ESAs to be effective. Patients undergoing dialysis are often treated with additional parenteral iron along with ESAs even if they are not overtly iron deficient. Although supplemental iron with darbepoetin may be required in this patient, iron therapy alone, either by oral or parenteral routes of administration, will not correct anemia in this patient who has no laboratory findings to support the diagnosis of iron deficiency.

KEY POINT

- Patients with symptomatic anemia of chronic kidney disease may be treated with erythropoiesis-stimulating agents to reduce transfusion requirements with a target hemoglobin level of 11 to 12 g/dL (110-120 g/L) to avoid increased risk of adverse cardiovascular events.

Bibliography

Palmer SC, Saglimbene V, Craig JC, Navaneethan SD, Strippoli GF. Darbepoetin for the anaemia of chronic kidney disease. Cochrane Database Syst Rev. 2014:CD009297. [PMID: 24683046] doi:10.1002/14651858.CD009297.pub2

Item 34 Answer: E

H

Educational Objective: Manage minor bleeding in a patient taking a non-vitamin K antagonist oral anticoagulant.

Observation is most appropriate in this patient at this time. She has no major or clinically relevant bleeding; therefore, a conservative treatment approach is reasonable. Her hemoglobin level is normal, she is hemodynamically stable, and she has no other signs of bleeding. The elimination half-life of dabigatran is 12 hours with anticoagulant effect for 24 hours in patients with normal kidney function. Dabigatran should be withheld for 24 hours or longer in this patient pending evaluation of her urinary tract. She has nonglomerular hematuria (no proteinuria, casts, or dysmorphic erythrocytes) and requires an evaluation of the upper and lower urinary tract for a cause of the hematuria. The necessity to fully evaluate hematuria is not influenced by the use of anticoagulant therapy.

Fresh frozen plasma has been used in patients experiencing major bleeding while taking a non-vitamin K antagonist oral anticoagulant, but it is not typically adequate monotherapy in patients experiencing severe bleeding; it is often combined with four-factor prothrombin complex concentrate (4F-PCC). However, neither fresh frozen plasma nor 4F-PCC would be necessary in this patient because she is hemodynamically stable, the bleeding is not life threatening, and the anticoagulant effect of dabigatran will dissipate in 24 hours.

Idarucizumab is a humanized monoclonal antibody fragment with a very high affinity for dabigatran. It is approved for dabigatran reversal for emergency surgery, for urgent procedures, or in patients experiencing life-threatening or uncontrolled bleeding. Severe adverse effects may include thromboembolic events and possible hypersensitivity reactions, such as bronchospasm and pruritus. Because this patient does not have life-threatening bleeding, idarucizumab is not indicated.

Vitamin K administration has no effect on bleeding caused by non-vitamin K antagonist oral anticoagulants such as dabigatran. Vitamin K can be used to reverse over-anticoagulation with warfarin.

KEY POINT

- Minor bleeding in patients taking a non–vitamin K antagonist oral anticoagulant can be managed by discontinuation of the anticoagulant alone without additional therapy.

Bibliography

Pollack CV Jr, Reilly PA, Eikelboom J, Glund S, Verhamme P, Bernstein RA, et al. Idarucizumab for dabigatran reversal. N Engl J Med. 2015;373:511-20. [PMID: 26095746] doi:10.1056/NEJMoa1502000

Item 35 Answer: C

Educational Objective: Manage preoperative transfusion in sickle cell anemia.

The patient should receive preoperative simple transfusion to achieve a hemoglobin level of 10 g/dL (100 g/L). Transfusions may have significant adverse effects, including infection, alloimmunization, and cumulative risk of iron overload. Therefore, persons with sickle cell disease (SCD) should not receive transfusions unless they have significant symptoms or signs of end-organ failure from their anemia or are preparing for surgery. Patients with SCD are at increased risk for perioperative pulmonary, infectious, and thrombotic complications. In 1994, a landmark study was published showing that simple transfusion to a target hemoglobin level of 10 g/dL (100 g/L) was equivalent to exchange transfusion in low- to medium-risk surgeries (low-risk surgeries include adenoidectomy and inguinal-hernia repair; medium-risk surgeries include cholecystectomy and joint replacement) in reducing surgical complications in patients with SCD with less risk, reduced cost, and increased convenience. More recently, guidelines have been published on the care of patients with SCD that strongly recommend simple transfusion to a target hemoglobin level of 10 g/dL (100 g/L) in patients requiring general anesthesia. In addition to transfusion, the use of incentive spirometry has also been shown in a randomized trial to improve surgical outcomes in patients with SCD. Overtransfusion should be avoided in these patients because of complications arising from increased blood viscosity. Typically, hemoglobin levels are kept at or below 10 g/dL (100 g/L).

Exchange transfusion is used for acute stroke or retinal artery occlusion or in patients with severe acute chest syndrome. When indicated, the target hemoglobin S level should be less than 30%.

KEY POINT

- Simple transfusion to achieve a hemoglobin level of 10 g/dL (100 g/L) in patients having low- to moderate-risk surgery reduces surgical complications equivalent to exchange transfusion with less risk and cost.

Bibliography

Yawn BP, Buchanan GR, Afenyi-Annan AN, Ballas SK, Hassell KL, James AH, et al. Management of sickle cell disease: summary of the 2014 evidence-based report by expert panel members. JAMA. 2014;312:1033-48. [PMID: 25203083] doi:10.1001/jama.2014.10517

Item 36 Answer: C

H

Educational Objective: Diagnose protein C deficiency.

The most likely diagnosis is protein C deficiency. The patient's skin condition is most likely retiform purpura. The term "retiform" describes the angulated or netlike configuration that reflects the vascular structure in the skin. The color is often a dark brick-red or purple. Retiform purpura is caused by local skin ischemia caused by occlusion or breakdown of vascular integrity that may lead to necrosis, which may become life-threatening if not aggressively treated. Various conditions can cause retiform purpura, many of which disrupt arterial blood flow. Thrombotic and embolic causes should be considered first. Thrombotic causes include alterations to the coagulation cascade such as disseminated intravascular coagulation, thrombotic thrombocytopenic purpura, and drug-induced thrombosis (warfarin or heparin).The patient's clinical presentation is consistent with warfarin-induced skin necrosis, which is a rare complication of warfarin therapy. The pathophysiology is thought to be caused by a transient hypercoagulable state resulting from protein C deficiency, which can be inherited or acquired. A family history of pulmonary embolism suggests the possibility of inherited protein C deficiency. Congenital protein C deficiency is an autosomal dominant inherited thrombophilia associated with an increased risk of venous thromboembolism. When protein C is activated, it inactivates the activated coagulation factors V and VIII, which are needed for factor X activation. When warfarin is initiated, an initial reduction in protein C activity of 50% occurs, which leads to a transient hypercoagulable state. If the patient is receiving heparin and warfarin therapy, the lesions may appear when the heparin is discontinued, which likely accounts for the appearance of the rash on day 3 of her hospitalization. Treatment involves the discontinuation of warfarin, continuation of alternate anticoagulation (such as a non–vitamin K antagonist oral anticoagulant), vitamin K for warfarin reversal, and fresh frozen plasma in an attempt to improve decreased protein C levels.

Warfarin-induced skin necrosis is not associated with factor V Leiden mutation, plasminogen activator inhibitor 1 deficiency, or prothrombin gene mutation.

KEY POINT

- Protein C or S deficiency is associated with warfarin-associated skin necrosis.

Bibliography

Thornsberry LA, LoSicco KI, English JC 3rd. The skin and hypercoagulable states. J Am Acad Dermatol. 2013 Sep;69(3):450-62. doi:10.1016/j.jaad.2013.01.043. [PMID: 23582572]

Item 37 Answer: D

Educational Objective: Evaluate a patient with dyspnea using the Pulmonary Embolism Rule-Out Criteria.

The patient requires no further testing for pulmonary embolism. Many patients present to the emergency department

with shortness of breath or chest pain. Inappropriate use of D-dimer testing and CT angiography led to the development of new American College of Physicians guidelines regarding the evaluation of patients with possible pulmonary embolism (PE). These guidelines use clinical decision tools (such as the Pulmonary Embolism Rule-Out Criteria [PERC]) to help risk stratify patients who present with shortness of breath or chest pain.

The PERC are defined as

- Age younger than 50 years
- Heart rate less than 100/min
- Oxygen saturation 95% or greater
- No hemoptysis
- No estrogen use
- No previous deep venous thrombosis or PE
- No unilateral leg swelling
- No surgery or trauma requiring hospitalization in the last 4 weeks

To avoid unnecessary testing, patients with a low pretest probability using a validated prediction tool such as the Wells Criteria for Pulmonary Embolism and negative PERC should undergo no further evaluation. In patients with intermediate pretest probability or positive PERC, the D-dimer level should be obtained. Patients with a high pretest probability should proceed directly to imaging, without D-dimer testing.

Because this patient has a low pretest probability and the PERC are negative, neither D-dimer testing nor CT angiography of the chest should be performed. A study of multiorgan ultrasonography was shown to be helpful in the diagnosis of PE in adults with a Wells score of 4 or greater or a positive D-dimer test. A positive test was defined by any one of the following: one or more pulmonary subpleural infarctions on lung ultrasonography; right ventricular dilatation or thrombi on heart ultrasonography; or deep venous thrombosis on lower extremity ultrasonography. Multiorgan ultrasonography was found to be 90% sensitive and 86% specific compared with CT angiography. Multiorgan ultrasonography was significantly more sensitive than individual ultrasonographic examinations of the lungs, heart, or lower extremities.

Echocardiography is unlikely to be helpful in this patient because her pretest probability of pulmonary embolism was very low, and echocardiography alone is an insensitive test.

KEY POINT

- Patients identified as low risk and meeting the Pulmonary Embolism Rule-Out Criteria do not require D-dimer testing to eliminate the need for further diagnostic imaging.

Bibliography

Kline JA, Courtney DM, Kabrhel C, Moore CL, Smithline HA, Plewa MC, et al. Prospective multicenter evaluation of the pulmonary embolism rule-out criteria. J Thromb Haemost. 2008;6:772-80. [PMID: 18318689] doi:10.1111/j.1538-7836.2008.02944.x

Item 38 Answer: C

Educational Objective: Treat chronic myeloid leukemia with an oral tyrosine kinase inhibitor.

This patient should be treated with imatinib, a tyrosine kinase inhibitor (TKI); he has chronic myeloid leukemia (CML) presenting in the chronic phase and requires therapy targeting the *BCR-ABL* fusion gene. Translocation of the long arm of chromosomes 9 and 22 leads to the fusion gene of *BCR-ABL*, which is characteristic of CML. CML is divided into the chronic phase, accelerated phase, or blast crisis depending on clinical and pathologic characteristics. Approximately 90% of patients with CML present in the chronic phase with less than 10% blasts in the blood and bone marrow. TKIs are effective in the treatment of the chronic phase of CML and are usually first-line treatment. The three TKIs approved for initial treatment of CML are imatinib, dasatinib, and nilotinib. Other newer generation TKIs are approved for patients who are intolerant of these first three TKIs or who have CML resistant to them. Although TKIs have some unique adverse effects and drug interactions, they are well tolerated compared with chemotherapy and transplantation.

Bone marrow transplantation for CML in the chronic phase is reserved for patients with resistant disease or who are intolerant of TKIs.

Chemotherapy with idarubicin and cytarabine is used for patients with CML in blast crisis with more than 20% blasts and is not intended for the chronic phase as in this patient. This therapy is similar to the treatment of acute myeloid leukemia.

Part of the differential diagnosis for extreme granulocytic leukocytosis (leukocyte count >50,000/µL [50×10^9/L]) is the leukemoid reaction. When sepsis occurs, the bone marrow responds by releasing early cells into circulation, and a leukemoid reaction may be difficult to distinguish from CML in an acutely ill patient. However, few patients with typical sepsis, even gram-negative bacillary bacteremia, develop such counts. Blasts and basophils are much less likely with a leukemoid reaction. This patient has been chronically, not acutely, ill, and CML is a much more likely explanation of the leukocytosis than is sepsis; therefore, antibiotics are not needed.

KEY POINT

- Tyrosine kinase inhibitors such as imatinib are effective for initial treatment of chronic myeloid leukemia in the chronic phase.

Bibliography

Cortes J, Kantarjian H. How I treat newly diagnosed chronic phase CML. Blood. 2012;120:1390-7. [PMID: 22613793] doi:10.1182/blood-2012-03-378919

Item 39 Answer: B

Educational Objective: Diagnose paroxysmal nocturnal hemoglobinuria.

Flow cytometry is the most appropriate test to perform next. This patient has pancytopenia with significant intravascular

hemolysis and hemoglobinuria, most likely caused by paroxysmal nocturnal hemoglobinuria (PNH). Patients with PNH commonly note fatigue and nonspecific abdominal pain, which worsens during times of increased hemolysis. These patients have a mutation in the gene that regulates production of glycophosphatidylinositol-anchoring proteins. Flow cytometry will demonstrate the absence of glycophosphatidylinositol-linked proteins, such as CD55 and CD59, on leukocytes; these proteins normally prevent complement activation on the erythrocyte surface. Bone marrow aplasia and corresponding pancytopenia in these patients are common, and they have an increased risk of evolving to a myelodysplastic syndrome or acute leukemia. Patients with PNH also have an increased risk for thrombotic complications, including thrombi in unusual sites, such as the portal venous system or sagittal veins in the central nervous system.

Hereditary angioedema is caused by the unregulated activation of the complement cascade owing to lack of or ineffective function of C1 esterase inhibitor, leading to increased vascular permeability. C1 esterase inhibitor deficiency has no role in the pathogenesis of PNH.

While complement-mediated hemolysis is a core feature of PNH, the complement system functions normally. Neither excess of complement nor IgG antibodies are noted on the erythrocyte surface that would be revealed by a direct antiglobulin test.

Vitamin B_{12} deficiency can cause pancytopenia and is commonly associated with some features of intramedullary hemolysis resulting from ineffective erythropoiesis. However, vitamin B_{12} deficiency is associated with macrocytic anemia, which is not present in this patient. Hemoglobinuria is present in PNH but not seen in vitamin B_{12} deficiency. The first step in diagnosing vitamin B_{12} deficiency is a cobalamin measurement. Methylmalonic acid and homocysteine measurements may be helpful in cases of diagnostic uncertainty because they are elevated in 98% of patients with cobalamin deficiency. Methylmalonic acid measurement is unnecessary in this patient.

KEY POINT

- Diagnosis of paroxysmal nocturnal hemoglobinuria is based on flow cytometry results, which can detect CD55 and CD59 deficiency on the surface of peripheral erythrocytes or leukocytes.

Bibliography

Sutherland DR, Illingworth A, Keeney M, Richards SJ. High-sensitivity detection of PNH red blood cells, red cell precursors, and white blood cells. Curr Protoc Cytom. 2015:72:6.37.1-30. [PMID: 25827482] doi:10.1002/0471142956.cy0637s72

H

Item 40 Answer: C

Educational Objective: Treat coagulopathy of liver disease.

This patient should receive a transfusion with cryoprecipitate. He has the coagulopathy of liver disease, characterized by thrombocytopenia, prolonged activated partial thromboplastin time (aPTT) and prothrombin time (PT), elevated D-dimer level, and hypofibrinogenemia. The patient's hemodynamic instability is addressed with fluids and erythrocyte transfusion. Vitamin K will help correct the PT, but he may also need fresh frozen plasma (FFP). Thrombocytopenia is addressed with platelet transfusion. Fibrinogen levels less than 100 mg/dL (1 g/L) associated with active bleeding should be corrected. Cryoprecipitate contains more fibrinogen than FFP and is the blood component of choice for treating this patient. It is often difficult to distinguish between disseminated intravascular coagulation (DIC) and the coagulopathy of liver disease, but a normal or increased factor VIII level points to liver disease instead of DIC. Somewhat paradoxically, factor VIII levels are supranormal in the coagulopathy of liver disease because it is produced in extrahepatic endothelial cells, and a hepatically synthesized factor is required for factor VIII clearance. The management of these coagulopathies is often the same.

Recombinant activated factor VII is preferred for treating patients with acquired hemophilia associated with high titers of antibody directed against factor VIII. It may be used to treat uncontrolled bleeding in patients with liver disease unresponsive to replacement of platelets, FFP, vitamin K, and cryoprecipitate.

ε-Aminocaproic acid (EACA), an inhibitor of fibrinolysis, has been shown to reduce blood loss after cardiac and orthopedic surgery. Accelerated fibrinolysis plays some role in the coagulopathy of bleeding in liver disease, and EACA may reduce bleeding in some of these patients. No laboratory test correlates fibrinolysis with bleeding risk, and EACA should not be used before treating more objective measures of coagulopathy, such as low fibrinogen levels.

Four-factor prothrombin complex concentrate is used to treat patients with warfarin toxicity and life-threatening bleeding. It should not be used more routinely to treat patients with the coagulopathy of liver disease and bleeding until conventional component support proves ineffective.

KEY POINT

- Patients with coagulopathy of liver disease and low fibrinogen levels who are experiencing bleeding should receive immediate cryoprecipitate transfusion.

Bibliography

Tripodi A, Mannucci PM. The coagulopathy of chronic liver disease. N Engl J Med. 2011;365:147-56. [PMID: 21751907] doi:10.1056/NEJMra1011170

Item 41 Answer: B

H

Educational Objective: Prevent venous thromboembolism in a hospitalized patient with cancer.

This patient should receive prophylactic enoxaparin. Venous thromboembolism (VTE) is a major contributor to morbidity and mortality in patients with cancer. It is the second leading cause of death after the cancer itself. Hospitalized patients with cancer have an even greater thrombotic risk. The Prophylaxis in Medical Patients with Enoxaparin (MEDENOX)

H CONT.

trial enrolled 1102 medically ill patients who were randomly assigned to receive one of three subcutaneous regimens: enoxaparin sodium, 20 mg/d; enoxaparin sodium, 40 mg/d; or placebo. The frequency of VTE was reduced in a statistically significant manner in patients receiving enoxaparin sodium, 40 mg/d. For hospitalized patients with cancer and acute illness, pharmacologic prophylaxis should be used unless a clear contraindication exists.

Although aspirin has a role for prevention of recurrent VTE in patients without cancer, it does not have a place in primary prophylaxis.

The American College of Physicians guideline on VTE prophylaxis in hospitalized patients recommends against the use of graduated compression stockings because of the lack of difference in risk for mortality or symptomatic VTE. However, risk for lower-extremity skin damage was increased among patients treated with compression stockings.

The American College of Physicians guideline also noted that in patients at high risk for bleeding events or in whom heparin is contraindicated for other reasons, intermittent pneumatic compression may be a reasonable option because evidence suggests it is beneficial in surgical patients. However, intermittent pneumatic compression has not been sufficiently evaluated as a stand-alone intervention in medical patients to reliably estimate benefits and harms.

Warfarin is typically not used as VTE prophylaxis in hospitalized patients with cancer because of its delayed onset of antithrombotic action and the need for dose adjustment. Although low-molecular-weight heparin is more effective than warfarin for treatment of cancer-associated VTE, no randomized trials have compared the benefit of prophylactic heparin with warfarin in hospitalized medical patients.

KEY POINT

- In patients with cancer who are hospitalized, prophylactic anticoagulation with low-molecular-weight heparin should be provided to reduce the risk of venous thromboembolism.

Bibliography

Samama MM, Cohen AT, Darmon JY, Desjardins L, Eldor A, Janbon C, et al. A comparison of enoxaparin with placebo for the prevention of venous thromboembolism in acutely ill medical patients. Prophylaxis in Medical Patients with Enoxaparin Study Group. N Engl J Med. 1999;341:793-800. [PMID: 10477777]

Item 42 Answer: E

Educational Objective: Manage sickle cell disease in an uncomplicated pregnancy.

This patient requires no treatment other than expectant care. She should be closely monitored and treatment should be withheld until symptoms appear or some measurable parameter changes. Sickle cell disease (SCD) is associated with maternal morbidity and mortality from stroke, vaso-occlusive crisis, and acute chest syndrome. Furthermore, the risk of eclampsia is higher in pregnant women with SCD. Fetal complications are also more common in patients with SCD, including low birth weight, spontaneous abortion, early delivery, and growth retardation. No routine interventions have been proven to decrease these complications, so close follow-up by hematologic and obstetric specialists and prompt management of evolving problems is important. Pregnancy outcomes are difficult to predict in pregnant patients with SCD, but one of the best indicators is the outcome from a previous pregnancy, which is encouraging in this patient.

Antiplatelet drugs, such as clopidogrel, have been associated with increased risk of bleeding and ablatio placenta without any clear benefit in pregnant patients with SCD.

Although the role of transfusion in the management of pregnant patients with SCD lacks consensus, no clear benefit has been seen with either simple or exchange transfusion in patients with uncomplicated disease or pregnancy. However, pregnant patients with SCD who have worsening symptomatic anemia should undergo transfusion. Those with past or new severe obstetric or fetal complications, those with twins, or those with chronic organ dysfunction may also benefit from transfusion. The decision to transfuse must be balanced against the risks of transfusion, including alloimmunization and delayed transfusion reaction, as well as iron and volume overload. Because this patient has an uncomplicated pregnancy, exchange or simple transfusion is not indicated.

Hydroxyurea therapy results in decreased mortality in SCD and is indicated in patients with recurrent painful episodes, acute chest syndrome, and symptomatic anemia. However, because of its potential teratogenicity, hydroxyurea should not be administered during pregnancy. Proper contraception before hydroxyurea initiation should be discussed with the nonpregnant patient. This patient has no indication for hydroxyurea treatment.

KEY POINT

- Patients with sickle cell disease and uncomplicated pregnancy should be closely monitored and treatment withheld until symptoms appear or some measurable parameter changes.

Bibliography

Boga C, Ozdogu H. Pregnancy and sickle cell disease: a review of the current literature. Crit Rev Oncol Hematol. 2016;98:364-74. [PMID: 26672916] doi:10.1016/j.critrevonc.2015.11.018

Item 43 Answer: D

Educational Objective: Diagnose α-thalassemia trait.

The most likely diagnosis is α-thalassemia trait. This patient has a chronic microcytic anemia. Patients with α-thalassemia trait have inadequate production of two copies of the α gene on chromosome 16 (α-/α- or --/αα). Such patients have a chronic microcytic anemia with hemoglobin levels of approximately 10 g/dL (100 g/L). Hemoglobin A levels, although reduced in quantity, are otherwise normal in these patients and will migrate in a normal pattern

on electrophoresis. Furthermore, there is no increase in the minor hemoglobin components, hemoglobin A_2 and hemoglobin F. It is possible to identify specific chromosomal abnormalities that establish the diagnosis of α-thalassemia, but physicians typically make a clinical diagnosis based on family history, complete blood count, peripheral blood smear, and hemoglobin electrophoresis and by ruling out other causes of microcytic anemia. Patients with thalassemia should receive supplemental folate but should not receive iron supplementation; they are not iron deficient and they have an increased ability to absorb iron, which can lead to iron overload. Genetic counseling may be indicated in reproductive planning.

This patient's iron study results are normal, and her serum ferritin level is greater than 100 ng/mL (100 µg/L), essentially ruling out iron deficiency.

Inflammatory anemia, also known as anemia of chronic disease, is characterized by a low serum iron level and often a concomitant reduction in iron-binding capacity in the absence of iron deficiency. The iron studies in this patient are inconsistent with that diagnosis. Mild microcytosis may be seen in the anemia of inflammation but not as severely as in this patient.

Patients who are silent carriers for α-thalassemia have a defect in production of a single α gene. These patients have a normal hemoglobin level and no microcytosis. They are clinically healthy.

Patients with β-thalassemia minor also have a chronic microcytic anemia and a normal electrophoretic pattern for hemoglobin A. But in β-thalassemia, the excess α chains link with δ and γ chains to produce increased amounts of hemoglobin A_2 and hemoglobin F, respectively.

KEY POINT

- Patients with α-thalassemia trait have chronic microcytic anemia with hemoglobin levels of approximately 10 g/dL (100 g/L) and a normal hemoglobin electrophoresis pattern.

Bibliography

Brancaleoni V, Di Pierro E, Motta I, Cappellini MD. Laboratory diagnosis of thalassemia. Int J Lab Hematol. 2016;38 Suppl 1:32-40. [PMID: 27183541] doi:10.1111/ijlh.12527

Item 44 Answer: D

Educational Objective: Manage an elevated INR.

The patient's warfarin therapy should be withheld, and her INR should be remeasured in 2 days. Warfarin acts by inhibiting the synthesis of vitamin K-dependent clotting factors, which include factors II, VII, IX, and X. Variations in INR can occur with dietary changes. Other factors associated with prolonged elevation of INR include age 80 years or older, lower maintenance dose of warfarin, decompensated heart failure, active cancer, and use of medications known to potentiate the effect of warfarin. The 30-day risk of major bleeding is less than 1% with an INR between 5 and 9. Accordingly, warfarin should be withheld in patients with elevated INRs between 4.5 and 10 who are not bleeding and have no major risk factors for bleeding. Approximately one third of patients with an INR greater than 6 will still have an abnormal INR after withholding warfarin for two consecutive doses. Warfarin can be reinstituted when the INR returns to a therapeutic level.

The patient is asymptomatic, with no evidence of bleeding. Therefore, neither vitamin K nor fresh frozen plasma should be given. Patients who are not bleeding, are not at high risk for bleeding, and have an INR less than 10 can be managed simply by withholding warfarin. For patients with an INR greater than 10, oral vitamin K, 2.5 mg, should be given. Oral vitamin K and intravenous vitamin K appear equally effective and more effective than subcutaneous vitamin K or placebo for reversing excessive warfarin-induced anticoagulation.

The American Society of Hematology recommends against administering plasma or prothrombin complex concentrates for nonemergent reversal of vitamin K antagonists (including situations other than major bleeding, intracranial hemorrhage, or anticipated emergent surgery). However, the 30-day mortality is approximately 13% in patients with major bleeding during treatment with warfarin. In these patients with acute major bleeding as a result of warfarin therapy, in addition to vitamin K, prothrombin complex concentrates are preferred to fresh frozen plasma. Prothrombin complex concentrate is more effective than fresh frozen plasma for reducing 30-day all-cause mortality and the INR in patients with major bleeding or requiring surgical or invasive procedures.

KEY POINT

- Patients with asymptomatic INR elevation between 4.5 and 10 are managed by simply withholding warfarin.

Bibliography

Lee A, Crowther M. Practical issues with vitamin K antagonists: elevated INRs, low time-in-therapeutic range, and warfarin failure. J Thromb Thrombolysis. 2011;31:249-58. [PMID: 21274594] doi:10.1007/s11239-011-0555-z

Item 45 Answer: B

Educational Objective: Manage pre-eclampsia in a pregnant woman with thrombocytopenia.

The most appropriate management of this patient is emergency delivery of the fetus. Several disorders are characterized by microangiopathic hemolytic anemia (MAHA) and thrombocytopenia during pregnancy. Pre-eclampsia, HELLP (Hemolysis, Elevated Liver enzymes, and Low Platelets) syndrome, and thrombotic thrombocytopenic purpura-hemolytic uremic syndrome (TTP-HUS) have different clinical features but with significant overlap. Pre-eclampsia typically presents with hypertension, peripheral edema, and proteinuria, most commonly in the third

trimester of pregnancy. TTP-HUS is characterized by MAHA and thrombocytopenia developing in the first or second trimester. Additionally, neurologic findings and fever are more common in TTP-HUS than in the other syndromes. HELLP syndrome is characterized by right upper quadrant pain and elevated liver enzyme levels. Disseminated intravascular coagulation parameters may be found in patients with pre-eclampsia and HELLP syndrome but should be absent in those with TTP HUS. This patient has pre-eclampsia, defined as hypertension (systolic blood pressure >140 mm Hg or diastolic blood pressure >90 mm Hg) after the 20th week of gestation with edema and proteinuria, which requires immediate delivery. Symptoms usually resolve with delivery. HELLP syndrome is similarly treated.

Eculizumab is used to treat atypical hemolytic uremic syndrome (HUS), which is the most common form of HUS in pregnancy. It is associated with congenital defects in the alternate pathway of the complement system. Although this patient has proteinuria, the normal creatinine level makes this an unlikely diagnosis because marked kidney disease is a hallmark of this disorder.

High-dose glucocorticoids would be useful to treat immune thrombocytopenic purpura (ITP) in pregnancy, especially toward the end of the third trimester. ITP is diagnosed when an isolated thrombocytopenia is discovered, but it is not associated with hypertension, proteinuria, or schistocytes on the peripheral blood smear.

Although she has thrombocytopenia, fragmented erythrocytes, and headache, her elevated blood pressure, edema, and proteinuria point to pre eclampsia as a more likely diagnosis than TTP. Therefore, plasma exchange would not be appropriate.

KEY POINT

- Pre-eclampsia, HELLP (Hemolysis, Elevated Liver enzymes, and Low Platelets) syndrome, and thrombotic thrombocytopenic purpura hemolytic uremic syndrome can all present with microangiopathic hemolytic anemia and thrombocytopenia during pregnancy; pre-eclampsia is defined by hypertension, edema, and proteinuria after the 12th week of gestation.

Bibliography

Shatzel JJ, Taylor JA. Syndromes of thrombotic microangiopathy. Med Clin North Am. 2017;101:395-415. [PMID: 28189178] doi:10.1016/j.mcna.2016.09.010

Item 46 Answer: D

Educational Objective: Diagnose von Willebrand disease.

Von Willebrand disease (vWD) is the most common inherited hemostatic defect. Quantitative or qualitative abnormalities in the portion of the factor VIII molecule that facilitates binding of platelets to injured endothelium lead to bleeding. Often the hemostatic defect is mild, characterized as mucosal or endometrial bleeding, and requires an additional hemostatic insult, such as surgery, menstruation, or platelet injury from NSAIDs, to provoke bleeding. The patient's bleeding history and normal prothrombin time (PT), activated partial thromboplastin time (aPTT), and platelet count, along with an abnormal screening of platelet function, support the diagnosis of vWD. This diagnosis can be confirmed by finding a quantitative reduction in von Willebrand antigen and a qualitative reduction in von Willebrand ristocetin cofactor activity.

Congenital hemophilia A is an X-linked hereditary disorder of factor VIII deficiency. Although women may be carriers, they rarely have symptomatic bleeding. Laboratory features in inherited hemophilia would include a prolonged aPTT that corrects with mixing studies and a normal PT. Assay of individual factor levels would confirm factor VIII deficiency. Platelet function should be normal. These features are not present in this patient, making this diagnosis unlikely.

Factor XI deficiency is expressed in a clinically heterogeneous manner. Many patients are asymptomatic, even when stressed with major surgery, but some might have a bleeding history similar to this patient's. The diagnosis is more prevalent in patients of Jewish descent, and the aPTT should be prolonged and should correct with mixing. This patient's normal aPTT and platelet dysfunction make this an unlikely diagnosis.

The lupus anticoagulant is an acquired autoantibody to phospholipids that behaves like an inhibitor in the test tube. Typically, the aPTT is prolonged and does not correct when mixed with normal plasma. Despite the prolonged aPTT, lupus anticoagulants are associated with thrombosis, not bleeding. The patient's normal aPTT and abnormal Platelet Function Analyzer-100 result are not compatible with the presence of a lupus anticoagulant.

KEY POINT

- A history of mucosal or endometrial bleeding, normal prothrombin and activated partial thromboplastin times, and normal platelet count with evidence of a qualitative platelet defect suggest the diagnosis of von Willebrand disease.

Bibliography

Tcherniantchouk O, Laposata M, Marques MB. The isolated prolonged PTT. Am J Hematol. 2013;88:82-5. [PMID: 22811044] doi:10.1002/ajh.23285

Item 47 Answer: B

Educational Objective: Diagnose hemoglobin S β-thalassemia.

This patient most likely has hemoglobin S β thalassemia (Sβ thalassemia). Patients with Sβ thalassemia generally have milder disease than those homozygous for hemoglobin S (HbS). However, patients with Sβ-thalassemia can have painful crises of varied frequency and intensity. Some of the variability in presentation depends on the

relative expression of the β-globin gene (from β^+ to β^0), which in turn determines the relative amount of hemoglobin A (HbA). Most black persons with Sβ-thalassemia are β^+ and have between 5% and 30% HbA; the more HbA present, the less severe the symptoms and fewer the complications. Occasionally, with a milder disease course, patients do not present until adolescence or early adulthood. Hemoglobin electrophoresis is essential in making a specific diagnosis of a sickling disorder. Patients with Sβ-thalassemia have a slightly reduced hemoglobin level and microcytic erythrocytes. Characteristically, their HbS levels are about 60%. In contrast, patients with sickle cell trait have HbS levels well below 50%, typically closer to 30%, and proportionally more HbA. More notably, patients with sickle cell trait do not experience painful crises and have normal hemoglobin levels.

Patients with hemoglobin SS disease (sickle cell anemia) have greater than 90% HbS and no HbA. The clinical expression and severity of sickle cell anemia may be quite variable, and some patients may have few acute pain events and no other major complications, so that the diagnosis may not be suspected until later in life. The level of hemoglobin F detected in these patients may also vary, with increased hemoglobin F levels correlating with milder disease, but Hb A should be undetectable and no microcytosis should be seen.

Hemoglobin E disease results from a point mutation in the β-globin gene that causes decreased production of β-globin and results in a thalassemia-like syndrome. Hemoglobin E migrates in a different pattern than HbA and would be revealed on hemoglobin electrophoresis, in addition to increased levels of HbA2, as with other β-thalassemias. Although patients with hemoglobin E disease will have mild anemia, they do not experience acute pain events.

KEY POINT

- Patients who coinherit hemoglobin S and β-thalassemia genes typically have lifelong mild hemolytic anemia with microcytosis and detectable hemoglobin A on electrophoresis; the amount of hemoglobin A is inversely related to the severity of the symptoms and risk of complications.

Bibliography

Benites BD, Bastos SO, Baldanzi G, Dos Santos AO, Ramos CD, Costa FF, et al. Sickle cell/β-thalassemia: Comparison of Sβ(0) and Sβ(+) Brazilian patients followed at a single institution. Hematology. 2016;21:623-629. [PMID: 27237196]

H

Item 48 Answer: A

Educational Objective: Manage acute upper gastrointestinal bleeding with a restrictive transfusion strategy.

This patient should continue to receive crystalloid resuscitation. In the absence of symptoms of anemia, hemodynamic instability, or massive bleeding, a patient such as this one does not require a blood transfusion. A randomized controlled trial of 900 patients with acute upper gastrointestinal bleeding and a hemoglobin level less than 12 g/dL (120 g/L) compared a restrictive transfusion strategy (hemoglobin transfusion threshold of 7 g/dL [70 g/L]) to a liberal strategy (hemoglobin transfusion threshold of 9 g/dL [90 g/L]). Half of the patients had peptic ulcer disease as the source of bleeding. Mortality was lower in the restrictive group compared with the liberal transfusion group (5% versus 9%). Half of the patients in the restrictive group did not receive transfusion at all. Therefore, crystalloid volume resuscitation is appropriate and erythrocyte transfusion unnecessary in this patient.

Plasma transfusion is not indicated in the absence of coagulopathy. Fresh frozen plasma (FFP) contains all of the coagulation factors. FFP use is excessive in the United States and other countries despite published guidelines regarding its use. FFP is ineffective at treating mild coagulopathies. Indications for the use of FFP and other plasma-based products include treatment or prevention of coagulopathy from massive transfusion, bleeding associated with multiple acquired clotting factor deficiencies (liver disease, disseminated intravascular coagulation), and major warfarin-associated hemorrhage when a four-factor prothrombin complex concentrate is not available. There is no reason to suspect that this patient has a coagulopathy requiring replacement of clotting factors.

Platelet counts greater than 50,000/µL (50×10^9/L) do not warrant platelet transfusion in most situations when thrombocytopenia is the only hemostatic defect. The exception is neurosurgical patients, in whom platelet counts of approximately 100,000/µL (100×10^9/L) should be maintained.

KEY POINT

- A hemoglobin transfusion threshold of less than 7 g/dL (70 g/L) for hemodynamically stable patients is associated with less blood use and lower mortality compared with a more liberal hemoglobin transfusion threshold of 9 g/dL (90 g/L).

Bibliography

Villanueva C, Colomo A, Bosch A, Concepción M, Hernandez-Gea V, Aracil C, et al. Transfusion strategies for acute upper gastrointestinal bleeding. N Engl J Med. 2013;368:11-21. [PMID: 23281973] doi:10.1056/NEJMoa1211801

Item 49 Answer: B

Educational Objective: Prevent complications of sickle cell disease with hydroxyurea.

The most appropriate management for this patient is to begin hydroxyurea therapy. The benefits of hydroxyurea in reducing painful crises and complications of sickle cell disease (SCD) were discovered 20 years ago. Hydroxyurea acts as a nitric oxide donor and can decrease vascular and platelet

activity. It also increases levels of hemoglobin F, which, in turn, enhances hemoglobin oxygen avidity and decreases the likelihood of sickling. Hydroxyurea therapy is indicated for patients who experience frequent painful episodes or have a history of acute chest syndrome, severe vaso-occlusive events, or severe symptomatic anemia. It has been shown to decrease vaso-occlusive episodes and acute chest syndrome, to decrease transfusion requirements and hospitalizations, and to prolong overall survival. Unfortunately, hydroxyurea remains underused.

As in other hemolytic anemias, folate is consumed during active hemolysis, which could lead to a megaloblastic anemia. Folic acid supplementation, 1 mg/d, is recommended for most patients with chronic hemolytic anemia. This patient has an elevated mean corpuscular volume related to the reticulocytosis, so additional folate is not needed.

Incentive spirometry is useful in preventing acute chest syndrome in patients hospitalized with an acute pain event and chest symptoms, but it is unnecessary to continue treatment after the patient is pain free.

Although simple or exchange transfusion may be indicated in the therapy of acute chest syndrome, no evidence supports continuing transfusion therapy after the patient has recovered. Additionally, persons with SCD should not receive transfusions unless they have significant symptoms from their anemia (dizziness, shortness of breath, chest pain that is significantly worse than their typical vaso-occlusive symptoms) or they have signs of end-organ damage (such as acute neurologic symptoms, acute chest syndrome, multi-organ failure). Transfusions for simple vaso-occlusive pain are generally not indicated.

KEY POINT

- In patients with sickle cell disease, hydroxyurea therapy has been shown to decrease vaso-occlusive episodes and acute chest syndrome, to decrease transfusion requirements and hospitalizations, and to prolong overall survival.

Bibliography

Kato GJ. New insights into sickle cell disease: mechanisms and investigational therapies. Curr Opin Hematol. 2016;23:224-32. [PMID: 27055046] doi:10.1097/MOH.0000000000000241

Item 50 Answer: B

Educational Objective: Diagnose polycythemia vera.

The most appropriate diagnostic test to perform is for the *JAK2 V617F* mutation. Polycythemia vera (PV) is a disorder of the myeloid and erythroid stem cells that causes erythropoietin-independent proliferation of erythrocytes. This older adult patient has an elevated hematocrit level, a low erythropoietin level, and splenomegaly, indicating a likely diagnosis of PV. More than 97% of patients with PV have the *JAK2* mutation. The 2016 World Health Organization major criteria for PV include increased hemoglobin level (>16.5 g/dL [165 g/L] in men and >16 g/dL [160 g/L] in women), a bone marrow biopsy specimen showing hypercellularity and increased reticulin and collagen fibrosis, and positive findings for *JAK2* or exon 12 mutation. *JAK2* mutation testing can be done on peripheral blood granulocytes.

Calreticulin mutation has been recently found in *JAK2*-negative myeloproliferative disorders such as essential thrombocythemia and myelofibrosis. Evaluation for the calreticulin mutation would not be indicated in the absence of thrombocytosis or cytopenia.

Translocation of chromosomes 9 and 22, resulting in a *BCR-ABL* fusion gene, is seen in patients with chronic myeloid leukemia (CML). CML can present with elevated leukocyte and platelet counts, but polycythemia is not a typical presentation.

Most causes of secondary erythrocytosis share the mechanism of an elevated erythropoietin level, which is most commonly driven by hypoxemia. Polycythemia can be the presenting symptom of undiagnosed sleep apnea, and all patients with polycythemia should be screened for symptoms and signs of sleep apnea. However, in this patient with no symptoms, a low erythropoietin level, and splenomegaly, PV is much more likely, and *JAK2* mutational analysis should be performed first.

KEY POINT

- *JAK2 V617F* mutation is present in 97% of patients with polycythemia vera, so testing should be performed in patients in whom the disease is suspected.

Bibliography

Arber DA, Orazi A, Hasserjian R, Thiele J, Borowitz MJ, Le Beau MM, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood. 2016;127:2391-405. [PMID: 27069254] doi:10.1182/blood-2016-03-643544

Item 51 Answer: C

Educational Objective: Diagnose thrombotic thrombocytopenic purpura.

H

The finding of schistocytes on the peripheral blood smear is all that is needed to initiate therapy for presumed thrombotic thrombocytopenic purpura (TTP). This patient's clinical features of fever, change in mental status, thrombocytopenia, and features of hemolytic anemia (low haptoglobin level, elevated lactate dehydrogenase level, elevated reticulocyte count) suggest TTP. The presence of schistocytes on the peripheral blood smear will confirm the diagnosis of a microangiopathic hemolytic anemia (MAHA) and a presumptive diagnosis of TTP and allows for early treatment. Prompt diagnosis is critical because TTP is fatal in 90% of patients without therapy. Patients require emergent treatment with plasma exchange.

The most common cause of TTP results from a deficiency in the protease ADAMTS13, which cleaves the high-molecular-weight multimers of von Willebrand

H CONT.

factor (vWF). The decrease in ADAMTS13 activity leads to accumulation of clumps of ultra-large-molecular-weight vWF multimers, which bind to masses of platelets leading to microvascular occlusion and thrombocytopenia. If the peripheral blood smear supports the diagnosis of TTP, testing for ADAMTS13 activity is important to confirm the diagnosis and establish the autoimmune cause. However, the turn-around time for this test result is long, and therapy should not be delayed while awaiting results. This patient's clinical history, laboratory findings, and schistocytes on the peripheral blood smear are sufficient to initiate life-saving treatment.

Coagulation studies are almost always normal in patients with TTP. Tissue ischemia may result in laboratory findings consistent with disseminated intravascular coagulation, but neither normal nor abnormal coagulation studies affect the decision to initiate early therapy.

In a patient with thrombocytopenia, MAHA, and bloody diarrhea, stool cultures and toxin testing for Shiga toxin or Shiga toxin–producing organisms are indicated to differentiate TTP from hemolytic uremic syndrome. Because this patient does not have diarrhea, stool studies are not indicated, and results do not dictate when to initiate therapy.

KEY POINT

- In the proper clinical setting, a peripheral blood smear showing schistocytes in a patient with thrombocytopenia and hemolytic anemia establishes a presumptive diagnosis of thrombotic thrombocytopenic purpura and confirms the need to initiate early, life-saving therapy.

Bibliography

George JN, Nester CM. Syndromes of thrombotic microangiopathy. N Engl J Med. 2014;371:654-66. [PMID: 25119611] doi:10.1056/NEJMra1312353

Item 52 Answer: D

Educational Objective: Screen for hyperlipidemia and diabetes in adult survivors of pediatric leukemia.

A lipid profile and fasting blood glucose should be performed. Adult survivors of childhood leukemia (primarily acute lymphoblastic leukemia [ALL]) have health risks largely secondary to the cancer therapy they received. Requesting a treatment summary or referral to a survivor clinic at a comprehensive cancer center is the first step in providing care. Increased risks of cardiovascular disease, the metabolic syndrome, and secondary cancer are the most relevant concerns. Compared with control populations, survivors of ALL are more likely to have features of the metabolic syndrome, including high BMI, truncal obesity, dyslipidemia, insulin resistance, and hypertension. Screening for lipid profile, diabetes, and hypertension is recommended by multiple guidelines for adult survivors of childhood ALL.

Survivors of ALL in continuous remission for more than 20 years have virtually no risk for ALL recurrence, although they are at risk for therapy-associated myelodysplastic syndrome or acute myeloid leukemia up to 15 years after treatment. With normal complete blood count findings, surveillance bone marrow examinations and whole genome sequencing are not indicated.

Leukemia therapy in childhood does not typically compromise ovarian function, and the patient's regular periods attest to the presence of normal ovarian function; obtaining estrogen and progesterone levels is not necessary.

Anthracyclines, such as doxorubicin, are the most common cause of dose-dependent chemotherapy-induced cardiomyocyte damage, leading to late and irreversible chronic heart failure. Exposure to anthracycline chemotherapy during childhood can cause heart failure in adulthood. However, echocardiography, not an exercise stress test, is the appropriate test to evaluate for abnormal myocardial function that may be asymptomatic. Echocardiography before pregnancy may be particularly important in women previously treated with anthracyclines because they are at risk for further deterioration of myocardial function during pregnancy.

KEY POINT

- Survivors of acute lymphoblastic leukemia are at increased risk for the metabolic syndrome, including high BMI, truncal obesity, dyslipidemia, insulin resistance, and hypertension.

Bibliography

Diller L. Clinical practice. Adult primary care after childhood acute lymphoblastic leukemia. N Engl J Med. 2011;365:1417-24. [PMID: 21995389] doi:10.1056/NEJMcp1103645

Item 53 Answer: C

H

Educational Objective: Diagnose transfusion-associated circulatory overload.

The most likely diagnosis is transfusion-associated circulatory overload, which is an underrecognized and underreported transfusion reaction affecting 1% to 8% of transfusion recipients. Risk factors include older age, pre-existing cardiac or kidney disease, receipt of multiple blood components, and rapid administration rate. The definition includes respiratory distress within 6 hours of transfusion, positive fluid balance, elevated central venous pressure, elevated B-type natriuretic peptide, and radiographic findings of pulmonary edema. Management consists of transfusion discontinuation, diuretic therapy, and supportive care. Prevention includes a slower infusion rate (1 mL/kg/hour) and diuretic therapy between transfusions to maintain euvolemia for those at risk.

Intravascular acute hemolytic transfusion reactions are characterized by the immediate destruction of donor erythrocytes by recipient antibodies. Signs and symptoms include

H CONT.

fever, chills, dyspnea, red urine, flank pain, kidney injury, disseminated intravascular coagulation, and hypotension or shock; they do not include circulatory overload as seen in this patient.

Anaphylaxis is associated with respiratory distress. Manifestations include the sudden onset of respiratory distress, bronchospasm, angioedema, urticaria, nausea and vomiting, abdominal pain, tachycardia, and hypotension. It is not associated with pulmonary edema.

Transfusion-related acute lung injury (TRALI) is the leading cause of transfusion-related mortality. It is characterized by the development of acute lung injury within 6 hours of transfusion of erythrocytes, platelets, or fresh frozen plasma. TRALI is mediated by initial priming of neutrophils in the recipient's lung parenchyma followed by their activation by anti-HLA and antineutrophil antibodies present in donor plasma. Signs and symptoms escalate quickly and include dyspnea, hypoxia, fever, chills, and hypotension. The chest radiograph shows diffuse bilateral pulmonary infiltrates. The presence of circulatory overload is not consistent with TRALI. Management of TRALI is supportive.

KEY POINT

- Signs of transfusion-associated circulatory overload include respiratory distress within 6 hours of transfusion, positive fluid balance, elevated central venous pressure, elevated B-type natriuretic peptide, and radiographic findings of pulmonary edema.

Bibliography

Delaney M, Wendel S, Bercovitz RS, Cid J, Cohn C, Dunbar NM, et al; Biomedical Excellence for Safer Transfusion (BEST) Collaborative. Transfusion reactions: prevention, diagnosis, and treatment. Lancet. 2016;388:2825-2836. [PMID: 27083327] doi:10.1016/S0140-6736(15)01313-6

H

Item 54 Answer: B

Educational Objective: **Treat acute chest syndrome.**

The most appropriate management is to perform immediate exchange transfusion. The patient has acute chest syndrome (ACS), defined clinically by fever, respiratory findings that include tachypnea and hypoxia, and evolving infiltrates on chest radiograph. ACS is one of the most common complications of sickle cell disease and is the most common cause of death. ACS may occur secondary to infection, fat or bone marrow embolism, in situ thrombosis, or any combination of these. ACS remains a clinical diagnosis. Patients should receive supplemental oxygen, incentive spirometry, analgesics if they have concomitant pain, and antibiotics to treat common causes of pneumonia. The severity of ACS determines the need for transfusion and type of transfusion (simple versus exchange transfusion). Mild episodes require no transfusion, moderate episodes are managed with simple or exchange transfusion, and severe episodes require exchange transfusion. The target hemoglobin level is 10 g/dL (100 g/L). Most experts agree that patients requiring mechanical ventilation or experiencing shock or other signs of multiorgan dysfunction should receive exchange transfusion.

Venous thromboembolism is not a common precipitant of ACS, and filling defects in the pulmonary vasculature are more likely to be caused by bone marrow or fat emboli than by venous thromboembolism. Without evidence for venous thrombosis of the lower extremity or other risk factors, CT pulmonary angiography should not be obtained, and therapeutic anticoagulation with heparin should not be started. Similarly, duplex Doppler imaging of the lower extremities should not be performed in the absence of clinical features such as unilateral leg swelling or edema and dilatation of the venous pattern that suggest acute venous thrombosis.

Acute infection is a common precipitant of ACS, and antibiotics to treat common causes of pneumonia should be routinely administered. Although a broad range of bacterial and viral agents have been linked to ACS, infection with fungal organisms is rare, and amphotericin is not indicated.

KEY POINT

- Patients with sickle cell disease and acute chest syndrome with respiratory distress requiring mechanical ventilation should receive emergent exchange transfusion.

Bibliography

Novelli EM, Gladwin MT. Crises in sickle cell disease. Chest. 2016;149:1082-93. [PMID: 26836899] doi:10.1016/j.chest.2015.12.016

Item 55 Answer: C

H

Educational Objective: **Reverse non–vitamin K antagonist oral anticoagulation before emergent surgery.**

The most appropriate management of this patient is to administer idarucizumab. To proceed with urgent procedures or surgery in patients taking anticoagulants, the continued presence of the anticoagulant must be determined, and the anticoagulant effect must be reversed. Idarucizumab is a humanized monoclonal antibody fragment that binds with high affinity to free and thrombin-bound dabigatran. The REVERSE-AD study assessed the efficacy and safety of idarucizumab for patients with serious bleeding or requiring urgent procedures. Among the 36 patients in the study who underwent a procedure, normal hemostasis was reported in 92%. The half-life of dabigatran in patients with normal kidney function is 12 to 17 hours. Although the patient's last dose of dabigatran was 16 hours ago, her impaired kidney function (serum creatinine level, 1.7 mg/dL [150 µmol/L]) will likely extend the half-life of the drug. In patients taking dabigatran, prolongation of the activated partial thromboplastin time is a good indication of bleeding risk with emergency surgery. Low levels of dabigatran can be detected by elevation of the dilute thrombin time.

H CONT.

Dabigatran is cleared through the kidney, and dialysis has been used in patients experiencing bleeding. However, treatment duration is unclear, and a rebound increase in dabigatran levels after discontinuation of dialysis has been noted; therefore, dialysis would not be the best, or even the most practical, management choice for this patient who requires emergency surgery.

Fresh frozen plasma should not be used in this patient. It would require a large volume to overcome inhibition of factor Xa, putting the patient at great risk for transfusion-associated circulatory overload (TACO). TACO is a common adverse event in which hypervolemia develops toward completion or within several hours of a blood product transfusion.

Although three- and four-factor prothrombin complex concentrates (PCCs) have been used in bleeding associated with non-vitamin K antagonist oral anticoagulants, the benefit of PCCs has not been confirmed in randomized trials and remains unclear. Because idarucizumab is available as a reversal agent for dabigatran, its use would be first line in this setting.

KEY POINT

- Patients taking dabigatran and requiring urgent surgery should be given idarucizumab, a monoclonal antibody fragment that binds free and thrombin-bound dabigatran and neutralizes its activity.

Bibliography

Pollack CV Jr, Reilly PA, Eikelboom J, Glund S, Verhamme P, Bernstein RA, et al. Idarucizumab for dabigatran reversal. N Engl J Med. 2015;373:511-20. [PMID: 26095746] doi:10.1056/NEJMoa1502000

H

Item 56 Answer: B

Educational Objective: Diagnose folate deficiency.

The most likely diagnosis is folate deficiency. The patient has a macrocytic anemia associated with malnutrition and presumed decreased consumption of folate-rich foods and chronic alcoholism. A major source of folate is grains and green leafy vegetables, but folate absorption is decreased in the presence of chronic alcoholism. This patient is at risk for folate deficiency based on his homelessness, cachetic appearance suggesting malnutrition, and chronic alcoholism. Folate is not efficiently stored, and folate deficiency can develop within weeks of inadequate intake. Measuring the folate level is often of limited utility because of the ease and safety of initiating folate replacement. This patient should receive supplemental folate in addition to mental health and social service support.

Cobalamin deficiency will also produce a macrocytic anemia with hematologic features identical to that seen in folate deficiency. Unlike folate, cobalamin is effectively stored, and dietary inadequacy is not a common cause of deficiency. Alcohol dependence is not a risk factor for cobalamin deficiency. Although cobalamin deficiency is a conceivable cause of anemia in this patient, folate deficiency is much more likely.

Inflammatory anemia is caused by underlying proinflammatory states, such as infection, cancer, and autoimmune disease, and other conditions not traditionally characterized as proinflammatory, including chronic heart failure and diabetes mellitus. It is associated with a normocytic or microcytic anemia, not with macrocytosis or hypersegmented neutrophils as seen in this patient.

The hallmark of iron deficiency is a microcytic hypochromic anemia. Macrocytosis and hypersegmented neutrophils are not seen, making iron deficiency an unlikely diagnosis in this patient.

KEY POINT

- Folate deficiency should be suspected in patients with macrocytic anemia, malnutrition, and alcohol dependence.

Bibliography

Green R, Dwyre DM. Evaluation of macrocytic anemias. Semin Hematol. 2015;52:279-86. [PMID: 26404440] doi:10.1053/j.seminhematol.2015.06.001

Item 57 Answer: D

Educational Objective: Diagnose multiple myeloma.

Serum protein electrophoresis (SPEP) and serum free light chain analysis are the most appropriate next diagnostic steps. He has the classic signs and symptoms of multiple myeloma (MM) (hyperCalcemia, Renal failure, Anemia, and Bone lesions [CRAB]; the bone lesions in this instance manifest by a compression fracture). In addition to these features, he has elevated total protein and low serum albumin levels, which indicate an elevated globulin level that can be seen with MM. SPEP and serum free light chain assay are the initial screening tests for MM because they identify most myelomas, which secrete a clonal immunoglobulin, a light chain, or both. Rarely, some patients with MM do not secrete a protein, and bone marrow biopsy is required for diagnosis.

Bone scans are not obtained in MM because myeloma lesions are usually lytic and lack the associated increase in osteoblast activity that leads to positive bone scan findings typical of other forms of metastatic cancer. Plain radiography of the bones (skeletal surveys) is the most common imaging used to assess lytic lesions, but PET scan and MRI are more sensitive than skeletal survey at identifying MM bone lesions.

Prostate cancer with bone metastasis can cause hypercalcemia, bone pain, anemia, and, possibly, kidney failure from obstruction or hypercalcemia. But it would not cause the elevated protein seen in this patient.

Although primary hyperparathyroidism can cause hypercalcemia and decreased bone density leading to increased risk of vertebral body fractures, this patient's anemia and protein elevation do not fit with that diagnosis.

Answers and Critiques

KEY POINT

- Patients with hypercalcemia, renal failure, anemia, and bone disease should have further testing with serum protein electrophoresis and serum free light chain assay to evaluate for multiple myeloma.

Bibliography

Rajkumar SV, Dimopoulos MA, Palumbo A, Blade J, Merlini G, Mateos MV, et al. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. Lancet Oncol. 2014;15:e538-48. [PMID: 25439696] doi:10.1016/S1470-2045(14)70442-5

Item 58 Answer: B

Educational Objective: Evaluate megaloblastic anemia.

Serum cobalamin and folate levels should be obtained next. The clinical features, pancytopenia with macrocytic erythrocytes and hypersegmented neutrophils, suggest megaloblastic anemia, and serum levels of cobalamin and folate should be assessed. The patient described also has an elevated indirect bilirubin level and an elevated lactate dehydrogenase (LDH) level, which indicate ineffective erythropoiesis and intramedullary hemolysis seen in megaloblastic anemia. This constellation of findings is consistent with cobalamin deficiency, which often occurs simultaneously with other autoimmune conditions, such as Hashimoto thyroiditis. Similar hematologic findings are seen in folate deficiency, which would be more likely in patients with poor nutrition or alcohol dependence. A reasonable first step in evaluating suspected vitamin B_{12} deficiency is serum cobalamin measurement, with levels greater than 300 pg/mL (221 pmol/L) making deficiency unlikely and levels less than 200 pg/mL (148 pmol/L) strongly suggesting deficiency. If diagnostic uncertainty exists, methylmalonic acid and homocysteine measurement may be helpful. Both are elevated in 98% of patients with cobalamin deficiency, even in patients who have neurologic symptoms without anemia. Methylmalonic acid and total homocysteine levels are helpful in differentiating cobalamin deficiency (both levels are elevated) from folate deficiency (elevated homocysteine level but normal methylmalonic acid level).

Bone marrow biopsy is seldom indicated to diagnose megaloblastic anemia. Although a marrow sample may be useful to diagnose myelodysplasia, which can also present as a macrocytic anemia, a bone marrow biopsy would not be the appropriate next test for this patient without first excluding vitamin B_{12} and folate deficiency.

Flow cytometry would not be helpful in the absence of abnormal leukocytes or other findings that raise suspicion for myelodysplasia or leukemia (for example, immature cells, leukopenia, or leukocytosis).

Patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency do not have a macrocytic anemia or hypersegmented neutrophils. During episodes of hemolysis, peripheral blood smears show typical bite cells and Heinz bodies, which are not present in this patient's peripheral smear. Additionally, G6PD deficiency is an X-linked condition uncommon in women. Furthermore, patients with suspected G6PD deficiency should not have G6PD levels measured during an acute hemolytic event because G6PD levels are relatively preserved in the non-hemolyzed cells remaining in circulation, so false-negative results are common.

KEY POINT

- Patients with pancytopenia, macrocytic erythrocytes, hypersegmented neutrophils, and findings consistent with intramedullary hemolysis should have vitamin B_{12} and folate levels assessed to determine the cause of megaloblastic anemia.

Bibliography

Stabler SP. Clinical practice. Vitamin B12 deficiency. N Engl J Med. 2013;368:149-60. [PMID: 23301732] doi:10.1056/NEJMcp1113996

Item 59 Answer: A

Educational Objective: Diagnose acquired von Willebrand disease.

Acquired von Willebrand disease (vWD) should be suspected in a patient who has previously been well without bleeding symptoms but now has bleeding manifestations and laboratory features consistent with vWD. Acquired vWD typically occurs in patients who develop an autoantibody to von Willebrand factor, analogous to that seen with acquired factor VIII deficiency, and in conditions of high sheer pressure within the vasculature, traditionally in patients with a prosthetic heart valve that has become dislodged but also in patients with prosthetic heart valves that appear normal in function and in those with valvular heart disease who have not had surgery. More recently, this disorder has been linked to left ventricular assist devices (LVADs). This patient has the expected INR elevation associated with therapeutic-dose warfarin routinely prescribed after LVAD implantation. But the relatively abrupt onset of bleeding manifestations is associated with prolongation of the Platelet Function Analyzer-100 test, suggesting a new qualitative platelet defect. Acquired vWD can be confirmed by low levels of von Willebrand antigen or ristocetin cofactor activity.

The liver is responsible for synthesizing all clotting factors as well as anticoagulant and antifibrinolytic factors. Because of this fact, patients with severe liver disease will have significantly prolonged prothrombin and activated partial thromboplastin times (PT and aPTT) resulting from decreased levels of coagulation factors. This patient only has slightly prolonged aPTT and PT and no history or evidence of severe liver disease, making the coagulopathy of liver disease unlikely.

Acquired fibrinogen abnormalities are relatively common, whereas inherited fibrinogen disorders are rare. The most common causes include liver disease (dysfibrinogenemia), disseminated intravascular coagulation (hypofibrinogenemia), and certain medications. This patient has no evidence of liver disease, and his fibrinogen level is normal, which together exclude disseminated intravascular coagulation.

Immune thrombocytopenic purpura is associated with a low platelet count and not with a qualitative platelet abnormality.

KEY POINT

- High sheer force seen in some patients with prosthetic heart valves, abnormal native valves, and left ventricular assist device placement may cause an acquired von Willebrand disease with clinical bleeding.

Bibliography

Nascimbene A, Neelamegham S, Frazier OH, Moake JL, Dong JF. Acquired von Willebrand syndrome associated with left ventricular assist device. Blood. 2016;127:3133-41. [PMID: 27143258] doi:10.1182/blood-2015-10-636480

Item 60 Answer: B

Educational Objective: Diagnose myelodysplastic syndrome.

This older adult patient should undergo bone marrow biopsy. He has macrocytic anemia likely resulting from myelodysplastic syndrome (MDS), and a bone marrow biopsy will help confirm the diagnosis. The peripheral blood smear shows a dysplastic neutrophil with abnormal segmentation and hypogranularity and a nucleated erythrocyte, which are characteristic in patients with MDS. MDS is an acquired bone marrow failure syndrome with ineffective hematopoiesis and peripheral cytopenias. A bone marrow biopsy specimen showing hypercellular marrow with dysplastic myeloid progenitor cells and lack of orderly maturation is diagnostic. Bone marrow biopsy also helps with risk stratification of MDS, which determines treatment. Other causes of dysplasia, including chronic infections (HIV), vitamin B_{12} deficiency, alcohol use, and medications such as sulfamethoxazole, must be ruled out.

BCR-ABL translocation involving chromosomes 9 and 22 is pathognomonic for chronic myeloid leukemia (CML), a myeloproliferative neoplasm. CML typically presents in the chronic phase with elevated neutrophils or platelets, or both. CML cannot explain this patient's pancytopenia and abnormal peripheral blood smear findings.

Positivity for the *JAK2* mutation is seen in certain other myeloproliferative neoplasms, such as essential thrombocythemia, polycythemia vera, and primary myelofibrosis. Primary myelofibrosis can present with cytopenias, but patients usually have other systemic symptoms, such as fever, night sweats, and malaise; findings of splenomegaly; and a peripheral blood smear showing teardrop erythrocytes and a leukoerythroblastic picture. This patient's clinical presentation with cytopenias and dysplastic neutrophils does not fit that of CML or other myeloproliferative neoplasms, so performing *JAK2* mutation testing or polymerase chain reaction for *BCR-ABL* translocation is not necessary at this time.

Although patients with multiple myeloma may present with pancytopenia, anemia is more likely to be normochromic or normocytic and not megaloblastic as seen in this patient. Furthermore, patients with multiple myeloma do not have dysplastic leukocytes or nucleated erythrocytes in the peripheral blood.

KEY POINT

- Bone marrow biopsy can help confirm the diagnosis of myelodysplastic syndrome in patients with macrocytic anemia and other cytopenias and a peripheral blood smear showing dysplastic, hypogranular neutrophils and nucleated erythrocytes.

Bibliography

Fenaux P, Haase D, Sanz GF, Santini V, Buske C; ESMO Guidelines Working Group. Myelodysplastic syndromes: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2014;25 Suppl 3:iii57-69. [PMID: 25185242] doi:10.1093/annonc/mdu180

Item 61 Answer: B

Educational Objective: Diagnose pulmonary hypertension related to sickle cell disease.

Echocardiography is the most appropriate diagnostic test to perform next. The patient's symptoms, cardiac examination, and electrocardiography suggest pulmonary hypertension (PH). PH is associated with significant morbidity and a 30% to 50% mortality rate. Prevalence is approximately 10% in nonpregnant patients but increases in women with sickle cell disease (SCD) who become pregnant. Risk factors for development of PH include severity of anemia, iron overload from transfusions, and history of thromboembolic disease. Although cardiac ultrasonography may underestimate the severity of PH, it remains a useful initial noninvasive screening test even if right heart catheterization is eventually required to more definitively evaluate the hemodynamics.

Cardiac MRI would be useful in evaluating infiltrative cardiomyopathy from iron overload or amyloidosis. Secondary iron overload is seen in SCD but invariably in the setting of multiple blood transfusions over years of time, a history that is lacking in this patient.

Although chest pain could be associated with coronary artery disease and angina, patients with SCD are not especially predisposed to this complication. Exercise stress testing would be contraindicated in those with suspected severe PH and a recent episode of exertion-triggered syncope.

Although pregnancy is a risk factor for dissecting thoracic aortic aneurysm, it is somewhat debated whether additional conditions, such as sustained hypertension, Marfan syndrome, or other connective tissue disorders, are required. This patient's clinical features do not warrant aortography before additional tests are performed, including cardiac ultrasonography.

KEY POINT

- Pulmonary hypertension, a known complication in sickle cell disease, may worsen during pregnancy and should be initially evaluated by echocardiography.

Bibliography

Gordeuk VR, Castro OL, Machado RF. Pathophysiology and treatment of pulmonary hypertension in sickle cell disease. Blood. 2016;127:820-8. [PMID: 26758918] doi:10.1182/blood-2015-08-618561

Item 62 Answer: D

Educational Objective: Diagnose testosterone supplementation as a secondary cause for polycythemia.

This patient's polycythemia is likely caused by testosterone injections. Polycythemia is a common adverse effect of testosterone (and anabolic steroid) supplementation, and evaluating the hematocrit level at initiation, 3 to 6 months after testosterone initiation, and annually thereafter is recommended by Endocrine Society guidelines. Guidelines also recommend interrupting the testosterone supplementation if the hematocrit value is greater than 54%. Secondary polycythemia can cause symptoms, such as headaches and elevated blood pressure, and increase the risk of thromboembolism. The risk of venous thromboembolic disease is directly related to hematocrit level. In this patient, stopping the testosterone supplementation until his polycythemia improves and restarting at a lower dose is recommended. In patients with severe symptoms, phlebotomy can also be considered. Testosterone supplementation can also exacerbate undiagnosed sleep apnea, and evaluation for an underlying sleep disorder should be performed in these patients with polycythemia.

Anemia rather than erythrocytosis may be seen in patients with both hyperthyroidism and hypothyroidism, and levothyroxine, even if given at inappropriately high or low doses, does not cause polycythemia.

Lisinopril does not cause polycythemia. ACE inhibitors, such as lisinopril, are actually used to treat secondary polycythemia after kidney transplantation. Posttransplant erythrocytosis occurs in up to 15% of patients after kidney transplantation. ACE inhibitors reduce erythrocytosis in 90% of patients in a dose-response manner. The mechanism is unknown, but apoptosis of the erythroid precursors has been suggested as well as renin-angiotensin system inhibition that may decrease erythropoietin production.

Polycythemia vera (PV) is a disorder of the myeloid and erythroid stem cells that causes erythropoietin-independent proliferation of erythrocytes and splenomegaly. PV should be considered in all patients with polycythemia; however, in this patient who is receiving testosterone supplementation, has an elevated erythropoietin level, and does not have splenomegaly, PV is unlikely. If PV is suspected, mutational analysis for *JAK2 V617F* should be performed.

KEY POINT

- Polycythemia is a common adverse effect of testosterone injections, and testosterone supplementation should be interrupted if the hematocrit level exceeds 54%.

Bibliography

Bhasin S, Cunningham GR, Hayes FJ, Matsumoto AM, Snyder PJ, Swerdloff RS, et al; Task Force, Endocrine Society. Testosterone therapy in men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2010;95:2536-59. [PMID: 20525905] doi:10.1210/jc.2009-2354

Item 63 Answer: A

H

Educational Objective: Treat heparin-induced thrombocytopenia.

The most appropriate management is to discontinue heparin and initiate argatroban. This patient has heparin-induced thrombocytopenia (HIT). He was in the hospital 1 month ago for chronic heart failure and most likely received subcutaneous heparin at that time, so he has a history of heparin exposure. A scoring system for determining the pretest probability of a patient having HIT has been developed (4T score). High probability scores are associated with a 50% decrease in platelet count, onset between days 5 and 10 of heparin exposure, new thrombosis, and no other cause of thrombocytopenia. This patient's platelet count decreased more than 50% from admission 5 days ago, he has a new thrombotic event, and he has no other likely explanation for the thrombocytopenia. HIT can be a life-threatening condition if not addressed rapidly. Heparin must be discontinued and an alternate, immediately effective anticoagulant, such as argatroban, must be initiated. A strongly positive immunoassay for HIT antibody will help confirm the diagnosis. The risk of thrombosis persists after resolution of the thrombocytopenia, so treatment with warfarin should begin when the platelet count normalizes; most experts recommend 3 to 6 months of therapy.

Patients with HIT must have all heparin products stopped. Replacing low-molecular-weight heparin with unfractionated heparin does not mitigate the risk of additional thrombosis. Most experts advise delaying warfarin therapy until the platelet count has normalized.

Placement of an inferior vena cava filter will not prevent additional thrombotic events.

KEY POINT

- Patients with a high probability of heparin-induced thrombocytopenia should have heparin stopped, and therapy with an immediately effective anticoagulant, such as argatroban, should be initiated.

Bibliography

Greinacher A. Clinical practice. Heparin-induced thrombocytopenia. N Engl J Med. 2015;373:252-61. [PMID: 26176382] doi:10.1056/NEJMcp1411910

Item 64 Answer: B

Educational Objective: Diagnose hemolytic uremic syndrome.

This patient most likely has hemolytic uremic syndrome (HUS). HUS is a diarrhea-associated syndrome of microangiopathic hemolytic anemia, thrombocytopenia, and acute kidney injury caused by Shiga toxin–producing *Escherichia coli*, typically with serotypes O157:H7, O104:H4, and, less commonly, *Shigella dysenteriae*. Shiga toxin

binds to endothelial cells, triggering thrombosis and resulting in a thrombotic microangiopathy. It also binds to renal mesangial cells, podocytes, and renal tubular cells, causing direct damage. These actions lead to acute kidney injury. Although it is more commonly seen in children, it can also present in adults. Supportive care is a cornerstone of treatment, and fluid management with volume expansion is critical despite any existing oliguria.

Atypical HUS is a congenital syndrome caused by overwhelming complement activation that is not preceded by a diarrheal illness as typical HUS is. The distinction between thrombotic thrombocytopenic purpura and typical and atypical HUS is difficult but important to make because atypical HUS is effectively treated by infusions of eculizumab, a monoclonal antibody directed against the terminal components of the complement cascade.

The combination of an immune-mediated hemolytic anemia, usually warm antibody, IgG mediated, and immune thrombocytopenic purpura is known as Evans syndrome. Although this patient has evidence of a hemolytic anemia and thrombocytopenia, the direct antiglobulin test is negative, and schistocytes, reflecting microangiopathic hemolysis, were noted on the peripheral blood smear. Spherocytes would be expected in IgG-mediated autoimmune hemolytic anemia.

Patients with rapidly progressive glomerulonephritis (RPGN) typically present with the nephritic syndrome and may sometimes be in advanced kidney failure at the time of presentation. Other symptoms and clinical findings related to an underlying cause may also be present, such as systemic signs of vasculitis (arthritis, epistaxis, hemoptysis) or lung hemorrhage (Goodpasture syndrome). The absence of active urinary sediment and the presence of microangiopathic hemolytic anemia make RPGN an unlikely diagnosis.

KEY POINT

- Classic hemolytic uremic syndrome is a diarrhea-associated syndrome of microangiopathic hemolytic anemia, thrombocytopenia, and acute kidney injury caused by Shiga toxin–producing *Escherichia coli* and, less commonly, *Shigella dysenteriae*.

Bibliography

Mele C, Remuzzi G, Noris M. Hemolytic uremic syndrome. Semin Immunopathol. 2014;36:399-420. [PMID: 24526222] doi:10.1007/s00281-014-0416-x

Item 65 Answer: D

Educational Objective: Diagnose valve hemolysis.

This patient most likely has valve hemolysis. She has a persistent mild anemia with laboratory features consistent with intravascular hemolysis (undetectable haptoglobin levels and elevated lactate dehydrogenase levels). The peripheral blood smear shows rare schistocytes, which are fragmented erythrocytes consistent with micro- or macroangiopathic hemolysis. Patients with artificial valves or those with left ventricular assist devices can develop anemia resulting from erythrocyte fragmentation known as macroangiopathic hemolysis. A normal echocardiographic examination does not exclude mild valve hemolysis; in fact, the peripheral blood smear is more sensitive than echocardiography for detecting valve dysfunction. In addition to the peripheral blood smear, the most sensitive laboratory test is the serum haptoglobin level, but this test lacks specificity. Although the peripheral blood smear is a reliable indicator of the integrity of valve function, it is a less reliable indicator of the degree of hemodynamically significant perivalvular regurgitation. As such, the presence of mild hemolysis may not necessitate valve replacement, and the timing of valve replacement would become a clinical decision based on patient and valve characteristics, pattern and pace of hemolysis, and changes in echocardiographic findings over time.

This patient is taking no medications associated with drug-induced hemolytic anemia (for example, cephalosporins, penicillins, NSAIDs, quinidine, isoniazid). In addition, schistocytes are not present in drug-induced hemolysis, making this a very unlikely diagnosis.

The peripheral blood smear does not show features, such as microcytosis or anisopoikilocytosis, found in iron deficiency from blood loss, making gastrointestinal bleeding unlikely. However, patients with significant intravascular hemolysis and hemoglobinuria may excrete enough iron in the urine to become iron deficient. This patient does not have such severe hemolysis nor does she have any hematologic features of iron deficiency.

This patient lacks the peripheral blood smear findings associated with glucose-6-phosphate dehydrogenase deficiency, including bite cells and Heinz bodies. Similarly, none of the medications prescribed (for example, sulfonamides, some antimalarials, rasburicase) are associated with glucose-6-phosphate dehydrogenase deficiency, an X-linked condition that is uncommon in women.

KEY POINT

- Patients with artificial valves or those with left ventricular assist devices can develop anemia resulting from erythrocyte fragmentation known as macroangiopathic hemolysis.

Bibliography

Beris P, Picard V. Non-immune hemolysis: diagnostic considerations. Semin Hematol. 2015;52:287-303. [PMID: 26404441] doi:10.1053/j.seminhematol.2015.07.005

Item 66 Answer: A

Educational Objective: Treat provoked deep venous thrombosis.

The most appropriate management is to continue anticoagulation for a 3-month course. Decisions on anticoagulation therapy duration depend on the recurrent venous thromboembolism (VTE) risk without anticoagulation, the bleeding risk

with anticoagulants, and the patient's preference. In patients with proximal leg deep venous thrombosis (DVT) or pulmonary embolism, the cumulative VTE recurrence risk after discontinuation of anticoagulation is (1) 1% after 1 year and 3% after 5 years for VTE provoked by major surgery; (2) 5% after 1 year and 15% after 5 years for VTE provoked by a nonsurgical reversible risk factor; and (3) 10% after 1 year and 30% after 5 years for unprovoked VTE. This patient experienced a provoked DVT after major surgery. In provoked thrombosis with reversible risk factors, guidelines recommend 3 months of anticoagulation.

Because of the high risk of recurrence with discontinuation of anticoagulant therapy, an unprovoked VTE is a consideration for extended anticoagulant therapy. When extended (long-term) anticoagulation therapy is chosen, the risks, benefits, and burden of long-term therapy must be re-evaluated periodically. This patient's DVT was provoked by surgery; therefore, extended anticoagulation is not a reasonable option.

Identifying an inherited thrombophilia often does not change treatment decisions in a patient with VTE. Recent guidelines recommend against routine thrombophilia testing because identification of inherited abnormalities does not alter the duration of recommended anticoagulation or reliably predict risk of VTE recurrence. Finally, the American Society of Hematology's Choosing Wisely Campaign specifically recommends against thrombophilia testing in adults with VTE that occurs in the setting of a major transient risk factor, such as surgery, prolonged immobility, or trauma.

In patients with unprovoked DVT, a common strategy has been to measure D-dimer levels 2 weeks after discontinuation of a 3-month course of anticoagulant therapy. Patients with elevated D-dimer levels were considered for further anticoagulation. However, although elevated levels of D-dimer can identify persons at risk, this test has low specificity, and a normal D-dimer level cannot safely rule out the possibility of future recurrence, thus limiting the utility of this testing strategy. Furthermore, this patient had a provoked DVT, which is another reason not to perform follow-up D-dimer testing.

KEY POINT

- In provoked deep venous thrombosis with reversible risk factors, 3 months of anticoagulation is recommended.

Bibliography

Kearon C, Akl EA, Ornelas J, Blaivas A, Jimenez D, Bounameaux H, et al. Antithrombotic therapy for VTE disease: CHEST Guideline and Expert Panel Report. Chest. 2016;149:315-52. [PMID: 26867832] doi:10.1016/j.chest.2015.11.026

Item 67 Answer: D

Educational Objective: Diagnose pseudothrombocytopenia.

The most likely diagnosis in this patient is pseudothrombocytopenia. A review of the peripheral blood smear is the first step in evaluating a patient with thrombocytopenia. Platelet clumping, or pseudothrombocytopenia, is caused by antibodies directed against the anticoagulant ethylenediaminetetraacetic acid and is not associated with any medical problem. Additionally, in the absence of platelet clumping, review of the peripheral blood smear might show schistocytes or abnormal leukocytes, suggesting possible diagnoses accounting for true thrombocytopenia. An accurate platelet count would be obtained by drawing a blood sample in a heparinized tube.

Patients with essential thrombocythemia may have large platelets and platelet clumping, but the platelet count would be elevated, not normal as was found with the heparinized blood specimen.

Immune thrombocytopenic purpura is an autoimmune disorder that results in a low platelet count. The peripheral smear typically shows scant large platelets that do not form clumps, and the platelet count would be consistently low, even when drawn in a heparinized tube.

The diagnosis of myelodysplastic syndrome should be suspected in patients with macrocytic anemia or pancytopenia in whom vitamin B_{12} and folate deficiency have been excluded. Abnormal erythrocyte forms with basophilic stippling or Howell-Jolly bodies and dysplastic neutrophils with decreased nuclear segmentation and granulation may be present. Increased myeloblasts can be seen in more advanced disease. This patient's microcytic anemia, thrombocytopenia with platelet clumping, and correction of the thrombocytopenia by using a heparinized tube is not consistent with the diagnosis of myelodysplastic syndrome.

KEY POINT

- Evaluation of the peripheral blood smear to assess platelet clumping should be done in patients with isolated thrombocytopenia; if clumping is detected, the platelet count should be repeated in a heparinized blood specimen.

Bibliography

Lippi G, Plebani M. EDTA-dependent pseudothrombocytopenia: further insights and recommendations for prevention of a clinically threatening artifact [Editorial]. Clin Chem Lab Med. 2012;50:1281-5. [PMID: 22868791] doi:10.1515/cclm-2012-0081

Item 68 Answer: C

Educational Objective: Treat multiple myeloma and skeletal lesions.

All patients with multiple myeloma (MM) requiring therapy should be given intravenous bisphosphonates, such as zoledronic acid or pamidronate, in addition to antimyeloma therapy. Zoledronic acid and pamidronate have been shown to prevent new skeletal-related events in patients with MM, but only zoledronic acid has been shown to improve survival. Close monitoring of kidney function and calcium level should be performed in all patients taking zoledronic acid; monitoring for pain and swelling that may be early signs of osteone-

crosis of the jaw is also essential. Calcium and vitamin D supplementation is usually given to patients taking intravenous bisphosphonates unless a contraindication exists. Patients with MM are given intravenous zoledronic acid every 3 to 4 weeks. Experts have not reached a consensus on duration of therapy, but indefinite bisphosphonate therapy is often used. It is reasonable to consider remission status, extent of skeletal disease, kidney function, and patient preference when determining the duration of bisphosphonate therapy. In patients who stop therapy, bisphosphonates should be restarted at disease relapse.

In patients with monoclonal gammopathy of undetermined significance and smoldering MM, dual-energy x-ray absorptiometry (DEXA) is performed to evaluate for osteoporosis or osteopenia in determining bisphosphonate therapy. This patient has MM requiring therapy with lytic lesions. Bone density scanning with DEXA is unnecessary to determine treatment.

With the advent of effective antimyeloma therapy, limited use of radiation is recommended to preserve the bone marrow. Radiation therapy is recommended to control pain or prevent impending pathologic fracture or spinal cord compression. In this patient with adequate pain control, no evidence of spinal cord compression, and no neurologic symptoms, radiation therapy is not appropriate.

Patients with MM requiring therapy are at high risk for recurrent skeletal-related events. Therefore, continuing with antimyeloma therapy alone without specifically addressing the bone disease is not adequate.

KEY POINT

- Zoledronic acid has been shown to prevent new skeletal-related events and improve survival in patients with multiple myeloma requiring therapy.

Bibliography

Terpos E, Morgan G, Dimopoulos MA, Drake MT, Lentzsch S, Raje N, et al. International Myeloma Working Group recommendations for the treatment of multiple myeloma-related bone disease. J Clin Oncol. 2013; 31:2347-57. [PMID: 23690408] doi:10.1200/JCO.2012.47.7901

H

Item 69 Answer: C

Educational Objective: Treat cold agglutinin disease.

The most appropriate treatment for this patient is rituximab. She has profound anemia and evidence of intravascular (decreased haptoglobin, hemoglobinuria, elevated lactate dehydrogenase) and extravascular (elevated indirect hyperbilirubinemia level) hemolysis. The positive direct antiglobulin test showing C3 on erythrocytes with agglutinated erythrocytes on the peripheral blood smear suggests cold agglutinin autoimmune hemolytic anemia. The improbably high mean corpuscular volume (MCV) calculated by the Coulter counter likely reflects measurement of agglutinated cells, although the reticulocytosis will also elevate the MCV. This disease can be primary, with no other underlying disorders, but may be associated with lymphoproliferative disorders, such as Waldenström macroglobulinemia, other B cell non-Hodgkin lymphomas, and IgM monoclonal gammopathy of undetermined significance. Cold agglutinin disease may also be precipitated by infections, typically *Mycoplasma pneumoniae* or Epstein-Barr virus. In cold agglutinin disease, IgM antibodies are directed against erythrocyte antigens, resulting in complement fixation and intravascular hemolysis as well as clearance of complement-coated erythrocytes by Kupffer cells in the liver. Rituximab, a monoclonal antibody to the B-cell antigen CD20, has shown efficacy in case series of patients with cold agglutinin disease. Additionally, all patients with cold agglutinin disease should be kept warm, and all infusions should be administered at body temperature.

Unlike in patients with warm antibodies, prednisone and intravenous immune globulin do not decrease the hemolytic process in patients with cold agglutinin disease.

Because cold agglutinin disease does not involve splenic clearance of erythrocytes, splenectomy is not effective at reducing this type of hemolysis compared with warm antibody-mediated hemolysis.

KEY POINT

- Cold avoidance and rituximab are effective treatments for cold agglutinin disease; glucocorticoids, splenectomy, and intravenous immune globulin are not helpful.

Bibliography

Barcellini W. Immune hemolysis: diagnosis and treatment recommendations. Semin Hematol. 2015;52:304-12. [PMID: 26404442] doi:10.1053/j.seminhematol.2015.05.001

Item 70 Answer: B

H

Educational Objective: Diagnose antithrombin deficiency as a cause of heparin resistance.

The most likely diagnosis is antithrombin deficiency (ATD). This patient's clinical presentation is consistent with heparin resistance, which occurs when the activated partial thromboplastin time (aPTT) does not increase into the therapeutic range despite increasing doses of heparin or when unusually high doses of heparin are required to achieve a therapeutic aPTT. Heparin achieves its anticoagulant effect through antithrombin. The heparin-antithrombin complex then inactivates thrombin, activated factor X (fXa), and other activated clotting factors. If the amount of available antithrombin is decreased, a reduced response to heparin is seen. Heparin resistance can also occur with increased clearance of heparin or an increase in acute phase reactant proteins such as factor VIII, which can bind to and neutralize heparin. ATD is diagnosed by assaying antithrombin activity. Acquired causes must be ruled out.

Antiphospholipid antibodies are acquired autoantibodies against phospholipids and phospholipid-binding proteins, such as cardiolipin and β_2-glycoprotein I. In vitro, they can prolong clotting tests, but in vivo, they increase the

H CONT.

risk of venous and arterial thrombosis. Antiphospholipid syndrome (APS) can be a primary disorder with no underlying comorbidity or a secondary disorder associated with autoimmune diseases, malignancy, or drugs. This patient's clotting test fails to prolong with heparin therapy; this finding is incompatible with APS.

Factor V Leiden mutation is the most common inherited thrombophilia. Factor V Leiden mutation is associated with about 95% of cases of activated protein C (APC) resistance. APC is a naturally occurring anticoagulant; the primary manifestation of APC resistance is venous thromboembolism. Patients with factor V Leiden mutation are not resistant to the effects of heparin.

Protein C is a vitamin K-dependent natural anticoagulant; it is converted during the coagulation process to APC, which inactivates coagulation factors Va and VIIIa. Protein C deficiency is inherited in an autosomal dominant fashion. Protein C deficiency is a risk factor for venous thromboembolism and arterial thromboembolism. Patients with protein C deficiency are not resistant to the effects of heparin.

KEY POINT

- Antithrombin deficiency is a cause of heparin resistance.

Bibliography

Gaman AM, Gaman GD. Deficiency of antithrombin III (AT III) - case report and review of the literature. Curr Health Sci J. 2014;40:141-3. [PMID: 25729597] doi:10.12865/CHSJ.40.02.12

Item 71 Answer: A

Educational Objective: Treat acquired factor VIII deficiency.

The most appropriate management of this patient is to administer activated factor VII. She has an acquired hemophilia A with an autoantibody against factor VIII. An association of this disorder with hematologic malignancies such as chronic lymphocytic leukemia has been recognized. The prolonged activated partial thromboplastin time (aPTT) did not fully correct with mixing, suggesting the presence of an inhibitor. Acquired hemophilia typically presents in adults older than 60 years, and women are affected more often than men. Patients present with ecchymoses and subcutaneous or muscle bleeding. Treatment with factor VIII infusion is not successful because the inhibitor will interfere with factor efficacy, so an activated factor product is required. Recombinant activated factor VII (or activated prothrombin complex concentrate) promotes clotting by bypassing several coagulation steps.

Bleeding associated with a prolonged aPTT should raise concern for disseminated intravascular coagulation (DIC) with hypofibrinogenemia requiring cryoprecipitate; however, severe factor VIII deficiency (1%) is unusual in DIC, and the normal prothrombin time and platelet count also argue against that diagnosis. Finally, the patient has none of the common triggers of DIC, such as sepsis, metastatic cancer, or systemic immune response syndrome.

Desmopressin is used in the treatment of von Willebrand disease (vWD) and causes preformed stores of von Willebrand factor and factor VIII to be released from endothelial cells. However, in patients with vWD, the aPTT would correct in a mixing study. This patient's aPTT did not correct, making the diagnosis of vWD unlikely.

Fresh frozen plasma is used to treat patients with massive bleeding and dilutional coagulopathy and has been used in patients with warfarin toxicity. It would be ineffective in treating hemophilia with acquired factor VIII inhibitor because the inhibitor will interfere with factor efficacy.

KEY POINT

- A prolonged activated partial thromboplastin time that does not fully correct with a mixing study suggests the presence of a factor inhibitor and the diagnosis of acquired hemophilia A; treatment is with activated factor VII.

Bibliography

Franchini M, Mannucci PM. Acquired haemophilia A: a 2013 update. Thromb Haemost. 2013;110:1114-20. [PMID: 24008306] doi:10.1160/TH13-05-0363

Item 72 Answer: A

H

Educational Objective: Treat vitamin K deficiency.

Administering vitamin K is the most appropriate management at this time. This patient has developed vitamin K deficiency from poor oral intake and a prolonged course of antibiotics combined with diarrhea from concurrent *Clostridium difficile* infection. Although vitamin K is found in many foods, most vitamin K needed for coagulation is derived from saprophytic bacteria in the colon, and antibiotics destroy these bacteria. Diarrhea (from any cause) results in decreased absorption of vitamin K. Vitamin K is needed to activate certain factors (II, VII, IX, and X), and the prothrombin time (PT), which is most sensitive to a decrease in factor VII levels, will be elevated out of proportion to the activated partial thromboplastin time (aPTT), which will be normal or only mildly elevated. Vitamin K deficiency can be managed with oral or parenteral vitamin K, and the coagulopathy will begin to correct within 1 day.

Although atorvastatin can cause an elevation in liver enzyme levels, this patient's coagulopathy is not a result of liver disease, because the factor V level is in the normal range. With the exception of factor VIII, all clotting factors are produced in the liver, and liver disease results in a decrease in all factors with corresponding abnormalities in aPTT and PT.

Discontinuing this patient's low-dose heparin is unnecessary because this heparin formulation will not prolong the PT.

Although fresh frozen plasma will correct the underlying vitamin K deficiency, it is not the safest or most cost-effective treatment option, and the duration of effect is limited by the short half-life of factor VII. Vitamin K is a safer, more cost-effective intervention and will last much longer.

KEY POINT

- Vitamin K deficiency, which can be recognized by a normal activated partial thromboplastin time and an elevated prothrombin time, should be expected in patients who have poor oral intake and are taking prolonged courses of antibiotics.

Bibliography

Brenner B, Kuperman AA, Watzka M, Oldenburg J. Vitamin K-dependent coagulation factors deficiency. Semin Thromb Hemost. 2009;35:439-46. [PMID: 19598072] doi:10.1055/s-0029-1225766

Item 73 Answer: D

Educational Objective: Determine when a thrombophilia evaluation should be performed.

The ideal testing strategy is to temporarily stop rivaroxaban in 1 year and test 2 weeks later. Long-term anticoagulation is indicated in the setting of idiopathic thrombosis. Because of the unprovoked nature of this patient's thrombotic event, his thrombotic risk remains high even after 3 months of anticoagulation. Therefore, it is safer to continue anticoagulation for 1 year before testing. Testing for inherited thrombophilia remains controversial. Guidelines and systematic reviews recommend against routine population screening or screening in most adults with idiopathic venous thromboembolism (VTE) and in asymptomatic family members of patients with VTE and known factor V Leiden or prothrombin *G20210A* gene mutation. Most experts agree that thrombophilia evaluation can be considered in select populations, such as patients with thromboses at unusual sites or recurrent idiopathic thrombosis, patients younger than 45 years with unprovoked thrombosis, patients with VTE and a clear family history of thrombosis in one or more first-degree relatives, and patients with warfarin-induced skin necrosis. After an informed discussion of the risks and benefits of testing, patients who desire evaluation should receive genetic counseling before testing. Testing typically focuses on factor V Leiden mutation; prothrombin *G20210A* mutation; protein C, protein S, and antithrombin deficiencies; and antiphospholipid antibody syndrome. However, the thrombophilia evaluation should not be performed during an acute episode of thrombosis. Additionally, although genetic tests such as factor V Leiden and prothrombin gene mutation can be performed at any time, the other assays can be variably affected by the presence of an acute thrombosis, heparin, and other anticoagulants. For example, during the acute phase of thrombosis, plasma levels of antithrombin and occasionally proteins C and S may transiently decrease, and fibrinogen and factor VIII levels may increase. Depending on the assay used, dabigatran therapy may result in increased measurements of antithrombin and protein S and C levels, whereas the factor Xa inhibitors (for example, rivaroxaban and apixaban) may result only in increased measurements of antithrombin. Warfarin therapy reduces vitamin K-dependent factors, including proteins C and S, which do not resolve for 4 to 6 weeks after discontinuation. Most experts agree that with the exception of testing for genetic mutations, testing should not be done in the acute setting or while receiving anticoagulant therapy and should be delayed at least 2 weeks after discontinuation of anticoagulant therapy to minimize diagnostic error.

KEY POINT

- With the exception of testing for genetic mutations, thrombophilia testing should not be performed in the acute setting or while receiving anticoagulant therapy and should be delayed at least 2 weeks after discontinuation of anticoagulant therapy to minimize diagnostic error.

Bibliography

Meyer MR, Witt DM, Delate T, Johnson SG, Fang M, Go A, et al. Thrombophilia testing patterns amongst patients with acute venous thromboembolism. Thromb Res. 2015;136:1160-4. [PMID: 26477821] doi:10.1016/j.thromres.2015.10.019

Item 74 Answer: D

Educational Objective: Diagnose a myeloproliferative neoplasm in a patient with hepatic vein thrombosis.

This patient should be evaluated for the *JAK2 V617F* gene mutation. This mutation is present in more than 95% of patients with polycythemia rubra vera and 50% of patients with essential thrombocytosis, even without the presence of erythrocytosis or thrombocytosis. Thromboses, including abdominal vein thromboses, are a major cause of morbidity and mortality in patients with myeloproliferative neoplasms (MPNs). Approximately 50% of cases of Budd-Chiari syndrome and 25% of cases of portal vein thrombosis are the result of an MPN, and *JAK2 V617F* gene mutations should be evaluated even in the absence of erythrocytosis or thrombocytosis. Portal hypertension and splenomegaly are often found, which may account for the relatively normal blood counts seen in some patients.

Although hepatocellular carcinoma, which could possibly be diagnosed by α-fetoprotein, can be associated with the development of abdominal thrombosis, this diagnosis is unlikely in this patient, considering her viral studies are negative and she has no evidence of cirrhosis or malignancy on imaging.

Factor VIII testing is not considered a standard component of a thrombophilia evaluation because of its mixed results regarding long-term implications. It would be inappropriate to evaluate the patient's factor VIII level at this time.

Paroxysmal nocturnal hemoglobinuria is also associated with abdominal vein thrombosis, but her normal haptoglobin level and absence of indirect hyperbilirubinemia indicate no evidence of hemolysis. Performing flow cytometry to evaluate for loss of CD 55/59 would not be appropriate.

KEY POINT

- Patients with abdominal thrombosis, splenomegaly, and portal hypertension should be evaluated for the presence of a myeloproliferative neoplasm, specifically the *JAK2 V617F* gene mutation, even in the absence of erythrocytosis or thrombocytosis.

Bibliography

Smalberg JH, Arends LR, Valla DC, Kiladjian JJ, Janssen HL, Leebeek FW. Myeloproliferative neoplasms in Budd-Chiari syndrome and portal vein thrombosis: a meta-analysis. Blood. 2012;120:4921-8. [PMID: 23043069] doi:10.1182/blood-2011-09-376517

H

Item 75 Answer: B

Educational Objective: Diagnose drug-induced autoimmune hemolytic anemia.

This patient most likely has drug-induced hemolysis. She has an acute anemia in association with ceftriaxone treatment for Lyme-related meningoencephalitis. Acute anemia in hospitalized patients should raise the suspicion for blood loss (including from laboratory testing) or hemolysis. An elevated lactate dehydrogenase level along with the positive direct antiglobulin test (DAT) and spherocytes on the peripheral blood smear should further raise suspicion for hemolysis from an IgG autoantibody. Many drugs are associated with drug-induced hemolytic anemia, and antibiotics are the most frequently encountered cause of this condition, with ceftriaxone being one of the most common. It is believed that ceftriaxone may become affixed to the erythrocyte membrane, leading to an immune reaction resulting in erythrocyte hemolysis. Treatment of drug-induced hemolysis involves stopping the offending drug. Importantly, Lyme disease itself is not associated with hemolysis.

Although warm antibody hemolysis can cause a hemolytic anemia that is DAT positive for IgG, cold agglutinin disease is DAT positive for C3. The peripheral blood smear would show agglutinated cells, and spherocytes would not be present. Furthermore, cold agglutinin disease is not associated with Lyme disease. Cold agglutinin disease can be primary or associated with lymphoproliferative disorders and certain infections, typically *Mycoplasma pneumoniae* or Epstein-Barr virus.

Glucose-6-phosphate dehydrogenase (G6PD) deficiency can cause acute hemolysis with certain medications (for example, sulfonamides, some antimalarials, rasburicase), but ceftriaxone is not a drug associated with G6PD deficiency-induced hemolysis. Also, G6PD-mediated hemolysis is an X-linked disease and is uncommon in women. Finally, the positive DAT and presence of spherocytes on the peripheral blood smear are inconsistent with G6PD deficiency; bite cells and Heinz bodies, which are denatured oxidized hemoglobin visualized as intranuclear inclusions seen on supravital stain, are the expected finding.

KEY POINT

- Many drugs are associated with drug-induced hemolytic anemia, and antibiotics are the most frequently encountered cause of this condition, with ceftriaxone being one of the most common causative agents.

Bibliography

Mayer B, Bartolmäs T, Yürek S, Salama A. Variability of findings in drug-induced immune haemolytic anaemia: experience over 20 years in a single centre. Transfus Med Hemother. 2015;42:333-9. [PMID: 26696803] doi:10.1159/000440673

Item 76 Answer: A

H

Educational Objective: Diagnose transfusion-transmitted babesiosis.

The patient most likely has transfusion-transmitted babesiosis. This tickborne disease, caused primarily by *Babesia microti* in the United States, can be transmitted through transfusion but is not routinely screened for in blood donors. *Babesia* is endemic in New England and regions of the upper Midwest. Although blood donors who report a history of babesiosis are excluded from donating, 80% of infected persons are asymptomatic and may be parasitemic for months. The incubation period for transfusion-related babesiosis ranges from 11 to 176 days. Risk factors for severe disease include older age, splenectomy, or compromised immune function. Symptoms include fatigue, malaise, fever, nausea, anorexia, myalgia, abdominal pain, and diarrhea. Hemolytic anemia, thrombocytopenia, and elevated serum aminotransferase and alkaline phosphatase levels are common. The first clue often comes on the blood smear examination from the unexpected detection of the protozoal ring forms within erythrocytes; babesiosis is then confirmed by polymerase chain reaction.

Bacterial contamination in blood components is much less common in erythrocytes compared with platelets, and symptoms and signs, such as fever and hypotension, begin during or within hours of the transfusion. This patient's illness, beginning 3 weeks after transfusion, would not be consistent with bacterial contamination.

The transmission of cytomegalovirus is associated with a generally benign mononucleosis-like syndrome in immunocompetent patients. Patients typically have lymphocytosis and atypical lymphocytosis but would not have hemolytic anemia or erythrocyte inclusions.

West Nile virus infection has an incubation period of only 2 weeks or less and is associated with fever and headaches. Zika virus may be transmitted through transfusion, but the incubation period is 2 weeks or less. Symptoms typically include rash and arthralgia. Neither West Nile virus nor Zika virus would be associated with hemolytic anemia, elevated liver chemistry test results, or erythrocyte inclusions.

KEY POINT

- *Babesia microti* is a transfusion-transmissible pathogen that can be responsible for malaria-like symptoms, hemolytic anemia, thrombocytopenia, and abnormal liver chemistry study results.

Bibliography

Manian FA, Barshak MB, Lowry KP, Basnet KM, Stowell CP. Case records of the Massachusetts General Hospital. Case 27-2016. N Engl J Med. 2016;375:981-91. [PMID: 27602671] doi:10.1056/NEJMcpc1607091

Item 77 Answer: D

Educational Objective: Treat chronic immune thrombocytopenic purpura during pregnancy.

No management beyond monitoring her platelet count and treating her urinary tract infection is needed for this patient.

Women with immune thrombocytopenic purpura (ITP) can be safely monitored during their pregnancy without intervention as long as they are asymptomatic and the platelet count remains greater than 30,000/µL (30×10^9/L). If the platelet count drops unexpectedly, other diagnoses, in addition to worsening ITP, must be considered, such as pre-eclampsia, HELLP syndrome (Hemolysis, Elevated Liver enzymes, and Low Platelets), thrombotic thrombocytopenic purpura (TTP), or hemolytic uremic syndrome (HUS). This patient's normal blood pressure, absence of proteinuria, and normal liver chemistry tests make pre-eclampsia and HELLP syndrome unlikely. The absence of schistocytes on her peripheral blood smear excludes TTP, HUS, and HELLP syndrome. Her currently decreased platelet count is probably related to her intercurrent infection. However, her platelet count should be monitored closely because it is close to the cut-off for treatment.

Intravenous immune globulin is a first-line therapy option in treating ITP in pregnancy, but treatment is unnecessary when the platelet count is greater than 30,000/µL (30×10^9/L).

This patient does not require therapy at this time. If treatment is needed, prednisone is another first-line option in ITP. Orofacial abnormalities have been reported in neonates when used in the first trimester, but prednisone is safe to use after the 12th week of gestation. However, this patient is only at 10 weeks' gestation, so prednisone would not be preferred if treatment were needed.

Patients with ITP should not receive platelet transfusions because autoantibodies will cross-react with the transfused platelets, interfering with any potential improvement in platelet counts. However, their use in patients with severe bleeding is not disputed.

KEY POINT

- Pregnant women with immune thrombocytopenic purpura can be safely monitored during their pregnancy without intervention as long as they are asymptomatic and the platelet count remains greater than 30,000/µL (30×10^9/L).

Bibliography

Gernsheimer T, James AH, Stasi R. How I treat thrombocytopenia in pregnancy. Blood. 2013;121:38-47. [PMID: 23149846] doi:10.1182/blood-2012-08-448944

Oncology Answers

Item 78 Answer: C

Educational Objective: Treat limited small cell lung cancer with combined chemotherapy and radiation.

The most appropriate treatment is combined chemotherapy and radiation. This patient has limited small cell lung cancer. Limited disease is defined as nonmetastatic disease that can be encompassed within a single radiation portal. Because this patient's cancer is confined to the left chest and is not metastatic, it meets this definition. Although surgery can be considered for patients with small isolated tumors, this cancer most commonly presents with large centrally located tumors that are not amenable to resection, as it did in this patient. For these patients, standard management is combined chemotherapy and radiation, which can result in cure for about 20% to 30% of patients. Chemotherapy consists of a cisplatin-based combination (usually cisplatin and etoposide) and is started at the same time as radiation. It is important to integrate radiation early in the course of chemotherapy, as delaying radiotherapy has been shown to result in inferior outcomes. Chemotherapy typically continues for a total of four to six cycles.

Chemotherapy alone does not sufficiently control local disease and is also not curative in small cell lung cancer, even in the limited-stage setting.

There is no proven role for chemotherapy followed by radiation. Studies of the use of sequential versus concurrent chemotherapy and radiation have found that concurrent treatment seems to be more effective than sequential treatment. Although in the one reported randomized trial the improvement in survival did not reach statistical significance, the preponderance of available evidence suggests that concurrent treatment is superior to sequential treatment. Therefore, it remains standard care for this patient population.

Radiation alone is not effective and does not result in cure. Small cell lung cancer has a high predilection for metastatic spread, which cannot be prevented by radiation therapy.

KEY POINT

- For patients with small cell lung cancer who have large centrally located tumors that are not amenable to resection, standard management is combined chemotherapy and radiation, which can result in cure for about 20% to 30% of patients.

Bibliography

Tam K, Daly M, Kelly K. Treatment of locally advanced non-small cell lung cancer. Hematol Oncol Clin North Am. 2017 Feb;31(1):45-57. doi:10.1016/j.hoc.2016.08.009. [PMID: 27912833]

Item 79 Answer: C

Educational Objective: Treat high-risk prostate cancer with a gonadotropin-releasing hormone agonist plus radiation.

The most appropriate treatment is a gonadotropin-releasing hormone (GnRH) agonist plus radiation. High-risk prostate cancer is defined as a prostate-specific antigen (PSA) level greater than 20 ng/mL (20 µg/L), a Gleason score of 8 to 10, or evidence of extraprostatic extension of the cancer. Imaging studies, such as pelvic CT or MRI, can be used to assess regional lymph node enlargement in selected patients. Imaging is reserved for patients with a PSA level greater 20 ng/mL (20 µg/L), a Gleason score 8 or greater, and other factors. Patients with high-risk prostate cancer have a significant risk of eventually developing metastatic disease, and they

all require treatment unless significant medical comorbidity precludes treatment. In this patient population, there is significant risk of both local recurrence and distant metastatic disease. Studies have shown that the addition of androgen deprivation therapy (most commonly with a GnRH agonist, such as leuprolide) to radiation results in an improvement in 10-year disease-free and overall survival compared with radiation alone in men with high-risk prostate cancer. Based on this data, the combination of radiation with a GnRH agonist for up to 2 to 3 years is the standard care for this patient population.

Brachytherapy is not indicated in patients with high-risk prostate cancer because no evidence supports the efficacy of brachytherapy in this setting. Brachytherapy is typically only recommended for men with low-risk and limited-volume cancer.

Use of a GnRH agonist alone has no role in the treatment of nonmetastatic prostate cancer. In this patient, local treatment (with either radiation or surgery) is definitively indicated, and treatment with a GnRH agonist alone provides no local treatment.

Radiation alone is not recommended given the survival advantage associated with combined GnRH agonist and radiation treatment in men with high-risk and very-high-risk prostate cancer.

KEY POINT

- Combination therapy with radiation and a gonadotropin-releasing hormone agonist for up to 2 to 3 years results in an improvement in 10-year disease-free and overall survival and is the standard care for patients with high-risk and very-high-risk prostate cancer.

Bibliography

Bolla M, Van Tienhoven G, Warde P, et al. External irradiation with or without long-term androgen suppression for prostate cancer with high metastatic risk: 10-year results of an EORTC randomized study. Lancet Oncol. 2010 Nov;11(11):1066-73. [PMID: 20933466]

H

Item 80 Answer: B

Educational Objective: Treat locally advanced head and neck cancer.

The most appropriate treatment is cetuximab plus radiation. Several options exist for treatment of locally advanced head and neck cancer. However, in many cases, surgery is not recommended as first-line treatment. In addition, significant morbidity is expected with open surgery to resect large, locally advanced cancers. For these reasons, nonsurgical treatment is often recommended in this setting. The standard treatment of such patients is a combination of radiation with systemic therapy, most commonly either cisplatin or cetuximab. Randomized trials have clearly demonstrated improved survival in patients treated with either cisplatin or cetuximab plus radiation compared with those treated with radiation alone. For example, 3-year survival in a pivotal randomized trial was 55% in patients receiving cetuximab and radiation compared with 45% in patients treated with radiation alone. No study to date has determined whether cetuximab or cisplatin is preferred in this setting. However, because of long-term experience with cisplatin and the significantly higher cost of cetuximab, cisplatin is preferred unless there is a contraindication to use of this agent. For this patient, who has chronic kidney disease with a baseline creatinine level of 1.8, cisplatin is clearly contraindicated and, therefore, cetuximab combined with radiotherapy is the most appropriate treatment.

There is no evidence to support a role for bevacizumab, a monoclonal antibody directed against vascular endothelial growth factor, in the treatment of locally advanced head and neck cancer.

Although radiation alone can be used for treatment of very early stage disease, this patient has locally advanced disease, and radiation alone is not sufficient treatment based on data clearly identifying an improvement in survival with combined radiation and systemic therapy, as discussed above.

KEY POINT

- The standard treatment for locally advanced head and neck cancer is a combination of radiation with systemic therapy, most commonly cisplatin or cetuximab.

Bibliography

Bonner JA, Harari PM, Giralt J, et al. Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. N Engl J Med. 2006 Feb 9;354(6):567-78. [PMID: 16467544]

Item 81 Answer: A

Educational Objective: Manage early-stage cervical cancer while maintaining fertility.

The most appropriate management for this patient with early-stage cervical cancer and concerns about future fertility is conization, which consists of excision of a cone-shaped portion of the cervix. Discussion of the impact of treatment options on fertility is important for reproductive-age patients with cancer and especially relevant for women with cervical cancer, almost half of whom are younger than 45 years of age. Patients with early-stage cervical cancer, which includes stage IA (microscopic disease without visible tumor), and stage IB1 (visible tumor less than 4 cm in size confined to the cervix) who desire future childbearing are candidates for fertility-sparing surgery. Conization is an option limited to stage IA disease without vascular invasion.

Patients with stage IA1 disease with vascular invasion and patients with stage IA2 or IB1 disease are candidates for radical trachelectomy. Vaginal radical trachelectomy is a fertility preservation surgery that involves removal of the cervix with conservation of the uterus. A permanent cerclage is placed in the uterine isthmus. In one study of patients who underwent vaginal radical trachelectomy, the 5-year recurrence-free survival was 95.8%. Fifty-eight of 125 women conceived a total of 106 pregnancies, with 75% of the pregnancies carried to term.

Neoadjuvant chemotherapy in women with early-stage cervical cancer is not needed; its use in more advanced-stage disease has not been well studied.

Radiation therapy can be used for early-stage cervical cancer, particularly in patients with poor performance status who are not candidates for surgery, but radiation would result in infertility and is thus not the best option in this patient.

Similarly, in early-stage cervical cancer, there is no difference in the rate of recurrence or mortality with more limited surgery that allows future child-bearing compared to radical or simple hysterectomy.

KEY POINT

- Conization, or excision of a cone-shaped portion of the cervix, is a fertility preservation surgery for patients who have stage IA cervical cancer, defined as microscopic disease without visible tumor.

Bibliography

Qian Q, Yang J, Cao D, You Y, Chen J, Shen K. Analysis of treatment modalities and prognosis on microinvasive cervical cancer: a 10-year cohort study in China. J Gynecol Oncol. 2014;25:293-300. [PMID: 25142622] doi:10.3802/jgo.2014.25.4.293

Item 82 Answer: A

Educational Objective: Treat early-stage hormone receptor–positive breast cancer with tamoxifen in a premenopausal patient.

The most appropriate management for this patient with early-stage hormone receptor–positive breast cancer is to continue tamoxifen for 5 more years. Two large randomized controlled studies have confirmed the benefit of extending tamoxifen to 10 years in decreasing breast cancer recurrence and breast cancer mortality. Ten years of tamoxifen compared with 5 years reduces breast cancer mortality by one third in the first 10 years and by one half after 10 years. The major adverse event with 5 additional years of tamoxifen use was a small increase in the risk for endometrial cancers with no increase in endometrial cancer deaths. There were no increases in fatal pulmonary emboli, stroke, or ischemic heart disease.

In postmenopausal women, estrogen is no longer made in the ovaries but rather in other tissues, such as fat and muscle, through the aromatase enzymes. Use of aromatase inhibitors alone, therefore, is an ineffective strategy in premenopausal women who still have ovarian estrogen production. Because this patient is still having periods, anastrozole will be ineffective; aromatase inhibitors should be used in postmenopausal women only.

Ovarian suppression with leuprolide or other gonadotropin releasing hormone agonists combined with aromatase inhibitors has been shown to decrease the risk for breast cancer recurrence in premenopausal patients with early hormone receptor–positive breast cancer who receive chemotherapy for higher-risk cancers. Based on recent large randomized controlled trials, ovarian suppression does not improve disease-free or overall survival in patients with lower-risk cancers who did not receive initial chemotherapy.

KEY POINT

- In patients with low-risk, early-stage hormone receptor–positive breast cancer, use of tamoxifen for 10 years has been shown to decrease the risk for breast cancer recurrence and breast cancer mortality.

Bibliography

Burstein HJ, Temin S, Anderson H, et al. Adjuvant endocrine therapy for women with hormone receptor–positive breast cancer: American Society of Clinical Oncology clinical practice guideline focused update. J Clin Oncol. 2014 Jul 20;32(21):2255-69. [PMID: 24868023]

Item 83 Answer: B

Educational Objective: Treat classic Hodgkin lymphoma.

The most appropriate management for this young man with Hodgkin lymphoma is chemotherapy. Hodgkin lymphoma encompasses four classic histologic subtypes (nodular sclerosing, mixed cellularity, lymphocyte predominant, and lymphocyte depleted) and one nonclassic subtype (nodular lymphocyte predominant subtype expressing the CD20 cell surface antigen). The presentation is consistent among subtypes and is characterized by palpable, firm lymph nodes and, in some patients, B symptoms (fever, night sweats, weight loss). Other physical examination findings include splenomegaly (30%) and hepatomegaly (5%). Hodgkin lymphoma is a highly curable disease, and the best outcomes are achieved with systemic therapy, sometimes in combination with radiation therapy. In the United States, doxorubicin, bleomycin, vinblastine, and dacarbazine is the most commonly used chemotherapy regimen for classic Hodgkin lymphoma. The need for radiation after chemotherapy for early-stage disease depends on the initial bulk of disease, the response to treatment, and patient and institutional preference.

Bone marrow biopsy, in the absence of unexplained blood abnormalities, is not indicated in the evaluation of patients with Hodgkin lymphoma. Staging no longer includes routine bone marrow biopsy, lymphangiography, or staging laparotomy and splenectomy. High-resolution CT, PET, and the routine use of systemic therapy in even early-stage disease have obviated the need for these staging modalities. Patients with extensive lymph node involvement above the diaphragm are now typically treated with chemotherapy; therefore, there is no need for staging laparotomy and splenectomy to determine the presence of microscopic disease below the diaphragm as the treatment would be no different. With this approach, the short-term morbidity of the staging surgery and long-term risk of overwhelming sepsis from asplenia can be avoided.

Radiation therapy may have a role in this patient's management; however, it is given after completion of chemotherapy for consolidation. Although radiation therapy alone may have a high cure rate for classic Hodgkin lymphoma, the cure rate is higher and toxicity is reduced when chemotherapy is used as the primary treatment modality.

KEY POINT

- All patients with classic Hodgkin lymphoma, regardless of stage, receive chemotherapy, usually the doxorubicin, bleomycin, vinblastine, and dacarbazine regimen, obviating the need for staging laparotomy and splenectomy.

Bibliography

Ansell SM. Hodgkin lymphoma: diagnosis and treatment. Mayo Clin Proc. 2015;90:1574-83. [PMID: 26541251] doi:10.1016/j.mayocp.2015.07.005

Item 84 Answer: B

Educational Objective: Treat advanced ovarian cancer with germline *BRCA1* and *BRCA2* mutations using olaparib.

The most appropriate treatment is an oral poly (adenosine diphosphate [ADP]-ribose) polymerase (PARP) inhibitor. Olaparib is an oral PARP inhibitor that is FDA-approved monotherapy for patients with germline *BRCA*-mutated advanced ovarian cancer previously treated with three or more lines of chemotherapy. PARP inhibition leads to the formation of double-stranded DNA breaks that in *BRCA*-competent tumors are repaired by homologous recombination. Tumors with germline *BRCA* mutations are unable to repair these defects, leading to cell death (referred to as synthetic lethality). A study of 298 patients with germline *BRCA1*- or *BRCA2*-associated cancers showed responses in ovarian, breast, pancreatic, and prostate cancers, with a 31% response rate and median duration of response of 7 months in platinum-resistant ovarian cancers. The most common side effects of olaparib were fatigue, nausea, vomiting, and anemia. In addition to the 15% of ovarian cancers with germline *BRCA1* and *BRCA2* mutations, up to 50% of high-grade serous ovarian cancers may be deficient in homologous recombination repair due to somatically acquired *BRCA1* and *BRCA2* mutations, epigenetic inactivation of *BRCA1*, or other defects in the homologous recombination pathway. These ovarian cancers with a "BRCAness" phenotype are also responsive to PARP inhibitors.

High-dose chemotherapy with hematopoietic stem cell transplantation is not recommended for the treatment of ovarian cancer, neither as initial treatment nor after recurrence.

Intraperitoneal chemotherapy is not effective in patients with recurrent ovarian cancer.

Given the activity of olaparib in the setting of a germline *BRCA1* mutation and this patient's good performance status, it is reasonable to recommend continuing cancer-directed therapy at this time. In patients who did not benefit from previous treatment and with poor performance status (Eastern Cooperative Oncology Group performance status, 3-4) or in those with bowel obstruction in the setting of refractory ovarian cancer, changing to supportive care would be appropriate.

KEY POINT

- Olaparib is FDA approved as monotherapy for patients with germline *BRCA*-mutated advanced ovarian cancer previously treated with three or more lines of chemotherapy.

Bibliography

Kaufman B, Shapira-Frommer R, Schmutzler RK, et al. Olaparib monotherapy in patients with advanced cancer and a germline BRCA1/2 mutation. J Clin Oncol. 2015 Jan 20;33(3):244-50. [PMID: 25366685]

Item 85 Answer: C

Educational Objective: Manage fertility in a female patient with cancer.

The most appropriate option for this patient is to meet with a fertility specialist. Young women with cancer who may wish to bear children after cancer treatment can be seen emergently and counseled about their options. An established fertility preservation option for a woman with a partner is in vitro fertilization with embryo freezing. Newer options include freezing of unfertilized eggs and ovarian cryopreservation with future reimplantation. Delaying initiation of chemotherapy for a brief time in a stable patient so she can be assessed and eggs or embryos harvested if appropriate is acceptable. Premenopausal women with breast cancer who do not wish to become pregnant should use a nonhormonal method of birth control.

Although a hormone receptor–negative, *HER2*-positive cancer is potentially aggressive and initiation of her neoadjuvant treatment should not be unnecessarily delayed, it is not an emergency and there is time for her to meet with a fertility specialist. With the use of chemotherapy and anti-*HER2* therapy in combination with appropriate local therapy, she should have a reasonably high likelihood of cure. Restricting her therapy to only local therapy with surgery and radiation decreases her chance for cure and is not the best option.

There is no evidence that women who become pregnant after a diagnosis of breast cancer have a higher rate of recurrence than similarly staged patients who do not become pregnant. Therefore, there is no reason to counsel this patient against future pregnancies.

KEY POINT

- For women who desire future childbearing who are medically stable, initiation of chemotherapy can be delayed for a brief time to allow assessment by a fertility specialist.

Bibliography

Lambertini M, Del Mastro L, Pescio MC, et al. Cancer and fertility preservation: international recommendations from an expert meeting. BMC Med. 2016 Jan 4;14:1. doi: 10.1186/s12916-015-0545-7. [PMID: 26728489]

Item 86 Answer: C

Educational Objective: Evaluate a woman with ovarian cancer with *BRCA1* and *BRCA2* genetic testing.

This patient should be referred to a genetic counselor for genetic testing for *BRCA1* and *BRCA2* mutations. Current guidelines recommend *BRCA1* and *BRCA2* genetic testing for all women with epithelial ovarian cancer, regardless of age of onset, family history, or ancestry. Of women with ovarian

cancer, 10% to 15% carry a mutation in one of these genes. Approximately 75% of epithelial ovarian cancers are serous histology–the type most likely to be associated with a *BRCA1* or *BRCA2* mutation. This patient has a family history of breast cancer in a paternal aunt who was age 52 years, but even with no family history of breast or ovarian cancer, *BRCA1* and *BRCA2* genetic testing would still be recommended. Although she had her ovaries removed, positive test results for a *BRCA1* or *BRCA2* mutation would have implications for breast cancer risk and screening, with annual mammography and breast MRI recommended. She may also consider prophylactic mastectomies. If she carries a *BRCA1* or *BRCA2* mutation, her siblings and children have a 50% chance of inheriting the same mutation. Genetic testing is best performed by a genetic counselor, with appropriate pre- and post-test counseling.

Routine surveillance imaging studies are not recommended for monitoring patients in clinical remission after initial treatment; therefore, neither annual chest radiography nor an abdominal-pelvic CT scan in 3 months would be recommended unless the patient develops signs or symptoms suggestive of recurrent disease.

Hereditary nonpolyposis colon cancer (HNPCC), also known as Lynch syndrome, is an autosomal dominant disorder caused by a germline mutation in one of the DNA mismatch repair genes. Patients with Lynch syndrome have a 3% to 14% lifetime risk of ovarian cancer, and the possibility of HNPCC mutation testing should be considered in patients with ovarian cancer. However, testing for HNPCC mutations is usually only offered to patients who have a personal or family history, or both, of additional HNPCC-related cancers, particularly colorectal, small bowel or endometrial cancers, or transitional cell cancers of the renal pelvis or ureters. This patient has no personal or family history of these cancers and would not usually be offered HNPCC testing based on her history of ovarian cancer alone. Models such as $PREMM_{1,2,6}$ can be used to determine if a patient is eligible for HNPCC testing.

KEY POINT

- Current guidelines recommend *BRCA1* and *BRCA2* genetic testing for all women with epithelial ovarian cancer, regardless of age of onset, family history, or ancestry.

Bibliography

Alsop K, Fereday S, Meldrum C, et al. BRCA mutation frequency and patterns of treatment response in BRCA mutation-positive women with ovarian cancer: a report from the Australian Ovarian Cancer Study Group. J Clin Oncol. 2012 Jul 20;30(21):2654-63. Erratum in: J Clin Oncol. 2012 Nov 20;30(33):4180. [PMID: 22711857]

Item 87 Answer: D

Educational Objective: Treat gastric MALT lymphoma associated with *Helicobacter pylori* infection.

The appropriate treatment for this patient with gastric mucosa-associated lymphoid tissue (MALT) lymphoma associated with *Helicobacter pylori* infection is proton pump inhibitor and dual antibiotic therapy, such as clarithromycin and amoxicillin, for 7 to 14 days. Chronic antigen stimulation can lead to clonal expansion of MALT and progress to malignant transformation manifesting as lymphoma. The lymphoma originates in B cells in the marginal zone of MALT and expresses the CD20 surface antigen. Eradication of *H. pylori* infection is associated with a high rate of response and long-term remission for these tumors and is the treatment of choice given its efficacy and ease of use. Regression of these lymphomas occurs slowly, and serial endoscopy will be needed to document this patient's response to therapy.

For MALT lymphoma that is not localized to the stomach or, rarely, that is localized to the stomach but does not respond to eradication of *H. pylori* infection, anti-CD20-directed therapy with rituximab may be effective. However, the initial treatment for this patient is eradication of *H. pylori* infection.

Although surgery can be used to treat localized gastrointestinal lymphomas, it is generally performed in the setting of a complication, such as hemorrhage or perforation, because other therapies are less invasive and may be as effective as or more effective than surgery.

Obtaining a PET scan to complete staging before making treatment recommendations is not needed for this patient. Marginal zone lymphomas are less likely to be detected by PET than follicular and aggressive lymphomas; therefore, the test is less sensitive and is unlikely to change management in the absence of other abnormal findings on CT scanning or clinical examination.

Radiation therapy is quite effective in the treatment of gastric marginal zone lymphoma, with high local control rates and relatively low toxicity. However, radiation would generally be reserved for patients for whom *H. pylori* eradication therapy has failed, those with residual or recurrent disease, or those who are *H. pylori*-negative and thus not likely to respond to antibiotic therapy.

KEY POINT

- The initial treatment for gastric mucosa-associated lymphoid tissue lymphoma associated with *Helicobacter pylori* infection is proton pump inhibitor and antibiotic therapy.

Bibliography

Zucca E, Bertoni F. The spectrum of MALT lymphoma at different sites: biological and therapeutic relevance. Blood. 2016;127:2082-92. [PMID: 26989205] doi:10.1182/blood-2015-12-624304

Item 88 Answer: A

Educational Objective: Provide chemoprevention in a patient at high risk for breast cancer.

Exemestane is the most appropriate preventive measure. This postmenopausal woman has lobular carcinoma in situ and atypical hyperplasia. These atypical lesions are associated with a 30% to 35% lifetime risk of breast cancer, and patients with these findings on breast biopsy are

candidates for chemoprophylaxis with antiestrogens. Antiestrogen options include tamoxifen in both premenopausal and postmenopausal women as well as raloxifene and aromatase inhibitors (such as exemestane or anastrozole) in postmenopausal women. Because this patient had a deep venous thrombosis while taking oral contraceptives in the past, both tamoxifen and raloxifene are contraindicated, and exemestane is the best option if she is willing to take chemoprophylaxis.

Exemestane prophylaxis decreased the risk of invasive breast cancer by 65% in the National Cancer Institute of Canada (NCIC) Clinical Trials Group MAP.3 trial. Compared with placebo, there were no significant differences between the two arms in terms of skeletal fractures, cardiovascular events, other cancers, or treatment-related deaths. There were minimal differences in quality-of-life symptoms, such as vasomotor symptoms or arthralgia. Unlike tamoxifen and raloxifene, exemestane does not increase the risk for venous thromboembolic disease or endometrial cancer. Anastrozole, another aromatase inhibitor, has also been shown to decrease the risk of breast cancer in patients with high-risk conditions and is an alternate option for this patient.

Although vitamin D deficiency has been associated with a higher risk of breast cancer, there are no studies supporting high-dose vitamin D as an effective method to decrease the risk of breast cancer.

A low-fat diet has been shown to decrease breast cancer recurrence in patients with a diagnosis of estrogen receptor-negative invasive breast cancer but has not been shown to be of benefit in decreasing the risk of breast cancer in patients with atypical breast lesions or other high-risk conditions.

Both raloxifene and tamoxifen are contraindicated due to this patient's history of a deep venous thrombosis.

KEY POINT

- Patients with lobular carcinoma in situ and atypical hyperplasia are candidates for chemoprophylaxis with antiestrogens.

Bibliography

Goss PE, Ingle JN, Alés-Martinez JE, Cheung AM, Chlebowski RT, Wactawski-Wende J, et al; NCIC CTG MAP.3 Study Investigators. Exemestane for breast-cancer prevention in postmenopausal women. N Engl J Med. 2011;364:2381-91. [PMID: 21639806] doi:10.1056/NEJMoa1103507

Item 89 Answer: A

Educational Objective: **Stage colorectal cancer.**

A contrast-enhanced CT scan is the most appropriate imaging modality for staging of patients with a new diagnosis of colorectal cancer. The preoperative staging evaluation for colorectal cancer should include a complete colonoscopy (if technically feasible) and contrast-enhanced CT scans of the chest, abdomen, and pelvis. Preoperative measurement of serum carcinoembryonic antigen (CEA) levels is also routinely done. In addition to imaging the abdomen and pelvis, the chest should be imaged with CT to rule out pulmonary metastases and to establish a baseline for surveillance. CT imaging with contrast provides the most reliable means of detecting the presence of metastatic disease to the lungs, liver, intra-abdominal lymph nodes, and peritoneum, which are the most common sites of metastatic spread; CT is also useful in planning appropriate therapy. Patients with local or locoregional rectal cancer require further preoperative staging with endorectal ultrasonography or a pelvic MRI to assess the depth of tumor penetration (T stage), degree of lymph node involvement (N stage), and any metastasis (M stage). Staging using the TNM cancer staging system is the most accurate predictor of outcome in patients with colorectal cancer.

CT colonography would not add to the information obtained from a completed colonoscopy. It is an acceptable alternative to a screening colonoscopy for healthy individuals at low risk but is not appropriate for individuals at high risk with unexplained microcytic anemia because it will not provide the option for biopsy if an abnormal result is found.

Liver MRI is a sensitive tool to identify liver metastases and is especially useful in the background of fatty liver, a condition that decreases the sensitivity of contrast CT. In clinical practice, liver MRI is reserved for patients with suspicious but not diagnostic lesions on CT or with contraindications to CT contrast agents.

National guidelines specifically do not recommend PET/CT scans for either preoperative staging or for postoperative surveillance. PET/CT scans have a higher false-positive and false-negative rates than is often appreciated, and have not been shown to improve the accuracy of preoperative staging.

KEY POINT

- Staging of patients with colorectal cancer should include a contrast-enhanced CT scan of the chest, abdomen, and pelvis to determine the extent of the cancer and to establish a baseline for surveillance.

Bibliography

Meyerhardt JA, Mangu PB, Flynn PJ, Korde L, Loprinzi CL, Minsky BD, et al; American Society of Clinical Oncology. Follow-up care, surveillance protocol, and secondary prevention measures for survivors of colorectal cancer: American Society of Clinical Oncology clinical practice guideline endorsement. J Clin Oncol. 2013;31:4465-70. [PMID: 24220554] doi:10.1200/JCO.2013.50.7442

Item 90 Answer: A

Educational Objective: **Treat ductal carcinoma in situ.**

Anastrozole is the most effective adjuvant therapy for ductal carcinoma in situ (DCIS) in postmenopausal women younger than 60 years. In the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-35 clinical trial, 5 years of anastrozole was found to be more effective than 5 years of tamoxifen at decreasing both ipsilateral and contralateral breast cancer in postmenopausal women with DCIS who were younger than 60 years when starting treatment. Almost 95% of the anastrozole group was free from local or contralateral recurrence compared to 88% of the tamoxifen group. Overall 10-year survival, approximately 90%, was comparable between the

two groups. In women age 60 years or older, anastrozole and tamoxifen yielded equivalent results. All women in this trial were postmenopausal and underwent lumpectomy and breast radiation. Unlike in invasive breast cancer, there is no survival advantage to treatment with antiestrogens for patients with DCIS, and such treatment is discussed as an option for patients who wish to decrease their risk of local recurrence and contralateral breast cancers. Because this patient is younger than 60 years, anastrozole is the most effective adjuvant antiestrogen option to achieve this goal.

Raloxifene is a selective estrogen receptor modulator (SERM) that can be used for breast cancer prophylaxis in patients with atypical breast lesions or in patients with a strong family history of breast cancer, but it is not an effective option for hormonal therapy in patients who have DCIS or invasive cancers.

Chemotherapy is not indicated in the treatment of DCIS. Chemotherapy is used as adjuvant treatment to decrease the risk of distant metastases in many invasive breast cancers, but in DCIS the risk of distant metastases is only 1%. Tamoxifen alone is an option for DCIS and could be discussed as an alternative to anastrozole, particularly in patients who wish to avoid potential anastrozole side effects, such as arthralgia and decreased bone density.

The 21-gene recurrence score testing is used in invasive cancers to determine the benefit of adding adjuvant chemotherapy in patients with estrogen receptor-positive cancers who will be treated with antiestrogen treatment. It is not helpful at determining the benefit of antiestrogen therapy in DCIS. The use of the 21-gene recurrence score in DCIS to determine if radiation can be safely omitted has been studied, but it is not yet approved for this use.

KEY POINT

- Anastrozole adjuvant therapy for ductal carcinoma in situ in postmenopausal patients younger than age 60 years decreases the risk of recurrent ipsilateral and contralateral breast cancer but does not decrease overall survival.

Bibliography

Margolese RG, Cecchini RS, Julian TB, Ganz PA, Costantino JP, Vallow LA, et al. Anastrozole versus tamoxifen in postmenopausal women with ductal carcinoma in situ undergoing lumpectomy plus radiotherapy (NSABP B-35): a randomised, double-blind, phase 3 clinical trial. Lancet. 2016;387:849-56. [PMID: 26686957] doi:10.1016/S0140-6736(15)01168-X

Item 91 Answer: E

Educational Objective: Evaluate for activating mutations in newly diagnosed metastatic nonsquamous non-small cell lung cancer.

The most appropriate management is to test for epidermal growth factor receptor (EGFR), *ALK*, and *ROS1* alterations. Mutations in *EGFR*, translocation of the *ALK* and *EML-4* genes, or mutation of the *ROS1* gene have been identified in a few non-squamous cell lung cancers, usually adenocarcinomas. Patients with *EGFR* mutations have been found to derive significant benefit from treatment with erlotinib, whereas those with *ALK* translocations and *ROS1* mutations derive similar benefit from crizotinib; these agents are recommended as initial therapy in these patients when mutation status is known before treatment is initiated. In patients who must start treatment before mutation test results are available, these agents can be used later in treatment. Current standard care is to test for these molecular alterations in any patient diagnosed with nonsquamous metastatic non-small cell lung cancer. Although testing can also be considered in patients with squamous histologic findings, the likelihood of finding an alteration is very low.

Erlotinib would not be appropriate for this patient in the absence of a confirmed *EGFR* mutation because there is no evidence it is effective in patients without the mutation.

Prophylactic cranial irradiation is a standard treatment for patients with metastatic small cell lung cancer after chemotherapy. It is not indicated at the time of diagnosis in patients with non-small cell lung cancer.

Because this patient's thoracic spine lesion is not causing pain, there is no role for palliative radiotherapy at this time.

Patients are often treated with chemotherapy while the results of mutation testing are pending, but it is critical to obtain testing as soon as possible after diagnosis. For this reason, it is most appropriate to perform mutation testing before initiation of chemotherapy.

KEY POINT

- For nonsquamous metastatic non-small cell lung cancer, testing for molecular alterations in the epidermal growth factor receptor (EGFR), *ALK*, and *ROS1* genes informs treatment options; patients with *EGFR* mutations derive significant benefit from treatment with erlotinib, whereas those with *ALK* translocations and *ROS1* mutations derive similar benefit from crizotinib.

Bibliography

Dholaria B, Hammond W, Shreders A, Lou Y. Emerging therapeutic agents for lung cancer. J Hematol Oncol. 2016 Dec 9;9(1):138. [PMID: 27938382]

Item 92 Answer: A

Educational Objective: Manage very-low-risk prostate cancer with active surveillance.

The most appropriate management is active surveillance. The American College of Physicians recommends that clinicians inform men between 50 and 69 years of age about the limited potential benefits and substantial harms of screening for prostate cancer. The decision to screen should be based on the patient's general health and life expectancy and patient preferences. This patient has very low-risk prostate cancer based on his biopsy findings and prostate-specific antigen (PSA) level at diagnosis. Management of such patients has evolved during the past several years. Although treatment is a reasonable consideration, recent literature supports the use of active

surveillance, which is a program of scheduled assessments that include digital rectal examination, PSA measurement, and prostate biopsy. The purpose of active surveillance is to identify early evidence of cancer progression in an effort to limit treatment to those most likely to benefit. It is appropriate only for men with low-risk or very-low-risk prostate cancer who have a life expectancy of at least 10 years. Although no randomized data are available to support this strategy, available data indicate that the 15-year metastasis-free survival in appropriately selected patients is up to 97%. Active surveillance is currently considered appropriate standard care in this patient population.

Bone scan is not indicated for this asymptomatic patient because he has a very low likelihood of occult metastatic disease. A bone scan would be indicated only if there were signs or symptoms suggestive of osseous metastatic disease.

Leuprolide would be indicated for treatment of metastatic disease, and it can also be combined with radiation for treatment of high-risk or very-high-risk prostate cancer. However, it has no role in the treatment of an asymptomatic patient with very-low-risk prostate cancer.

Observation, sometimes called "watchful waiting," is distinct from active surveillance. These patients are provided palliative care if and when symptomatic progression requires medical intervention for control of symptoms. Observation is appropriate for elderly men with significant medical comorbidities that limit life expectancy. Treatment is not appropriate for these men based on their relatively short predicted life expectancy.

KEY POINT

- Active surveillance is a reasonable option in men with low-risk or very-low-risk prostate cancer who have a life expectancy of at least 10 years; active surveillance consists of scheduled assessments that include digital rectal examination, prostate-specific antigen measurement, and prostate biopsy.

Bibliography

Klotz L, Vesprini D, Sethukavalan P, Jethava V, Zhang L, Jain S, et al. Long-term follow-up of a large active surveillance cohort of patients with prostate cancer. J Clin Oncol. 2015;33:272-7. [PMID: 25512465] doi:10.1200/JCO.2014.55.1192

Item 93 Answer: B

Educational Objective: Perform lung cancer screening after treatment for head and neck cancer.

The most appropriate diagnostic test to perform next is low-dose noncontrast CT scan of the chest. Following definitive treatment for head and neck cancer, patients require ongoing surveillance to look for evidence of recurrence as well as evidence of second primary head and neck cancer. Especially in patients with smoking-related cancers, the risk of a second primary cancer is substantial. Surveillance consists of history, physical examination, and laryngoscopy to examine the entire upper aerodigestive tract.

This patient meets the criteria for screening for lung cancer, independent of the previous head and neck cancer. The U.S. Preventive Services Task Force (USPSTF) recommends annual low-dose CT imaging of the thorax for all patients 55 to 80 years of age who have a 30-pack-year history of smoking and are continuing to smoke or who have quit within the past 15 years. The history of head and neck cancer further increases the risk for subsequent lung cancer in this patient and heightens the importance of such screening.

There is currently no established role for imaging studies of the head and neck or PET/CT scan in the absence of signs or symptoms indicative of metastatic disease. Imaging is indicated, however, for evaluation of concerning signs or symptoms suggestive of cancer recurrence or a new primary cancer.

The most clearly defined risk factor for thyroid cancer is radiation exposure of the thyroid during childhood. Radiation treatment of childhood cancers is the most likely source of exposure, but other sources include fallout from atomic weapons and nuclear power plant accidents. There are no recommendations for thyroid cancer screening after radiation exposure in adulthood. Such patients should be screened periodically for hypothyroidism with a serum thyroid-stimulating hormone level, but routine thyroid ultrasonography is not recommended.

KEY POINT

- Many patients with head and neck cancer have significant smoking histories and should be offered lung cancer screening if they meet high-risk criteria.

Bibliography

Humphrey LL, Deffebach M, Pappas M, et al. Screening for lung cancer with low-dose computed tomography: a systematic review to update the US Preventive Services Task Force recommendation. Ann Intern Med. 2013 Sep 17;159(6):411-20. [PMID: 23897166]

Item 94 Answer: C

Educational Objective: Evaluate lymphadenopathy.

In this patient with multiple enlarged lymph nodes that have persisted for several weeks and with negative results on fine-needle aspiration, a surgical lymph node biopsy should be performed. A surgical biopsy is preferable to less invasive biopsy techniques because it provides more tissue for a definitive diagnosis and allows study of nodal architecture, provided the nodes being evaluated are easily and safely accessible (for example, cervical, axillary, or inguinal).

Although a core biopsy of lymph nodes can be performed and may be diagnostic, it may not provide adequate tissue, particularly if the samples are small and there is necrosis, fibrosis, or only partial or patchy involvement of the node. In the case of lymphoma, which is likely in this patient, up to 35% of core biopsies of lymph nodes must be followed by an excisional lymph node biopsy to fully classify lymphoma. However, core biopsy may be an appropriate next step if the nodes are deep (for example, retroperitoneal) in an attempt to avoid a more invasive procedure.

A PET/CT scan in this patient may be abnormal but will not be diagnostic and may be positive for inflammatory or infectious conditions as well as lymphoma and other malignancies. Although staging with PET/CT may eventually be needed in this patient, that test would be more appropriate after a diagnosis of lymphoma has been made.

Patients with soft, small, freely movable lymph nodes that are limited to the cervical or inguinal area and who have no other significant history or physical examination findings can be followed with serial examinations over 6 to 8 weeks and require no additional investigation. However, from 30% to 50% of patients with supraclavicular lymphadenopathy have an associated malignancy. Right supraclavicular lymphadenopathy is associated with cancer in the thorax, including the mediastinum, lungs, or esophagus. Left supraclavicular lymphadenopathy is associated with abdominal malignancy and lymphoma. Because fine-needle aspiration cytology is an insensitive test, particularly in the diagnosis of lymphoma, further evaluation with lymph node excision is indicated.

KEY POINT

- Diagnosis and classification of lymphoma are generally established based on lymph node biopsy.

Bibliography

Frederiksen JK, Sharma M, Casulo C, Burack WR. Systematic review of the effectiveness of fine-needle aspiration and/or core needle biopsy for subclassifying lymphoma. Arch Pathol Lab Med. 2015;139:245-51. [PMID: 25611108] doi:10.5858/arpa.2013-0674-RA

H Item 95 Answer: A

Educational Objective: Manage metastatic non–small cell lung cancer with palliative care.

The most appropriate management in addition to platinum-based chemotherapy is palliative care consultation. In patients with metastatic non-small cell lung cancer, early institution of palliative care has been shown to improve both quality of life and survival. Palliative care does not preclude aggressive cancer treatment with platinum-based combination chemotherapy and other interventions. Palliative care complements cancer treatment through its emphasis on controlling both cancer- and treatment-related symptoms that may interfere with effective treatment. It also makes it easier for patients and treating physicians to decide when treatment is no longer indicated, either because of insufficient efficacy or problematic toxicity. Current standard care is to offer palliative care services at the time of diagnosis with metastatic non-small cell lung cancer and, by extension, in patients diagnosed with any advanced incurable cancer.

PET/CT scan plays no role in this patient's management, as CT and bone scans have already been performed and have already documented the extent of metastatic disease.

Prophylactic cranial irradiation is indicated in selected patients with small cell lung cancer, but it is not appropriate in patients with non-small cell lung cancer.

Epidermal growth factor receptor (*EGFR*) mutation testing is not indicated because this patient has squamous cell carcinoma and has a smoking history. The incidence of *EGFR* mutation in such a patient is very low, and routine testing is not indicated.

KEY POINT

- In patients with metastatic non–small cell lung cancer, early institution of palliative care has been shown to improve both quality of life and survival; palliative care does not preclude aggressive cancer treatment.

Bibliography

Temel JS, Greer JA, Muzikansky A, et al. Early palliative care for patients with metastatic non-small-cell lung cancer. N Engl J Med. 2010 Aug 19;363(8):733-42. [PMID: 20818875]

Item 96 Answer: B

Educational Objective: Treat mismatch repair-deficient colorectal cancer.

An immune checkpoint inhibitor is the most reasonable treatment. This patient now has metastatic colorectal cancer with a mismatch repair-deficient tumor. Tumors may be mismatch repair deficient either because of a germline mutation (Lynch syndrome) or a somatic mutation or epigenetic silencing that is limited to the tumor. In either case, these mismatch repair-deficient tumors represent the very limited subset of metastatic colorectal cancers that have shown substantial benefit in a few small studies from treatment with immune checkpoint inhibitors, such as pembrolizumab or nivolumab. Unfortunately, these mismatch repair-deficient tumors represent only a small minority of patients with metastatic cancer. For most patients with metastatic colorectal disease (greater than 95%), immune checkpoint inhibitors have thus far been essentially ineffective.

Epidermal growth factor receptor inhibitors such as panitumumab or cetuximab are inappropriate for consideration in a patient with a mutation in *KRAS* or any other *RAS* gene because they are potentially active only in tumors with nonmutated *KRAS*, *NRAS*, and *BRAF* genes.

Several trials have examined the efficacy of simultaneously targeting both vascular endothelial growth factor and the endothelial growth factor receptor with dual antibody therapy. However, this synergic approach has not been shown to be effective, and the results suggest that dual antibody therapy for this patient is not the next most reasonable treatment option.

Although supportive comfort care only should be considered in patients who are either too sick for treatment or who have exhausted all reasonable treatment options, such a course of action would not be the first consideration in a fully functional patient with a meaningful treatment option.

KEY POINT

- An immune checkpoint inhibitor, such as pembrolizumab, shows benefit in patients with metastatic mismatch repair–deficient colorectal cancer.

Bibliography

Le DT, Uram JN, Wang H, Bartlett BR, Kemberling H, Eyring AD, et al. PD-1 Blockade in Tumors with Mismatch-Repair Deficiency. N Engl J Med. 2015;372:2509-20. [PMID: 26028255] doi:10.1056/NEJMoa1500596

Item 97 Answer: A

Educational Objective: Prevent recurrent pneumonia in a patient with chronic lymphocytic leukemia.

This patient with chronic lymphocytic leukemia (CLL) has had three hospitalizations for pneumonia in the past year, and assessing his immunoglobulin levels would be appropriate. Patients with CLL frequently are hypogammaglobulinemic and are prone to sinus and pulmonary infection. Intravenous immunoglobulin G replacement therapy has been shown to reduce the risk of infections in patients with CLL with documented hypogammaglobulinemia. Surveillance for viral infections and early initiation of antimicrobial agents for presumed bacterial infections are also essential.

Although this patient has lymphocytosis, lymphadenopathy, and splenomegaly, their presence alone is not an indication to treat his underlying CLL in the absence of symptoms or more significant cytopenias.

Although the patient has only 5% neutrophils and 1% bands, his total leukocyte count is 34,000/µL (34×10^9/L), and thus he is not significantly neutropenic. Even if he were neutropenic, long-term granulocyte colony-stimulating factor (G-CSF) injections would not be appropriate.

Ibrutinib is an appropriate therapy for CLL that requires treatment because it is taken orally, is relatively easy for most patients to tolerate, and is associated with high response rates in both untreated and previously treated patients. However, there is no clear benefit to immediate initiation of ibrutinib therapy in asymptomatic patients.

KEY POINT

- Intravenous immunoglobulin G replacement therapy reduces the risk of infections in patients with chronic lymphocytic leukemia with documented hypogammaglobulinemia.

Bibliography

Sánchez-Ramón S, Dhalla F, Chapel H. Challenges in the role of gammaglobulin replacement therapy and vaccination strategies for hematological malignancy. Front Immunol. 2016;7:317. [PMID: 27597852] doi:10.3389/fimmu.2016.00317

Item 98 Answer: D

Educational Objective: Evaluate recurrent colorectal cancer.

The *RAS* mutation status of an archived primary tumor specimen should be tested next. This patient has colon cancer that has metastasized to the liver and lungs in a pattern that is not surgically curable. Chemotherapy is the treatment of choice, and several different agents will be considered. This patient may be a candidate for treatment with an epidermal growth factor receptor inhibitor, such as cetuximab or panitumumab. All patients with metastatic colorectal cancer should have tumor genotyping to identify mutations in the *KRAS* and *NRAS* genes because cetuximab and panitumumab are inactive in the 40% to 50% of tumors that harbor these mutations. It is therefore standard practice to obtain *RAS* mutational status of tumors of patients with metastatic disease. *RAS* mutations, when they occur, occur early in carcinogenesis, such that the *RAS* mutation status of the primary tumor and a subsequent recurrence are very highly concordant, and rebiopsy of the tumor for *RAS* status is not necessary. The absence of *KRAS* or *NRAS* mutations does not predict therapeutic success with cetuximab or panitumumab; up to 40% of tumors with wild type (nonmutated) genes will not respond to these agents. Multigene sequencing may open some experimental options, but it does not yield actionable information in terms of standard management options at this time. Thus, the expense is not warranted outside of a potential research setting.

The presentation and imaging of this patient, who was at high risk for recurrence, are virtually diagnostic of metastatic colon cancer, and an invasive procedure, such as needle biopsy, for pathologic confirmation is neither required nor appropriate.

A PET/CT scan would not provide any additional information to the imaging that is already available and would not change management.

KEY POINT

- The *RAS* mutational status of tumors should be tested in patients with metastatic disease to determine if they are candidates for treatment with an epidermal growth factor receptor inhibitor, such as cetuximab or panitumumab.

Bibliography

Allegra CJ, Rumble RB, Hamilton SR, Mangu PB, Roach N, Hantel A, et al. Extended RAS gene mutation testing in metastatic colorectal carcinoma to predict response to anti-epidermal growth factor receptor monoclonal antibody therapy: American Society of Clinical Oncology provisional clinical opinion update 2015. J Clin Oncol. 2016;34:179-85. [PMID: 26438111] doi:10.1200/JCO.2015.63.9674

Item 99 Answer: C

Educational Objective: Treat non–small cell lung cancer that responds to first-line chemotherapy with maintenance chemotherapy.

The most appropriate treatment is pemetrexed maintenance chemotherapy. In the absence of a driver mutation, the current standard for management of patients with metastatic non–small cell lung cancer and good performance status is platinum-based chemotherapy. Many combinations can be used, including carboplatin and pemetrexed, which was used for this patient. Treatment is given for four to six cycles depending on response. There is no evidence to support continuation of treatment after six cycles. However, maintenance chemotherapy, such as with single-agent

pemetrexed, has been shown to improve progression-free survival and, in some studies, overall survival. Therefore, maintenance chemotherapy is an appropriate option for patients with metastatic non–small cell lung cancer who respond to first-line platinum-based chemotherapy. Either the nonplatinum agent used for first-line treatment is continued as a single agent ("continuation maintenance") or an alternative agent, most commonly docetaxel, is used ("switch maintenance").

Continuation of platinum-based chemotherapy with a different partner agent is not indicated for this patient. There is no evidence supporting the use of carboplatin beyond six cycles in patients with metastatic non–small cell lung cancer. In addition, this patient has been diagnosed with adenocarcinoma, and currently available evidence indicates that gemcitabine is not effective in patients with adenocarcinoma.

Because this patient did not have an epidermal growth factor receptor (*EGFR*) mutation, there is no role for erlotinib treatment. Erlotinib is effective only in patients with an identified activating *EGFR* mutation.

For patients with metastatic disease, radiation is reserved for palliation of cancer-related symptoms, most commonly pain. It has no role in treatment of the cancer.

KEY POINT

- Maintenance chemotherapy is an appropriate option for patients with metastatic non–small cell lung cancer who respond to first-line platinum-based chemotherapy.

Bibliography

Ciuleanu T, Brodowicz T, Zielinski C, et al. Maintenance pemetrexed plus best supportive care versus placebo plus best supportive care for non-small-cell lung cancer: a randomised, double-blind, phase 3 study. Lancet. 2009 Oct 24;374(9699):1432-40. [PMID: 19767093]

Item 100 Answer: C

Educational Objective: Treat early-stage laryngeal cancer.

The most appropriate treatment in this patient with early-stage laryngeal cancer is radiation therapy. In early-stage laryngeal cancer, it is important to consider predicted efficacy and anticipated voice quality and other potential functional impairments when deciding on a treatment plan. For patients with early-stage disease, cure rates are high with surgery and with radiation. For patients treated with surgery, the use of adjuvant radiation or combined chemotherapy and radiation is recommended based on findings at surgery. However, open hemilaryngectomy results in suboptimal functional outcomes and is associated with complications, including bleeding, infection, laryngocutaneous fistula, and aspiration. Radiation is highly effective with low morbidity, and functional outcomes are generally superior in patients with laryngeal cancer who are treated with radiation compared with those treated with surgery. Radiation therapy often causes xerostomia, thickening of saliva, mucositis, dysphagia, odynophagia, and malnutrition.

Use of combined chemotherapy and radiation is appropriate for patients with locally advanced laryngeal cancer who need total laryngectomy for effective treatment. The most commonly used agent is high-dose cisplatin. Cetuximab, a monoclonal antibody directed against the epidermal growth factor receptor, is also an accepted care option in this setting. However, these therapies are not indicated in patients with early-stage laryngeal cancer, who are effectively treated with radiation alone.

KEY POINT

- Early-stage laryngeal cancer is most appropriately treated with radiation alone because it is highly effective in that area, has low morbidity, and is associated with superior voice quality compared with patients who are treated with surgery.

Bibliography

Chera BS, Amdur RJ, Morris CG, Kirwan JM, Mendenhall WM. T1N0 to T2N0 squamous cell carcinoma of the glottic larynx treated with definitive radiotherapy. Int J Radiat Oncol Biol Phys. 2010;78:461-6. [PMID: 20153124] doi:10.1016/j.ijrobp.2009.08.066

Item 101 Answer: E

Educational Objective: Treat stage I rectal cancer.

The most appropriate treatment is surgery. Based on the information available, this person has a T2N0, stage I midrectal cancer. Patients with rectal tumors that are not full thickness and do not have lymph node involvement (stage I) on pretreatment imaging usually undergo surgery, with a total mesorectal excision being the preferred procedure. The mesorectum is a fatty sheath covering the rectum that contains the regional lymph nodes. A total mesorectal excision entails a sharp dissection of the pelvis outside of the mesorectum to allow removal of the mesorectum fully intact en bloc with the rectum. Because this patient's tumor is 8 cm from the anal verge, this is a midrectal tumor. Resection of such a tumor would be anticipated to be sphincter sparing and so would not be anticipated to require a permanent colostomy. However, considerable expertise is required to avoid complications with this procedure, which should be performed only by a subspecialized surgeon.

If postoperative findings upstage the tumor to stage II or III, then consideration of further interventions, such as radiation or chemotherapy, may be warranted. However, data do not support a role for adding either chemotherapy or radiation therapy to the management of surgically confirmed stage I rectal cancer.

KEY POINT

- Rectal cancers without full thickness penetration of the bowel wall or involved lymph nodes are stage I and are treated with surgical resection.

Bibliography

Allegra CJ, Yothers G, O'Connell MJ, Beart RW, Wozniak TF, Pitot HC, et al. Neoadjuvant 5-FU or capecitabine plus radiation with or without oxaliplatin in rectal cancer patients: a phase III randomized clinical trial. J Natl Cancer Inst. 2015;107. [PMID: 26374429] doi:10.1093/jnci/djv248

H

Item 102 Answer: C

Educational Objective: Prevent chemotherapy-induced neutropenia.

This patient has fever and neutropenia caused by her chemotherapy and should start granulocyte colony-stimulating factor (G-CSF) with her next cycle of chemotherapy. Febrile neutropenia is defined as a single fever (101 °F [38.3 °C]) or sustained elevated temperature (38 °C [100.4 °F]) in a patient with a current or anticipated absolute neutrophil count less than 500 cells/µL (0.5×10^9/L). Most infections are believed to arise from the patient's endogenous flora. Neutropenia typically occurs 5 to 15 days after administration of chemotherapy. G-CSF and granulocyte-macrophage colony-stimulating factor can be given prophylactically to patients receiving chemotherapeutic regimens that carry a high risk of neutropenia and as secondary prophylaxis in patients such as this one, who have had a previous episode.

In this patient, initiating G-CSF or pegylated G-CSF on day 2 of her next cycle of chemotherapy would reduce the risk of another bout of febrile neutropenia and help maintain the dose intensity of her chemotherapy.

Reducing this patient's dose of chemotherapy for the next cycle would not be an appropriate strategy to avoid neutropenia because she is a young patient being treated with curative intent, and reducing her chemotherapy dosages might compromise her outcome. The prophylactic use of G-CSF is a better strategy.

There is little benefit to starting G-CSF once a patient already has fever and neutropenia. Although there may be a slightly more rapid return of neutrophils, the benefit is minimal, and there is no demonstrated reduction in mortality.

Fluoroquinolone prophylaxis is typically reserved for high-risk patients with ongoing neutropenia. High-risk patients typically include those undergoing allogeneic hematopoietic cell transplantation or receiving induction chemotherapy for acute leukemia. Neither of these applies to this patient.

KEY POINT

- Granulocyte colony-stimulating factor is effective for prophylaxis and secondary prophylaxis of neutropenia in patients undergoing chemotherapy but has little benefit in patients who are currently neutropenic.

Bibliography

Smith TJ, Bohlke K, Lyman GH, et al; American Society of Clinical Oncology. Recommendations for the use of WBC growth factors: American Society of Clinical Oncology Clinical practice guideline update. J Clin Oncol. 2015 Oct 1;33(28):3199-212. doi: 10.1200/JCO.2015.62.3488. [PMID: 26169616]

Item 103 Answer: B

Educational Objective: Treat a gastrointestinal stromal tumor with imatinib.

The most appropriate management for this patient is oral imatinib for 3 years. Gastrointestinal stromal tumors (GISTs) most commonly occur in the stomach, although they can arise anywhere in the digestive tract. Although rare, they are the most common sarcoma of the digestive tract. Location outside of the stomach, larger size, and higher mitotic index are all factors that increase the risk of recurrence after resection and indicate use of adjuvant therapy. Almost all GISTs have an activating mutation in the c-KIT proto-oncogene, leading to constitutive activation of the KIT receptor tyrosine kinase. Therefore, she should be treated with the small-molecule receptor tyrosine kinase inhibitor imatinib, which blocks c-KIT tyrosine kinase phosphorylation. In such high-risk patients, recurrence-free survival and overall survival are superior in patients who receive 3 years of imatinib therapy compared with 1 year of therapy.

Rituximab is a genetically engineered chimeric monoclonal antibody against CD20, a B-cell specific surface antigen. CD20 regulates cell cycle initiation. Rituximab binds to the antigen on the cell surface, activating complement-dependent B-cell cytotoxicity, and binds to human Fc receptors, mediating cell killing through an antibody-dependent cellular toxicity. Rituximab is used in the treatment of rheumatoid arthritis, ANCA-related vasculitis, chronic lymphocytic leukemia, and non-Hodgkin lymphoma. As predicted by its mechanism of action, it is not effective in the treatment of GIST.

Because GISTs are relatively resistant to radiation therapy, such treatment is not used after a complete resection.

Small gastric GISTs with low mitotic indices may often be managed with surgery alone, but because this patient has a GIST with several factors that increase the risk of recurrence, observation without further therapy is not sufficient.

KEY POINT

- High-risk gastrointestinal stromal tumors should be treated with surgery and 3 years of adjuvant imatinib.

Bibliography

Joensuu H, Eriksson M, Sundby Hall K, Hartmann JT, Pink D, Schütte J, et al. One vs three years of adjuvant imatinib for operable gastrointestinal stromal tumor: a randomized trial. JAMA. 2012;307:1265-72. [PMID: 22453568] doi:10.1001/jama.2012.347

Item 104 Answer: B

H

Educational Objective: Manage superior vena cava syndrome.

This patient has symptoms, signs, and CT scan findings consistent with superior vena cava (SVC) syndrome due to a mediastinal malignancy, with symptoms developing over 2 weeks, and should receive a mediastinoscopy. It is important to establish a tissue diagnosis before treatment. There are no peripheral sites to biopsy in this case; the only abnormal result found on imaging and examination is the mediastinal mass. Although some patients may be unable to have surgery if they are in severe respiratory distress, are hemodynamically unstable, or have evidence of cerebral edema, most patients who present with SVC syndrome can tolerate a surgical biopsy. Mediastinoscopy with biopsy

H CONT.

has a diagnostic yield of over 90% and is more likely than core biopsies to obtain specimens adequate for determining nodal architecture and histologic subtype if a lymphoma is present. SVC syndrome is caused by thrombosis or other nonmalignant obstructions in about 35% of cases. Of malignant causes, approximately 75% are due to lung cancers, with non-small cell lung cancers most common. Lymphoma and metastatic cancer each cause about 10% of cases; thymoma, germ cell cancer, and mesothelioma are each present in 1% to 3% of cases.

Dexamethasone is often used to treat SVC syndrome and, particularly in lymphomas, may decrease symptoms. However, dexamethasone may obscure histologic findings in lymphomas, and a biopsy should be done before starting the patient on glucocorticoids.

Percutaneous intravascular stents can be placed in patients with respiratory distress before tissue biopsy, but this patient is not having respiratory distress and does not require stent placement.

Radiation requires an initial tissue diagnosis and is used as initial treatment in some but not all malignancies that cause SVC syndrome. If this patient has a lymphoma, as is clinically most likely, she would be treated with initial chemotherapy.

KEY POINT

- Most patients with superior vena cava syndrome do not require emergency intervention, and a tissue biopsy should be obtained.

Bibliography

Wilson LD, Detterbeck FC, Yahalom J. Clinical practice. Superior vena cava syndrome with malignant causes. N Engl J Med. 2007;356:1862-9. Erratum in: N Engl J Med. 2008 Mar 6;358(10):1083. [PMID: 17476012]

Item 105 Answer: C

Educational Objective: Treat locally advanced head and neck cancer.

The most appropriate treatment is cisplatin plus radiation. Treatment of head and neck cancer in the adjuvant setting depends heavily on the results of pathologic analysis of the resection specimen. This should include assessment of human papillomavirus (HPV) status based on tumor staining for p16, a viral protein. HPV has been found to be responsible for most oropharynx cancers (tonsil and base of tongue). Most patients diagnosed with HPV-associated head and neck cancer are younger than expected and do not have traditional risk factors, such as the patient in this case. Positivity for HPV has a significant impact on prognosis but does not yet affect treatment decision making. Options for treatment include no adjuvant therapy, radiation alone, and combined chemotherapy and radiation. No adjuvant therapy is required for early-stage cancers with no high-risk pathologic features, such as poorly differentiated histology and lymphovascular invasion. For early-stage cancers with high-risk features and for some locally advanced cancers (specifically any node-positive cancer), radiation alone is appropriate. Combined chemotherapy and radiation has been shown to improve survival in patients with locally advanced cancer after surgery when there are positive surgical margins or evidence of nodal metastases with extracapsular extension. Extracapsular extension refers to squamous cell carcinoma that breaks through the outer capsule of the lymph node and extends into surrounding tissues. Notably, the number of lymph nodes involved has not been clearly shown to be a predictor of benefit with combined chemotherapy and radiation adjuvant therapy. This patient underwent surgery and had evidence of extracapsular extension; therefore, combined cisplatin and radiation is the most appropriate adjuvant treatment.

Chemotherapy alone, either with single-agent cisplatin or cisplatin-based combination chemotherapy, is not indicated. Adjuvant chemotherapy has not been shown to improve survival or other treatment outcomes in this setting.

Vaccination of children before sexual activity is important in the primary prevention of HPV infection and the reduction of the incidence of oropharyngeal, cervical, and anal cancers associated with this virus. Immunization plays no role in patients who are already infected with HPV.

Radiation alone is not indicated owing to the presence of extracapsular extension.

KEY POINT

- Combined chemotherapy and radiation improves survival in patients with locally advanced head and neck cancer after surgery when there are positive surgical margins or evidence of nodal metastases with extracapsular extension.

Bibliography

Adelstein D, Gillison ML, Pfister DG, Spencer S, Adkins D, Brizel DM, et al. NCCN guidelines insights: head and neck cancers, version 2.2017. J Natl Compr Canc Netw. 2017;15:761-770. [PMID: 28596256] doi:10.6004/jnccn.2017.0101

Item 106 Answer: B

Educational Objective: Treat stage II non-small cell lung cancer with adjuvant chemotherapy after resection.

The most appropriate treatment is adjuvant chemotherapy. Most (80%) lung cancers are non-small cell lung cancers (NSCLCs), with the most common type being adenocarcinoma of the lung. Current treatment options for NSCLCs include surgical resection, radiation therapy, chemotherapy, and targeted therapies. Several studies have found a small but significant survival benefit associated with adjuvant chemotherapy in patients with stage II and stage III NSCLC. Although both cisplatin- and carboplatin-based chemotherapy regimens have been studied, only cisplatin-based chemotherapy has been shown to improve survival. At least four

different cisplatin-based combination regimens can be used for adjuvant chemotherapy treatment; however, patients must be selected carefully because toxicity can be substantial. Based on this survival benefit, cisplatin-based chemotherapy is recommended after surgery for stage II and stage III NSCLC in patients such as this one without contraindications to chemotherapy.

Combined chemotherapy and radiation has not been shown to improve outcomes in patients with NSCLC after surgery with negative margins. Combined chemotherapy and radiation is used, however, as a primary therapy for patients with stage III lung cancer with clinically evident mediastinal lymphadenopathy noted at the time of initial evaluation; this is because this group of patients does not typically fare well with surgery.

Radiation as a single modality has no role in the adjuvant treatment of resected NSCLC in the absence of positive surgical margins. In the presence of positive margins, it is reasonable to recommend radiation.

Observation is not recommended as a routine management strategy because of the survival benefit associated with chemotherapy treatment. Observation would be appropriate only for a patient who could not be treated with chemotherapy owing to medical contraindications or personal preference.

KEY POINT

- Adjuvant cisplatin-based chemotherapy for stage II and stage III non–small cell lung cancer provides a survival advantage.

Bibliography

Pignon JP, Tribodet H, Scagliotti GV; LACE Collaborative Group. Lung adjuvant cisplatin evaluation: a pooled analysis by the LACE Collaborative Group. J Clin Oncol. 2008 Jul 20;26(21):3552-9. [PMID: 18506026]

Item 107 Answer: D

Educational Objective: Manage cancer of unknown primary site in a patient with poor performance status.

This patient should receive supportive management and hospice care. He has moderately differentiated adenocarcinoma of unknown primary site with extensive metastatic disease and severe debilitation, jaundice, and evidence of substantial nutritional deficiency as indicated by cachexia, bitemporal wasting, and hypoalbuminemia. This is a patient who is too debilitated and deconditioned to have a realistic chance of benefit from chemotherapy, and the most appropriate management is to focus on symptom control and comfort. Hospice care would be the most effective means of accomplishing these goals.

In a more medically fit patient with adenocarcinoma in a predominantly abdominal pattern, treatment with a gastrointestinal chemotherapy regimen, such as 5-fluorouracil (5-FU), leucovorin, and oxaliplatin (FOLFOX); 5-FU, leucovorin, and irinotecan (FOLFIRI); or 5-FU, leucovorin, irinotecan, and oxaliplatin (FOLFIRINOX) would be a reasonable consideration; however, this patient is too debilitated to tolerate these treatments.

A platinum-based germ cell regimen would be appropriate for a younger patient with a midline poorly differentiated carcinoma, but this patient does not meet these criteria and, again, is too sick to tolerate this treatment.

Hepatic arterial embolization is an appropriate consideration for patients with well-differentiated neuroendocrine tumors or primary liver cancer who are well enough to tolerate such treatments and whose disease is largely confined to the liver.

KEY POINT

- Patients with several comorbidities and poor performance status are unlikely to benefit from aggressive chemotherapy, and such treatment is likely to cause serious or life-threatening toxicity.

Bibliography

Fizazi K, Greco FA, Pavlidis N, Daugaard G, Oien K, Pentheroudakis G; ESMO Guidelines Committee. Cancers of unknown primary site: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2015;26 Suppl 5:v133-8. [PMID: 26314775] doi:10.1093/annonc/mdv305

Item 108 Answer: C

Educational Objective: Diagnose renal cell carcinoma in a patient with erythrocytosis.

The most appropriate diagnostic test to perform next is CT scan of the abdomen. Although symptomatic erythrocytosis is most commonly associated with myeloproliferative neoplasms, such as polycythemia vera, it is important to assess for all possible causes. This patient has symptomatic erythrocytosis in the setting of a markedly elevated erythropoietin level and in the absence of organomegaly. This combination of findings is most consistent with autonomous production of erythropoietin, most commonly by an underlying tumor. Tumors known to be associated with this paraneoplastic syndrome include kidney cancer and, less frequently, hepatocellular carcinoma, cerebellar hemangioblastoma, pheochromocytoma, and uterine myomata. Clues to tumor-related erythrocytosis may include microscopic hematuria (kidney cancer); abnormal liver chemistry test results, hepatitis B, hemochromatosis, or cirrhosis (hepatocellular); headache, abnormal neurological findings (hemangioblastoma); hypertension, abnormal electrolyte levels, or hyperglycemia (pheochromocytoma); and menorrhagia (uterine myomata). In the absence of suggestive symptoms or findings, a CT scan of the abdomen is indicated as the first study for further evaluation of this patient.

Bone marrow biopsy and serum *JAK-2* mutation testing can be done to evaluate for possible underlying polycythemia vera. However, polycythemia vera is most commonly seen in the setting of a low or an undetectable erythropoietin level, not with a markedly elevated level as seen in this patient. In addition, polycythemia vera is commonly

associated with an elevated leukocyte and platelet count, as well as hepatosplenomegaly, but these are not present in this patient. These findings make the diagnosis of polycythemia vera less likely; therefore, testing to evaluate for that diagnosis is not indicated as initial management.

Chest radiography has no role in this patient's evaluation because lung cancer is not associated with paraneoplastic erythrocytosis. In addition, chest radiography cannot evaluate for any of the cancers that are associated with erythrocytosis.

KEY POINT

- Erythrocytosis is a common paraneoplastic syndrome associated with kidney cancer.

Bibliography

Morais C, Johnson DW, Vesey DA, Gobe GC. Functional significance of erythropoietin in renal cell carcinoma. BMC Cancer. 2013 Jan 10;13:14. [PMID: 23305401]

Item 109 Answer: D

Educational Objective: Treat oligometastatic liver metastases of colorectal cancer.

The most appropriate management is resection of all lesions. The role of postoperative surveillance in patients with colorectal cancer is to identify surgically curable recurrence, such as oligometastatic liver disease or lung metastases. The liver is the primary metastatic site for patients with colorectal cancer. About one third of patients with metastatic disease will have it confined to the liver and will be amenable to surgical resection and cure, with or without adjuvant chemotherapy. The criteria for surgical resection of hepatic metastases have expanded from the "three lesions or less" rule. Most patients with good performance status can be considered for surgical resection unless they have one of three conditions: tumor involvement of the common artery or portal vein or common bile duct; more than 70% liver involvement, more than six involved segments, or involvement of all three hepatic veins; and a predicted inadequate hepatic reserve after resection. This patient has recurrent colorectal cancer in a single organ in an oligometastatic pattern. As such, he is a candidate for surgery with curative intent.

Hepatic arterial embolization is not routinely used to treat colorectal cancer because colorectal tumors tend not to be very vascular. Further, it is a palliative, noncurative intervention. It is more appropriately considered in the management of unresectable neuroendocrine tumors or primary liver cancers.

A needle biopsy should not be done because it will not change management. The clinical presentation in this patient is compelling enough to diagnose recurrent colorectal cancer; a negative needle biopsy specimen would be assumed to be a false negative and would not alter management. Surgical resection would be the appropriate intervention regardless of the results of a biopsy.

Because this cancer is potentially curable, palliative chemotherapy should not be considered.

KEY POINT

- Patients with recurrent colorectal cancer in a single organ in an oligometastatic pattern are candidates for surgery with curative intent.

Bibliography

Smith JJ, D'Angelica MI. Surgical management of hepatic metastases of colorectal cancer. Hematol Oncol Clin North Am. 2015;29:61-84. [PMID: 25475573] doi:10.1016/j.hoc.2014.09.003

Item 110 Answer: A

Educational Objective: Treat carcinoma of unknown primary site in a woman with isolated axillary lymph node metastases.

The most appropriate management is to treat an axillary presentation of adenocarcinoma in a woman as a likely primary breast cancer. Patients with cancer of unknown primary involving a single lymph node or single lymph node region may have potentially treatable disease. Women with isolated axillary lymphadenopathy that is found to be an adenocarcinoma or a poorly differentiated carcinoma should be assumed to have locoregional breast cancer until proved otherwise. Breast MRI is indicated in this setting and reveals a primary breast mass in 50% to 70% of patients. In addition, immunohistochemical staining for estrogen receptor, progesterone receptor, *HER2* expression, and other breast cancer–specific markers should be performed on the biopsy specimen to help establish the diagnosis of breast tumor and guide therapy.

If the breast MRI scan is normal, the patient should be managed as for primary breast cancer and should undergo axillary lymph node dissection. Although in the past mastectomy was typically recommended in this setting, if no primary cancer is detected on the mammogram or breast MRI scan, axillary dissection with subsequent breast and axillary radiation is an accepted alternative to mastectomy. In patients with triple-negative breast cancer with axillary node involvement, adjuvant chemotherapy is indicated and can be given either before or after axillary dissection.

The management and prognosis are similar whether or not a primary breast cancer is identified, and, in the absence of distant metastases, patients should be treated with curative intent. Women who are found to have other sites of metastatic adenocarcinoma in addition to the axillary lymph node should be treated for metastatic breast cancer.

Letrozole is a hormonal therapy used for hormone receptor–positive breast cancers. This patient's cancer is estrogen and progesterone receptor–negative, and she would not receive any benefit from adjuvant hormonal therapy.

Radiation to the breast and axilla will be recommended after completing surgery and adjuvant chemotherapy but is not given as initial management before these other modalities.

Given the potential curability of this cancer, observation alone would also be inadequate.

KEY POINT

- Women with isolated axillary lymph-node adenocarcinoma metastases should be presumptively considered to have locoregional breast cancer and should be treated as such.

Bibliography

Fizazi K, Greco FA, Pavlidis N, Daugaard G, Oien K, Pentheroudakis G; ESMO Guidelines Committee. Cancers of unknown primary site: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2015;26 Suppl 5:v133-8. [PMID: 26314775] doi:10.1093/annonc/mdv305

H

Item 111 Answer: D

Educational Objective: Prevent tumor lysis syndrome in a patient with Burkitt lymphoma.

The most appropriate treatment is the administration of rasburicase along with intravenous hydration with normal saline and furosemide. Malignancies associated with rapid cell turnover can release large quantities of electrolytes and procoagulants into the circulation, causing the potentially life-threatening complication of tumor lysis syndrome. Spontaneous tumor lysis syndrome occurs commonly in patients with leukemia and Burkitt lymphoma and after treatment of bulky large B-cell lymphoma or advanced chronic lymphocytic leukemia. Rapid cell breakdown results in hyperkalemia, hyperphosphatemia, hyperuricemia, hypocalcemia, and disseminated intravascular coagulation. Hyperuricemia can lead to uric acid nephropathy and acute kidney injury. In this patient, proceeding with rasburicase, intravenous hydration, and furosemide with plans for prompt initiation of systemic therapy is appropriate. Rasburicase can rapidly and effectively lower serum urate levels and reduce the risk of acute uric acid nephropathy seen with tumor lysis syndrome. Because of its rapid onset of action and ability to lower urate levels quickly, which may be renoprotective, rasburicase should be administered before initiation of chemotherapy in patients with underlying kidney disease or those with signs of kidney disease, including an elevated serum creatinine level and a low urine output. Intravenous hydration with diuretics to maintain a high urine output is also key to reducing the risk of kidney failure and managing hyperkalemia and hyperphosphatemia, as well as hyperuricemia.

Large-volume intravenous hydration with normal saline plus administration of allopurinol to limit hyperuricemia is usually effective to prevent tumor lysis syndrome. However, this patient has hyperuricemia and an elevated serum creatinine level, making rasburicase preferred to allopurinol.

Whereas glucocorticoids and radiation therapy may be effective at shrinking this patient's tumors, such therapy will not prevent and will likely exacerbate tumor lysis syndrome.

KEY POINT

- Burkitt lymphoma often presents with early signs of tumor lysis, and it is important to institute tumor lysis syndrome prophylaxis before initiation of chemotherapy.

Bibliography

Casulo C, Friedberg J. Treating Burkitt lymphoma in adults. Curr Hematol Malig Rep. 2015;10:266-71. [PMID: 26013028] doi:10.1007/s11899-015-0263-4

Item 112 Answer: C

Educational Objective: Treat breast cancer using ovarian suppression along with aromatase-inhibitor therapy.

The most appropriate treatment is leuprolide and an aromatase inhibitor. Two prospective randomized clinical trials have shown the superiority of ovarian suppression with leuprolide plus an aromatase inhibitor, such as exemestane, over ovarian suppression plus tamoxifen or tamoxifen alone in premenopausal women with higher risk hormone receptor–positive early breast cancer.

Analyzing the trials together, disease-free survival at 5 years was 91.1% in the ovarian-suppression-plus-exemestane group and 88.3% in the ovarian-suppression-plus-tamoxifen group. Overall survival was the same in both groups. Compared with tamoxifen alone, ovarian suppression with tamoxifen improved disease-free survival, which was further improved by ovarian suppression plus exemestane. The benefit was particularly dramatic in women younger than 35 years who had a 15.7% absolute improvement in 5-year disease-free survival with the use of ovarian suppression and exemestane compared to tamoxifen alone. Adverse effects were seen more frequently in the patients on ovarian suppression, and by 4 years, 21% of patients had stopped ovarian suppression due to side effects. In patients who do not tolerate initial treatment with ovarian suppression and exemestane, ovarian suppression with tamoxifen can be used, transitioning to an aromatase inhibitor after 2 to 3 years if tolerated.

An aromatase inhibitor is ineffective in premenopausal women unless concomitant ovarian suppression is given.

The benefit of ovarian suppression alone is similar to tamoxifen alone and inferior to the option of ovarian suppression and an aromatase inhibitor.

In patients who require initial chemotherapy and remain premenopausal, treatment with tamoxifen alone has a higher risk of breast cancer recurrence than ovarian suppression plus an aromatase inhibitor.

KEY POINT

- Ovarian suppression along with antiestrogen therapy is recommended to decrease breast cancer recurrence in women with high-risk, early-stage, hormone receptor–positive breast cancer who remain premenopausal after chemotherapy.

Bibliography

Pagani O, Regan MM, Walley BA, Fleming GF, Colleoni M, Láng I, et al; TEXT and SOFT Investigators. Adjuvant exemestane with ovarian suppression in premenopausal breast cancer. N Engl J Med. 2014;371:107-18. [PMID: 24881463] doi:10.1056/NEJMoa1404037

Item 113 Answer: E

Educational Objective: Manage a residual mass after treatment of diffuse large B-cell lymphoma.

For this patient with a residual mass after treatment for diffuse large B-cell lymphoma, the appropriate management is observation with serial CT scanning to ensure that the mass is stable. This patient's current CT and PET scan results demonstrate an excellent response to therapy. Her disease was characterized by bulky retroperitoneal lymphadenopathy, and it is probable that the residual mass found on CT scan represents scar tissue rather than viable tumor. Bulky lymphoma masses, when treated with effective systemic therapy, often do not show complete resolution by CT scan. The PET scan results also suggest the absence of active disease, although PET scan is not 100% sensitive or specific. In this circumstance, observation by serial CT (with or without further PET scanning) is most appropriate.

An autologous stem cell transplant could be an appropriate option for a patient with relapsed or residual disease. Even if the PET scan showed higher residual uptake, given the potential for false-positive CT and PET scan results, proceeding to further therapy without tissue documentation of recurrence would not be appropriate.

Although biopsy could be considered to document the presence or absence of viable lymphoma (and should be done to definitively document disease before initiation of any salvage treatment), this procedure could be deferred in a patient with a low suspicion for disease who has a favorable CT scan and metabolic response by PET, unless there are reasons to expect residual or progressive disease.

Consolidative radiation therapy has been used for patients with large cell lymphoma and initial bulky disease and residual mass. This treatment can decrease the risk of local recurrence; however, routine use has not been proven to improve survival or cure, and many patients without active disease would be irradiated.

KEY POINT

- In a patient with a residual mass after treatment of bulky diffuse large B-cell lymphoma, observation with serial CT scanning is appropriate if diagnostic testing shows a low likelihood of active disease.

Bibliography

Thanarajasingam G, Bennani-Baiti N, Thompson CA. PET-CT in staging, response evaluation, and surveillance of lymphoma. Curr Treat Options Oncol. 2016;17:24. [PMID: 27032646] doi:10.1007/s11864-016-0399-z

Item 114 Answer: B

Educational Objective: Treat advanced ovarian cancer with intravenous and intraperitoneal chemotherapy.

The most appropriate initial treatment for this patient with advanced ovarian cancer is intravenous (IV) and intraperitoneal (IP) cisplatin and paclitaxel chemotherapy. This treatment is associated with a 16-month improvement in median overall survival in women with stage III ovarian cancer and no residual mass greater than 1 cm after surgical debulking compared with intravenous chemotherapy alone. Patients receiving IP/IV chemotherapy have a higher incidence of toxicities, including leukopenia, thrombocytopenia, fever, infection, fatigue, pain, and gastrointestinal events. Less than half of patients starting IP/IV therapy can complete all six cycles of therapy. However, the National Cancer Institute encourages the use of IP/IV chemotherapy for optimally debulked stage III ovarian cancer. Obstacles to the widespread adoption of IP/IV chemotherapy include not only the higher toxicities but also placement of an IP catheter and training of nursing staff in IP chemotherapy administration. The original IP/IV regimen required hospitalization for the first 3 days of each cycle. Modified regimens that allow all treatment to be given on an outpatient basis are now accepted options.

High-dose chemotherapy with hematopoietic stem cell transplantation is not recommended for the treatment of ovarian cancer, neither as initial treatment nor after recurrence.

Patients with left colon or rectosigmoid resections had a higher risk of discontinuing IP therapy, so this approach is no longer recommended in patients who undergo bowel resection. The types of catheters used have improved, with fewer catheter-related problems.

Olaparib is approved for use to treat relapsed ovarian cancer in women with *BRCA1* or *BRCA2* germline mutations. This oral poly(ADP-ribose) polymerase (PARP) inhibitor is FDA approved as monotherapy for patients with germline *BRCA*-mutated advanced ovarian cancer previously treated with three or more lines of chemotherapy. Patients with germline *BRCA1*- or *BRCA2*-associated cancers show responses in ovarian, breast, pancreatic, and prostate cancers, with a 31% response rate and median duration of response of 7 months in platinum-resistant ovarian cancers. Olaparib is not used as initial therapy in ovarian cancer.

KEY POINT

- Intravenous and intraperitoneal cisplatin and paclitaxel chemotherapy is a treatment option for patients with advanced ovarian cancer.

Bibliography

Wright AA, Cronin A, Milne DE, et al. Use and effectiveness of intraperitoneal chemotherapy for treatment of ovarian cancer. J Clin Oncol. 2015 Sep 10;33(26):2841-7. [PMID: 26240233]

Item 115 Answer: C

Educational Objective: Treat a patient with a metastatic well-differentiated gastrointestinal neuroendocrine tumor.

The most appropriate management for this patient is to not intervene now and repeat the CT scan in 3 months. Neuroendocrine tumors can arise from the endocrine cells of the pancreas or neuroendocrine cells of the aerodigestive tract. These two entities look and behave similarly; however, several anticancer agents that show activity against pancreatic neuroendocrine tumors show little or no activity against aerodigestive tumors. This patient is asymptomatic with an incidental finding of a well differentiated, low-grade, small-bowel gastrointestinal neuroendocrine tumor (previously known as carcinoid) with multiple small metastases to the liver. The liver is overwhelmingly the most common site of metastasis, and diagnosis is often established through an incidental finding of hepatomegaly or abnormal findings on an imaging study. Such tumors are often asymptomatic and indolent, and asymptomatic patients may do well, with minimal growth and no symptoms for years, even with metastatic disease. As such, there is no urgency to intervene. Follow-up examination and imaging at approximately 3 months is appropriate. Although perhaps 25% of metastatic gastrointestinal neuroendocrine tumors will elaborate serotonin, a hormone causing diarrhea or facial flushing (carcinoid syndrome), most patients have a hormonally nonfunctional tumor and thus do not require treatment for these symptoms. In patients whose disease appears stable on the 3-month CT scan, further monitoring with serial imaging at 3- to 6-month intervals is appropriate.

Hepatic arterial embolization may be helpful in shrinking liver metastases or reducing hormonal output from functional tumors and may be considered in a patient with progressive or symptomatic disease.

Obstruction of the bowel from a well-differentiated neuroendocrine primary tumor is very uncommon, so prophylactic surgery to remove the primary bowel tumor in an asymptomatic patient with metastases is not indicated.

Chemotherapy for gastrointestinal neuroendocrine tumors is of limited utility in asymptomatic patients with small volume disease that has not been demonstrated to be progressive. In these patients, the toxicities of treatment outweigh the benefit.

KEY POINT

- Well-differentiated, low-grade, metastatic gastrointestinal neuroendocrine tumors are often indolent and asymptomatic and do not require immediate treatment.

Bibliography

Singh S, Asa SL, Dey C, Kennecke H, Laidley D, Law C, et al. Diagnosis and management of gastrointestinal neuroendocrine tumors: an evidence-based Canadian consensus. Cancer Treat Rev. 2016;47:32-45. [PMID: 27236421] doi:10.1016/j.ctrv.2016.05.003

Item 116 Answer: D

Educational Objective: Treat hormone receptor-positive breast cancer in a premenopausal patient with primary breast radiation and tamoxifen.

In addition to primary breast radiation, this patient should receive adjuvant tamoxifen. She has a 2.5-cm, node-negative, hormone receptor-positive, *HER2*-negative breast cancer. Gene expression assays, such as the 21-gene recurrence score, are helpful in determining the benefit of adding adjuvant chemotherapy to tamoxifen in patients with node-negative, hormone receptor-positive, *HER2*-negative breast cancer. The 21-gene recurrence score has been shown to be not only prognostic for the risk of distant recurrence but also predictive for the magnitude of benefit of adding chemotherapy to tamoxifen.

A prospective trial of patients with hormone receptor-positive, *HER2*-negative, node-negative breast cancers with 21-gene recurrence scores of 0 to 10 was published in November 2015. The 5-year rate of freedom from recurrence of breast cancer at a distant or local site was 98.7% with endocrine therapy alone. This is standard care for patients with early breast cancer with these characteristics.

Adjuvant chemotherapy, given either alone or followed by tamoxifen, does not improve the disease-free or overall survival in patients with hormone receptor-positive, node-negative breast cancers with low-risk recurrence scores. The SOFT (Suppression of Ovarian Function Trial) study showed that the combination of ovarian suppression and an aromatase inhibitor is superior to tamoxifen in patients with higher risk early breast cancer who require initial chemotherapy and remain premenopausal, but it is not superior to tamoxifen alone in women with low-risk breast cancers who do not need adjuvant chemotherapy.

KEY POINT

- Primary breast radiation and tamoxifen are indicated for premenopausal patients with node-negative, hormone receptor-positive, *HER2*-negative breast cancer with low-risk recurrence scores.

Bibliography

Tevaarwerk AJ, Wisinski KB, O'Regan RM. Endocrine therapy in premenopausal hormone receptor-positive breast cancer. J Oncol Pract. 2016 Nov;12(11):1148-1156. [PMID: 27858538]

Item 117 Answer: E

Educational Objective: Manage prostate cancer in a patient with significant comorbidities.

The most appropriate management in this patient with early-stage prostate cancer and significant medical comorbidities is observation. His medical history is consistent with a predicted life expectancy of less than 5 years, his voiding symptoms are better after treatment with an α-blocker, and

he has no other symptoms attributable to his cancer. Based on the typically indolent course of a low-grade localized prostate cancer, this patient will most likely die as a result of one of his other medical conditions rather than his prostate cancer. He is also at significant risk for complications associated with treatment. These issues should all be discussed with the patient so he can understand the competing issues involved and thereby permit him to be an active participant in decision making.

Observation is distinct from active surveillance. Observation consists of periodic follow-up to assess symptoms related to cancer progression that require palliation. Active surveillance, however, is a plan to defer definitive prostate cancer therapy until there is evidence of cancer progression based on evidence from systematic monitoring, including changes in prostate-specific antigen level and findings on digital rectal examination, biopsy results, or both. Because this patient's early-stage cancer is not appropriate for treatment, he is not a candidate for active surveillance.

Androgen deprivation therapy is not a recommended treatment for early-stage prostate cancer and will expose this patient to unnecessary side effects, including decreased libido and erectile dysfunction, osteoporosis, fatigue, gynecomastia, and hot flushes.

Bone scan is very unlikely to reveal bone metastases in asymptomatic men who have low-risk prostate cancer and, therefore, is not indicated.

Radiation is not appropriate for this patient because of his short predicted life expectancy, the indolent course of early-stage prostate cancer, and prostate radiation side effects, including bladder, bowel, and rectum injury along with erectile dysfunction.

KEY POINT

- For men with early-stage prostate cancer who have limited life expectancy or significant medical comorbidities, observation is the most appropriate management.

Bibliography

Daskivich TJ, Fan KH, Koyama T, et al. Effect of age, tumor risk, and comorbidity on competing risks for survival in a U.S. population-based cohort of men with prostate cancer. Ann Intern Med. 2013 May 21;158(10):709-17. [PMID: 23689764]

Item 118 Answer: D

Educational Objective: Avoid unnecessary imaging in a patient with stage IIB invasive breast cancer.

No imaging studies are necessary for this patient with stage IIB invasive breast cancer. Patients with clinical stages I and II invasive breast cancers are at low risk for metastases at the time of diagnosis of their initial breast cancer. There is a lack of evidence suggesting that routine imaging studies improve the detection of metastatic disease or survival. Clinical staging based on history, physical examination, and serum liver chemistry tests and alkaline phosphatase measurements is the standard for confirming that patients have early-stage breast cancer. Staging imaging studies are recommended only if signs or symptoms suggest metastatic disease.

Bone scan is indicated for patients with localized bone pain or elevated serum alkaline phosphatase levels.

Chest CT is recommended for patients who have pulmonary symptoms or abnormal results on lung examination. Abdominal and possibly pelvic CT is indicated in patients with abnormal results on serum liver chemistry tests or with abnormal alkaline phosphatase levels, abdominal symptoms, or abnormal findings on physical examination of the abdomen or pelvis.

PET scan is not indicated in the staging of clinical stage I, II, or operable stage III breast cancer. In patients with large stage III cancers or inflammatory breast cancer, staging imaging studies are indicated and detect occult distant metastases in 10% to 21% of patients.

Despite a campaign to educate physicians about the lack of benefit of staging imaging studies in clinical stages I to II breast cancer, these tests continue to be done in a large percentage of patients with early breast cancer. A study from Ontario showed that after publication of the American Clinical Society's "Top Five" 2012 guidelines recommending against routine imaging studies in stages I and II breast cancer, 84% of patients with operable early-stage cancer had at least one imaging staging study. Radiologically evident metastases were found in only 2 of 200 patients, both of whom had clinical stage III breast cancer.

KEY POINT

- Clinical staging based on history, physical examination, and serum liver chemistry tests and alkaline phosphatase measurements is the standard to confirm early-stage breast cancer; staging imaging studies are recommended only if signs or symptoms suggest metastatic disease.

Bibliography

Schnipper LE, Smith TJ, Raghavan D, Blayney DW, Ganz PA, Mulvey TM, et al. American Society of Clinical Oncology identifies five key opportunities to improve care and reduce costs: the top five list for oncology. J Clin Oncol. 2012;30:1715-24. [PMID: 22493340] doi:10.1200/JCO.2012.42.8375

Item 119 Answer: A

Educational Objective: Treat hairy cell leukemia.

This patient has hairy cell leukemia, a low-grade B-cell disorder characterized by cytopenia and splenomegaly without lymphadenopathy. Hairy cells (classic appearance of thread-like projections emanating from the cell surface) are typically seen in the peripheral blood smear, and findings on flow cytometry demonstrate positivity for surface markers CD20, CD11c, CD25, and CD103. Cladribine is an appropriate initial therapy for hairy cell leukemia.

Cladribine, as well as another purine nucleoside analogue, pentostatin, is associated with complete response rates exceeding 80% to 90%. A single 5- or 7-day course of cladribine is often all that is required. Many patients have durable remissions, although a significant minority do relapse and require retreatment with the same or alternate agents.

Interferon alfa therapy is active in the treatment of hairy cell leukemia but is rarely used anymore given its toxicity and inferior response rate compared to other agents.

Hairy cell leukemia is typically CD20 positive and should respond to rituximab. However, clinical trials of rituximab have shown mixed results. Many experts reserve rituximab for patients failing two cycles of a purine nucleoside analogue. Rituximab is not given as initial therapy.

Hypersplenism in hairy cell leukemia may play a larger role in the mechanism of cytopenias compared to other lymphoproliferative disorders. Splenectomy can be an effective treatment for relieving symptoms and ameliorating cytopenias associated with hairy cell leukemia. Before effective systemic therapies were available, splenectomy was the initial treatment of choice. However, splenectomy does not treat the underlying marrow infiltration and is no longer considered appropriate initial therapy.

Some patients with hairy cell leukemia are asymptomatic and do not require immediate therapy. However, this patient has fatigue and anemia, so observation would not be appropriate.

KEY POINT

- Initial therapy for hairy cell leukemia is a purine nucleoside analogue, either cladribine or pentostatin.

Bibliography

Getta BM, Park JH, Tallman MS. Hairy cell leukemia: past, present and future. Best Pract Res Clin Haematol. 2015;28:269-72. [PMID: 26614906] doi:10.1016/j.beha.2015.10.015

Item 120 Answer: A

Educational Objective: Diagnose transformed follicular lymphoma.

This patient has a 7-year history of follicular lymphoma with a recent onset of systemic symptoms and a rapidly enlarging right inguinal lymph node. Biopsy of the right inguinal node would be appropriate to evaluate for histologic progression of disease. Transformation to diffuse large B-cell lymphoma occurs in approximately 30% of patients with follicular lymphoma. Transformation may be suggested by a change in the clinical pattern of disease, such as the development of new systemic symptoms or rapid progression of a localized area of disease. In addition, a rise in serum lactate dehydrogenase level or markedly higher areas of standardized uptake values on PET scanning should raise suspicion of transformation. In such cases, a new lymph node biopsy is required to establish the occurrence of transformation. In this patient, rapid progression in just one area of disease, the onset of systemic symptoms, and a high serum lactate dehydrogenase level raise suspicion for transformation. If transformation to another, more aggressive lymphoma is demonstrated, a more aggressive course of treatment would be appropriate. Thus, a new biopsy in this setting is important to optimize management.

Idelalisib, a PI3K kinase inhibitor, is an oral agent that has shown significant activity for the treatment of relapsed follicular lymphoma. It has a reasonably high rate of partial response. It would be appropriate in this patient if transformation is excluded.

Radiation for palliation to a single symptomatic site can be considered for relapsed follicular lymphoma. However, this patient has systemic symptoms, and active systemic options are available; therefore, single-site palliative radiation would not be preferred at this time.

Treating with additional chemotherapy would be a reasonable option for this patient, given her excellent and prolonged initial response, if she has documented relapse of follicular lymphoma and requires retreatment. However, transformation to a large B-cell lymphoma should first be excluded because it may require a different treatment strategy.

KEY POINT

- Transformation of follicular lymphoma to an aggressive non-Hodgkin lymphoma may be suggested by a change in the clinical pattern of disease, such as the development of new systemic symptoms or rapid progression of a localized area of disease.

Bibliography

Casulo C, Burack WR, Friedberg JW. Transformed follicular non-Hodgkin lymphoma. Blood. 2015;125:40-7. [PMID: 25499449] doi:10.1182/blood-2014-04-516815

Item 121 Answer: A

Educational Objective: Evaluate isolated inguinal lymphadenopathy.

The most appropriate diagnostic test to perform is an anoscopy. In the United States, approximately 35,000 patients receive a diagnosis of cancer of unknown primary (CUP) annually. The clinical evaluation should not involve an exhaustive search for a primary site because detection of an asymptomatic and occult primary tumor does not improve outcome. In a patient with CUP, it is important to look for treatable subgroups. Patients with CUP who have lymphadenopathy in a single lymph node or single lymph node region belong to a potentially more treatable subgroup of patients with CUP. Most patients with carcinoma, especially squamous cell carcinoma, involving inguinal lymph nodes have a primary site in the genital or anorectal area. In women this necessitates a careful examination of the vulva, vagina, and cervix. Men require a careful examination of the penis. Men and women should have a careful examination of the perineal skin, a digital rectal examination, and an anoscopy. This patient's examination is complete except for digital rectal examination and anoscopy. The anal region drains directly to the inguinal lymph nodes.

Cancers of the anus that metastasize to the inguinal nodes are local-regionally advanced but not distantly metastatic and are potentially curable with a combination of chemotherapy and radiation therapy.

A bone scan would not be useful in identifying a treatable primary source and would not be indicated in a patient with an enlarged inguinal lymph node in the absence of specific bone pain.

Colonoscopy and upper endoscopy would be indicated in a patient presenting with gastrointestinal symptoms, unexplained anemia, or blood in the stool.

Although PET scans may sometimes suggest the location of a primary tumor, these findings are rarely definitive and do not improve long-term outcome.

Measurement of serum tumor marker levels, such as carcinoembryonic antigen, CA-19-9, CA 15-3, and CA-125, is rarely helpful and virtually never diagnostic.

KEY POINT

- Squamous cell carcinoma or poorly differentiated carcinoma presenting as isolated inguinal lymphadenopathy should prompt a careful examination of the vulva, vagina, and cervix in women, penis in men, and perineal skin and anus in both men and women.

Bibliography

Fizazi K, Greco FA, Pavlidis N, Daugaard G, Oien K, Pentheroudakis G; ESMO Guidelines Committee. Cancers of unknown primary site: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2015;26 Suppl 5:v133-8. [PMID: 26314775] doi:10.1093/annonc/mdv305

Item 122 Answer: D

Educational Objective: Treat stage II colon cancer without high-risk features.

No further treatment is needed. This patient has stage II colorectal cancer (invades full thickness of the bowel [T3]), and lymph nodes are not involved [N0]). Patients with stage II colon cancer do not have a clear survival advantage with administration of adjuvant chemotherapy; consequently, surgery alone is the acceptable standard practice for most patients. Exceptions are patients with stage II colon cancer with characteristics associated with a high risk for recurrence (T4 primary tumor [invasion into adjacent structures or through the peritoneum], lymphovascular invasion, inadequate lymph node sampling [fewer than 12 lymph nodes examined], poorly differentiated histology, elevated postoperative carcinoembryonic antigen (CEA), or clinical perforation or obstruction). In these patients, the prognosis is similar to that of patients with stage III disease, and adjuvant chemotherapy may be appropriate. Exposing this patient to the toxicity of chemotherapy is not warranted, as data do not support a survival benefit in such patients. For patients with stage II disease and a high risk for recurrence, treatment with 5-fluororuracil/leucovorin or capecitabine may be appropriate. Patients with stage II disease with a substantial number of high-risk features may at times be considered for oxaliplatin-containing chemotherapy, such as parenteral 5-fluorouracil, leucovorin, and oxaliplatin (FOLFOX).

Patients with stage III disease (lymph node metastases) are routinely treated with oxaliplatin-containing regimens, such as FOLFOX, after resection. The combination of capecitabine plus intravenous oxaliplatin is also an acceptable regimen for adjuvant treatment of patients with stage III colon cancer.

Because local recurrence of colon cancer rarely develops and because it can be difficult to isolate the small bowel from the radiation field, radiation therapy, either alone or in combination with chemotherapy, does not have a role in the routine management of patients with stage III colon cancer. In addition, radiation to the small bowel may cause substantial toxicity.

KEY POINT

- Patients with stage II colon cancer without high-risk features are unlikely to benefit from adjuvant treatment.

Bibliography

Dotan E, Cohen SJ. Challenges in the management of stage II colon cancer. Semin Oncol. 2011;38:511-20. [PMID: 21810510] doi:10.1053/j.seminoncol.2011.05.005

Item 123 Answer: C

Educational Objective: Treat melanoma with a solitary brain metastasis.

Surgical resection of the brain lesion in this patient with previous melanoma would be the most appropriate treatment. Assuming the lesion is surgically accessible, resection would provide a tissue diagnosis confirming the suspicion of metastatic melanoma, provide the best long-term local control, and offer the best potential for cure. Postoperative radiosurgery to the tumor bed may be considered to reduce the risk for recurrence. Melanoma may be associated with solitary or oligometastatic disease, and metastasectomy can be curative in a significant minority of these patients. Metastasectomy with or without systemic medical therapy is associated with increased overall survival compared to systemic medical therapy alone in patients with stage IV melanoma. Based on a cohort analysis of data from a randomized clinical trial, surgery was associated with a median overall survival of 15.8 months compared to 6.9 months with systemic therapy alone. The 4-year overall survival also favored the surgery group, 20.8% versus 7% in the group receiving systemic therapy alone.

Immunotherapy with nivolumab, pembrolizumab, or ipilimumab plus nivolumab is used in the treatment of metastatic melanoma but would not be recommended as first-line therapy if there is a resectable isolated metastasis, as in this patient.

Gamma knife or other forms of radiosurgery can provide high rates of local control while minimizing radiation exposure to the rest of the brain. With a large mass, however, surgical resection would provide a better probability of long-term control.

Treatment with BRAF/MEK inhibitor combination therapy, such as dabrafenib plus trametinib or vemurafenib plus cobimetinib, is effective for *BRAF*-mutated melanoma and can target disease in the brain, but these agents would not be preferred as initial therapy here because they are less effective than metastasectomy in increasing survival and offering a chance of cure.

Whole brain radiation therapy is reserved for patients with multiple metastases that are not amenable to focal therapies (surgery or radiosurgery). Although whole brain radiation therapy does decrease the risk of newer metastases, it is associated with an increased risk of late neurologic dysfunction.

KEY POINT

- Melanoma may be associated with solitary or oligometastatic disease, and metastasectomy will prolong survival and can be curative in these patients.

Bibliography

Deutsch GB, Kirchoff DD, Faries MB. Metastasectomy for stage IV melanoma. Surg Oncol Clin N Am. 2015;24:279-98. [PMID: 25769712] doi:10.1016/j.soc.2014.12.006

Item 124 Answer: C

Educational Objective: Treat locally advanced anal cancer.

Pelvic radiation therapy with concurrent chemotherapy is the most appropriate treatment. Anal carcinoma is a rare but increasing cause of cancer and accounts for approximately 2% of gastrointestinal cancers. Most anal cancers are squamous cell carcinomas and are associated with human papillomavirus (HPV) infection, particularly HPV 16 and HPV 18. Risk factors for anal cancer include HPV infection; sexually transmitted infections; multiple sex partners; men having sex with men; receptive anal intercourse; history of vaginal, cervical, or vulvar cancer; immunosuppression due to hematologic malignancy; solid organ transplantation; or HIV infection. Most patients present with a perianal lesion or mass associated with rectal bleeding or anal discomfort. This patient has locally invasive, node positive squamous cell cancer of the anus. Curative-intent treatment with the combination of pelvic radiation therapy and concurrent systemic chemotherapy is indicated. This would be appropriate for patients with stages I, II, and III anal cancer. Mitomycin plus fluorouracil has been the standard chemotherapy regimen in patients with anal cancer for the past 50 years, although capecitabine, an oral fluorouracil prodrug, is now often used instead of parenteral fluorouracil.

Randomized studies of anal cancer treatment have shown radiation plus chemotherapy to be superior to radiation alone and 5-fluorouracil plus mitomycin to be superior to 5-fluorouracil alone.

Surgery for anal cancer is reserved as a salvage treatment for either local recurrence or incomplete response to chemotherapy plus radiation therapy, and is potentially curative. However, because definitive surgery must remove the anal sphincter, a placement of a permanent colostomy would be required.

HPV vaccine is approved for and has been shown to prevent anal HPV infection and anal intraepithelial neoplasia, precursors of anal cancer. However, HPV immunization is not an effective therapy for anal cancer once it has developed.

KEY POINT

- Anal cancer is often curable with combined chemotherapy and radiation, avoiding surgery.

Bibliography

James RD, Glynne-Jones R, Meadows HM, Cunningham D, Myint AS, Saunders MP, et al. Mitomycin or cisplatin chemoradiation with or without maintenance chemotherapy for treatment of squamous cell carcinoma of the anus (ACT II): a randomised, phase 3, open-label, 2×2 factorial trial. Lancet Oncol. 2013;14:516-24. [PMID: 23578724] doi:10.1016/S1470-2045(13)70086-X

Item 125 Answer: B

Educational Objective: Treat early-stage breast cancer with extended aromatase-inhibitor therapy.

The most appropriate management for this patient with early-stage breast cancer is to continue anastrozole for 5 years. In the North America Breast Cancer Group MA.17R trial, 1918 postmenopausal women with hormone receptor-positive early breast cancer who had completed 5 years of an aromatase inhibitor were randomly assigned to 5 years of letrozole or placebo. Most of the women had also received 5 years of tamoxifen before starting aromatase inhibitor therapy. The 5-year disease-free survival rate was 95% with letrozole versus 91% with placebo. Overall survival was the same in both groups. Patients on letrozole had a higher incidence of bone pain, bone fractures, and new-onset osteoporosis. This patient has tolerated anastrozole therapy well, has preserved bone density, and remains at higher risk (tumor size greater than 2 cm and pathologically involved lymph nodes). Extending aromatase inhibitor therapy to 10 years is reasonable for this patient.

Tamoxifen can be used sequentially with an aromatase inhibitor during the first 5 years of hormonal therapy. Studies have demonstrated equivalent results between sequential therapy (2 years of either tamoxifen or an aromatase inhibitor followed by 3 years of the other agent) compared with 5 years of an aromatase inhibitor. However, no data show benefit of tamoxifen, either as a single agent or in combination with an aromatase inhibitor, after completing 5 years of an aromatase inhibitor.

KEY POINT

- Extending aromatase-inhibitor therapy beyond 5 years to 10 years in postmenopausal women with hormone receptor-positive early breast cancer is associated with an increase in the 5-year disease-free survival rate but not overall survival.

Bibliography

Goss PE, Ingle JN, Pritchard KI, Robert NJ, Muss H, Gralow J, et al. Extending aromatase-inhibitor adjuvant therapy to 10 years. N Engl J Med. 2016;375:209-19. [PMID: 27264120] doi:10.1056/NEJMoa1604700

H

Item 126 Answer: B

Educational Objective: Manage metastatic lung cancer in a patient with poor performance status.

The most appropriate management is palliative care consultation. This patient has advanced metastatic non–small cell lung cancer and very poor performance status, and he had several months of symptoms before hospitalization. Although systemic chemotherapy and other treatments can help many patients with advanced non–small cell lung cancer, data clearly indicate that not all patients benefit. In particular, patients with poor performance status have not been shown to benefit from systemic treatment of their cancer. In those patients, the most appropriate intervention is palliative care consultation. Evidence suggests that patients with metastatic non–small cell lung cancer who have palliative care consultation at the time of diagnosis have decreased depression and prolonged life by 2.7 months. In addition, goals of care should be discussed, as well as the low likelihood of efficacy associated with systemic treatment.

Ablation of liver metastases plays no role in the management of patients with non–small cell lung cancer and poor performance status, particularly in the setting of extensive extrahepatic cancer, such as in this patient.

Platinum-based chemotherapy is associated with significant potential toxicity in patients with poor performance status and is not recommended.

Given the presence of obvious extensive metastatic disease, radiation treatment would be recommended only for palliation. However, this patient is experiencing systemic effects from his cancer and does not have any specific lesion needing local palliation.

KEY POINT

- Patients with non–small cell lung cancer and poor performance status do not benefit from systemic treatment of their cancer; in such patients, the most appropriate intervention is palliative care consultation.

Bibliography

Rade BC, Silvestri GA. Palliative care in lung cancer: a review. Semin Respir Crit Care Med. 2016 Oct;37(5):750-759. [PMID: 27732996]

Item 127 Answer: B

Educational Objective: Treat neoplastic epidural spinal cord compression.

This patient should receive immediate decompressive surgery. Once spinal cord compression is diagnosed, treatment must be started urgently to prevent irreversible loss of neurologic function. Glucocorticoids should be given immediately and promptly followed by surgery, external beam radiation, or stereotactic body radiation. A study of 101 patients with epidural spinal cord compression showed that patients who received surgery followed by radiotherapy had better outcomes and lower morbidity and mortality than those who received radiotherapy alone. Candidates for surgery include those with a life expectancy of at least 3 months and the absence of comorbidities that would otherwise be a contraindication to surgery.

Radiation therapy would never be done electively in a patient with epidural cord compression because delays in treatment lead to further neurologic deterioration.

Palliative care and supportive care alone might be appropriate in a patient with a very poor prognosis who does not want any further active antineoplastic therapy. Patients in this situation must be aware of the high likelihood of neurologic deterioration, including loss of ambulation and loss of control of bowel and bladder function. In most patients with metastatic cancer, treatment to avoid these complications is recommended.

Urgent radiation would be appropriate in patients who are not surgical candidates because of comorbidities, who have an expected survival of less than 3 months, or who refuse surgery. This patient has a life expectancy of more than 3 months and has no medical contraindications to surgery.

KEY POINT

- Initial administration of dexamethasone followed by decompressive surgery for epidural spinal cord compression is recommended in patients who are acceptable surgical candidates and who have an expected survival of at least 3 months.

Bibliography

Patchell RA, Tibbs PA, Regine WF, et al. Direct decompressive surgical resection in the treatment of spinal cord compression caused by metastatic cancer: a randomised trial. Lancet. 2005 Aug 20-26;366(9486):643-8. [PMID: 16112300]

Item 128 Answer: B

Educational Objective: Manage a *BRCA2* mutation carrier with prophylactic bilateral salpingo-oophorectomy.

The most appropriate recommendation for this patient is bilateral salpingo-oophorectomy by age 40 to 45 years. This patient has tested positive for a pathogenic *BRCA2* mutation. Although she has no family history of ovarian cancer, she has a 12% lifetime risk for ovarian cancer. Prophylactic bilateral salpingo-oophorectomy (BSO) is strongly recommended for both *BRCA1* and *BRCA2* mutation carriers. Risk-reducing BSO markedly reduces the risk for ovarian cancer and, if done while premenopausal, decreases the risk for breast cancer by 50%. For *BRCA1* mutation carriers, the risk for ovarian cancer increases substantially after age 35 years, and thus prophylactic BSO is recommended between the ages of 35 and 40 years and after completion of childbearing. *BRCA1* carriers who delay BSO until age 40 years will have a 4% risk of being diagnosed with an ovarian cancer. For *BRCA2* carriers, however, the risk of ovarian cancer before age 50 is only 1%. Therefore, it is reasonable to delay risk-reducing BSO until age 40 to

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45 years in *BRCA2* mutation carriers, particularly if they have already undergone prophylactic bilateral mastectomy. BSO can reduce the risk of ovarian, fallopian tube, or primary peritoneal cancers by 80% and decrease all-cause mortality to age 70 years by 77%.

Because this patient desires further childbearing and is only 38 years old, she can safely delay BSO until age 40 to 45 years and until childbearing is complete.

Screening with annual or semiannual pelvic ultrasonography and CA-125 is not effective and has been removed as a screening recommendation from *BRCA1* and *BRCA2* management guidelines.

Oral contraceptive use decreases the risk for ovarian cancer by as much as 50% with prolonged use and can be used in *BRCA1* and *BRCA2* carriers but is not an adequate substitute for prophylactic BSO.

KEY POINT

- Prophylactic bilateral salpingo-oophorectomy is recommended for both *BRCA1* and *BRCA2* mutation carriers, which markedly reduces the risk for ovarian cancer and, if done while premenopausal, decreases the risk for breast cancer by 50%.

Bibliography

Finch AP, Lubinski J, Møller P, Singer CF, Karlan B, Senter L, et al. Impact of oophorectomy on cancer incidence and mortality in women with a BRCA1 or BRCA2 mutation. J Clin Oncol. 2014;32:1547-53. [PMID: 24567435] doi:10.1200/JCO.2013.53.2820

Item 129 Answer: D

Educational Objective: Diagnose chronic lymphocytic leukemia.

This patient's elevated lymphocyte count and the identification of smudge cells on the peripheral blood smear, together with the presence of lymphadenopathy on physical examination, point to a possible diagnosis of chronic lymphocytic leukemia (CLL). B-cell CLL is the most common form of adult leukemia, accounting for 10% of hematologic malignancies. Patients are usually asymptomatic at presentation, with CLL identified by a lymphocytosis on a routine complete blood count. Flow cytometry is the most appropriate test to make an initial diagnosis of CLL. It can be easily performed on peripheral blood and will show B-cell antigens (CD19, CD20, and CD23), coexpression of CD5 (usually a T-cell marker), and low levels of a monoclonal surface immunoglobulin. In most cases, CLL can be suspected based on the complete blood count and review of a peripheral blood smear. However, other conditions may present with lymphocytosis, which flow cytometry can help distinguish from typical CLL. Other conditions include reactive lymphocytosis, T-cell leukemias, and other B-cell lymphoproliferative disorders involving the blood, such as mantle cell and marginal zone lymphomas and hairy cell leukemia.

A bone marrow aspiration and biopsy can be used to diagnose CLL and will provide prognostic information based on the extent of marrow involvement. However, flow cytometry has replaced bone marrow examination, which is not routinely needed as part of diagnosing or staging the disease, although it may still be useful in evaluating atypical cases or the mechanisms of cytopenia in patients with CLL.

A CT scan may show lymphadenopathy or nonpalpable splenomegaly in patients with CLL; however, it does not provide additional information that is helpful in the management of disease in asymptomatic patients.

Prognosis for patients with CLL is determined by gene mutation status (immune globulin variable heavy chain mutation) and fluorescence in situ hybridization or array-based karyotyping. In patients with CLL, a deletion of chromosome 17p is concerning because it is associated with a short median survival (less than 3 years). These cytogenetic and molecular genetic studies may have implications in choice of therapies. However, these studies would not typically be ordered until a definitive diagnosis of CLL is obtained.

KEY POINT

- Flow cytometry on peripheral blood is the most appropriate test to make an initial diagnosis of chronic lymphocytic leukemia.

Bibliography

Strati P, Shanafelt TD. Monoclonal B-cell lymphocytosis and early-stage chronic lymphocytic leukemia: diagnosis, natural history, and risk stratification. Blood. 2015;126:454-62. [PMID: 26065657] doi:10.1182/blood-2015-02-585059

Item 130 Answer: A

Educational Objective: Treat metastatic renal cell carcinoma.

The most appropriate management is left radical nephrectomy. Renal cell carcinomas arise in the renal cortex and are the most common type of tumors affecting the kidney. Patients with renal cell carcinoma are often asymptomatic until they have advanced disease, but possible symptoms include hematuria, an abdominal mass, abdominal pain, and unexplained weight loss. However, the classic triad of flank pain, hematuria, and a palpable abdominal mass occurs in only approximately 9% of patients. This patient most likely has metastatic kidney cancer based on identification of a large kidney mass associated with a suspicious pulmonary nodule and anemia. However, there is no histologic diagnosis of cancer at this point. Debulking nephrectomy has been shown to improve survival in patients diagnosed with metastatic kidney cancer, particularly in those with limited metastatic disease. Patients with lung-only metastasis and good performance status benefit most. In this patient, therefore, nephrectomy would serve two purposes. It would confirm the diagnosis and also serve as treatment for her metastatic kidney cancer. Following nephrectomy it would be appropriate to consider metastasectomy for removal of the isolated pulmonary lesion.

Nivolumab, a monoclonal antibody directed against programmed death receptor 1, is currently FDA approved for treatment of advanced clear cell carcinoma of the kidney. However, nivolumab is not recommended as first-line treatment and should not be started before establishing a histologic diagnosis of clear cell carcinoma. Clear cell carcinoma has not been confirmed in this patient, so the use of nivolumab would be premature.

PET/CT scan plays no role in the evaluation of a patient suspected of having kidney cancer. The presence or absence of fluorodeoxyglucose avidity would not influence management.

External beam radiation does not play a role in the treatment of metastatic kidney cancer except for palliative treatment of metastatic sites, such as painful osseous metastatic lesions. In this patient with a large kidney mass and one site of metastatic disease, surgery is indicated. Radiation has not been shown to improve outcomes in this setting and is not recommended.

KEY POINT

- Debulking nephrectomy improves survival in patients diagnosed with metastatic kidney cancer, particularly in those with limited metastatic disease.

Bibliography

Flanigan RC, Salmon SE, Blumenstein BA, et al. Nephrectomy followed by interferon alfa-2b compared with interferon alfa-2b alone for metastatic renal-cell cancer. N Engl J Med. 2001 Dec 6;345(23):1655-9. [PMID: 11759643]

Item 131 Answer: D

Educational Objective: Manage advanced-stage follicular lymphoma in an asymptomatic patient.

For this 75-year-old man with advanced-stage follicular lymphoma who is asymptomatic and does not have bulky disease, observation is an appropriate management strategy. There is no proof that earlier therapy for stage III to IV (nodes on both sides of the diaphragm [III]; noncontiguous extranodal involvement [IV]) follicular lymphoma provides benefit over deferring therapy until needed, provided the patient is comfortable with a strategy of surveillance. Patients with nonbulky follicular lymphoma who are not symptomatic may survive many years without the need for therapy.

Spontaneous tumor lysis syndrome occurs commonly in patients with leukemia and Burkitt lymphoma and after treatment of bulky large B-cell lymphoma or advanced chronic lymphocytic leukemia. Tumor lysis syndrome results in hyperkalemia, hyperphosphatemia, hyperuricemia, hypocalcemia, and disseminated intravascular coagulation. Hyperuricemia can lead to urate nephropathy and acute kidney injury. Prevention of tumor lysis syndrome is accomplished with large-volume intravenous hydration with normal saline plus administration of allopurinol to limit hyperuricemia. Because this patient will not likely be receiving chemotherapy, there is no need for allopurinol to prevent tumor lysis syndrome. Even if he were to be treated, tumor lysis is not common in low-grade lymphomas in the absence of bulky disease or preexisting renal disease or hyperuricemia.

Although follicular lymphomas are sensitive to radiation, and radiation therapy may be used for palliation of symptomatic bulky sites of disease or for cure in patients with localized (stage I to II) follicular lymphoma, this patient clearly has disseminated disease with diffuse lymphadenopathy, and systemic therapy would be appropriate if needed.

Follicular lymphoma associated with symptomatic systemic disease requires multiagent therapy that traditionally includes rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP); rituximab plus cyclophosphamide, vincristine, and prednisone (R-CVP); or rituximab and bendamustine. This patient is asymptomatic and does not yet require systematic therapy.

KEY POINT

- Patients with nonbulky follicular lymphoma who are not symptomatic may survive many years without the need for therapy.

Bibliography

Blood. 2016 Apr 28;127(17):2055-63. doi: 10.1182/blood-2015-11-624288. Epub 2016 Mar 17. Follicular lymphoma: evolving therapeutic strategies. Kahl BS, Yang DT.

Item 132 Answer: D

Educational Objective: Screen for breast cancer in a patient with previous chest wall radiation.

Annual mammography or breast MRI starting now is the most appropriate screening strategy in this patient. She has a history of radiation to the chest wall to treat Hodgkin lymphoma at age 19 years and is at high risk for breast cancer. Among this group, the cumulative breast cancer incidence by age 40 to 45 years ranges from 13% to 20% and is similar to that in *BRCA* gene mutation carriers. The risk varies with the dose of radiation used, and the strength of the screening recommendation is highest for women who received the highest dose of radiation (20 Gy or higher). For women with low- to moderate-dose chest radiation (less than 20 Gy), the decision to screen should be an individual one, taking into account additional risk factors and patients' values. The increased risk for breast cancer begins within 8 years after treatment. The International Late Effects of Childhood Cancer Guideline Harmonization Group recommends that for women who received chest wall radiation before the age of 30 years, screening should begin at age 25 years or 8 years after completion of radiation therapy, whichever is last. The Guideline Harmonization Group notes that the ideal screening modality is unknown because of a lack of sufficient

evidence, but breast MRI, mammography, or a combination of mammography and breast MRI are all reasonable choices. National Comprehensive Cancer Network guidelines recommend annual mammography and MRI starting after age 25 for patients receiving radiation between ages 10 and 30, beginning 8 to 10 years after irradiation.

This patient completed radiation at the age of 19 years. According to the Guideline Harmonization Group, her breast cancer screening should start at age 27 years (8 years after radiation or age 25 years, whichever is last), not 30 years.

Patients at average risk for breast cancer should start screening every 2 years by age 50 years, with the option to start mammographic screening between ages 40 and 50 years being an individualized decision. This patient, however, is at high, not average, risk.

KEY POINT

- The International Late Effects of Childhood Cancer Guideline Harmonization Group recommends that for women who received chest wall radiation before the age of 30 years, breast screening should begin at age 25 years or 8 years after completion of radiation therapy, whichever is last.

Bibliography

Mulder RL, Kremer LC, Hudson MM, et al; International Late Effects of Childhood Cancer Guideline Harmonization Group. Recommendations for breast cancer surveillance for female survivors of childhood, adolescent, and young adult cancer given chest radiation: a report from the International Late Effects of Childhood Cancer Guideline Harmonization Group. Lancet Oncol. 2013 Dec;14(13):e621-9. doi:10.1016/S1470-2045(13)70303-6. [PMID: 24275135]

Item 133 Answer: B

Educational Objective: Manage fertility in a patient with early-stage breast cancer.

Fertility specialist consultation before chemotherapy is appropriate for this patient with early-stage breast cancer. Current guidelines recommend addressing the possibility of chemotherapy-related infertility with all patients treated with chemotherapy during their reproductive years and referring them as early as possible in the treatment process to reproductive specialists. The risk of infertility after chemotherapy for breast cancer is related to patient age, treatment type and doses, and pretreatment fertility. Even if women resume menses after chemotherapy, they may have infertility and are at risk for premature menopause. In women, embryo cryopreservation is a proven fertility preservation method. Current methods allow egg harvesting to occur at any point in the menstrual cycle. Patients who carry deleterious *BRCA1* or *BRCA2* mutations have the option of preimplantation genetic selection and implanting only embryos that do not have the deleterious mutation. Studies to date show no increase in the risk for disease recurrence with fertility preservation methods.

Fertility consultation after chemotherapy is less likely to be beneficial given the exposure of ovarian follicles to the chemotherapy agent. The ovarian response to ovarian stimulation and the quality of the oocytes decrease after even one round of chemotherapy.

There is insufficient evidence regarding the use of a gonadotropin-releasing hormone agonist such as goserelin during chemotherapy to preserve ovarian function, and it should not replace established methods of fertility preservation.

There is no reason to recommend against future childbearing in patients with early-stage breast cancer. Pregnancy after breast cancer diagnosis is associated with no difference in disease-free survival and a slightly reduced risk of death.

KEY POINT

- Fertility specialist consultation is recommended for all patients before chemotherapy during their reproductive years.

Bibliography

Loren AW, Mangu PB, Beck LN, Brennan L, Magdalinski AJ, Partridge AH, et al; American Society of Clinical Oncology. Fertility preservation for patients with cancer: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol. 2013;31:2500-10. [PMID: 23715580] doi:10.1200/JCO.2013.49.2678

Item 134 Answer: B

Educational Objective: Treat localized gastroesophageal cancer.

The most reasonable treatment strategy is neoadjuvant chemotherapy plus radiation therapy. Although only 30% to 40% of patients with gastroesophageal cancer have potentially resectable disease at presentation, patients with local and locoregional disease are typically treated surgically. Unfortunately, recurrence rates are high, and cure rates with surgical resection alone remain low. Studies have shown that administration of neoadjuvant chemotherapy improves outcome to a modest but statistically significant degree. Neoadjuvant chemotherapy plus radiation therapy is given before a planned curative-intent surgery to patients who are believed to have fully resectable disease to eradicate any micrometastatic disease that might be present outside of the surgical field and thus increase the chance for cure. There is often confusion between neoadjuvant chemotherapy and conversion chemotherapy. The key distinction between neoadjuvant chemotherapy and conversion chemotherapy is that in conversion chemotherapy, the patient's tumor is not believed to be currently resectable but could possibly become resectable if adequate tumor regression can be accomplished with chemotherapy. Thus, both neoadjuvant and conversion chemotherapy are given with a plan for surgery to follow; however, neoadjuvant therapy is administered to patients with micrometastatic disease thought to be resectable, whereas conversion therapy is given to shrink visible tumors in patients with unresectable disease in whom disease might become resectable with adequate tumor regression.

Adjuvant therapy is given after curative-intent surgery to eradicate any residual micrometastatic disease and

increase the chance for cure. Because of the low cure rates for locoregional therapy for esophageal cancer, chemotherapy has been added to many treatment regimens, and many patients are currently treated with combination chemoradiation following surgery for resectable disease. However, the optimal treatment regimen and the overall effectiveness of different treatment approaches have not yet been established. However, there is no evidential support for adjuvant radiation therapy (surgery followed by radiation therapy) for patients with localized gastroesophageal cancer.

Palliative therapy is given to patients with incurable cancer to prolong survival or control symptoms. Palliative care should be considered for patients with poor performance status due to chronic medical comorbidities, for those who have not been able to tolerate initial treatment attempts, or for those who have exhausted standard treatment options.

KEY POINT

- Neoadjuvant therapy is given before a planned curative-intent surgery to patients with fully resectable disease to eradicate micrometastatic and increase the chance for cure.

Bibliography

van Hagen P, Hulshof MC, van Lanschot JJ, Steyerberg EW, van Berge Henegouwen MI, Wijnhoven BP, et al; CROSS Group. Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med. 2012;366:2074-84. [PMID: 22646630] doi:10.1056/NEJMoa1112088

Item 135 Answer: B

Educational Objective: Treat superficial bladder cancer.

The most appropriate treatment is intravesicular bacillus Calmette Guérin (BCG) for six treatments followed by periodic cystoscopy. Bladder cancer is the most commonly diagnosed cancer of the urinary tract. In the United States, almost all bladder cancer is transitional cell carcinoma. Risk factors include advanced age, white ethnicity, various occupational exposures, and cigarette smoking. Smoking is the most important risk factor and encompasses current and former smokers and persons exposed to secondhand smoke. Persons at occupational risk include metal workers, painters, miners, textile workers, and leather workers. The most common presenting symptom of bladder cancer is gross hematuria. Most patients diagnosed with bladder cancer will be found to have non-muscle invasive disease, which can be purely exophytic or can involve limited bladder wall invasion. For patients with non-muscle invasive cancer, transurethral resection of the bladder tumor (TURBT) is the standard initial management. For those with high-grade or recurrent low-grade cancer, standard care is to follow TURBT with six rounds of intravesical chemotherapy, most commonly BCG or mitomycin given directly into the bladder. This procedure is done both for treatment of the identified lesion and to help prevent additional bladder tumors from developing. The risk of either recurrent cancer or a new bladder cancer arising elsewhere is significant. Therefore, after BCG or mitomycin treatment, it is essential to perform cystoscopy 3 months after treatment and subsequently at 3- to 6-month intervals to look for new cancers. Patients with noninvasive bladder cancer have an excellent prognosis, and cancer related deaths rarely occur. Patients who develop recurrent disease with favorable tumor characteristics may be retreated with intravesicular therapy but, if higher-risk tumors are found, may require cystectomy.

Cisplatin-based chemotherapy has no role in the treatment of non-muscle invasive cancer. It is used most often as a neoadjuvant treatment before surgery in patients with muscle-invasive cancer. The role of adjuvant chemotherapy in muscle-invasive cancer is much less clear.

Partial cystectomy is not needed for the treatment of early stage, non-muscle invasive bladder cancer. However, it has a role in selected patients with muscle-invasive cancer.

KEY POINT

- Initial treatment for high-grade or recurrent low-grade bladder cancer is transurethral resection of the bladder tumor followed by intravesical chemotherapy and periodic cystoscopy.

Bibliography

Hall MC, Chang SS, Dalbagni G, et al. Guideline for the management of nonmuscle invasive bladder cancer (stages Ta, T1, and Tis): 2007 update. J Urol. 2007 Dec;178(6):2314-30. [PMID: 17993339]

Item 136 Answer: D

Educational Objective: Properly apply the results of clinical oncology trials to individual patients.

The patient would most likely achieve efficacy results inferior to those in the published trial. Patients who participate in clinical trials typically have a good to excellent performance status, performing most of their normal activities of living. Patients who are sedentary, with limited exercise tolerance and limited caloric intake, are substantially less likely to benefit from treatment than patients who are more medically fit. Patients with a poor performance status, such as this one, would also be more likely to experience greater toxicity with aggressive treatment than would a more medically fit patient. Consequently, the results of clinical trials, which typically comprise medically fit patients with a good performance status, cannot be directly extrapolated to patients with poor health and poor performance status, such as this one.

KEY POINT

- Results of clinical trials in patients with cancer, usually encompassing medically fit patients with good performance status, cannot be extrapolated to patients with poor health and performance status.

Bibliography

Tinetti ME. The gap between clinical trials and the real world: extrapolating treatment effects from younger to older adults. JAMA Intern Med. 2014;174:397-8. [PMID: 24424303] doi:10.1001/jamainternmed.2013.13283

Answers and Critiques

Item 137 Answer: B

Educational Objective: Treat advanced breast cancer using palbociclib with antiestrogen therapy.

Letrozole plus palbociclib is the most appropriate treatment for this patient with advanced breast cancer that recurs after completing previous adjuvant aromatase inhibitor therapy. Palbociclib is an oral cyclin-dependent kinase 4 and 6 (CDK4 and CDK6) inhibitor that is synergistic with endocrine therapies in vitro. In vitro studies suggest that breast cancer that has become resistant to hormonal therapy remains dependent on cyclin D1-CDK4 for proliferation. Two studies have shown benefit to the combination of antiestrogen therapy with palbociclib for hormone receptor–positive, *HER2*-negative advanced breast cancer, with an increased response rate and an approximate doubling of progression-free survival compared to hormonal therapy alone. Therapy with palbociclib was associated with increased adverse effects, including fatigue, nausea, and neutropenia.

Based on these studies, palbociclib has been approved for use with either letrozole as first-line therapy or fulvestrant for women with hormone receptor-positive, *HER2*-negative advanced breast cancer. As first-line therapy, an aromatase inhibitor with palbociclib is typically preferred.

The aromatase inhibitor exemestane alone is unlikely to be effective in a patient who has relapsed a few years after receiving treatment with another aromatase inhibitor and is an inferior choice to combination hormonal therapy and palbociclib.

Raloxifene can be used as chemoprophylaxis to lower the risk of breast cancer in patients with increased risk due to atypical breast lesions or strong family history but is not an active agent for treatment of breast cancer.

Tamoxifen is not typically recommended as first-line therapy for advanced hormone receptor–positive, *HER2*-negative breast cancer. As a second-line agent after previous aromatase inhibitor treatment, it has an overall response rate of only 10%.

KEY POINT

- Patients with widely metastatic hormone receptor-positive, *HER2*-negative breast cancer can benefit from combination antiestrogen therapy with palbociclib.

Bibliography

Turner NC, Ro J, André F, et al; PALOMA3 Study Group. Palbociclib in hormone-receptor-positive advanced breast cancer. N Engl J Med. 2015 Jul 16;373(3):209-19. [PMID: 26030518]

Item 138 Answer: A

Educational Objective: Treat stage III colon cancer.

The most appropriate treatment is the FOLFOX regimen of 5-fluorouracil (5-FU), leucovorin, and oxaliplatin. This patient has stage IIIC colon cancer. Stage III is defined by metastases to the local-regional lymph nodes, and stage IIIC is defined by metastases to four or more nodes. Stage III colon cancer is potentially curable, although the risk of treatment failure increases with the number of nodes, and four or more positive nodes is a worrisome prognostic indicator. Currently all patients with stage III cancer are recommended to receive adjuvant chemotherapy after definitive surgery, as large randomized trials have shown that this modestly improves the likelihood of cure. For over a decade, the combination of oxaliplatin plus a fluoropyrimidine, such as 5-FU or its oral prodrug, capecitabine, have been the accepted standard management for stage III colon cancer. The drug 5-FU is usually given with the reduced folate leucovorin, which is inactive alone but causes 5-FU to bind more tightly to its target enzyme.

Oxaliplatin with oral capecitabine (CAPOX) is also an acceptable regimen for adjuvant treatment of stage III colon cancer. Use of oral capecitabine requires a highly reliable, motivated patient who is able to adhere to a complex oral medication schedule.

Local recurrence in colon cancer, unlike rectal cancer, is rare, so radiation therapy is not a routine part of the management of colon cancer. Further, it can be difficult to isolate the small bowel from the radiation field, which results in unnecessary toxicity. Therefore, radiation therapy does not have a role in the routine management of patients with stage III colon cancer, either alone or combined with chemotherapy.

KEY POINT

- The FOLFOX regimen of 5-fluorouracil, leucovorin, and oxaliplatin or oxaliplatin with oral capecitabine (CAPOX) is the most appropriate adjuvant therapy for stage III colon cancer.

Bibliography

André T, de Gramont A, Vernerey D, Chibaudel B, Bonnetain F, Tijeras-Raballand A, et al. Adjuvant fluorouracil, leucovorin, and oxaliplatin in stage II to III colon cancer: updated 10-year survival and outcomes according to BRAF mutation and mismatch repair status of the MOSAIC study. J Clin Oncol. 2015;33:4176-87. [PMID: 26527776] doi:10.1200/JCO.2015.63.4238

Item 139 Answer: C

Educational Objective: Evaluate anemia in a patient with chronic lymphocytic leukemia.

Obtaining a direct antiglobulin (Coombs) test would be the appropriate initial diagnostic step to help guide management in this patient with chronic lymphocytic leukemia (CLL) with anemia. Concomitant autoimmune disease, including immune thrombocytopenia and hemolytic anemia, is common among patients with CLL. Anemia in patients with CLL can have many mechanisms, including myelophthisis (replacement of normal marrow elements by fibrosis or tumor) from the CLL itself, hypersplenism, chemotherapy, pure red cell aplasia, and autoimmune hemolytic anemia. The patient's reticulocytosis is strongly suggestive of a hemolytic anemia. Identifying

the mechanism of anemia can help guide therapy. If the patient has a positive direct antiglobulin test result suggestive of a secondary immunohemolytic anemia, glucocorticoids would be the appropriate first treatment for this patient.

Parvovirus has a tropism for erythrocyte precursors and is a known cause of aplastic crisis in patients with underlying hematologic disorders, iron deficiency, and immunosuppression. Patients with CLL and others with immunosuppression can have prolonged infections resulting in persistent anemia. However, reticulocytopenia (as opposed to the reticulocytosis as seen in this patient) would be characteristic for this complication.

A bone marrow aspiration and biopsy can help determine the mechanism of anemia in patients with CLL to assess for the extent of marrow replacement, for evaluation of hypoplasia from chemotherapy, to look for secondary myelodysplasia or pure red cell aplasia, or suggest evidence of erythroid hyperplasia, which could be seen in hypersplenism or an immunohemolytic disease. However, if the result of a direct antiglobulin test is positive and reticulocytosis is present, bone marrow aspiration and biopsy would not be needed.

Ibrutinib, an oral Bruton kinase inhibitor, is effective in CLL and mantle cell lymphoma. Although ibrutinib can cause some marrow suppression, this is not typical and would not be associated with reticulocytosis.

Hypersplenism (with or without immunohemolysis) may have a role in this patient's anemia, and eventually splenectomy may be an appropriate treatment. However, establishing the mechanism of the anemia and initiating systemic treatment would be preferable and a less invasive option.

KEY POINT

- Autoimmune hemolytic anemia is common in patients with chronic lymphocytic leukemia; a direct antiglobulin (Coombs) test can confirm the diagnosis and guide treatment.

Bibliography

Molica S, Polliack A. Autoimmune hemolytic anemia (AIHA) associated with chronic lymphocytic leukemia in the current era of targeted therapy. Leuk Res. 2016;50:31-36. [PMID: 27657651] doi:10.1016/j.leukres.2016.09.002

Item 140 Answer: B

Educational Objective: Screen for *PD-L1* expression in metastatic non–small cell lung cancer

Up until recently, the accepted front-line treatment for patients with metastatic non–small cell lung cancer was platinum-based chemotherapy in all patients except those found to have a driver mutation, in whom small molecule inhibitors, such as erlotinib, are indicated. However, pembrolizumab has recently been approved by the FDA for the initial treatment of metastatic non–small cell lung cancer positive for expression of programmed cell death ligand 1 (*PDL1*). Pembrolizumab is a monoclonal antibody directed against *PDL1*, and it blocks binding of this ligand to the programmed death receptor 1 receptor, preventing the cancer from silencing cellular immunity. This agent was found to improve overall survival compared to platinum-based chemotherapy in a phase III trial that enrolled 305 patients with advanced non-small cell lung cancer who had at least 50% tumor cell positivity for *PD-L1*. In this study, overall survival was 10.3 months with pembrolizumab compared to 6 months with platinum-based chemotherapy. Based on this data, it has now become standard practice to test all patients newly diagnosed with metastatic non–small cell lung cancer for *PD-L1* expression.

Liver biopsy can help confirm the presence of metastatic disease but is not indicated in patients with imaging findings consistent with metastatic disease whose diagnosis has been confirmed by biopsy of the primary lesion.

PET/CT scan has no role in the evaluation or management of patients with known metastatic disease and would not be indicated for this patient.

Pulmonary function tests also play no role in the management of patients with metastatic disease. They are typically indicated in patients who are being considered for surgery for early-stage disease.

KEY POINT

- It has now become standard practice to test all patients newly diagnosed with metastatic non–small cell lung cancer for programmed cell death ligand 1 expression.

Bibliography

Reck M, Rodríguez-Abreu D, Robinson AG, Hui R, Csoszi T, Fülöp A, et al; KEYNOTE-024 Investigators. Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. N Engl J Med. 2016;375:1823-1833. [PMID: 27718847]

Item 141 Answer: B

Educational Objective: Treat midline poorly differentiated carcinoma of unknown primary site.

The most appropriate treatment is a germ cell chemotherapy regimen of cisplatin and etoposide. Cancer of unknown primary (CUP) is a diagnosis of exclusion established in patients with a solid metastatic tumor after a detailed medical history and physical examination have been done and imaging studies or other diagnostic studies have not identified a primary tumor site. Diagnostic efforts should focus on identifying whether a patient is among the approximately 20% of patients with CUP who fall into identifiable subgroups with a more favorable prognosis and who can benefit from a specific treatment strategy. A biopsy obtained from the site that can be sampled in the safest, least invasive manner is done, and specimens are often evaluated by immunohistochemical stains consistent with the tumor's pattern of presentation to attempt to establish a diagnosis of a more treatable subtype of CUP. The patient

is a young man with a poorly differentiated CUP site that is predominantly midline in presentation. In the absence of an identified primary tumor, these patients should be treated presumptively for metastatic germ cell tumor. The absence of abnormal findings on testicular examination or ultrasonography or the absence of germ cell specific markers, such as α-fetoprotein and β-human chorionic gonadotropin, does not exclude this diagnosis or this course of action. Even if these evaluation results are negative, an unrecognized germ cell tumor may still exist, and these patients should be treated for this possibility with a platinum-based chemotherapy regimen.

A chemotherapy regimen focused on digestive tract malignancies, such as fluorouracil and irinotecan, would be appropriate palliation for a pattern of CUP consistent with a gastrointestinal primary tumor, such as disease predominantly below the diaphragm with liver or peritoneal involvement. However, this patient has bulky lymphadenopathy below and above the diaphragm, making a digestive malignancy unlikely.

The extent of retroperitoneal lymphadenopathy and mediastinal lymphadenopathy makes initial treatment with either radiation therapy or surgery inappropriate.

KEY POINT

- Young men with poorly differentiated carcinoma that is characterized by centrally located bulky retroperitoneal or mediastinal lymphadenopathy may have an unrecognized germ cell tumor and are best treated with a platinum-based chemotherapy regimen.

Bibliography

Fizazi K, Greco FA, Pavlidis N, Daugaard G, Oien K, Pentheroudakis G; ESMO Guidelines Committee. Cancers of unknown primary site: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2015;26 Suppl 5:v133-8. [PMID: 26314775] doi:10.1093/annonc/mdv305

Item 142 Answer: C

Educational Objective: Define an inclusionary predictive tumor marker.

The finding of a *BRAF* V600E mutation is best described in this situation as an inclusionary predictive marker. Predictive markers help identify specific aspects of the tumor that can guide clinicians in determining which therapies are or are not appropriate for particular patients. For example, specific *BRAF*-targeted treatment, such as vemurafenib and dabrafenib, is indicated only in the subset of patients in whom the *BRAF* V600E mutation is found, and patients with this mutation are predicted to respond favorably to these agents. Conversely, the absence of the *BRAF* V600E mutation in patients with metastatic melanoma excludes consideration of such therapy and strongly predicts an absence of benefit from such a treatment.

An exclusionary predictive marker excludes patients from treatment that otherwise might have been used. Examples of exclusionary predictive markers are the *KRAS* or *NRAS* mutations in patients with colorectal cancer, the presence of which would exclude the activity of an anti-epidermal growth factor receptor (EGFR)-targeted therapy. Patients with these gene mutations have disease that is not only found to be highly resistant to these agents, but they can also experience accelerated tumor growth with the use of such treatments.

Prognostic markers would quantitate a patient's risk of recurrence but would not indicate whether the outcome was more or less likely to be influenced by a certain treatment or intervention. Whereas predictive markers provide actionable information that is useful in guiding therapy, prognostic markers do not provide actionable information and therefore typically do not guide therapy and provide little to no value in clinical management.

KEY POINT

- Inclusionary predictive tumor markers identify which therapies are more likely to be effective.

Bibliography

Nair M, Sandhu SS, Sharma AK. Prognostic and predictive biomarkers in cancer. Curr Cancer Drug Targets. 2014;14(5):477-504. [PMID: 24807144]

Item 143 Answer: D

Educational Objective: Recommend genetic counseling to an asymptomatic patient with a family history of *BRCA*-related cancers.

The most appropriate management for this patient is referral to a genetic counselor. This patient has a family history suggestive of an inherited breast and ovarian cancer susceptibility gene and is interested in genetic testing. Both her mother and maternal aunt had cancers suggestive of a *BRCA1* or *BRCA2* mutation. Women with triple-negative breast cancers diagnosed before age 60 years are recommended to have *BRCA1* and *BRCA2* genetic testing, as are women with ovarian cancer diagnosed at any age. Referral to a genetic counselor or other suitably trained health care provider is the best option for genetic risk assessment. The U.S. Preventive Services Task Force has published guidelines for risk assessment and recommends referral to a genetic counselor for asymptomatic women who have not been diagnosed with a *BRCA*-related cancer but have a family history of *BRCA*-related cancers. These guidelines include screening tools designed to identify a family history that may be associated with an increased risk for *BRCA1* or *BRCA2* mutations. Family history factors suggesting an increased likelihood of *BRCA* mutations include breast cancer diagnosis before age 50 years, bilateral breast cancer, family history of breast and ovarian cancer, presence of breast cancer in one or more male family members, multiple cases of breast cancer in the family, one or more family member with two primary types of *BRCA*-related cancer, and Ashkenazi Jewish ethnicity. Genetic counseling should always occur before any genetic test is performed. The essential components of counseling include informing the patient of the test purpose, implications of diagnosis, alternative testing

options (including foregoing testing), and any possible risks and benefits. The National Society of Genetic Counselors Web site (http://nsgc.org) can be used to locate a genetic counselor.

Direct-to-consumer tests may not include the appropriate type of genetic testing. In addition, genetic testing should be done after pretest genetic counseling, which is not always available in patients being tested by direct-to-consumer commercial genetic tests.

Although *BRCA1* and *BRCA2* testing for the three mutations most common in the Ashkenazi Jewish population (called multisite testing) is recommended for Ashkenazi Jewish women with breast cancer diagnosed at any age, comprehensive *BRCA1* and *BRCA2* testing is recommended if additional criteria for *BRCA1/2* testing are met.

KEY POINT

- Asymptomatic patients with a family history of *BRCA*-related cancers should receive genetic counseling for genetic risk assessment.

Bibliography

Moyer VA; U.S. Preventive Services Task Force. Risk assessment, genetic counseling, and genetic testing for BRCA-related cancer in women: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2014;160:271-81. [PMID: 24366376]

Item 144 Answer: A

Educational Objective: Evaluate suspected testicular cancer.

The most appropriate management is to measure β-human chorionic gonadotropin and α-fetoprotein levels. In the setting of unilateral testicular swelling or a palpable testicular mass in a young man, cancer is a diagnosis of exclusion. This patient has unilateral testicular swelling. Physical examination and ultrasonography both point to the presence of a testicular mass. Although extrinsic processes can cause testicular swelling, ultrasonography is very accurate in differentiation of intrinsic from extrinsic testicular pathology. In a patient found to have a testicular mass, the diagnosis of cancer must be confirmed histologically. Germ cell tumors are the most common type of testicular cancer. These tumors can be pure seminomas or nonseminomas. However, before histologic confirmation, α-fetoprotein and β-human chorionic gonadotropin levels should be measured to most accurately determine stage and prognosis. The serum α-fetoprotein level is never elevated in patients with pure seminomas, and β-human chorionic gonadotropin is elevated in only approximately 20% of patients with pure seminomas. Nonseminomatous germ cell tumors can contain elements of seminoma, but those elements are mixed with tumors with nonseminomatous histologies, which include yolk sac tumor, choriocarcinoma, and embryonal carcinoma. This distinction is important for determining the correct treatment. However, these measurements do not determine diagnosis and are not a substitute for histologic evaluation. Because levels will fall after orchiectomy, measurement before surgery is recommended. Failure of the levels to fall suggests inadequate therapy, and elevation of the levels after treatment suggests recurrent disease.

Needle biopsy is contraindicated in the evaluation of testicular masses owing to the risk of biopsy tract seeding.

Chest radiography and CT of the abdomen and pelvis are done after a diagnosis is established. CT of the chest is indicated if the chest radiograph is abnormal or lung metastases are strongly suspected. PET-CT has little role in the evaluation of men with confirmed testicular cancer in part because of a high rate of false-positive results. It would not be indicated before establishing a diagnosis.

Radical inguinal orchiectomy is essential for establishing a diagnosis of testicular cancer in the most expeditious and safest way possible. However, it should be performed after tumor markers are measured.

KEY POINT

- Before histologic confirmation of testicular cancer, α-fetoprotein and β-human chorionic gonadotropin levels should be measured to most accurately determine stage and prognosis.

Bibliography

Mir MC, Pavan N, Gonzalgo ML. Current clinical applications of testicular cancer biomarkers. Urol Clin North Am. 2016 Feb;43(1):119-25. doi:10.1016/j.ucl.2015.08.011. [PMID: 26614034]

Item 145 Answer: A

Educational Objective: Treat symptomatic brain metastases.

This patient has evidence of brain metastases in the setting of metastatic hormone receptor-negative, *HER2*-positive breast cancer and should receive dexamethasone. She has headache and ataxia but no signs or symptoms of severe intracranial edema or impending herniation. Glucocorticoids are indicated as initial treatment in all patients with symptomatic brain metastases; they improve neurologic symptoms in 75% of patients, usually reducing intracranial pressure and improving neurologic symptoms within hours. Dexamethasone given either intravenously or orally is typically used because of its minimal mineralocorticoid effect and long half-life. Doses should be tapered to the lowest effective dose after stereotactic radiation and then tapered over several weeks. For patients on glucocorticoids for longer than 6 weeks, prophylaxis against pneumocystis pneumonia is recommended. Patients should be monitored for symptoms of gastritis or peptic ulcer, but there is no evidence that prophylaxis with H_2-blockers or proton-pump inhibitors is effective at preventing these complications. Patients should also be monitored for steroid myopathy.

Only about 25% of patients with brain metastases have seizures, and prophylactic antiepileptic therapy is not recommended in patients who have not had seizures. When antiepileptic drug therapy is used, newer agents, such as levetiracetam, are preferred to older agents, given the more

favorable safety profiles and less potential for drug-drug interactions.

Mannitol and mechanical hyperventilation would be used in patients with severe edema at risk for herniation but are not indicated in this patient. Similarly, neurosurgical decompression would be recommended in patients with severe edema or impending herniation unable to wait for a response to dexamethasone or unresponsive to other treatments.

Whole brain radiation is less desirable in patients with good prognostic tumors and a limited number of brain metastases; stereotactic radiation would be recommended instead, but only after initial glucocorticoid treatment to improve peritumoral edema.

KEY POINT

- Patients with symptomatic brain metastases should be initially treated with glucocorticoids.

Bibliography

Lin X, DeAngelis LM. Treatment of brain metastases. J Clin Oncol. 2015;33:3475-84. [PMID: 26282648] doi:10.1200/JCO.2015.60.9503

Item 146 Answer: C

Educational Objective: Manage posttreatment surveillance for a patient with cervical cancer.

The most appropriate posttreatment surveillance for this patient with cervical cancer is a history, physical examination, and gynecologic examination every 3 months to monitor for local recurrence. Guidelines for posttreatment surveillance of patients with cervical cancer recommend a thorough history and examination every 3 to 6 months for the first 2 years, then every 6 to 12 months for years 2 through 5. Higher-risk patients, such as those treated with chemotherapy or radiation, should be evaluated every 3 months for 2 years, then every 6 months for years 2 through 5; those with lower-risk disease treated with surgery alone should be evaluated every 6 months for 2 years, then annually through year 5. The main goals of surveillance are to detect central pelvic (not involving the pelvic sidewall) recurrences that might be amenable to curative therapy and to address treatment-related symptoms. Treatment-related symptoms include bladder and bowel dysfunction; dyspareunia; difficulty achieving sexual arousal and orgasm; hot flushes; lymphedema of the lower extremities; fatigue; and mood disturbances related to fear of recurrence, altered body image, and loss of fertility. Patients also should be educated at these visits about symptoms that might indicate recurrence, including vaginal bleeding or new abdominal or pelvic pain. Most recurrences are symptomatic and are detected within 2 years of primary treatment, with nearly all detected by 5 years. Additional laboratory or imaging studies should be directed by signs or symptoms suggesting possible recurrence rather than done as routine studies in asymptomatic patients. Although annual cervical or vaginal cytology, or both, is recommended, it is unlikely that an asymptomatic recurrence will be found by cytology alone. In addition, pelvic radiation may alter tissue histology and make cytology interpretation difficult.

There is no evidence that routine imaging studies with either ultrasonography or CT results in better patient outcomes than clinical monitoring, or that the response to palliative therapy is improved by such surveillance techniques. Routine laboratory studies are also not recommended.

KEY POINT

- Posttreatment surveillance of patients with cervical cancer is limited to a thorough history and examination every 3 to 6 months for the first 2 years, then every 6 to 12 months for years 2 through 5; frequency of visits can be tailored to the patient's risk.

Bibliography

Elit L, Fyles AW, Devries MC, Oliver TK, Fung Kee Fung M; Gynecology Cancer Disease Site Group. Follow-up for women after treatment of cervical cancer: a systematic review. Gynecol Oncol. 2009 Sep;114(3):528-35. [PMID: 19560188]

Item 147 Answer: B

Educational Objective: Treat stage III lung cancer with combined chemotherapy and radiation.

The most appropriate treatment is combined chemotherapy and radiation. Treatment for stage III non–small cell lung cancer, which is defined in most cases by the presence of mediastinal lymphadenopathy, can vary significantly based on the extent of the primary tumor and the extent of associated lymphadenopathy. Patients with extensive primary tumors, such as this patient whose tumor invades the mediastinum, are not candidates for surgery. Patients with bulky, multistation (widespread mediastinal or hilar lymph node involvement) lymphadenopathy in the mediastinum do not fare well after surgery. These patients should be treated with combined chemotherapy and radiation, which has been shown to improve outcomes compared with either chemotherapy alone or radiation alone.

In highly selected patients with stage III disease, surgery may be considered an appropriate therapeutic option. For patients with T3N1 disease, surgery can be done as initial therapy, although the procedure should include mediastinal lymph node dissection. In patients with negative mediastinal lymph nodes, adjuvant chemotherapy should be given. In patients with positive mediastinal lymph nodes, sequential chemotherapy and radiation is recommended. However, this patient has bulky mediastinal disease and is clearly not a candidate for surgery.

Pembrolizumab is a monoclonal antibody directed against programmed death receptor 1 (PD-1) that is indicated for treatment of recurrent metastatic non–small cell lung cancer. It has no role in the treatment of locally advanced non–small cell lung cancer and would not be indicated for this patient.

Radiation alone is inferior to combined chemotherapy and radiation and is not typically recommended. It would be recommended only for patients who were not candidates for combined chemotherapy and radiation based on comorbid

conditions. However, this patient does not have any comorbid conditions that would preclude chemotherapy.

As noted previously, this patient has bulky mediastinal disease and is clearly not a candidate for surgery; therefore, surgical resection is not appropriate.

KEY POINT

- Patients with non–small cell lung cancer who have extensive primary tumors or bulky, multistation lymphadenopathy in the mediastinum are not candidates for surgery and instead should be treated with combined chemotherapy and radiation.

Bibliography

Tam K, Daly M, Kelly K. Treatment of locally advanced non-small cell lung cancer. Hematol Oncol Clin North Am. 2017 Feb;31(1):45-57. doi:10.1016/j.hoc.2016.08.009. [PMID: 27912833]

Item 148 Answer: B

Educational Objective: Evaluate metastatic gastroesophageal junction adenocarcinoma for *HER2* amplification.

This patient's tumor tissue should be assessed for human epidermal growth factor receptor 2 (*HER2*) amplification. He has metastatic adenocarcinoma of the distal esophagus. Approximately 25% of gastroesophageal cancers demonstrate *HER2* amplification; such tumors achieve a superior response to chemotherapy when the anti-*HER2* monoclonal antibody trastuzumab is added to standard chemotherapy. For this reason, determination of *HER2* amplification status is necessary when initiating chemotherapy for patients with a gastroesophageal tumor.

BRAF mutation status is of paramount importance in patients with melanoma, 40% of whom will have *BRAF*-mutated tumors that are highly likely to respond to tyrosine kinase inhibitors targeting *BRAF*. However, such mutations are exceedingly rare in upper gastrointestinal malignancies, and *BRAF*-targeting agents have thus far failed to show activity in *BRAF*-mutated gastrointestinal malignancies.

RAS mutation status is relevant to the use of anti-epidermal growth factor receptor (*EGFR*) monoclonal antibodies in colorectal cancer. These agents have not been shown to be active in upper gastrointestinal malignancies and are not part of the treatment paradigm.

Neither a PET/CT scan nor a barium swallow will add useful information for this patient because the available CT imaging is sufficient for establishing a treatment plan. Any further information regarding extent of disease that might be found on a PET/CT would not be expected to change management. A barium swallow is unlikely to provide clinically useful information about the extent of his tumor or additional information about his swallowing capacity.

KEY POINT

- Upper gastrointestinal tumors should be assessed for human epidermal growth factor receptor 2 (*HER2*) amplification to guide chemotherapy.

Bibliography

Iomrich G, Schoppmann SF. Targeting HER 2 and angiogenesis in gastric cancer. Expert Rev Anticancer Ther. 2016;16:111-22. [PMID: 26567753] doi:10.1586/14737140.2016.1121110

Item 149 Answer: B

Educational Objective: Treat castrate-sensitive metastatic prostate cancer with androgen deprivation therapy and docetaxel.

The most appropriate management is leuprolide plus docetaxel. Standard therapy for metastatic prostate cancer or evidence of disseminated disease based on an elevated serum prostate-specific antigen (PSA) is androgen deprivation therapy (ADT). ADT consists of inhibiting androgen synthesis by using a gonadotropin-releasing hormone (GnRH) agonist (such as leuprolide) or blocking the androgen receptor with an antiandrogen agent (such as flutamide or bicalutamide). Bilateral orchiectomy is a reasonable alternative to GnRH agonist therapy, particularly in the very elderly. ADT is typically combined with docetaxel chemotherapy in patients with extensive metastatic disease. This patient has castrate-sensitive metastatic prostate cancer. He presented with clinical metastatic disease and had a significant response to treatment with leuprolide, based on both a reduction in his PSA level and improvement in pain related to his metastatic lesion to the lumbar spine. Two randomized trials have confirmed a survival benefit associated with combined ADT and docetaxel chemotherapy for men with castrate-sensitive metastatic prostate cancer. Based on the observed improvement in survival, use of docetaxel in this setting is now accepted standard care and should be recommended unless a contraindication to chemotherapy exists. Myelosuppression is the most common side effect of docetaxel. Hepatic dysfunction or compromised bone marrow function are contraindications to its use. This patient's medical history does not indicate any contraindication to treatment with docetaxel.

Continuation of leuprolide alone would not be recommended in a patient who is a candidate for docetaxel chemotherapy based on the demonstrated improvement in survival in men treated with six cycles of docetaxel.

Although radiation to the lumbar spine would be indicated for pain control or for treatment of neurologic compromise due to nerve compression by metastatic disease, this patient has no evidence of neurologic compromise, and his pain improved with leuprolide treatment. Therefore, radiation is not indicated at this time.

KEY POINT

- In men with clinical metastatic prostate cancer that is castrate sensitive, docetaxel along with continuation of androgen deprivation therapy has been shown to improve survival and is accepted as standard care.

Bibliography

James ND, Sydes MR, Clarke NW, et al; STAMPEDE Investigators. Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multiarm, multistage, platform randomized controlled trial. Lancet. 2016 Mar 19;387(10024):1163-77. [PMID: 26719232]

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◯ Endocrinology and Metabolism	19
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CREDITS OR POINTS CLAIMED ON SECTION
1 hour = 1 credit or 1 point

Enter the number of credits earned on the test to the nearest quarter hour. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

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Enter your score here.

Instructions for calculating your own score are found in front of the self-assessment test in each book. You must receive a minimum score of 50% correct.

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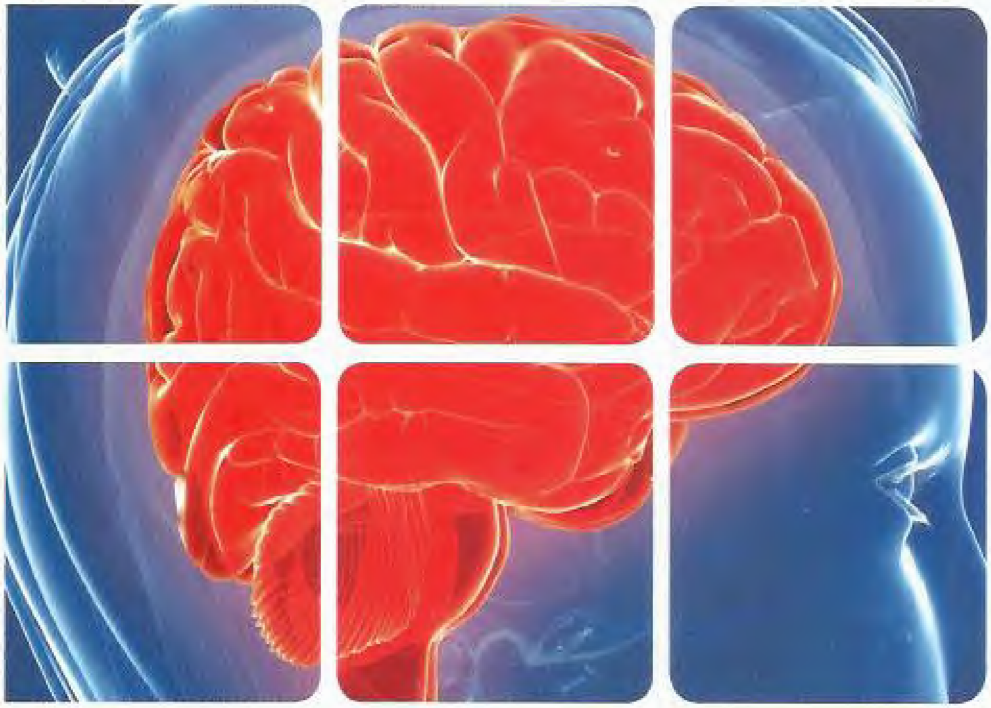

Neurology

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Medical Knowledge Self-Assessment Program®

Neurology

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Welcome to the Neurology Section of MKSAP 18!

In these pages, you will find updated information on headache and facial pain, head injury, epilepsy, stroke, cognitive disorders, movement disorders, multiple sclerosis, disorders of the spinal cord, neuromuscular disorders, and neuro-oncology. All of these topics are uniquely focused on the needs of generalists and subspecialists *outside* of neurology.

The core content of MKSAP 18 has been developed as in previous editions—all essential information that is newly researched and written in 11 topic areas of internal medicine—created by dozens of leading generalists and subspecialists and guided by certification and recertification requirements, emerging knowledge in the field, and user feedback. MKSAP 18 also contains 1200 all-new peer-reviewed, psychometrically validated, multiple-choice questions (MCQs) for self-assessment and study, including 96 in Neurology. MKSAP 18 continues to include *High Value Care* (HVC) recommendations, based on the concept of balancing clinical benefit with costs and harms, with associated MCQs illustrating these principles and HVC Key Points called out in the text. Internists practicing in the hospital setting can easily find comprehensive *Hospitalist*-focused content and MCQs, specially designated in blue and with the H symbol.

If you purchased MKSAP 18 Complete, you also have access to MKSAP 18 Digital, with additional tools allowing you to customize your learning experience. MKSAP Digital includes regular text updates with new, practice-changing information, 200 new self-assessment questions, and enhanced custom-quiz options. MKSAP Complete also includes more than 1200 electronic, adaptive learning–enhanced flashcards for quick review of important concepts, as well as an updated and enhanced version of Virtual Dx, MKSAP's image-based self-assessment tool. As before, MKSAP 18 Digital is optimized for use on your mobile devices, with iOS- and Android-based apps allowing you to sync between your apps and online account and submit for CME credits and MOC points online.

Please visit us at the MKSAP Resource Site (mksap.acponline.org) to find out how we can help you study, earn CME credit and MOC points, and stay up to date.

On behalf of the many internists who have offered their time and expertise to create the content for MKSAP 18 and the editorial staff who work to bring this material to you in the best possible way, we are honored that you have chosen to use MKSAP 18 and appreciate any feedback about the program you may have. Please feel free to send any comments to mksap_editors@acponline.org.

Sincerely,

Patrick Alguire

Patrick C. Alguire, MD, FACP
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Senior Vice President Emeritus
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Up to 22 *AMA PRA Category 1 Credits*™ are available from July 31, 2018, to July 31, 2021, for the MKSAP 18 Neurology section.

Learning Objectives

The learning objectives of MKSAP 18 are to:

- Close gaps between actual care in your practice and preferred standards of care, based on best evidence
- Diagnose disease states that are less common and sometimes overlooked and confusing
- Improve management of comorbid conditions that can complicate patient care
- Determine when to refer patients for surgery or care by subspecialists
- Pass the ABIM Certification Examination
- Pass the ABIM Maintenance of Certification Examination

Target Audience

- General internists and primary care physicians
- Subspecialists who need to remain up to date in internal medicine
- Residents preparing for the certifying examination in internal medicine
- Physicians preparing for maintenance of certification in internal medicine (recertification)

ABIM Maintenance of Certification

Check the MKSAP Resource Site (mksap.acponline.org) for the latest information on how MKSAP tests can be used to apply to the American Board of Internal Medicine (ABIM) for Maintenance of Certification (MOC) points following completion of the CME activity.

Successful completion of the CME activity, which includes participation in the evaluation component, enables the participant to earn up to 275 medical knowledge MOC points in the ABIM's MOC program. It is the CME activity provider's responsibility to submit participant completion information to ACCME for the purpose of granting MOC credit.

Earn Instantaneous CME Credits or MOC Points Online

Print subscribers can enter their answers online to earn instantaneous CME credits or MOC points. You can submit your answers using online answer sheets that are

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1. Use the printed answer sheet at the back of this book to record your answers. Go to mksap.acponline.org, access the appropriate online answer sheet, transcribe your answers, and submit your test for instantaneous CME credits or MOC points. There is no additional fee for this service.
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Errata

Errata for MKSAP 18 will be available through the MKSAP Resource Site at mksap.acponline.org as new information becomes known to the editors.

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Neurology High Value Care Recommendations

The American College of Physicians, in collaboration with multiple other organizations, is engaged in a worldwide initiative to promote the practice of High Value Care (HVC). The goals of the HVC initiative are to improve health care outcomes by providing care of proven benefit and reducing costs by avoiding unnecessary and even harmful interventions. The initiative comprises several programs that integrate the important concept of health care value (balancing clinical benefit with costs and harms) for a given intervention into a broad range of educational materials to address the needs of trainees, practicing physicians, and patients.

HVC content has been integrated into MKSAP 18 in several important ways. MKSAP 18 includes HVC-identified key points in the text, HVC-focused multiple choice questions, and, for subscribers to MKSAP Digital, an HVC custom quiz. From the text and questions, we have generated the following list of HVC recommendations that meet the definition below of high value care and bring us closer to our goal of improving patient outcomes while conserving finite resources.

High Value Care Recommendation: A recommendation to choose diagnostic and management strategies for patients in specific clinical situations that balance clinical benefit with cost and harms with the goal of improving patient outcomes.

Below are the High Value Care Recommendations for the Neurology section of MKSAP 18.

- Imaging is not indicated for patients with stable migraine and a normal neurologic examination.
- Imaging is not indicated for tension-type headache.
- Head CT is the most appropriate initial study for an unprovoked, first-time seizure (see Item 7).
- Lumbar puncture after a first seizure is recommended only if an infectious cause is suspected.
- Transesophageal echocardiography is not routinely indicated for the evaluation of acute stroke.
- Do not administer platelet transfusion for intracerebral hemorrhage in patients treated with antiplatelet agents.
- Internal carotid artery revascularization for primary prevention of stroke is not indicated unless stenosis is greater than 80% or rapid progression of stenosis is documented.
- Aspirin monotherapy is a first-line antiplatelet regimen for secondary stroke prevention.
- Do not stent symptomatic high-grade intracranial arterial stenosis.
- Do not obtain specialized genetic or cerebrospinal fluids tests for dementia unless diagnosis is uncertain.
- No treatments or primary prevention interventions are currently approved for mild cognitive impairment.
- A positive pull test is the most reliable predictor of backward falls in Parkinson disease.
- Proper application of diagnostic criteria for multiple sclerosis can prevent unnecessary neurologic testing, referrals, and misdiagnoses.
- Exclude transient symptoms associated with increased body temperature before treating an apparent multiple sclerosis exacerbation.
- Using agents other than ocrelizumab and mitoxantrone for progressive forms of multiple sclerosis increases cost and unnecessary risk.
- Routine electromyography is not necessary for patients with slowly progressive distal symmetric sensory neuropathy and a negative family history.
- Clinical diagnosis and supportive care is appropriate for carpal tunnel syndrome with mild symptoms.
- Brain imaging and laboratory testing is not required for the diagnosis of classic Bell palsy.
- Prophylactic antiepileptic drugs are not recommended for central nervous system tumors in the absence of seizures.
- Reassurance is the best management for periodic limb movements of sleep if no associated sleep disorder is present (see Item 46).
- Most patients with chronic cervical and lumbar stenosis do not require surgery (see Item 79).

Neurology

Headache and Facial Pain

Approach to the Patient with Headache

Formal classification of headache disorders identifies three headache subtypes: primary headaches, secondary headaches, and painful cranial neuralgias. Primary headaches, or those in which the symptoms are due to a specific headache disorder, are more commonly seen in practice, and are defined by clinical criteria. Primary headache disorders include migraine, tension-type headache, cluster headache, and the other trigeminal autonomic cephalalgias. Secondary headaches result from another underlying process and are defined by that causative disease process (**Table 1**); these headaches may be associated with significant morbidity and mortality and require early identification. Patients with serious secondary headaches typically have acute or subacute symptoms and a headache pattern that is progressive or unstable; suspicion of a secondary headache is heightened in the presence of the following clinical "red flags":

- First or worst headache
- Abrupt onset or thunderclap attack
- Progression or fundamental change in headache pattern
- Abnormal physical examination findings
- Neurologic symptoms lasting longer than 1 hour
- New headache in persons younger than 5 years or older than 50 years
- New headache in patients with malignancy, coagulopathy, immunosuppression, or pregnancy
- Association with alteration in or loss of consciousness
- Headache triggered by exertion, sexual activity, or Valsalva maneuver

A detailed headache history (**Table 2**) is the most valuable clinical assessment tool in the evaluation of headaches. Neurologic examination with funduscopic testing is essential, and brain imaging is the most important diagnostic study. Imaging is indicated for suspected secondary headaches and for some of the uncommon primary syndromes (such as trigeminal autonomic cephalalgias). Stable headaches meeting criteria for most primary headaches usually do not require imaging. Head CT is indicated in the assessment of acute, severe headaches, and brain MRI is used when indicated for subacute or chronic headaches, given its greater sensitivity and safety. Additional testing is determined by differential diagnostic considerations and may include erythrocyte sedimentation rate determination, C-reactive protein measurement, lumbar puncture, serum chemistries, or toxicology screens. There is no indication for electroencephalography in the assessment of headache disorders.

TABLE 1. Secondary Headache and Associated Syndromes
Posttraumatic headache
Head injury
Whiplash injury
Headache attributed to cranial or cervical vascular disorder
Ischemic stroke or transient ischemic attack
Parenchymal or subarachnoid hemorrhage
Unruptured vascular malformation or aneurysm
Intracranial or extracranial arteritis
Arterial dissection
Venous or sinus thrombosis
Headache attributed to nonvascular intracranial disorders
Intracranial hypotension or hypertension
Brain neoplasia
Noninfectious inflammatory disorders (sarcoidosis)
Chiari malformation
Headache attributed to substance use or withdrawal
Medication adverse event (nitrates)
Alcohol
Caffeine withdrawal
Medication overuse headache
Headache attributed to infection
Intracranial infection (meningitis, encephalitis, brain abscess)
Extracranial infection (systemic bacterial infection, viral syndrome)
Headache attributed to disorder of homeostasis
Hypertensive crisis, dialysis, hypoxia, hypercapnia, hypothyroidism
Headache attributed to disorder of the neck, eyes, ears, nose, sinuses, teeth, or mouth
Headache attributed to a psychiatric disorder

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TABLE 2. Headache History
Headache Temporal Profile
Onset of the condition
When did these headaches first develop?
How long have the headaches been occurring at the frequency reported presently?
Monthly headache frequency over past 3 months
Total headache days?
Severe headache days?
Headache days requiring medication?
Duration of headache episodes
Untreated?
Treated?
Headache Symptom Profile
Pain
Location of pain
Quality of pain
Severity of pain
Effect of routine physical activity on pain
Associated features
Precursor symptoms
Sensitivities to light, sound, smell
Nausea, vomiting
Neurologic or visual complaints
Cranial autonomic features (tearing, nasal congestion or rhinorrhea, ptosis, conjunctival injection)
Contributing Clinical Factors
Family history
Provocative or palliative features
Detailed medication history

KEY POINTS

- Early identification of secondary headaches is essential because of their potentially significant morbidity and mortality; patients with serious secondary headaches typically have acute or subacute symptoms and a headache pattern that is progressive or unstable.
- HVC Stable headaches meeting criteria for most primary headaches usually do not require imaging.

Secondary Headache

Thunderclap Headache

H Thunderclap headache is defined as a severe attack of headache pain developing abruptly and reaching maximum intensity within 1 minute. Although occasionally of primary origin, thunderclap headache is a medical emergency that warrants immediate diagnostic evaluation. Noncontrast head CT should be performed without delay. Lumbar puncture with measurement of opening pressure, cell counts, and xanthochromia should be performed if the head CT is nondiagnostic. Contrast-enhanced brain MRI and noninvasive vascular imaging (magnetic resonance angiography [MRA] or CT angiography [CTA]) of cranial and cervical vessels should be performed in patients with a normal CT scan and normal results of cerebrospinal fluid (CSF) analysis. **Table 3** lists essential considerations in the differential diagnosis.

Subarachnoid hemorrhage (SAH), the most common cause of thunderclap headache, is discovered in nearly 25% of affected patients. The headache associated with SAH may be described as the worst the patient has ever experienced, although the specificity of this finding is limited. Mortality is 50%, with an additional 25% of affected patients experiencing significant morbidity. In the presence of a normal neurologic examination, the following features increase the likelihood of a diagnosis of SAH: age 40 years or older, onset during exertion, witnessed loss of consciousness, or concomitant neck pain. Estimates vary widely, but many patients describe a past headache consistent with a sentinel leak within the previous 1 to 2 weeks; these leaks typically involve abrupt, severe, transient headaches that may be focal or global. Sensitivity of head CT is approximately 95% at 12 hours but decreases to 50% at 1 week. Lumbar puncture in SAH typically reveals a CSF erythrocyte count greater than 10,000/µL ($10{,}000 \times 10^6$/L) and an elevation in protein level. CSF xanthochromia may take 4 hours or more to develop but is nearly 100% sensitive

TABLE 3. Possible Causes of Thunderclap Headache
Secondary Headache Disorders
Subarachnoid or parenchymal hemorrhage
Intracranial venous or sinus thrombosis
Cervical artery dissection
Reversible cerebral vasoconstriction syndrome
Posterior reversible encephalopathy syndrome
Ischemic stroke or transient ischemic attack
Spontaneous intracranial hypotension
Subdural hematoma
Pituitary apoplexy
Pheochromocytoma
Colloid cyst of third ventricle
Acute hydrocephalus
Subdural hematoma
Acute angle-closure glaucoma
Primary Headache Disorders
Primary thunderclap headache
Primary stabbing headache

H CONT.

between 12 hours and 7 days. Urgent neurosurgical consultation is required.

Headache is the most common symptom and may be the only presenting manifestation with thrombosis of the intracranial veins and sinuses. The pain is typically of sudden onset and is unremitting. Clinical symptoms may be related to the resulting increase in intracranial pressure and include pain exacerbation with the Valsalva maneuver, pulsatile tinnitus, and diplopia. Nonspecific findings of increased intracranial pressure include papilledema, decreased mentation, and seizures. Abducens nerve (cranial nerve VI) palsy secondary to increased intracranial pressure may falsely indicate a focal lesion (falsely localizing abducens nerve palsy). Specific findings may help localize the thrombosis. Cavernous sinus thrombosis usually involves extension of dental or sinus bacterial infection and manifests as acute-onset headache, proptosis, periorbital edema, and ophthalmoplegia; this disorder requires immediate administration of antibiotics, often with surgical drainage. Other forms of cerebral venous thrombosis are not related to infection and often occur in the presence of hypercoagulable states, thrombophilia, pregnancy (and the puerperium), oral contraceptive use, or dehydration. Anticoagulation is recommended even in those patients with hemorrhagic parenchymal lesions. Treatment with low-molecular-weight heparin results in lower hospital mortality than treatment with unfractionated heparin. Anticoagulation with warfarin is generally continued for a minimum of 3 to 6 months. Extended anticoagulation should be considered in those with severe hypercoagulable states, myeloproliferative disorders, or recurrence and perhaps in those with idiopathic thrombosis.

Dissections of the cervical vessels (**Figure 1**) often present with acute pain in the head and neck, typically occur in younger patients, and may develop spontaneously or as a result of trauma, which may be minor. Risk factors include hypertension, migraine, polycystic kidney disease, and connective tissue disorders. Extracranial dissections are a common cause of stroke in persons younger than 50 years. Dissections of the carotid artery often present with orbital pain, partial Horner syndrome (ptosis and miosis only), and ipsilateral signs of cerebral or retinal ischemia. Those with dissections of the vertebral arteries may describe occipital and neck pain and posterior fossa symptoms, such as dysarthria, dysphagia, ataxia, and hemifield visual loss. Brain MRI may show a tapered arterial lumen or increased arterial diameter with an intramural hematoma. Noninvasive vessel imaging with MRA or CTA is typically sufficient. Comparative trials have not documented the superiority of anticoagulation in patients with dissections, and many are treated with aspirin.

Reversible cerebral vasoconstriction syndrome is characterized by recurrent thunderclap headache and multifocal constriction of intracranial vessels normalizing within 3 months of onset. Predisposing factors are listed in **Table 4**. It is the second most frequent source of thunderclap headache. The headaches may be triggered by exertion, Valsalva maneuvers, emotion, or bathing. Focal deficits, encephalopathy, and seizures are seen in a minority of patients. Diagnostic evaluation should include noninvasive imaging of the brain and neck vessels with MRA or CTA and CSF analysis. Digital subtraction angiography has been associated with transient neurologic deficits and is typically avoided. Results of head CT and lumbar puncture are both typically normal. Brain MRI is more sensitive and may show areas of white matter edema primarily in the occipital and parietal lobes compatible with posterior reversible encephalopathy syndrome. Areas of ischemia or hemorrhage may be seen in the parenchyma, and a subdural or subarachnoid hemorrhage also may be found in some patients. Management begins with resolution of predisposing factors, avoidance of physical exertion, and management of blood pressure. Verapamil and nimodipine are the drugs of choice. Glucocorticoids may worsen the clinical course and should be avoided. Repeat MRA or CTA is necessary at 12 weeks to document resolution of vasospasm, at which time medication is tapered. H

KEY POINTS

- Thunderclap headache is a medical emergency that warrants immediate diagnostic evaluation; noncontrast head CT should be performed without delay.
- Subarachnoid hemorrhage is the most common cause of thunderclap headache.
- Cavernous sinus thrombosis manifests as acute-onset headache, proptosis, periorbital edema, and ophthalmoplegia; usually involves extension of dental or sinus bacterial infections; and requires immediate administration of antibiotics and frequently surgical drainage.
- Dissections of the cervical vessels often present with acute pain in the head and neck and are a common cause of stroke in patients younger than 50 years.
- Reversible cerebral vasoconstriction syndrome is characterized by recurrent thunderclap headache and is the second most frequent source of thunderclap headache.

Idiopathic Intracranial Hypertension

H

Increased intracranial pressure in the absence of any vascular or space-occupying lesion is the hallmark of idiopathic intracranial hypertension (IIH) (also known as pseudotumor cerebri). Approximately 90% of affected persons are women of childbearing age with an elevated BMI. IIH is associated with the following conditions:

- Hypervitaminosis A
- Use of the tetracycline class of antibiotics
- Retinoic acid use
- Kidney failure
- Endocrine disorders (hypoparathyroidism, Addison disease)
- Use of estrogen and progesterone supplements and pregnancy
- Glucocorticoid use or withdrawal

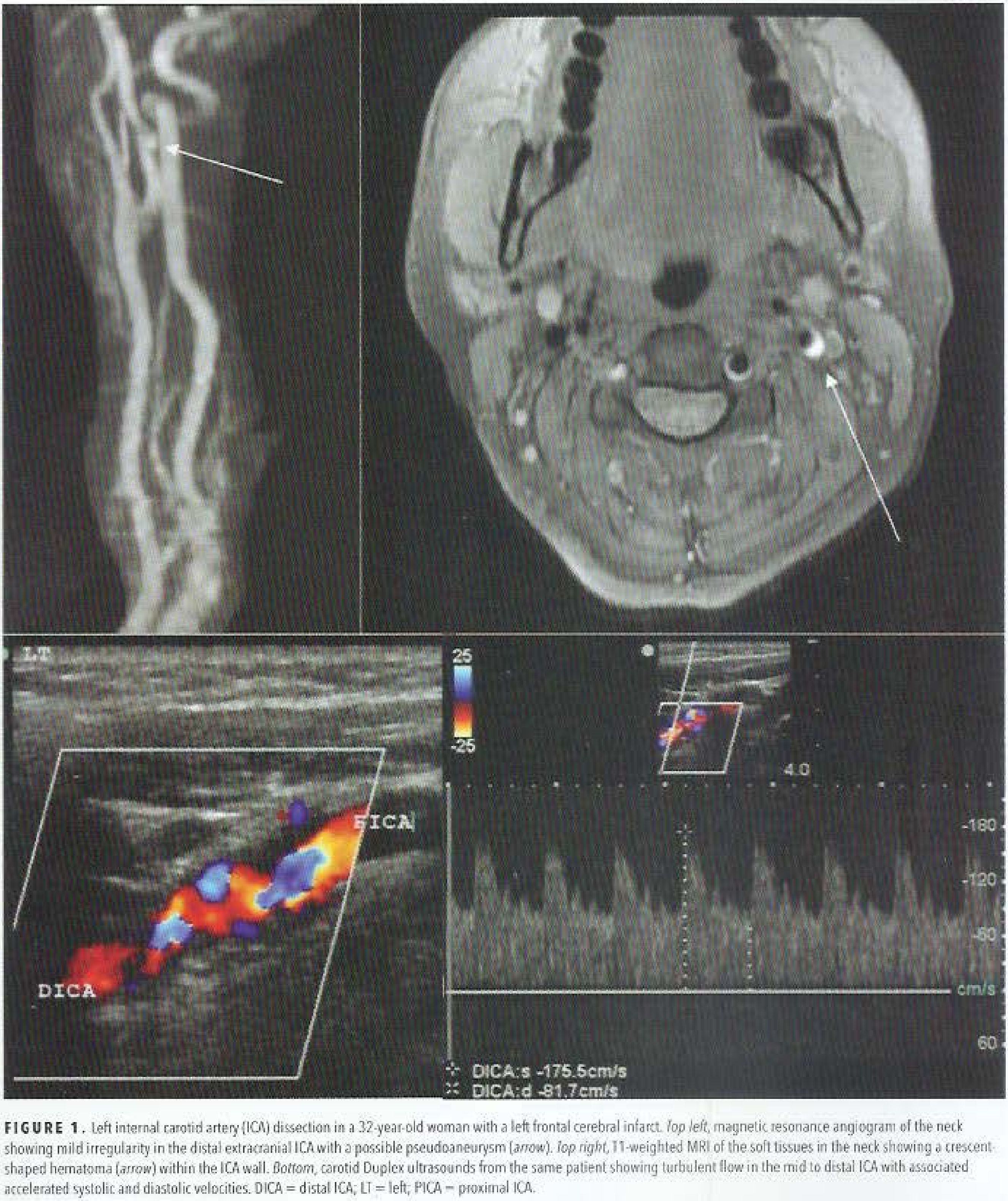

FIGURE 1. Left internal carotid artery (ICA) dissection in a 32-year-old woman with a left frontal cerebral infarct. *Top left*, magnetic resonance angiogram of the neck showing mild irregularity in the distal extracranial ICA with a possible pseudoaneurysm (*arrow*). *Top right*, T1-weighted MRI of the soft tissues in the neck showing a crescent-shaped hematoma (*arrow*) within the ICA wall. *Bottom*, carotid Duplex ultrasounds from the same patient showing turbulent flow in the mid to distal ICA with associated accelerated systolic and diastolic velocities. DICA = distal ICA; LT = left; PICA = proximal ICA.

H CONT.

Headaches, visual symptoms, and intracranial noises (pulsatile tinnitus) are the most common presenting symptoms of IIH. Head pain is nonspecific and may be similar to that of tension type headache or migraine. Vision may be blurred, doubled, or periodically dim in brief episodes known as visual obscurations. Visual field testing is essential in the initial and follow-up evaluations of IIH. Although only 25% of patients may report visual

TABLE 4. Predisposing Factors of Reversible Cerebral Vasoconstriction Syndrome
Vasoactive Drug Exposure
Sympathomimetic agents (amphetamines, pseudoephedrine, phenylpropanolamine)
Antidepressants (SSRIs, SNRIs, monoamine oxidase inhibitors)
Triptans or ergot alkaloid derivatives
Nicotine
Illicit drugs (cocaine, cannabis, ecstasy, methamphetamines)
Pregnancy and Puerperium
Preeclampsia, eclampsia
HELLP syndrome
Head and Neck Trauma and Surgery
Acute Cerebrovascular Disorders
Cervical artery dissection
Cerebral endovascular procedures or angiography
Cerebral vein or sinus thrombosis
Miscellaneous Conditions
Exposure to immunosuppressants or blood products
Meningitis
Catecholamine-secreting tumors

HELLP = Hemolysis, Elevated Liver enzymes, and Low Platelet count; SNRI = serotonin norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor.

H CONT.

symptoms, 90% have some abnormality on visual perimetry. Typical findings include blind spot enlargement and peripheral field reduction. Patients with atypical presentations (men older than 50 years, patients with normal BMIs) are less likely to report headaches and have a more benign visual prognosis.

Findings on neurologic examination include papilledema and, occasionally, ophthalmoplegia. Enhanced brain MRI with magnetic resonance venography may reveal widening of the optic nerve sheaths or flattening of the posterior optic globes but is otherwise unremarkable. An elevation in CSF opening pressure of greater than 250 mm H_2O with normal CSF composition confirms the diagnosis.

Treatment of IIH is aimed primarily at preservation of vision. Patients with BMI elevation require introduction of a weight-loss program. Bariatric procedures have been shown to be helpful, when necessary. Acetazolamide is the drug of choice. Topiramate may be less effective but carries the potential added benefit of weight loss. Paresthesias, kidney stones, and taste perversion are possible adverse effects of both drugs. More immediate reduction in intracranial pressure may be accomplished through repeated lumbar punctures. Decompressive procedures, such as lumboperitoneal shunting or optic nerve fenestration, should be considered in patients with medically refractory IIH. H

KEY POINTS

- Idiopathic intracranial hypertension, which is suggested by the presence of headache, visual symptoms, and pulsatile tinnitus, occurs most commonly in women of child-bearing age who have an elevated BMI.
- Treatment of idiopathic intracranial hypertension is aimed primarily at preservation of vision; weight loss in patients who have an elevated BMI and acetazolamide are the treatments of choice.

Headaches from Intracranial Hypotension

H

The most common source of intracranial hypotension is leakage of CSF after a lumbar puncture. The cardinal feature is a postural headache, typically worsening within 20 seconds of sitting or standing. Tinnitus, diplopia, neck pain, nausea, photophobia, and phonophobia are additional symptoms. Risk of developing symptoms may be reduced by using a small-caliber atraumatic needle but is unaffected by bed rest postprocedure. More than 50% of these headaches resolve spontaneously by day 4 postprocedure, and more than 75% by day 7. Persistent symptoms are treated with an autologous epidural blood patch (EBP), which causes resolution of symptoms in 80% to 90% of patients. H

Spontaneous intracranial hypotension also classically presents with an orthostatic headache, but the interval between postural change and headache development is highly variable. When present for a period of weeks to months, the orthostatic component may fade completely. Associated symptoms are similar to those of post-dural puncture headaches. Headache presentation may be thunderclap or subacute in nature. Diagnosis of intracranial hypotension can be confirmed by a CSF opening pressure of less than 60 mm H_2O, but lumbar puncture may introduce another site of potential CSF leakage. Most clinicians rely on the contrast-enhanced brain MRI finding of diffuse nonnodular pachymeningeal enhancement seen in nearly 80% of patients. Cerebellar tonsillar descent similar to that of a Chiari malformation, subdural fluid collections, decreased ventricular size, and engorgement of the pituitary gland are other common findings on MRI. Identification of the source of CSF leakage may be challenging. Most cases are empirically treated with lumbar EBP procedures. The success rate with "blind" patches is approximately 30%, and repeat procedures are commonly required. If two to three patches do not relieve the condition, attempts are made to further localize the site of CSF leakage using spinal CT myelography. Noncontrast spine MRI is a noninvasive alternative that also may show an extradural fluid collection at the site of the leak. Once identified, the site may be treated with targeted EBP or surgical repair. If no leak is identified, the studies can be repeated in 4 to 6 months.

KEY POINTS

- The headache associated with intracranial hypotension caused by leakage of cerebrospinal fluid after a lumbar puncture is treated with an autologous epidural blood patch.
- The diagnosis of spontaneous intracranial hypotension is associated with the contrast-enhanced brain MRI finding of diffuse nonnodular pachymeningeal enhancement in nearly 80% of patients.

Trigeminal Neuralgia

Trigeminal neuralgia is the most common and most intense cranial neuralgia. Incidence increases with advanced age. Multiple sclerosis should be considered in those with onset before age 50 years. Pain is typically unilateral and localized to the maxillary and mandibular branches of the trigeminal nerve (cranial nerve V). The pains are brief, "shock like," or electric, lasting seconds to minutes. Paroxysms may be spontaneous or triggered by innocuous stimulation of the face. Refractory periods are common after a series of paroxysms. Ipsilateral autonomic features are rare. Neurologic examination is typically normal. Contrast-enhanced brain MRI detects nonvascular structural pathology (such as compressing and demyelinating causes) in 15% of patients. In the other 85%, brain MRA often identifies neurovascular contact between a loop of the superior cerebellar artery and the trigeminal nerve. Contact causing displacement or atrophy of the nerve has been associated with a greater likelihood of symptom development.

Management of trigeminal neuralgia begins with carbamazepine administration. Pain may resolve within a few days, although mild dizziness and drowsiness are common. Other adverse effects of the medication, including hyponatremia and agranulocytosis, are less common but necessitate intermittent monitoring. Alternative drugs are oxcarbazepine, baclofen, gabapentin, and lamotrigine. Approximately 30% of patients do not respond to trials of monotherapy or combined therapy. For those refractory to two-drug trials, surgical intervention should be considered. Nonsurgical options are effective in 50% of patients and include percutaneous radiofrequency coagulation, glycerol injection, or focused stereotactic (Gamma Knife) radiation. Posterior fossa microvascular decompression of the neurovascular contact zone is a more invasive and more effective option. It should be prioritized in those with low surgical risk.

KEY POINTS

- Contrast-enhanced brain MRI detects nonvascular structural pathology in 15% of patients with trigeminal neuralgia, and brain magnetic resonance angiography often identifies neurovascular contact between a loop of the superior cerebellar artery and the trigeminal nerve in the other 85%.

(Continued)

KEY POINTS *(continued)*

- Initial management of trigeminal neuralgia is with carbamazepine; if medical therapy fails, focused stereotactic (Gamma Knife) radiation, glycerol injection, or posterior fossa microvascular decompression may be effective.

Medication-Induced Headache

Headache is a potential effect of medication exposure or withdrawal. Oral contraceptives, phosphodiesterase inhibitors, β-adrenergic agonists, and nitrates are among the most commonly implicated drugs; they may cause headache de novo or aggravate an existing primary headache disorder. Withdrawal from caffeine or antidepressants also frequently provokes headache. Medication overuse headache (MOH), previously called "rebound" headache, is a highly prevalent condition affecting 1% of adults. This clinical syndrome may result from overtreatment with acute medication in patients with underlying migraine or tension-type headache. Use of triptans, ergot alkaloids, opioids, or combination analgesics for 10 or more days per month or simple analgesics for 15 or more days per month constitutes medication overuse. Affected patients often report daily or near-daily headache that is refractory to numerous treatment options. MOH is more common in midlife, in women, and in those with high baseline headache frequency. In those with migraine, opioids are associated with a 44% increase and butalbital compounds with a 70% increase in the risk of headache progression. These medications should be avoided in patients with recurrent primary headache disorders. Management of MOH involves discontinuation of the overused medication and the introduction of appropriate preventive medication directed at the primary headache disorder.

KEY POINT

- Medication overuse headache can result from use of triptans, ergot alkaloids, opioids, or combination analgesic agents for 10 or more days per month or simple analgesic agents for 15 or more days per month; treatment includes discontinuation of the overused medication and use of appropriate preventive medication directed at the primary headache disorder.

Primary Headache

Migraine

Diagnosis

H

The International Classification of Headache Disorders (ICHD), third edition (beta version), recognizes several subtypes of migraine, including migraine without aura, migraine with aura, and chronic migraine. Each is characterized by episodes of disabling headache lasting hours to days. Accuracy of diagnosis and management is enhanced by the use of formal ICHD criteria, although the POUND mnemonic (Pulsatile quality of headache, One-day duration, Unilateral location, Nausea or vomiting, Disabling intensity) is a helpful means of recalling

CONT.

the symptoms typically associated with migraines. Because of the extensive phenotypic variation, nearly half of migraine presentations are misdiagnosed. Neck pain (75%) and "sinus" symptoms, such as tearing or nasal drainage (50%), are both more common than features felt to be characteristic of migraine, such as vomiting or aura. In the presence of a stable clinical pattern of migraine and a normal neurologic examination, brain imaging is not indicated.

Migraine without aura is the most prevalent migraine subtype (**Table 5**). Although clinicians often emphasize unilateral location or pulsatile characteristics, moderate to severe pain is the most sensitive feature, and worsening by routine physical activity is the most specific element among the pain criteria. Photophobia, phonophobia, and nausea are each reported by approximately 75% of patients with migraine without aura.

The diagnosis of migraine with aura is made after two discrete aura episodes have occurred (**Table 6**). Aura may occur in 20% to 30% of patients with migraine. It frequently precedes pain but may occur during or without head discomfort. Aura symptoms involve positive and negative neurologic phenomena developing gradually and evolving over a period of 5 to 60 minutes. Resolution is gradual and complete. ICHD criteria recognize a number of aura subtypes. Typical aura involves any combination of homonymous visual, hemisensory, or language symptoms. Brainstem aura is defined by the presence of two of the following brainstem symptoms: dysarthria, vertigo, tinnitus, hypacusis, diplopia, ataxia, or decreased level of consciousness. Hemiplegic aura comprises any aura involving motor weakness. Both hemiplegic and brainstem auras are listed as contraindications for triptan use. Retinal aura involves monocular visual compromise. These auras need to be distinguished from ocular pathologies, such as retinal ischemia or detachment. Given an associated increased risk of stroke, estrogen-containing oral contraceptives should be avoided in women with migraine aura of all subtypes. H

TABLE 5. International Headache Society Criteria for Migraine Without Aura

A. At least five attacks fulfilling criteria B-D

B. Headache attacks lasting 4-72 hours (untreated or unsuccessfully treated)

C. Headache with at least two of the following four characteristics:

1. Unilateral location
2. Pulsating quality
3. Moderate or severe pain intensity that inhibits or prohibits daily activities
4. Aggravation by walking up or down stairs or similar routine physical activity

D. During headache, occurrence of at least one of following symptoms:

1. Nausea/vomiting
2. Photophobia/phonophobia

E. Headache not better accounted for by another ICHD-3 diagnosis

ICHD-3 = International Classification of Headache Disorders, 3rd edition (beta version).

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TABLE 6. International Headache Society Criteria for Migraine With Aura

A. At least two attacks fulfilling criteria B and C

B. One or more of the following fully reversible aura symptoms:

1. Visual
2. Sensory
3. Speech and/or language
4. Motor
5. Brainstem
6. Retinal

C. At least two of the following four characteristics:

1. At least one aura symptom spreads gradually over >5 minutes, and/or two or more symptoms occur in succession
2. Each individual aura symptom lasts 5-60 minutes
3. At least one aura symptom is unilateral
4. The aura is accompanied, or followed within 60 minutes, by headache

D. Headache not better accounted for by another ICHD-3 diagnosis, and transient ischemic attack has been excluded

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Chronic migraine is defined as headache for 15 or more days per month (**Table 7**). Transformation from acute to chronic migraine occurs in the general population at an annual rate of 3%. Older age, female sex, head trauma, major life changes or stressors, obesity, chronic pain, mood and anxiety disorders, and inadequate acute migraine management are risk factors. Acute migraine medication or caffeine overuse and exposure to nicotine may also raise the risk of or exacerbate chronic migraine; some patients with chronic migraine may have a secondary diagnosis of MOH. Patients with chronic migraine are more disabled and more likely to report migraine-related comorbidities (mood or anxiety disorders, sleep dysfunction, irritable bowel syndrome, fibromyalgia) than are those with episodic migraine.

Acute Migraine Management

H

The acute treatment of migraine aims to eliminate pain and restore function. Goals of care involve freedom from pain,

TABLE 7. International Headache Society Criteria for Chronic Migraine

A. Headache (tension-type-like and/or migraine-like) on at least 15 days per month for greater than 3 months and fulfilling criteria B and C

B. Occurring in a patient who has had at least five attacks fulfilling criteria B-D for migraine without aura and/or criteria B and C for migraine with aura

C. On at least 8 days per month for greater than 3 months, fulfilling any of the following:

1. Criteria C and D for migraine without aura
2. Criteria B and C for migraine with aura
3. Believed by the patient to be a migraine at onset and relieved by a triptan or ergot alkaloid derivative
4. The aura is accompanied, or followed within 60 minutes, by headache

D. Headache not better accounted for by another ICHD-3 diagnosis

ICHD 3 = International Classification of Headache Disorders, 3rd edition (beta version).

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H CONT.

nausea, and sensory sensitivities within 1 to 2 hours and maintenance of such control through at least 24 hours. Because attack characteristics show significant inter-individual and intra-individual variability, different treatment options and strategies are required (**Table 8**). Guidelines recommend tailoring the treatments to the severity and symptomatology of the attack. Migraines awakening a patient from sleep or those associated with nausea and vomiting may require medication offered in parenteral or nasal formulations. Because consistency of response to any treatment rarely approaches 100%, most patients benefit from availability of two or more acute migraine therapies. Administration of medication at the time of mild pain has been shown to improve therapeutic outcomes when compared to treating moderate to severe headache; therefore, treatment should be started as early as possible in the disease course. Treatment should be limited to 10 days per month to avoid MOH.

Evidence-based guidelines recommend several simple and combination analgesic agents as first-line therapies for acute migraine. Acetaminophen has established efficacy only in migraine of mild to moderate intensity; data suggest the response may be enhanced by coadministration with metoclopramide. Aspirin administered alone or in combination with acetaminophen and caffeine also has established efficacy in acute migraine. The effectiveness of the NSAIDs ibuprofen, naproxen sodium, and diclofenac potassium is supported by strong evidence. Special formulations of these products have been shown to be more rapidly absorbed and effective than their standard tablet counterparts. These formulations include effervescent aspirin, solubilized ibuprofen, and diclofenac powder for oral solution.

Triptans are selective agonists at 5-hydroxytryptamine 1B and 1D receptors. They are migraine-specific agents with direct impact on trigeminovascular activation associated with migraine attacks. Triptans reverse intracranial vasodilation (1B) and provide neuronal inhibition at peripheral and central trigeminal nerve circuitry (1D). Guidelines recommend the use of triptans in patients with moderate to severe migraine who have not responded to NSAID therapy over a series of at least three migraine attacks. Current evidence suggests that all oral triptans possess nearly similar clinical efficacy. Orally dissolvable tablets are intestinally absorbed; their only advantage is use without the need to drink liquids. Nasal spray options may have more rapid onset, bypassing the gastrointestinal tract. Outcomes are similar to those of oral agents, but unpleasant taste, nasal congestion, or burning may be limiting factors. Subcutaneous sumatriptan provides the most rapid onset and achieves the highest response rates among all triptan agents and formulations. Local site reactions and more prominent "triptan" sensations characteristic of the class (flushing, chest or throat tightness, paresthesias) may be noted. All triptans are

TABLE 8. Acute Migraine Therapies

Drug	Recommended Dose
NSAIDs[a]	
Aspirin	325-900 mg
Ibuprofen	400-800 mg
Naproxen sodium	250-1000 mg
Combination of acetaminophen-aspirin-caffeine	2 tablets
Diclofenac potassium (oral solution)	50 mg
Migraine-Specific Oral Agents[a]	
Almotriptan	6.25-12.5 mg
Eletriptan	20-40 mg
Frovatriptan	2.5 mg
Naratriptan	1-2.5 mg
Rizatriptan	5-10 mg
Sumatriptan	25-100 mg
Sumatriptan-naproxen	85-500 mg
Zolmitriptan	2.5-5 mg
Nonoral Agents[a]	
Dihydroergotamine	1 mg nasally
Dihydroergotamine	1 mg subcutaneously
Prochlorperazine	10 mg intravenously
Sumatriptan	5-20 mg nasally
Sumatriptan	4-6 mg subcutaneously
Zolmitriptan	5 mg nasally

[a]Doses listed may be administered once or twice daily.

H CONT

contraindicated in the presence of coronary, cerebral, or peripheral vascular disease; uncontrolled hypertension; or migraine with brainstem or hemiplegic auras. Different formulations of one triptan may be used safely within the same day, but using a different triptan or an ergot alkaloid should be delayed by 24 hours. Despite labeling precautions, the concurrent use of triptans and selective serotonin reuptake inhibitors or serotonin norepinephrine reuptake inhibitor antidepressants is safe in most cases.

Other agents also are effective in the management of acute migraine. Ergot alkaloids have been used for years but have been largely replaced by triptans, which have preferable safety and tolerability profiles; parenteral and nasal formulations of dihydroergotamine are the most available and effective options among the ergot alkaloids. Dopamine D_2 receptor antagonists (metoclopramide, prochlorperazine) are often used as adjuncts to analgesics or triptans. In addition to antiemetic properties, these agents can reduce migraine pain when delivered parenterally. Guidelines recommend avoiding the use of opioids and butalbital-containing compounds for acute migraine. In addition to the potential for dependence or addiction, use of these agents has been linked to an increased risk of transformation from episodic to chronic migraine. They should be used sparingly and only when more appropriate acute therapies are contraindicated.

Migraine with a duration lasting longer than 72 hours is known as status migrainosus. Many patients with this condition can be treated with several days of glucocorticoids. Severe cases of acute migraine or status migrainosus may require emergency department or inpatient management. The cornerstone of care in these settings is intravenous delivery of a dopamine antagonist. These are typically combined with intravenous diphenhydramine (to limit dystonic reactions), intravenous ketorolac, and hydration. Opioids may be associated with prolonged length of hospital stay and should be avoided. A more extended course of treatment involving repetitive intravenous dihydroergotamine with antiemetics over 2 to 3 days is very effective in the management of refractory status migrainosus. H

Migraine Prevention

The goals of migraine prevention are the reduction of migraine frequency, intensity, and duration. None of the medications used for migraine prevention were designed for this specific purpose. The best agents may reduce migraine frequency by half in approximately half of the patients treated. Nonpharmacologic preventive measures are not only optimal but required. Trigger identification and avoidance are often helpful. Stress management techniques, such as relaxation therapy or biofeedback, have established efficacy. Regulation of sleep patterns, intake of small frequent meals, adequate hydration, and daily aerobic exercise are all extremely helpful. Regular work and school schedules should be encouraged. Stimulants (such as caffeine and nicotine) must be eliminated or limited. Diet should be modified to avoid additives or preservatives, such as monosodium glutamate and artificial sweeteners. There is good evidence to support the use of certain supplements, such as petasites (butterbur), magnesium, riboflavin, and feverfew.

Pharmacologic prophylaxis should be considered when the headache frequency reaches 5 days per month and almost always is initiated when the frequency exceeds 10 days per month. Data suggest preventive medication can reduce attack frequency and intensity, patient disability, and medical cost. Several weeks or months are often required before maximum benefit is achieved. Once a response occurs, the medications should be continued for a period of 6 to 12 months, at which point dose reduction or drug elimination may be considered. Evidence-based guidelines for pharmacologic prevention of episodic migraine have established Level A evidence supporting the use of five medications: three β-adrenergic blockers (propranolol, timolol, metoprolol) and two antiepileptic drugs (divalproex sodium and topiramate). Level B evidence is available for atenolol, two antidepressants (amitriptyline and venlafaxine), and several NSAIDs. No evidence supports the use of calcium channel blockers or selective serotonin reuptake inhibitor antidepressants in migraine prevention. Studies involving patients with chronic migraine are more limited, but efficacy in prevention has been shown with topiramate and onabotulinum toxin A. Treatment selection is informed by previous therapeutic trials, the presence of coexisting medical conditions, and patient preference.

KEY POINTS

- Because of the extensive phenotypic variation, nearly half of migraine presentations are misdiagnosed; the POUND mnemonic (Pulsatile quality of headache, One-day duration, Unilateral location, Nausea or vomiting, Disabling intensity) is a helpful means of recalling the symptoms typically associated with migraines. **HVC**
- In the presence of a stable clinical pattern of migraine and a normal neurologic examination, brain imaging is not indicated. **HVC**
- Given an associated increased risk of stroke, estrogen-containing oral contraceptives should be avoided in women with migraine aura of all subtypes.
- Triptans are migraine-specific agents that are useful in moderate to severe migraine that has not responded to NSAID therapy; they are contraindicated in the presence of coronary, cerebral, or peripheral vascular disease; uncontrolled hypertension; or migraine with brainstem or hemiplegic auras.
- Pharmacologic prophylaxis for migraine should be considered when headache frequency reaches 5 days per month and almost always is initiated when the frequency exceeds 10 days per month; propranolol, timolol, metoprolol, divalproex sodium, and topiramate are most effective for migraine prophylaxis.

Tension-Type Headache

The most prevalent primary headache condition, tension-type headache is defined by clinical criteria as a headache disorder that, unlike migraine, is mild to moderate in intensity and is not associated with nausea, severe sensory sensitivities, or neurologic symptoms (**Table 9**). Imaging is not indicated. Subclassification is based on monthly headache frequency: infrequent episodic (<1 day), frequent episodic (1-14 days), and chronic (15 or more days). Acetaminophen, aspirin, NSAIDs, and caffeine-containing compounds are effective acute treatments for tension-type headache. Amitriptyline and stress management techniques have modest benefit in prevention of tension-type headache, and some data support the use of acupuncture. Muscle relaxants, benzodiazepines, opioids, and onabotulinum toxin A have no role in the management of tension-type headache.

KEY POINTS

HVC
- Imaging is not indicated for tension-type headache.
- Acetaminophen, aspirin, NSAIDs, and caffeine-containing compounds are effective acute treatments for tension-type headache, but muscle relaxants, benzodiazepines, opioids, and onabotulinum toxin A have no role in the management of tension-type headache.

Trigeminal Autonomic Cephalalgias

Trigeminal autonomic cephalalgias (TACs) are the most severe and stereotypic primary headache disorders. Pain is severe, localized to the periorbital or temporal areas, and associated with pronounced ipsilateral cranial autonomic features, such as nasal congestion or rhinorrhea and ptosis or miosis. The TACs, which include cluster headache, chronic paroxysmal hemicrania (CPH), and short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT), are differentiated by episode duration, frequency, and periodicity.

Cluster headache may last 15 to 180 minutes and recur one to eight times daily over a span of weeks to months; the shorter duration distinguishes cluster headache from migraine (**Table 10**). This headache is characterized by a cyclical nature in which periods of recurrent headache activity are interrupted by months to years of headache remission. Many of the attacks are nocturnal, and some may be provoked by alcohol ingestion. Episodes of CPH last 2 to 30 minutes and recur up to 40 times per day, whereas those of SUNCT last 1 to 600 seconds and may recur more than 100 times daily. SUNCT may be confused with trigeminal neuralgia, which is more likely mandibular or maxillary and lacks autonomic features. Unlike cluster headache, both CPH and SUNCT typically continue without periods of remission. Brain MRI should be performed initially to exclude structural lesions mimicking TACs.

Cluster headache has several acute and preventive options. Oxygen inhalation and subcutaneous sumatriptan are both effective in the treatment of attacks. A 2-week course of glucocorticoids may help reduce attack frequency at the onset

TABLE 9. International Headache Society Criteria for Tension-Type Headache

A. At least 10 attacks fulfilling criteria B-E

B. Headache attacks (untreated or unsuccessfully treated) lasting from 30 minutes to 7 days

C. Headache with at least two of the following four characteristics:
  1. Bilateral location
  2. Pressing/tightening (nonpulsating) quality
  3. Mild or moderate intensity
  4. Not aggravated by walking stairs or similar routine physical activity

D. Headache characterized by both of the following:
  1. No nausea/vomiting
  2. No more than one episode of photophobia or phonophobia

E. Not better accounted for by another ICHD-3 diagnosis

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TABLE 10. International Headache Society Criteria for Cluster Headache

A. At least five attacks fulfilling criteria B-D

B. Severe or very severe unilateral orbital, supraorbital, and/or temporal pain lasting 15-180 minutes (when untreated)

C. Either or both of the following:
  1. At least one of the following symptoms or signs, ipsilateral to the headache:
     a) conjunctival injection and/or lacrimation
     b) nasal congestion and/or rhinorrhea
     c) eyelid edema
     d) forehead and facial sweating
     e) forehead and facial flushing
     f) sensation of fullness in the ear
     g) miosis and/or ptosis
  2. A sense of restlessness or agitation

D. Attack frequency from one every other day to eight per day when the disorder is active

E. Headache not better accounted for by another ICHD-3 diagnosis

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of the cycle. Verapamil is the drug of choice for longer-term prevention of cluster headache. CPH is uniquely and universally responsive to indomethacin. Reports have suggested a small benefit from lamotrigine, but SUNCT is largely refractory to medical management.

KEY POINTS

- Trigeminal autonomic cephalalgias are the most severe and stereotypic primary headache disorders and include cluster headaches, chronic paroxysmal hemicrania, and short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing.
- Cluster headache is treated with oxygen inhalation and subcutaneous sumatriptan.
- Chronic paroxysmal hemicrania is universally responsive to indomethacin; short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing is largely refractory to medical management.

Other Primary Headache Syndromes

Primary stabbing headaches ("ice-pick headaches") are episodes of stabbing head pain lasting seconds and occurring in isolation or in series. There are no associated autonomic features. The location of pain is fixed in one third of patients and extratrigeminal in most patients. Those with migraine may be more likely to describe these attacks. Indomethacin can be helpful during cycles of more frequent attacks.

Cough headache develops abruptly with cough or Valsalva maneuvers and typically lasts seconds to minutes. Mild headache may continue for 1 to 2 hours. The severity of pain correlates with cough frequency. Advancing age and male sex may be risk factors. Brain MRI is indicated because secondary pathologies, most commonly a Chiari malformation, may be found in half of those affected. Indomethacin may reduce headache frequency during cycles of increased activity.

KEY POINT

- Brain MRI is indicated in patients with cough headache to identify possible secondary pathologies (such as a Chiari malformation), which may be found in 50% of affected patients.

Head Injury

Traumatic Brain Injury

H Traumatic brain injury (TBI) results from biomechanical forces applied to the structures of the head and neck. Damage may be temporary or permanent and may arise from functional or structural alterations in the central nervous system. Severity is determined by clinical findings and imaging results. When indicated, noncontrast CT is the imaging modality of choice because it is more sensitive for bony injuries, less expensive, and more widely available than MRI. Mild TBI is associated with Glasgow Coma Scale (GCS) scores of 13 to 15 with no or only a brief initial loss of consciousness; results of head CT are typically normal. Moderate TBI is associated with GCS scores of 9 to 12 and/or an initial loss of consciousness of 30 minutes to 24 hours. Severe TBI is associated with GCS scores of 3 to 8 and/or an initial loss of consciousness of more than 24 hours (**Table 11**). In moderate and severe TBI, head CT may reveal a skull fracture, cerebral contusions and edema, and intracranial hemorrhage. H

Mild Traumatic Brain Injury

The terms mild TBI and concussion are often used interchangeably. Mild TBI is the most common presentation of TBI and frequently results from accidents, athletic activity, or military service activities. Guidelines for the use of head CT in mild TBI have been published by the Centers for Disease Activity and Prevention (**Table 12**). Although yet to be incorporated into management guidelines, serum measurements of brain-specific biomarkers released after mild TBI can help predict which patients may have intracranial lesions visible on CT scan. Elevated levels of ubiquitin carboxy-terminal hydrolase L1 and glial fibrillary acidic protein can be detected as early as 20 minutes after head injury. A recent study of patients within 12 hours of mild TBI (GCS scores of 9 to 15) showed that these elevated serum levels combined with certain clinical information had a sensitivity of 97.5% for predicting lesions visible on head CT scan; negative predictive value was 99.6%. Patients

TABLE 11. Glasgow Coma Scale

Eye Opening	Score
Spontaneous	4
Response to verbal command	3
Response to pain	2
No eye opening	1
Best Verbal Response	
Oriented	5
Confused	4
Inappropriate words	3
Incomprehensible sounds	2
No verbal response	1
Best Motor Response	
Obeys commands	6
Localizing response to pain	5
Withdrawal response to pain	4
Flexion to pain	3
Extension to pain	2
No motor response	1
Total	

Data from: Teasdale G, Jennett B. Assessment of coma and impaired consciousness. A practical scale. Lancet 1974 Jul 13;2(7872): 81-4. [PMID: 4136544]

TABLE 12. Indications for Head CT in Mild Traumatic Brain Injury[a]
Age >60 years
Vomiting
Headache
Posttraumatic seizure
Drug or alcohol intoxication
Persistent drowsiness or short-term memory deficit
"Dangerous" mechanisms of injury (fall from height greater than 3 feet or 5 steps, ejection from a vehicle, being struck by a vehicle as a pedestrian)
Glasgow Coma Scale score <15
Focal neurologic deficit
Physical evidence of significant trauma to the head and neck
Coagulopathy

[a]CT scan should be obtained if any of the following findings are present.

with mild TBI, a normal neurologic examination, and (when necessary) a normal head CT scan may be safely discharged from the emergency department.

Symptoms following a mild TBI may be divided into four domains: physical, cognitive, psychological, and sleep-associated (**Table 13**). Most symptoms resolve spontaneously within 7 to 10 days. Headache is consistently the most common symptom and is among the most disabling sequelae. Head trauma may cause new headache or worsen a preexisting headache condition. A previous history of migraine has been linked with increased incidence and severity of postconcussion symptoms. Posttraumatic headaches most commonly have the characteristics of migraine and tension-type headaches.

Treatment is matched to the headache phenotype. Acetaminophen, aspirin, NSAIDs, and triptans are effective acute therapies; opioids and butalbital products should be avoided. β-Blockers, antidepressants, and antiepileptic drugs may be useful for headache prevention in patients with persistent posttraumatic headache. Treatment of other postconcussion symptoms is largely symptomatic and based on little evidence. Visual, vestibular, and cognitive therapies may be helpful in certain settings. Stimulants, such as amantadine, are sometimes given to patients with cognitive symptoms. Regulated sleep, graded return to exercise, and temporary modification of school or work schedules are often recommended.

KEY POINTS

- The symptoms of mild traumatic brain injury, which usually involves brief or no loss of consciousness, typically resolve spontaneously within 7 to 10 days.
- NSAIDs and triptans are effective acute therapies for mild traumatic brain injury–related headache, but opioids and butalbital products should be avoided.

TABLE 13. Symptoms of Mild Traumatic Brain Injury
Physical
Headache
Nausea/vomiting
Dizziness/vertigo
Gait disturbance
Photophobia or phonophobia
Visual blurring
Dysarthria
Seizures
Cognitive
Poor concentration
Mental "fogginess" or confusion
Poor memory
Learning impairment
Slowed reaction times
Psychological
Irritability
Depression
Anxiety
Sleep Associated
Fatigue
Insomnia
Hypersomnia
Drowsiness
Vivid dreams

Severe Traumatic Brain Injury

H

Severe TBI may present with an alteration in consciousness, seizures, repeated vomiting, or focal neurologic deficits. Bilateral periorbital or mastoid bruising and hemotympanum may be signs of basilar skull fracture.

The primary goal of initial management is prevention of hypotension and hypoxia. Normalization of blood oxygenation (arterial P_{O_2} > 60 mm Hg [8.0 kPa]) and blood pressure (systolic > 90 mm Hg) has been shown to improve outcomes. Early management of elevated intracranial pressure with head elevation and mannitol may be required; continuous measurement of intracranial pressure also may be necessary. Head CT is the preferred imaging study, and serial scans may be necessary. Penetrating injuries, depressed skull fracture, and intracranial hemorrhage all may require urgent surgery.

Medical management includes mechanical thromboprophylaxis (with intermittent pneumatic compression) for deep venous thrombosis prevention, glycemic control, and treatment of infectious or gastrointestinal complications. Nutritional support with full caloric replacement by day 7

postinjury is recommended. Fever should be controlled aggressively, with some medical centers advocating induced hypothermia; acetaminophen is an appropriate initial treatment. Glucocorticoids worsen the prognosis of severe TBI and should be avoided.

KEY POINT

- Medical management in the treatment of severe traumatic brain injury includes normalization of blood oxygenation and blood pressure, correction of elevated intracranial pressure, mechanical thromboprophylaxis for deep venous thrombosis, glycemic control, and aggressive control of fever; glucocorticoids should be avoided.

Epidural and Subdural Hematoma

An epidural hematoma arises when an arterial structure is breached and blood collects between the dura mater and skull in a "lentiform" fashion (**Figure 2**). Most epidural hematomas involve a laceration of the middle meningeal artery from a temporal bone fracture. Lateral extension is limited by dural attachments at the skull sutures, and expansion occurs inward toward the brain parenchyma. Many patients with an epidural hematoma have a "lucid interval" followed by rapid neurologic compromise. Headache, vomiting, and declining mental status may occur early. Stupor or coma with ipsilateral oculomotor nerve (cranial nerve III) palsy and contralateral hemiparesis may signal transtentorial (uncal) herniation. Urgent surgical evacuation is recommended for those with a GCS score less than 9, anisocoria, or a hematoma greater than 30 mL in volume.

A subdural hematoma (**Figure 3**) is a collection of blood between the brain and dura mater. Rupture of bridging veins within this space is typically responsible. This may occur spontaneously, as a complication of anticoagulation, or after trauma. Because of cerebral atrophy and subsequent tension on the subdural bridging veins, older persons and those with alcoholism are particularly susceptible. Presentations may be acute, subacute, or chronic. Whereas acute subdural hematoma typically presents with coma or neurologic compromise, chronic hematoma may be associated with nonspecific symptoms, including altered mental status or somnolence, in addition to focal neurologic findings. In patients with acute subdural hematomas, a hematoma thickness greater than 10 mm, a score less than 9 on the GCS, and the presence of pupillary asymmetry or fixation are all indications for immediate surgical treatment. In patients with chronic hematomas, a hematoma thickness greater than 10 mm, a midline shift greater than 5 mm, and significant neurologic compromise are all indications for drainage.

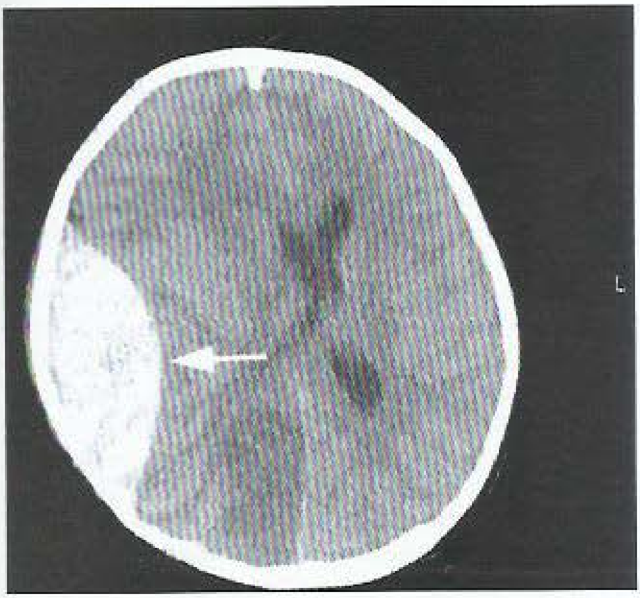

FIGURE 2. CT scan of an epidural hematoma. Note the biconvex lens appearance as blood under arterial pressure collects between the skull and outer margin of the dura (*arrow*).

FIGURE 3. CT scan of a subdural hematoma. Note the crescent shape as blood under venous pressure separates the dura from the arachnoid membrane (*arrow*).

KEY POINTS

- In patients with epidural hematoma, stupor or coma with ipsilateral occulomotor nerve palsy and contralateral hemiparesis may signal transtentorial herniation.
- Chronic subdural hematoma may be associated with nonspecific symptoms, including altered mental status or somnolence, in addition to focal neurologic findings.
- In patients with acute subdural hematomas, a hematoma thickness greater than 10 mm, a score less than 9 on the Glasgow Coma Scale, and the presence of pupillary asymmetry or fixation are indications for immediate surgical treatment.

Head Injury in Special Populations

Athletes

Any athlete suspected of sustaining a mild TBI should be immediately removed from play and assessed by a licensed health care provider trained in the evaluation and management of concussion. Guidelines recommend initial screening with a symptom checklist and neurologic examination involving specific cognitive evaluation and balance testing. Neuropsychological testing provides an objective and more sensitive measure of cognitive function; it should be employed as part of a comprehensive TBI management program for patients with persistent symptoms. Rest, both cognitive and physical, is required for the first days to weeks. Return to play requires the resolution of symptoms and normalization of cognition. The patient should progress through gradual stepwise increases in physical activity without the return of postconcussive symptoms before returning to play. There are no available guidelines for permanent disqualification from contact sports for athletes with mild TBI.

Chronic traumatic encephalopathy is being recognized with increasing frequency in athletes who play contact sports. The result of multiple concussions and head trauma, chronic traumatic encephalopathy may manifest as progressive neuropsychiatric symptoms, including depression and dementia, years after the inciting events. See Cognitive Impairment for more information.

KEY POINT

- Any athlete suspected of sustaining a mild TBI should be immediately removed from play and assessed by a licensed healthcare provider trained in the evaluation and management of concussion.

Military Personnel

TBI is a common consequence of service in the armed forces, particularly among those deployed to a combat theater. Mild TBI, which often lacks abnormalities on neurologic examination or imaging, is highly prevalent and accounts for 80% of TBI diagnoses. Guidelines recommend that military personnel undergo screening for TBI when exposed to trauma involving a direct blow to the head, a vehicular accident, or an explosive blast and when they are instructed to by a superior officer. The Military Acute Concussion Evaluation and a requisite 24-hour rest period are mandated, with return to duty requiring complete recovery. Headache is the most common symptom after TBI and the best prognostic indicator in returning service members. A posttraumatic headache still present at 1 year postinjury is likely to be permanent. Other sequelae of mild TBI in this population include posttraumatic stress disorder (PTSD), depression, anxiety, insomnia, and disorders of cognition and balance. The prevalence of PTSD is higher in military personnel with mild TBI than in civilians with mild TBI, and thus screening for PTSD in the former group is mandatory. Returning service members with any TBI are best managed through a multidisciplinary approach. Treatments are largely symptomatic and supportive.

KEY POINT

- The prevalence of posttraumatic stress disorder is higher in military personnel with mild traumatic brain injury (TBI) than in civilians with mild TBI.

Older Patients

Adults older than 75 years are at particular risk for hospitalization and death from TBI. Falls, motor vehicle accidents, and accidental blows to the head are the leading mechanisms of injury in this population. Prevention of these events is an essential aspect of geriatric medicine. See MKSAP 18 General Internal Medicine for more information.

Patients Receiving Anticoagulation

H

Anticoagulation is associated with an increased risk of intracranial hemorrhage after trauma. Intracranial hemorrhage in patients treated with warfarin has significant morbidity and a mortality as high as 50%; immediate correction of the INR limits hematoma expansion. Reversal of direct-acting anticoagulant agents with specific reversal agents, if available, also should be performed. The reinitiation of anticoagulation after intracranial hemorrhage is clinically challenging and is supported by scant empirical evidence. Hemorrhagic complications in this population appear to be greatest within the first 24 hours of injury, and the risk of thromboembolism is highest between days 3 through 5 after injury. For patients with lower risk of hematoma expansion (such as younger patients or those whose hemorrhage is small in size) and higher risk of thromboembolism (such as those with a mechanical heart valve), the optimal time to resume anticoagulation may be 72 hours after trauma. H

Seizures and Epilepsy

Clinical Presentation of Seizures

Epilepsy is defined as at least two unprovoked seizures more than 24 hours apart, or one unprovoked seizure with a risk of further seizures that is similar to the risk after two unprovoked seizures (at least 60%). The term "epileptic seizure" does not imply that the seizure is related to epilepsy; rather, it means that the seizure is "real"—that is, secondary to abnormal electrical activity in the brain and not to some other cause (such as syncope or psychiatric disease). The diagnosis of an epileptic seizure relies on a detailed patient history. The stereotyped nature of clinical events is characteristic of seizures; symptom variability from event to event suggests an alternative diagnosis. Epilepsy usually requires antiepileptic drug (AED) therapy, but isolated seizures may not, especially if provoked by reversible or preventable causes. The terminology of seizures is evolving, with more descriptive terms suggested as replacements for "simple partial seizures" and "complex partial seizures" (**Figure 4**).

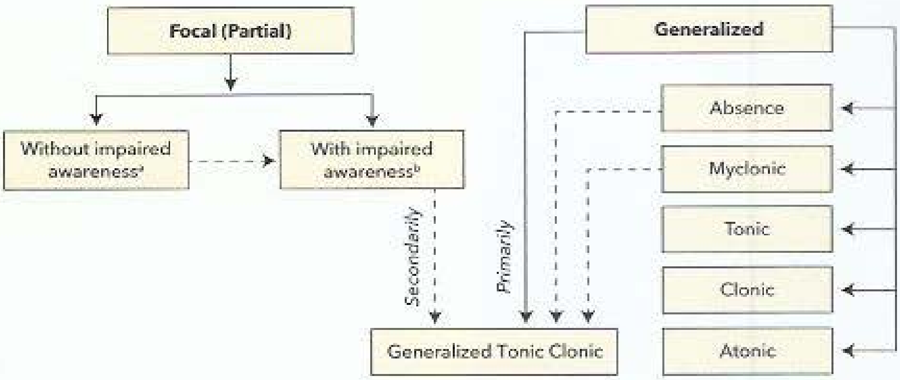

FIGURE 4. Common seizure types based on International League Against Epilepsy classification. The dashed arrows represent the possibility of one seizure type transitioning directly into another when a patient is seizing. Note that generalized tonic clonic seizures may start out focal or generalized.

[a]Formerly known as simple partial seizures.

[b]Formerly known as complex partial or focal dyscognitive seizures.

Focal Seizures

Focal seizures may occur without alteration of awareness (formerly, simple partial seizures) or with alteration of awareness (formerly, complex partial seizures). The first type includes auras, which are not just warning symptoms but actually very localized focal seizures (**Table 14**). Seizures involving impaired awareness may affect memory, responsiveness, language, or cognition. Both focal seizures and generalized absence seizures can present as "staring episodes" and must be carefully differentiated (**Table 15**).

Patients may not remember or volunteer a history of focal seizures because they may be unaware of the events. Therefore, it is important to ask about discrete episodes of memory loss or time lapses. A typical temporal lobe seizure, for example, may start with an aura of a rising feeling in the stomach, déjà vu, or fear, followed by altered awareness with staring, arrest of speech or behavior, and semipurposeful repetitive movements, called automatisms. Focal seizures also may present with autonomic symptoms, such as palpitations, sweating, and hot flashes. Whereas these symptoms also can be seen with psychiatric and cardiac disorders, focal seizures will typically have sudden onset, stereotyped symptoms, and a short duration.

Generalized Seizures

Generalized tonic-clonic seizures (GTCS) have a characteristic pattern of tonic activity followed by clonic activity. During the tonic phase, eyes are wide open while the entire body stiffens, and typically there is a single loud groan or "ictal cry" (not actual crying or sobbing). During the clonic phase, rhythmic jerking occurs synchronously in all limbs, initially at high frequency, with eventual slowing and cessation. This movement often is followed by stertor (deep, slow snoring). A postictal state with confusion, hypersomnolence, and fatigue is common and can persist for hours or even a day.

GTCS may be generalized at onset and are considered to be primarily generalized seizures. These may be preceded by

TABLE 14. Examples of Focal Seizures Without Altered Awareness[a]

Lobe	Clinical Presentation
Frontal	Focal contralateral motor activity (clonic jerking)
Temporal	Epigastric rising sensation (nausea, butterflies); aphasia; déjà vu; fear; elation; auditory, olfactory[b], and gustatory[b] sensations
Parietal	Focal contralateral pain, numbness, or paresthesias
Occipital	Contralateral homonymous visual loss or nonformed hallucinations (dots, lines, flashes of light)

[a]Formerly known as simple partial seizures, which includes auras.

[b]Altered smell and taste also can be seen in psychogenic nonepileptic events.

TABLE 15. Clinical Differentiation of Seizure Types Presenting As Staring Episodes

Seizure Feature	Absence Seizure	Focal Seizure With Altered Awareness[a]
Aura	No	Possible
Onset	Abrupt	Gradual or abrupt
Duration	<15 s	>30 s
Termination	Abrupt	Usually gradual
Postictal state	Normal	Lethargy, confusion
Frequency	Multiple daily	Once weekly or monthly
Precipitated by hyperventilation	Usually	Unlikely
Associated seizure types	Generalized onset seizures (myoclonic, primarily generalized tonic-clonic, tonic, atonic)	Focal onset seizures (simple partial or secondarily generalized tonic-clonic)

[a]Formerly known as complex partial seizure, or focal dyscognitive seizure.

other generalized events, such as absence or myoclonic seizures. Alternatively, GTCS may start as focal seizures with subsequent spread to both hemispheres (secondarily generalized). Aura or automatisms before GTCS and postictal unilateral weakness (Todd paralysis) suggest a focal onset.

Absence seizures are characterized by brief episodes of staring (see Table 15). Many patients are unaware of these seizures. They may occur as the only seizure type in school-age children and are often confused with attention deficit disorder. In adulthood, absence seizures most often occur in combination with other generalized seizure types, such as GTCS or myoclonic seizures.

Myoclonus is a single quick jerk of a limb or the entire body lasting less than a second and is not always associated with a seizure (see Movement Disorders). A diagnosis of myoclonic seizures can be confirmed by electroencephalography (EEG), with each jerk associated with a generalized spike-and-wave discharge (**Figure 5**). Myoclonic seizures also can occur repetitively and result in falls. Awareness is maintained and duration is very short (<1 second), which differentiates myoclonic seizures from GTCS.

Tonic seizures present as episodes of increased muscle tone, ranging from mild extension of the arms and head to a more severe stiffening of the entire body. Atonic seizures present with sudden loss of muscle tone. Both tonic and atonic seizures occur with no warning, last a few seconds, and cause altered awareness, which often leads to falls and physical injuries; they lack postevent confusion. Prolonged episodes of increased or decreased tone with long duration of loss of consciousness are unlikely to represent seizures.

KEY POINTS

- Epilepsy is defined as at least two unprovoked seizures more than 24 hours apart, or one unprovoked seizure with a risk of further seizures that is similar to the risk after two unprovoked seizures (at least 60%).
- Focal seizures may present with autonomic symptoms, such as palpitations, sweating, and hot flashes, but will have sudden onset, stereotyped symptoms, and a short duration, which differentiate them from psychiatric and cardiac disorders.
- Generalized seizures consist of tonic-clonic, absence, myoclonic, tonic, and atonic seizures.

Epilepsy Syndromes

Focal Epilepsies

Identifiable causes of focal epilepsies include structural lesions, such as mesial temporal sclerosis, cavernous

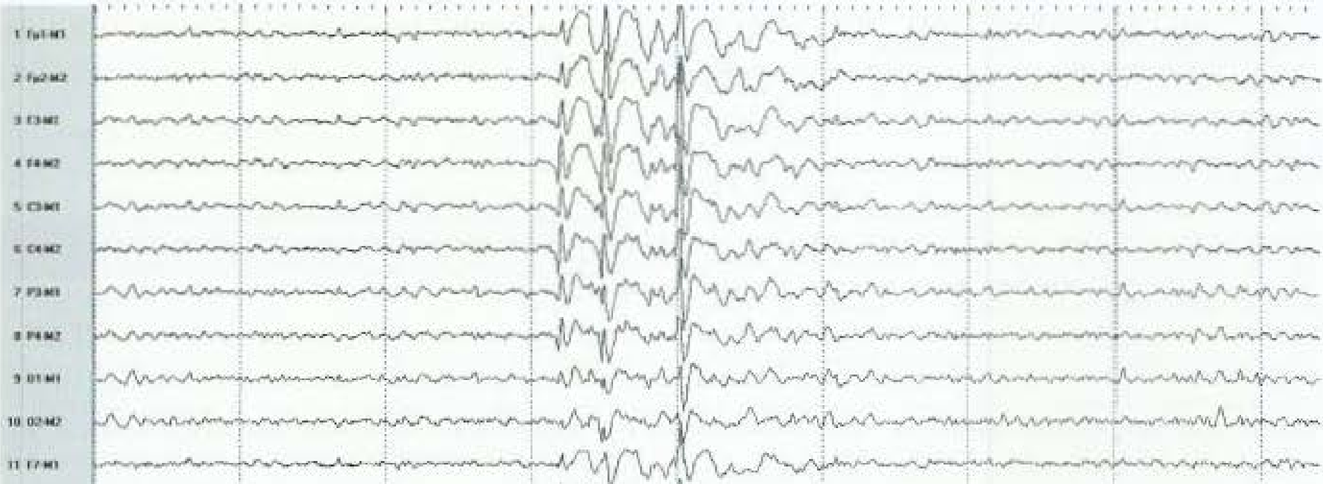

FIGURE 5. Electroencephalogram showing generalized spike-and-wave discharges. In an appropriate clinical setting, this strongly supports a diagnosis of generalized epilepsy.

malformations, cortical dysplasia, traumatic brain injury, stroke, and tumors, all of which may be seen on MRI (**Figure 6** and **Figure 7**). EEG may show focal spikes or sharp waves in the appropriate brain region (**Figure 8**). In most adults with focal epilepsy, however, brain MRI is normal and the cause is unknown.

Temporal lobe epilepsy is the most common adult onset focal epilepsy. Typical symptoms include aura, loss of awareness, staring, behavior arrest, and amnesia. Automatisms, repetitive semipurposeful movements (such as lip smacking, chewing, and swallowing), and picking or grabbing movements with the ipsilateral arm are common. Speech arrest may be seen with involvement of the dominant hemisphere. Mesial temporal sclerosis with hippocampal atrophy is the most common cause of medication resistant adult onset focal epilepsy.

KEY POINTS

- Temporal lobe epilepsy is the most common adult onset focal epilepsy; typical symptoms include aura, loss of awareness, staring, behavior arrest, and amnesia.
- Mesial temporal sclerosis with hippocampal atrophy is the most common cause of medication-resistant adult-onset focal epilepsy.

FIGURE 7. Focal cortical dysplasia with periventricular nodular heterotopia. Coronal MRI showing a focal area of thickened cortex in the right temporal region (*thick arrow*) and nodules of abnormal neuronal tissue along the ventricular surface (*thin arrow*).

FIGURE 6. Mesial temporal sclerosis. The coronal fluid-attenuated inversion recovery MRI shows increased signal intensity and atrophy of the left mesial temporal lobe (*arrow*).

Idiopathic (Genetic) Generalized Epilepsies

Idiopathic epilepsy is "pure" epilepsy without an underlying neurologic disorder. Newer classification schemes call this type of epilepsy "genetic," even in the absence of a positive family history, inheritability, or a single identifiable gene. In adults, juvenile myoclonic epilepsy (JME) is the most common form of idiopathic generalized epilepsy. JME seizures often are called "college seizures" because of the age of onset (teens or twenties) and associated triggers (sleep deprivation, alcohol use, and stress). Epilepsy may not be diagnosed until the first GTCS occurs because myoclonic seizures often remain unrecognized by patients, family, or friends until a physician takes a careful and complete history.

The presence of myoclonic seizures is required for the diagnosis of JME; patients may report dropping items from their hands, commonly a coffee cup or hairbrush, because myoclonic seizures in JME generally occur in the morning. Most affected patients have GTCS, and approximately 30% of patients have absence seizures. Patients are usually otherwise neurologically healthy and can live relatively normal lives because seizures are often controlled with one or two AEDs. Brain MRI is typically normal, and EEG may show generalized spike-and-wave discharges (see Figure 5). Lifelong AED therapy is typically required.

FIGURE 8. Electroencephalogram showing focal (left temporal) sharp waves. In an appropriate clinical setting, this strongly supports a diagnosis of temporal lobe epilepsy.

KEY POINTS

- The presence of myoclonic seizures is required for the diagnosis of juvenile myoclonic epilepsy (JME); JME often is not diagnosed, however, until the first generalized tonic-clonic seizure occurs because myoclonic seizures often remain unrecognized by patients, family, or friends until a physician takes a careful and complete history.
- Lifelong antiepileptic drug therapy is typically required for patients with juvenile myoclonic epilepsy.

Diagnostic Evaluation of Seizures and Epilepsy

Initial Approach to the Patient With a First Seizure

For any patient with a first seizure, obtaining a detailed history is crucial to distinguish seizures from other causes of symptoms. The distinction between seizure and nonseizure events and clarification of first-time versus recurrent episodes are key. A history of previous staring events or myoclonus may help identify patients with epilepsy and should be specifically sought out through careful questioning.

KEY POINT

- Obtaining a detailed history is critical in differentiating seizures from other causes of symptoms; a history of previous staring events or myoclonus may help identify patients with epilepsy.

Differential Diagnosis of Seizures

Many episodic disorders mimic seizures but are nonepileptic events. These include syncope, migraine, movement disorders (tremor, tics), sleep disorders, stroke, and psychogenic events. Seizures usually have positive symptoms, such as jerking, tingling, and visual flashes, whereas strokes have negative symptoms, such as weakness, numbness, and loss of vision. Normal mentation with a headache after the episode suggests migraine. Occurrence only in public suggests panic disorder with agoraphobia.

Associated lightheadedness or chest pain may suggest syncope or cardiac disease. Syncope often presents with shaking ("convulsive syncope") and must be differentiated from GTCS (**Table 16**). In one study, more than 90% of healthy volunteers had nonepileptic myoclonus (generalized or multifocal) when syncope was induced; only a minority had classic, motionless syncope. For distinguishing seizures from syncope

TABLE 16. Clinical Differentiation of Generalized Tonic-Clonic Seizures and Syncope

Seizure Feature	Generalized Tonic-Clonic Seizures	Syncope
Warning symptoms	Typical epileptic aura immediately before onset	Prodrome of lightheadedness, nausea, warmth, diaphoresis, blurred or tunnel vision, generalized weakness, palpitations, and a "faint" feeling
Self-protection	Aura may or may not be long enough to ensure patient safety, but seizure is not preventable	Lying or sitting down may prevent progression to LOC
Muscle tone	Generalized stiffening	Generalized loss of tone
Motor activity	Generalized clonic shaking (rhythmic, synchronous whole-body jerks)	Generalized myoclonic shaking (whole-body shaking or isolated subtle twitching of limbs)
Color	May have cyanosis	May have pallor
Duration of LOC	Usually >1 minute	Usually <1 minute
Postictal state	Confusion, lethargy, combativeness, somnolence	Normal, an other than situationally appropriate memory loss of event

LOC = loss of consciousness.

and psychogenic loss of consciousness, video EEG can be very useful, in combination with tilt-table testing, because it can specifically differentiate these events. H

H CONT.

Psychogenic Nonepileptic Spells/Events

Psychogenic nonepileptic spells/events (PNES) were formerly called pseudoseizures or psychogenic nonepileptic seizures. These latter terms should be avoided because seizure is a misnomer in this context, and "pseudo" implies falseness of the symptoms. PNES are most often related to posttraumatic stress disorder or conversion disorder. Factitious disorder and malingering are rare. Patients often have a history of military combat, sexual or physical abuse, chronic medical illness, or prominent life stressors. PNES often mimic GTCS, but certain features help distinguish the diagnoses (Table 17). Event capture during video EEG monitoring usually is required to confirm the diagnosis.

KEY POINT

- Psychogenic nonepileptic spells/events are most often related to posttraumatic stress disorder or conversion disorder; factitious disorder and malingering are rare.

Diagnostic Evaluation

H

Neuroimaging is recommended for all patients with a first seizure. CT of the head is adequate initially to rapidly exclude emergent pathology, including hemorrhage, but MRI is required in most patients. Contrast-enhanced CT or MRI may be deferred unless infection, tumor, or vascular lesions are suspected. Because temporal lobe epilepsy is common, MRI sequences focusing on the hippocampus and temporal lobes are useful (coronal T2-weighted, fluid-attenuated inversion recovery, and

TABLE 17. Clinical Differentiation of GTCS and PNES

Seizure Feature	GTCS	PNES
Stereotyped	Yes	No (varies from event to event)
Eyelids	Open	Closed (may resist opening)
Color	May have cyanosis	May turn red
Vocalization	Ictal cry (sharp, loud, deep single inspiration against contracted epiglottis)	Intermittent breath holding alternating with gasping/rapid breaths, or crying/sobbing
Muscle tone	Starts with stiffening of all limbs (tonic)	Patients usually limp or limber; may resist movement or make atypical postures (fists, claws)
Motor activity	Synchronous shaking of all limbs (clonic)	Asynchronous flailing of variable limbs, side-to-side head shaking, pelvic thrusting[a]
Motor pattern	Shaking starts at high frequency and gradually slows down	Shaking may speed up or vary in frequency
Duration	Usually ends within <5 min	Prolonged, or waxes and wanes over >5 min or even hours
Consciousness/memory	Impaired/lost	May be retained (may hear or remember but not respond)
Postictal state	Confused, lethargic	May have relatively normal mental status despite high frequency of "seizures"
Postictal breathing	Slow, deep, loud, snoring-like stertor	Normal or rapid panting

GTCS = generalized tonic-clonic seizure; PNES = psychogenic nonepileptic spell/event.

[a]These typically psychogenic symptoms may be seen in true epileptic frontal lobe seizures.

thin-slice T1-weighted imaging). Functional imaging (PET and single-photon emission CT) is considered when planning for epilepsy surgery but is not routinely indicated.

Outpatient EEG also is recommended in patients with a first seizure. Because capture of an actual seizure is unlikely, the physician must rely on "epileptiform" abnormalities, such as focal sharp waves (see Figure 8) or generalized spike-and-wave discharges (see Figure 5). These findings are considered relatively specific for epilepsy; although not diagnostic, they may help support the diagnosis in an appropriate clinical context. A single routine EEG is only 40% to 50% sensitive for such findings, but the yield can increase to 80% to 90% with repeated studies, prolonged studies, and studies that capture sleep.

MRI and EEG can be performed at a follow-up evaluation, but the yield of EEG is higher within 24 hours of GTCS. Emergent lumbar puncture is recommended in adults only if an infectious cause, such as meningitis or encephalitis, is suspected.

Epilepsy Monitoring Units

A normal EEG does not rule out epilepsy. Capturing events during continuous 24-hour video EEG monitoring is the gold standard in diagnosis. Continuous video EEG monitoring is performed in an epilepsy monitoring unit during a multiple-day elective hospitalization during which AEDs are decreased or withdrawn under close supervision. Patients who have not responded to two adequately dosed AEDs are considered to have refractory disease (see Intractable Epilepsy and Epilepsy Surgery) and also should be referred to an epilepsy center, where evaluation in an epilepsy monitoring unit can both confirm the diagnosis of epilepsy and determine candidacy for epilepsy surgery.

Other Continuous Electroencephalographic Monitoring

Continuous video EEG monitoring also is useful in the ICU (**Table 18**). It can determine if episodic events are truly seizures, particularly in sedated or confused patients who cannot provide a history. This type of EEG additionally is the only method of diagnosing nonconvulsive status epilepticus.

TABLE 18. Indications for Immediate Continuous Video Electroencephalographic Monitoring in the Critical Care Setting

AMS following CSE or clinical seizures
AMS with acute brain injury (such as hemorrhage, trauma, infection, stroke, hypoxia, cardiac arrest)
Unexplained AMS with subacute or chronic brain injury (tumor, history of epilepsy)
Unexplained AMS (or mental fluctuation) without acute brain injury (as in sepsis)
Unexplained AMS following a CNS procedure or CNS instrumentation
Pharmacologic coma and paralysis that limit the ability to perform a neurologic examination (as is used with therapeutic hypothermia, ECMO)
Clinical episodes concerning for seizures (such as unexplained muscle or eye movements)[a]

AMS = altered mental status; CNS = central nervous system; CSE = convulsive status epilepticus; ECMO = extracorporeal membrane oxygenation; EEG = electroencephalography.

[a]If CSE is suspected, treatment should begin before EEG is performed or results are available; if nonconvulsive status epilepticus is suspected, treatment most often should await EEG results.

KEY POINTS

HVC
- MRI and electroencephalography are recommended for all patients with a first seizure; lumbar puncture is recommended only if an infectious cause is suspected.
- A single routine electroencephalographic study is only 40% to 50% sensitive in diagnosing epilepsy, but the yield can increase to 80% to 90% with repeated studies, prolonged studies, and studies that capture sleep.
- Electroencephalography is the only method of diagnosing nonconvulsive status epilepticus.

Provoked, Unprovoked, and Triggered Seizures

Provoking factors, risk factors, and triggers all can all lead to seizures (**Table 19**), and differentiating among them is essential. Provoking factors can cause seizures in patients with or without epilepsy; avoidance of these provocations should prevent further seizures. Particular attention should be paid to the patient's medications, and drugs that can cause a seizure or lower seizure threshold (such as tramadol, meperidine, bupropion, fluoroquinolones, carbapenems, and cefepime) should be avoided. Risk factors increase the chance of developing epilepsy later in life; however, an acute symptomatic seizure (such as a seizure occurring in the first week after traumatic brain injury, stroke, or meningitis) may not necessarily lead to the development of epilepsy. Although triggers lead to seizures in patients with epilepsy, they are not the cause of epilepsy (and are not considered provoking factors).

Determining the risk of recurrence guides the decision to treat. The 2-year recurrence risk after a single unprovoked seizure is approximately 40%. Risk is lower (20%-30%) if there are no epilepsy risk factors and the MRI and EEG are normal. A first unprovoked seizure is often not treated; although treatment may reduce the risk of seizure over the next 2 years, it does not change a patient's long-term prognosis for developing epilepsy. In the setting of two unprovoked seizures or one unprovoked seizure with significant EEG or MRI abnormalities, recurrence risk is at least 60%, and treatment is recommended.

KEY POINTS

HVC
- After a single unprovoked seizure with no abnormalities on MRI or electroencephalography and with no risk factors for epilepsy, the 2-year recurrence risk is approximately 20% to 30%, and treatment is often withheld.
- In the setting of two unprovoked seizures or one unprovoked seizure with significant electroencephalographic or MRI abnormalities, the recurrence risk is at least 60%, and treatment is recommended.

TABLE 19. Potential Causes of Seizures or Epilepsy

Seizure-Provoking Factors	Epilepsy Risk Factors	Seizure Triggers
Hypo- or hypernatremia	Febrile seizures	Sleep deprivation[b]
Hypo- or hypercalcemia	Family history (especially first-degree relatives)	Fever
Hypomagnesemia	Past meningitis/encephalitis	Emotional stress
Hypoglycemia	History of structural brain lesion (such as stroke, tumor)	Acute infection (nonneurologic)
Hyperammonemia or hepatic failure	Past significant head trauma (loss of consciousness or amnesia >30 min, penetrating skull injury)	Hyperventilation
Uremia or kidney failure	Preterm birth	Photic stimulation
Acute head trauma, meningitis, encephalitis, stroke, or hypoxia/ischemia	Birth injury, asphyxia, or stroke	Music, reading, eating (only in specific reflex epilepsies)
Alcohol intoxication or withdrawal	Neurologic developmental delay	
Recreational drug use	Intellectual disability	
Benzodiazepine withdrawal	History of brain surgery	
Baclofen withdrawal		
Fluoroquinolones		
Carbapenems		
Cefepime		
Metronidazole		
Tramadol		
Meperidine		
Morphine		
Bupropion		
Clozapine[a]		
Lithium[a]		
Tricyclic antidepressants[a]		
Typical antipsychotic agents[a]		

[a]Can be used in patients with epilepsy, if needed.

[b]Typically does not trigger seizures in patients without epilepsy and is not considered a provoking factor.

Treatment of Epilepsy

Antiepileptic Drug Therapy

Empiric pharmacologic treatment generally is not recommended unless the patient's history is strongly suggestive of seizures or epilepsy. The exception is convulsive status epilepticus, which must be treated emergently if clinically suspected. Similarly, prophylactic treatment is avoided except in specific situations, such as during the week after severe head trauma or brain tumor resection. Alcohol or benzodiazepine withdrawal seizures typically are not treated with AEDs.

Selection and Adverse Effects of Antiepileptic Drugs

Many AEDs are available for patients with epilepsy (**Table 20**). Newer AEDs, although not more effective in controlling seizures than older AEDs, are often preferred because they have fewer adverse effects, fewer drug interactions, and a reduced need for laboratory monitoring. The higher cost and shorter length of experience with the newer AEDs are disadvantages. Most often, treatment is guided by the seizure type rather than AED mechanism or epilepsy cause. When a patient has GTCS and focal onset is not certain, a broad-spectrum AED should be used. Focal seizure medications are also used for secondarily generalized seizures.

Most dangerous AED toxicities (rash, pancytopenia, hepatotoxicity) are idiosyncratic and not necessarily dose related. **Table 21** lists common adverse effects and laboratory monitoring recommendations. Key dose-dependent adverse effects include oxcarbazepine-related hyponatremia and valproic acid-related thrombocytopenia. Hyponatremia is a particular concern with oxcarbazepine and carbamazepine in older patients, especially with concomitant diuretic use. Enzyme-inducing AEDs (**Table 22**) increase statin clearance and necessitate higher doses or alternative options; they also can increase bone catabolism. Therefore, bone density testing and

TABLE 20. Spectrum of Use of Antiepileptic Drugs

Population	First-Line Agent	Second-Line Agent	Considerations
Patients with focal seizures	Lamotrigine Levetiracetam Oxcarbazepine	Carbamazepine Gabapentin Pregabalin Topiramate Zonisamide	Includes treatment of secondarily generalized tonic-clonic seizures
Patients with generalized seizures	Ethosuximide (absence only) Lamotrigine (may worsen myoclonic seizures) Levetiracetam Valproate	Topiramate Zonisamide	May be worsened by gabapentin, pregabalin, carbamazepine, and oxcarbazepine
Woman of childbearing age	Lamotrigine Levetiracetam	Oxcarbazepine	Avoid carbamazepine, phenobarbital, phenytoin, topiramate, and valproate
Older patients	Gabapentin Lamotrigine Levetiracetam		Higher risk for hyponatremia with carbamazepine and oxcarbazepine, especially with concomitant diuretics

TABLE 21. Adverse Effects of Selected Antiepileptic Drugs and Recommended Laboratory Monitoring

Drug	Common Adverse Effects	Serious Adverse Effects	Recommended Laboratory Monitoring
Phenobarbital	Sedation (but paradoxical hyperactivity in children)	Rash, pancytopenia, osteoporosis, hepatotoxicity	CBC, liver chemistry studies, bone density, serum drug level
Phenytoin	Sedation, nausea, ataxia, tremor, diplopia, imbalance, headache, and dose-dependent dizziness; if given IV, tissue necrosis (with extravasation), bradycardia, hypotension, and asystole	Rash, gingival hyperplasia, cerebellar atrophy, peripheral neuropathy, pancytopenia, osteoporosis, hepatotoxicity	CBC, liver chemistry studies, bone density, serum drug level
Valproic acid	Sedation, nausea, ataxia, tremor, diplopia, imbalance, headache, and dose-dependent dizziness; weight gain, hair loss, PCOS, and reversible parkinsonism with dementia	Pancytopenia, osteoporosis, hepatotoxicity, pancreatitis, hyperammonemia	CBC, liver chemistry studies, bone density, serum drug level, serum ammonia level in select cases
Carbamazepine and oxcarbazepine	Sedation, nausea, ataxia, tremor, diplopia, imbalance, headache, and dose-dependent dizziness	Hyponatremia, rash, pancytopenia, osteoporosis, hepatotoxicity	CBC, liver chemistry studies, bone density, serum drug level
Felbamate	Insomnia, weight loss, nausea, vomiting, and diarrhea	Aplastic anemia and hepatotoxicity[a]	CBC, liver chemistry studies
Lamotrigine	Sedation, nausea, ataxia, tremor, diplopia, imbalance, headache, insomnia, and dose-dependent dizziness	Rash	Serum drug level
Gabapentin and pregabalin	Sedation, weight gain, edema, and dose-dependent dizziness	—	—
Topiramate and zonisamide	Sedation, nausea, ataxia, tremor, diplopia, imbalance, headache, word finding difficulty, poor concentration, paresthesias, weight loss, anhidrosis, and dose-dependent dizziness	Nephrolithiasis, acute angle glaucoma, psychosis	BMP in select cases
Levetiracetam	Sedation, irritability, psychosis, and depression	Suicidal ideation[b] and thrombocytopenia (rare)	—
Tiagabine	Sedation, nausea, ataxia, tremor, diplopia, imbalance, headache, and dose-dependent dizziness	Acute confusion and encephalopathy	—
Lacosamide	Sedation, nausea, ataxia, tremor, diplopia, imbalance, headache, dose-dependent dizziness, and PR-interval prolongation	Atrioventricular block, atrial fibrillation	Electrocardiography
Perampanel	Dizziness, headache, and sedation	Homicidal ideation	—

BMP = basic metabolic profile; CBC = complete blood count; IV, intravenously; PCOS = polycystic ovary syndrome.

[a]A serious and potentially fatal adverse effect that limits this drug's use (and requires close monitoring).

[b]A concern with all antiepileptic drugs, but especially levetiracetam.

TABLE 22. Key Pharmacologic Issues with Selected Antiepileptic Drugs

Inducers of Hepatic Enzymes[a,b]	Inhibitors of Hepatic Enzymes[a]	Requires Dose Adjustment in Kidney Dysfunction	Avoid in Hepatic Dysfunction	Highly Albumin Bound[c]	No Significant Drug-Drug Interactions
Carbamazepine	Valproate	Gabapentin	Carbamazepine	Phenytoin	Levetiracetam
Oxcarbazepine		Pregabalin	Phenytoin	Valproate	Lacosamide
Phenobarbital		Levetiracetam	Phenobarbital		Gabapentin
Phenytoin			Valproate		Pregabalin
Topiramate					Zonisamide

[a]May cause osteoporosis and interact with lamotrigine.

[b]May decrease statin and oral contraceptive efficacy.

[c]Warrants checking unbound (free) blood level, especially in kidney failure and hypoalbuminemia.

supplementation of calcium and vitamin D are recommended with enzyme-inducing AEDs (and with valproic acid).

Phenytoin, carbamazepine, phenobarbital, and lamotrigine are AEDs that commonly cause rash, which usually resolves with discontinuation of the drug. AED-related rashes, however, are sometimes severe and life threatening. For example, rapid titration of lamotrigine has been associated with the development of Stevens-Johnson syndrome, toxic epidermal necrolysis, and drug reaction with eosinophilia and systemic symptoms. These AEDs also should be avoided in patients of Asian heritage unless testing for genetic predisposition (presence of HLA-B*1502 allele) is negative. Nevertheless, lamotrigine is one of the most safe and effective AEDs used today, when titrated slowly.

All AEDs carry a warning about worsening depression and suicidality, and all patients must be screened and monitored for these symptoms. Levetiracetam may cause depression, anxiety, anger, or agitation. Perampanel may cause homicidal ideation. Topiramate may cause psychosis. Lamotrigine and valproic acid, on the other hand, are known to be mood stabilizing.

Monitoring and Discontinuing Antiepileptic Drugs

Measuring serum levels of certain AEDs (phenytoin, carbamazepine, valproic acid, phenobarbital, oxcarbazepine, lamotrigine) is useful, given their known therapeutic windows and predictable dose-related adverse effects. However, in a patient whose epilepsy is well controlled without clinical adverse effects, dose reduction because of high levels usually is not warranted.

Generic AEDs are appropriate for most patients, given recent guidelines. Well-designed studies have not shown differences in AED bioequivalence (on the basis of FDA standards) when switching between generic drugs or switching from a brand to a generic drug for patients with epilepsy. Generic substitution reduces cost and does not compromise efficacy. Patients need to be informed of changes in the color and shape of pills.

In addition, phenytoin, carbamazepine, and valproic acid do not have a 1:1 conversion between immediate-release and extended-release formulations. Monitoring for AED toxicity and seizures is advised if a change is made.

Tapering of AEDs can be considered in patients remaining seizure free for at least 2 to 5 years. The best predictor of seizure freedom is time; a prolonged period of seizure freedom predicts further seizure freedom. Factors prohibiting AED weaning include the presence of JME, a history of difficulties in early seizure control, and the presence of significant epilepsy risk factors (see Table 19). Relevant MRI abnormalities, significant EEG abnormalities (especially when not taking AEDs), risk of physical injury, and loss of driving privileges (if unacceptable to the patient) are additional considerations. There are no accepted standards for tapering schedules for AEDs.

KEY POINTS

- Newer antiepileptic drugs (AEDs), although not more effective in controlling seizures than older AEDs, are often preferred because they have fewer adverse effects, fewer drug interactions, and a reduced need for laboratory monitoring.
- Epilepsy treatment usually is guided by the seizure type rather than drug mechanism or epilepsy cause.
- Enzyme-inducing antiepileptic drugs increase statin clearance and thus necessitate higher doses or alternative options; because they also can increase bone catabolism, bone density testing and supplemental calcium and vitamin D are recommended.
- Tapering of antiepileptic drugs can be considered in most patients who remain seizure free for 2 to 5 years; factors prohibiting weaning include the presence of juvenile myoclonic epilepsy, a history of difficulties in early seizure control, and the presence of significant epilepsy risk factors.

Counseling and Lifestyle Adjustments

All patients experiencing a seizure, even a single provoked seizure, must be instructed about seizure precautions, including driving restrictions. Most states restrict driving in patients with any episode of altered awareness or motor control, with the restriction varying by state from 3 to 12 months (see www.epilepsy.com/driving-laws). Additionally, patients should avoid common triggers and provoking factors (see Table 19). Most patients with epilepsy can work, even if they are not completely seizure free. Patients should avoid operating heavy machinery, using firearms, lifting more than 9 kg (20 lb), taking tub baths, swimming in unsupervised locations, and being near open flames or heights (such as rooftops).

Comorbidities and Complications of Epilepsy

Sudden Unexpected Death in Epilepsy Patients

Besides the risk of trauma, asphyxia, and death from a seizure or status epilepticus, epilepsy patients are at risk for unexplained death. This risk is approximately 1 in 1000 and increases to approximately 1 in 100 in patients with intractable seizures, especially those with uncontrolled GTCS and those taking multiple AEDs. Mechanisms are unknown and may involve cardiac, respiratory, and autonomic dysregulation. Studies show that patients prefer to discuss sudden unexplained death in epilepsy openly; doing so can encourage medication adherence and home safety planning (such as using webcams and bed monitors and sharing of bedrooms).

KEY POINT

- The risk of sudden unexpected death in epilepsy is approximately 1 in 1000 and increases to approximately 1 in 100 in patients with intractable seizures, especially those with uncontrolled generalized tonic clonic seizures and those taking multiple antiepileptic drugs.

Intractable Epilepsy and Epilepsy Surgery

Any patient who does not achieve seizure freedom for at least 1 year after treatment with two adequately dosed, appropriately chosen AEDs is considered to have medically intractable (drug-resistant) epilepsy and should be referred to an epilepsy center to both confirm the diagnosis and evaluate the patient for surgical candidacy, starting with video EEG monitoring. The chance of achieving seizure control from additional medications (a regimen of three or more AEDs) is less than 10%; therefore, other treatment options must be considered. In appropriately chosen surgical candidates, especially those with temporal lobe epilepsy due to mesial temporal sclerosis, resection can lead to seizure freedom in 60% to 70% of patients. Implantable vagus nerve stimulators and the ketogenic diet are available palliative therapies but do not result in complete seizure control.

KEY POINT

- Any patient who does not achieve seizure freedom after treatment with two adequately dosed, appropriately chosen antiepileptic drugs is considered to have medically intractable (drug-resistant) epilepsy and should be referred to an epilepsy center to both confirm the diagnosis and evaluate the patient for surgical candidacy.

Seizures and Epilepsy in Specific Populations

Older Adults

Incidence of new-onset epilepsy is highest in older adults (age > 60 years). Because recurrence after a new-onset seizure in this age group is more likely (50% to 60%) than in younger adults (40%), treatment after one seizure is sometimes considered. Major risk factors for seizure recurrence include stroke and dementia. Older adults usually require lower AED doses and are at increased risk of interactions and decreased drug clearance. Data suggest that levetiracetam, lamotrigine, and gabapentin are better tolerated and no less effective when compared with older AEDs. Valproic acid should be avoided because it can cause (reversible) parkinsonism and cognitive dysfunction.

KEY POINT

- In older patients, levetiracetam, lamotrigine, and gabapentin are better tolerated and no less effective when compared with older antiepileptic drugs.

Patients with Organ Failure

In patients with epilepsy and chronic kidney disease, dosages of levetiracetam, gabapentin, and pregabalin must be reduced because decreased clearance can lead to toxicity. Phenytoin is highly albumin bound; dosage should be reduced, and free (unbound) levels should be monitored. Gabapentin and pregabalin can cause encephalopathy and nonepileptic myoclonus, thus mimicking seizures. Valproic acid is typically avoided in patients with hepatic insufficiency. Because topiramate and zonisamide can cause acidosis and nephrolithiasis, they also should be avoided in patients with a predisposition to these disorders.

KEY POINT

- In patients with epilepsy and chronic kidney disease, dosages of levetiracetam, gabapentin, and pregabalin must be reduced, because decreased clearance can lead to toxicity.

Posttraumatic Epilepsy

H AEDs are prophylactically given during the first week after severe head trauma (loss of consciousness > 12-24 hours, intracranial hemorrhage, depressed skull fracture, or brain contusion) to prevent acute seizure complications (hemorrhage, edema, or elevated intracranial pressure). As with acute stroke, such treatment does not reduce the risk of developing epilepsy later, and prophylaxis beyond 1 week is not recommended. H

A single unprovoked seizure that occurs more than 1 month after a stroke or significant head trauma has a high enough recurrence risk to be considered epilepsy and requires treatment. Patients with a history of moderate or severe head trauma (skull fracture, penetrating head injury, or loss of consciousness > 30 minutes) are at increased risk of epilepsy.

Returning combat veterans who develop seizures require careful evaluation, often including video EEG monitoring. Many have had head trauma and are at increased risk for epilepsy, but many also have posttraumatic stress disorder and may have PNES. Assuming a diagnosis of epilepsy and empirically treating the patient can be detrimental, especially because veterans tend to have a delay in the diagnosis of PNES compared with the general population.

KEY POINTS

- Antiepileptic drugs are prophylactically given during the first week after severe head trauma (loss of consciousness > 12-24 hours, intracranial hemorrhage, depressed skull fracture, or brain contusion).
- A single unprovoked seizure that occurs more than 1 month after a stroke or significant head trauma has a high enough recurrence risk to be considered epilepsy and requires treatment.

Women with Epilepsy

Women with epilepsy may experience catamenial seizures (related to menstrual cycle), which may occur around menstruation or ovulation or because of an inadequate luteal phase. Some studies suggest adding progestin-containing oral contraceptives or acetazolamide to the AED regimen, but oophorectomy is not recommended to improve seizure control.

Reproductive Issues

Findings from various studies are contradictory about whether women with epilepsy have decreased fertility rates. Valproic acid, however, is associated with anovulation and polycystic ovary syndrome.

Pregnancy and Nursing

Most women with epilepsy have normal, healthy children. The rate of major congenital malformations (MCMs) in untreated women with epilepsy is likely similar to that of the general population. All women with epilepsy who are of childbearing age and are taking AEDs should receive preconception counseling and folate supplementation. Women with epilepsy who take AEDs are unlikely to have an increased risk of cesarean section, late pregnancy bleeding, or premature delivery, unless they smoke; however, they may be at increased risk of having a newborn who is small for gestational age. The best predictor of seizure control during pregnancy is seizure frequency in the previous 9 to 12 months (especially for patients who have been seizure free).

In women with epilepsy who are of child-bearing age, levetiracetam and lamotrigine have minimal evidence of teratogenicity and are the preferred treatment options. Select patients, however, may need to continue potentially teratogenic medications, such as valproic acid, especially if seizures cannot be otherwise controlled. Discovery of pregnancy alone is not a sufficient reason to stop AEDs in women with epilepsy whose disease is well controlled. Women with epilepsy must balance risk of teratogenicity with risk of uncontrolled seizures, particularly GTCS, which can result in fetal anoxia and death.

Valproic acid, phenobarbital, and phenytoin are associated with MCMs and lower IQ in offspring; these drugs should be avoided if possible in pregnant women with epilepsy. Topiramate, carbamazepine, and AED polypharmacy also should also be avoided because of increased MCM risk. Valproic acid is associated with neural tube defects, and topiramate with cleft lip and palate.

Serum levels of lamotrigine, oxcarbazepine, and levetiracetam are known to decrease significantly during pregnancy. For lamotrigine, a dose escalation of approximately 50% is needed to maintain therapeutic levels and prevent seizures; levels should be followed at least monthly during pregnancy. Once delivery occurs, the lamotrigine dose should be rapidly decreased to avoid a sudden increase in serum levels, which would increase toxicity and risk of Stevens-Johnson syndrome.

Because the benefits of breastfeeding most often outweigh the risks, breastfeeding is recommended in most women with epilepsy who take AEDs. Sedation of the infant is a potential complication, but AED exposure through breast milk is usually minimal and probably less than that in utero.

Contraception

Enzyme-inducing AEDs (see Table 22) increase the metabolism of oral contraceptives, which decreases their effectiveness and thus increases chances of pregnancy occurring (while taking potentially teratogenic medications). Alternate methods of contraception, such as intrauterine devices or barrier methods, are thus recommended. Oral contraceptives also increase lamotrigine metabolism, which necessitates dosage increases.

KEY POINTS

- In women with epilepsy who are of child-bearing age, levetiracetam and lamotrigine have minimal evidence of teratogenicity and are the preferred treatment options.
- Discovery of pregnancy alone is not a sufficient reason to stop antiepileptic drugs in women with epilepsy whose disease is well controlled; women with epilepsy must balance risk of teratogenicity with risk of uncontrolled seizures, particularly generalized tonic-clonic seizures, which can result in fetal anoxia and death.
- Valproic acid, phenobarbital, phenytoin, topiramate, carbamazepine, and antiepileptic drug polypharmacy are associated with major congenital malformations and, if possible, should be avoided in pregnant women with epilepsy.

H Status Epilepticus

Not all seizures require emergent treatment. Most GTCS will cease spontaneously within 2 to 3 minutes, and, if the patient has stopped shaking, treatment is not necessarily indicated. Treatment also differs depending on the type of status epilepticus. Convulsive status epilepticus (CSE) is analogous to ventricular fibrillation (that is, a true medical emergency). Nonconvulsive status epilepticus (NCSE) is analogous to atrial fibrillation with or without rapid ventricular response (management varies with symptom severity). The cause of a seizure most often determines the outcome; thus, evaluation for serious causes (meningitis, intracranial hemorrhage) must occur emergently and in parallel with treatment.

Convulsive Status Epilepticus

CSE is defined as a generalized tonic-clonic seizure lasting more than 5 minutes, or two GTCS occurring within 5 minutes of each other without a return to baseline mental status. CSE is diagnosed clinically and presents as continuous generalized clonic jerking of the entire body. Unless PNES is strongly suspected, empiric therapy is indicated without awaiting results of EEG, imaging, serum studies, or lumbar puncture because a longer duration of CSE is strongly linked to worse outcomes.

Securing the airway and obtaining intravenous (IV) access are the first steps in CSE management (**Figure 9**). If point-of-care glucose testing is not available, thiamine should be given, followed by IV glucose. First-line treatment is IV lorazepam, IV diazepam, or intramuscular midazolam. If IV access is not available, diazepam may be given rectally or intramuscularly, although absorption is erratic; intranasal and buccal midazolam also are available in some centers. Fear of respiratory depression should not limit treatment; there is clear evidence that respiratory depression is less common when CSE is treated with benzodiazepines than with placebo.

In a patient who is not already on AEDs, benzodiazepines should be followed by an IV AED to avoid seizure recurrence when the initial treatment wears off. Fosphenytoin is preferred over phenytoin because it can be infused more rapidly and has a lower incidence of skin necrosis (such as purple glove

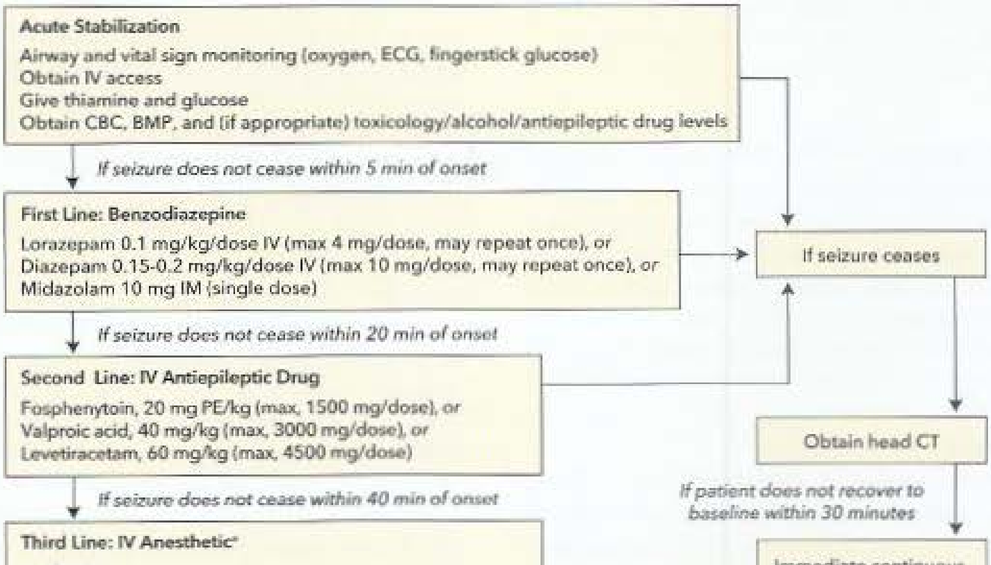

FIGURE 9. Management guidelines for convulsive status epilepticus. BMP = basic metabolic panel; CBC = complete blood count; ECG = electrocardiology; EEG = electroencephalographic; IM = intramuscularly; IV = intravenous(ly); max = maximum; PE = phenytoin equivalents.

*Or choose an appropriate second line agent.

H CONT.

syndrome due to drug extravasation). However, both fosphenytoin and phenytoin can cause acute bradycardia and hypotension. Alternative second-line therapies include IV valproic acid (especially in generalized epilepsy) or IV levetiracetam. There is not enough evidence to support the use of lacosamide as a standard treatment in CSE.

Simultaneously with treatment, emergent evaluation for the cause of CSE should be underway, including provoking factors and triggers. A complete blood count, comprehensive metabolic profile, and evaluation for infection (with urinalysis, chest radiography, and lumbar puncture) should be considered. Head CT is usually indicated before lumbar puncture, but no test should delay the administration of antibiotics if meningitis is suspected.

If convulsions stop but the patient does not either improve within 10 minutes or return to baseline within 30 minutes, immediate continuous EEG is required to diagnose NCSE. NCSE after CSE is still a medical emergency and should be treated aggressively. If convulsive seizure activity does not cease, intubation is typically required, and third-line therapy with IV anesthesia should be initiated. IV anesthesia carries considerable risk, including prolonged ICU hospitalization and associated morbidity (infection, deep venous thrombosis) because patients are typically placed in a drug-induced coma for 24 to 48 hours. Therefore, concomitant continuous EEG monitoring is mandatory. Infusion of propofol, midazolam, or pentobarbital may be considered for NCSE that follows CSE. Hypotension is most common with pentobarbital, which may accumulate in tissues and require many days for clearance. Midazolam is least likely to cause hypotension but often leads to tolerance and tachyphylaxis. Because risk is determined by dose and duration of drug therapy, treatment should be limited to less than 48 hours. H

KEY POINTS

- In patients with likely convulsive status epilepticus (CSE), empiric therapy is indicated without awaiting results of electroencephalography, imaging, serum studies, or lumbar puncture because a longer duration of CSE is strongly linked to worse outcomes.
- First-line treatment of convulsive status epilepticus is intravenous benzodiazepines typically followed by an intravenous antiepileptic drug to avoid seizure recurrence when the initial treatment wears off.

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Nonconvulsive Status Epilepticus

NCSE refers to episodes of electrical seizure activity without clinically evident seizure activity. It should be suspected when a patient, particularly a critically ill patient, has altered mental status with an unclear cause. NCSE may occur in as many as 48% (more typically, 15% to 25%) of patients with encephalopathy who are in the ICU. Certain situations should prompt consideration of NCSE and immediate continuous EEG monitoring (see Table 18). Although EEG is required for diagnosis of NCSE, appropriate clinical correlation of EEG findings is necessary to confirm NCSE and guide treatment. EEG of a few hours duration typically is inadequate because many patients experience intermittent rather than continuous seizures. At least 24 hours of monitoring is recommended in noncomatose patients, and at least 48 hours is recommended in comatose patients.

NCSE that does not occur directly after GTCS or CSE may not necessarily carry as high a risk to the patient as NCSE that follows these seizure types, but evidence is lacking. Treatment is based on clinical examination and not on EEG alone. If the patient is not comatose, initiating aggressive therapy with intubation and an IV anesthetic-induced coma is usually avoided because risks may outweigh benefits. Outcome is typically based more on cause and less on severity or duration of seizures.

Absence status epilepticus is a form of NCSE that typically occurs in patients with a history of generalized epilepsy but sometimes is seen in healthy older patients. Patients with this condition have days to weeks of mild confusion, despite being able to speak and walk ("walking wounded"); EEG confirms the presence of continuous generalized spike-and-wave discharges. Prognosis is excellent because treatment with IV benzodiazepines, valproic acid, or levetiracetam will usually resolve the problem, even in patients with days or weeks of seizing. H

KEY POINTS

- Nonconvulsive status epilepticus should be suspected when a patient, particularly a critically ill patient, has altered mental status with an unclear cause.
- Although electroencephalography is required for diagnosis of nonconvulsive status epilepticus (NCSE), appropriate clinical correlation of electroencephalographic findings is necessary to confirm NCSE and guide treatment.
- Nonconvulsive status epilepticus is diagnosed by continuous electroencephalographic monitoring; at least 24 hours of monitoring is recommended in noncomatose patients, and at least 48 hours is recommended in comatose patients.

Stroke

Definition of Stroke

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Stroke is the leading cause of serious disability among adults and the fifth leading cause of death in the United States. Its incidence increases with each decade of life. The World Health Organization defines stroke as a disease of sudden-onset focal neurologic deficits associated with dysfunction in the brain, retina, or spinal cord due to occlusion or rupture of a cerebral or spinal artery. Ischemic stroke, which results from occlusion of an artery, is the most common type of stroke and can be further subclassified on the basis of its underlying cause. Transient ischemic attack (TIA) was formerly defined as a neurologic impairment lasting less than 24 hours but now is recognized as a transient neurologic

H CONT

deficit without the presence of infarction on neuroimaging. Hemorrhagic strokes comprise a small proportion of all strokes but are associated with higher short-term mortality. Intracerebral hemorrhage (ICH) presents with focal neurologic deficits and may also include headache or impairment in consciousness. Subarachnoid hemorrhage (SAH) commonly presents with sudden onset severe headache and impairment in consciousness without focal neurologic deficits. Although their clinical manifestations often overlap with stroke, subdural and epidural hematomas are not considered to be strokes and are discussed in Head Injury. Determining the exact subtype of stroke a patient experiences has important implications for acute therapeutics, prevention strategies, and prognosis. H

KEY POINT

- Determining the exact subtype of stroke (ischemic or hemorrhagic) has important implications for acute therapeutics, prevention strategies, and prognosis.

Diagnosis of Stroke

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Stroke is a clinical diagnosis supported by neuroimaging. The clinical manifestations of stroke are highly variable. Although most strokes commonly manifest as rapid onset of specific neurologic symptoms, such as weakness, aphasia, dysphagia, and sensory changes, stroke also may present with more nonspecific symptoms, such as dizziness, altered mental status, or sudden unexplained coma. Examination will often show focal neurologic deficits. In the acute setting, rapid assessment is required to inform treatment, and validated scales, such as the National Institutes of Health Stroke Scale (NIHSS), are commonly used (**Table 23**). The neurologic examination, however, is not reliable enough to distinguish ischemic from hemorrhagic stroke, and neuroimaging is required before initiation of treatment. Noncontrast head CT is the most widely used test, given its rapid acquisition, low cost, wide availability, and high sensitivity for diagnosing hemorrhagic stroke (**Figure 10**). In ischemic stroke, the initial

TABLE 23. National Institutes of Health Stroke Scale

Parameter (Testing Method)	Scores[a]
1a. Level of consciousness	0 = normal 1 = not alert but arousable by minor stimulation 2 = not alert and requires constant verbal or painful stimuli to remain interactive 3 = unresponsive or responds with only reflexive movements
1b. Level of consciousness questions (state month and age)	0 = answers both correctly 1 = answers one correctly 2 = answers neither correctly
1c. Level of consciousness commands (close and open eyes; make fist or close one hand)	0 = performs both tasks correctly 1 = performs one task correctly 2 = performs neither task correctly
2. Best gaze (track a finger in a horizontal plane)	0 = normal 1 = partial gaze palsy or isolated cranial nerve paresis 2 = forced gaze deviation or total gaze paresis
3. Visual fields (each eye tested individually)	0 = no visual loss 1 = partial hemianopia 2 = complete hemianopia 3 = bilateral hemianopia
4. Facial palsy (show teeth, raise eyebrows, close eyes)	0 = normal 1 = minor paralysis (flattening of the nasolabial fold or asymmetry on smiling) 2 = partial paralysis (paralysis of the lower face only) 3 = complete paralysis (upper and lower face)
5. Arm strength (hold arm with palms down or lift arm for 10 s; each arm scored separately)	0 = no drift 1 = some drift but does not hit bed 2 = drifts down to bed 3 = no effort against gravity 4 = no movement
6. Leg strength (hold leg at 30 degrees for 5 s; each leg scored separately)	0 = no drift 1 = some drift but does not hit bed 2 = drifts down to bed 3 = no effort against gravity 4 = no movement

(Continued on the next page)

TABLE 23. National Institutes of Health Stroke Scale *(Continued)*

Parameter (Testing Method)	Scores[a]
7. Limb ataxia (finger-nose-finger test, heel-knee-shin slide)	0 = absent 1 = present in one limb 2 = present in two limbs
8. Sensation (pinch/pinprick tested in face, arm, and leg)	0 = normal 1 = mild to moderate sensory loss or loss of sensation in only one limb 2 = complete sensory loss
9. Best language (describe a picture, name six objects, and read five sentences)	0 = no aphasia 1 = mild to moderate aphasia (difficulty with fluency and comprehension; meaning can be identified) 2 = severe aphasia (fragmentary language, meaning cannot be clearly identified) 3 = global aphasia or mute
10. Dysarthria (repeat or read words)	0 = normal 1 = mild to moderate 2 = severe (speech not understandable)
11. Extinction/inattention (visual and tactile stimuli applied on right and left sides)	0 = normal 1 = visual or tactile extinction or mild hemispatial neglect 2 = profound hemi-inattention or extinction to more than one modality

[a]Score interpretation (based on total score): 0 = no stoke; 1-4 = minor stroke; 5-15 = moderate stroke; 16-20 = moderate to severe stroke; 21-42 = severe stroke (maximum score, 42).

Adapted from www.ninds.nih.gov/sites/default/files/NIH_Stroke_Scale_Booklet.pdf. Accessed January 17, 2018.

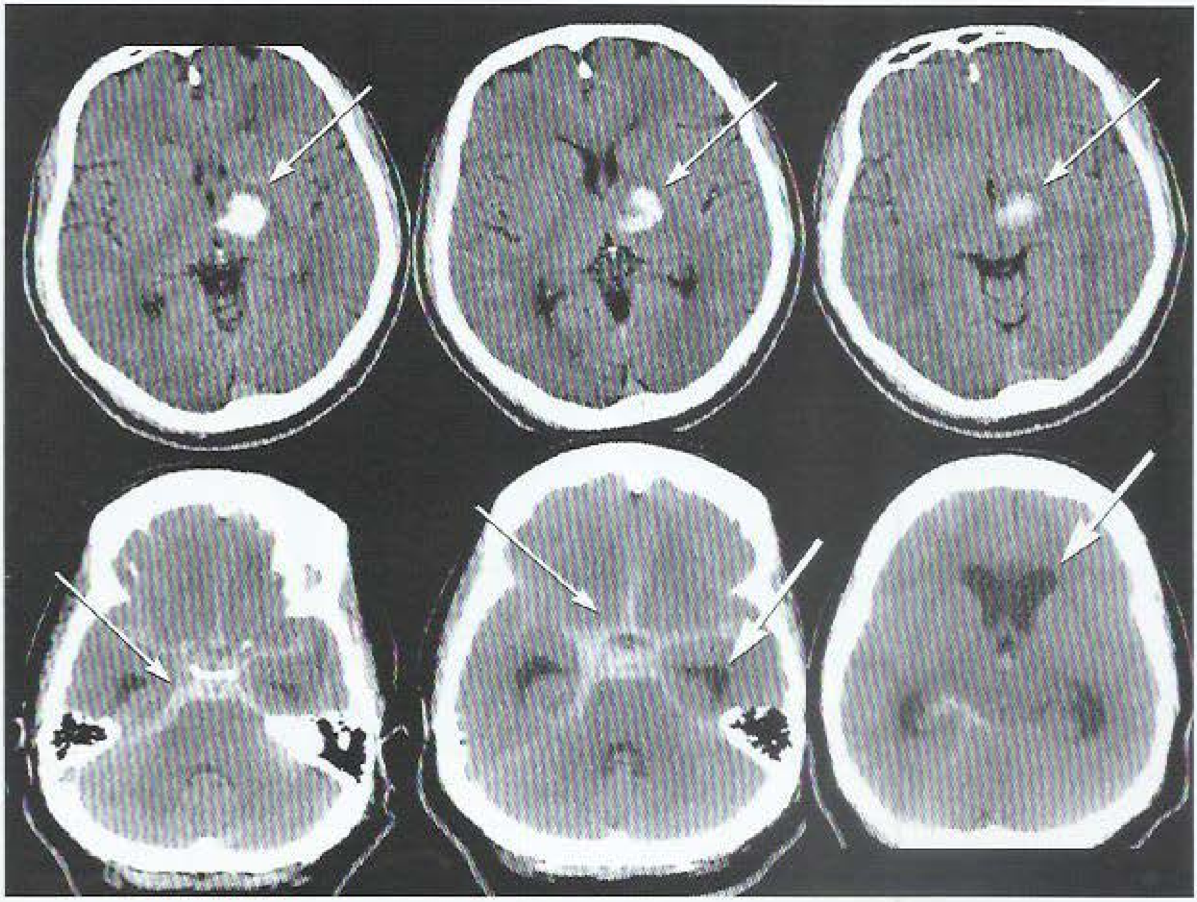

FIGURE 10. Noncontrast CT scans of the head. *Top panel*, an acute left thalamic intracerebral hemorrhage (*arrows*) without hydrocephalus or intraventricular extension is shown. *Bottom panel*, an acute subarachnoid hemorrhage is shown that involves the basal cisterns (*thinner arrows*) with associated enlargement of the lateral horn of the lateral ventricles, consistent with obstructive hydrocephalus and elevated intracranial pressure (*thicker arrows*).

H CONT.

noncontrast head CT scan is often normal, especially in patients seen within 3 hours of symptom onset (although some patients with larger deficits can exhibit early findings) (**Figure 11**). Even 24 hours after onset, a noncontrast head CT scan may not show evidence of infarction, given the poor resolution of small infarcts and those located in the brainstem. CT of the head with contrast rarely is indicated in the initial evaluation of a patient with stroke. CT angiography (CTA) of the head and neck, however, may be performed acutely if endovascular therapy is considered or in otherwise unexplained acute coma to rule out basilar artery thrombosis.

MRI is more sensitive than CT for acute infarction, with changes on the diffusion-weighted imaging sequence apparent within minutes from onset (**Figure 12**). The advantages of MRI include the ability to visualize small strokes, multifocal or bilateral infarcts that may suggest an embolic cause, and the presence of microbleeding. MRI, however, is never the initial test of choice in acute suspected stroke because of its longer acquisition time; if indicated, it is obtained after the initial noncontrast head CT.

Among patients with ICH seen on a noncontrast head CT scan, MRI or CTA is considered if clinical factors are present that raise the suspicion of a cause of hemorrhage other than hypertension or amyloid angiopathy, such as arteriovenous malformation. Likewise, if a patient has symptoms suggestive of SAH and noncontrast head CT findings are normal, lumbar puncture is required to evaluate for the presence of blood or xanthochromia (yellow color stemming from erythrocyte breakdown). If SAH is confirmed,

FIGURE 11. Imaging findings in acute ischemic stroke. *Top left panel*, CT scan of the head without contrast obtained 4 hours after acute onset of left-sided weakness and hemiparesis. The *arrow* points to a dense middle cerebral artery sign suggestive of a thrombus. *Top middle panel*, CT scan of the head showing hypodensity in the right insula (*oval*). *Top right panel*, CT scan of the head from the same patient showing early loss of the gray-white matter differentiation in the right middle cerebral artery territory distribution (*oval*). *Bottom left panel*, CT angiogram of the head showing abrupt cessation of filling in the right middle cerebral artery (*arrow*). *Bottom middle and right panels*, CT scans of the head from the same patient as above 36 hours after symptom onset showing more prominent hypodensity (*middle panel*, *oval*) and cerebral edema (*right panel*, *oval*).

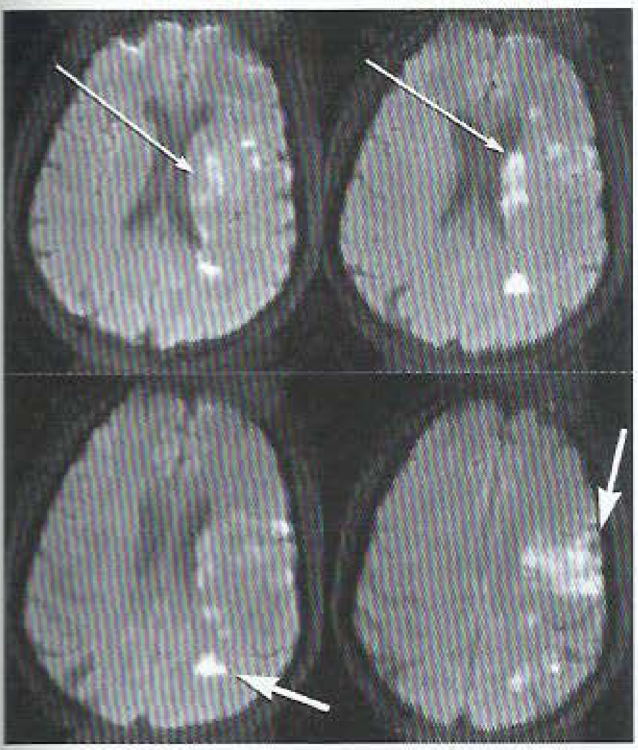

FIGURE 12. Diffusion-weighted MRIs from a patient with symptomatic atherosclerosis of the left middle cerebral artery reveal an acute infarction in deep (*thinner arrows*) and superficial (*thicker arrows*) structures in the left cerebral hemisphere.

catheter-based angiography is required to diagnose, and potentially treat, a cerebral aneurysm.

Results of the physical and neurologic examination most likely will suggest the cause of ischemic stroke, such as the presence of atrial fibrillation or a carotid bruit. Further evaluation with cardiac testing or vessel imaging is required to confirm these causes. H

KEY POINTS

- Neuroimaging, preferably noncontrast head CT, is required before initiating treatment for stroke.
- Although MRI is more sensitive than CT for diagnosing acute infraction, it is not the initial test of choice to exclude hemorrhagic stroke or to make treatment decisions about thrombolysis for ischemic stroke because of its longer acquisition time.

Stroke Subtypes

Transient Ischemic Attack

TIA is characterized by a temporary focal neurologic deficit with an absence of infarction on neurologic imaging. Similar to those of acute ischemic stroke, symptoms of TIA include hemiparesis, mono-ocular or visual field loss, dysarthria, aphasia, and sensory loss. The presence of paresthesia, isolated dizziness or vertigo, or memory loss is more consistent with migraine or seizure. Patients with TIA are at high risk of stroke within the first 48 hours after symptom onset and should be evaluated promptly.

Several post-TIA stroke prediction scoring systems have been developed, with the most widely used being the $ABCD^2$ score, which is based on Age, Blood pressure, Clinical presentation, Duration of symptoms, and the presence of Diabetes mellitus (**Table 24**). TIA scoring systems, however, do not identify with sufficient sensitivity the highest risk patients for whom treatment can ameliorate the risk of stroke. Patients with high-grade extracranial internal carotid artery (ICA) stenosis who have a TIA in a downstream neurologic territory have the greatest short-term risk of stroke. This risk is highest within 2 weeks of TIA for those with greater than 70% stenosis, although 50% to 70% stenosis also carries significant associated risk. In the long term, the risk of stroke is high among patients with atrial fibrillation or other cardioembolic sources requiring anticoagulation.

Expedited vascular imaging of the ICA and cardiac evaluation for atrial fibrillation are required for all patients with TIA. The initial test of choice for evaluating ICA stenosis is duplex ultrasonography because of its wide availability, low cost, and low risk; if high-grade ICA stenosis is detected and the patient is a candidate for surgery or stenting, confirmatory testing is required before intervention. Cardiac evaluation should include electrocardiography for atrial fibrillation, which may be followed by longer-term monitoring. Echocardiography is performed if there is a clinical suspicion of a cardioembolic source or structural heart disease. H

TABLE 24. $ABCD^2$ Score[a]

Patient Characteristics	Score[b]
Age ≥60 y	1
Blood pressure ≥140/90 mm Hg	1
Clinical symptoms	
Focal weakness with the TIA	2
Speech impairment without weakness	1
Duration of TIA	
≥60 min	2
10-59 min	1
Diabetes mellitus present	1

TIA = transient ischemic attack.

[a]Based on Age, Blood pressure, Clinical presentation, Duration of symptoms, and the presence of Diabetes mellitus.

[b]The 48-hour stroke risk based on total score: 0-1 = 0%; 2-3 = 1.3%; 4-5 = 4.1%; 6-7 = 8.1%.

Data from Johnston SC, Rothwell PM, Nguyen-Huynh MN, Giles MF, Elkins JS, Bernstein AL, et al. Validation and refinement of scores to predict very early stroke risk after transient ischaemic attack. Lancet. 2007;369:283-92. [PMID: 17258668]

KEY POINTS

- Patients with a greater than 70% extracranial stenosis of the internal carotid artery who have a transient ischemic attack in a downstream neurologic territory have the highest risk of stroke within 2 weeks.
- Expedited vascular imaging of the internal carotid artery and cardiac evaluation for atrial fibrillation are required for all patients with transient ischemic attack.

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Ischemic Stroke

Large Artery Atherosclerosis

The main mechanism of stroke due to large-artery atherosclerosis is plaque rupture with artery-to-artery embolism. The extracranial carotid artery is frequently involved; the intracranial arteries most commonly affected are the intracranial ICA, middle cerebral arteries, vertebral-basilar arterial junction, and midbasilar artery. Patients with stenoses of the extracranial ICA and the intracranial arteries are at high short-term risk for recurrent stroke and require prompt evaluation. As with TIAs, the extracranial carotid arteries are best evaluated with duplex ultrasonography. Magnetic resonance angiography (MRA) and CTA are both appropriate confirmatory tests after ultrasonography to inform intervention or if duplex examination is not available (**Figure 13**). Transcranial Doppler ultrasonography may help diagnose large-vessel intracranial atherosclerosis, although MRA and CTA are more sensitive tests and can help confirm the diagnosis. Catheter-based angiography is rarely used to diagnose either extracranial or intracranial vessel disease and is associated with a small risk of stroke.

Cardioembolic Stroke

A cardioembolic cause is suggested by clinical and radiologic factors, including infarcts that occur in multiple arterial territories or are located near the cortical surface of the brain with normal arterial imaging. Atrial fibrillation is the most common cardioembolic cause of stroke. Other potential

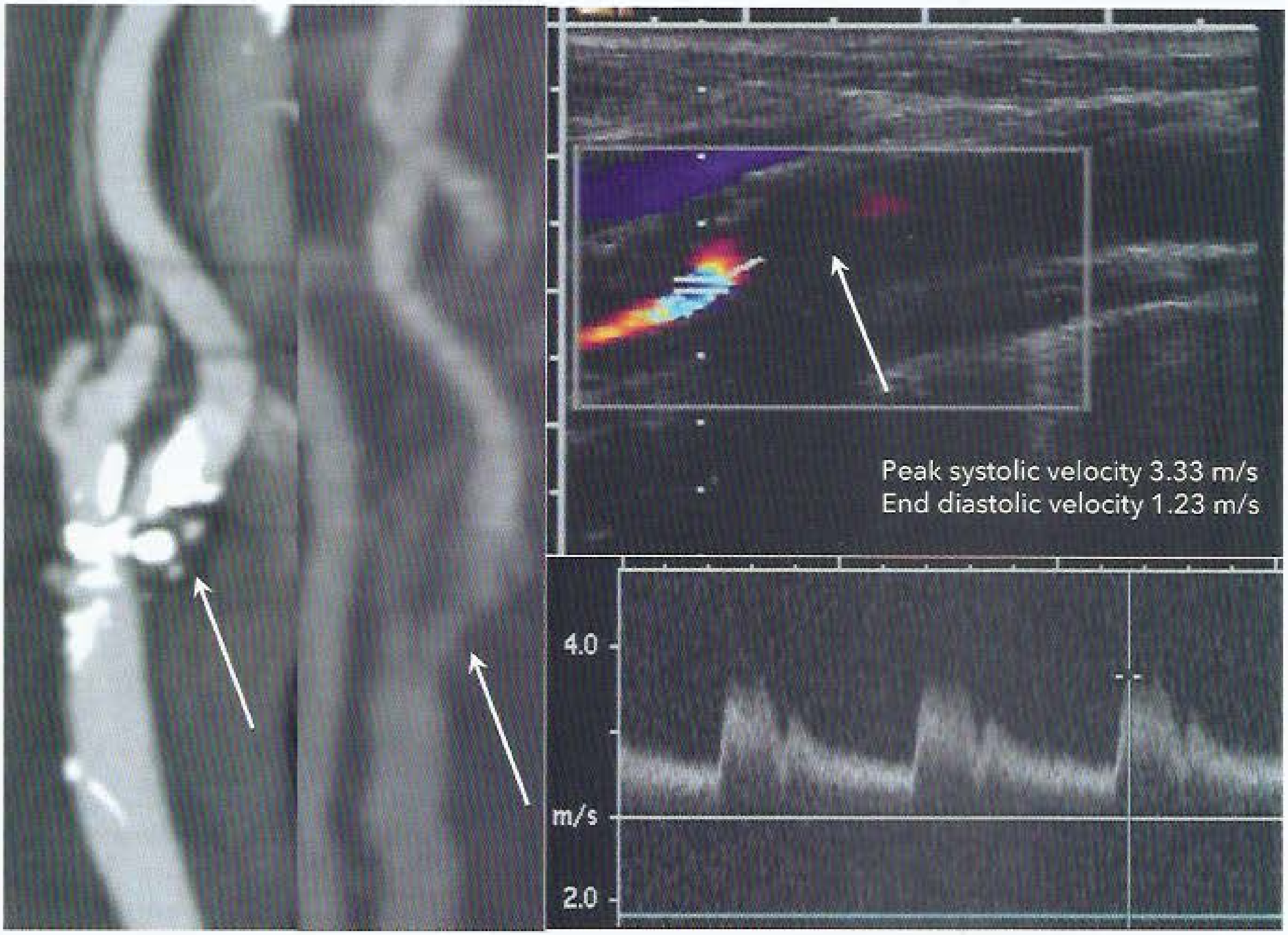

FIGURE 13. Diagnostic imaging modalities in a patient with a symptomatic extracranial internal carotid artery atherosclerotic plaque and associated 90% stenosis. The CT angiogram (*left panel*) and magnetic resonance angiogram (*middle panel*) show high grade stenosis at the origin of the internal carotid artery (*arrows*). Carotid ultrasounds (*right panel*) of the extracranial proximal internal carotid artery show a large plaque at the origin (*arrow*) of the artery, with associated elevated systolic (3.33 m/s) and diastolic (1.23 m/s) velocities consistent with 80% to 99% stenosis.

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cardioembolic sources include new ventricular thrombus after myocardial infarction and severe valvular disease (for example, rheumatic disease, infective endocarditis, and bioprosthetic and mechanical heart valves).

Radiographic findings suggestive of a cardioembolic source, however, are insufficient grounds for initiating anticoagulation. Patients admitted to the hospital with ischemic stroke should have telemetry monitoring to assess for atrial fibrillation. Similarly, when a clinical suspicion of structural heart disease or embolic stroke exists, transthoracic echocardiography is indicated to evaluate for a cardiac source that may require anticoagulation. Echocardiography also may reveal other findings suggesting the cause of stroke, such as a reduced ejection fraction or patent foramen ovale (PFO), although anticoagulation is not routinely indicated for patients with these conditions. The use of transesophageal echocardiography to evaluate for an intracardiac source of stroke is not routinely indicated, given the low yield for findings that require anticoagulation or surgery. In younger patients without stroke risk factors or in whom suspicion of endocarditis or an intracardiac tumor (such as myxoma or fibroelastoma) exists, transesophageal echocardiography may be considered on a case-by-case basis. For further details on anticoagulation criteria, see MKSAP 18 Cardiovascular Disease.

Small Subcortical Infarcts (Lacunar Infarcts)

Lacunar infarcts commonly lead to isolated motor or sensory syndromes; they rarely affect cognition or mental status. These infarcts (which are < 1.5 cm in diameter) involve the deep white matter, basal ganglia, or brainstem. Pathologically, these infarcts are due to occlusion of small penetrating arteries arising from ICAs (most commonly the middle cerebral and basilar arteries). The main risk factor is hypertension, which leads to local damage at the level of the penetrating artery with subsequent occlusion. Other stroke sources include artery-to-artery embolic thrombi from more proximal sources. Patients with lacunar infarcts still require vessel imaging of the extracranial ICAs to inform secondary prevention.

Cryptogenic Causes of Stroke

In many patients with ischemic stroke, a clear cause is not apparent: there is no lacunar infarct, arterial imaging is normal, and no clear cardioembolic source of stroke (such as atrial fibrillation) is found. When this occurs, the patient's clinical syndrome, underlying medical comorbidities, and neuroimaging characteristics can inform which additional diagnostic testing should be considered.

In a younger patient without risk factors for cardiovascular disease, an evaluation for autoimmune and hypercoagulable disorders should be considered, particularly with nonneurologic systemic findings. Hypercoagulable disorders, PFO, and other rare cardioembolic causes may present with an infarct pattern similar to that of atrial fibrillation. A PFO with a right-to-left shunt (diagnosed with a bubble study on transthoracic echocardiography) may explain stroke in a younger patient but is associated with a low risk of recurrent stroke. For further information, including recent recommendations regarding percutaneous PFO closure to prevent a secondary stroke, see MKSAP 18 Cardiovascular Disease. Cerebral vasculitis is an extremely rare cause of stroke and presents with numerous infarcts affecting multiple arterial distributions.

Many patients with cryptogenic stroke may have undiagnosed paroxysmal atrial fibrillation. Neuroimaging findings are similar to those of atrial fibrillation without abnormalities on telemetry or electrocardiography. Prolonged cardiac monitoring with either surface electrodes or an implantable monitor can reveal paroxysmal atrial fibrillation in approximately one third of these patients. In patients with an implantable pacemaker, interrogation of the device may also reveal episodes consistent with atrial fibrillation. The benefit of anticoagulation for stroke prevention if atrial fibrillation is not found on monitoring is unclear. H

KEY POINTS

- Carotid and transcranial Doppler ultrasonography may help diagnose large vessel atherosclerosis in a patient with ischemic stroke, although magnetic resonance angiography and CT angiography may provide additional information; catheter-based angiography is rarely used to diagnose either extracranial or intracranial vessel disease and is associated with a small risk of stroke.
- Atrial fibrillation is the most common cardioembolic cause of stroke, and anticoagulation is indicated; radiographic findings suggestive of a cardioembolic source, however, are insufficient grounds for initiating anticoagulation.
- The use of transesophageal echocardiography to evaluate for an intracardiac source of stroke is not routinely indicated, given the low yield for findings that require anticoagulation or surgery. HVC
- Lacunar (or small subcortical) infarcts resulting in isolated motor or sensory syndromes are caused by occlusion of the small penetrating arteries arising from intracranial arteries; the main risk factor for lacunar infarcts is hypertension.
- Many patients with cryptogenic stroke may have undiagnosed paroxysmal atrial fibrillation, and prolonged cardiac monitoring should be considered.

Hemorrhagic Stroke

H

Subarachnoid Hemorrhage

Examination findings suggestive of SAH include altered mental status, nuchal rigidity, pupillary dilation from compression of the occulomotor nerve (cranial nerve III) by a posterior communicating artery aneurysm, or subhyaloid hemorrhages on funduscopy. The most common cause of subarachnoid hemorrhage is saccular (berry) aneurysm rupture, with intracranial arterial dissection and mycotic aneurysm rupture occurring less commonly. Other rare causes of SAH are the reversible cerebral vasoconstriction syndromes, dural

H CONT.

sinus thrombosis, vascular malformations, and cerebral amyloid angiopathy. Saccular aneurysms often can be visualized with CTA or MRA, although the resolution is not sufficient to detect smaller aneurysms; catheter-based angiography is necessary for the definitive diagnosis of aneurysms and other causes of SAH.

Elevated intracranial pressure from obstructive hydrocephalus and/or global cerebral edema is a common consequence of SAH. Examination findings that raise concern for elevated intracranial pressure include impairment in consciousness, loss of brainstem reflexes, and stereotyped posturing movements to painful stimuli. The presence of hydrocephalus on neuroimaging is associated with high mortality and should prompt neurosurgical placement of an external ventricular drain to relieve (and measure) elevated intracranial pressure. Impaired consciousness due to nonconvulsive status epilepticus also may occur and requires electroencephalographic monitoring for diagnosis.

Intracerebral Hemorrhage

ICH can present similarly to ischemic stroke, with headache and impaired consciousness as distinguishing characteristics. The most common cause of ICH that affects deep structures of the brain (thalamus, basal ganglia, pons, cerebellum) is hypertension. Lobar hemorrhages near the cortical surface may have various causes, including hypertension, hemorrhagic tumors, and cortical vein thrombosis. In patients older than 55 years, especially in those without hypertension, lobar ICH may be due to cerebral amyloid angiopathy. In this syndrome, amyloid protein similar to that seen pathologically in Alzheimer disease deposits in cerebral arterioles near the cortical surface, thereby weakening the arterial wall and making it prone to rupture.

The mainstay of acute treatment and prevention is control of blood pressure. Clinical and radiologic features can be used to calculate a patient's ICH score, which informs 30-day mortality and is recommended in the assessment of patients with ICH (**Table 25**). The main cause of early neurologic deterioration is hematoma expansion. Another leading cause of death is early withdrawal of care. Guidelines caution against termination of care within the first 48 hours. H

KEY POINTS

- Catheter-based angiography is necessary for the definitive diagnosis of aneurysms and other causes of subarachnoid hemorrhage.
- In subarachnoid hemorrhage, the presence of hydrocephalus on neuroimaging is associated with high mortality and should prompt neurosurgical placement of an external ventricular drain to relieve elevated intracranial pressure.
- The most common cause of intracerebral hemorrhage that affects deep structures of the brain (thalamus, basal ganglia, pons, cerebellum) is hypertension; the mainstay of prevention is control of blood pressure.

TABLE 25. Intracerebral Hemorrhage Score[a,b]

Clinical and Imaging Findings		Points
Glasgow Coma Scale score	3-4	2
	5-12	1
	13-15	0
Age	80 y or older	1
	Younger than 80 y	0
Infratentorial (brainstem, cerebellum)	Yes	1
	No	0
Volume	Greater than 30 mL	1
	Less than 30 mL	0
Intraventricular hemorrhage	Yes	1
	No	0

[a]30-Day mortality based on total score: 0 = 0%; 1 = 13%; 2 = 26%; 3 = 72%; 4 = 97%; 5 and 6 = 100%.

[b]Adapted with permission from: Hemphill JC 3rd, Bonovich DC, Besmertis L, Manley GT, Johnston SC. The ICH score: a simple, reliable grading scale for intracerebral hemorrhage. Stroke. 2001;32:891-7. [PMID: 11283388]

In-Hospital Stroke Considerations

H

In-hospital stroke is most often ischemic and frequently observed perioperatively. Patients undergoing cardiac surgery involving cardiopulmonary bypass, particularly multivalve procedures, are at highest risk for stroke in the postoperative setting. The most common cause is atrial fibrillation.

The modifiable preoperative risk factors for in-hospital stroke are similar to those causing stroke in the short term without surgery, including symptomatic extracranial ICA stenosis of greater than 70%. Patients with a recent stroke secondary to ICA stenosis who are undergoing nonemergent surgery are likely to benefit from revascularization beforehand. The presence of asymptomatic ICA stenosis, however, is not clearly associated with perioperative stroke, and routine prophylactic ICA revascularization is not indicated.

Stroke within 30 days of surgery, regardless of cause, increases the risk of perioperative stroke; elective surgeries within this time period should be avoided. Patients with stroke involving a large brain volume or with a recent hemorrhagic stroke also are at risk of cerebral hemorrhage if placed on cardiopulmonary bypass and/or anticoagulation. If possible, nonemergency major cardiac procedures should be avoided. H

KEY POINTS

- Patients undergoing cardiac surgery involving cardiopulmonary bypass, particularly multivalve procedures, are at highest risk for stroke in the postoperative setting, most commonly from atrial fibrillation.
- Stroke within 30 days of surgery, regardless of cause, increases the risk of perioperative stroke, and elective surgeries within this time period should be avoided.

H Acute Stroke Therapy

Ischemic Stroke Treatment

Thrombolysis and Endovascular Therapy

Intravenous recombinant tissue plasminogen activator (alteplase) is the only thrombolytic agent approved for use in acute ischemic stroke. Alteplase is most effective when administered early, and treatment within 3 hours of ischemic stroke onset with disabling symptoms is associated with a significant reduction in disability at 3 months. Although treatment within 4.5 hours also may have clinical benefit, treatment beyond 3 hours is not approved by the FDA. Because of the associated delays, obtaining advanced imaging or laboratory values should be avoided before treatment unless coagulopathy or thrombocytopenia is suspected. Treatment should start within 60 minutes of arrival at the emergency department or detection of in-hospital stroke, with best practices recommending treatment within 45 minutes. Contraindications for treatment with alteplase have evolved over the years, with the latest guidelines clarifying relative exclusion criteria and defining nondisabling symptoms (Table 26).

The main complication of alteplase treatment is symptomatic ICH, which can present with headache or worsening of NIHSS score or level of consciousness. Symptomatic hemorrhage occurs in up to 6% of treated patients, and mortality can be as high as 50% when present. The main risk factors for symptomatic hemorrhage are treatment after 4.5 hours and hypertension before and after treatment. Accordingly, before treatment with alteplase, the patient's blood pressure should be less than 185/110 mm Hg. Higher readings should prompt administration of intravenous labetalol or nicardipine before alteplase. Nitrates should be avoided because of their potential to increase intracranial pressure.

After treatment with alteplase, frequent monitoring of neurologic status and vital signs is required in the first 24 hours. Neurologic worsening should prompt urgent neuroimaging. Blood pressure should be maintained below 180/105 mm Hg, and both antiplatelet and anticoagulant agents should be held for the first 24 hours after alteplase administration. After 24 hours, antiplatelet agents for stroke prevention and anticoagulant agents for deep venous thrombosis prevention can be started if hemorrhage is absent on imaging.

Endovascular therapy (primarily with intra-arterial mechanical thrombectomy) within 24 hours of stroke onset can be considered for select patients with a clinically suspected large-vessel occlusion and specific examination and radiologic findings, such as a measurable neurologic deficit and small but radiographically evident ischemic changes. In patients for whom endovascular therapy is considered, prompt noninvasive vessel imaging with CT or MRA is recommended. The evaluation for endovascular stroke therapy with vessel imaging, however, should not replace or delay the administration of

TABLE 26. Contraindications to Intravenous Alteplase in Adults With Acute Ischemic Stroke

Absolute Exclusion Criteria	Relative Exclusion Criteria
Significant head trauma or prior stroke in the previous 3 months	Minor or rapidly improving nondisabling symptoms[a]
Suspicion of subarachnoid hemorrhage	Pregnancy
Noncompressible site arterial puncture within 7 days	Seizure at onset
Intracranial neoplasm, arteriovenous malformation, aneurysm	Major surgery or serious trauma within 14 days
Recent intracranial or spinal surgery	Recent gastrointestinal or genitourinary bleeding within 21 days
Blood pressure ≥185/110 mmHg despite treatment	Recent acute myocardial infarction
Active internal bleeding	
Active bleeding diathesis	
Platelet count <100,000/µL (100 × 10^9/L)	
Heparin within 48 hours with an activated partial thromboplastin time above normal range	
Current use of anticoagulant with INR >1.7	
Current use of non-vitamin K antagonist anticoagulants (within 48 hours) with associated elevated relevant laboratory tests	
Blood glucose less 50 mg/dL (2.8 mmol/L)	
Noncontrast head CT demonstrated multi-lobar infarction with >1/3 of the hemisphere involved	

[a]Disabling symptoms are defined as complete hemianopia (score of 2-3 on National Institutes of Health Stroke Scale [NIHSS] question 3), visual or sensory extinction (score of 1-2 on NIHSS question 11), any weakness against gravity (score of 2-4 on NIHSS question 6 or 7), and total NIHSS score >5.

Adapted with permission from: Demaerschalk BM, Kleindorfer DO, Adeoye OM, Demchuk AM, Fugate JE, Grotta JC, et al; American Heart Association Stroke Council and Council on Epidemiology and Prevention. Scientific Rationale for the Inclusion and Exclusion Criteria for Intravenous Alteplase in Acute Ischemic Stroke: A Statement for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke. 2016;47:581-641. [PMID: 26696642] doi:10.1161/STR.0000000000000086

H CONT.

alteplase in otherwise eligible patients. A treatment algorithm for stroke within 6 hours of onset is provided in **Figure 14**.

Antiplatelet Therapy, Anticoagulation, and Medical Management

For the many patients with acute ischemic stroke who are not eligible for thrombolysis or endovascular stroke therapy, antiplatelet therapy is the mainstay of acute treatment. When administered either orally or rectally within 48 hours of stoke, aspirin reduces the short-term risk of recurrent stroke, and its use in the acute setting is a stroke-specific quality-of-care core measure. Monotherapy with clopidogrel, however, has no established benefit in the acute stroke setting.

The patient with TIA or minor stroke, usually defined as an NIHSS score of 5 or less, has been the focus of recent trials of antiplatelet therapy because of the high short-term risk of recurrent events. In one recent trial, aspirin was compared to ticagrelor within 24 hours of stroke onset, and no difference between the two medications in the risk of recurrent stroke during 90 days of treatment was noted. Another study compared aspirin monotherapy for 90 days with aspirin and clopidogrel combined for 21 days followed by clopidogrel monotherapy as long as 69 days. The combination arm had a 3% absolute reduction in recurrent ischemic stroke at 90 days, with no difference in hemorrhagic stroke. Further clinical trials are ongoing to evaluate the safety and efficacy of dual antiplatelet agents in the settings of acute minor stroke and TIA.

Acute administration of anticoagulation in ischemic strokes (whether related to atrial fibrillation or not) does not reduce the short-term risk of recurrent stroke and increases the risk of hemorrhage into the territory of cerebral infarction (hemorrhagic conversion).

Management of acute hypertension in ischemic stroke differs when thrombolysis is not involved. Blood pressure should not be treated within the first 48 hours unless it is greater than 220/120 mm Hg or there is evidence of end-organ dysfunction. Acute antihypertensive therapy has been associated with neurologic worsening in patients with ischemic stroke and should be started slowly after the first 48 hours until secondary prevention targets are reached. Statins have not been shown to reduce the risk of recurrent stroke when administered within 30 days but can be considered after a dysphagia evaluation has been completed, especially in those patients with an atherosclerotic stroke subtype. See Dyslipidemia section in MKSAP 18 General Internal Medicine. H

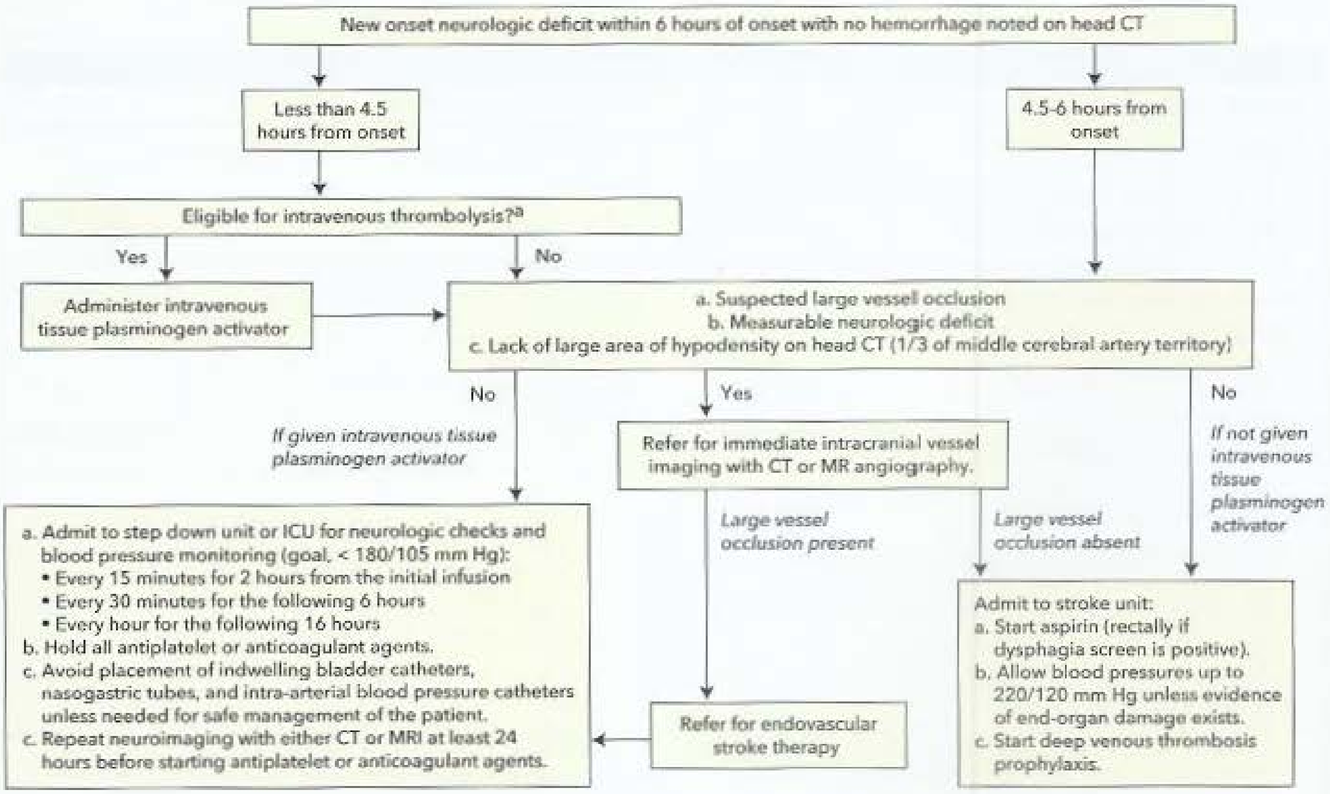

FIGURE 14. Proposed pathway for the evaluation and treatment of an acute stroke within 6 hours of onset.

[a]See Table 26 for exclusion criteria for alteplase (tissue plasminogen activator).

KEY POINTS

- Treatment with intravenous recombinant tissue plasminogen activator (alteplase) within 3 hours of ischemic stroke onset is associated with a significant reduction in disability at 3 months after stroke; treatment within 4.5 hours of onset also may have clinical benefit but is not FDA approved.
- Endovascular therapy within 24 hours of stroke onset can be considered for select patients with a clinically suspected large-vessel occlusion and specific examination and radiologic findings, such as a measurable neurologic deficit and small but radiographically evident ischemic changes.
- When administered within 48 hours of ischemic stroke that is not eligible for thrombolysis, aspirin reduces the short-term risk of recurrent stroke; its use in the acute setting is a stroke-specific quality-of-care core measure.
- Acute administration of anticoagulation for ischemic stroke (whether related to atrial fibrillation or not) does not reduce the short-term risk of recurrent stroke and increases the risk of hemorrhage into the territory of cerebral infarction (hemorrhagic conversion).

Hemorrhagic Stroke Treatment

Intracerebral Hemorrhage Treatment

Treatment of acute ICH is centered on preventing hematoma expansion. The primary predictor of early hematoma expansion is elevated blood pressure. Treatment of blood pressure is recommended for patients with ICH who have a systolic blood pressure greater than 180 mm Hg, although the most appropriate agent for the blood pressure control in this circumstance is not well established. Parenteral medications delivered by intravenous infusion with frequent blood pressure monitoring have the benefit of close titration to the intended target. Intravenous nitrates (such as nitroglycerin) and nitroprusside may raise intracranial pressure and reduce blood flow to the ischemic region and should be avoided in patients with ICH. Guidelines for the treatment of ICH indicate that acutely treating the systolic blood pressure in a specialized intensive care unit until it is 140 mm Hg is reasonable if the presenting systolic pressure is 150 to 220 mm Hg.

A recently completed trial compared a goal systolic blood pressure of 110 to 140 mm Hg with one of 140 to 180 mm Hg in patients with a systolic blood pressure of greater than 180 mm Hg who were seen within 4.5 hours of ICH onset. The more intensive control arm achieved a mean systolic blood pressure of 128 mm Hg versus 141 mm Hg in the usual care arm. No difference in mortality or neurologic outcomes was seen, but a significantly higher rate of adverse renal events occurred with intensive control. Treating systolic blood pressure if greater than 180 mm Hg is still advised but should be performed cautiously, and systolic blood pressure goals of less 140 mm Hg should be avoided.

Another risk factor for hematoma expansion is coagulopathy due to either antiplatelet agent use or anticoagulation. The use of platelet transfusion has been specifically studied in ICH in the setting of antiplatelet agent use, and no clinical benefit has been shown. Guidelines advise against its routine use. Anticoagulation should be reversed, although this incurs an increased risk of thrombotic events. For patients without coagulopathy, recombinant factor VII has no neurologic benefit and is associated with high rates of venous thromboembolic events.

Another source of neurologic decline in patients with ICH is nonconvulsive status epilepticus, which may present with impaired consciousness. Use of prophylactic antiepileptic medications in patients with ICH is not recommended, however, unless there are definitive clinical or electroencephalographic seizures.

Elevated intracranial pressure is a major determinant of morbidity and mortality in ICH. Osmotherapy with mannitol or hypertonic saline may temporarily reduce intracranial pressure in ICH; glucocorticoids are ineffective in reducing cerebral edema in ICH and should not be routinely administered. External ventricular drainage is indicated with hydrocephalus and impaired consciousness; other surgical measures are not routinely indicated unless as life saving measures in rapidly deteriorating patients. Cerebellar hemorrhages greater than 3 centimeters in diameter are the exception because early surgical evacuation is necessary to prevent hydrocephalus, brainstem compression, and neurologic deterioration.

KEY POINTS

- Treatment of blood pressure is recommended for patients with intracerebral hemorrhage whose systolic blood pressure is greater than 180 mm Hg; intravenous nitrates should be avoided.
- Routine use of platelet transfusion in patients with intracerebral hemorrhage who are being treated with antiplatelet agents is not indicated. HVC
- Osmotherapy with mannitol or hypertonic saline may temporarily reduce intracranial pressure in patients with intracerebral hemorrhage; glucocorticoids are ineffective and should not be routinely administered.
- In patients with intracerebral hemorrhage, early surgical evacuation of cerebellar hemorrhages greater than 3 cm in diameter is necessary to prevent hydrocephalus, brainstem compression, and neurologic deterioration.

Subarachnoid Hemorrhage Treatment

Treatment of SAH focuses on prevention of early (≤48 hours) and late neurologic complications. Within the first 48 hours, a major cause of morbidity is aneurysmal rebleeding; early surgical exclusion of the ruptured aneurysm and maintenance of a blood pressure of less than 140/80 mm Hg is required. Elevated intracranial pressure from obstructive hydrocephalus, cerebral edema, seizures, and cerebral vasospasm are other leading causes of poor outcomes.

H CONT.

Cerebral vasospasm with resultant cerebral ischemia and neurologic worsening may develop beginning near day 5. The degree of hemorrhage on a head CT may predict the risk of vasospasm, but frequent monitoring and daily transcranial Doppler imaging is recommended in all patients. Nimodipine should be started as early as possible to improve neurologic outcomes. The drug is continued for 21 days or until hospital discharge. If there is a high clinical suspicion of vasospasm, CTA or catheter-based angiography may be needed to establish vasospasm as the cause of neurologic worsening. The latter has the added benefit of potential endovascular treatment, including use of intra-arterial vasodilators and angioplasty. Another treatment option for vasospasm in patients with a treated aneurysm is induced hypertension, although the exact treatment targets are not well established.

Medical complications are a significant source of morbidity and mortality in patients with SAH. Patients with impaired consciousness and coma at presentation are at highest risk for stunned myocardium (with a decrease in left ventricular ejection fraction) and pulmonary edema due to the large sympathetic surge in SAH. Other medical complications include pulmonary and urinary tract infections, dysphagia, the syndrome of inappropriate antidiuretic hormone secretion, and cerebral salt wasting. Because of these possible medical and neurologic complications, patients with SAH require care in a specialized ICU with experience in treating SAH. H

KEY POINTS

- Within the first 48 hours of a subarachnoid hemorrhage, aneurysmal rebleeding is a major cause of morbidity; early surgical exclusion of the ruptured aneurysm and maintaining a blood pressure of less than 140/80 mm Hg is required.
- In aneurysmal subarachnoid hemorrhage, cerebral vasospasm with resultant cerebral ischemia and neurologic worsening may develop beginning near day 5, and all patients should be treated with nimodipine to prevent poor neurological outcomes.

Stroke Prevention

Primary Prevention

MKSAP 18 General Internal Medicine provides information on the treatment of cardiovascular risk factors related to primary prevention of stroke. Patients with asymptomatic ICA stenosis require primary prevention strategies similar to those used for patients with asymptomatic atherosclerotic disease. Contemporary best medical therapy, including high-intensity statin therapy, is associated with a low risk of first stroke, likely less than 2% per year. ICA revascularization may reduce the risk of stroke further, but the risk of the procedure itself must be weighed against the potential benefit. ICA revascularization for primary prevention is not warranted unless high-risk stroke features are present, such as stenosis greater than 80% or rapid progression of stenosis. For patients with high-risk predictors, the decision to refer for revascularization should be made on an individual basis. Ongoing clinical trials may provide more information on the relative advantages of revascularization and medical therapy.

The main modifiable risk factors for intracranial arterial aneurysm growth and rupture are hypertension and active tobacco use. Treatment of both is indicated. Surgical treatment of aneurysms with either endovascular therapy or craniotomy is associated with sufficiently high neurologic morbidity that treatment is reserved for patients at high risk of rupture and low surgical risk. The location and size of the aneurysm are the primary determinants of rupture risk, and both MRA and CTA can show these features noninvasively. Aneurysms less than 7 millimeters in diameter in the posterior circulation and less than 12 millimeters in the anterior circulation have a low risk of rupture and can be managed conservatively. Patients with these aneurysms should undergo annual noninvasive imaging because aneurysmal growth is a risk factor for rupture and may be an indication for surgery. Patients with two or more relatives with intracranial aneurysms or SAH also should be offered screening with noninvasive neuroimaging. Other predictors of aneurysmal rupture that should prompt surgical consideration include a previous aneurysmal SAH or the presence of cranial nerve palsy.

KEY POINTS

- Routine internal carotid artery revascularization for primary prevention of stroke is not warranted unless high-risk stroke features are present, such as stenosis greater than 80% or rapid progression of stenosis. HVC
- Aneurysms less than 7 millimeters in diameter in the posterior circulation and less than 12 millimeters in the anterior circulation have a low risk of rupture and can be managed conservatively with annual noninvasive neuroimaging. HVC

Secondary Prevention

Lifestyle Modifications and Medical Management

The risk factors for a second stroke are similar to those for ischemic heart disease and other atherosclerotic disease. Patients with stroke benefit from diet and exercise changes to maintain cardiometabolic health. Patients with ICH are at high risk for recurrent stroke due to hypertension; after the acute in hospital setting, a target blood pressure of less than 130/80 mm Hg is advised. Similarly, patients with small subcortical infarcts in whom hypertension is the primary risk factor may also benefit from a systolic blood pressure of less than 130 mm Hg. High-intensity statin therapy reduces the risk of stroke among patients with ischemic stroke or TIA presumed to be of atherosclerotic origin and an LDL-cholesterol level greater than 100 mg/dL (2.6 mmol/L).

The choice of an antiplatelet agent for long-term (>90 days from stroke) secondary stroke prevention in the absence of atrial fibrillation has been the subject of several clinical trials. Consistent across trials is the finding that long-term use of aspirin and clopidogrel combined, versus a single antiplatelet agent, is associated with no reduction in risk of stroke but an increased risk of hemorrhage and death. Aspirin monotherapy is a reasonable first-line antiplatelet regimen for secondary stroke prevention, although clopidogrel or aspirin-dipyridamole is often prescribed because of their small absolute risk benefits over aspirin. Clopidogrel monotherapy, when compared with aspirin monotherapy in a trial involving ischemic stroke, peripheral arterial disease, and myocardial infarction, was associated with a 0.9% per year absolute benefit; however, the results of this trial were driven by peripheral arterial disease outcomes, with no clear difference in recurrent stroke. The combination of aspirin and dipyridamole versus aspirin alone has been associated with a modestly lower risk of recurrent stroke in the long term, although the combination is associated with high risk of discontinuation because of headache and other adverse effects. Clopidogrel has been compared with the aspirin-dipyridamole combination in one large clinical trial, with both having similar efficacy in stroke prevention. Cilostazol has been compared to aspirin in clinical trials in Japan and China; it has had similar efficacy in reducing ischemic stroke and resulted in slightly lower hemorrhagic complications, although its use is limited by adverse effects. Other antiplatelet agents, such as ticagrelor or prasugrel, have not been examined in long-term trials of secondary stroke prevention, although prasugrel is associated with a high risk of hemorrhage when used in patients with coronary artery disease who have a history of stroke. No data are available on blood assays examining a lack of response to antiplatelet agents in secondary stroke prevention or on the choice of antiplatelet agent after an additional clinical event.

Warfarin also has been compared to aspirin for secondary stroke prevention in the absence of atrial fibrillation, with no difference in stroke outcomes reported. In a trial of patients with intracranial atherosclerosis, warfarin was associated with increased mortality compared with aspirin. Non–vitamin K antagonist anticoagulants have not been tested in clinical trials of stroke not involving atrial fibrillation and are not routinely indicated in this setting. For a review of anticoagulation in atrial fibrillation–related stroke, see MKSAP 18 Cardiovascular Medicine.

Whether to start antithrombotic agents after hemorrhagic stroke has not been as well studied. Patients with cerebral amyloid angiopathy are at particularly high risk of recurrent lobar ICH, and the use of antiplatelet agents should only be considered in those with clear secondary prevention indications, such as coronary stents. Similarly, anticoagulation-related lobar ICH has a high risk of recurrence, and further anticoagulation should be avoided in patients with this type of hemorrhage. Anticoagulation also should be avoided in most patients with indications of low thromboembolic risk, such as atrial fibrillation with a low CHA_2DS_2 Vasc score (with one point each given for heart failure, hypertension, diabetes, vascular disease [previous myocardial infarction, peripheral arterial disease, aortic plaque], female sex, and age 65 to 74 years and two points each for previous stroke/transient ischemic attack/thromboembolic disease and for age ≥75 years), and used with caution in higher-risk scenarios (such as pulmonary emboli). Finally, with adequate control of hypertension, anticoagulation and antiplatelet treatment can be considered for appropriate indications 4 weeks after a deep ICH secondary to hypertension.

Surgical Management

The use of surgical approaches for secondary stroke prevention has been examined in patients with extracranial ICA stenosis, ICA occlusion, intracranial atherosclerosis, and PFO-related stroke. In extracranial ICA disease, patients with nondisabling stroke or TIA due to ICA stenosis of greater than 70% are at high risk for recurrent stroke and may benefit from early revascularization. The choice of endarterectomy or angioplasty with stenting is dictated by several patient-specific factors and by local surgical experience. A consistent finding in trials has been a higher risk of perioperative stroke with stenting and a higher risk of perioperative myocardial infarction with endarterectomy. In patients with a complete symptomatic occlusion of the ICA, however, direct revascularization is not feasible, and external carotid–to–internal carotid bypass is not effective for stroke prevention.

Symptomatic intracranial arterial stenosis of greater than 70% is associated with a high risk of recurrent stroke and should be treated with a statin. Stenting of the affected artery, however, is associated with a high risk of procedural stroke and should be avoided. Endovascular closure of a PFO for secondary stroke prevention may be considered in select patients (see MKSAP 18 Cardiovascular Disease).

KEY POINTS

- Long-term use of combination aspirin-clopidogrel is associated with no reduction in risk of stroke but an increased risk of hemorrhage and death when compared with single-agent antiplatelet use; aspirin monotherapy is a reasonable first line antiplatelet regimen for secondary stroke prevention. **HVC**
- Patients with nondisabling stroke or TIA due to greater than 70% stenosis of the internal carotid artery (ICA) may benefit from early revascularization; in those with a complete symptomatic occlusion of the ICA, however, direct revascularization is not feasible. **HVC**
- Symptomatic high-grade intracranial arterial stenosis is associated with a high risk of recurrent stroke, but stenting of the affected artery is associated with a high risk of procedural stroke and should be avoided. **HVC**

Standardized Discharge Orders

Adherence to secondary stroke prevention guidelines is inconsistent after hospital discharge. Standardized discharge orders, aligned with recommended core measures for patients with ischemic stroke, can reduce the risk of both hospital readmission and recurrent stroke. These standardized orders ensure that appropriate antiplatelet or anticoagulation agents and high-intensity statin therapy are started on hospital discharge. They include the essential component of patient education about diet, exercise, smoking cessation, and other healthy lifestyle choices to reduce the risk of recurrent events. Lastly, these discharge orders allow for stroke-specific education regarding typical stroke symptoms and the importance of rapid return to care if symptoms occur so that acute stroke therapeutics can be initiated.

Prognosis and Recovery

Neurologic Complications

Patients with stroke are at high risk for developing in-hospital and long-term neurologic complications beyond those previously outlined. Patients with ischemic stroke may develop worsening deficits from hemorrhagic conversion of the infarct, usually within 48 hours. Antiplatelet agents should be held for at least 1 week in most patients with hemorrhagic conversion (for example, a hematoma seen on brain imaging that is associated with mass effect or edema). Patients with hemorrhagic conversion not involving a hematoma and with stable repeat imaging can be started on antiplatelet agents within 48 hours. Patients with a large hemispheric ischemic stroke are at risk for neurologic deterioration from cerebral edema starting on day 2 after a stroke. Patients with significant symptomatic cerebral edema and increased intracranial pressure after an ischemic stroke have a survival advantage with decompressive hemicraniectomy, although neurologic compromise may be significant. Finally, patients with ischemic and hemorrhagic stroke may show neurologic worsening from seizures and systemic infections.

KEY POINTS

- Patients with ischemic stroke may develop worsening deficits from hemorrhagic conversion of the infarct, usually within 48 hours; antiplatelet agents should be held in the setting of hemorrhagic conversion involving a hematoma for at least 1 week and for a shorter period of time if there is no hematoma seen on imaging and repeat imaging is stable.
- Patients with significant symptomatic cerebral edema and increased intracranial pressure after an ischemic stroke have a survival advantage with decompressive hemicraniectomy, although neurologic compromise may be significant.

Medical Complications and Stroke Units

In-hospital medical complications are a leading cause of morbidity and mortality in patients with stroke. Admission to a specialized stroke unit is associated with a reduced long-term risk of all-cause mortality. Specialized stroke units are effective because they use multidisciplinary care teams focused on early mobilization and adherence to protocols, such as removing indwelling catheters to prevent urinary tract infection, preventing aspiration pneumonia by addressing/preventing dysphagia, and instituting oral hygiene protocols. Care protocols in stroke units also emphasize early initiation of pharmacologic prophylaxis of deep venous thrombosis in patients with ischemic stroke and prophylaxis initiation within 48 hours in patients with hemorrhagic stroke who have no evidence of active bleeding.

Long-Term Prognosis and Recovery

Long-term survivors of stroke are at high risk for delayed neurologic complications. Cognitive impairment, vascular dementia, and seizures all may occur. Most stroke survivors exhibit neurologic impairment and disability 1 year poststroke and beyond. Fatigue can arise from a high prevalence of sleep-disordered breathing. Depression is highly prevalent in stroke survivors and is one of the leading modifiable risk factors for long-term disability. Many stroke survivors require ongoing rehabilitative care to improve mobility, prevent falls, and treat spasticity.

KEY POINT

- Most stroke survivors exhibit neurologic impairment and disability 1 year poststroke and beyond; depression is highly prevalent in stroke survivors and is one of the leading modifiable risk factors for long-term disability.

Cognitive Impairment

Definition

Cognitive impairment is the progressive loss of cognitive function in at least one major category: memory, language, executive function, visuospatial function, or behavior. When the level of cognitive impairment is progressive, involves more than one cognitive function, and results in a loss of independent function, it is considered a dementia syndrome. Fixed cognitive disorders occurring after a brain lesion, such as stroke or traumatic brain injury, are excluded from the dementia category.

General Approach to the Patient With Cognitive Impairment

Dementia syndromes are chronic disorders that typically develop over years; intervention when dementia is well established is likely too late to have a meaningful effect on the

disorder. Although definitive evidence that earlier diagnosis improves patient outcomes is lacking, screening for dementia has become the subject of increased interest. At this time, however, there are no accepted standards for dementia screening. The U.S. Preventive Services Task Force does not endorse screening, but the Association of Gerontology and Geriatrics recommends that some form (objective or subjective) of cognitive screening be performed annually in patients age 70 and older.

In the absence of screening, certain signs and behaviors may raise clinical suspicion of a cognitive disorder and provoke evaluation in a primary care setting. Examples include concerns expressed by family members or caregivers, frequent missed (or late arrival to) appointments, changes in medication adherence, unexplained weight loss, presence of a partner or family member at patient appointments when the patient previously was seen alone, and withdrawal from previously enjoyed hobbies.

Many bedside cognitive evaluation tools have demonstrated adequate sensitivity and specificity for detecting cognitive impairment in population-based settings. The most common are the Mini-Mental State Examination, the Montreal Cognitive Assessment, the Ascertain Dementia 8 questionnaire, the Mini-Cog test, and the five-word memory test. Each of these tests can be performed in less than 5 to 10 minutes; no compelling data support the superiority of one test over another. These tests are increasingly used to justify billing and medication authorization decisions by insurers.

After cognitive impairment is diagnosed, determining whether it is reversible or nonreversible is imperative in the initial evaluation of the patient. Essential elements in this determination are the time course of symptom onset and progression, the principal cognitive domain or function affected and its functional impact, and other associated neurologic and nonneurologic symptoms (**Figure 15**). Access to a reliable informant familiar with the patient's condition is critical in the evaluation of the cognitive disorder. The signs and symptoms of a cognitive disorder also may have an anatomic correlate that can be used to help guide the diagnosis and treatment. For example, a progressive loss of language function localizes to a different anatomic location than does a primary memory problem, which may be helpful in determining the underlying cause of the impaired function. The age of the patient also is an important consideration; for example, both atypical presentations of typical dementia syndromes and nonneurodegenerative causes are more common in younger patients.

For a slowly progressive dementia syndrome in an older patient, the American Neurological Association recommends that a minimum evaluation include the following elements:

- General neurologic examination, including a cognitive screening evaluation
- Evaluation for depression, sleep disorders, alcohol use, and family history of dementia
- Detailed medication review
- Serum chemistries, including plasma glucose level
- Complete blood count
- Determination of vitamin B_{12} and thyroid-stimulating hormone levels
- A rapid plasmin reagent test to evaluate for syphilis in high-risk populations
- Basic neuroimaging (MRI or CT without contrast)

In the older population, increasing evidence also suggests that chronic vitamin D deficiency increases the odds of developing dementia. Therefore, measuring serum 25-hydroxyvitamin D levels is a recommended part of the evaluation. When patient age, disease progression, or other associated symptoms

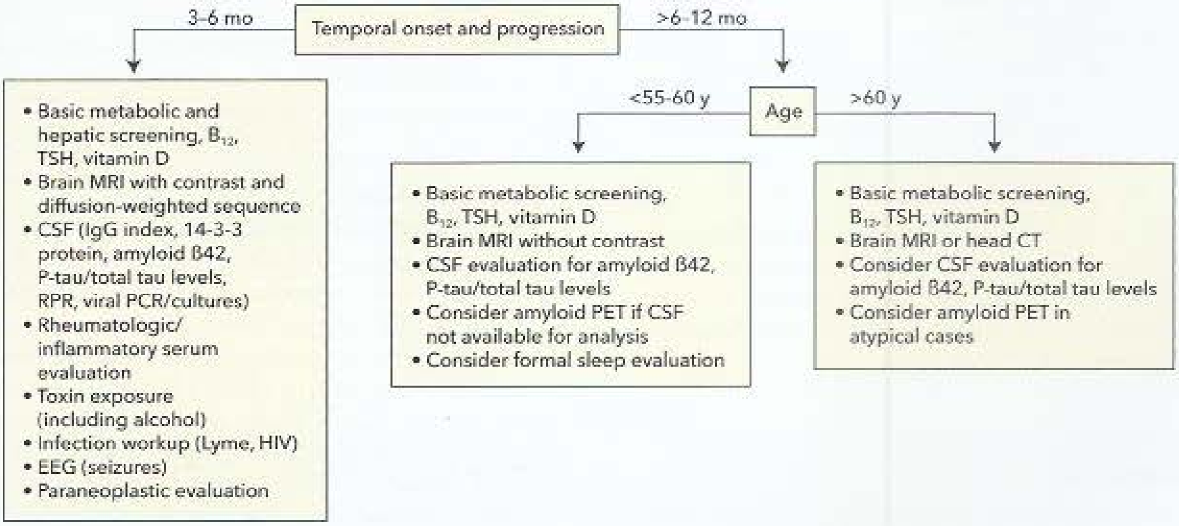

FIGURE 15. Diagnostic test consideration in patient with a dementia syndrome. CSF = cerebrospinal fluid; EEG = electroencephalography; PCR = polymerase chain reaction; PET = positron emission tomography; P-tau = phosphorylated tau; RPR = rapid plasma reagin test; TSH = thyroid-stimulating hormone.

raise the possibility of a more uncommon type of dementia, additional diagnostic tests and early referral to a specialist should be considered (see Figure 15).

Several more specialized testing modalities are available. These tests should be reserved for patients with an uncertain diagnosis (for example, to distinguish dementia from pseudodementia), for an atypical progression of a previously established diagnosis (such as an excessively slow course of Alzheimer disease), and for discriminating between two types of dementia with overlapping features (such as the detection of Alzheimer disease-specific biomarkers). These tests, if required, are typically ordered by a dementia specialist.

These specialized diagnostic tests fall into two categories:

1. Disease-specific tests: measurement cerebrospinal fluid (CSF) levels of the tau protein and 42 residue form of amyloid-β peptide ($A\beta_{42}$) in patients with Alzheimer disease; prion-specific PET (using ^{18}F fluorodeoxyglucose [FDG]) to detect amyloid plaques in Alzheimer disease; and dopamine-transporter single-photon emission CT (SPECT) in patients with cognitive impairment and symptoms of parkinsonism (see Movement Disorder chapter).
2. Disease nonspecific tests: FDG-PET to measure cerebral metabolism; SPECT measuring cerebral blood flow to detect disease-relevant patterns; MRI to detect and measure brain atrophy; and CSF analysis to detect inflammation, infection, neuronal injury, and paraneoplastic antibodies.

KEY POINTS

- Many bedside cognitive evaluation tools have demonstrated adequate sensitivity and specificity for detecting cognitive impairment in population-based settings; no compelling data support the superiority of one test over another.
- The minimum evaluation in slowly progressive dementia syndrome in an older patient includes assessment for a reversible cause with a general neurologic examination; evaluation for depression, sleep disorders, alcohol use, and a family history of dementia; a detailed medication review; basic laboratory studies, including vitamin B_{12} and thyroid-stimulating hormone measurement; and basic neuroimaging (MRI or CT without contrast).
- HVC Specialized tests for dementia–including cerebrospinal fluid tests, single-photon emission CT and PET scans–should be reserved for uncertain diagnoses or atypical presentations; they are usually ordered in conjunction with dementia specialists.

Dementias

Dementia syndromes can be divided into neurodegenerative and nonneurodegenerative categories. Neurodegenerative dementias involve a progressive loss of the underlying brain tissue related to a pathologically identifiable pattern of protein accumulation. Distinction between syndromes typically can be made through careful consideration of the temporal onset and progression, the core cognitive dysfunction, and the associated neurologic and nonneurologic signs and symptoms.

Neurodegenerative Diseases

Mild Cognitive Impairment

Within the framework of early detection of dementia, the diagnosis of mild cognitive impairment (MCI) is a commonly used measure to identify patients with clear symptoms of cognitive decline who do not meet criteria for dementia. The formal criteria for MCI are a subjective report (from either the patient or a witness) of a decline in cognitive abilities with relative preservation of day-to-day function and evidence of cognitive impairment on cognitive testing.

The annual risk of MCI progressing to dementia ranges from 5% to 15%, but a significant percentage of patients (as many as 20%) have normal findings on subsequent examinations. The risk of progression depends on the number of cognitive domains affected and the presence of markers of an underlying neurodegenerative process. Because of wide variability in the risk of progression, steps should be taken to confirm the underlying cause of the symptoms. The initial diagnostic approach should follow that used in patients with dementia, and specialized testing (CSF analysis, PET) is not recommended unless a specific dementia syndrome is suspected. Abnormalities on these studies may help more accurately predict the risk of progression.

Treatment

No specific treatments are currently approved for MCI, and no medications have been shown to prevent progression to dementia. All conditions that can contribute to cognitive impairment, however, should be aggressively treated.

KEY POINT

- No specific treatments are currently approved for mild cognitive impairment, and no medications have been shown to prevent progression to dementia. HVC

Alzheimer Disease

The most common memory-predominant dementia is Alzheimer disease, which likely accounts for 60% to 80% of neurodegenerative dementias. Age is the greatest risk factor; after age 65 years, the prevalence doubles every 5 years. A second major risk factor is the presence of one or two copies of the apolipoprotein-E ε4 (APOE ε4) allele. Additional risk factors include a family history of dementia, female sex, history of stroke, and (to a lesser extent) head injury and cardiovascular disease. Evidence suggests that education, regular exercise, a Mediterranean diet, and cognitively stimulating leisure activities provide protection against developing Alzheimer disease.

The pathophysiology of Alzheimer disease is unclear. The principal pathologic findings, however, include brain volume loss, extracellular fibrillar Aβ plaques, and intracellular neurofibrillary tau tangles. Notably, the development of Aβ pathologic features begins as early as 15 to 20 years before symptom onset.

The typical presentation of Alzheimer disease is that of an insidious worsening of memory, language, and visuospatial abilities. Manifestations include forgetfulness (misplacing objects, missing appointments, frequently repeating questions or statements, missing bill payments), word-finding difficulties, hesitation in speech, and navigational problems (difficulty with directions while driving, even to familiar places, or disorientation in unfamiliar places). These symptoms are often followed by problems with executive function (organizational abilities and multitasking), problems with calculations (managing finances), and behavioral and mood symptoms (apathy, depression, anxiety, irritability, and agitation). In most instances, the patient's insight remains well preserved early in the disease. As the disease progresses, behavioral symptoms, including delusions, become more common. In contrast to dementia with Lewy bodies, however, hallucinations are rare. Motor symptoms and gait problems also do not typically occur until well into the moderate stages of the disease when daily function is significantly impaired. Early hallucinations and motor problems suggest the presence of a disorder other than Alzheimer disease (**Table 27**).

In younger-onset Alzheimer disease, nonmemory symptoms are more frequently the predominant pattern and include language-predominant, executive function-predominant (impaired organizational abilities, disorganized thoughts, poor attention span), and visual/perceptive-predominant (impaired depth perception, navigational problems, problems with coordination) forms. Memory impairment is initially minimal.

Evaluation

MRI of the brain supports the diagnosis of Alzheimer disease when it shows evidence of decreased volume of the

TABLE 27. Features That Distinguish Alzheimer Disease From Other Dementias

Dementia Type	Clinical Features
Alzheimer disease	Impaired memory or forgetfulness as prominent early symptom
	Minimal motor symptoms until disease reaches moderate severity (that is, at the point of significant impairment of activities of daily living)
	Rare visual hallucinations
	Delusions not common at early stages of disease (that is, at the point of relatively preserved activities of daily living)
Dementia with Lewy bodies	Severe autonomic symptoms (such as orthostatic hypotension, constipation, and erectile dysfunction)
	Sleep disorders (such as rapid eye movement sleep behavior disorder and daytime hypersomnia)
	Severe fluctuations in mental status or seizure-like activity
	Early visual hallucinations
	Syncopal events or unexplained episodes of severe alteration in mentation
	Repeated falls
	Severe sensitivity to medications that act on the central nervous system
Frontotemporal dementia	Poor insight into impairment or denial of impairment, especially when cognitive impairment is mild
	New-onset obsessive-compulsive behaviors
	Criminal behaviors
	Gluttonous eating behaviors or adoption of bizarre food restrictions or fads
	Motor neuron disease (such as muscle wasting)
Vascular cognitive impairment	Pronounced gait disorder and repeated falls, especially early in the disease course (at mild dementia stage)
	Emotional incontinence (explosive crying, laughter)
	Pronounced apathy
	Severe cognitive slowing
Normal pressure hydrocephalus	Pronounced gait disorder and repeated falls, especially early in the disease course (at mild dementia stage)
	Minimal cognitive impairment, compared with much greater gait disorder and non-memory-predominant pattern
	Pronounced bladder incontinence proximate to onset of gait changes

hippocampi (**Figure 16**), although this is a nonspecific finding. When seen in MCI, decreased hippocampal volume predicts a higher likelihood of progression to Alzheimer disease. When the MRI is normal and the diagnosis is in question or a non-Alzheimer disease process is being considered, functional brain scans (FDG-PET or perfusion SPECT) can be used to look for the Alzheimer disease pattern of decreased brain function in the bilateral parietal and temporal regions.

In situations involving an uncertain diagnosis or a younger patient, Alzheimer disease–specific biomarkers also can be sought. A CSF test for Alzheimer disease biomarkers is FDA approved and frequently covered by insurers. In the presence of dementia, a pattern of decreased $A\beta_{42}$ and increased tau and phosphorylated tau levels is highly specific for Alzheimer disease; conversely, a normal $A\beta_{42}$ level has a high negative-predictive probability for Alzheimer disease. Three Aβ plaque PET scans are FDA approved for detecting these findings, but their role in the diagnosis of dementia is unclear. Trials are currently underway that may further delineate the role of amyloid scanning in the evaluation of dementia and Alzheimer disease.

Treatment

The nonpharmacologic management of Alzheimer disease includes aggressively treating possible factors contributing to disease progression, such as sleep disorders (including obstructive sleep apnea) and cardiovascular disease; risk factors for cardiovascular disease also should be addressed. Adhering to an exercise program should be encouraged. Dietary recommendations for slowing cognitive decline in Alzheimer disease or MCI remain uncertain. Given the links between cardiovascular disease risk factors and Alzheimer disease, it is generally recommended that affected patients follow a "heart healthy" diet (a diet rich in whole grains, fruits, and vegetables and low in simple carbohydrates, polyunsaturated or trans fatty acids, nitrates, and alcohol). The use of nutraceuticals (supplements enriched with nutrient precursors of many substrates for healthy brain function) has shown benefit in some, but not all, trials and remains controversial. If homocysteine levels are elevated, folic acid supplementation is recommended. There is moderate evidence showing a benefit of vitamin E (200-400 U/d) for moderate Alzheimer disease but not for MCI. No conclusive data have shown a link between statin use and development of Alzheimer disease, and meta analyses of randomized controlled trials have shown no clear benefit or harm to cognition from statins. However, given the numerous case reports of cognitive decline after statin therapy, the FDA has issued a warning about possible worsening cognition after initiation of some statins. Clinicians should consider discontinuing statin therapy if there is a clear temporal link between starting this therapy and significant cognitive decline.

The acetylcholinesterase inhibitors donepezil, rivastigmine, and galantamine are approved for treating mild to moderate dementia in patients with Alzheimer disease and have demonstrated modest benefits in cognitive performance without clear improvements in daily functioning. These three drugs have differences in pharmacodynamics and pharmacokinetics but appear equally efficacious. Because of their possible adverse effects on conduction, acetylcholinesterase inhibitors should be used with caution or avoided in patients with bradycardia or other conduction abnormalities. A transdermal form of rivastigmine is available but should be used

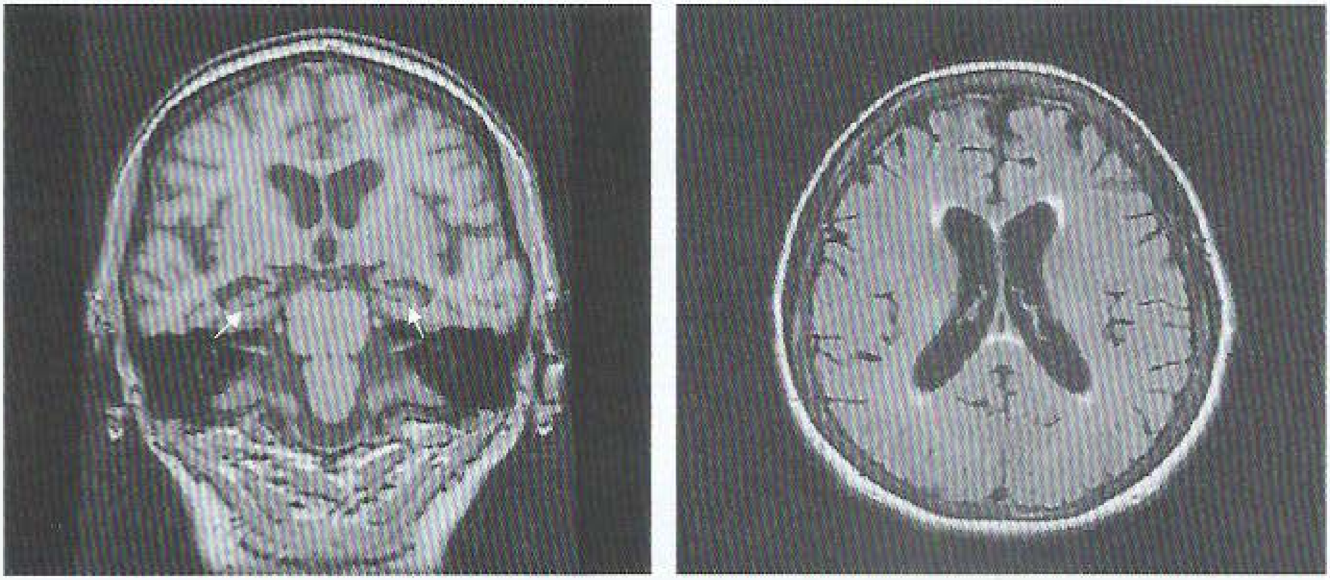

FIGURE 16. MRI findings showing bilateral hippocampal atrophy (*arrows*), which is a typical feature of Alzheimer disease, and diffuse cortical atrophy, which is recognized widening of the sulci and enlargement of the ventricles.

only after intolerance of oral forms has been established. The most common adverse effects are gastrointestinal issues, which result in discontinuation of the medication in nearly 20% of patients. Additional adverse effects include syncope, agitation, nocturnal cramps, and vivid dreams. Donepezil should be used with caution in patients with a history of seizures.

The *N*-methyl-D-aspartate receptor antagonist memantine is approved for moderate to severe dementia in patients with Alzheimer disease associated with significant functional impairment and is not associated with adverse cardiovascular effects. It has no established benefit in mild dementia. Some evidence suggests that combining an acetylcholinesterase inhibitor and *N*-methyl-D-aspartate receptor antagonist provides a synergistic benefit, but only when the latter is added at the moderate stage of dementia.

Antibodies targeting Aβ plaques represent another potential means of treatment and are the subject of current study. Preliminary clinical trials have shown that the antibody aducanumab reduces Aβ plaques in Alzheimer disease accompanied by a slowing of clinical decline.

KEY POINTS

- Evidence suggests that education, regular exercise, a Mediterranean diet, and cognitively stimulating leisure activities provide protection against developing Alzheimer disease.
- An MRI of the brain supports the diagnosis of Alzheimer disease when it shows evidence of decreased volume of the hippocampi.
- Acetylcholinesterase inhibitors have demonstrated modest benefits in cognitive performance in patients with mild to moderate Alzheimer disease without clear improvements in daily functioning; memantine is approved for moderate to severe dementia in patients with Alzheimer disease associated with significant functional impairment.

Frontotemporal Dementia

The frontotemporal dementias (FTDs), which comprise language variant and behavioral variant types, are the second most common cause of neurodegenerative dementia in patients younger than 65 years. The language variant FTDs consist of the primary progressive aphasias and are discussed separately in Language-Predominant Dementias. In behavioral variant FTD, there is a slight male predominance and shorter disease duration than in Alzheimer disease. As many as 10% of patients with behavior-variant FTD have a family history consistent with an autosomal-dominant inheritance of dementia, and as many as 30% to 40% have evidence of a family history of a dementia. Amyotrophic lateral sclerosis occurs in as many as 20% to 30% of patients with behavior-variant FTD and generally portends a much more rapid progression than other forms of FTD. The pathology underlying FTD involves neurofibrillary tau tangles or transactive response DNA-binding protein 43 inclusions.

The most prominent feature of behavioral-variant FTD is an alteration in personality and behavior that typically develops years before the onset of cognitive impairment. A clue to the diagnosis early in the disease is discordance between normal or near-normal performance on objective cognitive testing and a significant degree of functional impairment. Because these behaviors often manifest as obsessive-compulsive tendencies, impulsivity, apathy, and impaired judgment, patients with this disorder are often misdiagnosed as having bipolar disorder, obsessive compulsive disorder, and depression. Other common symptoms are emotional coldness, disinhibition, excessive spending, and excessive eating, particularly of high-caloric foods. These behaviors occasionally result in legal troubles. Unlike patients with Alzheimer disease, those with behavioral-variant FTD often have poor insight into their disease.

Diagnostic criteria have been proposed, with the diagnosis of behavioral-variant FTD being established when three of the following six criteria are met: early behavioral disinhibition, early apathy or inertia, early loss of sympathy or empathy, perseverative or compulsive behaviors, hyperorality and dietary changes, and neuropsychological deficits in executive function with memory and visuospatial sparing.

Evaluation

Because cognitive testing results can be normal early in the disease course, Alzheimer disease screening tools are not helpful for evaluating FTD. When this diagnosis is suspected, detailed cognitive testing by a neuropsychologist is indicated.

Because structural lesions of the frontal lobes can result in a syndrome similar to behavioral variant FTD, neuroimaging with MRI or CT is mandatory. Additionally, many patients with behavioral-variant FTD have frontotemporal lobe atrophy visible on imaging (**Figure 17**). If the MRI is normal, a functional brain scan (FDG-PET or perfusion SPECT) may show a pattern of prominent frontal lobe abnormalities.

A CSF evaluation also can be helpful in distinguishing FTD from Alzheimer disease because the $A\beta_{42}$ level is typically depressed in Alzheimer disease but normal in FTD.

Finally, because of the association with amyotrophic lateral sclerosis, all patients with a diagnosis of behavioral-variant FTD should be monitored closely for muscle weakness, cramping, or fasciculations.

Treatment

There are currently no approved therapies to treat behavioral-variant FTD, and clinical trials testing the effectiveness of acetylcholinesterase inhibitors and memantine have shown no benefit (and, in the case of memantine, possible detriment). Treatment is symptomatic and can involve collaboration with a psychiatrist.

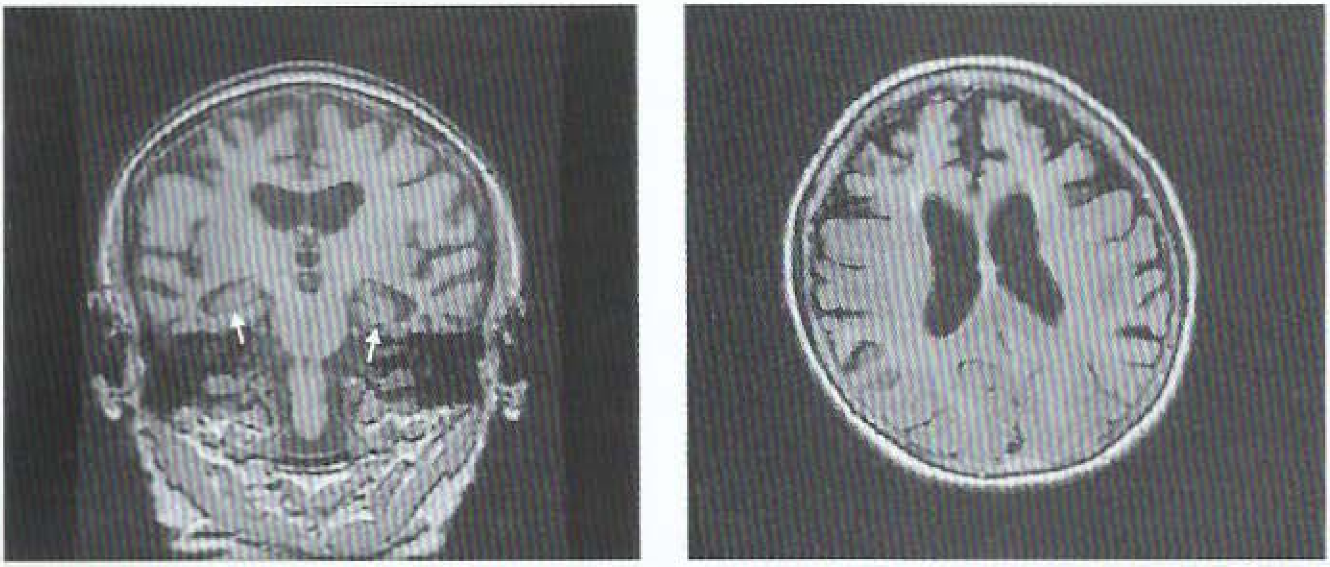

FIGURE 17. Brain MRI findings showing changes associated with frontotemporal dementia, including bilateral hippocampal atrophy (arrows) and more severe temporal and frontal cortical atrophy.

KEY POINT

- A clue to the diagnosis of behavioral variant frontotemporal dementia early in the disease course is discordance between normal or near-normal performance on objective cognitive testing and a significant degree of functional impairment.

Language-Predominant Dementias

The primary progressive aphasias (PPA) are a group of neurodegenerative dementia syndromes in which a progressive impairment in language is the principal cognitive deficit and cause of functional impairment. PPAs can be subdivided into nonfluent and fluent (semantic) variants. In nonfluent PPA, patients predominantly have problems with language production; those with fluent PPA largely have problems with comprehension. Although language decline is common in many dementia syndromes, in PPA it is the symptom noted first, and language is often the only cognitive domain affected for years before the development of additional cognitive deterioration. Pathologically, the PPAs are related to FTD and Alzheimer disease but typically occur at a younger age. Because of the relationship to FTD, the fluent (semantic) variant of PPA often has significantly more behavioral symptoms than the nonfluent variant.

Evaluation

The language components of the cognitive screening evaluation are disproportionately affected in language-predominant dementias. Sentence or phrase repetition, timed word production, and object naming are all impaired. Because most cognitive tests are language based, patients with PPA often perform worse than expected given their level of day-to-day functioning (the opposite of what is seen in behavioral variant FTD).

Structural imaging can be very helpful; attention should be paid to asymmetric involvement of the left temporal lobe, which controls language in most patients (**Figure 18**). Functional brain imaging (FDG-PET or perfusion SPECT) can identify a pattern of asymmetric hemispheric abnormality (left greater than right) in patients with inconclusive brain MRIs.

As with FTD, CSF evaluation can be helpful in diagnosing a language-predominant dementia if it identifies an Alzheimer disease pattern (decreased $A\beta_{42}$ with elevated levels of tau and phosphorylated tau), which may help with tailoring treatment.

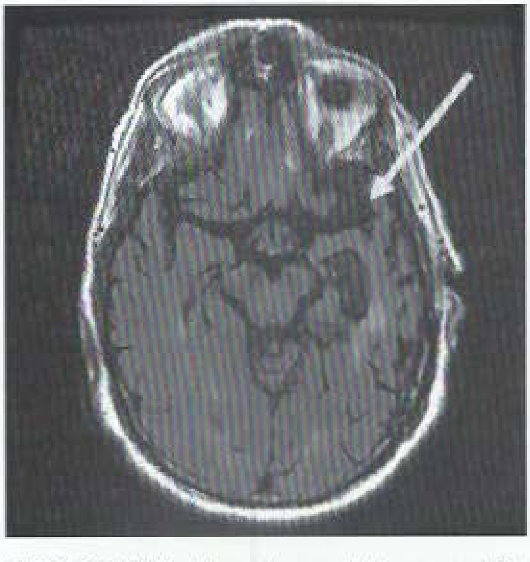

FIGURE 18. Brain MRI of a 64-year-old woman that shows severe left temporal lobe atrophy (arrow), consistent with fluent primary progressive aphasia.

Treatment

There are no pharmacologic therapies specifically approved for PPA. All affected patients should be assessed by a speech therapist. If language comprehension is an issue, assistive language devices can be helpful.

KEY POINT

- Because most cognitive tests are language based, patients with a primary progressive aphasia often perform worse than expected given their level of day-to-day functioning, in contrast to what is seen in behavioral-variant frontotemporal dementia.

Chronic Traumatic Encephalopathy

Chronic traumatic encephalopathy (CTE) is technically a pathologic diagnosis. Because of its relationship with a history of head injuries–most commonly, repeated head trauma–the term also is used clinically. The frontal and temporal lobes are most susceptible to damage from head trauma, and symptoms often reflect damage to these areas. CTE may develop over many years, which makes the diagnosis challenging, particularly when it occurs in patients in their sixties and seventies when the prevalence of other dementias also increases.

A major clinical feature of the disease is the greater frequency of somatic symptoms, particularly headache, that precede the onset of cognitive symptoms. Similarly, the behavioral and mood findings of apathy, irritability, impulsivity, emotional outbursts, and depression often occur before overt cognitive impairment. The cognitive pattern is often one of cognitive slowing and disorganized thought processing, with less involvement of memory and visuospatial function early in the disease course. As the disease progresses, symptoms of mild parkinsonism, such bradykinesia and gait changes, frequently occur.

Evaluation

A history of repeated head trauma is necessary for the diagnosis. Cognitive testing often will demonstrate a pattern of cognitive slowing (problems with timed tasks) as a prominent finding. In patients with more advanced disease, memory impairment may occur. No specific pattern of brain atrophy is seen on structural brain imaging, which can help differentiate CTE from FTD (which is associated with frontal lobe atrophy).

Treatment

No clinical trials comparing various treatments have been performed in CTE. Cholinergic deficits have been identified pathologically, which suggests that acetylcholinesterase inhibitors might be useful. As in behavioral-variant FTD, treatment is often symptom directed and includes Parkinson disease medications for motor symptoms, antidepressants, mood stabilizers, and (occasionally) stimulants for severe apathy. Close monitoring for suicidality also should be part of treatment strategy for patients with CTE.

KEY POINT

- The cognitive pattern typical of chronic traumatic encephalopathy is often one of cognitive slowing and disorganized thought processing, with less involvement of memory and visuospatial function early in the disease course; as the disease progresses, symptoms of mild parkinsonism, such as bradykinesia and gait changes, frequently occur.

Dementia with Lewy Bodies and Parkinson Disease Dementia

Because Parkinson disease is a progressive neurodegenerative disorder, cognitive symptoms frequently develop at some point in the disease course. When dementia occurs well after the motor symptoms, it is considered Parkinson disease dementia. When dementia and motor symptoms develop within 1 to 2 years of each other, it is classified as dementia with Lewy bodies (DLB).

DLB is the second most common neurodegenerative dementia after Alzheimer disease. α Synuclein deposits, or Lewy bodies, are the chief pathologic feature of DLB and commonly coexist with pathologic features of Alzheimer disease. The prevalence of DLB significantly increases with age, and this dementia often progresses more rapidly than Alzheimer disease. The clinical diagnosis rests on the key features of dementia, parkinsonian motor features (particularly gait problems and slowness of movements), visual hallucinations, and frequent fluctuations in attention (**Table 28**). The latter may manifest as acute confusional episodes or brief, focal seizures with alteration of awareness (formerly known as complex partial seizures).

Distinguishing DLB from Alzheimer disease on the basis of cognition alone can be difficult, but other symptoms can help differentiate the two. Delusions and hallucinations are common and frequently occur at the mild stages of DLB. Additionally, significant sleep problems, especially daytime sleepiness, can be a debilitating feature of DLB, and rapid eye movement sleep behavior disorder is much more common.

TABLE 28. Diagnostic Features of Dementia With Lewy Bodies

Features	Specific Symptoms
Central feature	Dementia
Core features	Parkinsonism, fluctuations in attention, and recurrent visual hallucinations
Suggestive features	Rapid eye movement sleep behavior disorder and (typically) severe neuroleptic sensitivity
Supportive features	Transient episodes of loss of consciousness, significant daytime somnolence, severe delusions (especially early in dementia course), apathy, repeated falls, and orthostatic hypotension

Making the diagnosis of DLB as early as possible is important because the behavioral problems associated with this condition frequently result in the use of antipsychotic agents. Many patients with DLB are extremely sensitive to neuroleptic medications, particularly first-generation agents, and are at high risk for developing a severe worsening of symptoms resembling neuroleptic malignant syndrome.

Evaluation

The evaluation of DLB is similar to that of the other dementia syndromes, and the cognitive impairment is often similar to that of Alzheimer disease. CSF evaluation is often inconclusive in DLB. The best diagnostic tools remain the clinical history and examination.

Treatment

Although not formally approved for DLB, acetylcholinesterase inhibitors can be effective in treating the cognitive symptoms of the disorder, according to expert opinion. Rivastigmine has been approved for treating Parkinson disease dementia but not DLB; there is no evidence that memantine is beneficial. The treatment of behavioral symptoms is often necessary, but first-generation antipsychotic agents are strongly contraindicated. In the case of severe hypersomnolence, stimulant type medications can be considered.

KEY POINTS

- The clinical diagnosis of dementia with Lewy bodies rests on the key features of dementia, parkinsonian motor features (particularly gait problems and slowness of movements), visual hallucinations, and frequent fluctuations in attention.
- Many patients with dementia with Lewy bodies are extremely sensitive to neuroleptic medications, particularly first-generation agents, and are at high risk for developing a severe worsening of symptoms resembling neuroleptic malignant syndrome.

Treatment Approach to Neurobehavioral Symptoms of Dementia

Behavioral and psychiatric symptoms of dementia are a common problem in patients with dementia disorders and are among the most common reasons for admission to long term care facilities. Nonpharmacologic environmental and behavioral treatments should be emphasized for these patients, although some pharmacologic therapies may improve function and patient safety. Antidepressant agents should be considered the first-line therapy for symptoms related to mood and anxiety. If appropriate, acetylcholinesterase inhibitors also may be tried early in the disease course. Benzodiazepines should be avoided, except in cases of extreme anxiety.

The use of antipsychotic agents to treat behavioral and psychiatric symptoms of dementia should be considered on an individual basis. Strong evidence links use of antipsychotic agents with increased mortality in older persons with dementia. At the same time, there is evidence of benefit for certain antipsychotic agents (such as risperidone, aripiprazole, and olanzapine). If antipsychotic agents are needed, newer generation medications should be started at low doses with a regimented titration and a plan for regular follow up evaluation and dose decreases. These drugs are associated with an increased risk of sudden death (likely cardiac), especially in the first 3 to 6 months of taking the medication; this risk should be clearly discussed with families before initiating the therapy and only after all other treatments have been tried. It is also advisable to obtain an electrocardiogram before the first dose to ensure that the patient's QT interval is normal; if the corrected QT interval is prolonged (>450 ms for men and >470 ms for women), antipsychotic agents should not be used.

Nonneurodegenerative Dementias

Two of the most common nonneurodegenerative dementias are normal pressure hydrocephalus (NPH) and vascular cognitive impairment. Both share the symptoms of prominent gait impairment and a pattern of cognitive slowing with less memory impairment.

Normal Pressure Hydrocephalus

NPH is characterized by the triad of gait changes, urinary incontinence, and cognitive impairment. Gait impairment, the most prominent feature, is characterized by a wide based gait, short step length, and often problems with starting ambulation (hesitation).

Evaluation

Gait changes can occur for multiple reasons and in several neurodegenerative diseases, so recognition of the gait pattern specific for NPH is crucial. Similarly, alternative causes for urinary incontinence should be excluded. Cognitive testing typically reveals a pattern of slowing and executive cognitive impairment; some patients may require formal neuropsychological testing.

A brain MRI or CT scan should be obtained because NPH cannot be diagnosed without evidence of ventriculomegaly (**Figure 19**). Lumbar puncture with high-volume (30 50 mL) CSF removal and determination of opening pressure also is required. A timed gait evaluation should be performed just before CSF removal and within 60 minutes after removal. Objective improvement in gait after CSF removal is an accurate predictor of NPH improvement with shunting.

Treatment

CSF diversion through a ventriculoperitoneal shunt is the definitive treatment. Gait disturbance is the clinical symptom most amenable to ventricular shunting. The longer cognitive impairment has been present and the more pronounced the memory problem, the less certain is the response to shunting. If response to high volume CSF removal is uncertain, referral to a neurosurgeon for a lumbar drain can be pursued. In the

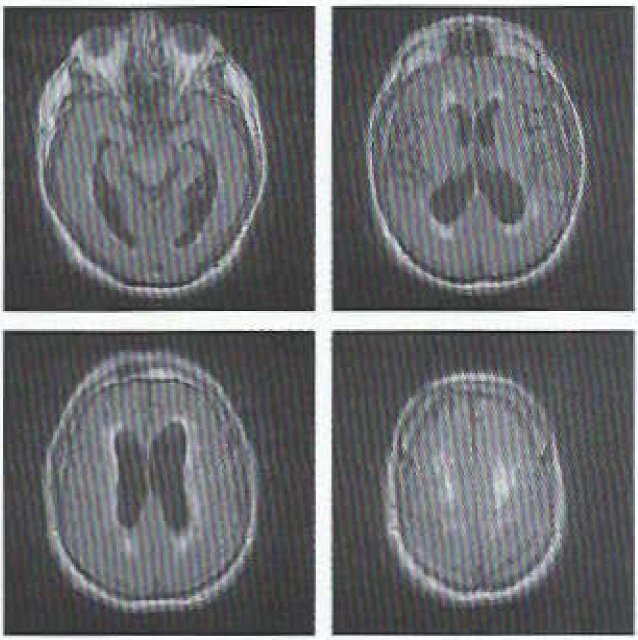

FIGURE 19. Multiple axial fluid-attenuated inversion recovery (FLAIR) MRIs of a 68-year-old man that show ventriculomegaly, little cortical atrophy, and mild periventricular FLAIR hyperintensities, all consistent with normal pressure hydrocephalus.

absence of a clear response to either high-volume CSF removal or lumbar drainage, a permanent ventricular shunt should not be pursued, and another diagnosis should be considered.

KEY POINTS

- Normal pressure hydrocephalus is characterized by the triad of gait changes, urinary incontinence, and cognitive impairment.
- Normal pressure hydrocephalus cannot be diagnosed without evidence of ventriculomegaly (enlarged cerebral ventricles) on a brain MRI or CT scan of the head; cerebrospinal fluid diversion through a ventriculoperitoneal shunt is the definitive treatment.

Vascular Cognitive Impairment

Vascular cognitive impairment encompasses a category of disorders in which the causal link between cerebrovascular disease and cognitive impairment is strong. In older populations, vascular cognitive impairment is likely second only to Alzheimer disease as the most common primary cause of dementia (but not of neurodegenerative dementia; see earlier discussion of dementia with Lewy bodies). This disorder may occur concurrently with Alzheimer disease in older patients.

The likelihood of vascular cognitive impairment increases with age and is associated with systemic vascular risk factors and a history of stroke (either clinically diagnosed or based on neuroimaging evidence). Several features distinguish vascular cognitive impairment from Alzheimer disease (see Table 27). Two major signs of vascular cognitive impairment are early gait impairment and pseudobulbar affect ("emotional incontinence") that can manifest as excessive crying or laughter disproportionate to the context of the situation and is abrupt in onset and discontinuation.

Evaluation

Evaluation of vascular cognitive impairment relies on identification of vascular risk factors and, particularly, previous stroke. Abrupt changes in cognition and a cognitive pattern of disproportionate cognitive slowing compared with memory impairment are often noted.

As with NPH, brain imaging is a critical component supporting the diagnosis. In vascular cognitive impairment, MRIs typically display a pattern of diffuse and confluent changes in the white matter of the brain (**Figure 20**), cerebral microhemorrhages, and/or cortical infarcts beyond the mild periventricular hyperintensities commonly seen in older patients. The presence of severe extracranial or intracranial vascular disease also supports this diagnosis.

Treatment

Medications useful in treating Alzheimer disease are not approved for use in vascular cognitive impairment. However, some evidence suggests a modest benefit of the acetylcholinesterase inhibitors in vascular cognitive impairment, and treatment with this class of medications is generally recommended. Trials with memantine additionally indicated a modest cognitive benefit. However, aggressive treatment of vascular risk factors may be most beneficial.

KEY POINT

- Two major signs of vascular cognitive impairment are early gait impairment and pseudobulbar affect.

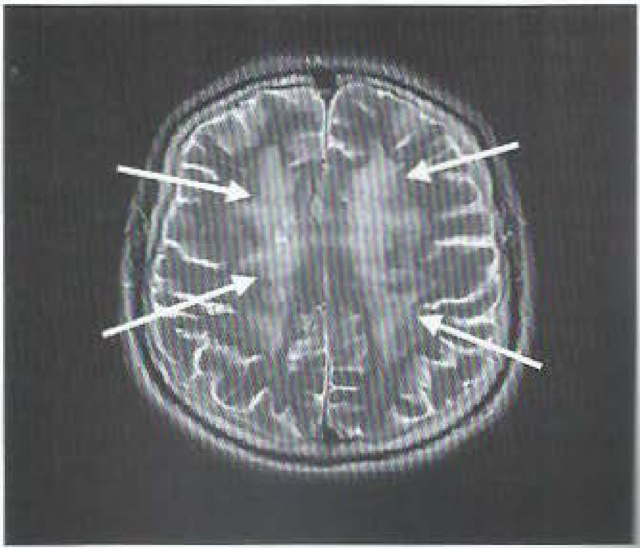

FIGURE 20. Axial T2-weighted MRI of the brain showing diffuse subcortical white matter hyperdensities (*arrows*) in the bilateral hemispheres. These findings are consistent with a severe microangiopathy seen in advanced vascular cognitive impairment.

Rapidly Progressive Dementia

Because of the many possibly treatable causes of rapidly progressive dementia, a systematic approach is required and can identify the underlying cause in most patients. The differential diagnosis includes Creutzfeldt-Jakob disease (CJD), paraneoplastic syndromes, autoimmune/inflammatory encephalopathy (lupus encephalopathy, Sjögren syndrome, Hashimoto encephalopathy, multiple sclerosis), granulomatous disease (central nervous system sarcoidosis, Behçet syndrome, neurosyphilis), vasculitis (primary or secondary), some infections (HIV, herpes simplex virus, *Borrelia burgdorferi*-caused disease), and toxicities (from alcohol or drug abuse, exposure to heavy metals).

CJD is a potentially transmissible prion-related disorder that often presents with rapidly progressive dementia. Time from disease onset to death is approximately 12 months in as many as 80% of patients with CJD. The rapid cognitive decline seen with this disorder is associated with myoclonus, gait problems, and interruption of the circadian rhythm. MRI is one of the most sensitive diagnostic tools for CJD, typically showing a pattern of increased intensity in the diffusion-weighted sequence in the basal ganglia and various cortical regions. Periodic sharp wave complexes are often seen on electroencephalography and are helpful but not necessary in making the diagnosis. CSF testing may establish the presence of 14-3-3 protein and an elevation in total tau protein levels.

Paraneoplastic syndromes can also present with rapidly progressive dementia, and many of these disorders are treatable if diagnosed early (see Neuro-oncology for further discussion of these syndromes).

KEY POINT

- MRI is one of the most sensitive diagnostic tools for Creutzfeldt-Jakob disease and typically shows a pattern of an increased intensity in the diffusion-weighted sequence in the basal ganglia and various cortical regions.

H Delirium

Although rarely considered in the same light as acute dysfunction of other major organs, delirium is an acute alteration of brain function and should be approached with the same intent of alleviating the dysfunction as rapidly as possible. The clinical consequences of delirium are substantial because delirium is associated with greater hospital morbidity, more medical complications, longer lengths of stay, and a higher rate of discharge to long-term care facilities. The frequency of delirium depends on the setting and the patient population. Postsurgical and ICU patients, particularly older populations, have the highest prevalence of delirium. Risk also increases with the presence of baseline dementia, multiple medical problems, polypharmacy, and hypoxia.

Prevention of delirium is likely more effective than treatment of established delirium. In hospitalized patients, providing patients with assistive visual and hearing devices, adequately controlling pain, limiting psychoactive medications, frequent orientation, encouraging mobility, and enabling uninterrupted sleep on a normal sleep-wake cycle may help decrease the likelihood of developing delirium.

Delirium presents with numerous and variable symptoms and signs (**Table 29**). The core of delirium is an alteration in the arousal system (that is, in the ascending reticular activating system of the midbrain, thalamus, and hypothalamus that modulates sleep-wake transitions). Fluctuations in mental status, altered circadian rhythm, and poor attention are the hallmarks of the clinical syndrome. The Confusion Assessment Method is a useful tool with good sensitivity for diagnosing delirium. It includes assessment of onset and course, inattention, disorganized thinking, and level of consciousness.

Delirium also has a multitude of causes (**Table 30**), and almost any acute medical condition may provoke delirium in a susceptible patient. Evaluation for the underlying cause of delirium is mandatory but often difficult because the patient may not be able to direct the evaluation. Consideration should always be given to life-threatening causes of delirium, including vascular events and infection. Neuroimaging may be necessary, and in the appropriate setting, electroencephalography can be used to ensure that seizures are not the cause of the confusion.

Treatment

The primary treatment of delirium is identification and treatment of the underlying cause. Use of sedating medications, such as benzodiazepines and haloperidol, should be avoided because they may cause or worsen delirium. In severe cases, and especially when safety is a concern, newer-generation antipsychotic agents may help control behavior. Additionally, increasing evidence suggests that the melatonin receptor agonist ramelteon may be useful. The effectiveness of acetylcholinesterase inhibitors remains uncertain. H

TABLE 29. Clinical Features of Delirium
Fluctuations in mentation
Hypervigilance more than hypovigilance
Disorganized thoughts
Delusions
Hallucinations
Poorly sustained attention
Altered circadian rhythm
Tremors (with occasional myoclonus)
Hyperreflexia
Motor restlessness more than stupor
Amnesia
Increased sympathetic tone (particularly with alcohol withdrawal)

TABLE 30. Causes of Delirium

Drugs
Prescription medications (such as psychotropic medications, opioids, sedative hypnotics, anticonvulsants, antiparkinsonian agents, glucocorticoids, immunosuppressants, antiarrhythmics, antihypertensive agents, skeletal muscle relaxants, antibiotics)
Nonprescription medications (such as NSAIDs, antihistamines)
General anesthesia
Alcohol or drug withdrawal
Central nervous system diseases
Seizure, including nonconvulsive status epilepticus
Acute ischemic infarction
Intracranial hemorrhage
Head injury
Metabolic disorders
Electrolyte disturbance
Hyperglycemia or hypoglycemia
Hypoxemia
Hypercarbia
Organ failure (such as cardiac failure, kidney impairment, liver failure)
Endocrine (such as hypothyroidism, hyperthyroidism, hyperparathyroidism, Cushing syndrome, adrenal insufficiency)
Nutritional (such as malnourishment, vitamin B_{12} deficiency, thiamine deficiency, niacin deficiency)
Cardiovascular disease
Myocardial infarction
Hypertensive emergency
Dysrhythmias
Infections[a]
Surgery
Trauma
Environment
Post-acute care setting
ICU
Other
Acute blood loss
Uncontrolled pain
Fecal impaction
Urinary retention

[a]Such as urinary tract infections, respiratory infections, cellulitis, meningitis or encephalitis, and sepsis.

KEY POINT

- The confusion assessment method is a useful tool with good sensitivity for diagnosing delirium; treatment is identification and treatment of the underlying causes.

Movement Disorders

Overview of Movement Disorders

Movement disorders are characterized by hypokinetic and hyperkinetic patterns of motor output. The most typical hypokinetic pattern, parkinsonism, is characterized by paucity and slowness of movements. Hyperkinetic disorders are categorized on the basis of the type of involuntary excessive movements displayed (**Table 31**).

Neurologic examination of movement disorders should include detailed assessment of motor function and gait. The key features in the classification of movement disorders are the speed, amplitude, and fatigability of voluntary movements and the rhythmicity, suppressibility, randomness, and directionality of hyperkinetic movements. Muscle tone should be assessed for rigidity, which is an increase in resistance to passive movements that is independent of the velocity and direction of those movements. Gait examination should consider the base of standing, pace of ambulation, stride length, foot clearance off the ground, postural stability, and arm swing.

KEY POINT

- The key features in the classification of movement disorders are the speed, amplitude, and fatigability of voluntary movements and the rhythmicity, suppressibility, randomness, and directionality of hyperkinetic movements.

Hypokinetic Movement Disorders

The most common type of hypokinetic movement disorder is parkinsonism. Parkinson disease is the most common form of parkinsonism; Parkinson-plus syndromes combine features of parkinsonism with other features found in the patient's history or physical examination. Vascular parkinsonism results from microvascular disease or large strokes and is characterized by predominant gait impairment with relative sparing of upper extremities. Parkinsonism also may arise as an adverse effect of medication. Some patients with normal pressure hydrocephalus exhibit parkinsonism with gait instability, dementia, and urinary incontinence (see Cognitive Impairment).

Parkinson Disease

Parkinson disease is a slowly progressive neurodegenerative disorder involving the gradual loss of dopamine-producing neurons in the substantia nigra. Pathologic findings include the aggregation of α-synuclein protein and formation of Lewy body inclusions in the substantia nigra and other brain regions. Both genetic influences and exposure to certain environmental factors, including pesticides, can increase the risk for Parkinson disease. Aging is a major risk factor.

Clinical Features of Parkinson Disease

Parkinson disease has four cardinal signs: tremor at rest, bradykinesia, rigidity, and gait/balance impairment. Resting

TABLE 31. Classification of Movement Disorders

Movement Type	Clinical Features	Examples
Hypokinetic		
Parkinsonism	Cardinal features: bradykinesia/hypokinesia, rigidity, rest tremor, postural instability Additional features: freezing gait, stooped posture, masked face, hypophonia, micrographia	Parkinson disease, Parkinson-plus syndromes, dementia with Lewy bodies, vascular parkinsonism, hydrocephalus, medication-induced parkinsonism, Wilson disease, young-onset Huntington disease
Hyperkinetic		
Tremor	Rhythmic oscillations of a body part, can occur at rest or with action (including postural or kinetic) Intention tremor is characterized by marked increase in tremor amplitude near target	Rest tremor: parkinsonism Postural and kinetic tremor: essential tremor, enhanced physiologic tremor Intention tremor: cerebellar
Dystonia	Sustained or intermittent, stereotyped, and directional twisting and posturing movements of various body parts; can be associated with sensory trick ("geste antagoniste" or movement or touch that interrupts dystonia)	Primary: primary generalized dystonia (DYT1), dopa-responsive dystonia, torticollis, blepharospasm, writer's cramp Secondary: basal ganglia lesion, anoxic injury, postencephalitic, cerebral palsy, medications
Chorea	Random, nonrepetitive, quick, unsustained, purposeless movements with a flowing dance-like pattern	Huntington disease, neuroacanthocytosis, poststreptococcal, chorea gravidarum, autoimmune, metabolic, vascular, medications
Hemiballismus	Unilateral high-amplitude proximal flailing, ballistic, choreiform movements of limbs	Lesions of contralateral subthalamic or adjacent parts of basal ganglia (often stroke)
Athetosis	Slow convoluted writhing movements of digits and toes Pseudoathetosis similar but elicited by eye closure	Early-life damage to basal ganglia (hypoxia, kernicterus, vascular event) Pseudoathetosis caused by lesions of proprioceptive pathway
Tic	Stereotyped, brief, purposeless, rapid movements that break the flow of normal movements; can be simple or complex, motor or vocal; premonitory sensory urges, suggestibility, and suppressibility Stereotypy is a coordinated ritualistic and highly repetitive movement	Tourette syndrome, autism, developmental delay syndromes, Huntington disease, medications Stereotypy can be normal in young children or associated with developmental delay and neurometabolic syndromes
Myoclonus	Rapid, shock-like, jerky movement of isolated body parts or whole body	Metabolic, medications, infections, autoimmune, myoclonic epilepsies, benign essential myoclonus, corticobasal degeneration, Alzheimer disease, prion disease, sleep-related (hypnic jerks)
Akathisia	Inner restlessness associated with repetitive movements	Drug-induced, restless legs syndrome
Psychogenic	Highly variable, inconsistent, distractible, acute onset, episodic, with variable frequency of tremor, with fixed dystonia, with acrobatic uneconomic gait (astasia-abasia)	Conversion disorder (functional neurological symptom disorder), malingering, somatoform disorder

tremor is characteristically unilateral at onset and remains asymmetric. The tremor typically emerges after few seconds of outstretched posturing of the arms and during ambulation. Bradykinesia is characterized by slowness and gradual lessening of the amplitude of repetitive movements. This feature often is associated with reductions in facial expression and arm swing. Small handwriting (micrographia) is common, and patients may report difficulty with both fine and gross movements. Rigidity, manifesting as increased resistance to movement, is often asymmetric and may occur on the same side as tremor. It may be "cogwheel" with intermittent release of the rigidity with passive movement, resulting in a jerking or ratcheting quality of movement. As many as 30% of patients with Parkinson disease have a tremor-free akinetic rigid syndrome at presentation. Gait disturbance manifests as a slow, narrow-based, and shuffling gait with associated reduced arm swings, stooped posture, and imbalance when turning. As the disease progresses, severe freezing of gait and postural instability are noted. In contrast, cerebellar ataxic gait is characterized by a wide base, frequent truncal swaying and veering, and impaired tandem walking in a straight line. Additional cerebellar signs, such as nystagmus, scanning speech, and extremity dysmetria, also may be seen in cerebellar disorders. Early prominent postural instability with frequent falls suggests a Parkinson-plus condition.

Parkinson disease also is associated with various nonmotor symptoms, ranging from autonomic dysfunction to problems with sleep, mood, and cognition (**Table 32**). Premotor symptoms, including hyposmia (diminished sense

TABLE 32. Nonmotor Symptoms of Parkinson Disease

Category	Nonmotor Symptoms
Cognitive	Bradyphrenia (slow processing), mild subcortical cognitive impairment (slow processing speed, impaired short-term memory, and attention deficits with relative sparing of cortical functions, such as language and declarative memory), dementia possible at advanced stages
Affective and behavioral	Primary: depression, anxiety, apathy, pseudobulbar affect (emotional incontinence)
	Medication-induced: psychosis, impulse control disorder, punding (purposeless stereotyped behavior), dopamine dysregulation syndrome (craving for dopaminergic medications)
Sleep related	Sleep fragmentation, sleep-wake reversal, rapid eye movement sleep behavior disorder, restless legs syndrome, medication-related sedation and sleep attacks, fatigue
Autonomic	Constipation, postural hypotension, bladder and sexual dysfunction, sialorrhea, seborrhea, excessive sweating, hyposmia or anosmia
Musculoskeletal	Truncal and cervical stooped posturing, camptocormia (truncal flexion during standing and walking), frozen shoulder, dystonic joint deformities in hands and toes, and fall-related injuries
Pain related	Painful dystonia, painful rigidity, mechanical pain, central and visceral pain

of smell), constipation, and rapid eye movement (REM) sleep behavior disorder, may precede onset of motor symptoms by years.

Cognitive impairment in Parkinson disease is not uncommon and initially involves mild subcortical deficits, especially in processing speed, short-term memory, and attention domains. Cortical functions, such as language and declarative memory, are relatively spared. As many as a third of patients may develop dementia in the later stages of Parkinson disease, but early cognitive impairment is a red flag pointing to other diagnoses, such as dementia with Lewy bodies (see Cognitive Impairment).

Diagnosis of Parkinson Disease

The diagnosis of Parkinson disease requires the presence of bradykinesia and at least one other cardinal feature and the absence of red flags for atypical forms of parkinsonism (**Table 33**). Brain imaging is recommended to rule out

TABLE 33. Red Flags for Atypical Forms of Parkinsonism

Red Flags	Features	Likely Alternative Diagnosis
Dysautonomia	Prominent orthostatic hypotension, urinary incontinence, impotence, inappropriate sweating (mild autonomic deficits can been seen in early Parkinson disease)	MSA
Abnormal eye movements	Supranuclear vertical gaze palsy (which can be overcome by oculocephalic maneuver), slowness of vertical saccades	PSP
Prominent early cognitive impairment	Dementia within first year of onset (mild cognitive impairment common in Parkinson disease; dementia may develop in a notable subgroup of patients in advanced stages)	DLB but sometimes PSP or vascular parkinsonism
Visual hallucinations	Early and not provoked by medications (levodopa-induced hallucinations can be seen in Parkinson disease, especially in later stages)	DLB
Early prominent postural instability and falls	Within first year of onset	MSA, PSP
Prominent gait ataxia	With or without additional cerebellar deficits (dysmetria, nystagmus)	MSA
Symmetric or markedly asymmetric involvement	In Parkinson disease, characteristically asymmetric at onset and throughout its course	
	Lack of asymmetry indicative of atypical parkinsonism	MSA, PSP
	Very severe asymmetric involvement, possibly suggestive of corticobasal degeneration, and usually associated with severe fixed dystonic posturing, myoclonus, apraxia, and sensory cortical deficits	CBD
Rapid onset and step-wise deterioration	More suggestive of vascular parkinsonism (Parkinson disease is associated with slow onset and gradual course)	Vascular parkinsonism
Lack of response to levodopa*	Most important red flag of atypical parkinsonism	MSA, PSP, CBD, vascular parkinsonism

CBD = corticobasal degeneration; DLB = dementia with Lewy bodies; MSA = multiple system atrophy; PSP = progressive supranuclear palsy.

*Must not be secondary to adverse effects or insufficient dosing of medication.

vascular disease and hydrocephalus. A dopamine transporter scan, such as a single-photon emission CT scan of the brain using ioflupane-123 ligand, can be used as a confirmatory test. Its use, however, should be limited to select patients in whom the differentiation between Parkinson disease and essential tremor or drug-induced parkinsonism is not possible on clinical grounds. The test cannot distinguish between Parkinson disease and Parkinson-plus conditions. A therapeutic trial of levodopa also can help when the diagnosis is in question; patients with Parkinson disease usually respond well, but other disorders rarely improve with levodopa.

Depression and Fall Screening

All patients with Parkinson disease should be screened for depression and be assessed for fall risk. Depression and anxiety are common nonmotor symptoms of Parkinson disease and can be detected by using common clinical mood and anxiety scales. Treatments include psychotherapy, antidepressants (excluding antipsychotic agents), and dopaminergic medications (when mood symptoms correlate with motor symptoms). Depression should be distinguished from apathy, a state of reduced motivation and goal-directed behavior that is not associated with emotional distress.

Falls in Parkinson disease may be related to postural imbalance, insufficient control of motor symptoms, or orthostatic hypotension. Detection of risk factors for falling and implementation of a multidisciplinary approach—including medications, therapy, supportive devices, and education—can reduce morbidity and costs related to falls. Postural stability can be best assessed by the pull test, in which an examiner throws the patient off balance by pulling backward on the shoulders. A positive test, characterized by toppling into examiner's arms or taking more than two corrective steps, is the most reliable predictor of a risk of backward falls.

Treatment of Parkinson Disease

Currently, no medication with established efficacy is available to slow the progression of Parkinson disease. Rigorous daily exercise can improve the quality of gait and balance and also may provide disease-modifying benefits.

Symptomatic treatments include medications (**Table 34**), surgical therapy, and supportive measures. Dopaminergic medications (various formulations of the dopamine precursor levodopa, pramipexole, ropinirole, and rotigotine) are the mainstay in the treatment of motor symptoms. Several other medications can supplement the dopaminergic agents and help reduce the medication-induced complications that may emerge over time as Parkinson disease progresses (see Table 34).

Dopamine agonists, such as pramipexole and ropinirole, are the preferred initial first-line dopaminergic medications in patients younger than 65 years and may be used with levodopa as an adjunct treatment at any point in the disease course. Many experts encourage the use of dopamine agonists in younger patients to decrease long-term exposure to levodopa and to delay the onset of levodopa-related complications. Patients taking dopamine agonists should be warned about impulse control disorder, which manifests as a tendency to engage in out-of-character impulsive behaviors, such as excessive gambling, overspending, and hypersexuality. Other adverse effects include sleep attacks, dependent edema, nausea, hallucinations, and confusion.

Eventually, all patients with Parkinson disease will require levodopa. The drug should be started as initial therapy in older patients and as replacement or additional therapy in younger patients with insufficient response to dopamine agonists. Carbidopa, a peripheral decarboxylase inhibitor, blocks the adverse effects of levodopa outside the brain and is used in combination with levodopa. Motor fluctuations, such as the "wearing-off" phenomenon (loss of the beneficial effect of the medication before the next dose is administered) and medication-induced dyskinesia (involuntary choreic movements), are common problems with levodopa. These complications emerge in as many as 50% of patients treated for more than 5 years with levodopa and may reflect disease progression rather than duration of exposure to levodopa.

Several formulations of levodopa are commercially available, including oral immediate-release, extended-release, and rapidly disintegrating formulations; an enteral gel infusion also has recently become available (see Table 34). The immediate-release formulations of levodopa have a rapid peak dose effect that many patients find helpful. The newer extended-release formulations may provide a more sustained control of symptoms throughout the day, which can prove beneficial by reducing any wearing off between doses. Wearing off also can be lessened by frequent dosing of levodopa and by the addition of dopamine agonists, catechol-*O*-methyltransferase inhibitors, or monamine oxidase B inhibitors. Amantadine can be added to the treatment regimen to prevent dyskinesia. Anticholinergic medications also can be added to provide additional benefit in patients with prominent tremor or dystonia; adverse events, such as urinary retention, constipation, tachycardia, and memory impairment, are limiting factors, especially in older patients with dementia. Finally, droxidopa, a norepinephrine precursor, can improve neurogenic orthostatic hypotension.

Medication-induced psychosis, especially visual hallucinations, also can occur with use of dopaminergic medications. Treatment strategies include addressing any systemic trigger, simplifying the medication regimen (including removal of non-levodopa medications and decreasing the levodopa dosage), and, if needed, using antipsychotic agents. Pimavanserin, a selective serotonin 5-HT2b receptor inverse agonist, is the

TABLE 34. Medications for Parkinson Disease

Class	Forms	Clinical Indication
Dopamine precursor	Levodopa	Most effective treatment for motor deficits
		Initial therapy in patients older than 65 years or those with severe motor symptoms, freezing, or falls
		Second-line treatment in younger patients who have failed dopamine agonists
Oral	Immediate-release levodopa	Maintenance therapy during waking hours, peak effect provides good "on"-time benefit
	Continued-release levodopa	Nighttime therapy
	Extended-release carbidopa-levodopa	Maintenance therapy if immediate-release formulation causes motor fluctuations and dyskinesia
	Orally disintegrating levodopa	Rapid relief of sudden "off"-time
Enteral gel	Enteral levodopa	Maintenance therapy in advanced Parkinson disease associated with severe motor complications of immediate-release levodopa, provides sustained levodopa release, can cause a higher rate of gastrointestinal complications
Decarboxylase inhibitors	Carbidopa, benserazide[a]	Suppression of peripheral adverse effects of levodopa
Dopamine agonists		
Oral	Pramipexole, ropinirole, cabergoline[a]	First-line treatment in younger patients, adjuvant therapy to limit total dose of levodopa
Patch	Rotigotine	Similar to oral forms
Subcutaneous injection	Apomorphine	Rapid relief of sudden "off"-time
Catechol-O-methyltransferase inhibitors	Entacapone (often used), tolcapone (hepatic toxicity)	Counteracting of wearing-off phenomenon, prolongation of levodopa effect
Monoamine oxidase type B inhibitors	Selegiline, rasagiline, safinamide	Initial therapy in mild cases, potentiation of levodopa effect, tremor
Glutamate NMDA antagonist	Amantadine, rimantidine	Dyskinesia, tremor, fatigue
Anticholinergic agents	Trihexyphenidyl, benztropine	Tremor, mild benefit against parkinsonism, higher adverse effect profile in old age and dementia
Antipsychotic agents	Pimavanserin, quetiapine	Medication-induced psychosis, medication-reduction strategies should be prioritized, increased mortality risk in patients with dementia
Norepinephrine precursor	Droxidopa	Neurogenic orthostatic hypotension, requires coadministration with carbidopa; other measures (including liberal salt intake, fludrocortisone, and midodrine) also are effective

NMDA = *N*-methyl-D-aspartate.

[a]Available in Europe but not the United States.

only FDA-approved medication for Parkinson psychosis; quetiapine and clozapine also are often used as less expensive, albeit off-label, options.

In patients with severe motor complications, enteral infusion of carbidopa-levodopa gel through a jejunal tube with a portable pump can provide more sustained levodopa release and reduce motor complications. High rates of gastrointestinal and tube-related complications are limiting factors.

Deep brain stimulation (DBS) is a surgical therapy that involves the delivery of electrical stimulation to key brain targets, such as the subthalamic nucleus and the globus pallidus interna. The stimulation disrupts the abnormal neurophysiologic activity within the basal ganglia and simulates a patient's response to medications. This mode of treatment is indicated for patients who continue to benefit from levodopa but experience severe motor fluctuations or have a refractory tremor. An algorithm for selection of appropriate candidates for DBS surgery is shown in **Figure 21**. Given the evidence of improved quality of life after early implementation of DBS, the FDA has expanded the indication for this procedure to patients with Parkinson disease of 4 years' duration who experience early motor fluctuations.

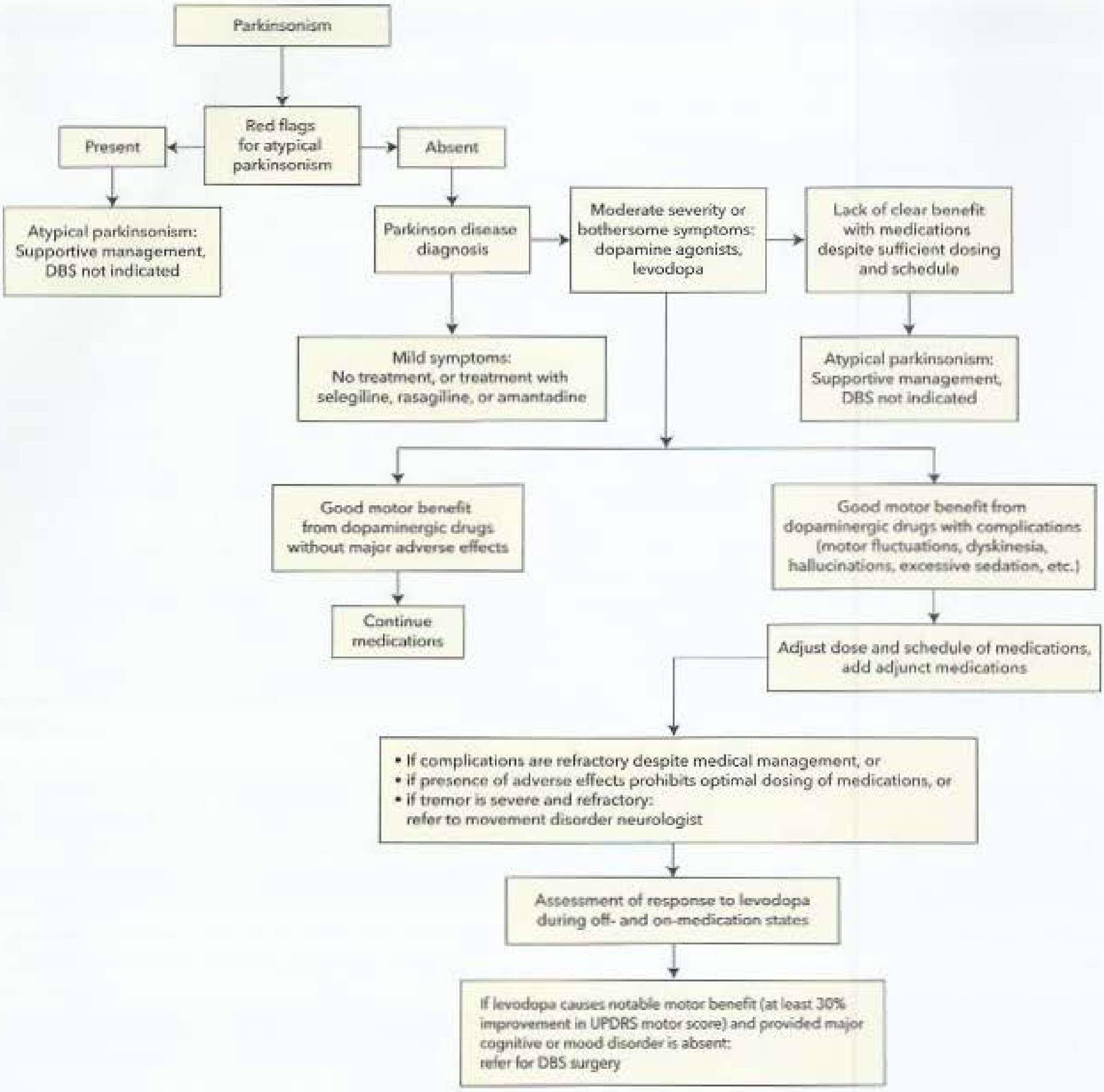

FIGURE 21. Algorithm for evaluation of candidacy for deep brain stimulation in Parkinson disease. DBS = deep brain stimulation; UPDRS = Unified Parkinson Disease Rating Scale.

KEY POINTS

- The diagnosis of Parkinson disease requires the presence of bradykinesia and at least one of the other cardinal features of the disorder (tremor at rest, cogwheel rigidity, and gait or balance impairment) and the absence of red flags for atypical forms of parkinsonism.
- HVC In Parkinson disease, a dopamine transporter scan, such as single-photon emission CT of the brain, is unnecessary except to differentiate between Parkinson disease and essential tremor or drug-induced parkinsonism if the distinction cannot be made on clinical grounds.

(Continued)

KEY POINTS *(continued)*

- Detection of risk factors for falling and implementation of a multidisciplinary approach—including medications, therapy, supportive devices, and education—can reduce morbidity and costs related to falls; a positive pull test is the most reliable predictor of a risk of backward falls in Parkinson disease. HVC
- Dopamine agonists are the preferred initial first-line medication in patients younger than 65 years and levodopa is the preferred initial therapy in older patients.
- Deep brain stimulation is indicated for patients who continue to benefit from levodopa but experience severe motor fluctuations or have a refractory tremor.

Parkinson-Plus Syndromes

Parkinson-plus syndromes typically present with a combination of parkinsonism and additional features that are atypical for idiopathic Parkinson disease. These conditions often are more rapidly progressive than Parkinson disease and less responsive to standard therapies, particularly levodopa. The primary syndromes include progressive supranuclear palsy, multiple system atrophy (formerly Shy-Drager syndrome, acquired olivopontocerebellar atrophy, and striatonigral degeneration), and corticobasal degeneration. Patients with progressive supranuclear palsy have parkinsonism, impairment in both ocular range of movement and saccades (very fast jumps from one eye position to another, particularly in the vertical direction), facial dystonia, axial rigidity, and prominent postural instability with early falls. Multiple system atrophy presents with a combination of parkinsonism, ataxia, and severe dysautonomia and also is associated with early falls. Corticobasal degeneration often presents with markedly asymmetric parkinsonism and frequently is associated with dystonia, myoclonus, cortical sensory deficits, cognitive deficits, and apraxia (impaired motor planning).

KEY POINT

- Parkinson-plus syndromes often are more rapidly progressive than Parkinson disease, have additional features that are atypical for idiopathic Parkinson disease, and are less responsive to standard antiparkinsonian therapies, particularly levodopa.

Drug-Induced Parkinsonism

A number of drugs, especially dopamine receptor–blocking antipsychotic agents, can cause parkinsonism (**Table 35**). Drug-induced parkinsonism is symmetric, lacks nonmotor features, and is reversible after removal of the causative agent. Several other extrapyramidal complications of dopamine-receptor blockers have also been described (**Table 36**).

TABLE 35. Medications Causing Drug-Induced Parkinsonism

Medication Class	Examples
Common	
Antipsychotics	Typical: haloperidol, chlorpromazine
	Atypical: risperidone, olanzapine, ziprasidone, aripiprazole
Antiemetics	Metoclopramide, prochlorperazine
Dopamine depleters	Tetrabenazine, reserpine
Uncommon	
Mood stabilizers, antiepileptic agents	Lithium, valproic acid
Other	Amiodarone, flunarizine, SSRIs (including fluoxetine)

SSRI = selective serotonin reuptake inhibitor.

TABLE 36. Extrapyramidal Complications of Dopamine Receptor Blockers

Type of Movement Disorder	Symptoms
Acute reactions (reversible)	
Acute dystonia	Immediate dystonic spasms; often involves neck, face, larynx, and eyes (oculogyric crisis); rapid reversal with intravenous diphenhydramine
Acute akathisia	Immediate sensation of restlessness with urge to constantly move and pace
Subacute or chronic syndromes (reversible)	
Parkinsonism	Similar to Parkinson disease, dose dependent, resolves within months after removal of the offending agent, symmetry and absence of nonmotor features favors a drug-induced over an idiopathic cause
Tardive syndromes (late onset, may be irreversible)	
Tardive dyskinesia	Repetitive stereotyped choreiform movements, oral-buccal-lingual predominance (tongue protrusion, lip smacking, puckering and chewing movements), also can affect the extremities (piano playing movements, foot tapping) and trunk (including respiratory muscles)
Tardive dystonia	Sustained dystonic posturing commonly affecting the face, neck, trunk, and arms; extensor cervical and axial dystonia
Tardive akathisia	Chronic sensation of inner restlessness with urge to constantly move and pace, leg crossing, body rocking
Tardive tics	Clinical presentation similar to Tourette syndrome but triggered after exposure to dopamine blockers
Other Disorders	
Withdrawal emergent syndrome (reversible)	Choreiform dyskinesia starting after sudden withdrawal from a neuroleptic agent and stopping with reinstitution of the causative agent (or another agent from same class) and a subsequent slow taper within a few months; differential diagnosis of tardive dyskinesia that may be masked by antipsychotic agents and only unmasked after their removal (and may become persistent)
Neuroleptic malignant syndrome (treatable emergency)	Idiosyncratic, rapid onset and progressive, rigidity, dystonia, hyperthermia, rhabdomyolysis, altered mental status

Hyperkinetic Movement Disorders

Essential Tremor

Tremor is an oscillatory movement of a body part that is classified on the basis of its presence at rest or with action (**Table 37**). Essential tremor is the most common movement disorder and often presents with a bilateral upper extremity postural and action tremor. This type of tremor also can involve the voice, head, or legs. Common features include a positive family history (50% of patients), slow progression, and onset at either adolescence or middle age. The tremor may be alleviated by alcohol and may be aggravated by stress, illness, fatigue, or the use of caffeine or other stimulants. A minority of affected patients experience substantial progression, leading to marked disability.

The differential diagnosis includes enhanced physiologic tremor, which is a low-amplitude tremor that is unnoticeable in most people but may become prominent because of physical and psychological stressors, medications, thyroid disease, or caffeine. Assessment of any form of action tremor should include thyroid function studies and review of medications (**Table 38**). Patients younger than 40 years should undergo screening for Wilson disease with serum ceruloplasmin and 24-hour urine copper measurements, and slit-lamp examination for Kayser-Fleischer rings should be considered. Other rare causes of action tremor include dystonic tremor, rubral tremor, and fragile X–associated tremor/ataxia syndrome (see Table 37).

The treatment of essential tremor is symptomatic. Weighted utensils and wrist weights can help reduce tremor amplitude during feeding. The most effective pharmacologic treatments for essential tremor are propranolol, primidone, and topiramate. Additional second-line options include atenolol, sotalol, clonazepam, gabapentin, and nimodipine.

TABLE 37. Classification of Tremors

Tremor Type	Disease Association	Features
Resting tremor[a]		
Parkinsonian rest tremor	Parkinson disease	Reemergence of tremor after a short delay with outstretched posturing and during ambulation, associated with other parkinsonian signs (rigidity, bradykinesia, gait impairment)
	Atypical, drug-induced, and vascular parkinsonism	Similar to Parkinson disease; tremor sometimes symmetric; red flags for atypical parkinsonism sometimes present
Dystonic tremor	Dystonia	Associated with dystonic posturing; seen both at rest and with action; task specificity seen with action; position dependent, with a null point at which tremor stops
Action tremor		
Postural and kinetic tremor[b]	Essential tremor	Present in the outstretched arm position and with various actions; commonly (but not universally) associated with a positive family history and an improvement in symptoms with ethanol
	Enhanced physiologic tremor	Normal low-amplitude, high-frequency tremor seen in association with triggers, such as stress, drugs, and thyroid disease; similar to essential tremor but resolves with resolution of underlying physiologic stressor
Intention tremor[c]	Cerebellar disease	Tremor during movements that increases in amplitude as hand approaches target (also known as terminal tremor); possible association with other cerebellar symptoms, including dysmetria
	Severe essential tremor	Terminal tremor can be seen but often without prominent cerebellar dysmetria
	Fragile X-associated tremor/ataxia syndrome	Neurodegenerative disease seen in older men who are carriers of a premutation in the fragile X intellectual disability 1 gene; typically, there is a family history of intellectual disability in young males and premature ovarian failure in females; symptoms of (intention) tremor, ataxia, parkinsonism, neuropathy and dementia
Rubral tremor	Cerebellar outflow disorders (multiple sclerosis, stroke, traumatic brain injury)	Coarse proximal tremor present at rest, worse with posturing (especially large-amplitude and proximal tremors in the wing-beating position with elbows flexed), and most severe during movements
Task-specific tremor	Primary writing tremor	Only present with specific task
Orthostatic tremor	Orthostatic tremor	High-frequency tremor emerging in the legs only during standing (orthostatic position); resolving with sitting or action

[a]Tremor present with the affected extremity resting unsupported.

[b]Postural tremor is present with the arm in an outstretched position, and kinetic tremor is present during reaching, writing, and other movements.

[c]Intention tremor is a specific subtype of kinetic tremor that becomes very prominent near target, exhibiting a crescendo of increased severity at the terminal section of the movement path.

TABLE 38. Medications Causing Drug-Induced Action Tremor

Medication Class	Examples
β-Adrenergic agonists	Albuterol, terbutaline, theophylline
Stimulants	Amphetamines, methylphenidate, nicotine, caffeine
Mood stabilizers/ antiepileptic drugs	Lithium, valproic acid, carbamazepine
Neuroleptic agents	Haloperidol, olanzapine (postural and at rest)
Tricyclic antidepressants	Amitriptyline
Selective serotonin reuptake inhibitors	Fluoxetine
Immunosuppressant agents	Cyclosporine, tacrolimus
Other agents	Amiodarone, procainamide, mexiletine, levothyroxine, verapamil, atorvastatin, glucocorticoids

Botulinum toxin injection can help with some tremors, especially those involving the neck and voice, but its benefit for limb tremor is limited by local weakness. Medication-refractory tremor can be effectively treated by targeting the ventral intermediate nucleus of the thalamus with DBS or thalamotomy.

KEY POINTS

- Essential tremor is the most common movement disorder and often presents with a bilateral upper extremity postural and action tremor; common features include a positive family history, slow progression, and onset at either adolescence or middle age.
- The treatment of essential tremor is symptomatic; the most effective pharmacologic agents are propranolol, primidone, and topiramate.

Dystonia

Dystonia involves sustained or intermittent muscle contractions leading to stereotyped and directional twisting and posturing movements of various body parts. Dystonias are classified according to age of onset, body distribution, temporal pattern, associated features, and cause (**Table 39**). Generalized dystonias involve multiple body parts, including the trunk, whereas focal and segmental dystonias have a more restricted distribution and usually spare the lower extremities. Hemidystonia is limited to one side of the body. Generalized dystonias often start at a young age (<25 years) and have inherited, metabolic, or vascular causes. The most common type of generalized dystonia involves mutation in the dystonia 1 gene (*DYT1*). Patients with primary generalized dystonia should be challenged by a short trial of levodopa to screen for dopa-responsive dystonia, a rare but treatable cause of generalized dystonia. Young adults with progressive dystonia should be screened for Wilson disease, especially in the presence of other associated findings (such as tremor and parkinsonism).

Focal adult-onset dystonias include cervical dystonia (spasmodic torticollis), eyelid dystonia (blepharospasm), vocal cord spasmodic dysphonia, and task-specific hand dystonia (writer's cramp). Cervical dystonia often involves involuntary deviation of the head from midline, an irregular head tremor that lessens with positional changes (null point), and transient improvement of movements by specific sensory tricks (such as gently touching the face with the hand). Treatment includes anticholinergic agents, benzodiazepines, baclofen, and levodopa.

TABLE 39. Classification of Dystonia

Clinical Feature	Subtype
Age of onset	Infancy, childhood (<13 years), adolescence (13-18 years), young adulthood (18-40 years), late adulthood (>40 years)
Temporal pattern	Persistent, paroxysmal, action induced
Associated neurologic features	Isolated dystonia (no other deficits), dystonia plus (with parkinsonism or myoclonus)
Anatomic distribution	Focal, segmental (contiguous regions), multifocal (noncontiguous regions), hemidystonia, generalized (trunk plus two other regions)
Paroxysmal	Primary genetic paroxysmal dyskinesia (kinesigenic, nonkinesigenic, exercise induced, hypnogenic), secondary paroxysmal dyskinesia (stroke, demyelination)
Diurnal variation (better in morning)	Dopa-responsive dystonia
Cause	**Example**
Genetic	Autosomal dominant (DYT1, DYT6), autosomal recessive (Wilson disease), X-linked (Lesch-Nyhan syndrome), mitochondrial (Leigh syndrome)
Structural lesion	Hemidystonia secondary to stroke, vascular malformation or lesion in contralateral basal ganglia, postencephalitis, posttraumatic
Neurodegeneration	Parkinson disease, Parkinson-plus syndromes, Huntington disease
Perinatal brain injury	Dystonia associated with cerebral palsy, delayed-onset dystonia
Sporadic	Adult-onset focal dystonia (torticollis, blepharospasm, writer's cramp, musician's cramp, spasmodic dysphonia), Meige syndrome (facial and oromandibular segmental dystonia)
Psychological	Psychogenic dystonia
Medications	Neuroleptic-induced tardive dystonia, antiemetic-induced acute dystonic reaction, antiepileptic drug-induced dystonia

Injection with botulinum toxin targeting the most active muscles in focal dystonia also is beneficial. In genetic or idiopathic dystonia, DBS of the globus pallidus interna can markedly improve symptoms. The benefit of DBS is more variable in secondary dystonia with the exception of tardive dystonia, which responds well.

KEY POINTS

- Dystonia involves sustained or intermittent muscle contractions leading to stereotyped and directional twisting and posturing movements of various body parts.
- Treatment of cervical dystonia includes anticholinergic agents, benzodiazepines, baclofen, and levodopa; injection with botulinum toxin targeting the most active muscles in focal dystonia also is beneficial.

Choreiform Disorders and Huntington Disease

Chorea manifests as random, nonrepetitive, flowing dance-like movements and can be caused by medications, endocrine derangement, streptococcal infection (as in Sydenham chorea in rheumatic fever), autoimmune disease, pregnancy, and neurodegenerative disorders involving the basal ganglia (**Table 40**). The most common neurodegenerative cause of generalized chorea is Huntington disease, which involves symptoms of progressive parkinsonism, gait impairment, impulsiveness, psychiatric disease, and dementia. Substance abuse also has been associated with Huntington disease. An autosomal dominant condition, this disorder is caused by a trinucleotide repeat expansion in the *huntingtin* gene. Age of onset has a reverse correlation with length of repeat expansion and may be younger with paternal transmission (anticipation phenomenon). Huntington disease is invariably fatal. Symptomatic treatments of chorea include the dopamine depleters tetrabenazine and deutetrabenazine, antipsychotic agents, clonazepam, and antiepileptic drugs.

TABLE 40. Causes of Chorea

Cause	Example
Medications	Antipsychotic agents, estrogen-containing drugs, levodopa, amphetamines, methylphenidate, lithium, phenytoin
Pregnancy	Chorea gravidarum
Endocrine	Hyperglycemia (especially acute), thyrotoxicosis
Infection	Streptococcal (Sydenham chorea), prion disease, herpes encephalitis, HIV
Autoimmune	Systemic lupus erythematous, antiphospholipid syndrome, anti-GAD antibody
Paraneoplastic	Anti-CRMP5 antibody, anti-NMDA antibody, voltage-gated potassium channel antibody
Genetic	Benign hereditary chorea, neuroferritinopathy
Neurodegenerative	Huntington disease, Huntington-like disease 2, spinocerebellar ataxia 17 and 8, C9orf72 expansion syndrome, Friedreich ataxia, chorea-acanthocytosis, neurodegeneration with brain iron accumulation

CRMP5 = collapsin response mediator protein 5; GAD = glutamic acid decarboxylase; NMDA = *N*-methyl-D-aspartate

KEY POINT

- Huntington disease is an autosomal dominant condition marked by symptoms of progressive parkinsonism, gait impairment, impulsiveness, psychiatric disease, and dementia.

Myoclonus

Myoclonus is a brief, shock-like, jerky movement that can be physiologic (hiccups, hypnic jerks at sleep onset) or pathologic (caused by medications, toxins, or systemic or central disease) (**Table 41**). Myoclonus can originate from various parts of the nervous system, including the cortex, subcortical structures, the spine, or peripheral nerves. Cortical myoclonus is often epileptic. Negative myoclonus is caused by sudden loss of muscle tone, as seen in asterixis and in the legs after hypoxia (Lance-Adams syndrome). Treatment of myoclonus includes addressing the underlying systemic or toxic cause and administering antimyoclonic agents, such as clonazepam, valproic acid, levetiracetam, zonisamide, or topiramate.

KEY POINT

- Treatment of myoclonus includes addressing the underlying systemic or toxic cause and administering antimyoclonic agents, such as clonazepam, valproic acid, levetiracetam, zonisamide, or topiramate.

Tic Disorders and Tourette Syndrome

Tics are stereotyped, rapid movements interrupting the flow of normal movements. Tics may provide transient relief in response to premonitory unconformable sensations and are at least partially suppressible. Tics usually start during childhood and subside during adulthood, but they may persist in a minority of those affected.

Tourette syndrome is characterized by childhood-onset motor and phonic tics with a duration of at least 1 year. Phonic tics include vocalizations and, less commonly, echolalia (repetition of others' words) and coprolalia (utterance of obscenities). Tic severity may range from minimal to very disruptive. Tourette syndrome is considered a network disease in which basal ganglia and prefrontal cortex interactions are dysregulated. Common comorbidities include attention-deficit/hyperactivity disorder, obsessive-compulsive disorder, and mood disorders. Diagnosis is clinical. Treatment options include reassurance (often appropriate in mild disease), cognitive

TABLE 41. Causes of Acquired Myoclonus

Cause	Example	Features
Metabolic	Kidney, hepatic or respiratory failure, sleep apnea, hyponatremia, hypocalcemia, hyperglycemia	Both positive and negative myoclonus (asterixis)
Endocrine	Hyperthyroidism	With tremor and ophthalmopathy
Toxic	Opioids, gabapentin, amiodarone, SSRIs	Prominent in serotonin syndrome
Infectious	Lyme disease, Whipple disease, viral encephalitis (especially herpes)	Oculomasticatory myorhythmia (rhythmic movements of eye convergence with chewing) in Whipple
Paraneoplastic	Opsoclonus-myoclonus syndrome	Anti-Ri antibody
Autoimmune	Celiac disease, associated with thyroid antibodies	With other symptoms, such as ataxia or encephalopathy
Cortical pathology	Epileptic myoclonus (primary and secondary myoclonic epilepsies), posthypoxic myoclonus (Lance-Adams syndrome), corticobasal degeneration, advanced Alzheimer disease	Epileptic activity on EEG, giant somatosensory evoked potentials
Basal ganglia pathology	Myoclonus dystonia	Genetic, associated with dystonia, ethanol-sensitive
Brainstem pathology	Brainstem reticular myoclonus	Stimulus-sensitive (noise or action) myoclonus, coordinated flexion of trunk and limbs
Cord pathology	Segmental spinal myoclonus, propriospinal myoclonus, multiple sclerosis, cord tumor or trauma	Jerks in limited myotomes (segmental) or spreading distally and proximally (propriospinal), associated with myelopathy signs
Peripheral nerve pathology	Hemifacial spasm	Focal compression or irritation of the facial nerve (cranial nerve VII)

EEG = electroencephalography; SSRI = selective serotonin reuptake inhibitor.

behavioral therapy (including tic diversion techniques), and addressing psychiatric comorbidities. Anti-tic medications are indicated when tics interfere with daily functioning, education, or work. First-line treatments are clonidine, guanfacine, topiramate, levetiracetam, and tetrabenazine. Antipsychotic agents (aripiprazole, pimozide, ziprasidone, risperidone, and haloperidol) can help in the treatment of refractory tics, but the risk of tardive dyskinesia should be considered in adults. Botulinum toxin may be useful for focal tics and severe refractory disease; DBS may also be beneficial in severe disease.

KEY POINTS

- Tics are stereotyped, rapid movements interrupting the flow of normal movements and may provide transient relief in response to premonitory unconformable sensations.
- Tourette syndrome is characterized by childhood-onset motor and phonic tics with a duration of at least 1 year.

Restless Legs Syndrome and Sleep-Related Movement Disorders

Restless legs syndrome (RLS) is a common movement disorder characterized by an urge to move the legs. Patients report an uncomfortable sensation that is worse at rest and at night and is transiently relieved by movement. Patients with RLS should be screened for iron deficiency because iron supplementation in the presence of low-normal ferritin levels (15-75 ng/mL [15-75 µg/L]) may resolve the symptoms. Other risk factors for RLS include uremia, sleep apnea, pregnancy, and certain medications (including selective serotonin reuptake inhibitors, antipsychotic agents, and stimulant drugs). Nonpharmacological measures include improvement of sleep hygiene, exercise, and the use of a vibrational device. First-line pharmacologic treatments include dopamine agonists (especially pramipexole and the rotigotine patch). Additional options include ropinirole, gabapentin, pregabalin, levodopa, and opioid agonists (prolonged release oxycodone-naloxone and methadone). Chronic use of dopamine agonists, however effective, may lead to either augmentation (that is, symptoms start earlier in the day) or rebound (that is, symptoms return with greater severity after the medication wears off). Use of long-acting formulations can lessen both of these complications. Gabapentin enacarbil, an $\alpha_2\delta$ calcium channel ligand, is a slow-release prodrug of gabapentin that is also FDA approved for the treatment of RLS.

Periodic limb movements of sleep are brief triple flexion movements of the legs that repeat in 20-second cycles during sleep. This disorder is very common and can occur independently of or be associated with RLS, sleep-disordered breathing, or narcolepsy. The diagnosis is made by using polysomnography. Treatment of this disorder is only required if it causes marked sleep fragmentation.

REM sleep behavior disorder is caused by loss of normal paralysis during the REM phase of sleep, leading to

dream-enactment behavior. Patients with this condition tend to shout, kick, punch, and jump while dreaming. Diagnosis is based on either the report of a bed partner or polysomnography. The main differential diagnosis is nocturnal epilepsy. REM sleep behavior disorder responds well to clonazepam and melatonin. It is a strong predictor of future development of synuclein-related neurodegeneration, such as Parkinson disease, multiple system atrophy, or dementia with Lewy bodies.

KEY POINTS

- Patients with restless legs syndrome should be screened for iron deficiency because iron supplementation in the presence of low-normal ferritin levels may resolve the symptoms.
- The diagnosis of periodic limb movements of sleep is made by using polysomnography; treatment is only required if the disorder causes marked sleep fragmentation.

Other Drug-Induced Movements

Tardive Dyskinesia

Tardive dyskinesia is an extrapyramidal complication of dopamine receptor-blocking medications (see Table 36). It is associated with characteristic choreiform and dystonic craniofacial movements, which often involve other body parts, such as the neck and trunk. Treatment involves removal of the offending medication. Symptoms of dyskinesia, however, can take months to resolve or become permanent. Longer duration and higher doses of medication exposure, older age, and female gender increase the risk of irreversibility. Risk is highest with typical antipsychotic agents, but many atypical antipsychotic and antiemetic agents also can cause tardive dyskinesia. All patients receiving these agents must be warned about the risk of this complication. Recently, valbenazine, a monoamine depleter, was the first medication to receive FDA approval for treatment of tardive dyskinesia. Other pharmacologic therapies include tetrabenazine, amantadine, clonazepam, and anticholinergic agents. In severe cases, DBS of the globus pallidus may be effective, although it lacks FDA approval for this indication.

H Neuroleptic Malignant Syndrome

Neuroleptic malignant syndrome is an acute life-threatening disorder caused by an idiosyncratic reaction to therapeutic doses of dopamine-blocking agents. Its pathophysiology involves a sudden decrease in dopamine D_2 receptor activity. Patients present with fever, rhabdomyolysis, altered mental status, rigidity, and dystonia. The creatine kinase level often is remarkably elevated. The most effective treatment is removal of the offending agent and supportive management. Treatment options include dopamine agonists and the muscle relaxant dantrolene, although there is weak evidence supporting their effectiveness. Mortality may be as high as 10%. Patients who have dementia with Lewy bodies are particularly susceptible to neuroleptic malignant syndrome. A similar syndrome can be triggered by rapid withdrawal of dopaminergic medication in patients with Parkinson disease, including when medications are stopped in the hospital before surgery. See MKSAP 18 Pulmonary and Critical Care Medicine for more information about neuroleptic malignant syndrome. H

KEY POINTS

- Tardive dyskinesia is an extrapyramidal complication of dopamine receptor-blocking medications characterized by choreiform and dystonic craniofacial movements; symptoms can take months to resolve or become permanent.
- Neuroleptic malignant syndrome is an acute life-threatening disorder caused by exposure to therapeutic doses of dopamine-blocking agents; it presents with fever, rhabdomyolysis, altered mental status, rigidity, and dystonia.

Multiple Sclerosis

Presenting Signs and Symptoms

Multiple sclerosis (MS) is an autoimmune disorder of the central nervous system (CNS) that causes inflammatory damage to the brain, spinal cord, and optic nerve. Most of the overt clinical symptoms of MS occur as a direct consequence of functional interruption of critical axonal pathways by inflammatory lesions. Relapses or flares involve development of neurologic symptoms over the course of hours to days and often peak in severity over the course of days to weeks. This is typically followed by a period of remission lasting weeks to months. Remyelination and recruitment of other brain regions to functionally substitute for the damaged area may result in clinical improvement during times of remission.

The most common clinical manifestations of MS are optic neuritis, myelitis, and brainstem/cerebellar syndromes. Patients with optic neuritis typically have subacute visual deficits in one eye that are occasionally associated with pain with eye movement and/or flashing lights (photopsia). Formal ophthalmologic examination shows a reduction in visual acuity, a scotoma or visual field deficit, difficulty with color discrimination, and an afferent pupillary defect. Papillitis (flared appearance of the optic disc caused by inflammatory changes; **Figure 22**) can sometimes be seen, although this finding only occurs with involvement of the head of the nerve. Optic disc pallor (**Figure 23**) is usually seen as a late consequence of optic neuritis and is secondary to atrophy of the optic nerve.

Spinal cord involvement or myelitis results in sensory and/or motor symptoms below the affected spinal level. Unlike other spinal cord processes, MS generally causes a partial myelitis, and symptoms of full-cord transection are rare; crossed sensory-motor symptoms may also occur (as in

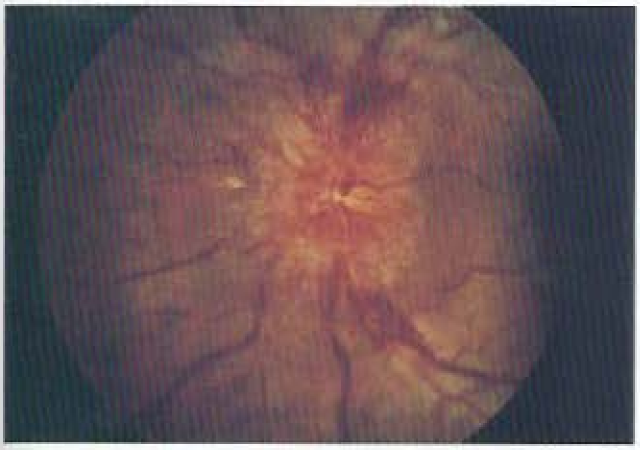

FIGURE 22. Optic nerve papillitis is characterized by hyperemia and swelling of the disk, blurring of disk margins, and distended veins. Papillitis is seen in one-third of patients with optic neuritis.

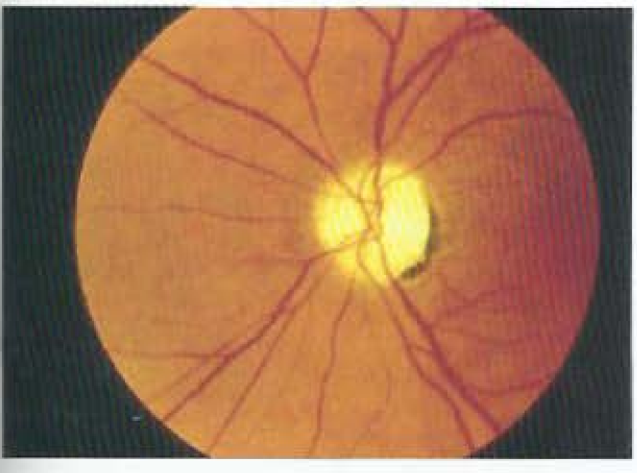

FIGURE 23. A pale, flat optic disk characteristic of optic nerve atrophy.

partial Brown-Séquard syndrome). Neurologic examination generally reveals focal weakness and/or reduced sensation below a specific spinal dermatome. Muscle tone can be reduced acutely, whereas spasticity and hyperreflexia often are delayed findings. During acute inflammation, some patients will also experience a tight, band-like sensation around the body involving the affected spinal level ("MS hug"). Lhermitte sign, which also can occur with upper cervical cord lesions from other causes, manifests as a shock-like sensation radiating down the spine or limbs with flexion of the neck. Urinary frequency, urgency, hesitancy, or retention also may be seen.

Brainstem syndromes often involve pathways for eye movement and result in diplopia or oscillopsia (a sensation of jerking of the visual field). Examination may reveal dysconjugate eye movements, nystagmus, and/or internuclear ophthalmoplegia (inability to adduct one eye and nystagmus in the abducting eye). Disruption of vestibular or cerebellar pathways may result in ataxia and/or vertigo. Neurologic examination will reveal appendicular or truncal ataxia, dysmetria on finger-to-nose testing, difficulty with rapid alternating movements, and impairment of tandem gait.

Most patients with MS also develop subtle, chronic symptoms that occur as a consequence of more widespread cortical demyelination and nonlesional axonal pathology. At least 50% of patients with MS experience cognitive deficits, typically in domains of short-term memory, visuospatial function, and processing speed. Many patients with MS also report fatigue, which can manifest as a feeling of exhaustion despite adequate sleep, a feeling of brain fog, and easy physical fatigability.

H Many patients with MS also experience Uhthoff phenomenon, a transient worsening of baseline neurologic symptoms in the setting of hot weather, physical exertion, or fever. This worsening occurs because of a temporary reduction in neuronal electrical conductance at higher temperatures, which causes magnification of symptoms from previously demyelinated pathways. Any patient with a suspected relapse should be screened for causes of Uhthoff phenomenon masquerading as a relapse (or "pseudorelapse") to avoid unnecessary treatment. Patients often need reassurance and counseling that such events are not indicative of new inflammatory damage. H

KEY POINTS

- Most of the overt clinical symptoms of multiple sclerosis (MS) occur as a direct consequence of functional interruption of critical axonal pathways by inflammatory lesions; the most common clinical manifestations of MS are optic neuritis, myelitis, and brainstem/cerebellar syndromes.
- HVC Any patient with a suspected relapse should be screened for causes of Uhthoff phenomenon (transient worsening of neurologic symptoms associated with increased body temperature) masquerading as a relapse (or "pseudorelapse") to avoid unnecessary treatment.

Diagnosis of Multiple Sclerosis

Diagnostic Criteria and Testing

Because no specific genetic or serologic diagnostic biomarker is available for diagnosing MS, the diagnosis is made through rigorous application of diagnostic criteria that integrate clinical and radiologic findings. The McDonald criteria require symptoms of CNS demyelination separated in space and time from a series of clinical relapses or progression, signs on physical examination, distribution of lesions on MRI, and (if necessary) the presence of cerebrospinal fluid (CSF)-unique oligoclonal bands. Proper application of the diagnostic criteria can prevent unnecessary neurologic testing, referrals, and misdiagnoses. A standardized MRI brain protocol should be used for

all diagnostic evaluations of potential MS. Spinal cord imaging also should be performed in patients with symptoms of myelitis, patients with insufficient features on a brain MRI to support the diagnosis, and patients older than 40 years with nonspecific brain MRI findings. Strict adherence to the McDonald criteria for MS-specific lesions is critical because many other disorders (migraine, head trauma, and cerebrovascular disease) also can cause brain (but not spinal) lesions on MRI. **Figure 24** shows examples of periventricular, juxtacortical, and infratentorial lesions that are specific to MS and satisfy the McDonald criteria; if visible, lesions in the cortex may substitute for juxtacortical lesions, according to the official diagnostic criteria. Ancillary testing can show objective clinical evidence of a demyelinating lesion. Demyelinating lesions of the optic nerve can be electrophysiologically confirmed with visual evoked potentials. Optic coherence tomography, which uses near-infrared light to quantify the thickness of the retinal nerve fiber layer and macula, also can confirm optic nerve damage in acute or previous optic neuritis. Conductance delay in brainstem auditory evoked potentials and somatosensory evoked potentials can act as surrogate markers of demyelination in brainstem and spinal cord pathways. Despite the usefulness of such testing for determining anatomic localization, however, MRI is the only objective measure that fulfills the diagnostic criteria.

CSF testing is not required for a diagnosis of MS if the McDonald criteria are otherwise met. However, CSF findings can be used to support the diagnosis when the MRI criteria are not fully met. The normally functioning blood-brain barrier excludes immunoglobulins from the CSF in healthy persons, which results in a blood to CSF IgG ratio of 500:1 or greater. Oligoclonal bands indicate elevations in oligoclonal immunoglobulin concentrations in the CSF and may result from disruption of the blood-brain barrier or intrathecal production of IgG. The presence of oligoclonal bands in the CSF that are absent in the serum occurs in 85% to 90% of persons with MS. An elevated IgG blood-to-CSF index and an elevated IgG synthesis rate also are possible. Nonspecific mild elevations in the CSF leukocyte count or protein level are sometimes seen.

KEY POINTS

- The McDonald criteria for diagnosing multiple sclerosis require symptoms of central nervous system demyelination separated in space and time from a series of clinical relapses or progression, signs on physical examination, distribution of lesions on MRI, and (if necessary) the presence of CSF-unique oligoclonal bands.
- Proper application of diagnostic criteria can prevent unnecessary neurologic testing, referrals, and misdiagnoses in patients suspected of having multiple sclerosis. **HVC**

Differential Diagnosis of Multiple Sclerosis

Knowledge of the various rheumatologic, inflammatory, infectious, and metabolic disorders with the potential to mimic the clinical signs/symptoms and radiologic changes of MS is important when considering the diagnosis (**Table 42**).

Clinical Course of Multiple Sclerosis

The clinical phenotypic definitions of MS recently have been modified to acknowledge that manifestations of MS are heterogeneous and can evolve over time (**Figure 25**). Approximately 85% of patients with MS experience an initial relapsing-remitting course. Those with a first demyelinating event that does not meet the definition of clinically definite MS are said to have a clinically isolated syndrome. Any future disease activity, defined as a clinical relapse or a new or contrast-enhancing lesion on MRI, results in conversion to a diagnosis of clinically definite relapsing-remitting MS. Because disease-modifying

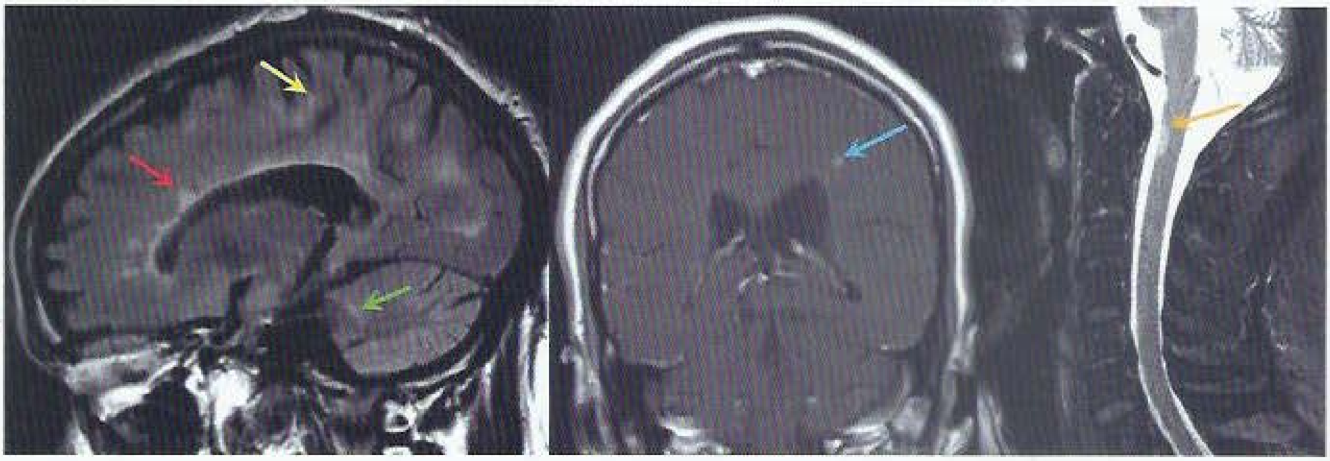

FIGURE 24. *Left*, fluid-attenuated inversion recovery brain MRI that shows periventricular (*red arrow*), juxtacortical (*yellow arrow*), and infratentorial (*green arrow*) lesions specific to multiple sclerosis (MS); if visible, lesions in the cortex can substitute for juxtacortical lesions, according to official diagnostic criteria. *Middle*, coronal T1-weighted postcontrast MRI of the brain showing a contrast-enhancing MS lesion (*blue arrow*). *Right*, sagittal T2-weighted MRI of the spinal cord showing an MS lesion (*gold arrow*).

TABLE 42. Differential Diagnosis of Multiple Sclerosis (*Continued*)

Disorder	Notes
Neoplasia (primary CNS neoplasm [gliomas or lymphomas] or metastatic disease)	Neoplasms with progressively worsening symptoms and neuroimaging findings Brain biopsy indicated when imaging cannot differentiate neoplasms from demyelinating disease
Paraneoplastic syndromes	May cause progressive cerebellar ataxia or myeloneuropathy (neuropathy affecting the spinal cord and peripheral nerves) Personality and mental status changes in addition to seizures and movement disorders possible with paraneoplastic limbic encephalitis Diagnosis often made on the basis of cancer screening and antibody testing
Somatoform disorders	Psychiatric disorders presenting with neurologic-like symptoms that are due to somatization, conversion, and similar conditions Neurologic evaluation findings entirely normal

ADEM = acute disseminated encephalomyelitis; CADASIL = cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; CNS = central nervous system; HTLV = human T-lymphotropic virus; MS = multiple sclerosis; NMO = neuromyelitis optica; SLE = systemic lupus erythematosus.

[a]For more information on idiopathic transverse myelitis, see Disorders of the Spinal Cord.

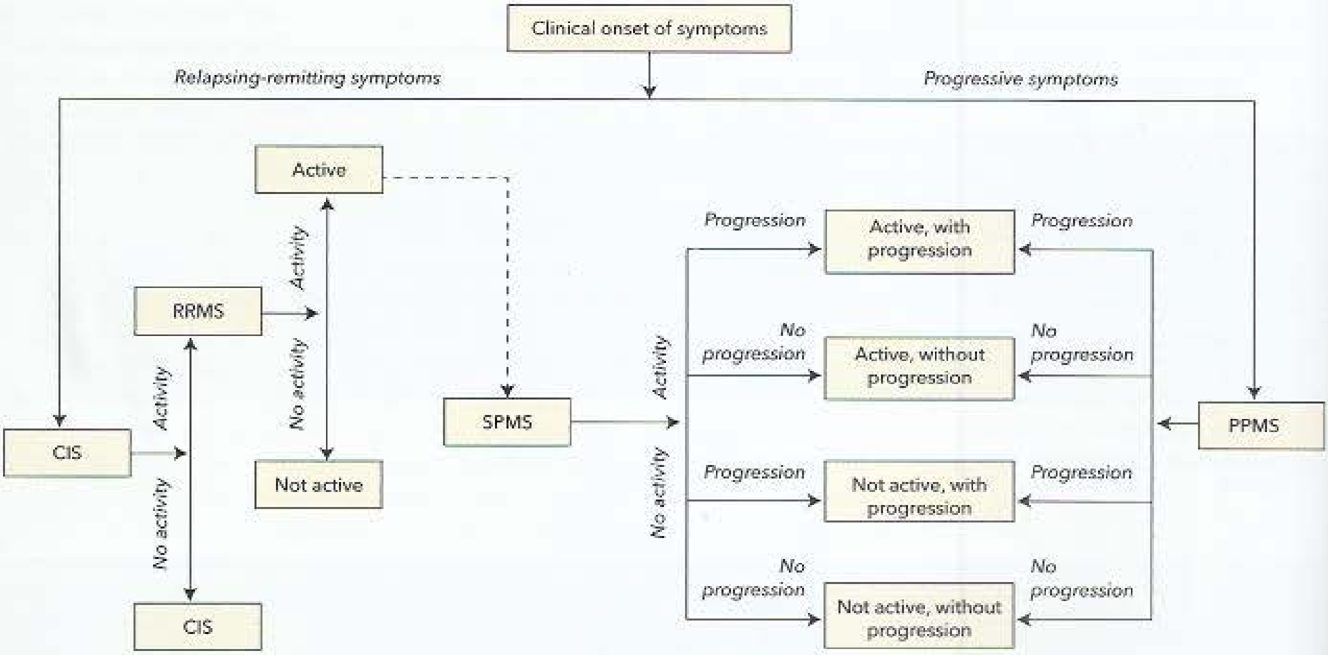

FIGURE 25. At clinical onset, multiple sclerosis (MS) can be either relapsing or progressive in nature. An initial, isolated demyelinating event results in a preliminary diagnosis of a clinically isolated syndrome. Any further activity (defined as a clinical relapse, new or enlarging T2-weighted lesion on MRI, or gadolinium-enhancing lesion on MRI) results in a diagnosis of relapsing-remitting MS (RRMS). Over time, RRMS can either be classified as active (if evidence of activity exists) or not active. Some patients with RRMS can later exhibit signs of progression (defined as slowly progressive accumulation of disability), and their condition can be reclassified as secondary progressive MS (SPMS). An initial clinical onset of progressive, nonrelapsing symptoms is diagnosed as primary progressive MS (PPMS). Any patients with progressive MS (PPMS or SPMS) can later exhibit signs of activity and/or progression, which allows for further stratification into four categories based on the presence or absence of these qualities.

CIS = clinically isolated syndrome; MS = multiple sclerosis; PPMS = primary progressive MS; RRMS = relapsing-remitting MS; SPMS = secondary progressive MS.

therapies reduce the risk of conversion from a clinically isolated syndrome to relapsing-remitting MS by approximately 50%, stratification of risk for conversion can inform treatment decisions. Patients with brain lesions on MRI at the time of their clinically isolated syndrome have a 10-year risk of conversion to relapsing-remitting MS of approximately 90%, whereas patients without brain lesions have a much lower risk (10%–20%).

Determination of activity status may also inform treatment decisions in relapsing-remitting MS. In the first few

years that a patient has this type of MS, significant or complete recovery from relapse is common. Over time, however, postrelapse recovery generally diminishes, and permanent disability accumulates. Without treatment, half of patients with relapsing-remitting MS develop secondary progressive MS after a median of 10 to 15 years. Data now suggest that the introduction of disease-modifying therapies has decreased the proportion of patients converting to secondary progressive MS. In secondary progressive MS, relapses become infrequent or cease completely, but slowly progressive neurologic disability continues to accrue in multiple domains.

Approximately 15% of patients with MS have primary progressive MS at presentation. This subtype often develops later in life (in the fifth or sixth decade) compared with the younger age of onset (third or fourth decade of life) in typical relapsing-remitting MS. Because patients with both primary and secondary progressive MS can have periods of disability progression or stability (with some even having permanent halting of progression), adding the modifiers "with progression" and "without progression" to these diagnostic terms has been suggested. Occasionally, patients with these types of MS may meet criteria for relapsing activity (clinical relapses, new or contrast-enhancing lesions on MRI) and thus can be further stratified into "active" and "not active" categories.

Patients with a radiologically isolated syndrome have no clinical symptoms of MS but are found incidentally to have MRI findings that meet the radiologic criteria for MS. Although an MS diagnosis cannot be made in the absence of demyelinating signs and symptoms, it has been shown that patients with a radiologically isolated syndrome are at high risk for later conversion to clinically definite MS and should be monitored closely.

KEY POINTS

- Disease-modifying therapies reduce the risk of conversion from a clinically isolated syndrome to relapsing-remitting multiple sclerosis by approximately 50%.
- Approximately 85% of patients with multiple sclerosis (MS) experience an initial relapsing-remitting course; 15% have primary progressive MS at presentation.
- Without treatment, half the patients with relapsing-remitting multiple sclerosis (MS) develop secondary progressive MS after a median of 10 to 15 years; the proportion of patients converting to secondary progressive MS has decreased since the introduction of disease-modifying therapies.

Treatment of Multiple Sclerosis

Lifestyle Modifications and General Health Care

Although some patients with MS may avoid physical activity because of disability, fatigue, and the Uhthoff phenomenon, repeated studies have shown multiple benefits from both strengthening and aerobic exercise programs. Patients with significant Uhthoff phenomenon induced by exercise should be reassured that neurologic injury will not result from exercise; they also can be counseled on strategies to minimize discomfort, such as heat avoidance or external cooling (cold water, fans, body-cooling devices) during exercise.

Exercise also can help preserve bone health. Patients with MS have a three- to sixfold increased risk of reduced bone mineral density, most likely from a combination of reduced physical activity, repeated use of glucocorticoids, and vitamin D deficiency. Vitamin D deficiency is common in MS patients, and reduced serum levels of vitamin D are predictive of MS development and future accumulation of lesions on MRI. A randomized trial of vitamin D supplementation added to interferon beta treatment resulted in reduced accumulation of lesions seen on MRI compared with placebo. Vitamin D supplementation is now recommended for all patients, although the ideal dosing regimen and serum 25-hydroxyvitamin D level are still being investigated.

Measures to prevent infection are needed for patients receiving more aggressive, immunosuppressive MS treatments, especially given the increased risk of MS relapse at the time of systemic infection. Current MS treatment guidelines recommend vaccination against influenza (with inactivated vaccine) and maintenance of standard immunizations. Patients with MS-related bladder dysfunction are at higher risk of recurrent urinary tract infection, and thus strategies to reduce the frequency of bladder infections are necessary.

Smoking cessation is advised for all patients with MS because of the threefold risk of conversion from relapsing-remitting MS to secondary progressive MS and faster rates of disability accumulation in cigarette smokers.

Many patients with MS are women in their childbearing years. The estrogenic state of pregnancy has an immunomodulatory effect that tends to reduce MS disease activity during pregnancy, often precluding the need for treatment during this period. Although the risk of relapse is increased slightly in the first 3 months of pregnancy, this does not seem to contribute negatively to prognosis; multiple studies have shown that pregnancy does not result in additional permanent disability and that multiparous women have better long-term MS outcomes than nulliparous or uniparous women. Data on the effect of breastfeeding on MS relapse risk are inconclusive.

KEY POINTS

- Studies have shown multiple benefits from both strengthening and aerobic exercise programs in patients with multiple sclerosis. **HVC**
- Current multiple sclerosis (MS) treatment guidelines recommend vaccination against influenza and maintenance of standard immunizations; smoking cessation also is advised because of the threefold risk of conversion from relapsing-remitting MS to secondary progressive MS and faster rates of disability accumulation in cigarette smokers. **HVC**

H Treatment of Acute Exacerbations

An MS relapse is defined as new or worsening neurologic symptoms lasting more than 24 hours. Symptoms lasting only minutes to hours should not be considered or treated as a relapse. The possibility of a pseudorelapse should always be considered before initiating treatment; suspicion of this condition should trigger clinical investigation for an underlying cause. The subsequent treatment of any infection or metabolic disturbance often results in improvement in neurologic symptoms.

The standard treatment for MS relapses is high dose glucocorticoids, typically intravenous methylprednisolone (1 g/d for 3 to 5 days). Multiple trials have shown that bioequivalent doses of oral glucocorticoids (such as prednisone, 1250 mg/d) are equally effective and well tolerated, with reduced cost. Adverse effects of high dose glucocorticoids include insomnia, hyperglycemia, metallic taste, gastritis, fluid retention, irritability, and (rarely) psychosis. These effects are typically short lived, given the brief duration of treatment. Frequent or prolonged glucocorticoid treatment should be avoided to minimize the risks of osteopenia and early cataracts.

MS relapses also can be treated with administration of a short course of intramuscular adrenocorticotropin hormone gel. This approach has a more favorable adverse-effect profile compared with external glucocorticoid administration. Use of this gel is limited by prohibitive pricing.

Patients not responding to glucocorticoid treatment may respond to plasmapheresis, administered as five consecutive exchanges. H

KEY POINT

- The standard treatment for MS relapses is high-dose glucocorticoids, typically intravenous methylprednisolone; frequent or prolonged glucocorticoid treatment should be avoided to minimize the risks associated with long-term glucocorticoid use.

Disease-Modifying Therapies

Prevention of MS relapse is vital. Various immunomodulatory or immunosuppressive medications have been shown to reduce the risk of relapse, disability progression, and new MRI lesion formation. Currently, many disease modifying therapies are approved and available for use in relapsing-remitting MS (**Table 43**), each differing in its route of administration, mechanism of action, and potential adverse effects. Interferon beta preparations, glatiramer acetate, and teriflunomide have additional utility in clinically isolated syndrome for prevention of conversion to clinically definite MS. Despite many options for those with relapsing disease, the options for patients with progressive forms of MS are limited. Mitoxantrone is currently the only FDA approved therapy for secondary progressive MS, and ocrelizumab is the only FDA approved therapy for primary progressive MS. Clinical trials of interferon beta, glatiramer acetate, fingolimod, and natalizumab in progressive forms of MS have failed to show benefit, and thus prescribing these medications in progressive MS not only increases cost but burdens patients with unnecessary adverse effects.

Selection of an appropriate disease modifying therapy involves consideration of comorbidities, patient tolerability, risk stratification, and disease activity. Treatment decisions often are made in consultation with a neurologist or MS specialist. There is no clear consensus about how to select the appropriate therapy, what defines treatment failure, or how to decide in what order medications should be introduced. Generally, most physicians recommend self-injection medications (an interferon beta or glatiramer acetate) as first line agents, given their favorable risk profiles. Patients who exhibit disease breakthrough on these medications or who are unable to tolerate their adverse effects are often switched to agents with better efficacy profiles. Although the oral therapies and monoclonal antibodies provide greater efficacy, they are associated with greater risk and the need for more intensive monitoring.

Interferon beta (available as interferon beta-1a and interferon beta-1b) is an immunomodulatory cytokine treatment that shifts immune responses away from autoimmunity and increase the integrity of the blood-brain barrier. Interferons beta-1a and beta-1b are available in multiple formulations and are administered via subcutaneous or intramuscular injection on schedules varying from every other day to twice monthly. They reduce relapse rates by approximately one-third compared with placebo and have positive effects on disability progression and MRI findings. Head-to-head studies show general equivalence of the formulations, although those requiring frequent injections have slightly higher efficacy in some studies. Interferon beta may exacerbate depression, and care should be taken when administering it to patients with a history of psychiatric disease.

Glatiramer acetate exerts its immunomodulatory effect through modification of the nonbinding sites of major histocompatibility complex molecules. Structurally similar to myelin basic protein, it also may work through molecular mimicry. Glatiramer acetate is available for daily or three times weekly subcutaneous injection. Reduction in relapse rates is similar to that of the interferon beta formulations. Combining glatiramer acetate with interferon beta provides no added benefit.

Fingolimod is an oral agent that results in sequestration of activated lymphocytes within lymph nodes. Fingolimod reduces relapse rates by approximately one-half compared with placebo and also reduces the risk of disability progression and the development of new MRI lesions. However, intensive monitoring is mandatory with fingolimod because of its rare adverse effects, including infection and heart block.

TABLE 43. Disease-Modifying Therapies for Relapsing-Remitting Multiple Sclerosis

Medication	Route of Administration	Potential Adverse Effects	Recommended Monitoring	Pregnancy Category[a]
Interferon beta-1a (three formulations) and interferon beta-1b (two formulations)	Intramuscular or subcutaneous injection	Flu-like symptoms, fatigue, depression, increased spasticity, transaminitis, rare autoimmune hepatitis, and injection-site reactions	CBC and liver enzymes every 3-6 months	C
Glatiramer acetate (three formulations)	Subcutaneous injection	Injection-site reactions, lipoatrophy of skin at injection sites, and rare systemic panic attack-like syndrome	None	B
Fingolimod	Oral	Transaminitis, lymphopenia, increased risk of serious herpesvirus infection, hypertension, bradycardia (usually only with the first dose), macular edema, basal cell carcinoma, PML	Cardiac monitoring (for bradycardia) after administration of first dose, ophthalmologic screening (for macular edema), liver enzymes, CBC monitoring (for excessive lymphopenia), yearly skin examination (for basal cell carcinoma)	C
Dimethyl fumarate	Oral	Diarrhea, nausea, abdominal cramping, flushing, lymphopenia, PML	Frequent monitoring of CBC in first 6 months after administration and then every 6 months thereafter	C
Teriflunomide	Oral	Alopecia, gastrointestinal distress, respiratory infections, transaminitis, lymphopenia, hypertension, and peripheral neuropathy	Monitoring of CBC for lymphopenia, liver enzymes, and blood pressure frequently in the first 6 months, every 6 months thereafter	X
Natalizumab	Intravenous	Black-box warning of increased risk of PML, common adverse effects of headache and chest discomfort, and rare hepatotoxicity, infusion reactions, and anaphylactic reactions	Rigorous, regimented, industry-sponsored monitoring (TOUCH program) and JC virus antibody testing (both screening and intermittent monitoring)	C
Alemtuzumab	Intravenous	Infusion reactions (including anaphylaxis), infections (especially herpes virus and fungal), autoimmune thyroiditis, ITP, glomerular nephropathy, increased risk of dermatologic malignancy	Rigorous, regimented, industry-sponsored monitoring program (Lemtrada REMS); monthly CBC, serum creatinine measurement, and urinalysis; quarterly thyroid function for 48 months after first infusion; yearly skin examination	C
Ocrelizumab	Intravenous	Allergic infusion reactions (such as urticaria, pruritus, anaphylaxis), infections (especially herpesvirus or hepatitis B virus reactivations); possible increased risks for PML and cancer	Preinfusion screening with CBC and hepatitis B serologies; consider preinfusion vaccinations (against, for example, zoster, streptococcal pneumonia, hepatitis B)	No assigned category, with some risk seen in animal studies; contraception suggested for 6 months after each infusion
Mitoxantrone	Intravenous	Black-box warnings for cardiotoxicity and acute myelogenous leukemia; other adverse effects of infection, nausea, oral sores, alopecia, menstrual irregularities, and blue discoloration of urine	Required monitoring of cardiac function by echocardiography or multigated radionucleotide angiography before each infusion and regular CBC	D

CBC = complete blood count; HYP = high-yield process; ITP = immune thrombocytopenic purpura; PML = progressive multifocal leukoencephalopathy; REMS = risk evaluation and migraine strategy.

[a]Pregnancy categories: A, no disclosed fetal effects; B, animal studies failed to demonstrate fetal risk; C, animal studies suggest adverse fetal effects; D, evidence of human fetal risk; X = documented fetal abnormalities. The FDA is no longer using these letter categories for newly approved drugs; for prescription drugs that were previously approved, these changes will be phased in gradually.

Dimethyl fumarate is an oral agent that activates the nuclear factor-like 2 transcriptional pathway and results in immunomodulation. It reduces relapse rates by slightly less than half and reduces the risk of disability progression and MRI lesion development. Infectious risks of dimethyl fumarate correlate with prolonged lymphopenia, and frequent blood-count monitoring is required.

Teriflunomide is an oral medication that inhibits a mitochondrial enzyme involved in pyrimidine synthesis in rapidly dividing cells. This drug reduces relapse rates by a third compared with placebo and also reduces the risk of disability progression and new MRI lesion development. Dual-method contraception is recommended with teriflunomide because of its known teratogenic effects.

Natalizumab is a monoclonal antibody targeting a cellular adhesion molecule on activated T-cells required for transmigration into the CNS. Administered intravenously once monthly, natalizumab is a highly effective treatment, resulting in a two-thirds reduction in relapse rates, slowing of disability progression by approximately 40%, and a reduction in MRI activity of approximately 90% compared with placebo. Despite this high efficacy, natalizumab is typically limited to use as a second-line agent because of the risk of progressive multifocal leukoencephalopathy (PML), a CNS demyelinating infection caused by reactivation of the JC virus. Duration of treatment, seropositivity for the JC virus, and previous exposure to chemotherapy or immunosuppressants increase PML risk. PML is uncommon in time-limited treatment in patients without other risk factors.

Alemtuzumab is an anti-CD52 monoclonal antibody that causes complement-mediated lysis of circulating lymphocytes. It is administered as an intravenous infusion with an initial course of once daily for 5 days, followed by 3 consecutive days 1 year later. Alemtuzumab reduces relapse rates and disability progression by approximately half and reduces new lesions and brain atrophy on MRI compared with interferon beta. Despite high efficacy, use of this drug also is limited due to significant safety concerns (see Table 43), all of which require intensive safety monitoring and potential prophylaxis.

Ocrelizumab is a monoclonal antibody against the CD20 antigen that causes lysis of circulating B cells. This drug is administered through intravenous infusion, initially as two infusions 2 weeks apart followed by a one-time infusion every 6 months. Ocrelizumab is the first medication to show benefit for patients with both relapsing-remitting MS (reductions in relapse rates, MRI disease burden, and disability accumulation) and primary progressive MS (reduced chance of disability progression). Safety concerns include allergic infusion reactions and increased risk for treatment-related infections.

Mitoxantrone is an anthracenedione chemotherapy drug that exerts an immunosuppressive effect by reducing lymphocyte proliferation. Although mitoxantrone is highly effective for relapsing-remitting MS and is the only drug approved for use in secondary progressive MS, it has fallen out of favor given its significant risks of cardiac toxicity and treatment-related leukemia.

KEY POINTS

- Generally, self-injection medications (interferon beta or glatiramer acetate) are recommended as first-line agents for relapsing-remitting multiple sclerosis because of their favorable risk profiles.
- Ocrelizumab is the only available therapy for primary progressive multiple sclerosis (MS), and mitoxantrone is the only FDA-approved therapy for secondary progressive MS; given the lack of benefit of other MS therapies in these disease subtypes, using agents other than ocrelizumab and mitoxantrone in patients with progressive forms of MS not only increases cost but burdens patients with unnecessary risk. **HVC**
- Natalizumab is a highly effective treatment in multiple sclerosis that causes a two-thirds reduction in relapse rates, slowing of disability progression by approximately 40%, and a reduction in MRI activity of approximately 90% compared with placebo; it is typically limited to use as a second-line agent because of the risk of progressive multifocal leukoencephalopathy.

Symptomatic Management

Despite the use of disease-modifying therapies, many patients still experience both chronic and intermittent neurologic symptoms. Proper management of these symptoms with pharmacologic and nonpharmacologic approaches can increase quality of life for patients with MS.

MS spasticity is due to corticospinal tract damage, resulting in increased muscle tone, painful muscle cramps, spasms, and contractures. The use of muscle relaxants, such as baclofen, tizanidine, cyclobenzaprine, and the benzodiazepines may be helpful. Gabapentin, medical marijuana, synthetic tetrahydrocannabinol compounds, and cannabis extract are beneficial in reducing painful spasms. Strategic use of botulinum toxin and intrathecal baclofen pumps may help in patients whose disease is refractory to oral therapies. Physical therapy, stretching, and massage therapy can be used as nonpharmacologic alternatives or additions to therapy.

Neuropathic pain is a common MS-related symptom and can be addressed with many of the same pharmacologic agents used to treat painful diabetic neuropathy (see MKSAP 18 Endocrinology and Metabolism). Nonpharmacologic approaches, such as transcutaneous electrical nerve stimulation, also can be integrated into the management plan.

Chronic fatigue is a common and life-impairing symptom in MS. Although fatigue is sometimes related to concurrent depression, insomnia, or other comorbid conditions, patients with MS without any of these issues also can experience disabling fatigue. Improved sleep hygiene, regular exercise, and treatment of underlying depression can be beneficial. The stimulant medications modafinil, armodafinil, amantadine, and amphetamines may be helpful. Complementary and alternative medicine approaches, such as magnetic therapy and ginkgo biloba, also have shown efficacy in some studies.

Depression is far more common in MS patients than in those without the disorder. Furthermore, the suicide rate for patients with MS and depression is elevated compared with that of patients with depression only. MS-related depression is likely multifactorial, involving the emotional response to dealing with a chronic disease, the consequence of demyelinating lesions and inflammatory cytokines on neurotransmitter function, and the adverse effects of treatments (such as interferon beta). Clinicians should be vigilant for the signs of depression, screen for suicidality if present, and have a low threshold for initiating antidepressants and offering referrals to psychiatry or psychology for counseling.

Cognitive dysfunction occurs in at least half of patients with MS, affecting employability and quality of life. Typical findings include deficits in short-term memory and processing speed, although almost any domain can be impaired. Trials of pharmacologic therapy, such as memantine, donepezil, and methylphenidate, have not shown efficacy. Exercise, formal neuropsychological testing, and cognitive rehabilitative and accommodative strategies (such as creating checklists to overcome memory deficits) are sometimes beneficial.

Maintenance of mobility in MS patients is essential to maintaining quality of life. An active healthy lifestyle is necessary to help stave off future disability. Physical and occupational therapy can provide gait safety training and improve balance and endurance. Assistive devices, such as braces, canes, walkers, and electrostimulatory walk-assist devices, can provide additional benefit. Pharmacologic therapy with dalfampridine, a voltage-gated potassium channel antagonist, can improve walking speed, leg strength, and gait in patients with MS and baseline gait impairment. Dalfampridine has a rare risk of seizures and should not be used in patients with known epilepsy or with kidney impairment.

Bladder dysfunction occurs in many patients with MS. Urinary frequency and urgency can be ameliorated with abstinence from caffeine, timed voids, and anticholinergic medications (solifenacin, oxybutynin, tolterodine). Patients with urinary hesitancy or retention can be more difficult to treat. Anticholinergic agents can worsen retention and increase the risk of urinary tract infection. Patients with a mixed pattern of bladder symptoms should be evaluated by a urologist; intermittent catheterization or an indwelling catheter may be necessary.

Limb tremor can occur in patients with MS and is often difficult to treat. Occupational therapy and botulinum toxin may be helpful.

Pseudobulbar affect is a rare complication of MS that can be a significant impediment to social interaction for affected patients. This symptom manifests as uncontrolled fits of laughter or crying that occur without distinct or appropriate triggers. Dextromethorphan-quinidine can help reduce this symptom.

KEY POINTS

- Muscle relaxants, such as baclofen, tizanidine, cyclobenzaprine, and the benzodiazepines, can help treat multiple sclerosis–associated spasticity due to corticospinal tract damage.
- Clinicians should be vigilant for the signs of depression in patients with multiple sclerosis; if present, they should screen for suicidality and have a low threshold for offering therapy and referrals to psychiatry.

Disorders of the Spinal Cord

Presenting Symptoms and Signs of Myelopathy

Myelopathy (any disorder involving the spinal cord) arises from extrinsic (external compression) and intrinsic (intramedullary) pathologic causes. Recognition and treatment of spinal cord injury in a timely manner is crucial, given the vital anatomy contained within this small-diameter structure.

Determining the location and mechanism of injury is crucial for rapidly deciding on the accurate site and type of neuroimaging required and the kind of specialty consultation (such as neurosurgical) needed. Spinal cord injury often presents with symptoms and signs at or below the site of a lesion. Corticospinal tract injury results in spastic paresis or paralysis, with weakness, hyperreflexia, muscle spasticity, and extensor plantar responses. There is often loss of sensation at or below the site of injury. Performance of a detailed sensory examination, with ascending pinprick testing throughout the entire torso and neck, is essential. Gait is abnormal in most patients with myelopathy; a sensory ataxia or spastic gait sometimes can be an isolated presenting sign. Involvement of the distal spinal cord and lower roots (cauda equina syndrome) results in decreased muscle tone, areflexia, and loss of perianal sensation.

Many patients with myelopathy report pain at the level of the compressive disease. Squeezing or banding sensations around the chest or abdomen near the level of spinal cord

compression may be reported. Focal tenderness to percussion over the spinal column may be elicited. Disruptions in bowel and bladder function and loss of sphincter tone also are often noted. These varied symptoms may lead to unnecessary cardiac, pulmonary, gastrointestinal, or urinary tract evaluations and to a delayed diagnosis.

KEY POINTS

- Corticospinal tract injury results in spastic paresis or paralysis, with weakness, hyperreflexia, muscle spasticity, and extensor plantar responses; there is often loss of sensation at or below the site of injury.
- Injury to the distal spinal cord and lower roots (cauda equina syndrome) results in decreased muscle tone, areflexia, and loss of perianal sensation.

Compressive Myelopathy

Clinical Presentation

H Spinal cord compression often presents with neck or back pain, followed by weakness, sensory changes, and bladder or bowel dysfunction. Examination typically reveals upper motor neuron signs (weakness, spasticity, hyperreflexia, and extensor planar responses), but lower motor neuron signs (atrophy, hyporeflexia) sometimes can occur near the level of compression. Specific signs and symptoms can provide clues as to the cause of compression. The presence of fever and focal back pain and tenderness, especially in patients who have had recent back instrumentation or have a history of intravenous drug use, may indicate an epidural abscess (see MKSAP 18 Infectious Diseases for more information on cranial and spinal epidural abscesses). A history of neoplasia and focal back pain should raise concern for metastatic disease (**Figure 26**) or pathologic vertebral fracture. Anticoagulant use raises the risk of compression from an epidural hematoma, particularly in the setting of recent back instrumentation. H

Patients with chronic spinal stenosis due to osteoarthritic degenerative spinal disease frequently present with chronic myelopathic symptoms. Compressive myelopathy should thus be considered in older patients with gait dysfunction or weakness. Degenerative spinal disease often affects the cervical and lumbar regions, but thoracic cord involvement is quite rare. Most patients with chronic compressive myelopathy initially report progressive leg weakness, spasticity, distal numbness, and bladder impairment. Some with lumbar stenosis describe symptoms similar to vascular claudication (pseudoclaudication), with exertional groin, thigh, or buttock pain, and possibly also of weakness or numbness.

H Diagnosis

Initial MRI of the spinal cord at the suspected region of injury is the preferred means of diagnosing compressive myelopathy and will often reveal the cause. Imaging should be performed

FIGURE 26. MRI of the spine showing metastatic cancer with collapse of the vertebral body and compression of the spinal cord from the posteriorly displaced bony fragments (*red arrow*).

emergently in cord compression thought to be secondary to abscess or malignancy because neurologic compromise can progress rapidly. CT myelography can show compressive myelopathy when MRI is not feasible but often does not reveal the cause of compression. Additionally, this type of imaging may be difficult to arrange emergently and is problematic in patients with allergies to contrast dyes or impaired kidney function. H

KEY POINTS

- In patients with compressive myelopathy, a history of neoplasia and focal back pain should arouse concern for metastatic disease; the presence of fever and focal back pain and tenderness may indicate an epidural abscess.
- An initial MRI of the spinal cord at the suspected region of injury is the preferred means of diagnosing compressive myelopathy and will often reveal the cause.

Treatment

Surgical decompression is typically required to treat spinal cord compression, but medical therapies can complement surgical treatment, depending on the underlying cause. Emergent treatment usually is indicated because the most important indicator of long-term neurologic function is the neurologic function at the time of decompression. Neurologic H

H CONT.

function is rarely regained as a result of therapy, but further deterioration may be prevented.

Adjunctive therapy is important; an epidural hematoma may first require management of the bleeding diathesis, and cord compression caused by epidural abscess requires antibiotics. The use of glucocorticoids in traumatic spinal cord compression is controversial. They generally are not indicated with hematoma and abscess. A joint panel of the American Association of Neurological Surgeons and the Congress of Neurological Surgeons has argued against the use of high-dose glucocorticoids in acute spinal cord trauma, given the lack of definitive evidence of benefit and some evidence of potential harm. Despite these recommendations, this issue remains controversial, and many physicians still offer glucocorticoid treatment for this select patient population because of the lack of alternative beneficial strategies.

Spinal cord compression from metastatic disease requires emergent use of high-dose glucocorticoids and urgent surgical decompression, followed by radiation for most tumor types. Clinical trials have shown the superiority of surgical decompression in optimizing ambulation. Certain radiosensitive tumor types, such as leukemia, lymphoma, myeloma, and germ cell tumors, may not require initial surgical decompression and instead may be treated urgently with radiation therapy. Surgical intervention also is sometimes deferred in patients with a completed neurologic deficit, patients with a poor prognosis or functional status, and patients without a distinct neurologic deficit. For more information on spinal cord compression due to metastatic disease, see MKSAP18 Hematology and Oncology. H

For chronic cervical or lumbar stenosis or acute disk herniation, symptomatic management can control symptoms in most patients. Surgical decompression may be required for patients with myelopathy refractory to medical management. See MKSAP 18 General Internal Medicine for more information about treating musculoskeletal pain.

KEY POINT

- Spinal cord compression from metastatic disease requires emergent use of high-dose glucocorticoids and urgent surgical decompression, followed by radiation for most tumor types.

Noncompressive Myelopathy

Noncompressive myelopathy can be caused by many inflammatory, infectious, metabolic, vascular, and genetic disorders. Inflammatory causes are most common, including multiple sclerosis (see Multiple Sclerosis), neuromyelitis optica, and sarcoidosis.

Idiopathic Transverse Myelitis

Idiopathic transverse myelitis (ITM) (**Figure 27**) is a monophasic, inflammatory, and demyelinating disorder of the spinal

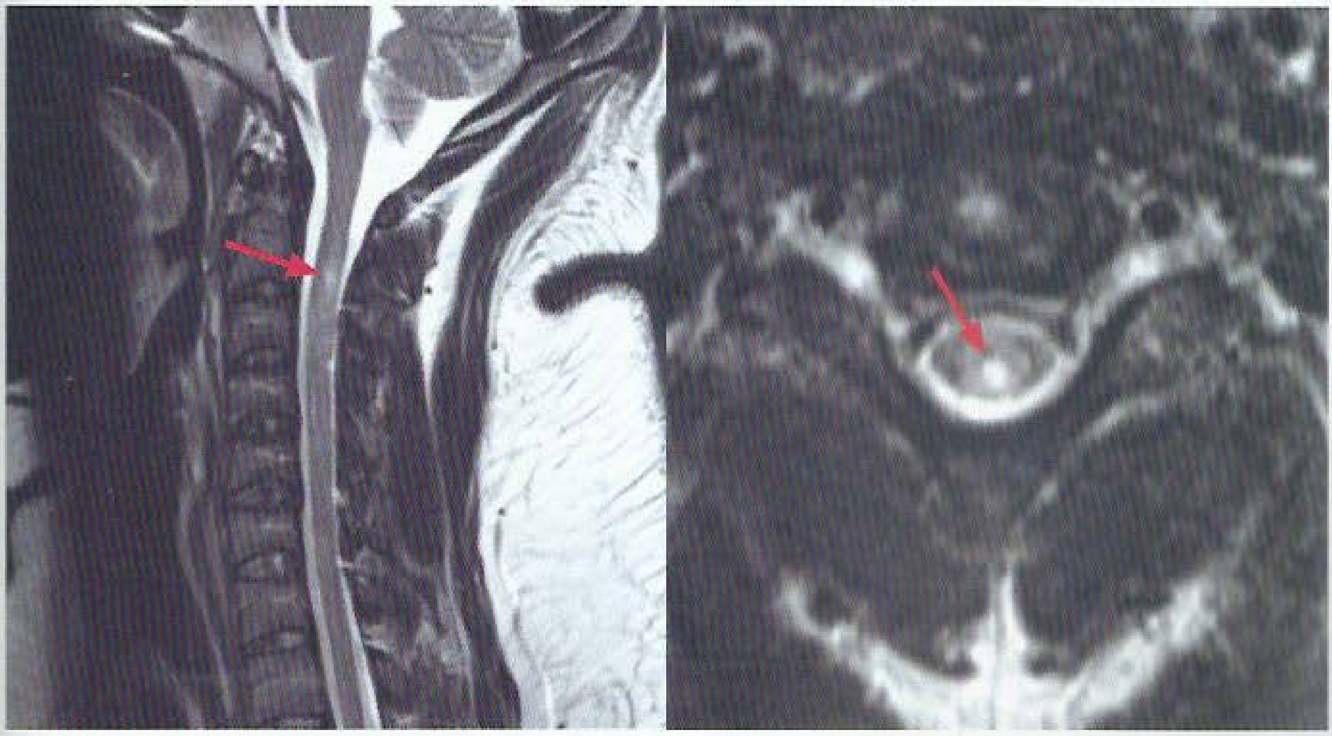

FIGURE 27. MRI of the cervical spine in a patient with transverse myelitis. Sagittal T2-weighted (*left*) and axial T2-weighted (*right*) images both demonstrate hyperintensity within the parenchyma of the spinal cord (*red arrows*).

cord. ITM typically affects only one region of the spinal cord and is considered to be a para- or postinfectious inflammatory response. Affected patients frequently experience subacute weakness, sensory changes, and bladder or bowel dysfunction. Some patients experience an initial prodrome of back pain or a thoracic banding sensation.

The diagnostic criteria for ITM require presence of clinical features of the syndrome, evidence of inflammation (either cerebrospinal fluid leukocytosis or contrast enhancement on spinal cord MRI), and exclusion of other potential causes. Those with complete myelitis (symptoms referable to complete rather than partial cord transection), a lack of elevated oligoclonal bands or IgG index in the cerebrospinal fluid, and no lesions on brain MRI are much more likely to have ITM than other disorders, such as multiple sclerosis. This is a crucial distinction because ITM is not a recurrent disorder and does not require long-term immunomodulatory therapy. Recurrence of symptoms or new symptoms beyond a 30-day period should arouse suspicion for multiple sclerosis or other recurrent disorders.

The consensus-based treatment of ITM is intravenous methylprednisolone, 1 g/d for 3 to 7 days. This therapy is intended to stop inflammatory damage of the spinal cord and allow for recovery of neurologic function. Patients whose disease is refractory to glucocorticoids may benefit from plasmapheresis or cyclophosphamide.

Infectious causes of transverse myelitis should always be considered when evaluating patients for possible ITM. Herpes simplex virus, varicella zoster virus, West Nile virus, human T-lymphotropic virus, Lyme disease, and neurosyphilis infections can affect the spinal cord. HIV infection can cause a transverse myelitis-like syndrome at the time of seroconversion or result in a chronic degenerative vacuolar myelopathy in patients with chronic low CD4 cell counts. Mycobacterium tuberculosis can infect the meninges and spinal cord and present with a transverse myelitis-like syndrome. Treatment should be directed against a particular infection if present. The addition of glucocorticoids to treat these disorders is controversial but may be indicated when infections are associated with significant spinal cord edema.

KEY POINTS

- Patients with complete myelitis, no oligoclonal bands or IgG index in the cerebrospinal fluid, and no lesions on brain MRI are much more likely to have idiopathic transverse myelitis than multiple sclerosis.
- Treatment of idiopathic transverse myelitis is intravenous methylprednisolone; secondary causes of transverse myelitis, including infection, should first be excluded.

Subacute Combined Degeneration

Severe and prolonged vitamin B_{12} deficiency can result in subacute combined degeneration, which refers to a dysfunction of the corticospinal and dorsal sensory tracts of the spinal cord that manifests as spastic paresis with reduced vibration and position sense and ataxia. MRI can show increased signal in the affected white matter pathways without associated inflammatory changes. Laboratory study results show a low serum vitamin B_{12} level with elevated levels of serum methylmalonic acid and homocysteine. Macrocytic anemia may be present, but the neurologic manifestations of B_{12} deficiency may precede development of anemia. The clinical symptoms of vitamin B_{12} deficiency can sometimes occur with low-normal serum B_{12} levels, and thus supportive laboratory studies should be performed in patients with a high index of clinical suspicion. Vitamin B_{12} replacement usually halts progression of the disease but may not necessarily reverse existing symptoms.

Nitrous oxide abuse also can cause a relative vitamin B_{12} deficiency that results in subacute combined degeneration. Supplementation of vitamin B_{12} in those circumstances without cessation of the drug may impede improvement in symptoms.

Copper deficiency (due to malabsorption, nutritional deficiency, or zinc toxicity) can also cause subacute combined degeneration. This entity should be considered in patients with suggestive symptoms who have normal vitamin B_{12} levels. Myelopathy from such nutritional deficiencies should specifically be considered in patients with previous bariatric surgical procedures.

KEY POINT

- Severe and prolonged vitamin B_{12} deficiency can result in subacute combined degeneration; in patients with suggestive symptoms of this disorder and normal vitamin B_{12} levels, copper deficiency should be considered.

Vascular Disorders

H Infarcts in the territory of the anterior spinal artery typically present as sudden-onset flaccid paralysis with preservation of vibration and position sense because of the lack of dorsal column involvement. Prolonged hypotension during cardiovascular or aortic surgery can also sometimes result in lack of perfusion to watershed regions of the spinal cord, especially in the area where the anterior spinal artery meets the most prominent radicular artery (artery of Adamkiewicz) in the upper thoracic cord. H

Dural arteriovenous fistulas of the spinal vascular supply can either result in chronic myelopathy due to venous congestion or cause infarction of the cord due to altered vascular dynamics or thromboses. Fistulas are most common in men older than 50 years and in persons with previous spinal surgery. Abnormal vascular flow voids often are seen on careful review of spinal MRIs. Diagnosis is often challenging and typically requires digital subtraction angiography of all radicular vessels along the entire spine.

Genetic Disorders

Although rare, several genetic disorders can result in chronic myelopathy. Some of these disorders have clear familial

inheritance, but others may result from de novo mutations. Hereditary spastic paraplegia comprises hereditary disorders that result in chronic, progressive, ascending weakness and spasticity, often beginning in childhood or adolescence. Genetic screening is available, but no treatment currently exists. Female carriers of X-lined adrenoleukodystrophy sometimes develop adrenomyeloneuropathy, a degenerative condition of the spinal cord and peripheral nerves. These patients can be diagnosed through alterations in the serum very-long-chain fatty acid profiles or genetic testing. Genetic counseling is indicated in such settings.

Neuromuscular Disorders

Overview

Peripheral and central nervous system disorders can be differentiated on the basis of history and neurologic examination findings (**Table 44**). Neuromuscular disorders include myopathies, neuromuscular junction disorders, peripheral neuropathies, plexopathies, radiculopathies, and motor neuron diseases (**Table 45** and **Table 46**).

Peripheral Neuropathies

Classification, Findings, and Diagnosis

Symptoms of peripheral neuropathy include negative (sensory loss) or positive (paresthesia, dysesthesia, and pain) sensory symptoms, weakness, or autonomic dysfunction. Neuropathies are classified on the basis of distribution of sensorimotor deficits (symmetry, distal versus proximal, focal versus generalized), pathology (demyelinating versus axonal), family history, and autonomic involvement (**Figure 28**, on page 78).

For all patients with a suspected peripheral neuropathy, a complete blood count, an erythrocyte sedimentation rate determination, serum protein electrophoresis with immune fixation, thyroid function tests, hemoglobin A_{1c}/fasting plasma glucose determination, and vitamin B_{12} measurement are necessary. In specific clinical settings, additional

TABLE 44. Features Distinguishing Peripheral From Central Nervous System Disorders

Features	PNS Disorder	CNS Disorder
Onset	Subacute or insidious	Sudden (stroke) or gradual (mass lesions)
Pattern of weakness	Focal or multifocal (in the territory of the affected nerve, plexus, or root) or generalized	Entire limb, unilateral, or a pyramidal pattern of weakness[a]
Atrophy	Yes (at times prominent)	No (or mild, and related to disuse)
Fasciculations	Yes	No
Tone	Decreased or normal	Increased (spasticity or rigidity[b]) or normal
Pattern of sensory symptoms	Focal or multifocal (in the territory of the affected nerve, plexus, or root) or stocking-glove in distribution	Entire limb or unilateral
Type of sensory symptoms	Positive symptoms (paresthesia, dysesthesia, or allodynia[c]) more frequent, but negative symptoms (numbness) possible	Negative symptoms more frequent, but positive symptoms possible
Dissociated sensory loss	Pain/temperature and vibration/proprioception deficits travel together	Dissociation of pain/temperature and vibration/proprioception deficits possible with spinal and brainstem lesions
Deep tendon reflexes	Diminished or normal	Increased
Pathologic reflexes	Absent	Present, including extensor plantar response, Hoffman sign,[d] knee cross adduction, jaw jerk, snout, and clonus
Additional localizing symptoms	Cramps	Headache, seizures, and visual and language-related symptoms
EMG	Abnormal	Normal

CNS = central nervous system; EMG = electromyography; PNS = peripheral nervous system.

[a]Pyramidal weakness is caused by upper motor neuron lesions and affects extensors more than flexors in the upper limbs and flexors more than extensors in the lower limbs.

[b]Spasticity is a direction- and velocity-dependent increase in tone and is associated with pyramidal lesions; rigidity is an increase in tone that is independent of velocity and direction and is associated with extrapyramidal lesions.

[c]Paresthesia is an abnormal spontaneous sensation, such as tingling, burning, or electrical sensation. Dysesthesia is an unpleasant sensation provoked by neutral stimuli, such as light touch or contact of clothes. Allodynia is pain provoked by nonnoxious stimuli.

[d]Hoffman sign is positive if the thumb is flexed in response to a flicking or snapping of the distal phalanx of the middle finger.

TABLE 45. Classification of Neuromuscular Disorders

Type	Features	Examples
Myopathy		
Acquired	Proximal greater than distal weakness, absence of sensory and autonomic symptoms, symmetric, late hyporeflexia after atrophy, adult onset	Inflammatory, toxic, systemic, and endocrine myopathies
Inherited	Similar to acquired myopathy, onset in childhood or early adulthood, positive family history, some possibly associated with distal or multifocal (scapuloperoneal, oculopharyngeal) weakness and atrophy, myotonia, exercise-induced pain	Muscular dystrophies; mitochondrial, metabolic, and congenital myopathies
Neuromuscular junction disorder	Fluctuating weakness; fatigue; absence of sensory and autonomic symptoms; symmetric, bulbar, and respiratory involvement	Myasthenia gravis, Lambert-Eaton myasthenic syndrome
Peripheral neuropathy		
Axonal	Symmetric distal sensory and sensorimotor impairment, possible involvement of autonomic nerves, early or late hyporeflexia	Diabetic, toxic, hypothyroid, uremic, nutritional polyneuropathy
Demyelinating	Proximal and distal symmetric or multifocal weakness with variable sensory loss, early areflexia, low back radicular pain; hereditary forms associated with foot deformities and slow progression	GBS, CIDP, hereditary (CMT1)
Mononeuropathy	Sensory and motor deficits within the distribution of a single nerve, symptoms distal to site of compression	Carpal tunnel syndrome, ulnar neuropathy, peroneal neuropathy
Plexopathy	Motor and sensory deficits in multiple contiguous nerves in upper or lower extremities, asymmetric, severe pain at onset with autoimmune and diabetic types	Idiopathic brachial plexitis, idiopathic lumbosacral radiculoplexus neuropathy, diabetic amyotrophy, postradiation and carcinomatous plexopathy
Radiculopathy	Motor, sensory, and reflex deficits in the area innervated by affected nerve root, radicular pain and paresthesia, neck or low back pain	Cervical and lumbar radiculopathy
Ganglionopathy	Severe loss of vibration and joint position sense in single limb, no motor deficit	Paraneoplastic and autoimmune ganglionopathy
Motor neuron disease	Concomitant signs of upper motor neuron (hyperreflexia, pyramidal signs, and spasticity) and lower motor neuron (weakness, atrophy, and fasciculation) dysfunction, no sensory deficit, asymmetric onset, bulbar and respiratory involvement	ALS
Myelopathy[a]	Lower motor neuron signs at the level of compression and upper motor neuron signs below it, sphincter dysfunction, sensory symptoms present, sensory level	Cervical cord compression

ALS = amyotrophic lateral sclerosis; CIDP = chronic inflammatory demyelinating polyradiculoneuropathy; CMT1 = Charcot-Marie-Tooth disease type 1; GBS = Guillain-Barré syndrome.

[a]Myelopathy is a key differential diagnosis for neuromuscular disorders.

tests, including CSF analysis, genetic testing, and other specialized laboratory testing, can help clarify the diagnosis (**Table 47**, on page 79).

Electromyography (EMG), including both nerve conduction studies and needle electrode examination, can differentiate neuropathy from other neuromuscular disorders. In neuropathy, motor unit potentials are high amplitude and prolonged, whereas in myopathy, these potentials are low amplitude and brief. If neuropathy is present, EMG also can determine whether it is demyelinating or axonal. In demyelinating neuropathies, velocity of nerve conduction decreases, but in axonopathy, velocity remains unchanged. The presence of weakness, asymmetry, proximal findings, rapid course, or atypical features should prompt EMG testing. In patients with a slowly progressive distal symmetric sensory neuropathy with negative family history, however, EMG may not be required.

Nerve biopsy should only be considered in rare settings in which concern for a vasculitic, infectious, or infiltrative neuropathy exists. Autonomic tests, including

TABLE 46. Common Symptoms and Signs of Neuromuscular Disorders

Symptoms and Signs	Differential Diagnosis
Weakness	
Distal extremities	Diabetic, toxic and systemic polyneuropathy, hereditary neuropathy
Proximal extremities	Myopathy, polyradiculopathy, inflammatory demyelinating neuropathy, diabetic amyotrophy
Multifocal with pain (mononeuropathy multiplex)	Vasculitis, rheumatoid arthritis, diabetes
Focal asymmetric	ALS, inclusion body myositis, radiculopathy, multifocal motor neuropathy
Fluctuating	Myasthenia gravis
Muscles of eye movement	Myasthenia gravis, mitochondrial myopathy, thyroid disease
Bulbar (tongue, palate, lips)	ALS, myasthenia gravis, inclusion body myositis
Cranial nerves (especially seventh and third)	Diabetes, Lyme disease, sarcoidosis, HIV infection, Sjögren syndrome
Neck extensors	ALS, myasthenia gravis (especially with anti-MuSK antibody)
Fasciculation	ALS, radiculopathy, benign fasciculation syndrome
Sensory	
Stocking-glove gradient	Diabetic, toxic, systemic, or cryptogenic polyneuropathy; hereditary neuropathy
Dermatomal pattern	Radiculopathy, peripheral nerve lesion
Distal pain without hyporeflexia	Small fiber neuropathy (diabetes mellitus, alcoholism, Sjögren syndrome, sarcoidosis)
Marked proprioceptive loss in single limb	Dorsal root ganglionopathy (paraneoplastic, Sjögren syndrome, HIV)
Autonomic	
Orthostatic hypotension, resting tachycardia, excessive or impaired sweating, gastroparesis, constipation, erectile dysfunction	Diabetes, alcoholism, amyloidosis, autoimmune dysautonomia with antiganglionic acetylcholine receptor antibody, paraneoplastic antibodies

ALS = amyotrophic lateral sclerosis; MuSK = muscle-specific kinase.

quantitative sudomotor axon reflex and tilt table tests, can help confirm autonomic neuropathy but are rarely performed in practice.

KEY POINTS

HVC
- Electromyography (EMG) can differentiate neuropathy from other neuromuscular disorders, and if neuropathy is present, EMG can determine whether it is axonal or demyelinating; EMG may not be necessary in patients with a slowly progressive distal symmetric sensory neuropathy and a negative family history.
- The presence of weakness, asymmetry, proximal findings, a rapid course, or atypical features should prompt testing with electromyography in a patient with a suspected peripheral neuropathy.

Mononeuropathies

Mononeuropathies involve a single nerve and can cause both motor and sensory symptoms within the territory of the affected nerve. Sequential involvement of multiple nerves may be seen in mononeuropathy multiplex, a condition most often associated with pain and caused by vasculitis. Plexopathies originate at the level of the brachial or lumbosacral plexus and involve multiple sensory and motor nerves simultaneously.

Carpal Tunnel Syndrome

Carpal tunnel syndrome results from focal compression of the median nerve at the wrist. Most often, paresthesia and pain are experienced in the first three digits but may radiate to the entire hand or proximally. With milder symptoms, diagnosis of carpal tunnel syndrome can be made clinically, and treatment is supportive, including neutral positioning, wrist splints, and pain control. The presence of weakness, thenar atrophy, refractory pain, or active denervation evident on EMG should prompt surgical decompression. See MKSAP 18 General Internal Medicine for further information about carpal tunnel syndrome.

KEY POINT

- In patients with carpal tunnel syndrome and mild symptoms, a clinical diagnosis and supportive care is appropriate; the presence of weakness, thenar atrophy, refractory pain, or active denervation evident on electromyography should prompt decompression surgery. HVC

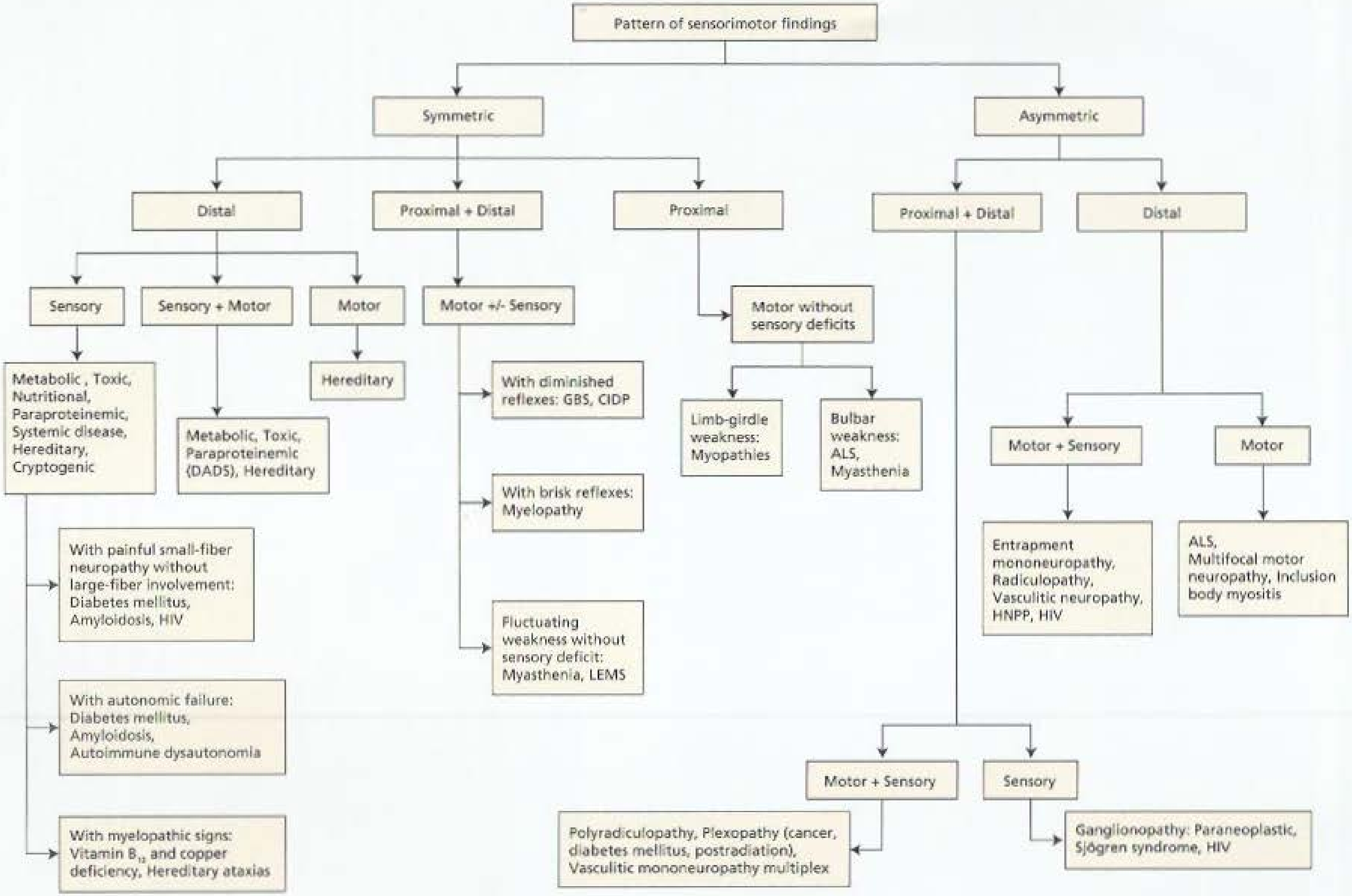

FIGURE 28. Algorithmic approach to peripheral neuropathies. ALS = amyotrophic lateral sclerosis; CIDP = chronic inflammatory demyelinating polyradiculoneuropathy; DADS = distal acquired demyelinating symmetric neuropathy; GBS = Guillain-Barré syndrome; HNPP = hereditary neuropathy with predisposition to pressure palsy; LEMS = Lambert-Eaton myasthenic syndrome.

TABLE 47. Laboratory Testing in Peripheral Neuropathy

Underlying Cause	Clinical Presentation	Laboratory Testing
Diabetes mellitus, impaired glucose tolerance	Distal symmetric polyneuropathy, mononeuropathy, lumbosacral radiculoneuropathy	Glucose tolerance test, hemoglobin A_{1c} measurement
Uremia, thyroid disease, anemia, liver disease	Distal symmetric polyneuropathy	Serum creatinine, TSH, and free thyroxine (T_4) levels; hematocrit, liver chemistry tests
Connective tissue disease, polyarteritis nodosa, vasculitis, Sjögren syndrome, cryoglobulinemia	Vasculitic mononeuropathy multiplex, Sjögren ganglionopathy	ESR and rheumatoid factor determination; antinuclear antibody, ANCA, anti-Ro/SSA antibody, anti-LA/SSB antibody, and cryoglobulin measurements
Syphilis	Posterior column disease resembling large-fiber neuropathy	RPR, CSF VDRL
MGUS, amyloidosis, multiple myeloma, lymphoproliferative disease, POEMS syndrome	Paraproteinemic neuropathy	SPEP, UPEP, IFE, serum free light chain assay
Vitamin B_{12}, folate, vitamin E, or copper deficiency	Myeloneuropathy with brisk reflexes	Serum copper, vitamin B_{12}, folate, vitamin E, methylmalonic acid/homocysteine levels
CIDP, GBS	Progressive symmetric proximal and distal motor and sensory polyradiculoneuropathy	CSF cell and protein, serum antiganglioside antibodies
Miller-Fisher variant of GBS	Ophthalmoplegia, ataxia, areflexia	Serum anti-GQ1B antibody
Multifocal motor neuropathy	Asymmetric pure motor weakness	Serum anti-GM1 antibody
Distal acquired demyelinating symmetric neuropathy	Distal sensory loss, tremor, sensory ataxia	SPEP, IFE, serum anti-MAG antibody
Amyloidosis	Autonomic and small-fiber neuropathy	Serum free light chains, abdominal fat pad biopsy (acquired), transthyretin gene testing (familial)
Infectious neuropathy	Variable, cranial nerve palsy, myelopathy with flaccid weakness in West Nile virus	Serum HIV antibody, serum Lyme antibody with Western blot confirmation, CSF West Nile virus antibody, skin biopsy in leprosy, IGRA, CSF acid-fast smear
Toxic neuropathy	Symmetric sensory or sensorimotor neuropathy, acute motor neuropathy (lead)	Serum lead, arsenic, mercury, and thallium measurements; 24-hour urine toxicology; history of exposure to ethanol, chemotherapy agents, colchicine, amiodarone, quinolones
Celiac disease	Sensory neuropathy and ataxia	IgA tissue transglutaminase antibodies and endomysial antibodies
Porphyria	Acute painful polyradiculopathy	Urine porphobilinogen and δ-aminolevulinic acid
Paraneoplastic disease	Subacute progressive sensory neuropathy, asymmetric ganglionopathy	Serum anti-Hu and anti-CRMP5 measurement; CSF oligoclonal bands

ANCA = anti-neutrophil cytoplasmic antibody; CIDP = chronic inflammatory demyelinating polyradiculoneuropathy; CRMP5 = collapsin response mediator protein 5; CSF = cerebrospinal fluid; ESR = erythrocyte sedimentation rate; GBS = Guillain-Barré syndrome, IFE = immune fixation electrophoresis; IGRA = interferon-γ release assay; MAG = myelin-associated glycoprotein; MGUS = monoclonal gammopathy of unknown significance; POEMS = polyneuropathy, organomegaly, endocrinopathy, monoclonal protein plasma cell disorder, and skin lesions ; RPR = rapid plasma reagin; SPEP = serum protein electrophoresis; SSA = Sjögren syndrome-related antigen A; SSB = Sjögren syndrome-related antigen B; TSH = thyroid-stimulating hormone; UPEP = urine protein electrophoresis; VDRL = Venereal Disease Research Laboratory test.

Bell Palsy

Bell palsy is idiopathic paralysis of the facial nerve (cranial nerve VII) that leads to unilateral paralysis of upper and lower facial muscles. In contrast, upper facial muscles are spared in central facial weakness (stroke) because of their bilateral innervation. Altered taste and hyperacusis also may occur in Bell palsy because of involvement of chorda tympani and stapedius muscles. Between 70% and 90% of patients with Bell palsy fully recover within a few weeks. In classic Bell palsy, initial brain imaging and laboratory testing are not required. Treatment with a 10-day course of oral prednisone, started within 72 hours of onset, is recommended to expedite both the rate and speed of full recovery. The utility of adding antiviral treatment to prednisone is controversial, and guidelines differ in their recommendations. There may be a small benefit to adding antiviral treatment in patients with severe palsy. Use of an eye patch and artificial tears to prevent corneal dryness are recommended. Synkinesis (concomitant movement of

perioral and periorbital muscles) may result from aberrant reinnervation after Bell palsy.

Secondary causes for facial nerve palsy include diabetes mellitus, Lyme disease, sarcoidosis, HIV, vasculitis, and malignancy. If a secondary cause is suspected on the basis of history (subacute onset over days, comorbidities, rash) or clinical examination (deficits unrelated to the facial nerve), additional testing is indicated and prednisone is typically avoided. Brain MRI with contrast also is recommended in patients with lingering or worsening weakness after 2 months.

KEY POINT

HVC
- In classic Bell palsy, initial brain imaging and laboratory testing is not required; treatment with a 10-day course of oral prednisone, started within 72 hours of onset, may expedite both the rate and speed of full recovery.

Brachial and Lumbosacral Plexopathies

Common causes of brachial and lumbosacral plexopathy include diabetes, malignancy, radiation, and trauma. Imaging is mandatory to rule out structural lesions and malignancy. Idiopathic brachial plexitis (also known as neuralgic amyotrophy) presents with subacute severe scapular pain followed by pronounced weakness and atrophy in shoulder-girdle and upper extremity muscles. It is likely immune mediated, and a triggering event, such as infection or surgery, usually precedes this presentation, although the infection or surgery is not in the region of the brachial plexus. EMG can confirm the diagnosis, and imaging can rule out alternative causes. Treatment is supportive. Gradual recovery (90% by 3 years) is common. Idiopathic lumbosacral radiculoplexus neuropathy is immune mediated and very similar in presentation to diabetic amyotrophy. (See Neuropathies of Diabetes Mellitus and Impaired Glucose Tolerance.)

Polyneuropathies

Polyneuropathies arise from various disorders causing injury to peripheral nerves (see Table 47). Polyneuropathies may affect either large nerve fibers (and lead to impaired proprioception, hyporeflexia, and weakness) or small nerve fibers (and cause pain, dysesthesia, and dysautonomia). Additionally, they may be primarily axonal or demyelinating. If axonal, the distal axonal segments are affected first, which leads to a length-dependent stocking-glove pattern of involvement. A sensory-predominant distal symmetric neuropathy is typically seen with metabolic, toxic, and systemic neuropathies. Demyelinating neuropathies, which result from injury to the myelin sheath of the peripheral nerve, can cause non-length-dependent weakness and sensory loss.

Neuropathies of Diabetes Mellitus and Impaired Glucose Tolerance

Diabetes mellitus causes various types of neuropathy (**Table 48**). The most common presentation is symmetric distal neuropathy involving small and large sensory fibers and, to a lesser extent, distal motor nerves. Clinical examination may reveal length-dependent loss of light touch and vibration sensation, loss of the ankle reflex, and—in advanced disease—distal weakness. Pain and paresthesia may predominate, especially when small fibers are involved. Patients with a pure small-fiber variant of symmetric distal neuropathy may have normal distal sensory and reflex findings on examination and normal results on EMG at presentation; this pattern also can be seen at various stages of diabetes and even in patients with impaired glucose tolerance. Between 11% and 25% of patients with glucose intolerance have evidence of small-fiber neuropathy on specialized testing, but only a minority (5%-10%) are symptomatic.

Autonomic diabetic neuropathy can cause orthostatic hypotension, erectile dysfunction, abnormal hidrosis, and gastroparesis. Dysautonomia also can mask symptoms of hypoglycemia and may predispose patients to silent myocardial infarction. Diabetic mononeuropathy can involve the cranial nerves (especially III, VI, and VII) and truncal nerve roots (with a dermatomal pattern of pain and paresthesia in the chest or abdomen) and predispose patients to entrapment neuropathies, such as carpal tunnel syndrome.

Diabetic amyotrophy, also known as proximal lumbosacral radiculoneuropathy, is associated with subacute painful involvement of the lumbosacral plexus followed by resolution of pain and onset of marked asymmetric weakness with atrophy and weight loss. The differential diagnosis of diabetic amyotrophy includes polyradiculopathy, retroperitoneal hematoma, neoplasm, carcinomatous meningitis, and inflammatory neuropathy. Spontaneous recovery over 1 to 3 years is typical but may be incomplete.

Tight glycemic control, exercise, and management of dyslipidemia, obesity, and metabolic syndrome can slow the progression and improve the symptoms of diabetic polyneuropathy. Management of diabetic amyotrophy consists of supportive measures, physical therapy, and pain control but does not involve immunosuppression. See MKSAP 18 Endocrinology and Metabolism for further information about diabetic neuropathy, including neuropathic pain treatment.

KEY POINTS

- The most common form of neuropathy secondary to diabetes is a symmetric distal neuropathy involving small and large sensory fibers and, to less extent, distal motor nerves; examination may reveal length-dependent loss of light touch and vibration sensation, loss of the ankle reflex, and—in advanced disease—distal weakness
- Tight glycemic control, exercise, and management of dyslipidemia, obesity, and metabolic syndrome can slow the progression and improve the symptoms of diabetic polyneuropathy.

TABLE 48. Peripheral Nerve Dysfunction in Diabetes Mellitus

Classification	Sign and Symptoms	Diagnosis	Management
Autonomic neuropathy	Orthostatic hypotension, early satiety, nausea and vomiting (gastroparesis), constipation (colonic dysmotility), erectile dysfunction, hyperhidrosis or hypohidrosis	Orthostatic blood pressure determination, QSART, tilt table	Fludrocortisone; midodrine; compression stocking; supportive management of bowel, bladder, and sexual symptoms; glycemic control
Diabetic lumbosacral radiculoneuropathy (diabetic amyotrophy)	Severe pain followed by weakness and muscle wasting in proximal lower extremities; weight loss, with or without proximal sensory loss	Clinical examination, EMG, lumbar spinal MRI, CT of abdomen and pelvis (to rule out retroperitoneal hematoma)	Pain control, physical therapy, supportive measures, not associated with level of glycemic control, not responsive to immunotherapy
Mononeuropathy	Sensory loss; paresthesia or pain in the distribution of a single nerve, followed by weakness (median or peroneal nerve); cranial nerve palsy (especially cranial nerves III, VI, or VII)	Clinical examination, EMG, brain MRI	Avoidance of compressive positions, bracing, pain control, decompressive surgery, observation in cranial palsies
Radiculopathy	Sensory loss, pain, and weakness in the distribution of nerve roots; thoracic radiculopathy causing patchy truncal numbness is common	Clinical examination, EMG, MRI of nerve roots (to rule out root compression)	Pain control, glycemic control, observation
Sensorimotor peripheral neuropathy	Asymptomatic (sometimes); distal length dependent; sensory loss and weakness; often painful; possible loss of ankle reflex	Clinical, EMG, oral glucose tolerance test, hemoglobin A_{1c}	Regular monitoring of feet, supportive measures, neuropathic pain medication (see Small-fiber neuropathy below)
Small-fiber neuropathy	Burning distal extremity pain without weakness, may be non-length-dependent, sparing of ankle reflex	Clinical, QSART, skin biopsy (intraepidermal nerve fiber density)	Pregabalin, duloxetine, tapentadol (FDA-approved), tricyclic antidepressants, venlafaxine, gabapentin, and topical capsaicin

EMG = electromyography; QSART = quantitative sudomotor axon reflex test.

Hereditary Neuropathies

Charcot-Marie-Tooth disease consists of more than 70 genetic disorders in which peripheral neuropathy is the only or main clinical manifestation. The most common inherited neuropathy, Charcot-Marie-Tooth disease type 1 is an autosomal dominant demyelinating neuropathy presenting with early onset, slowly progressive distal weakness, areflexia, and sensory loss without pain or paresthesia. Foot deformities, such as hammer toes, high arches, and distal leg atrophy (stork legs) are common (**Figure 29**). EMG typically reveals a uniform slowing of nerve conduction velocities, and genetic testing is confirmatory.

Inflammatory Polyradiculoneuropathies

Guillain-Barré Syndrome

H Guillain-Barré syndrome (GBS) is an acute autoimmune demyelinating polyradiculoneuropathy that presents with rapidly progressive flaccid weakness. Onset is often preceded by a respiratory or gastrointestinal infection, triggering a T-cell–mediated autoimmune attack against peripheral nerve and root myelin. Weakness is ascending, starting in the lower extremities, spreading to the upper limbs and bulbar and respiratory muscles, and reaching its nadir in less than 4 weeks. The weakness may occur first in the proximal muscles. Paresthesias and early low back pain are common. Dysautonomia can be severe and predispose patients to labile blood pressure and arrhythmias. Progressive respiratory and bulbar weakness may lead to rapid respiratory failure. On examination, diffuse areflexia is a key finding; there is not marked sensory loss, even in the setting of paresthesias. GBS variants include demyelinating polyradiculoneuropathy involving only or sparing the legs and the Miller-Fisher variant, which presents with ataxia, cranial neuropathies, and antibodies to GQ1b ganglioside protein (a highly sensitive finding).

The differential diagnosis of GBS includes botulism (descending weakness), myasthenic crisis (without pain and paresthesia), acute myelopathies (hyperreflexia and upper motor neuron signs), West Nile virus (asymmetric paralysis), carcinomatous and sarcoid meningitis (slower course), Lyme disease, HIV seroconversion, porphyria, and tick paralysis.

FIGURE 29. High arches, hammertoes, and distal leg atrophy in a patient with inherited neuropathy.

H CONT.

CSF analysis shows a pattern of a highly elevated protein level with a normal or mildly elevated leukocyte count (albuminocytologic dissociation) in 90% of patients. EMG is the confirmatory test and shows a predominantly demyelinating pattern; sensitivity is initially low but 90% by week 5. Initiation of treatment should not await EMG confirmation; a negative early study should be repeated later if the diagnosis remains suspected. Additional studies, such as spinal MRI and serologic testing for Lyme disease, HIV, and myasthenia antibodies, may be considered in appropriate clinical settings.

Therapy includes supportive management and immunotherapy. All patients with GBS should be hospitalized for close respiratory and cardiovascular monitoring. Decisions about intubation should be guided by measurement of forced vital capacity and negative inspiratory force and be made before emergence of hypoxemia. Both plasmapheresis and intravenous immune globulin (IVIG) have equal efficacy in shortening the time to recovery and the duration of ventilation. Serial treatment with IVIG after plasma exchange is not superior to either treatment alone and should not be considered unless symptoms worsen after initial improvement or stabilization. Glucocorticoids are contraindicated in GBS and may worsen outcome. Prognosis is favorable, with 80% of patients resuming ambulation by 6 months after onset. Relapse occurs in 6% of patients with GBS and requires repeated treatment. H

KEY POINTS

- Guillain-Barré syndrome is an acute autoimmune demyelinating polyradiculoneuropathy that presents with rapidly progressive ascending flaccid weakness.
- All patients with Guillain-Barré syndrome should be hospitalized for close respiratory and cardiovascular monitoring; plasmapheresis and intravenous immune globulin have equal efficacy in shortening the time to recovery and the duration of ventilation.
- Glucocorticoids are contraindicated in Guillain-Barré syndrome and may worsen outcome.

Chronic Inflammatory Demyelinating Polyradiculoneuropathy

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is a potentially treatable autoimmune neuropathy. CIDP often presents with a progressive or relapsing symmetric proximal and distal weakness and sensory symptoms with diffuse areflexia. Its temporal course is often subacute with progression after 8 weeks of onset. Atypical forms include multifocal asymmetric and distal symmetric variants, but respiratory failure is rare. CIDP may be isolated or occur in the setting of several other systemic conditions, including diabetes mellitus, lymphoma, and HIV. CSF findings are similar to those of GBS, and a demyelinating pattern on EMG is the key to diagnosis. Nerve

biopsy is often unnecessary but, in complex presentations, can differentiate CIDP from vasculitis or amyloidosis. First-line treatments include glucocorticoids, periodic IVIG, or plasma exchange, which all have similar efficacy. Treatment is typically continued for at least 6 months. Half of patients achieve remission, but the other half relapse and require resumption of immunotherapy. Second-line therapies, including azathioprine, mycophenolate mofetil, cyclosporine, or cyclophosphamide, are often used off-label to treat refractory disease.

Critical Illness Neuropathy

Prolonged intensive care treatment, particularly in association with sepsis and multiorgan failure, can lead to diffuse weakness, an inability to wean patients from ventilators, and prolonged posthospitalization weakness. Weakness may be secondary to critical illness myopathy, critical illness axonal polyneuropathy, or a combination of the two. Critical illness myopathy is more common, less severe, and potentially caused by channelopathy (a disease involving dysfunction of a cellular ion channel) triggered by sepsis and systemic disease. Critical illness neuropathy, on the other hand, is associated with microcirculatory axonal damage and a more protracted recovery. EMG can differentiate between the two, but often components of both are simultaneously present; in rare cases, nerve and muscle biopsy may be necessary. Differential diagnosis includes GBS, myasthenia gravis, vasculitis, and central weakness. No definitive treatment is available, but appropriate glycemic control, early mobilization and therapy, and minimizing glucocorticoid use improve prognosis. One third of patients with critical illness neuropathy die during the acute phase of the disease, with the remainder experiencing a full or partial slow recovery within months to years.

KEY POINTS

- Critical illness axonal polyneuropathy often coexists with critical illness myopathy and can lead to diffuse weakness, an inability to wean patients from ventilators, and prolonged posthospitalization weakness.
- No definitive treatment is available for critical illness neuropathy, but appropriate glycemic control, early mobilization and therapy, and minimizing glucocorticoid use improve prognosis.

Paraproteinemic Neuropathy

Paraproteinemic neuropathy frequently presents as a symmetric distal sensory neuropathy, but sensorimotor, multifocal motor, or cranial nerve variants also are possible. Therefore, all patients with peripheral neuropathy should be screened for paraproteinemia. Neuropathies associated with monoclonal proteins occur in monoclonal gammopathy of undetermined significance, multiple myeloma, Waldenström macroglobulinemia, amyloidosis, and other hematologic malignancies. (See MKSAP 18 Hematology and Oncology). Diagnosis depends on the detection of monoclonal proteins, and treatment is based on the underlying condition. A CIDP-like severe polyneuropathy may occur in paraproteinemic neuropathy in association with organomegaly, endocrinopathy, monoclonal plasma cell disorder, and skin changes (POEMS syndrome); this syndrome always is associated with λ paraproteinemia. Treatment is similar to that of multiple myeloma and may reverse neuropathic symptoms. Another neuropathic disorder associated with paraproteins is distal acquired demyelinating symmetric neuropathy. Patients with this condition generally are responsive to immunosuppressive therapy (glucocorticoids, IVIG, and rituximab), except for those with antibodies to myelin-associated glycoprotein; their disease is medication refractory.

Autonomic Neuropathy

Autonomic neuropathies manifest as diffuse or focal impairment of cholinergic or sympathetic autonomic systems. Whereas diabetes, amyloidosis, and HIV are common disorders underlying secondary autonomic neuropathy, primary autoimmune ganglionopathy is an important and potentially treatable cause of autonomic neuropathy that is often associated with antibodies against ganglionic nicotinic acetylcholine receptors. The presentation may range from acute pandysautonomia to chronic focal autonomic dysfunction. Antibody testing and skin biopsy help with diagnosis. Response to IVIG, plasmapheresis, or immunosuppression is common.

Amyloid neuropathy is caused by extracellular deposition of amyloid protein in peripheral nerves and other tissues. Amyloidosis starts with painful small-fiber neuropathy and progressively causes major autonomic impairment and weakness and multiorgan involvement. Primary amyloidosis is associated with monoclonal proteins, whereas familial amyloidosis is secondary to transthyretin gene mutation. See MKSAP 18 Hematology and Oncology.

Amyotrophic Lateral Sclerosis

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease of motor neurons that causes progressive weakness, atrophy, and (eventually) death. This motor neuron disease often begins as isolated extremity or bulbar weakness (dysphagia, dysarthria) but relentlessly spreads to other regions. Upper (hyperreflexia, spasticity, and extensor plantar response) and lower (atrophy and fasciculation) motor neuron signs and the absence of sensory deficits are characteristic. Frontotemporal dementia occurs in 50% of affected patients, but oculomotor palsy, incontinence, and tremor are atypical. Diagnosis is based on clinical evidence of both upper and lower motor neuron signs on examination and EMG evidence of lower motor neuron signs in at least two (probable ALS) or more (definite ALS) regions. Alternative diagnoses also must be excluded by brain and cervical spinal imaging and laboratory testing: cervical cord compression (causing lower motor neuron signs at the level of compression and some upper signs below that level), vitamin B_{12} and copper deficiencies, Lyme disease, hyperparathyroidism, and

thyrotoxicosis must be excluded. Multifocal motor neuropathy is a treatable ALS mimic characterized by severe weakness with minimal atrophy, absence of upper motor neuron signs, and EMG evidence of motor conduction block. Benign fasciculation syndrome causes widespread fasciculation without weakness or upper motor neuron signs and should not be confused with ALS.

Treatment of ALS is supportive and should involve multidisciplinary care. Riluzole, a glutamate release blocker, is an FDA-approved treatment for ALS and may increase survival by 3 months. Edaravone, an intravenous free radical scavenger, recently received FDA approval on the basis of evidence showing that it slowed functional decline in ALS within a 6-month period. Whether this agent can slow the course of ALS over a longer period or can reduce mortality remains under investigation. Noninvasive ventilation, nutritional support (including percutaneous endoscopic gastrostomy), and treatment of pseudobulbar affect by dextromethorphan-quinidine also have shown some benefit. Prognosis and goals of care should be discussed with the patient early in the disease course to avoid unnecessary diagnostic and therapeutic measures.

KEY POINTS

- Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease of motor neurons that causes progressive weakness, atrophy, and (eventually) death; 50% of patients with ALS will develop frontotemporal dementia.
- Although treatment of amyotrophic lateral sclerosis (ALS) remains largely supportive, the glutamate release blocker riluzole may increase survival by 3 months, and the intravenous free radical scavenger edaravone has been shown to slow functional decline within a 6-month period; both drugs have received FDA approval for use in ALS.

Neuromuscular Junction Disorders

Myasthenia Gravis

H Myasthenia gravis (MG) is an autoimmune disease of the postsynaptic neuromuscular junction associated with antibodies to the postsynaptic acetylcholine receptors. Onset most commonly occurs in the third decade of life in women and after age 50 years in men. Ptosis and diplopia are the first manifestations in two thirds of patients, although only half of these patients develop generalized myasthenia, typically within 2 years. Early bulbar and cervical involvement is seen in 10% of patients. Fluctuating painless weakness without sensory loss is typical. Weakness may be missed on clinical examination unless fatigability is assessed by sustained or repeated activation of muscles. The presence of respiratory symptoms should prompt close monitoring of respiratory parameters because of the risk of rapid respiratory failure (myasthenic crisis). This crisis can occur as part of the natural history of bulbar or generalized myasthenia or be triggered by external factors, including infection, surgery, or certain medications (especially aminoglycosides, quinolones, magnesium, beta blockers, and hydroxychloroquine). H

Diagnosis of MG is based on clinical, serologic, and EMG findings. Disease-specific antibodies are found in 90% of patients; of these, 85% have typical MG with acetylcholine receptor antibodies, but 5% have anti–muscle-specific kinase (MuSK) antibodies. MuSK-positive myasthenia is more likely to cause focal or severe bulbar, cervical, or respiratory weakness. The characteristic EMG finding of MG is a decremental response to repetitive stimulation. All patients with MG should undergo chest CT to screen for thymoma, a tumor associated with the disease.

Symptomatic treatment of ocular and mild generalized myasthenia usually starts with the cholinesterase inhibitor pyridostigmine. In those with more advanced disease, immunosuppressive therapy is required. Oral glucocorticoids often are used as first-line treatment but can cause transient exacerbation at high doses and should be titrated upward slowly in patients with mild to moderate weakness. In the presence of prominent bulbar or generalized weakness and in myasthenic crisis, treatment with IVIG or plasmapheresis should precede initiation of glucocorticoids. The immunosuppressant agents azathioprine, mycophenolate mofetil, and cyclosporine are effective long-term maintenance therapies. However, these drugs have a delayed onset of action, and bridging therapy with concomitant glucocorticoids, IVIG, or plasmapheresis is usually required. H

Thymectomy should be performed in all patients with thymoma. Benefits of thymectomy in patients without thymoma are not firmly established, but a recent randomized controlled trial confirmed that thymectomy improves clinical outcome and reduces immunosuppression requirements in patients with generalized MG who are younger than 65 years and within 3 years of diagnosis.

MuSK-positive myasthenia responds well to plasmapheresis and glucocorticoids but requires aggressive maintenance immunosuppression. Prolonged remission has been reported with rituximab (off-label use); thymectomy and pyridostigmine are not helpful.

KEY POINTS

- Onset of myasthenia gravis (MG) most commonly occurs in the third decade of life in women and after age 50 years in men, with ptosis, diplopia, and fluctuating painless weakness without sensory loss being typical symptoms; all patients with MG should undergo chest CT to screen for thymoma, a tumor associated with the disease.
- Symptomatic treatment of ocular and mild generalized myasthenia gravis usually starts with the cholinesterase inhibitor pyridostigmine; in those with more advanced disease, immunosuppressive therapy is required, as is thymectomy for those with thymoma.

Lambert-Eaton Myasthenic Syndrome

Lambert-Eaton myasthenic syndrome is an autoimmune disorder of the presynaptic neuromuscular junction associated with antibodies against the voltage-gated calcium channel. This disorder presents similarly to MG, except that weakness improves with exercise, and hyporeflexia and dysautonomia are present. Diagnosis is confirmed by detection of serum anti-voltage-gated calcium channel antibodies (90%) and the EMG finding of augmented motor response to rapid repetitive stimulation. Malignancy, especially small cell lung cancer, is found in half of patients. Treatment consists of treating any underlying malignancy or, in nonparaneoplastic disease, immunosuppression, IVIG, or plasmapheresis.

Myopathies

Overview

Classification of myopathies is based on clinical and pathologic characteristics and acquired versus inherited causes (**Table 49**). Most myopathies involve symmetric weakness of the proximal limb muscles. A normal sensory and reflex

TABLE 49. Classification of Myopathies

Class	Examples	Features
Inherited myopathies		
Muscular dystrophies	Duchenne	Early onset, fulminant
	Becker, Emery-Dreifuss	Early onset, survival to adulthood, cardiac disease
	Limb-girdle, facioscapulohumeral, oculopharyngeal	Variable onset, slow course
Myotonic dystrophy	Type 1	Myotonia, distal weakness, ptosis with lower facial weakness, variable cognitive impairment, cataract, arrhythmia with cardiomyopathy, diabetes mellitus, thyroid disease
	Type 2	Myotonia, proximal weakness, milder course, systemic features similar to those of type 1
Congenital myopathies	Nemaline myopathy, centronuclear myopathy, central core myopathy, distal myopathies	Childhood onset, focal weakness in distal forms, predisposition to exercise-induced cramping and malignant hyperthermia in central core myopathy
Metabolic myopathies	Acid maltase deficiency (Pompe disease), CPT II deficiency, McArdle disease (myophosphorylase deficiency), other lipid and glycogen storage disorders	Exercise intolerance, myoglobinuria, myalgia, progressive proximal and respiratory weakness in acid maltase deficiency
Mitochondrial myopathies	MERRF, MELAS, MNGIE, Kearns-Sayre syndrome	Childhood or early adulthood onset, fluctuating course, wide spectrum with variable systemic comorbidity, ophthalmoplegia, bulbar symptoms, elevated serum lactic acid level
Acquired myopathies		
Inflammatory	Dermatomyositis, polymyositis, immune-mediated necrotizing myopathy	Highly elevated creatine kinase level, subacute course, association with malignancy, dermatologic signs in dermatomyositis
	Inclusion body myositis	Onset usually after age 50 years, asymmetric progressive weakness with atrophy, distal arm and quadriceps involvement
Endocrine-related	Hypothyroidism, hyperthyroidism, hyperparathyroidism, Addison disease, Cushing syndrome, acromegaly, vitamin D deficiency, hypokalemia	
Systemic disease	Systemic lupus erythematosus, mixed connective tissue disease, systemic sclerosis, critical illness, paraneoplastic	
Toxic and drug-related	Ethanol, statins, glucocorticoids, anti-HIV and antimalarial agents, interferons, amphotericin B, amiodarone, immunophilins	Statin myopathy as possible cause of mildly to highly elevated creatine kinase level

CPT II deficiency = carnitine palmitoyltransferase II deficiency; MELAS = mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes syndrome; MERRF = myoclonic epilepsy with ragged red fibers; MNGIE = mitochondrial neurogastrointestinal encephalopathy.

examination can differentiate myopathy from neuropathy. Additional features that can indicate a specific diagnosis include the clinical course; the presence of pain and stiffness; atypical distribution in ocular, bulbar, or distal limb muscles; and episodic symptoms (**Table 50**).

Diagnosis is based on systematic clinical assessment, muscle-related serum markers (creatine kinase [CK], aldolase), EMG findings, muscle biopsy, and, in certain cases, genetic testing. The serum CK level is elevated in many forms of myopathy and can be followed to monitor disease activity and response to treatment in inflammatory myopathies. Mild elevation of the serum CK level (<5 times normal) is not specific to myopathies and also can be seen in ALS, CIDP, muscle trauma, and persistent elevation of the serum CK level without weakness (benign hyperCKemia). EMG can confirm the presence of changes associated with myopathy (low amplitude, short duration, polyphasic shape of motor unit potentials), determine distribution of involved muscles, and rule out neuropathy or a neuromuscular junction disorder. The serum CK level should be checked before EMG to prevent procedure-related false positive results. Muscle biopsy is the most helpful test to confirm the diagnosis of myopathy, but in some hereditary myopathies, genetic testing can provide the confirmation without need for biopsy.

KEY POINT

- Diagnosis of a myopathy is based on systematic clinical assessment, muscle-related serum markers, electromyographic findings, muscle biopsy, and (sometimes) genetic testing.

TABLE 50. Clinical Features of Myopathies

Clinical Features	Differential Diagnosis
Pain	Metabolic, toxic, infectious, inflammatory, and mitochondrial myopathies
Stiffness	Myotonic dystrophy, myotonic channelopathies, hyperkalemic periodic paralysis, hypothyroidism; differential diagnosis: stiff person syndrome
Rapid course	Inflammatory, toxic, autoimmune, and endocrine myopathies
Very slow course, plus or minus focal atrophy	Muscular dystrophies, congenital myopathies, metabolic myopathies
Fluctuating weakness	Mitochondrial myopathy, myasthenia gravis
Myoglobinuria	Toxic and infectious myopathy, trauma, metabolic myopathies (CPT II deficiency, McArdle disease, central core myopathy)
Respiratory muscle involvement	Muscular dystrophies, inflammatory, mitochondrial, and metabolic myopathies (acid maltase deficiency, debrancher deficiency)

CPT II deficiency = carnitine palmitoyltransferase II deficiency.

Inflammatory Myopathy

Polymyositis, dermatomyositis, immune-mediated necrotizing myopathy, and inclusion body myositis are idiopathic inflammatory myopathies. Polymyositis and dermatomyositis present with acute or subacute proximal muscle weakness. Diagnosis is based on an elevated serum CK level, EMG findings, and muscle biopsy findings. Immune-mediated necrotizing myopathy typically presents with progressive proximal weakness and an elevated serum CK level; diagnosis is based on muscle biopsy findings of necrotic fibers with limited inflammation. Onset can be triggered by statins, but weakness continues to progress after removal of the drug. In this setting, the presence of the disease-specific serum antibody to hydroxymethylglutaryl coenzyme A reductase can support the diagnosis. Treatment with immunosuppression reverses the myopathy.

Inclusion body myositis has a slowly progressive course and causes early weakness and atrophy of distal upper extremity flexors, quadriceps, and bulbar muscles. Muscle biopsy reveals inflammation and characteristic inclusion bodies. See MKSAP 18 Rheumatology for further information on inflammatory myopathy.

Endocrine-Related Myopathy

Hypothyroid myopathy can cause diffuse myalgia, proximal weakness, and myoedema (muscle mounding after percussion). Hyperthyroidism also can cause myopathy in association with fasciculation, ophthalmoplegia and hyperreflexia.

Glucocorticoid-Induced Myopathy

Exposure to chronic high-dose exogenous glucocorticoids can cause myopathy of unclear mechanism. This disorder is associated with proximal weakness and myalgia but normal CK levels and (mostly) normal EMG findings. Dexamethasone is more likely than prednisone or hydrocortisone to cause this type of myopathy. In patients treated with glucocorticoids for inflammatory myopathies, persistence of weakness after normalization of the CK level may indicate glucocorticoid-induced myopathy, and a trial of glucocorticoid tapering may be warranted.

KEY POINT

- Glucocorticoid-induced myopathy is associated with proximal weakness and myalgia but normal creatine kinase levels and (mostly) normal electromyographic findings; dexamethasone is more likely than prednisone or hydrocortisone to cause this type of myopathy.

Toxic Myopathy

Toxic myopathy can be triggered by statins and other drugs (see Table 49). Statins can cause acute toxic myopathy associated with rhabdomyolysis. The lipophilic statins metabolized by the cytochrome P450 3A4 isozyme system (simvastatin,

atorvastatin, and lovastatin) have a higher propensity to cause myopathy than the hydrophilic agents pravastatin and rosuvastatin. The risk of myopathy increases with higher dosages, the addition of fenofibrate or gemfibrozil, and the addition of cytochrome P450 3A4 isozyme inhibitors. Serum CK levels can be mildly or highly elevated in toxic myopathy.

Inherited Myopathies

Inherited myopathies are listed in Table 49. Many of these disorders develop early in life, but some present in adulthood. Myotonic dystrophies are systemic diseases associated with myotonia, an impairment of muscle relaxation causing stiffness and a delayed hand-grip release. Myotonic dystrophy type 1 causes distal weakness and is associated with cataracts, frontal balding, cardiac and endocrine disease, and mild cognitive impairment. Progression of weakness is slow, but diagnosis should prompt close monitoring for cardiac and pulmonary disease that can cause premature mortality.

Mitochondrial myopathy presents with significant variability and can cause fatigue, myalgia, ophthalmoplegia, and various extramuscular manifestations. Mitochondrial myopathies should be suspected in the presence of a fluctuating course, multiorgan involvement, and maternal transmission.

Adult-onset metabolic myopathies may present with isolated exercise-induced weakness, cramps, and myoglobinuria and include many deficiencies of key metabolic pathways, such as glycogen storage and fatty acid oxidation; the most common types are carnitine palmitoyltransferase II deficiency and McArdle disease.

Acid maltase deficiency (Pompe disease) has an adult-onset form associated with proximal and respiratory muscle weakness. Diagnosis is based on assessment of α-glucosidase activity and genetic testing. Alglucosidase alfa is FDA approved to prevent progression of weakness.

Neuro-oncology

H Approach to Intracranial Tumors

Both benign and malignant intracranial tumors can have devastating neurologic consequences because of the obvious space constraints within the skull and potential surgical inaccessibility (if in the thalamus or brainstem, for example). Presenting symptoms of intracranial tumors appear in **Table 51**. Intracranial tumors most often present with a slow, progressive course of neurologic symptoms. Acute symptoms typically occur when a tumor causes seizure or hemorrhage.

Headache is a common symptom, although the classic early morning headache is uncommon. Elevated intracranial pressure (ICP) can cause the headache to increase with coughing, sneezing, straining, or the Valsalva maneuver. Elevated ICP also is associated with nausea, vomiting, blurry vision, papilledema, and an inability to abduct the eyes (bilateral abducens nerve [cranial nerve VI] palsy). Elevated ICP also can lead to life-threatening herniation, syncope, or cerebellar "fits" (episodic extension, flexion and stiffening of limbs; loss of consciousness; slowed or irregular respiration; and pupil dilation), which may be confused with seizures.

Head CT without contrast may be useful emergently to assess for hemorrhage or herniation but is not very sensitive for detecting the presence of a mass lesion, especially in the posterior fossa. Brain MRI is the preferred diagnostic modality; contrast administration improves diagnostic sensitivity. Management is determined by tumor location and pathology. H

TABLE 51. Presenting Symptoms/Findings of Central Nervous System Tumors

Tumor Location	Symptoms/Findings
Brainstem	Cranial nerve findings, elevated intracranial pressure[a]
Cerebellum	Ataxia, falls, imbalance, elevated intracranial pressure[a]
Frontal lobe	Weakness, personality change, cognitive symptoms, or psychiatric symptoms
Occipital lobe	Homonymous hemianopia
Parietal lobe	Numbness, paresthesia
Temporal lobe	Amnesia
Dominant hemisphere	Aphasia

[a]Symptoms of elevated intracranial pressure include nausea, vomiting, blurry vision, papilledema, and inability to abduct the eyes (bilateral abducens nerve [cranial nerve VI] palsy).

KEY POINT

- Head CT without contrast may be useful emergently to assess for hemorrhage or herniation, but brain MRI is the preferred diagnostic modality for the evaluation of intracranial tumors.

Metastatic Brain Tumors

Brain metastases are the most common intracranial tumors. The most likely sources are lung, breast, and kidney cancers and melanoma. Metastases can be solitary but are more often multiple. These metastases typically appear as ring-enhancing lesions on postcontrast MRIs, usually at the gray-white cortical junction. Survival is generally measured in weeks to months. Most brain metastases are treated with whole-brain or more targeted radiation (stereotactic radiosurgery). Resection may increase survival in younger patients with good baseline function and a single or limited number of metastases; it may also be considered when the underlying diagnosis is uncertain.

Carcinomatous meningitis is a rare diagnosis that requires a high index of suspicion to identify; presenting symptoms are

variable and include headache, neurologic deficits, and altered mental status. MRI typically shows nodular meningeal enhancement. Patients with leukemia or lymphoma whose initial symptoms are cranial nerve deficits or radiculopathy may have evidence of nerve root enhancement on postcontrast MRI of the brain and/or spine. Cerebrospinal fluid (CSF) analysis with cytology and often flow cytometry is required to make the diagnosis; because of limited sensitivity of CSF cytology, repeat lumbar puncture is sometimes needed to establish the diagnosis.

KEY POINTS

- Brain metastases are the most common intracranial tumors that typically appear as ring-enhancing lesions on postcontrast MRIs at the gray-white cortical junction.
- Most brain metastases are treated with whole-brain or more targeted radiation (stereotactic radiosurgery), but resection of a single or limited number of intracranial metastases may increase survival in younger patients with good baseline function.

Primary Central Nervous System Tumors

Meningiomas

Meningioma is the most common primary type of central nervous system (CNS) tumor. Often found incidentally, meningiomas are benign dural-based tumors that typically show homogenous enhancement on postcontrast MRI. They have a smooth, rounded shape and often a "tail" that tracks along the dura outside the brain parenchyma (**Figure 30**). On noncontrast images, meningiomas may be hypointense or isointense and thus not readily seen. Because of their characteristic MRI appearance, many meningiomas are followed clinically, without resection or biopsy, unless they are accompanied by significant clinical deficits, drug-resistant seizures, severe headaches, or peritumoral edema.

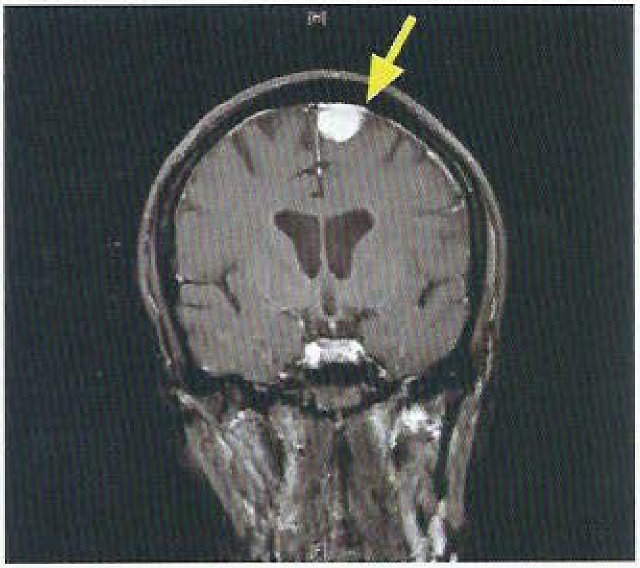

FIGURE 30. Coronal postcontrast T1-weighted MRI showing a left parafalcine meningioma. The tumor enhances homogeneously with contrast, which makes it look like a "lightbulb." Note the "dural tail" (*arrow*).

KEY POINT

- Meningioma is the most common primary type of central nervous system tumor and has a characteristic MRI appearance; the tumor is resected only if accompanied by significant clinical deficits, drug-resistant seizures, severe headaches, or peritumoral edema.

Glioblastoma Multiforme

Glioblastoma multiforme (**Figure 31**) is the most common and most aggressive glioma subtype in adults. Previous exposure to medical therapeutic radiation is the only consistent risk factor for developing gliomas. There is no evidence that environmental electromagnetic fields, cell phones, or smoking increase tumor risk. Gliomas rarely metastasize, and routine evaluation of patients with glioblastoma multiforme with lumbar puncture or MRI of the spinal cord is not recommended unless dictated by focal findings.

An MRI typically shows a large, space-occupying lesion with central necrosis, mass effect, and surrounding edema. Lower grade gliomas may not enhance. Treatment is usually resection, if possible, followed by radiation and chemotherapy. Temozolomide, nitrosoureas, and bevacizumab can be used. Prognosis is dependent on pathologic type; 5-year survival rates for glioblastoma multiforme are less than 10%, and survival is often measured in months. Prognosis is better in patients who are younger than 45 years, have an excellent functional status, have minimal residual tumor after resection, and receive chemotherapy and radiation after surgery.

KEY POINTS

- Previous exposure to medical therapeutic radiation is the only consistent risk factor for developing gliomas, including glioblastoma multiforme.
- Prognosis in glioblastoma multiforme is better in patients who are younger than 45 years, have an excellent functional status, have minimal residual tumor after resection, and receive chemotherapy and radiation after surgery.

Primary Central Nervous System Lymphoma

Primary central nervous system lymphoma (PCNSL) initially occurs without systemic or lymph node involvement. Its typical pathologic appearance is diffuse large B-cell lymphoma. Immunodeficiency is the most consistent risk factor, but PCNSL incidence is increasing in older, immunocompetent patients. On MRI, PCNSL appears as a single, well-demarcated, deep white matter (periventricular) lesion without mass effect or edema. The radiologic appearance of PCNSL can be confused with inflammatory or demyelinating lesions.

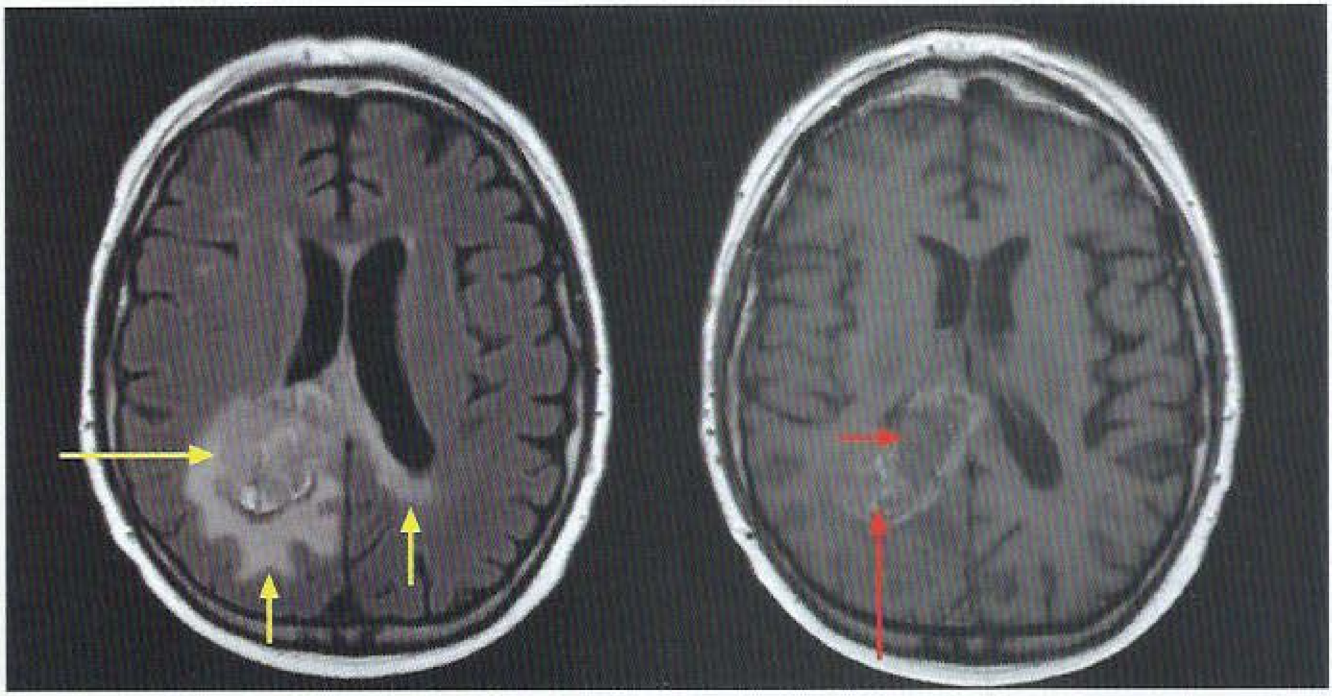

FIGURE 31. MRI showing a right parieto-occipital glioblastoma multiforme. *Left*, T2-weighted fluid-attenuated inversion recovery sequence shows a heterogenous intensity mass lesion (*longer yellow arrow*) with surrounding hyperintense edema that extends into both hemispheres (*shorter yellow arrows*). *Right*, T1-weighted sequence shows a hypointense core suggestive of central necrosis (*shorter red arrow*) with heterogenous enhancement (*longer red arrow*).

H CONT.

PCNSL evaluation should include HIV testing, lumbar puncture (if not contraindicated because of elevated ICP), and ophthalmologic evaluation with vitreous fluid sampling. Lymphomatous cells in vitreous or CSF samples (from cytology and flow cytometry) can add to diagnostic sensitivity and may obviate the need for biopsy. Systemic staging should include bone marrow biopsy, testicular ultrasonography, and whole-body PET or CT. Empiric glucocorticoids should be avoided before biopsy because they can temporarily suppress lymphoma and prevent or delay a tissue diagnosis.

Surgery and typical chemotherapeutic regimens for systemic lymphoma are usually ineffective in PCNSL. High-dose intravenous (IV) methotrexate combined with rituximab is the mainstay of treatment and at times is followed by subsequent radiation. Intrathecal chemotherapy has not been prospectively studied. Despite being chemo- and radiosensitive, PCNSL typically has multiple recurrences and a generally poor prognosis. H

KEY POINTS

- Immunodeficiency is the most consistent risk factor for primary central nervous system lymphoma, but its incidence is increasing in older, immunocompetent patients.
- Empiric glucocorticoids should be avoided before biopsy because they can temporarily suppress lymphoma and prevent or delay a tissue diagnosis.

Medical Management of Complications of Central Nervous System Tumors

H

Seizures

Seizures are more common in low-grade than high-grade tumors. Tumors near the cortex, especially the temporal lobe or primary motor cortex, are especially associated with seizures. White matter and posterior fossa tumors, on the other hand, typically do not cause seizures. Gangliogliomas and dysembryoplastic neuroepithelial tumors provoke medication-resistant seizures in more than 90% of patients, and these tumors should be resected, if possible. Seizures may not be directly caused by the CNS tumor but rather by associated conditions or treatment, such as electrolyte disturbances, infection, chemotherapy, or paraneoplastic encephalitis.

In patients with CNS tumors not associated with seizures, prophylactic antiepileptic drugs (AEDs) are not recommended, although they may be used for 1 week immediately postresection. In patients with seizures, older AEDs (phenobarbital, phenytoin, valproic acid, carbamazepine) should be avoided because of drug interactions and adverse effects. Levetiracetam and lacosamide are the preferred AEDs because of their lack of drug interactions, IV availability, better tolerability, and rapid titration to a therapeutic dose. Unprovoked seizures occurring after resection typically require lifelong AED treatment. H

KEY POINTS

- Gangliogliomas and dysembryoplastic neuroepithelial tumors provoke medication-resistant seizures in more than 90% of patients; therefore, patients with these tumors should be referred for resection, if possible.
- HVC In patients with central nervous system tumors not associated with seizures, prophylactic antiepileptic drugs are not recommended, although they may be used for 1 week immediately postresection.

H CONT.

Edema and Herniation

Brain edema can lead to focal neurologic deficits, elevated ICP, or herniation. Brain herniation inevitably leads to death if unrecognized. It manifests as an abrupt decline in mental status, unreactive dilated pupils, and motor weakness with flexor or extensor posturing. Emergent treatment includes elevation of the head of the bed to 30 degrees, hyperventilation (usually with mechanical ventilation) to an arterial P_{CO_2} greater than 26 mm Hg (3.5 kPa), infusion of either hypertonic saline or mannitol, and administration of glucocorticoids. These treatments can be life-saving and often are used as a bridge to emergent surgery. Among the glucocorticoids, dexamethasone is preferred because of its lack of mineralocorticoid effects. Antiangiogenic agents, such as bevacizumab, can be used as glucocorticoid-sparing agents but take weeks or months to have an effect. Both glucocorticoids and antiangiogenic agents may seal the blood-brain barrier and thus "hide" the previously contrast-enhancing residual tumor. H

KEY POINTS

- In patients with central nervous system tumors, brain herniation inevitably leads to death if unrecognized.
- Emergent treatment of brain herniation includes elevation of the head of the bed, hyperventilation, infusion of either hypertonic saline or mannitol, and administration of glucocorticoids.

H

Venous Thromboembolism

Certain characteristics are associated with increased risk of venous thromboembolism in patients with CNS tumors (**Table 52**). Despite the risk of intracranial hemorrhage, therapeutic anticoagulation is generally recommended in confirmed thromboembolic disease. Anticoagulation has historically been avoided in melanoma, choriocarcinoma, papillary thyroid carcinoma, and renal carcinoma because of an assumed increased risk of hemorrhage. However, recent studies have not shown that anticoagulation increases hemorrhage risk in patients with these cancers. Besides the usual contraindications, anticoagulation should be avoided in patients with previous intracranial hemorrhage and a platelet count less than 50,000/µL (50×10^9/L). The presence of a CNS tumor is a contraindication for thrombolytic therapy in pulmonary embolism, although exceptions may be made for low-risk tumors, such as meningiomas. Although evidence does not support routine use of preanticoagulation neuroimaging to assess for hemorrhage, noncontrast head CT is the most cost-effective test in this situation.

TABLE 52. Risk Factors for Venous Thromboembolism in Patients with Central Nervous System Tumors

Age >75 years
Prolonged immobility or leg weakness
Indwelling vascular catheter
Prior venous thromboembolism
Glioblastoma multiforme
Glioma >5 cm
Chemotherapy, particularly hormonal or antiangiogenic agents
Recurrent tumor
Incomplete resection
Immediate postresection period

Low-molecular-weight heparin is generally preferred over unfractionated heparin. Exceptions include kidney impairment and a higher hemorrhage risk when rapid reversal may be required. Inferior vena cava filters have considerably high rates of complications and should be reserved for patients with an absolute contraindication to anticoagulation. Warfarin or low-molecular-weight heparin may be considered for long-term therapy, although medication interactions between warfarin and chemotherapy or AEDs are a concern. Evidence is insufficient to recommend the non–vitamin K antagonist oral anticoagulants for patients with CNS tumors.

Prophylactic anticoagulation in combination with mechanical devices is recommended in hospitalized patients with CNS tumors as soon as possible after resection. Chronic outpatient prophylactic anticoagulation is not recommended. H

KEY POINTS

- Despite the risk of intracranial hemorrhage, therapeutic anticoagulation is generally recommended in confirmed venous thromboembolic disease.
- Prophylactic anticoagulation in combination with mechanical devices is recommended in hospitalized patients with central nervous system tumors as soon as possible after resection.

Paraneoplastic Neurologic Syndromes

H

Antibody-mediated neurologic syndromes may occur as primary autoimmune or paraneoplastic disorders. Various syndromes have been described with different neurologic manifestations and findings on serum and CSF studies (**Table 53**). Suggestive symptoms include new-onset status epilepticus in a patient without epilepsy, acute psychosis in a healthy patient, acute movement disorder (ataxia, chorea,

TABLE 53. Common Autoimmune and Paraneoplastic Neurologic Disorders

Clinical Presentation	Associated Cancers	Autoantibody Targets
Psychosis, chorea, dysautonomia[a]	Ovarian teratoma	NMDA receptor[b]
Executive dysfunction, personality change, brainstem/limbic encephalitis, myoclonus, neuropathy, hyponatremia[a]	SCLC	VGKC receptor complex[b] (includes LGI1, CASPR2, contactin-2)
Brainstem encephalitis, autonomic or sensory neuropathy[a]	SCLC	ANNA-1 (Hu)
Ataxia, brainstem encephalitis	Breast cancer, SCLC, gynecologic cancer	ANNA-2 (Ri)
Ataxia	Gynecologic cancer, breast cancer	PCA-1 (Yo)
Brainstem encephalitis[a]	Testicular cancer	Ma1, Ma2
Dementia, personality change, chorea, ataxia, neuropathy	SCLC, thymoma	CRMP5
Stiff-person syndrome, type 1 diabetes mellitus, ataxia, brainstem encephalitis, ophthalmoplegia, parkinsonism	Thymoma, breast cancer	GAD[b]

ANNA = antineuronal nuclear antigen; CASPR = contactin associated protein-like; CRMP = collapsin response mediator protein; GAD = glutamic acid decarboxylase; LGI = leucine-rich, glioma inactivated; NMDA = *N*-methyl-D-aspartate; PCA = Purkinje-cell antibody; SCLC = small cell lung cancer; VGKC = voltage-gated potassium channel.

[a]May present with limbic encephalitis (acute or subacute mood and behavioral changes, short term memory problems, cognitive dysfunction), in addition to the presentations listed.

[b]Not necessarily associated with paraneoplastic syndromes; may be primary autoimmune, without cancer.

H CONT

myoclonus, tremor), acute progressive peripheral neuropathy, and systemic signs of malignancy (severe anorexia, weight loss, lymphadenopathy).

Evaluation should include brain MRI with contrast, antibody testing of the blood and CSF, and imaging (full-body CT, body and brain PET, and ultrasonography, as appropriate) for tumor detection. Treating the symptoms directly is ineffective without appropriate tumor resection and immunotherapy. Even when the tumor is removed, immunotherapy may be needed. Acute management with IV immune globulin or IV methylprednisolone is often helpful. Chronic treatment with azathioprine, mycophenolate, cyclophosphamide, or rituximab may be considered. H

KEY POINT

- Treatment of paraneoplastic neurologic syndromes usually requires appropriate tumor resection and immunotherapy.

Bibliography

Headache and Facial Pain

Becker WJ. Acute migraine treatment in adults. Headache. 2015;55:778-93. [PMID: 25877672] doi:10.1111/head.12550

Chiang CC, Schwedt TJ, Wang SJ, Dodick DW. Treatment of medication-overuse headache: A systematic review. Cephalalgia. 2016;36:371-86. [PMID: 26122645] doi:10.1177/0333102415593088

Ducros A, Wolff V. The typical thunderclap headache of reversible cerebral vasoconstriction syndrome and its various triggers. Headache. 2016;56:657-73. [PMID: 27015869] doi:10.1111/head.12797

Maarbjerg S, Gozalov A, Olesen J, Bendtsen L. Trigeminal neuralgia—a prospective systematic study of clinical characteristics in 158 patients. Headache. 2014;54:1574-82. [PMID: 25231219] doi:10.1111/head.12441

Markey KA, Mollan SP, Jensen RH, Sinclair AJ. Understanding idiopathic intracranial hypertension: mechanisms, management, and future directions. Lancet Neurol. 2016;15:78-91. [PMID: 26700907] doi:10.1016/S1474-4422(15)00298-7

Marmura MJ, Silberstein SD, Schwedt TJ. The acute treatment of migraine in adults: the American Headache Society evidence assessment of migraine pharmacotherapies. Headache. 2015;55:3-20. [PMID: 25600718] doi:10.1111/head.12499

Mokri B. Spontaneous CSF leaks: low CSF volume syndromes. Neurol Clin. 2014;32:397-422. [PMID: 24703536] doi:10.1016/j.ncl.2013.11.002

Nye BL, Ward TN. Clinic and emergency room evaluation and testing of headache. Headache. 2015;55:1301-8. [PMID: 26422648] doi:10.1111/head.12648

Orr SL, Friedman BW, Christie S, Minen MT, Bamford C, Kelley NE, et al. Management of adults with acute migraine in the emergency department: The American Headache Society evidence assessment of parenteral pharmacotherapies. Headache. 2016;56:911-40. [PMID: 27300483] doi:10.1111/head.12835

Pareja JA, Álvarez M. The usual treatment of trigeminal autonomic cephalalgias. Headache. 2013;53:1401-14. [PMID: 24090529] doi:10.1111/head.12193

Silberstein SD, Holland S, Freitag F, Dodick DW, Argoff C, Ashman E; Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society. Evidence-based guideline update: pharmacologic treatment for episodic migraine prevention in adults: report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society. Neurology. 2012;78:1337-45. [PMID: 22529202] doi:10.1212/WNL.0b013e3182535d20

Head Injury

Giza CC, Kutcher JS, Ashwal S, Barth J, Getchius TS, Gioia GA, et al. Summary of evidence-based guideline update: evaluation and management of concussion in sports: report of the Guideline Development Subcommittee of the American Academy of Neurology. Neurology. 2013;80:2250-7. [PMID: 23508730] doi:10.1212/WNL.0b013e31828d57dd

Harmon KG, Drezner JA, Gammons M, Guskiewicz KM, Halstead M, Herring SA, et al. American Medical Society for Sports Medicine position statement: concussion in sport. Br J Sports Med. 2013;47:15-26. [PMID: 23243113] doi:10.1136/bjsports-2012-091941

Holtkamp MD, Grimes J, Ling G. Concussion in the military: an evidence-base review of mTBI in US military personnel focused on posttraumatic headache. Curr Pain Headache Rep. 2016;20:37. [PMID: 27084376] doi:10.1007/s11916-016-0572-x

Jaramillo CA, Eapen BC, McGeary CA, McGeary DD, Robinson J, Amuan M, et al. A cohort study examining headaches among veterans of Iraq and Afghanistan wars: Associations with traumatic brain injury, PTSD, and depression. Headache. 2016;56:528-39. [PMID: 26688427] doi:10.1111/head.12726

Lucas S, Hoffman JM, Bell KR, Dikmen S. A prospective study of prevalence and characterization of headache following mild traumatic brain injury. Cephalalgia 2014 Feb;34(2):93-102. Epub 2013 Aug 6. [PMID: 23921798] doi:10.1177/0333102413499645

Seizures and Epilepsy

Fisher RS, Acevedo C, Arzimanoglou A, Bogacz A, Cross JH, Elger CE, et al. ILAE official report: a practical clinical definition of epilepsy. Epilepsia. 2014;55:475–82. [PMID: 24730690] doi:10.1111/epi.12550

Glauser T, Shinnar S, Gloss D, Alldredge B, Arya R, Bainbridge J, et al. Evidence-based guideline: treatment of convulsive status epilepticus in children and adults: Report of the Guideline Committee of the American Epilepsy Society. Epilepsy Curr. 2016;16:48–61. [PMID: 26900382] doi:10.5698/1535-7597-16.1.48

Herman ST, Abend NS, Bleck TP, Chapman KE, Drislane FW, Emerson RG, et al; Critical Care Continuous EEG Task Force of the American Clinical Neurophysiology Society. Consensus statement on continuous EEG in critically ill adults and children, part I: indications. J Clin Neurophysiol. 2015;32:87–95. [PMID: 25626778] doi:10.1097/WNP.0000000000000166

Jobst BC, Cascino GD. Resective epilepsy surgery for drug-resistant focal epilepsy: a review. JAMA. 2015;313:285–93. [PMID: 25602999] doi:10.1001/jama.2014.17426

Krumholz A, Wiebe S, Gronseth GS, Gloss DS, Sanchez AM, Kabir AA, et al. Evidence-based guideline: Management of an unprovoked first seizure in adults: Report of the Guideline Development Subcommittee of the American Academy of Neurology and the American Epilepsy Society. Neurology. 2015;84:1705–13. [PMID: 25901057] doi:10.1212/WNL.0000000000001487

Vélez-Ruiz NJ, Pennell PB. Issues for women with epilepsy. Neurol Clin. 2016;34:411–25, ix. [PMID: 27086987] doi:10.1016/j.ncl.2015.11.009

Vossler DG, Anderson GD, Bainbridge J. AES position statement on generic substitution of antiepileptic drugs. Epilepsy Curr. 2016;16:209–11. [PMID: 27330454] doi:10.5698/1535-7511-16.3.209

Stroke

Demaerschalk BM, Kleindorfer DO, Adeoye OM, Demchuk AM, Fugate JE, Grotta JC, et al; American Heart Association Stroke Council and Council on Epidemiology and Prevention. Scientific rationale for the inclusion and exclusion criteria for intravenous alteplase in acute ischemic stroke: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2016;47:581–641. [PMID: 26696642] doi:10.1161/STR.0000000000000086

Hemphill JC 3rd, Greenberg SM, Anderson CS, Becker K, Bendok BR, Cushman M, et al; American Heart Association Stroke Council. Guidelines for the management of spontaneous intracerebral hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2015;46:2032–60. [PMID: 26022637] doi:10.1161/STR.0000000000000069

Kernan WN, Ovbiagele B, Black HR, Bravata DM, Chimowitz MI, Ezekowitz MD, et al; American Heart Association Stroke Council, Council on Cardiovascular and Stroke Nursing, Council on Clinical Cardiology, and Council on Peripheral Vascular Disease. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2014;45:2160–236. [PMID: 24788967] doi:10.1161/STR.0000000000000024

Meschia JF, Bushnell C, Boden-Albala B, Braun LT, Bravata DM, Chaturvedi S, et al; American Heart Association Stroke Council. Guidelines for the primary prevention of stroke: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2014;45:3754–832. [PMID: 25355838] doi:10.1161/STR.0000000000000046

Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, et al; American Heart Association Stroke Council. 2018 Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2018 Jan 24. [Epub ahead of print] [PMID: 29367334] doi:10.1161/STR.0000000000000158

Thompson BG, Brown RD Jr, Amin-Hanjani S, Broderick JP, Cockroft KM, Connolly ES Jr, et al; American Heart Association Stroke Council, Council on Cardiovascular and Stroke Nursing, and Council on Epidemiology and Prevention. Guidelines for the management of patients with unruptured intracranial aneurysms: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2015;46:2368–400. [PMID: 26089327] doi:10.1161/STR.0000000000000070

Yaghi S, Willey JZ, Khatri P. Minor ischemic stroke: triaging, disposition, and outcome. Neurol Clin Pract. 2016;6:157–163. [PMID: 27104067] doi:10.1212/CPJ.0000000000000234

Whelton PK, Carey RM, Aronow WS, Casey DE Jr, Collins KJ, Dennison Himmelfarb C, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2017 Nov 7. pii: S735-1097(17)41519-1. [PMID: 29146535] doi:10.1016/j.jacc.2017.11.006

Cognitive Impairment

Corbett A, Smith J, Creese B, Ballard C. Treatment of behavioral and psychological symptoms of Alzheimer's disease. Curr Treat Options Neurol. 2012;14:113–25. [PMID: 22328204] doi:10.1007/s11940-012-0166-9

Geschwind MD, Shu H, Haman A, Sejvar JJ, Miller BL. Rapidly progressive dementia. Ann Neurol. 2008;64:97–108. [PMID: 18668637] doi:10.1002/ana.21430

Inouye SK, van Dyck CH, Alessi CA, Balkin S, Siegal AP, Horwitz RI. Clarifying confusion: the confusion assessment method. A new method for detection of delirium. Ann Intern Med. 1990;113:941–8. [PMID: 2240918]

Lin JS, O'Connor E, Rossom RC, Perdue LA, Eckstrom E. Screening for cognitive impairment in older adults: A systematic review for the U.S. Preventive Services Task Force. Ann Intern Med. 2013;159:601–12. [PMID: 24145578]doi:10.7326/0003-4819-159-9-201311050-00730

Morley JE, Morris JC, Berg-Weger M, Borson S, Carpenter BD, Del Campo N, et al. Brain health: the importance of recognizing cognitive impairment: an IAGG consensus conference. J Am Med Dir Assoc. 2015;16:731–9. [PMID: 26315321] doi:10.1016/j.jamda.2015.06.017

Ott BR, Daiello LA, Dahabreh IJ, Springate BA, Bixby K, Murali M, et al. Do statins impair cognition? A systematic review and meta-analysis of randomized controlled trials. J Gen Intern Med. 2015;30:348–58. [PMID: 25575908] doi:10.1007/s11606-014-3115-3

Rascovsky K, Hodges JR, Knopman D, Mendez MF, Kramer JH, Neuhaus J, et al. Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. Brain. 2011;134:2456–77. [PMID: 21810890] doi:10.1093/brain/awr179

Ritter A, Pillai JA. Treatment of vascular cognitive impairment. Curr Treat Options Neurol. 2015;17:367. [PMID: 26094078] doi:10.1007/s11940-015-0367-0

Ströhle A, Schmidt DK, Schultz F, Fricke N, Staden T, Hellweg R, et al. Drug and exercise treatment of Alzheimer Disease and mild cognitive impairment: a systematic review and meta-analysis of effects on cognition in randomized controlled trials. Am J Geriatr Psychiatry. 2015;23:1234–49. [PMID: 26601726] doi:10.1016/j.jagp.2015.07.007

Movement Disorders

Albanese A, Bhatia K, Bressman SB, Delong MR, Fahn S, Fung VS, et al. Phenomenology and classification of dystonia: a consensus update. Mov Disord. 2013;28:863–73. [PMID: 23649720] doi:10.1002/mds.25475

Ali K, Morris HR. Parkinson's disease: chameleons and mimics. Pract Neurol. 2015;15:14–25. [PMID: 25253895] doi:10.1136/practneurol-2014-000849

Fasano A, Deuschl G. Therapeutic advances in tremor. Mov Disord. 2015;30:1557–65. [PMID: 26293405] doi:10.1002/mds.26383

Hermann A, Walker RH. Diagnosis and treatment of chorea syndromes. Curr Neurol Neurosci Rep. 2015;15:514. [PMID: 25620691] doi:10.1007/s11910-014-0514-0

Mills K, Mari Z. An update and review of the treatment of myoclonus. Curr Neurol Neurosci Rep. 2015;15:512. [PMID: 25398378] doi:10.1007/s11910-014-0512-2

Okun MS. Deep-brain stimulation for Parkinson's disease. N Engl J Med. 2012;367:1529–38. [PMID: 23075179] doi:10.1056/NEJMct1208070

Postuma RB, Berg D, Stern M, Poewe W, Olanow CW, Oertel W, et al. MDS clinical diagnostic criteria for Parkinson's disease. Mov Disord. 2015;30:1591–601. [PMID: 26474316] doi:10.1002/mds.26424

Todorova A, Jenner P, Ray Chaudhuri K. Non-motor Parkinson's: integral to motor Parkinson's, yet often neglected. Pract Neurol. 2014;14:310–22. [PMID: 24699931] doi:10.1136/practneurol-2013-000741

Trenkwalder C, Winkelmann J, Inoue Y, Paulus W. Restless legs syndrome-current therapies and management of augmentation. Nat Rev Neurol. 2015;11:434–45. [PMID: 26215616] doi:10.1038/nrneurol.2015.122

Saifee TA, Edwards MJ. Tardive movement disorders: a practical approach. Pract Neurol. 2011;11:341–8. [PMID: 22100943] doi:10.1136/practneurol-2011-000077

Multiple Sclerosis

Burton JM, O'Connor PW, Hohol M, Beyene J. Oral versus intravenous steroids for treatment of relapses in multiple sclerosis. Cochrane Database Syst Rev.

2012;12:CD006921. [PMID: 23235634] doi:10.1002/14651858.CD006921.pub3

Haselkorn JK, Hughes C, Rae-Grant A, Henson LJ, Bever CT, Lo AC, et al. Summary of comprehensive systematic review: rehabilitation in multiple sclerosis: report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. Neurology. 2015;85:1896-903. [PMID: 26598432] doi:10.1212/WNL.0000000000002146

Lublin FD, Reingold SC, Cohen JA, Cutter GR, Sorensen PS, Thompson AJ, et al. Defining the clinical course of multiple sclerosis: the 2013 revisions. Neurology. 2014;83:278-86. [PMID: 24871874] doi:10.1212/WNL.0000000000000560

Minden SL, Feinstein A, Kalb RC, Miller D, Mohr DC, Patten SB, et al; Guideline Development Subcommittee of the American Academy of Neurology. Evidence-based guideline: assessment and management of psychiatric disorders in individuals with MS: report of the Guideline Development Subcommittee of the American Academy of Neurology. Neurology. 2014;82:174-81. [PMID: 24376275] doi:10.1212/WNL.0000000000000013

Soilu-Hänninen M, Aivo J, Lindström BM, Elovaara I, Sumelahti ML, Färkkilä M, et al. A randomised, double blind, placebo controlled trial with vitamin D_3 as an add on treatment to interferon ß-1b in patients with multiple sclerosis. J Neurol Neurosurg Psychiatry. 2012;83:565-71. [PMID: 22362918] doi:10.1136/jnnp-2011-301876

Thompson AJ, Banwell BL, Barkhof F, Carroll WM, Coetzee T, Comi G, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurol. 2018 Feb;17(2):162-173. [Epub 2017 Dec 21] [PMID: 29275977] doi:10.1016/S1474-4422(17)30470-2

Traboulsee A, Simon JH, Stone L, Fisher E, Jones DE, Malhotra A, et al. Revised recommendations of the consortium of MS centers task force for a standardized MRI protocol and clinical guidelines for the diagnosis and follow-up of multiple sclerosis. AJNR Am J Neuroradiol. 2016;37:394-401. [PMID: 26564433] doi:10.3174/ajnr.A4539

Tramacere I, Del Giovane C, Salanti G, D'Amico R, Filippini G. Immunomodulators and immunosuppressants for relapsing-remitting multiple sclerosis: a network meta-analysis. Cochrane Database Syst Rev. 2015:CD011381. [PMID: 26384035] doi:10.1002/14651858.CD011381.pub2

Yadav V, Bever C Jr, Bowen J, Bowling A, Weinstock-Guttman B, Cameron M, et al. Summary of evidence-based guideline: complementary and alternative medicine in multiple sclerosis: report of the guideline development subcommittee of the American Academy of Neurology. Neurology. 2014;82:1083-92. [PMID: 24663230] doi:10.1212/WNL.0000000000000250

Disorders of the Spinal Cord

Al-Qurainy R, Collis E. Metastatic spinal cord compression: diagnosis and management. BMJ. 2016 May 19;353:i2539. [PMID: 27199232] doi:10.1136/bmj.i2539

Briani C, Dalla Torre C, Citton V, et al. Cobalamin deficiency: clinical picture and radiological findings. Nutrients. 2013 Nov 15;5(11):4521-39. [PMID: 24248213] doi:10.3390/nu5114521

Evaniew N, Belley-Côté EP, Fallah N, Noonan VK, Rivers CS, Dvorak MF. Methylprednisolone for the treatment of patients with acute spinal cord injuries: a systematic review and meta-analysis. J Neurotrauma. 2016 Mar 1;33(5):468-81. [PMID: 26529320] doi:10.1089/neu.2015.4192

Hurlbert RJ, Hadley MN, Walters BC, et al. Pharmacological therapy for acute spinal cord injury. Neurosurgery. 2013 Mar;72 Suppl 2:93-105. [PMID: 23417182] doi:10.1227/NEU.0b013e31827765c6

Narvid J, Hetts SW, Larsen D, et al. Spinal dural arteriovenous fistulae: clinical features and long-term results. Neurosurgery. 2008 Jan;62(1):159-66. [PMID: 18300903] doi:10.1227/01.NEU.0000311073.71733.C4

Scott TF, Frohman EM, De Seze J, Gronseth GS, Weinshenker BG; Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Evidence-based guideline: clinical evaluation and treatment of transverse myelitis: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology. 2011 Dec 13;77(24):2128-34. Epub 2011 Dec 7. [PMID: 22156988] doi:10.1212/WNL.0b013e31823dc535

Neuromuscular Disorders

Barohn RJ, Amato AA. Pattern-recognition approach to neuropathy and neuronopathy. Neurol Clin. 2013;31:343-61. [PMID: 23642713] doi:10.1016/j.ncl.2013.02.001

Fuller G, Morgan C. Bell's palsy syndrome: mimics and chameleons. Pract Neurol. 2016. [PMID: 27034243] doi:10.1136/practneurol-2016-001383

Kress JP, Hall JB. ICU-acquired weakness and recovery from critical illness. N Engl J Med. 2014;370:1626-35. [PMID: 24758618] doi:10.1056/NEJMra1209390

Latov N. Diagnosis and treatment of chronic acquired demyelinating polyneuropathies. Nat Rev Neurol. 2014;10:435-46. [PMID: 24980070] doi:10.1038/nrneurol.2014.117

Levine TD, Saperstein DS. Laboratory evaluation of peripheral neuropathy. Neurol Clin. 2013;31:363-76. [PMID: 23642714] doi:10.1016/j.ncl.2013.01.004

Mammen AL. Statin-associated autoimmune myopathy. N Engl J Med. 2016;374:664-9. [PMID: 26886523] doi:10.1056/NEJMra1515161

Peltier A, Goutman SA, Callaghan BC. Painful diabetic neuropathy. BMJ. 2014;348:g1799. [PMID: 24803311] doi:10.1136/bmj.g1799

Silvestri NJ, Wolfe GI. Myasthenia gravis. Semin Neurol. 2012;32:215-26. [PMID: 23117946] doi:10.1055/s-0032-1329200

van den Berg B, Walgaard C, Drenthen J, Fokke C, Jacobs BC, van Doorn PA. Guillain-Barré syndrome: pathogenesis, diagnosis, treatment and prognosis. Nat Rev Neurol. 2014;10:469-82. [PMID: 25023340] doi:10.1038/nrneurol.2014.121

Neuro-oncology

Englot DJ, Magill ST, Han SJ, Chang EF, Berger MS, McDermott MW. Seizures in supratentorial meningioma: a systematic review and meta-analysis. J Neurosurg. 2016 Jun;124(6):1552-61. Epub 2015 Dec 4. [PMID: 26636386] doi:10.3171/2015.4.JNS142742

Hoang-Xuan K, Bessell E, Bromberg J, Hottinger AF, Preusser M, Rudà R, et al; European Association for Neuro-Oncology Task Force on Primary CNS Lymphoma. Diagnosis and treatment of primary CNS lymphoma in immunocompetent patients: guidelines from the European Association for Neuro-Oncology. Lancet Oncol. 2015 Jul;16(7):e322-32. [PMID: 26149884] doi:10.1016/S1470-2045(15)00076-5

Jo JT, Schiff D, Perry JR. Thrombosis in brain tumors. Semin Thromb Hemost. 2014 Apr;40(3):325-31. [PMID: 24599439] doi:10.1055/s-0034-1370791

Leung D, Han X, Mikkelsen T, Nabors LB. Role of MRI in primary brain tumor evaluation. J Natl Compr Canc Netw. 2014 Nov;12(11):1561-8. [PMID: 25361803]

McKeon A. Autoimmune encephalopathies and dementias. Continuum (Minneap Minn). 2016 Apr;22(2 Dementia):538-58. [PMID: 27042907] doi:10.1212/CON.0000000000000299

Nabors LB, Portnow J, Ammirati M, Baehring J, Brem H, et al. Central nervous system cancers, version 1.2015. J Natl Compr Canc Netw. 2015 Oct;13(10):1191-202. [PMID: 26483059]

Owonikoko TK, Arbiser J, Zelnak A, Shu HK, Shim H, et al. Current approaches to the treatment of metastatic brain tumours. Nat Rev Clin Oncol. 2014 Apr;11(4):203-22. Epub 2014 Feb 25. [PMID: 24569448] doi: 10.1038/nrclinonc.2014.25

Sayegh ET, Fakurnejad S, Oh T, Bloch O, Parsa AT. Anticonvulsant prophylaxis for brain tumor surgery: determining the current best available evidence. J Neurosurg. 2014 Nov;121(5):1139-47. Epub 2014 Aug 29. [PMID: 25170671] doi: 10.3171/2014.7.JNS132829

Schiff D, Lee EQ, Nayak L, Norden AD, Reardon DA, Wen PY. Medical management of brain tumors and the sequelae of treatment. Neuro Oncol. 2015 Apr;17(4):488-504. Epub 2014 Oct 30. [PMID: 25358508] doi: 10.1093/neuonc/nou304

Weller M, van den Bent M, Hopkins K, Tonn JC, Stupp R, Falini A, et al; European Association for Neuro-Oncology (EANO) Task Force on Malignant Glioma. EANO guideline for the diagnosis and treatment of anaplastic gliomas and glioblastoma [erratum in: Lancet Oncol. 2014 Dec;15(13):e587]. Lancet Oncol. 2014 Aug;15(9):e395-403. [PMID: 25079102] doi: 10.1016/S1470-2045(14)70011-7

Neurology Self-Assessment Test

This self-assessment test contains one-best-answer multiple-choice questions. Please read these directions carefully before answering the questions. Answers, critiques, and bibliographies immediately follow these multiple-choice questions. The American College of Physicians (ACP) is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

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CME credits and MOC points are available from the publication date of July 31, 2018, until July 31, 2021. You may submit your answer sheet or enter your answers online at any time during this period.

Directions

*Each of the numbered items is followed by lettered answers. Select the **ONE** lettered answer that is **BEST** in each case.*

Item 1

A 19-year-old man is evaluated for a 2-week history of shaking episodes sometimes associated with falling that are followed by a period of unresponsiveness. He reports having a 30-minute episode just before getting in the car to go to this appointment. Episodes have been occurring daily, sometimes as often as four times per day, and last 20 to 45 minutes. According to the patient's mother, the episodes involve limb shaking with the eyes closed, intermittent cessation of breathing, and a reddening of the face. The patient remains standing for a few seconds after the shaking starts but on occasion becomes limp and falls. He does not respond when his name is called or his arms or legs are lightly touched. The shaking, which gradually increases and decreases in intensity, typically involves both arms and sometimes the legs. He is exhausted but oriented and responsive afterward and has rapid breathing.

All physical examination findings are normal.

Which of the following is the most likely diagnosis?

(A) Convulsive status epilepticus
(B) Generalized tonic clonic seizure
(C) Myoclonic seizure
(D) Psychogenic nonepileptic spell/event

H Item 2

A 75-year-old man is hospitalized for treatment of extreme agitation and delirium after developing a urinary tract infection (UTI). He has a 1-year history of dementia with Lewy bodies. According to his wife, the patient has nighttime visual hallucinations 4 or 5 times per week but is rarely bothered by them. Home medications are simvastatin and aspirin.

On physical examination, blood pressure is 150/92 mm Hg and pulse rate is 98/min; other vital signs are normal. The patient is agitated and disoriented and appears to be having visual hallucinations. Although his agitation steadily increases, he does not become aggressive. His UTI is being treated appropriately. No other clear sources of the delirium are present.

Environmental interventions are instituted to help abate his symptoms.

Which of the following medications is most likely to be effective in treating his acute agitation?

(A) Alprazolam
(B) Diphenhydramine
(C) Donepezil
(D) Haloperidol

Item 3

A 59-year-old woman comes to the office for a follow-up evaluation of Parkinson disease, which was diagnosed 8 years ago and has been treated with carbidopa-levodopa, amantadine, and rasagiline. Primary symptoms are tremor, slowness, shuffling of the feet, and intermittent freezing of gait, which has caused her to fall several times; the tremor and slowness substantially improve after administration of carbidopa-levodopa, but she exhibits prominent involuntary, nonpatterned, dance-like movements for approximately 2 hours after a dose. She has tried increasing the carbidopa-levodopa dosage but could not tolerate the resultant nausea and orthostatic hypotension.

On initial physical examination, which takes place before she takes her scheduled dose of carbidopa-levodopa, a prominent tremor is noted. The patient's spontaneous and repetitive movements are very slow, and she has difficulty taking more than a few steps before needing assistance to maintain balance. A repeat examination performed 1 hour after she takes the medication reveals suppression of the tremor, remarkable improvement of speed and gait, and the presence of diffuse high-amplitude flowing involuntary movements in all extremities.

An MRI of the brain is unremarkable.

Which of the following is the most appropriate next step in her treatment?

(A) Apomorphine
(B) Deep brain stimulation
(C) Droxidopa
(D) Rotigotine patch

Item 4 H

A 22-year-old man is evaluated in the hospital after sustaining a traumatic brain injury in a motorcycle accident 4 hours earlier. The patient lost consciousness briefly at the scene but was wearing a helmet. He is now awake and reports a severe headache, nausea, vertigo, left-ear tinnitus and deafness, and rhinorrhea when he sits upright.

On physical examination, temperature is 38.1 °C (100.6 °F), blood pressure is 110/60 mm Hg, pulse rate is 104/min, and respiration rate is 20/min. Oxygen saturation is 95% with the patient breathing ambient air. Right hemotympanum and deafness are noted. Bruising is shown.

H CONT.

Results of laboratory studies show a normal complete blood count, comprehensive metabolic profile, and urinalysis; a urine drug screen is positive for opiates.

A noncontrast head CT scan shows a small right temporal bone fracture but no intracranial hemorrhage. Chest radiographs and a cervical spine CT scan are normal.

Which of the following is the most appropriate initial treatment?

(A) Acetaminophen
(B) Ceftriaxone
(C) Dexamethasone
(D) Naloxone
(E) Norepinephrine

H Item 5

A 48-year-old man is hospitalized with new-onset right hemiparesis and difficulty speaking. He was well when last seen 20 hours earlier.

On physical examination, blood pressure is 138/76 mm Hg, pulse rate is 72 and regular, and respiration rate is 12/min. The patient has aphasia. A right visual field deficit and right facial, arm, and leg weakness are noted. Decreased pinprick sensation is present on the right. Reflexes also are decreased on the right; a right plantar extensor response is noted.

An electrocardiogram shows sinus rhythm. A CT scan of the head shows a hypodensity in the left frontal and parietal lobes, and a CT angiogram of the head and neck shows patent internal carotid arteries and 80% stenosis of the left middle cerebral artery.

Results of laboratory studies include a serum LDL cholesterol level of 108 mg/dL (2.80 mmol/L) and a hemoglobin A_{1c} value of 6.8%.

The patient is given aspirin.

Which of the following is the most appropriate next step in treatment?

(A) Atorvastatin
(B) Intracranial stenting
(C) Methylphenidate
(D) Warfarin

Item 6

A 51-year-old woman is evaluated for a 1-year history of daily afternoon fatigue that necessitates frequent naps and impairs her concentration at the office, where she works as a lawyer. Lifestyle adjustments, such as improving sleep hygiene, getting regular exercise, yoga, and vitamin supplementation have not resolved this symptom. She has a 5-year history of multiple sclerosis. Medications are glatiramer acetate and a vitamin D supplement.

On physical examination, vital signs are normal. Depression screening is negative. The remainder of the physical examination is noncontributory.

Results of laboratory studies, including hemoglobin and serum thyroid-stimulating hormone levels, are unremarkable.

Which of the following is the most appropriate management?

(A) Baclofen
(B) Memantine
(C) Modafinil
(D) Substitution of an interferon beta for the glatiramer acetate
(E) Tetrahydrocannabinol-cannabidiol combination

Item 7 H

A 22-year-old man is evaluated in the emergency department 40 minutes after having a first-time generalized tonic-clonic seizure. According to his mother, the patient exhibited shaking for 5 minutes. He has never had a seizure previously or any episode of jerking, staring, confusion, or memory loss. He has had no recent illness and has no history of neurologic problems. Birth and development were normal. There is no family history of seizures or epilepsy. He takes no medication and does not use illicit drugs.

On physical examination, vital signs are normal. Neurologic examination findings are unremarkable.

Results of laboratory studies show a normal complete blood count and comprehensive metabolic panel and a negative urine drug screen.

Which of the following is the most appropriate initial step in management?

(A) Head CT
(B) Intravenous levetiracetam
(C) Intravenous lorazepam
(D) Lumbar puncture

Item 8

A 53-year-old woman is brought to the office by her husband for follow-up evaluation of behavioral-variant frontotemporal dementia, which was diagnosed 9 months ago. Her clinical symptoms of occasional aphasia, minor memory impairment, behavioral disinhibition, and obsessive-compulsive behaviors have worsened since diagnosis and have become disruptive. She is currently estranged from her son and his family after bringing a large bag filled with plastic bottles collected from his neighbors' trash cans to her granddaughter's birthday party 2 weeks ago. Her husband asks about possible medications to control her symptoms.

Which of the following is the most appropriate medication to recommend?

(A) Citalopram
(B) Donepezil
(C) Memantine
(D) Methylphenidate
(E) Olanzapine

Item 9 H

A 72-year-old woman is evaluated in the emergency department 5 hours after developing difficulty speaking and facial weakness on the right. She takes no medication.

H CONT.

On physical examination, vital signs are normal. The patient is awake and attentive. Spontaneous speech is slow. Right sided facial weakness and dysarthria are noted.

Hemoglobin level, platelet count, and coagulation profile are within normal limits.

An electrocardiogram is normal. A CT scan of the head shows an acute left frontal ischemic stroke. A carotid duplex ultrasound reveals less than 40% stenosis in both internal carotid arteries; a transcranial Doppler ultrasound is normal. A transthoracic echocardiogram shows an ejection fraction of 50% but is otherwise unremarkable.

Aspirin and rosuvastatin are initiated, and the patient is admitted to the telemetry unit for 3 days, during which time she remains in sinus rhythm.

Which of the following is the most appropriate next step in management?

(A) Addition of clopidogrel
(B) Outpatient cardiac telemetry
(C) Substitution of apixaban for aspirin
(D) Transesophageal echocardiography

H

Item 10

A 47 year old woman is evaluated in the emergency department for abrupt onset severe headaches lasting 6 to 8 hours that have occurred three times in the past 4 days. The pain developed spontaneously, reached maximum intensity within 10 seconds, and is holocranial and throbbing. She reports associated nausea and photophobia but no changes in mentation, vision, sensation, or motor function. The first two episodes occurred while showering and the third while at the dinner table 2 hours ago. The patient has anxiety but no personal or family history of headache. She started taking sertraline 1 month ago for anxiety but discontinued it after headache onset.

On physical examination, temperature is 37.8 °C (100.0 °F), blood pressure is 130/80 mm Hg, and pulse rate is 72/min. All other physical examination findings, including those from a neurologic examination, are normal.

A head CT scan and results of lumbar puncture also are normal.

Which of the following is the most appropriate management?

(A) Digital subtraction angiography
(B) Magnetic resonance angiography of the brain
(C) Methylprednisolone sodium succinate
(D) Sumatriptan
(E) Valproic acid

H

Item 11

A 39 year old woman is evaluated in the emergency department for a 3 day history of worsening imbalance, falling, and vertigo. Multiple sclerosis was diagnosed 5 years ago and has been treated with interferon beta 1a since that time. She also takes gabapentin for neuropathic pain.

On physical examination, temperature is 37.3 °C (99.1 °F); all other vital signs are normal. Internuclear ophthalmoplegia is noted on the left. The patient exhibits imbalance in her primary gait and is unable to perform tandem gait or to maintain balance during Romberg testing when she opens her eyes.

Which of the following is the most appropriate immediate treatment?

(A) High dose oral prednisone
(B) Low dose oral prednisone
(C) Plasmapheresis
(D) Vitamin D administration

Item 12

A 41-year-old woman is evaluated for a 2-year history of tremor in the dominant right hand. She says that the tremor has begun interfering with her work as a hairdresser, especially when she uses scissors. She also reports tightness in the forearm. The patient is able to eat, write, and type without difficulty and has had no trauma, imbalance, slowness of movement, or change in gait speed. Alcohol has no effect on the tremor. There is no family history of tremor.

On physical examination, vital signs are normal. A right upper extremity tremor is noted, as are rhythmic flexion of the wrist, involuntary flexion of the fingers, and pronation of the forearm. The tremor is present both at rest and during action and resolves by changing the position of an outstretched arm. No dysmetria, dysdiadochokinesia, bradykinesia, rigidity, shuffling gait, or reduced arm swing is noted. Her handwriting is neither tremulous nor micrographic.

An MRI of the brain is unremarkable.

Which of the following is the most likely diagnosis?

(A) Cerebellar tremor
(B) Dystonic tremor
(C) Essential tremor
(D) Parkinson disease
(E) Rubral tremor

Item 13

H

A 21 year old man is evaluated in the emergency department for persistent convulsive status epilepticus that began 30 minutes before his arrival. An airway has been secured, and he has received intravenous glucose, thiamine, and two doses of intravenous lorazepam. After receiving the second dose of lorazepam, he continues shaking for another 5 minutes. Medications are levetiracetam and acetaminophen; the patient is allergic to phenytoin.

On physical examination, temperature is normal, blood pressure is 155/89 mm Hg, pulse rate is 108/min, respiration rate is 16/min, and oxygen saturation with the patient breathing 6 L of oxygen via a nasal cannula is 97%. The pupils are reactive but he remains comatose.

Results of a urine drug screen are negative.

H CONT.

Which of the following is the most appropriate next step in management?

(A) Brain MRI
(B) Electroencephalography
(C) Fosphenytoin
(D) Lacosamide
(E) Valproic acid

Item 14

A 78-year-old man is evaluated for recent difficulty with memory. The patient has hypertension treated with hydrochlorothiazide. He reports decreased appetite, problems falling asleep, and withdrawal from social activities since his wife's death 13 months ago, at which time he had to assume several new responsibilities, including managing the finances and cooking. He is concerned because he received a missed payment notice on last month's utility bill and is worried that he is developing dementia; his 85-year-old brother has Alzheimer disease that was diagnosed 2 years ago. On a screening evaluation 6 months ago, the patient scored 28/30 (normal, ≥24) on a Mini-Mental State Examination, and his Geriatric Depression Scale Short Form score was 9 (normal, <6); he has lost 2.3 kg (5.1 lb) since that time.

Physical examination findings, including vital signs and results of neurologic examination, are unremarkable.

Results of laboratory studies, including a complete blood count and measurement of thyroid-stimulating hormone and vitamin B_{12} levels, are normal.

Which of the following is the most appropriate next step in management?

(A) Begin an acetylcholinesterase inhibitor
(B) Begin treatment for depression
(C) Obtain a brain MRI without contrast
(D) Obtain neuropsychological testing

H

Item 15

A 51-year-old woman is evaluated in the emergency department for a 1-month history of new-onset abnormal movements, paranoia, hallucinations, and progressive confusion. She was healthy before onset of symptoms and takes no medication.

On physical examination, vital signs are normal. The patient is alert but oriented to person and place only, recalls none of three objects after 5 minutes, requires constant redirection to follow commands and sustain attention, is having ongoing visual and auditory hallucinations, and exhibits intermittent slow, writhing (choreiform) movements of the arms. Muscle strength is normal, as are sensation and deep tendon reflexes.

Results of standard laboratory studies, including a complete blood count and comprehensive metabolic panel, are unremarkable. Results of brain MRI and lumbar puncture are normal. Subsequent testing for serum anti-N-methyl-D-aspartate receptor antibody is positive.

Which of the following is the most likely diagnosis?

(A) Breast adenocarcinoma
(B) Non-small cell lung cancer
(C) Ovarian teratoma
(D) Small cell lung cancer

Item 16

A 24-year-old woman has a 4-year history of monthly headaches. The pain is bitemporal, throbbing, and worsened by bending or ascending stairs. Approximately half of the headaches have been severe with associated nausea. She has no precursor symptoms, no photophobia or phonophobia, and no visual or neurologic symptoms. Over the past year, the headaches have not changed in character but have gradually become more frequent, increasing from 4 to 10 days per month. Episodes last as long as 8 hours and typically respond to ibuprofen within 1 hour. She takes no other medication.

All physical examination findings, including vital signs and those from a neurologic examination, are unremarkable.

Which of the following is the most appropriate treatment?

(A) Citalopram
(B) Gabapentin
(C) Metoprolol
(D) Onabotulinum toxin A
(E) Rizatriptan

Item 17

A 29-year-old woman is evaluated before attempting pregnancy. Juvenile myoclonic epilepsy was diagnosed 11 years ago, at which time she started taking valproic acid; she has had no symptoms for 10.5 years. Her only other medication is an oral contraceptive agent. She is concerned about taking her medications if she becomes pregnant.

All physical examination findings are normal, as was her most recent electroencephalogram.

A plan is made to discontinue the oral contraceptive, start folic acid, and then taper the valproic acid.

Which of the following is the most appropriate additional step in treatment?

(A) Gabapentin
(B) Levetiracetam
(C) Oxcarbazepine
(D) Topiramate
(E) No additional treatment is necessary

Item 18

H

A 58-year-old man is evaluated in the emergency department for a 3-week history of worsening pain in the middle back and a 2-day history of increasing leg weakness that has made ambulation difficult. He has metastatic prostate cancer treated with leuprolide.

On physical examination, vital signs are normal. Muscle strength testing shows 4/5 weakness in the hip flexors. Reflexes are 3+ in both legs.

An MRI of the thoracic spine shows a contrast-enhancing mass originating in the T8 vertebral body with invasion into the epidural space that causes moderate cord compression.

H CONT.

After administration of high-dose glucocorticoids, which of the following is the most appropriate next step in management?

(A) Decompressive surgery with radiation
(B) Laminectomy
(C) Radiation only
(D) Spinal angiography

H

Item 19

A 47-year-old woman is evaluated in the hospital for a 4-month history of increasingly frequent falls and episodes of confusion. She was fired from her job 3 months ago because of poor performance. Since that time, she also has had occasional anxiety, problems sleeping, and visual hallucinations. For the past 2 weeks, she has had repeated falls, exhibited erratic behavior, and been unable to prepare even a cup of coffee.

On physical examination, vital signs are normal. The patient is agitated and disoriented to place and time. She exhibits word-finding difficulty and intermittent myoclonic movements of the arms and legs. She scores 8/30 (normal, ≥24) on the Mini–Mental State Examination.

Results of laboratory studies are normal, including cerebrospinal fluid findings of a normal leukocyte count and normal glucose and protein levels.

An electroencephalogram shows periodic sharp wave complexes. Diffusion-weighted brain MRIs show high-signal changes in the basal ganglia and cerebral cortex.

Which of the following is the most likely diagnosis?

(A) Creutzfeldt-Jakob disease
(B) HIV encephalopathy
(C) Lyme disease
(D) Wernicke encephalopathy

Item 20

A 49-year-old-man is evaluated 1 day after having an episode of right arm weakness without pain that lasted 5 minutes. He is now asymptomatic. The patient has type 2 diabetes mellitus and dyslipidemia. Medications are aspirin, metformin, and atorvastatin.

On physical examination, blood pressure is 126/68 mm Hg, pulse rate is 86/min and regular, and respiration rate is 12/min. No carotid bruits or cardiac murmurs are heard on cardiac auscultation. All other physical examination findings are normal.

An electrocardiogram shows normal sinus rhythm with no ST-segment or T-wave changes.

Which of the following is the most appropriate initial imaging test?

(A) Carotid duplex ultrasonography
(B) CT angiography of the neck
(C) MRI of the brain
(D) Transesophageal echocardiography

Item 21

A 64-year-old man is evaluated for an abnormal gait and twitching. He is brought to the office by his wife, who reports that the patient has depression and that he has abused drugs and alcohol for the past 15 years; she further states that within the past year, he has developed impulsivity, imbalance, and incoordination and often appears restless. His father had major depressive disorder and committed suicide at age 60 years.

On physical examination, vital signs are normal. Orientation, language, memory, and attention are intact. Speech is dysarthric. The patient cannot perform multistep tasks and cannot sit still on command. He exhibits frequent and variable flowing movements of the limbs and trunk that he incorporates into purposeful gestures. Reflexes are brisk, and gait is rapid, wide based, and uncoordinated.

Which of the following is the most likely diagnosis?

(A) Creutzfeldt-Jakob disease
(B) Frontotemporal dementia
(C) Huntington disease
(D) Parkinson disease

Item 22

H

A 62-year-old man is evaluated in the emergency department after being struck by a vehicle while crossing the street 3 hours earlier and hitting his head on the pavement. He did not lose consciousness. The patient now reports a moderate headache. He describes the headache as global, dull, and aching without photophobia or phonophobia. He has had no nausea, visual changes, or neurologic symptoms since the incident.

On physical examination, vital signs are normal, as are findings from a neurologic examination.

Which of the following is the most appropriate initial step in management?

(A) Head CT with contrast
(B) Head CT without contrast
(C) Hospital observation
(D) Prochlorperazine administration

Item 23

A 71-year-old woman is evaluated for difficulty holding her head upright. She notes that her head feels heavy and reports intermittent difficulty with swallowing and speech that is worse in the evening. She has had no pain, sensory changes, weakness in the extremities, or cognitive or visual symptoms. She has no other medical problems and takes no medication.

On physical examination, vital signs are normal. Speech is mildly dysarthric. Cervical extension is weak. No ptosis, ophthalmoplegia, sensory deficit, or weakness in the extremities is noted.

Results of laboratory studies show a normal serum creatine kinase level; no acetylcholine receptor antibodies are detected.

Findings from routine nerve conduction and needle electromyography studies of the limbs are unremarkable, but a repetitive stimulation protocol reveals a decremental response. An MRI of the brain is normal.

Which of the following is the most likely diagnosis?

(A) Bulbar amyotrophic lateral sclerosis
(B) Inclusion body myositis
(C) Multiple sclerosis
(D) Myasthenia gravis
(E) Polymyositis

Item 24

A 72-year old woman is evaluated for a 12-month history of increasing forgetfulness. The patient is retired from her position as a professor of economics at a local university. She takes no medication and drinks no alcoholic beverages. Her husband says that his wife's occasional forgetfulness has caused no major problems and that she is able to function normally.

On physical examination, vital signs are normal. Her Geriatric Depression Scale score is normal and Montreal Cognitive Assessment score is 25/30 (normal, ≥26), with a score of 1/5 on the delayed recall section and 5/6 on the orientation section. All other physical and neurologic examination findings are normal.

Results of laboratory studies show normal vitamin B_{12}, thyroid-stimulating hormone, and 25-hydroxyvitamin D levels.

Complete neuropsychological testing findings indicate normal global cognition, language function, and attention, but verbal learning and memory performance are 2 SDs below that of an age- and education-matched control population.

An MRI of the brain shows a slight loss of hippocampal volume that is greater on the right than the left but is otherwise normal.

Which of the following is the most likely diagnosis?

(A) Alzheimer disease
(B) Depression
(C) Mild cognitive impairment
(D) Normal aging

Item 25

A 59-year-old woman comes to the office for a follow-up evaluation of a 2-year history of worsening urinary urgency and frequency. Episodes of urinary incontinence have occurred more often in the past 6 months because she cannot walk fast enough to get to the bathroom in time. Recently, she also has experienced intermittent urinary hesitancy and a frequent feeling of incomplete emptying, sometimes requiring changing body position or manual pelvic pressure. The patient has a 5-year history of secondary progressive multiple sclerosis. She takes no disease-modifying therapy. Her only medication is a vitamin D supplement.

Physical examination findings are unremarkable.

Urinalysis results are normal.

Which of the following is the most appropriate next step in management?

(A) Dalfampridine administration
(B) Oxybutynin administration
(C) Solifenacin administration
(D) Urodynamic testing

Item 26

H

A 55-year-old woman is evaluated in the hospital after diagnosis of pulmonary embolism. She was admitted to the hospital 3 days ago for evaluation of a brain mass with imaging features characteristic of glioblastoma. Twenty-four hours after brain biopsy, the patient developed chest pain and dyspnea. Imaging confirmed a filling defect in the right pulmonary artery.

On physical examination, blood pressure is 110/60 mm Hg, pulse rate is 100/min, respiration rate is 18/min, and oxygen saturation is 93% with the patient receiving 2 L/min of nasal oxygen. Cardiopulmonary examination shows mild tachycardia but is otherwise normal. Right upper and lower facial numbness and right arm weakness and numbness are noted. Biceps, triceps, and brachioradialis reflexes are increased on the right, as is right-sided hyperreflexia. An extensor plantar response is present on the right.

Results of laboratory studies show a serum creatinine level of 1.7 mg/dL (150 µmol/L).

Which of the following is the most appropriate treatment?

(A) Apixaban
(B) Inferior vena cava filter placement
(C) Intravenous alteplase
(D) Intravenous heparin
(E) Subcutaneous low-molecular-weight heparin

Item 27

A 52-year-old man is evaluated for a 1-year history of progressive weakness that began as right foot drop and bilateral tingling in the feet. Within the past 2 months, the patient has developed progressive weakness, which makes walking difficult; he also notes weakness in the hands and burning below the knees but no autonomic symptoms. He has hypothyroidism treated with levothyroxine.

On physical examination, vital signs are normal. Motor strength is 4/5 in the intrinsic hand and quadriceps muscles and 3/5 in the tibialis anterior and gastrocnemius muscles; bulbar and facial muscle strength is normal. Deep tendon reflexes are absent in the lower extremities. Sensory perception of vibration is severely impaired at the knees. Pinprick testing shows reduced sensation below the ankles. Splenomegaly is present, as are patchy areas of hyperpigmentation and scattered angiomas on the trunk. Gait is broad based and wobbly, and a Romberg test has positive results.

Serum immunofixation reveals a λ light chain monoclonal protein.

Needle electromyography reveals a demyelinating sensorimotor polyneuropathy.

Which of the following is the most likely diagnosis?

(A) Amyotrophic lateral sclerosis
(B) Chronic inflammatory demyelinating polyradiculo neuropathy
(C) Mitochondrial myopathy
(D) POEMS syndrome

Item 28

A 19-year-old woman is evaluated for a 6-month history of recurrent episodes of confusion that occur approximately once monthly. Her boyfriend says she has periods of wide-eyed staring, chewing motions, and repetitive grabbing of her clothes with the right hand. The patient sometimes experiences a strange but familiar feeling before the episodes but does not remember the episodes themselves, which last approximately 45 to 60 seconds and are followed by exhaustion and sleepiness for 20 minutes.

All physical examination findings are normal.

Which of the following is the most likely diagnosis?

(A) Absence seizures
(B) Atonic seizures
(C) Focal seizures
(D) Myoclonic seizures

Item 29

A 42-year-old man comes to the office for a follow-up evaluation 4 weeks after undergoing laparoscopic abdominal surgery. Two days after the operation, he developed severe, unrelenting pain of the right shoulder and arm lasting 1 week followed by progressive weakness of the right shoulder and proximal arm. He currently has no pain but cannot maintain the right arm above his head. The patient reports numbness affecting the right arm and says that his grip has become weak. He has had no problem with speech, swallowing, or moving the lower extremities. He has hyperlipidemia treated with atorvastatin.

On physical examination, vital signs are normal. Motor examination reveals moderate weakness of arm abduction, forearm extension, and hand grip on the right side. Winging of the right scapula is present. Trapezius and deltoid muscle bulk is reduced on the right side compared with the left. Right biceps and brachioradialis reflexes are absent, but other deep tendon reflexes are intact. Patchy areas of sensory loss are noted over the right shoulder, forearm, and palm. The cranial nerves are intact, the lower extremities have normal strength bilaterally, and gait and balance are both normal.

Results of laboratory studies show an erythrocyte sedimentation rate of 18 mm/h, a serum creatine kinase level of 150 U/L, and a hemoglobin A_{1c} value of 5.7%.

MRI of cervical spine is unremarkable.

Which of the following is the most likely diagnosis?

(A) Compressive polyradiculopathy
(B) Idiopathic brachial plexopathy
(C) Lambert-Eaton myasthenic syndrome
(D) Statin myopathy

Item 30

An 18-year-old woman is evaluated for a 2-year history of repetitive fast movements of the neck that tilt the head to the right side. She reports that these movements are preceded by a feeling of discomfort in the right shoulder and that if she concentrates and taps the right foot immediately after this sensory cue, she usually can avoid the neck movements. She is a senior in high school and says she has not been able to use this method successfully in the classroom, especially during examinations, when she often experiences a cluster of movements that exhaust and distract her. Her mother notes that before onset of the neck symptoms, the patient used to roll her eyes and clear her throat frequently. She has obsessive-compulsive disorder treated with sertraline.

On physical examination, vital signs are normal. During the examination, the patient displays rapid tilting movements of the head followed by rolling of the head and shoulder; these movements repeat several times in a stereotyped manner. The patient can suppress these movements on request.

Which of the following is the most appropriate treatment?

(A) Botulinum toxin injection
(B) Clonidine administration
(C) Cognitive behavioral therapy
(D) Haloperidol administration

Item 31

A 38-year-old man is evaluated for a 6-month history of increasingly frequent episodes of migraine with aura. The patient has had migraine with aura since age 23 years. Auras involve 15 to 20 minutes of twinkling lights and visual blurring in either hemifield. On occasion, he has noted ipsilateral numbness and paresthesia of the face, tongue, and hand lasting another 15 to 20 minutes after the visual blurring has resolved. Migraine episode frequency has increased from once to twice monthly. Acetaminophen, ibuprofen, and naproxen were each discontinued after becoming ineffective, with headaches now lasting 24 hours.

On physical examination, all findings, including vital signs and results of a neurologic examination, are unremarkable.

Which of the following is the most appropriate next step in treatment?

(A) Hydrocodone
(B) Sumatriptan
(C) Topiramate
(D) Verapamil

Item 32

H

A 27-year-old woman is evaluated in the emergency department after a sudden, first-time episode of loss of consciousness while standing in line to board a tour bus. She had warning symptoms of tunnel vision and palpitations, after which she lost consciousness and fell. According to her father, who witnessed the episode, she was limp and unconscious for approximately 20 to 30 seconds, during which

H CONT.

time she displayed intermittent twitching of all four limbs, with the limbs shaking independently at separate times. After the patient regained consciousness, she was confused about why she was on the ground but answered questions appropriately and was oriented to self and place.

All physical examination findings are normal.

Which of the following is the most likely diagnosis?

(A) Atonic seizure
(B) Convulsive syncope
(C) Generalized tonic-clonic seizure
(D) Myoclonic seizure
(E) Tonic seizure

Item 33

A 66-year-old woman comes to the office for a follow-up evaluation 1 month after being hospitalized with an ischemic stroke of the pons. Neurologic deficits have improved steadily in the intervening weeks, but the patient now reports having difficulty with outpatient rehabilitation because of a diminished energy level and fatigue in the absence of depressed mood, anhedonia, or loss of interest. She also has hypertension, dyslipidemia, and depression. Medications are aspirin, amlodipine, chlorthalidone, atorvastatin, and citalopram.

On physical examination, vital signs are normal; BMI is 36. Right facial weakness and dysarthria are noted. Muscle strength is 4/5 in the right arm, 5/5 in the right leg, and 4/5 in the right ankle. The patient scores in the normal range on a two-point depression scale.

Results of laboratory studies, including a basic metabolic panel, liver chemistry and thyroid function studies, and serum creatine kinase measurement, are normal.

Which of the following is the most appropriate next step in management?

(A) Discontinuation of atorvastatin
(B) Fluoxetine initiation
(C) MRI of the brain
(D) Polysomnography

Item 34

A 38-year-old man comes to the office to discuss treatment of his recently diagnosed multiple sclerosis. The patient also has diabetes mellitus and nonalcoholic steatohepatitis. Medications are metformin and atorvastatin.

On physical examination, vital signs are normal; BMI is 30. All remaining physical examination findings are unremarkable.

A T2-weighted MRI of the brain obtained just before diagnosis shows three hyperintense lesions in the periventricular white matter, a hyperintense lesion in the pons, and three juxtacortical hyperintense lesions. The pontine lesion was enhanced with administration of intravenous contrast.

Which of the following is the most appropriate treatment?

(A) Fingolimod
(B) Glatiramer acetate
(C) Interferon beta
(D) Natalizumab

Item 35

A 70-year-old man is evaluated for a 6-month history of right upper extremity weakness, intermittent painful spasms in both calves, and occasional brief muscle twitches. The patient reports right arm and hand weakness and says that for the past 2 weeks, his right foot drags when he walks quickly. He has had no numbness, sensory loss, paresthesia, or problems with swallowing, sphincter control, or coordination.

On physical examination, vital signs are normal. Weakness and muscle wasting is noted in the thumb abductor and intrinsic hand muscles on the right side. Spontaneous muscle twitches are present in the bilateral thumb adductor, gastrocnemius, and paraspinal muscles. Minor weakness of right ankle dorsiflexion, a right Hoffman sign, and right foot clonus is noted. Deep tendon reflexes are brisk throughout. Cranial nerves are intact, as is sensory perception.

Electromyography and nerve condition studies reveal evidence of lower motor neuron involvement in the upper and lower extremities and paraspinal muscles. MRIs of the brain and cervical spine are unremarkable.

Which of the following is the most likely diagnosis?

(A) Amyotrophic lateral sclerosis
(B) Charcot-Marie-Tooth disease
(C) Granulomatosis with polyangiitis
(D) Miller Fisher variant of Guillain-Barré syndrome

Item 36

H

A 58-year-old man is evaluated in the emergency department for abrupt onset of a right retro-orbital throbbing headache and diplopia that have been present for the past 12 hours. The patient also reports occasional chills. He had a dental procedure 6 days ago. His only medication is hydrocodone.

On physical examination, temperature is 38.9 °C (102.0 °F), blood pressure is 138/90 mm Hg, and pulse rate is 88/min; BMI is 28. Right proptosis with lid edema is noted. The right pupil is dilated and sluggishly reactive. Oculomotor nerve (cranial nerve III), trochlear nerve (cranial nerve IV), and abducens nerve (cranial nerve VI) palsies are present on the right. Other findings from the physical examination are unremarkable.

Results of laboratory studies show an erythrocyte sedimentation rate of 60 mm/h and a leukocyte count of 13,400/µL (13.4×10^9/L), with 85% polymorphonuclear leukocytes.

Which of the following is the most likely diagnosis?

(A) Carotid artery dissection
(B) Cavernous sinus thrombosis
(C) Posterior communicating artery aneurysm
(D) Vertebral artery dissection

Item 37

H

A 51-year-old woman is evaluated in the hospital after having an ischemic stroke. She has hypertension treated with

H CONT.

candesartan and dyslipidemia treated with rosuvastatin. The patient is otherwise in good health.

On physical examination, blood pressure is 168/76 mm Hg. A right carotid bruit is heard. Left-sided weakness (including the face) is present.

An electrocardiogram shows sinus rhythm. A CT scan of the head shows a hypodensity in the right parietal lobe. A carotid duplex ultrasound shows greater than 80% stenosis in the right internal carotid artery. A magnetic resonance angiogram of the neck without contrast confirms greater than 80% stenosis.

Which of the following is the most appropriate next step in management?

(A) Carotid endarterectomy
(B) Carotid stenting
(C) Diagnostic cerebral angiography
(D) 30-Day outpatient telemetry

Item 38

A 68-year-old man is evaluated for increasing cognitive deficits, walking difficulties with occasional falls, and depression. He has become more forgetful over the past 5 years, has a 1-year history of shuffling his feet when walking, awakens three to four times each night to urinate (sometimes becoming incontinent), and generally has become more withdrawn and irritable. He also has difficulty remembering names and appointments, and his wife now manages their finances and his medications, which consist of hydrochlorothiazide for hypertension and metformin for type 2 diabetes mellitus.

On physical examination, vital signs are normal. The patient is slow to rise from a seated position. Gait examination reveals slow, short steps and difficulty turning. He scores 22/30 (normal, ≥24) on the Mini–Mental State Examination, losing four points in the orientation sections, one point in the registration section, and three points in the attention/calculation section.

An MRI of the brain shows moderate generalized atrophy and prominent cerebral ventricles.

Which of the following is most likely to be diagnostic in this patient?

(A) Amyloid PET scan
(B) Fluorodeoxyglucose PET scan
(C) Lumbar puncture
(D) Neuropsychological testing

H

Item 39

A 33-year-old man is evaluated in the emergency department for a 10-week history of worsening confusion, memory loss, and difficulty speaking. He has become progressively more disorganized at work and can no longer complete routine tasks. His medical history is otherwise unremarkable, and he takes no medication.

On physical examination, vital signs are normal. The patient exhibits decreased attention, is able to follow only simple commands, and is oriented only to person. Speech is dysarthric. Intermittent myoclonic jerking of varying limbs also is noted.

Results of laboratory studies show a serum sodium level of 128 mEq/L (128 mmol/L) but are otherwise unremarkable, including a normal complete blood count, comprehensive metabolic panel, serum thyroid-stimulating hormone level, and free thyroxine (T_4) level.

An urgent electroencephalogram shows evidence of nonconvulsive status epilepticus with focal seizures arising independently from both temporal lobes. A contrast-enhanced brain MRI is normal.

Which of the following is the most likely diagnosis?

(A) Autoimmune limbic encephalitis
(B) Lyme disease
(C) Progressive multifocal leukoencephalopathy
(D) Rapidly progressive dementia

Item 40

A 79-year-old woman is evaluated for persistent depression, declining function, and memory changes. According to family members, she has been depressed ever since her husband died 3 years ago. They further report that the patient's memory has gotten much worse in the past year and that she no longer cooks or cleans her home, despite previously preparing lavish weekly family meals and keeping a meticulous house. The patient says she feels healthy but "just no longer cares" or sometimes "forgets." She started taking paroxetine at the time of her husband's death and switched to venlafaxine 1 year later because of no improvement in her depression; although symptoms are now slightly less severe, they have not abated.

On physical examination, vital signs are normal. The two-question depression screening test is positive, and her score on the Patient Health Questionnaire (PHQ)-9 is 11/30 (moderate depression). The patient scores 23/30 (normal, ≥24) on a Mini-Mental State Examination; an evaluation for reversible causes of memory impairment is unrevealing.

An MRI obtained 1 year ago was normal.

Which of the following is the most appropriate next step?

(A) Addition of mirtazapine
(B) Cerebrospinal fluid analysis
(C) Neuropsychological testing
(D) Repeat MRI of the brain

Item 41

A 35-year-old man is evaluated for a 3-year history of epilepsy. Seizures typically occur twice monthly, last 2 minutes, and are characterized by staring, lip smacking, and confusion; approximately once every 6 months, the patient experiences a whole-body convulsion marked by incontinence and prolonged confusion for several hours. Treatment with oxcarbazepine and lamotrigine, although initially reducing seizure frequency, has been largely ineffective. He no longer drives or works because of the seizures. He also has migraines, which are well controlled by sumatriptan.

On physical examination, vital signs are normal. All other physical examination findings, including those from a neurologic examination, are unremarkable.

Results of routine outpatient electroencephalography (EEG) are normal. An MRI of the brain shows right hippocampal atrophy.

Which of the following is the most appropriate next step in management?

(A) Levetiracetam
(B) Topiramate
(C) Vagus nerve stimulation
(D) Video EEG monitoring

Item 42

A 38-year-old woman is evaluated for recent onset of visual blurriness when looking straight ahead or reading. She has a 4-mm right posterior communicating artery aneurysm that was first detected 1 year ago. She has not had any recent headaches and is otherwise well. The patient's only medication is an oral contraceptive agent.

On physical examination, blood pressure is 138/78 mm Hg; other vital signs are normal. The neck is supple. Findings from funduscopic examination are normal. On neurologic examination, the right pupil is 5 millimeters in diameter and unreactive; left lateral gaze results in diplopia. The left pupil and right lateral gaze are normal.

A magnetic resonance angiogram (MRA) of the brain shows that her aneurysm has grown in size to 8 millimeters.

Which of the following is the most appropriate next step in management?

(A) Lisinopril administration
(B) MRA of the neck
(C) Neurosurgical intervention
(D) Repeat MRA of the brain in 6 months

Item 43

A 75-year-old man comes to the office for a follow-up evaluation of Parkinson disease, which was diagnosed 12 years ago. Worsening motor symptoms have been controlled with a combination of carbidopa-levodopa and pramipexole for the past 3 years. According to family members, the patient becomes rigid and slow before taking his next dose of Parkinson medications, but these symptoms resolve after he has taken them. He reports recent visual hallucinations that have been distressing, occasionally seeing small animals and unfamiliar people mostly at night, which sometimes frightens him. He has had no recent illness, fever, anhedonia, or depressive symptoms.

On physical examination, vital signs are normal. The patient performs well on screening cognitive testing. He reports no active hallucinations. Masked facies, mild dysarthria, resting tremor, bradykinesia, and cogwheel rigidity are noted. Gait is narrow based and shuffling. Other physical examination findings are unremarkable.

Results of laboratory studies, including a complete blood count, comprehensive metabolic panel, serum creatine kinase measurement, and urinalysis, are normal.

Which of the following is the most appropriate next step in treatment?

(A) Add aripiprazole
(B) Add pimavanserin
(C) Add risperidone
(D) Discontinue pramipexole

Item 44

H

A 37-year-old man is evaluated in the emergency department 12 hours after sudden onset of a global, severe headache with associated neck stiffness. The patient has a 5-year history of migraine treated with sumatriptan. He says that his current headache feels different from previous headaches and did not respond to sumatriptan.

On physical examination, temperature is normal, blood pressure is 148/72 mm Hg, heart rate 86/min and regular, respiration rate is 12/min, and oxygen saturation is 96% with the patient breathing ambient air. The patient has discomfort and appears restless. Funduscopic examination is normal. The left pupil is 2 millimeters larger than the right and poorly reactive to light. Neck stiffness is noted with passive movement.

A CT scan of the head is normal.

Which of the following is the most appropriate next diagnostic test?

(A) Lumbar puncture
(B) Magnetic resonance angiography of the neck
(C) MRI of the brain
(D) No further testing is necessary

Item 45

A 79-year-old man is evaluated for a 2-month history of progressively worsening headaches, nausea, visual disturbance, and difficulty speaking. He also has hypertension and gastroesophageal reflux disease. Medications are lisinopril and omeprazole.

On physical examination, vital signs are normal. Right oculomotor nerve (cranial nerve III) and bilateral abducens nerve (cranial nerve VI) palsies are noted, as is right upper and lower facial weakness.

An MRI of the brain shows a well-demarcated, homogeneously enhancing, hyperintense lesion that is suspicious for primary central nervous system lymphoma in the brainstem extending from the left pons to the medulla. Mass effect but no edema is present. The lesion obstructs the cerebral aqueduct, and hydrocephalus with enlargement of the lateral and third ventricles is noted.

Which of the following is the most appropriate next step in management?

(A) Brain biopsy
(B) Intravenous dexamethasone
(C) Lumbar puncture
(D) Vitreous fluid sampling

Item 46

A 56-year-old woman is evaluated for a 6-month history of nocturnal leg movements. According to her husband, she frequently kicks her legs during sleep but does not exhibit vocalizations or complex movements while asleep. The patient is unaware of these movements and has not had any sensory discomfort or urge to move the legs. She snores at night but has had no sudden loss of consciousness, sleep attacks, or excessive daytime sleepiness.

Results of physical examination and laboratory studies are unremarkable.

A polysomnogram shows good sleep efficiency, a low apnea-hypopnea index, and absence of motor activity during the rapid eye movement phase of sleep; no sleep fragmentation is evident, despite frequent leg movements. A video recording of her movements reveals slow flexion movements of the ankles, knees, and hips that repeat every 20 seconds in a stereotyped manner.

Which of the following is the most appropriate next step in management?

(A) Clonazepam administration
(B) Electroencephalography
(C) Ferritin level measurement
(D) No further testing or treatment is necessary

H

Item 47

A 25-year-old woman is evaluated in the emergency department (ED) 90 minutes after being struck in the right temple by a foul ball at a baseball game. Although knocked from her seat and initially dazed by the blow, the patient continued to watch the game for another 45 minutes until she developed a worsening headache with nausea and vomiting. On arrival in the ED, the patient was stuporous and became unresponsive during subsequent CT of the head.

On physical examination, blood pressure is 140/90 mm Hg, pulse rate is 100/min, and respiration rate is 14/min. The right pupil is dilated. Right occulomotor nerve (cranial nerve III) palsy and left hemiparesis are noted. A plantar extensor response is present on the left.

A CT scan of the head is shown (see top of next column).

Which of the following is the most likely diagnosis?

(A) Epidural hematoma
(B) Lobar hemorrhage
(C) Subarachnoid hemorrhage
(D) Subdural hematoma

ITEM 47

On physical examination, vital signs are normal. "Mild" muscle weakness (inability to hold a limb against full resistance) and pain is present in the shoulder and limb girdle muscles. Muscle tone and bulk are normal, as are all reflexes. Results of sensory examination are unremarkable. Normal relaxation after hand grip is noted.

Results of laboratory studies show a serum creatine kinase level of 500 U/L and a serum creatinine level of 1.8 mg/dL (159 µmol/L); urinalysis results are normal.

Which of the following is the most likely diagnosis?

(A) Acute intermittent porphyria
(B) Limb-girdle muscular dystrophy
(C) McArdle disease (metabolic myopathy)
(D) Myotonic dystrophy
(E) Polymyositis

Item 48

A 36-year-old man is evaluated for severe muscle cramping. The patient reports occasional painful muscle cramps, sometimes associated with brownish urine discoloration, after intense physical activity since he was a teenager and intermittent proximal muscle pain; he has had no stiffness, rigidity, or other muscle weakness or pain. He says that if he briefly interrupts his exercise routine after onset of cramping, he can continue further exercise without difficulty; eating carbohydrate-rich food also increases his exercise tolerance.

Item 49

A 59-year-old man is evaluated for recent cognitive problems resulting in worsening performance in his work as an electrician. He reports having increasing difficulty "running the numbers" when determining the materials needed for a job and increasing problems understanding the layout of plans when working on a new construction. He also notes occasional hand tremors when he works. According to his wife, his gait has slowed somewhat and he seems to have less of a response to things occurring around him in the past few weeks, stating that he "doesn't show any emotion in his face anymore." The patient also has a 5-year history of erectile dysfunction, a 4-year history of constipation, and episodes of lightheadedness when standing for long periods at work.

On physical examination, vital signs are normal. A general paucity of movements is noted, as are slowness of movement in the upper and lower extremities and a mildly stooped posture when walking. He scores 20/30 (normal, ≥26) on the

Montreal Cognitive Assessment, having significant difficulty with the cube drawing, clock drawing, and sustained attention portions of the test.

Which of the following additional clinical findings would be most helpful in establishing the diagnosis in this patient?

(A) Delusions
(B) Depression
(C) Rapid eye movement sleep behavior disorder
(D) Repeated falls

Item 50

A 71-year-old woman is evaluated in the emergency department 1 hour after acute onset of a severe headache and left-sided weakness. The patient had a myocardial infarction 3 years ago that was treated with a bare metal stent in the right coronary artery. She also has hypertension. Medications are carvedilol, atorvastatin, and aspirin.

On physical examination, blood pressure is 200/110 mm Hg, pulse rate 78/min, respiration rate is 20/min, and oxygen saturation is 98% with the patient breathing ambient air. The patient is awake and attentive to both sides and has normal language function. Funduscopic examination shows no papilledema or hemorrhage. Pupils are both 3 millimeters in size and reactive. Left facial weakness, dysarthria, and flaccid paralysis in the left arm and leg with loss of sensation are noted.

An emergent noncontrast CT scan shows an acute intracerebral hemorrhage, 1 centimeter in diameter, in the right basal ganglia without intraventricular hemorrhage or midline shift.

Which of the following is the most appropriate treatment?

(A) Hematoma evacuation
(B) Intravenous nicardipine
(C) Intravenous nitroprusside
(D) Platelet transfusion

Item 51

A 34-year-old man is evaluated for recurrent right-sided severe, sharp periorbital headache. Episodes have been occurring nocturnally for the past 2 weeks, typically last 90 minutes, and are associated with ipsilateral nasal congestion, tearing, nausea, and photophobia. He reports having had a similar series of headaches over a 2-month period 6 months ago. The patient has been taking combination acetaminophen, aspirin, and caffeine as needed for pain. He takes no other medication and has a 10-pack-year smoking history.

On physical examination, vital signs and all other physical examination findings, including those from a neurologic examination, are unremarkable.

An MRI of the brain is normal.

Which of the following is the most appropriate preventive treatment?

(A) Carbamazepine
(B) Fexofenadine
(C) Indomethacin
(D) Propranolol
(E) Verapamil

Item 52

A 47-year-old man is evaluated for recent weakness and loss of balance during ambulation, multiple episodes of orthostatic syncope, and a 2-year history of burning paresthesia in the lower extremities. He also reports dry mouth and dry eyes. The patient has glaucoma, erectile dysfunction, constipation, and carpal tunnel syndrome. His father had sensory neuropathy, and his father and paternal uncle died of restrictive cardiomyopathy. Medications are gabapentin, sildenafil, and docusate sodium.

On physical examination, blood pressure is 130/70 mm Hg sitting and 110/64 standing, and pulse rate is 110/min. Weakness in the distribution of the bilateral median nerves and in the proximal lower extremities is noted. Loss of sensation to pinprick is present in both hands and below the knees. Deep tendon reflexes are reduced in the lower extremities.

Electromyography, including nerve conduction studies and needle electrode examination, reveals diffuse axonal sensorimotor polyneuropathy.

Which of the following is the most likely diagnosis?

(A) Amyotrophic lateral sclerosis
(B) Cervical myelopathy
(C) Chronic inflammatory demyelinating polyradiculoneuropathy
(D) Familial amyloidosis
(E) West Nile virus infection

Item 53

A 65-year-old man is evaluated in the ICU for a 24-hour history of altered mental status with a fluctuating level of consciousness. He was admitted to the hospital 5 days ago for urosepsis and acute kidney injury and developed acute respiratory distress syndrome on hospital day 3. The patient is currently intubated, mechanically ventilated, and receiving continuous hemodialysis. Medications are cefepime, norepinephrine, and fentanyl.

On physical examination, temperature is 38.4 °C (101.1 °F), blood pressure is 105/71 mm Hg, pulse rate is 108/min, and respiration rate is 12/min; FIO_2 is 0.9. The patient opens his eyes to voice but does not fixate on the examiner or follow commands. Pupils are reactive, and gag and corneal reflexes are present. All limbs move intermittently but not on command. The patient withdraws from painful stimuli in all four limbs. Intermittent twitching of the shoulders and eyelids is noted.

Results of laboratory studies show a serum creatinine level of 5.4 mg/dL (477 µmol/L). Glucose, calcium, and electrolyte levels are within normal limits.

A 20-minute electroencephalogram shows generalized slow activity, a nonspecific finding compatible with encephalopathy, but no evidence of seizure activity.

A head CT scan is normal.

Which of the following is the most appropriate next step in management?

CONT.

(A) Continuous (24-hour) electroencephalography

(B) Intravenous fosphenytoin

(C) Intravenous lorazepam

(D) No treatment

Item 54

A 52-year-old man is evaluated for a 9-month history of progressively worsening gait, ataxia, and paresthesia in the legs. He is a dentist who was recently barred from practice because of chronic illicit drug use, specifically amphetamines and nitrous oxide.

On physical examination, vital signs are normal. Decreased vibration and position sense is noted in both feet. Reflexes are 3+ in both legs. Muscle strength is 4/5 in both hips.

A complete blood count is normal, as is a routine chemistry panel.

A T2-weighted MRI of the thoracic spinal cord shows hyperintensity in the posterior columns and throughout the cord. There is no associated contrast enhancement.

Measurement of which of the following serum levels is the most appropriate next diagnostic test?

(A) 25-Hydroxyvitamin D

(B) Thiamine

(C) Vitamin A

(D) Vitamin B_6

(E) Vitamin B_{12}

Item 55

A 51-year-old woman is evaluated for increasingly poor ambulation ever since having a relapse of multiple sclerosis 20 months ago. She was diagnosed with MS 4 years ago and has been tasking natalizumab, baclofen, and a vitamin D supplement since that time.

On physical examination, vital signs are normal. Muscle strength is 4/5 in the left hip flexor, knee flexor, and ankle dorsiflexor. Gait is slow and deliberate with the assistance of a cane; left leg swing is noted. All other physical examination findings are unremarkable.

Which of the following medications is the most appropriate treatment?

(A) Dalfampridine

(B) Dextromethorphan-quinidine

(C) Gabapentin

(D) Memantine

(E) Modafinil

Item 56

A 56-year-old man is evaluated for a 10-day history of pain in a patchy region to the right of the umbilicus. He says that the area is sensitive to light touch. He reports no recent systemic illness, weakness, or fever. The patient has hypertension and hyperlipidemia. Medications are losartan, aspirin, and atorvastatin.

On physical examination, vital signs are normal; BMI is 36. Sensory examination reveals a patchy area of paresthesia and allodynia on the right side of the abdomen that extends posteriorly but does not cross the midline. Abdominal swelling is noted on the right. No abdominal mass or tenderness is present. There is no skin rash. Results of cranial nerve, motor strength, coordination, and gait testing are normal, and deep tendon reflexes are preserved.

Results of laboratory studies show a serum creatinine level of 2.1 mg/dL (186 µmol/L) and a hemoglobin A_{1c} value of 7.8% (0.078).

Results of serum and urine protein electrophoresis and serum light chain measurement are unremarkable.

An MRI of the thoracic spine is normal.

Which of the following is the most likely diagnosis?

(A) Diabetic mononeuropathy

(B) Paraproteinemic neuropathy

(C) Uremic neuropathy

(D) Vitamin B_{12} deficiency

Item 57

A 78-year-old man is evaluated in the emergency department for a 2-day history of bilateral leg weakness and urinary retention. He has atrial fibrillation and hypertension. Medications are warfarin, lisinopril, and hydrochlorothiazide.

On physical examination, vital signs are normal. Muscle strength is 4/5 in both legs. Decreased sensation in the groin, medial buttocks, and rectal area is noted, as is decreased rectal tone. No spinal sensory level is detected in the abdomen or chest region. Gait is wide based.

Results of laboratory studies show an INR level of 5.3.

Which of the following is the most appropriate management?

(A) Administration of intravenous glucocorticoids

(B) CT myelogram

(C) MRI of the lumbosacral spine

(D) Radiograph of the lumbosacral spine

Item 58

A 19-year-old woman is evaluated in the emergency department for a 6-month history of headaches that initially were intermittent but have been occurring daily for the past 6 weeks. She describes the pain as bilateral, frontotemporal, and a steady pressure. Neck stiffness has been present for 8 weeks. Vision intermittently darkens for seconds. For the past 3 nights, she has noted pulsatile tinnitus. The patient has inflammatory acne treated with minocycline and topical benzoyl peroxide gel.

On physical examination, vital signs are normal; BMI is 22. Papilledema and left abducens nerve (cranial nerve VI) palsy are noted, but all other findings are normal.

Results of brain MRI and magnetic resonance venography are normal.

H CONT.

Which of the following is the most appropriate management?

(A) Amitriptyline
(B) Indomethacin
(C) Lumbar puncture
(D) Magnetic resonance angiography
(E) Temporal artery biopsy

Item 59

A 67-year-old man is evaluated for a carotid bruit detected on routine medical examination. He reports no history of previous focal neurologic symptoms or visual loss. He has type 2 diabetes mellitus and hyperlipidemia treated with metformin, moderate-intensity pravastatin, and aspirin.

On physical examination, blood pressure is 128/64 mm Hg, pulse rate is 78/min and regular, and respiration rate is 16/min. A left carotid bruit is heard on cardiac examination. All other physical examination findings, including those from a neurologic examination, are unremarkable.

Results of laboratory studies show an LDL cholesterol level of 82 mg/dL (2.12 mmol/L).

The carotid ultrasound report describes a mixed-density plaque at the origin of the left internal carotid artery with stenosis estimated to be 60% to 80%.

Which of the following is the most appropriate next step in management?

(A) Carotid endarterectomy
(B) Carotid stenting
(C) Magnetic resonance angiography of the neck
(D) Replacement of aspirin with clopidogrel
(E) No further treatment or intervention

H

Item 60

A 52-year-old woman is hospitalized for rapidly progressive weakness in the arms and respiratory muscle weakness that necessitates ventilatory support. Cerebrospinal fluid analysis reveals a cell count of 3/µL (3×10^6/L) and a protein level of 190 mg/dL (1900 mg/L). Electromyographic findings, including those from a nerve conduction study, reveal slowing of nerve conduction. Guillain-Barré syndrome is diagnosed and treated with a standard 10-day course of plasma exchange; at the end of treatment, motor strength is improved by 50%, and she is extubated.

On subsequent physical examination, vital signs are normal. There is full range of motion in all extremities. The patient's strength has improved in the upper and lower extremities, but residual weakness persists. Ambulation is possible only with assistance because of weakness. Deep tendon reflexes are absent throughout. The cranial nerves are intact.

Which of the following is the most appropriate next step in management?

(A) Continue hospital monitoring for another week
(B) Discharge to rehabilitation
(C) Repeat plasma exchange
(D) Treat with intravenous glucocorticoids
(E) Treat with intravenous immune globulin

Item 61

A 35-year-old man is evaluated for two breakthrough focal seizures in the past week. He started having focal and generalized tonic-clonic seizures 20 years ago. The seizures previously had been well controlled by phenytoin, which he has taken since age 16 years, but he missed three doses of medication this week. He has had no recent illnesses or fevers.

On physical examination, all findings, including vital signs, are normal.

Results of bone densitometry show osteoporosis (T-score of −2.8).

In addition to starting the patient on alendronate, which of the following drugs should be substituted for the phenytoin?

(A) Carbamazepine
(B) Lamotrigine
(C) Phenobarbital
(D) Valproic acid

Item 62

H

A 61-year-old woman is admitted to the ICU 1 hour after having a subarachnoid hemorrhage (SAH). An emergent CT scan of the head showed an SAH, and a cerebral angiogram revealed a 6-mm rupture of the anterior communicating artery. The patient has hypertension treated with amlodipine.

On physical examination, vital signs are stable, and oxygen saturation is 96% with the patient breathing ambient air. She is somnolent. Nuchal rigidity is present. Subhyaloid hemorrhages are seen on funduscopic examination. No motor or sensory deficits are present.

Administration of which of the following medications is the most appropriate treatment?

(A) Dexamethasone
(B) Magnesium sulfate
(C) Nimodipine
(D) Nitroglycerin
(E) Verapamil

Item 63

A 76-year-old man is evaluated for recent worsening of balance. He has no dizziness or lightheadedness. The patient has an 8-year history of Parkinson disease treated with carbidopa-levodopa and entacapone.

On physical examination, vital signs are normal; no orthostatic decrease in blood pressure is noted. The patient has masked facies, a resting tremor, and bradykinesia. Gait assessment reveals mild shuffling without freezing. Findings from cognitive, cerebellar, and sensory examinations are unremarkable.

Which of the following is the most appropriate test to determine the patient's risk of falling backward?

(A) Head impulse test
(B) Pull test
(C) Romberg test
(D) Tandem gait test

Item 64

A 30-year-old man is evaluated for a 6-week history of repeated episodes of sharp pain isolated to the right parietal region lasting less than 10 seconds. The pain is intense, begins and ends spontaneously without a clear trigger, and can recur multiple times each day, sometimes in series. The patient has a history of migraine with aura from age 6 through 12 years but has had no headaches since that time. He has had no associated autonomic features and no symptoms of migraine. He has a family history of migraine with aura. The patient takes no medication.

All physical examination findings, including vital signs and those from a neurologic examination, are unremarkable.

An MRI of the brain is normal.

Which of the following is the most likely diagnosis?

(A) Cluster headache
(B) New daily persistent headache
(C) Primary stabbing headache
(D) Trigeminal neuralgia

Item 65

A 71-year-old man is evaluated for a 2-year history of episodes of staring, confusion, and repetitive left-arm movements (grabbing at his clothes or face). These events occur every 2 to 3 months, last approximately 2 minutes, and typically are followed by a 15-minute period of disorientation and fatigue. On one occasion, the episode was followed immediately by the patient's falling down, experiencing shaking of the entire body, and having urinary incontinence. He also has hypertension, nephrolithiasis, and mild cognitive impairment. Medications are hydrochlorothiazide and metoprolol.

All physical examination findings, including vital signs, are normal.

A routine electroencephalogram and brain MRI are normal.

Which of the following is the most appropriate treatment?

(A) Lamotrigine
(B) Oxcarbazepine
(C) Phenytoin
(D) Topiramate
(E) Valproic acid

Item 66

A 56-year-old man is evaluated for worsening memory and increasing behavioral problems. He was fired from his job as an accountant 6 months ago after forgetting to file necessary forms, making repeated calculation errors, and sending inappropriate emails to coworkers. He developed compulsive spending habits 3 years ago and completely depleted his retirement savings account; he has shown little concern about his financial losses. The patient was previously very physically active but now spends most of the day obsessively watching television. His wife says he eats high-calorie, nonnutritional food constantly and has gained 27.3 kg (60.1 lb) in the past 2 years. No other symptoms, including visual hallucinations, are reported.

On physical examination, the patient has a blunted affect and provides little information spontaneously. Vital signs are normal. He scores 18/30 (normal, ≥26) on the Montreal Cognitive Assessment and has significant difficulty with letter and number sequencing, word fluency, and memory, recalling only two of five items. Remaining physical examination findings are normal.

Which of the following is the most likely diagnosis?

(A) Alzheimer disease
(B) Dementia with Lewy bodies
(C) Frontotemporal dementia
(D) Parkinson disease

Item 67

A 56-year-old woman is evaluated for a 1-year history of tremor that is most notable on the right. She also has developed increasing problems with balance resulting in several falls, especially when she stands from a seated position or turns abruptly. The patient exhibits occasional shouting and arm flailing during sleep.

On physical examination, blood pressure is 128/75 mm Hg sitting and 105/70 mm Hg standing, pulse rate is 65/min sitting and 75/min standing, and respiration rate is 22/min. Decreased facial expression, full range of extraocular movements with dysmetric saccades, and hypophonic speech are noted. A low-amplitude resting tremor is more prominent on the right; the patient also has a more symmetric bilateral postural and kinetic tremor. On finger-to-nose testing, movements are slow and usually miss the target. Repetitive finger tapping movements become progressively smaller in amplitude. Gait is wide based, with frequent veering to the side, and the patient comes close to falling whenever she turns; gait speed is normal, but arm swing is decreased. The pull test results in the patient falling backward, and she is unable to walk a straight line.

An MRI of the brain is unremarkable.

Which of the following is the most likely diagnosis?

(A) Corticobasal degeneration
(B) Multiple system atrophy
(C) Parkinson disease
(D) Progressive supranuclear palsy
(E) Vascular parkinsonism

Item 68

H

A 64-year-old woman is evaluated in the emergency department 45 minutes after sudden onset of right-sided

H CONT

weakness and the loss of the ability to speak. An emergent noncontrast CT of the head shows no hemorrhage or early signs of infarct. The patient also has hypertension and atrial fibrillation. Medications are hydrochlorothiazide and warfarin.

On physical examination, blood pressure is 158/78 mm Hg, and pulse rate is 72/min and irregularly irregular. Global aphasia, left-gaze preference, right hemiparesis, and loss of pain sensation on the right side are noted.

Results of laboratory studies show an INR of 1.3.

The patient receives intravenous recombinant tissue plasminogen activator (alteplase) 1 hour after symptom onset. Blood pressure is now 168/86 mm Hg, but other vital signs are unchanged, as are results of repeat neurologic examination.

Which of the following is the most appropriate next step in management?

(A) Aspirin administration
(B) CT angiography of the head
(C) Intravenous labetalol administration
(D) MRI of the brain

Item 69

A 62-year-old man is evaluated in the emergency department because of progressive confusion. After his vital signs are obtained (normal temperature, blood pressure of 169/95 mm Hg, pulse rate of 44/min, and respiration rate of 12/min), he suddenly becomes unresponsive and comatose, with irregular respirations, and is emergently intubated.

On further physical examination, oxygen saturation is 93% with the patient receiving 100% oxygen. The pupils are large and unreactive bilaterally. The corneal reflex and oculocephalic reflex are absent on the right. The patient displays no spontaneous movements and withdraws his upper and lower limbs from noxious stimuli on the right but not on the left.

An emergent CT scan of the head without contrast shows a right temporal 4.1-cm heterogenous lesion with significant surrounding edema that is most consistent with a high-grade glioma. Mass effect and compression of the upper brainstem are noted without evidence of hemorrhage.

Which of the following is the most appropriate next step in management?

(A) Brain MRI
(B) Immediate brain biopsy
(C) Intravenous dexamethasone
(D) Intravenous levetiracetam

Item 70

H

A 54-year-old man is evaluated in the hospital for respiratory distress. The patient has well-controlled generalized epilepsy and was admitted 5 days earlier for a cervical discectomy, laminectomy, and fusion. On hospital day 4, he developed a productive cough, chills, and dyspnea. Medications are oxycodone, levetiracetam, and docusate sodium.

On physical examination, temperature is 38.4 °C (101.1 °F), blood pressure is 125/84 mm Hg, pulse rate is 108/min, respiration rate is 22/min, and oxygen saturation with the patient breathing ambient air is 93%. Crackles are heard in the right posterior thorax on pulmonary auscultation.

Results of laboratory studies show a leukocyte count of 18,400/µL (18.4×10^9/L).

A chest radiograph shows a right lower lobe infiltrate.

Which of the following is the most appropriate treatment?

(A) Cefepime
(B) Imipenem
(C) Levofloxacin
(D) Piperacillin-tazobactam

Item 71

A 39-year-old woman is evaluated for a 4-year history of headaches that typically occur twice weekly and last 8 to 12 hours when not treated early. The pain is bilateral, frontotemporal, vice-like, and aggravated by physical activity. Approximately half of the episodes have become severe and are associated with combined photophobia and phonophobia. She has had no associated nausea, vomiting, or visual or neurologic symptoms and reports no cranial autonomic features. Stress is the only clear trigger. Naproxen resolves the headache when administered early in the headache course. She takes no other medication.

On physical examination, vital signs are normal; BMI is 23. All other physical examination findings, including those from a neurologic examination, are unremarkable.

Which of the following is the most likely diagnosis?

(A) Medication-overuse headache
(B) Migraine
(C) Sinus headache
(D) Tension-type headache

Item 72

H

A 49-year-old woman is evaluated in the emergency department for a 12-hour history of new-onset right-sided visual loss. The patient has type 2 diabetes mellitus treated with metformin.

On physical examination, blood pressure is 138/72 mm Hg, and pulse rate is 102/min and irregularly irregular. Cardiac auscultation reveals no carotid bruits or cardiac murmurs. A visual field deficit is present on the right side of both eyes. No weakness or sensory loss is noted.

A CT scan of the head shows a hypodensity in the left occipital lobe, and a carotid duplex ultrasound shows less than 60% stenosis of both internal carotid arteries with normal vertebral artery flow. An electrocardiogram shows atrial fibrillation.

Which of the following medications should be administered now?

(A) Apixaban
(B) Aspirin
(C) Clopidogrel
(D) Intravenous heparin

Item 73

A 20-year-old woman comes to the office for follow-up evaluation 2 weeks after being involved in a head-to-head collision in a soccer game. She lost consciousness for several seconds on the field and was removed from play. On the sidelines, she reported a severe occipital headache, dizziness, "brain fog," and nausea. Subsequent neurologic examination and head CT findings were unremarkable. She was started on a 1-week course of ibuprofen and prochlorperazine, which she took regularly. Besides mild cognitive slowing and short-term memory issues, she has been completely asymptomatic without medication for 1 week.

On physical examination, blood pressure is 96/66 mm Hg and pulse rate is 62/min. All other physical examination findings, including those from a neurologic examination, are normal.

Which of the following is the most appropriate next step in management?

(A) Amantadine
(B) Brain MRI
(C) Neuropsychological testing
(D) Return to play

Item 74

An 85-year-old woman is evaluated for declining function. According to her son, her memory has been failing, her gait has slowed, she has fallen four times, and she often cries without apparent reason. He further reports that he does most of her cooking and has assumed responsibility for her finances. The patient had a right basal ganglia infarct 5 years ago and left cerebellar infarct 2 years ago. She also has atrial fibrillation and hypertension. Medications are rivaroxaban, hydrochlorothiazide, and metoprolol.

On physical examination, blood pressure is 155/80 mm Hg in both arms, and pulse rate is irregularly irregular at 90/min; other vital signs are normal. Cardiac examination shows findings consistent with atrial fibrillation. All other physical examination findings are normal. The patient says she has not been depressed but becomes tearful when discussing her medications. Depression screening has normal findings. She scores 20/30 (normal, ≥26) on the Montreal Cognitive Assessment. Bradykinesia with normal strength is noted in the legs bilaterally, as are increased deep tendon reflexes and an extensor plantar response on the left. Gait examination reveals a shuffling pattern.

Results of laboratory studies show normal thyroid-stimulating hormone and vitamin B_{12} levels.

An MRI shows diffuse white matter hyperintensities bilaterally and lacunar infarcts in the bilateral basal ganglia and left cerebellum.

Which of the following is most appropriate for this patient's cognitive impairment?

(A) Citalopram
(B) Donepezil
(C) Ginkgo biloba
(D) Methylphenidate

Item 75

A 65-year-old man comes to the office for follow-up evaluation of progressive weakness in the proximal muscles that has been present for the past 4 months. One month after symptom onset, an electromyogram showed myopathic changes without active denervation, and subsequent measurement of the serum creatine kinase level was 1500 U/L. The simvastatin he was taking to treat hyperlipidemia was stopped at that time, but his symptoms have persisted. He is otherwise well. He has no family history of neuromuscular disease.

On physical examination, vital signs are normal. Muscle strength is 5/5 in the facial, bulbar, and neck muscles and 3/5 in the proximal muscles of the upper and lower extremities. The proximal limbs are tender to palpation. Results of sensory and reflex examinations are normal.

Serum creatine kinase level is 4200 U/L.

Examination of a muscle biopsy specimen reveals evidence of muscle necrosis without inflammation.

Which of the following is the most appropriate next step in management?

(A) Azathioprine administration
(B) Clinical monitoring
(C) Coenzyme Q10 supplementation
(D) Prednisone administration

Item 76

A 52-year old woman is evaluated for a 3-week history of new onset daily headaches. The pain is absent nocturnally and on awakening but starts within 15 minutes of the patient's arising from bed and becomes progressively severe throughout the day. The headache is global, steady, and (when severe) associated with photophobia and mild nausea. Intermittent bilateral tinnitus and brief episodes of horizontal diplopia also have occurred. The pain improves within 15 to 20 minutes of the patient's lying down. Analgesic agents have been unhelpful. She has no other medical problems.

On physical examination, vital signs are normal; BMI is 26. Partial right abducens nerve (cranial nerve VI) palsy is noted.

An MRI of the brain shows diffuse nonnodular pachymeningeal enhancement, a cerebellar tonsillar descent of 3 mm, and clinically insignificant bilateral subdural fluid collections.

Which of the following is the most appropriate first step in management?

(A) Acetazolamide administration
(B) Epidural blood patch
(C) Lumbar puncture
(D) Subdural evacuation

Item 77

H

A 39-year-old woman is evaluated in the emergency department for a 2-day history of bilateral lower extremity weakness and numbness. The patient has no other

H CONT.

symptoms and no relevant medical history. She takes no medication.

On physical examination, temperature is 36.7 °C (98.1 °F); all other vital signs are normal. Muscle strength testing shows 4/5 weakness in hip flexion bilaterally and in foot dorsiflexion. Temperature sensation is partially reduced below spinal cord level T5. All other physical examination findings are normal.

A T2-weighted MRI of the thoracic spine shows a hyperintense lesion at the T4 level.

Which of the following is the most appropriate next test to evaluate for multiple sclerosis?

(A) Cerebrospinal fluid (CSF) analysis for antibodies to myelin basic protein
(B) CSF analysis for oligoclonal bands
(C) Erythrocyte sedimentation rate
(D) MRI of the brain
(E) Visual evoked potentials

H Item 78

A 56-year-old man is hospitalized 8 hours after developing difficulty speaking and left-sided weakness. An emergent CT scan of the head shows an acute right thalamic hemorrhage with no hydrocephalus or intraventricular hemorrhage; a follow-up CT scan obtained 48 hours later shows no changes. The patient also has hypertension and type 2 diabetes mellitus. Medications before admission were lisinopril, aspirin, and glipizide. On hospital admission, hydrochlorothiazide and lisinopril are continued, aspirin and glipizide are discontinued, and insulin is initiated.

On physical examination, blood pressure is 186/94 mm Hg, pulse rate is 74/min and regular, and respiration rate is 12/min. Left facial weakness with dysarthria and left-sided body weakness with no discernible movement are noted.

An electrocardiogram shows sinus rhythm without acute changes.

Which of the following is the most appropriate next step in management?

(A) Administration of low-molecular-weight heparin
(B) Administration of warfarin
(C) Application of thigh-high graduated compression stockings
(D) Resumption of aspirin

Item 79

A 68-year-old woman is evaluated for a 1-year history of neck stiffness and dull, achy neck pain. She also notes intermittent difficulty with dexterity while performing fine motor tasks at the hair salon where she works. Medications are ibuprofen as needed.

On physical examination, vital signs are normal. Range of motion of the neck is limited because of pain and stiffness. Fine finger movements exhibit subtle slowness. Reflex examination findings are normal, including a plantar flexor response. Muscle strength is 5/5 throughout. Gait is normal.

An MRI of the cervical spine shows multilevel cervical stenosis that is worst at C4/5 and C6/7. There is moderate deformation of the cord, but no signal change in the cord is noted.

Which of the following is the most appropriate next step in management?

(A) Gabapentin
(B) Neck immobilization in a hard cervical collar
(C) Neurosurgical intervention
(D) Physical therapy

Item 80

An 84-year-old woman is evaluated for dementia. She lives alone and is brought to the office by her son, who reports first noticing gradually progressive symptoms 4 years ago when his mother began having episodes of memory loss and a tendency to repeat herself excessively. He also notes increasing hygiene-related problems and says his mother recently called him several times in the middle of the night and asked him to pick her up "so she can go home." She can no longer manage her finances, keep appointments, or remember to take her medications; she stopped driving 1 year ago after getting lost several times. She has sick sinus syndrome and hypothyroidism treated with levothyroxine.

On physical examination, blood pressure is 155/60 mm Hg and pulse rate is 55/min and intermittently irregular. She scores 17/30 (normal, ≥24) on the Mini–Mental State Examination, but all other findings from neurologic examination are unremarkable.

Results of laboratory studies and brain imaging are normal.

Which of the following is the most appropriate treatment at this time?

(A) Alprazolam
(B) Donepezil
(C) Memantine
(D) Paroxetine
(E) Risperidone

Item 81

A 72-year-old man is evaluated for a 6-month history of headaches that have gradually increased in frequency and have been daily and constant for the past 6 weeks. The pain is bilateral, occipital, and described as a steady "pulling" sensation of mild to moderate intensity. Fatigue and neck discomfort are present. He has had no associated nausea, photophobia, phonophobia, or neurologic symptoms. The patient has atrial fibrillation treated with warfarin and verapamil and no other personal or family history of headache.

On physical examination, blood pressure is 128/88 mm Hg and pulse rate is 88/min and irregular. Decreased cervical range of motion is noted. Neurologic examination findings are unremarkable.

Results of laboratory studies show a normal erythrocyte sedimentation rate and complete blood count, a therapeutic INR, a normal comprehensive metabolic profile, and a normal serum level of C-reactive protein.

Which of the following is the most appropriate next step in management?

(A) Amitriptyline administration

(B) Brain MRI

(C) Cervical spine MRI

(D) Head CT

(E) Temporal artery biopsy

Item 82

A 40-year-old woman is evaluated after having two relapses of multiple sclerosis, which was diagnosed 3 years ago. She works as a human resource manager and has no other medical issues. The patient has been taking once weekly interferon beta-1a by intramuscular injection and a vitamin D supplement since diagnosis and has been adherent to the drug regimen. After reviewing her options, she elects to change her disease-modifying therapy to the oral medication fingolimod.

All physical examination findings, including vital signs, are normal.

Which of the following should now be a part of her drug monitoring program?

(A) JC virus antibody testing

(B) Ophthalmologic examinations

(C) Serum creatinine measurement

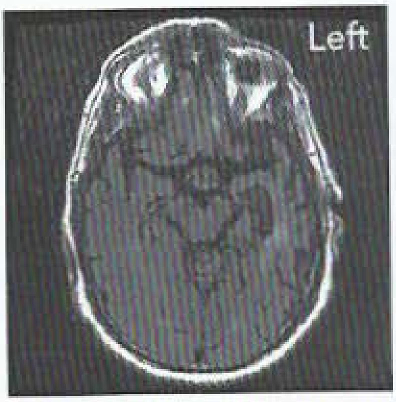
(D) Tuberculin skin testing

Item 83

A 63-year-old woman is evaluated for increasing difficulties with communication at work. She teaches mathematics at a local high school. Her most recent work evaluation cited a growing inability to provide clear instructions when assigning homework. She continues to manage the home finances and to drive, cook, and shop without difficulty.

On physical examination, vital signs are normal. The patient's speech pattern is fluent, but she has frequent problems with word finding and often repeats herself. She has difficulty understanding and following two-step commands. On the Montreal Cognitive Assessment, she scores 0/3 in the object-naming section, 0/1 in the letter-fluency section, and 4/5 in the recall section. All other physical examination findings are unremarkable.

An MRI of the brain is shown.



Which of the following is the most likely diagnosis?

(A) Alzheimer disease

(B) Behavioral-variant frontotemporal dementia

(C) Dementia with Lewy bodies

(D) Primary progressive aphasia

Item 84

A 62-year-old woman comes to the office for a follow-up evaluation of involuntary movements. She has a history of type 2 diabetes mellitus and gastroparesis for which she was taking long-term metoclopramide; the medication was stopped 6 months ago after she developed shuffling gait, involuntary facial movements, and a pill-rolling tremor. Since then, the gait problems and tremor have resolved, but she continues to experience persistent choreiform involuntary movements involving the face, lips, and hands. Medications are now metformin, insulin glargine, atorvastatin, and low-dose aspirin.

On physical examination, constant choreiform movements of the face, lips, and hands are noted. Vital signs and the remaining neurologic examination findings are unremarkable.

Which of the following is the most likely diagnosis?

(A) Akathisia

(B) Dystonic reaction

(C) Tardive dyskinesia

(D) Withdrawal emergent syndrome

Item 85

A 56-year-old man comes to the office for a follow-up evaluation after hospitalization for an intracerebral hemorrhage in the right thalamus. He reports feeling generally fatigued but has had no symptoms, such as depressed mood, since discharge. The patient has hypertension. His only medication is chlorthalidone.

On physical examination, blood pressure is 136/78 mm Hg, pulse rate is 68/min, and respiration rate is 12/min; BMI is 32. Neurologic examination reveals a left-sided loss of sensation and 4/5 muscle strength with mildly increased tone throughout the left side.

Results of laboratory studies show a serum creatinine level of 1.1 mg/dL (97.2 µmol/L), an LDL cholesterol of 86 mg/dL (2.23 mmol/L), and a hemoglobin A_{1c} value of 5.9%.

His calculated 10-year atherosclerotic heart disease risk for a major cardiovascular event is 4.3%.

Initiation of which of the following medications is the most appropriate next step?

(A) Aspirin

(B) Fluoxetine

(C) Lisinopril

(D) Rosuvastatin

Item 86

A 48-year-old woman is evaluated for an 8-hour history of facial paralysis. She reports having "droopiness" on the

right side of the face when she awoke this morning. She further says that her lunch tasted "odd" and that sounds on her right seem louder than usual.

On physical examination, vital signs are normal. A right facial droop associated with difficulty closing the eye and elevating the eyebrow is noted on the right side. Hearing is intact to whispering, but noises are more pronounced on the right side. The palate is symmetrically elevated, and the tongue protrudes at the midline. Taste is impaired on the right side of the tongue and intact on the left side. Muscle strength is intact on the left side of the face and in both extremities. Shoulder shrug and head turning are normal bilaterally. Facial sensation is intact bilaterally, as are all deep tendon reflexes. The neck is supple, no skin rash is visible, and coordination and gait are normal.

Which of the following is the most appropriate initial step in management?

(A) Brain MRI
(B) Intracranial magnetic resonance angiography
(C) Oral prednisone
(D) Oral valacyclovir

Item 87

A 37-year-old woman is evaluated for a 3-day history of recurrent episodes of severe, piercing right maxillary pain lasting several seconds. Attacks have become progressively more frequent, now occurring several times per hour, and can either arise spontaneously or be triggered by washing the face, chewing, or applying facial cosmetics. She has had no associated conjunctival injection, tearing, or nasal congestion or drainage. The patient has multiple sclerosis. Medications are glatiramer acetate and an oral contraceptive.

On physical examination, vital signs are normal; BMI is 22. A left afferent pupillary defect is noted, as is unsteadiness of tandem gait. All other physical examination findings are unremarkable, including normal facial sensation bilaterally.

A fluid-attenuated inversion recovery MRI reveals periventricular and brainstem hyperintensities that are not seen with contrast enhancement.

Which of the following is the most appropriate treatment?

(A) Acetazolamide
(B) Carbamazepine
(C) Indomethacin
(D) Lamotrigine

H Item 88

A 19-year-old man is evaluated in the hospital after admission for subacute onset of bilateral lower extremity paraplegia, urinary incontinence, and sensory deficits. His initial treatment was a 5-day course of high-dose intravenous methylprednisolone. Four days after completion of the infusions, no clinical improvement has occurred. The patient had flu-like symptoms for several days before onset of neurologic symptoms but otherwise has been healthy.

On physical examination, vital signs are normal. Muscle strength is 0/5 in both legs and 5/5 in both arms. Reflexes are absent in the lower extremities and normal in the upper extremities. Moderate sensory loss is noted below T3 bilaterally.

Cerebrospinal fluid analysis:

Erythrocyte count	2/µL (2×10^6/L)
Leukocyte count	38/µL (38×10^6/L), with a predominance of lymphocytes
Glucose	Normal
Protein	62 mg/dL (620 mg/L)

A T2-weighted MRI of the thoracic spine shows a hyperintense lesion in the thoracic cord at T2 with peripheral contrast enhancement. An MRI of the brain is normal.

Which of the following is the most appropriate next step in treatment?

(A) Antituberculosis drug regimen
(B) Inpatient rehabilitation only
(C) Intravenous immunoglobulin therapy
(D) Plasma exchange therapy

Item 89

A 41-year-old woman comes to the office for follow-up evaluation of relapsing-remitting multiple sclerosis, which was diagnosed 1 year ago. She has been taking the maximum dose of interferon beta-1a in three-times-weekly injections as disease-modifying therapy since that time. The patient currently has no symptoms and takes no other medication or supplement.

On physical examination, all findings are unremarkable.

A routine surveillance MRI of the brain shows two new lesions in the periventricular white matter, both of which enhance with contrast.

Which of the following is the most appropriate next step in management?

(A) Add dalfampridine
(B) Add glatiramer acetate
(C) Evaluate for cerebrospinal fluid JC virus antibody
(D) Measure serum 25-hydroxyvitamin D level

Item 90

A 64-year-old man comes to the office for a follow-up evaluation of mild cognitive impairment (MCI), which was diagnosed 6 months earlier after he scored 25/30 (normal, ≥26) on the Montreal Cognitive Assessment. The patient reports no worsening of symptoms. He now scores 24/30 on a repeat Montreal Cognitive Assessment, scoring 0/5 on the recall section. The patient wants to know if there are additional tests that would indicate whether his symptoms are caused by Alzheimer disease. A brain MRI obtained at the time of diagnosis was reported as normal.

Which of the following diagnostic studies is most likely to establish a diagnosis?

(A) Cerebrospinal fluid analysis
(B) Electroencephalography

(C) Fluorodeoxyglucose PET scan
(D) Repeat MRI
(E) Serum apolipoprotein E (*ApoE*) allele testing

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Item 91

A 47-year-old man is evaluated in the emergency department 2 hours after sudden onset of right-sided face, arm, and leg weakness and numbness. He has a history of hypertension. Medications are amlodipine and hydrochlorothiazide.

On physical examination, blood pressure is 166/72 mm Hg, pulse rate is 82/min, and respiration rate is 12/min. Right facial weakness, dysarthria, and loss of pinprick sensation in the right arm and leg are noted. The patient can lift the right arm and leg off the bed. The National Institutes of Health Stroke Scale score is 8 (moderate stroke).

A CT scan of the head without contrast shows no hemorrhage or early signs of infarct.

The patient receives intravenous recombinant tissue plasminogen activator (alteplase) 3 hours after symptom onset. One hour after treatment, blood pressure is 170/86 mm Hg; other physical examination findings are unchanged. A CT angiogram shows 80% stenosis of the left internal carotid artery and no intracranial arterial occlusion.

Administration of which of the following is the most appropriate next step in treatment?

(A) Amlodipine
(B) Clopidogrel
(C) Intravenous nitroprusside
(D) No further treatment is necessary

Item 92

A 52-year-old man is evaluated for a 3-year history of slowly progressive worsening gait, left leg weakness, spasticity, and fatigue without periods of improvement. Relapsing-remitting multiple sclerosis was diagnosed 20 years ago after an episode of optic neuritis from which he recovered fully. He takes interferon beta-1a as disease-modifying therapy. His disease was well controlled until symptom onset 3 years ago.

On physical examination, vital signs are normal. Muscle strength testing shows 3/5 left hip flexion and ankle dorsiflexion and 4/5 right hip flexion. Finger-to-nose testing elicits dysmetria on the right. The patient ambulates with the assistance of a cane and cannot perform tandem walking.

A T2-weighted MRI of the brain obtained 2 weeks ago showed a new lesion in the periventricular white matter that enhanced with gadolinium administration.

Which of the following best describes the current status of this patient's multiple sclerosis?

(A) Primary progressive, with progression but without activity
(B) Primary progressive, without progression but with activity
(C) Relapsing remitting, with activity
(D) Secondary progressive, with progression and activity
(E) Secondary progressive, without progression but with activity

Item 93

A 38-year-old man comes to the office for a routine follow-up evaluation of generalized tonic-clonic seizures, which he has experienced for the past year. He has had no improvement in seizures despite treatment with maximal doses of valproic acid. The patient also has depression with psychotic features. He attempted suicide 3 years ago. He has no additional medical problems. His only other medication is citalopram.

In addition to discontinuing the valproic acid, which of the following is the most appropriate treatment?

(A) Ethosuximide
(B) Lamotrigine
(C) Levetiracetam
(D) Topiramate

Item 94

A 49-year-old man is evaluated for a 6-month history of difficulty walking and frequent falls. He first noticed these symptoms after a prolonged hospitalization for pneumonia that was complicated by sepsis and cardiopulmonary arrest requiring intubation and antibiotic therapy. The patient also has hypothyroidism treated with levothyroxine.

On physical examination, vital signs are normal; BMI is 35. Muscle strength is normal in all limbs. At rest, few rapid jerky movements are noted in various limbs. On standing, rapid, nonrhythmic, shock-like movements are noted in the trunk and lower extremities, and there are brief lapses of muscle tone in the legs, which lead to loss of balance. These movements are not suppressible. Cognition, cranial nerves, reflexes, and sensation are normal. Plantar response is flexor bilaterally, and clonus is absent.

An MRI of the brain is unremarkable.

Which of the following most accurately describes this patient's abnormal movements?

(A) Ataxia
(B) Chorea
(C) Dystonia
(D) Myoclonus
(E) Orthostatic tremor

Item 95

A 51-year-old man is evaluated for morning headaches and increasing difficulty with focus and memory. He reports growing problems at work, including making occasional mistakes when updating spreadsheets, missing three recent appointments, and occasionally falling asleep during staff meetings. The patient has no other medical problems. He does not drink alcoholic beverages, smoke, or have a family history of dementia.

On physical examination, blood pressure is 150/90 mm Hg but other vital signs are normal; BMI is 33. He scores 25/30 (normal, ≥26) on the Montreal Cognitive Assessment, scoring 2/5 in the recall section, 0/1 in word generation, and 0/1 in letter identification. He scores normally on several clinical depression scales. Other physical examination

findings, including those from a neurologic examination, are unremarkable.

Which of the following is the most appropriate next step in evaluating this patient?

(A) Cerebrospinal fluid analysis
(B) Fluorodeoxyglucose PET scanning
(C) MRI of the brain
(D) Polysomnography

Item 96

A 55-year-old man is evaluated for increasing difficulty keeping track of tasks and performing his job adequately. The patient works as an accountant and lately has been making frequent calculation errors. He also has noticed some word-finding difficulties and marked difficulty with short-term memory. Symptoms have progressed over the past 18 months but recently have become more prominent. The patient has a 15-year history of multiple sclerosis and also has depression, which has been in remission. Medications are glatiramer acetate, vitamin D_3, and fluoxetine.

On physical examination, vital signs are normal. On neurologic examination, the patient can recall only one of three objects at 3 minutes, skips "August" when reciting the months backward, and makes one error when subtracting serial sevens.

Which of the following is the most appropriate treatment?

(A) Cognitive rehabilitation
(B) Increased dosage of fluoxetine
(C) Memantine
(D) Methylphenidate

Answers and Critiques

Item 1 Answer: D

Educational Objective: Diagnose a psychogenic nonepileptic spell/event.

This patient most likely is experiencing psychogenic nonepileptic spells/events (PNES). Although event capture during video electroencephalographic monitoring usually is required to confirm the diagnosis, the history is strongly suggestive of PNES because of the variability of symptoms (events not entirely stereotyped), eyes being closed, facial redness due to intermittent breath holding, shaking that starts with retained posture, long duration of shaking that waxes and wanes, limpness after falling, variable limb involvement, and rapid breathing without postictal confusion afterward.

Convulsive status epilepticus (CSE) is unlikely in this patient. The (relatively) long duration of symptoms without subsequent confusion or altered mental status places doubt on the diagnosis of CSE, which is not associated with a return to baseline mental status after seizures cease.

Unlike this patient's episodes, a generalized tonic-clonic seizure is characterized by stereotyped movements (essentially the same from one event to the next), eyes being open, cyanosis due to cessation of breathing, a duration of 2 to 5 minutes, stiffness and falling before symptoms of shaking, shaking that initially is fast but gradually slows and stops, and postictal confusion.

Myoclonic seizures are typically very brief (<1 second) and characterized by synchronous jerking or shaking of the limbs with retained awareness and no postictal confusion afterward. Given the duration and variable nature of this patient's seizures, they are not myoclonic.

KEY POINT

- Historical features that suggest the diagnosis of psychogenic nonepileptic spells/events include variability of symptoms, closing of eyes, long duration of shaking that waxes and wanes, and lack of postictal confusion; confirmation with video electroencephalographic monitoring usually is required.

Bibliography

LaFrance WC Jr, Baker GA, Duncan R, Goldstein LH, Reuber M. Minimum requirements for the diagnosis of psychogenic nonepileptic seizures: a staged approach: a report from the International League Against Epilepsy Nonepileptic Seizures Task Force. Epilepsia. 2013;54:2005-18. [PMID: 24111933] doi:10.1111/epi.12356

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Item 2 Answer: C

Educational Objective: Treat a patient who has dementia with Lewy bodies and acute agitation with donepezil.

This patient should be treated with donepezil. Delirium is a potentially preventable syndrome associated with other medical disorders, the adverse effects of medication, or drug withdrawal. Preexisting cognitive impairment is the major predisposing factor for delirium. With treatment, delirium typically resolves within days. Environmental interventions include orienting strategies (reliance on calendars, clocks, and familiar objects in the room), promoting a normal sleep-wake cycle (having no or limited interruptions during nocturnal sleeping hours, minimizing light and noise at night, and opening curtains and encouraging activity during the daytime), identifying and correcting sensory impairments, avoiding physical restraints, and early discontinuation of catheters and intravenous lines. This patient has dementia with Lewy bodies (DLB) and has developed acute agitation and delirium associated with a concurrent urinary tract infection (UTI). He should continue to receive therapy for the UTI until it resolves. The treatment of acute agitation in patients with dementia is challenging, and no medications are FDA approved for the treatment of delirium. Atypical and typical antipsychotic agents have a black box safety warning when used in patients with underlying dementia. Although not formally approved for DLB, donepezil can be effective in treating the behavioral and cognitive symptoms associated with the disorder; controlled clinical trials, however, remain inconclusive. Because donepezil (or any other medication) has not been shown to be efficacious for DLB in high-level, well-conducted trials, its use is based on expert opinion at this time. Nevertheless, donepezil is likely the safest and most efficacious medication for this patient.

Benzodiazepines (such as alprazolam) and diphenhydramine have a strong potential for worsening delirium symptoms in an older population and thus should be avoided in this patient.

Haloperidol is absolutely contraindicated in DLB because of the risk of significant worsening of the dementia syndrome. In addition, the patient is not aggressive at this point and is unlikely to harm himself or others, so antipsychotic agents are unnecessary, as are medications with a strong sedating effect (such as diphenhydramine).

KEY POINT

- Haloperidol is absolutely contraindicated in dementia with Lewy bodies; donepezil is a safer alternative and may improve the behavioral and cognitive symptoms associated with dementia.

Bibliography

Cummings J, Lai TJ, Hemrungrojn S, Mohandas E, Yun Kim S, Nair G, et al. Role of donepezil in the management of neuropsychiatric symptoms in Alzheimer's disease and dementia with Lewy bodies. CNS Neurosci Ther. 2016;22:159-66. [PMID: 26778658] doi:10.1111/cns.12484

Item 3 Answer: B

Educational Objective: Treat advanced Parkinson disease.

This patient should have deep brain stimulation, which is indicated for patients with advanced Parkinson disease who derive a continued benefit from carbidopa-levodopa but experience medication-related complications. The patient has two common levodopa-related complications: motor fluctuations (caused by the wearing off of the beneficial effects of the medication before the next dose is administered) and medication-induced dyskinesia (involuntary choreic movements). Attempting to increase the dose of levodopa to mitigate the "wearing off" phenomenon resulted in dyskinesia, nausea, and hypotension. Deep brain stimulation enables a persistent motor benefit and reduction of the total levodopa dosage, which would diminish the levodopa-induced adverse effects, including dyskinesia, nausea, and orthostatic hypotension.

Apomorphine is a fast-acting subcutaneous dopamine agonist that is indicated for rapid relief of symptoms caused by sudden wearing off of a Parkinson medication. It is inappropriate for this patient, who experiences predictable episodes of wearing off of the carbidopa-levodopa benefit before she takes the next dose. Apomorphine also does not address the dyskinesia or nausea.

Droxidopa has been approved for management of neurogenic orthostatic hypotension in Parkinson disease. This treatment, however, would not improve the wearing off of the dopaminergic medication before the next dose or the patient's other symptoms of gait freezing, dyskinesia, and medication-induced nausea.

Rotigotine, a dopamine agonist, can worsen both nausea and orthostatic hypotension. Additionally, an overall increase in dopaminergic medication dosing is likely to aggravate dyskinesia.

KEY POINT

- Deep brain stimulation is appropriate for patients with Parkinson disease who derive a continued benefit from carbidopa-levodopa but experience medication-related complications.

Bibliography

Okun MS. Deep-brain stimulation for Parkinson's disease. N Engl J Med. 2012;367:1529-38. [PMID: 23075179] doi:10.1056/NEJMct1208070

Item 4 Answer: A

H

Educational Objective: Treat severe traumatic brain injury.

This patient should be treated with acetaminophen. The patient has symptoms and signs of a severe head injury. Severe headache combined with nausea and focal neurologic symptoms, such as tinnitus and hearing loss, raises concerns of a major cranial injury. Bilateral periorbital bruising ("raccoon eyes"), mastoid bruising ("Battle sign"), and hemotympanum suggest the presence of a basilar skull fracture. Cerebrospinal fluid (CSF) rhinorrhea, epistaxis, and cranial nerve palsies also can be noted with these fractures, and fractures of the temporal bone occur in 75% of affected patients. Maintenance of an arterial Po_2 level of greater than 60 mm Hg (8.0 kPa) and a systolic blood pressure of greater than 90 mm Hg have been shown to improve outcomes in these patients. Fever worsens outcomes after stroke and possibly after severe head injury, most likely by promoting secondary brain injury, and acetaminophen is the most appropriate treatment at this time.

Prophylactic antibiotics, such as ceftriaxone, are inappropriate for this patient. Fever is a common complication of severe head injury and should be managed aggressively with antipyretic agents. There is no evidence of focal infection or sepsis. Although rhinorrhea in this patient most likely represents CSF drainage, no evidence supports the use of antibiotics without evidence of meningitis.

Dexamethasone is contraindicated in severe head injury because glucocorticoids have been shown to worsen its prognosis.

Naloxone is inappropriate for this patient. Although the urine drug screen was positive for opiates, there were no signs of central nervous system or respiratory depression. Naloxone also can worsen nausea and dizziness and occasionally cause sedation.

Norepinephrine is not required in this patient. Although blood pressure normalization in the presence of significant systolic hypotension (<90 mm Hg) has been shown to improve outcomes in severe closed head injury, this patient's systolic blood pressure does not require vasopressor support.

KEY POINT

- In patients with severe head injury, fever must be controlled aggressively with an agent such as acetaminophen.

Bibliography

Sheriff FG, Hinson HE. Pathophysiology and clinical management of moderate and severe traumatic brain injury in the ICU. Semin Neurol. 2015 Feb;35(1):42-9. [PubMed: 25714866] doi:10.1055/s-0035-1544238

Item 5 Answer: A

H

Educational Objective: Treat intracranial atherosclerosis.

This patient should receive high-intensity statin therapy with atorvastatin. The use of atorvastatin for secondary stroke prevention is associated with a reduced long-term risk of ischemic stroke, regardless of the baseline LDL cholesterol level. In addition to lowering the cholesterol level, high-intensity statin therapy has other benefits that are important in secondary stroke prevention, including plaque stabilization, anti-inflammatory properties, and slowing the progression of carotid arterial disease. A secondary-prevention randomized trial of high-dose statins established their efficacy among patients with LDL cholesterol levels greater than 100 mg/dL (2.59 mmol/L), irrespective of stroke subtype. Although this trial enrolled patients who were 30 days past stroke onset,

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statins are recommended to be part of a standardized hospital discharge order set for patients with ischemic stroke because this approach enhances patient adherence to medications. Standardized order sets, which also include antithrombotic agents and smoking cessation, focus on quality metrics of designated stroke centers.

Data have shown that stenting in patients with symptomatic intracranial atherosclerotic disease is associated with a nearly two-fold higher risk of stroke when compared with best medical therapy. Therefore, stenting is not routinely recommended or indicated for patients with intracranial atherosclerosis.

No clinical trial data support the use of methylphenidate, amphetamines, amantadine, bromocriptine, or similar agents for stroke recovery or prevention of stroke recurrence. Although these medications are not routinely recommended, they can be used on an individual basis in patients with behavioral syndromes, such as diminished wakefulness.

Compared with aspirin, warfarin has an increased risk of mortality when used for prevention of recurrence in patients with stroke due to intracranial atherosclerosis. Warfarin is indicated in patients with other stroke subtypes, such as those resulting from atrial fibrillation.

KEY POINT

- In ischemic stroke due to intracranial atherosclerosis, the use of high-intensity atorvastatin therapy for secondary stroke prevention is associated with a reduced long-term risk of ischemic stroke.

Bibliography

Kernan WN, Ovbiagele B, Black HR, Bravata DM, Chimowitz MI, Ezekowitz MD, et al; American Heart Association Stroke Council, Council on Cardiovascular and Stroke Nursing, Council on Clinical Cardiology, and Council on Peripheral Vascular Disease. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2014;45:2160-236. [PMID: 24788967] doi:10.1161/STR.0000000000000024

Item 6 Answer: C

Educational Objective: Treat fatigue in multiple sclerosis.

This patient should receive modafinil. Chronic fatigue is a common symptom in multiple sclerosis (MS). The fatigue associated with MS can have various causes, such as depression, insomnia, or other comorbid conditions. However, patients with MS without these conditions also can experience significant fatigue, which is often described as a sensation of mental exhaustion, frequently occurring in the midafternoon. Lifestyle adjustments, such as improving sleep hygiene, getting regular exercise, and treating depression, can sometimes resolve this symptom. For those with refractory fatigue, stimulant medications can be used. The most common medications of this type used (off-label) in MS are modafinil, armodafinil, and amantadine. For fatigue that is refractory to these medications, amphetamine stimulants, such as methylphenidate, also can be considered.

Spasticity is a frequent consequence of damage to the corticospinal tract in MS. This symptom manifests clinically as increased muscle tone, painful muscle cramps, spasms, and contractures. Spasticity can be reduced by using muscle relaxants, such as baclofen, tizanidine, or cyclobenzaprine. Antispasticity drugs, such as baclofen, are not effective agents for the management of fatigue.

Memantine has been evaluated as a means of treating MS-related cognitive deficits but has proved ineffective for this purpose. There is no reported benefit for MS-related fatigue with memantine.

Substituting an interferon beta for the glatiramer acetate would not be an appropriate step. Her fatigue is not an adverse effect of glatiramer acetate (which might necessitate a therapeutic switch), but rather a treatable symptom of an MS relapse.

Cannabinoids, such as tetrahydrocannabinol-cannabidiol, have been tested in clinical trials for a number of MS-related symptoms but have not improved outcomes. Trials have included the treatment of disease progression, spasticity, pain, and muscle stiffness. There are no data on the effect of cannabinoids on fatigue.

KEY POINT

- Multiple sclerosis-related fatigue is most appropriately treated with a stimulant medication, such as modafinil.

Bibliography

Tur C. Fatigue management in multiple sclerosis. Curr Treat Options Neurol. 2016;18:26. [PMID: 27087457] doi:10.1007/s11940-016-0411-8

Item 7 Answer: A

H

Educational Objective: Evaluate a first-time unprovoked seizure.

This patient should have CT of the head. Neuroimaging is indicated in all patients with a first-time seizure to rapidly exclude conditions requiring emergent intervention, including hemorrhage. Head CT is the most appropriate initial study because it typically is readily available in most emergency departments and can be performed rapidly. The patient will later require both MRI and electroencephalography, but CT is the best initial study.

Levetiracetam and other antiepileptic drugs are not recommended for first-time seizures until the results of further testing, such as head CT, brain MRI, and electroencephalography (EEG), are known and the recurrence risk of seizures can be determined. He had an unprovoked seizure but does not meet criteria for the diagnosis of epilepsy (at least two unprovoked seizures more than 24 hours apart, or one unprovoked seizure with a high risk of recurrence on the basis of abnormalities found on testing). The 2-year recurrence risk after a single generalized tonic-clonic seizure in patients with normal findings on clinical examination, no epilepsy risk factors, and a normal head CT scan is approximately 40%; that number decreases to about 20% if MRI and

H CONT.

EEG are normal. In the setting of two unprovoked seizures or one unprovoked seizure with significant EEG or MRI abnormalities, recurrence risk is at least 60% and treatment is recommended.

Although this seizure lasted 5 minutes and thus would meet the definition of convulsive status epilepticus (CSE) if seizure activity were ongoing, the patient has recovered completely and has normal findings on clinical examination. Therefore, he does not have CSE, and intravenous lorazepam is not indicated.

In adults, lumbar puncture is appropriate when meningitis is clinically suspected (for example, in the presence of neck stiffness, altered mental status, or fever) or when a patient has symptoms highly suggestive of subarachnoid hemorrhage in conjunction with normal noncontrast head CT findings. It otherwise is not indicated after a seizure in adults.

KEY POINT

- In a patient with an unprovoked, first-time seizure, head CT is the most appropriate initial study to rapidly exclude emergent pathologic issues.

Bibliography

Gavvala JR, Schuele SU. New-onset seizure in adults and adolescents: a review. JAMA. 2016;316:2657-68. [PMID: 28027373] doi:10.1001/jama.2016.18625

Item 8 Answer: A

Educational Objective: Treat the symptoms of behavioral-variant frontotemporal dementia.

This patient should be given the selective serotonin reuptake inhibitor citalopram to control her obsessive-compulsive behaviors. Early changes in social behavior and personality are the defining characteristics of behavioral-variant frontotemporal dementia (FTD). Apathy, diminished interest, loss of empathy, lack of initiative, increased emotionality, disinhibition, euphoria, impulsivity, changes in eating behaviors, hyperorality, and compulsiveness are the most common symptoms reported by families. Other changes include irritability, aggression, verbal abuse, hypomania, and restlessness. The treatment of behavioral-variant FTD is symptom based and should target the most troubling manifestations of the disorder. This patient's obsessive-compulsive tendencies not only have had embarrassing consequences but have resulted in a confrontation with family members. Selective serotonin reuptake inhibitors, such as citalopram, have the potential to alleviate these symptoms. Tricyclic antidepressants may also have this effect.

The acetylcholinesterase inhibitor donepezil is approved by the FDA to treat mild to moderate Alzheimer disease. This class of drug has shown modest benefit in improving cognitive performance in patients with this type of dementia without clear improvements in daily functioning. The body of evidence does not support acetylcholinesterase inhibitors as being beneficial in behavioral-variant FTD.

Similarly, the *N*-methyl-D-aspartate receptor antagonist memantine, which is approved for moderate to severe dementia in patients with Alzheimer disease associated with significant functional impairment, has shown no benefit in in patients with behavioral variant FTD and may, in fact, worsen symptoms.

In patients with severe apathy, which can be a common and sometimes debilitating symptom of behavioral variant FTD, stimulant medications, such as methylphenidate, are sometimes used. This patient has not exhibited apathy. More importantly, referral to a psychiatrist or neurologist is generally recommended before dispensing these medications.

Atypical antipsychotic agents (such as olanzapine) can be effective in treating agitation, aggression, delusions, and hallucinations. However, these drugs are not FDA approved for this clinical indication and have an associated black box warning due to increased cerebrovascular events and mortality rates in patients with dementia. Olanzapine can be considered if there are psychotic symptoms, such as hallucinations or psychotic delusions. This patient has exhibited no psychotic symptoms. In general, antipsychotic agents should be avoided in patients with dementia.

KEY POINT

- Because there are currently no disease-modifying treatments for behavioral variant frontotemporal dementia, treatment is symptom based and should target the disease's most troublesome manifestations.

Bibliography

Tsai RM, Boxer AL. Treatment of frontotemporal dementia. Curr Treat Options Neurol. 2014;16:319. [PMID: 25238733] doi:10.1007/s11940-014-0319-0

Item 9 Answer: B

H

Educational Objective: Evaluate a patient who has a cryptogenic stroke for atrial fibrillation.

This patient should have outpatient cardiac telemetry. She has a cryptogenic infarct with no clear source identified on arterial imaging, no evidence of atrial fibrillation (AF) or other high-risk embolic cause, and a stroke location that is not typical for lacunar infarcts. Accumulating data on patients with cryptogenic stroke indicate that an evaluation for AF with an outpatient rhythm monitor may yield a new diagnosis of AF in almost one third of patients. Given the high risk of recurrent stroke associated with AF, additional outpatient evaluation is warranted. The various options available for monitoring include mobile outpatient cardiac telemetry, 24-hour electrocardiographic monitoring, transtelephonic and event monitors, and implantable subcutaneous devices. Longer monitoring results in a higher diagnostic yield. In one study comparing 30-day monitoring to 24-hour monitoring, atrial fibrillation lasting for at least 30 seconds was found in 16.1% of patients monitored for 30 days vs. 3.2% of patients monitored for 24 hours, and AF lasting for at least 2.5 minutes

H CONT.

was found in 9.9% of patients with prolonged monitoring vs. 2.5% of patients with 24-hour monitoring.

The combination of clopidogrel and aspirin is associated in the long term with a higher risk of hemorrhagic complications compared with a single antiplatelet agent only. This combination additionally provides no reduction in the risk of ischemic stroke.

Apixaban and similar anticoagulants have not been shown to be effective for the routine prevention of cryptogenic stroke. Warfarin and aspirin have similar rates of recurrent stroke in patients with noncardioembolic stroke; warfarin is not indicated as first-line therapy for stroke prevention in cryptogenic stroke.

Transesophageal echocardiography is unnecessary because the patient is in sinus rhythm and already has had structural imaging of the valves and chamber sizes, which makes a transesophageal echocardiogram likely to be of low yield. This diagnostic test also is invasive and costly and is of higher yield when used to evaluate for unusual causes of cardiac emboli, such as valvular endocarditis or intracardiac tumors.

KEY POINT

- Evaluation of cryptogenic stroke with prolonged outpatient rhythm monitoring may yield a new diagnosis of atrial fibrillation in almost one third of patients.

Bibliography

Kernan WN, Ovbiagele B, Black HR, Bravata DM, Chimowitz MI, Ezekowitz MD, et al; American Heart Association Stroke Council, Council on Cardiovascular and Stroke Nursing, Council on Clinical Cardiology, and Council on Peripheral Vascular Disease. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2014;45:2160-236. [PMID: 24788967] doi:10.1161/STR.0000000000000024

H

Item 10 Answer: B

Educational Objective: Treat reversible cerebral vasoconstriction syndrome.

This patient should undergo magnetic resonance angiography of the brain. Her recent history of thunderclap headache is characteristic of reversible cerebral vasoconstriction syndrome (RCVS). The term thunderclap headache is applied to severe headaches that reach maximum intensity within 1 minute. Although subarachnoid hemorrhage (SAH) is the most frequent cause of thunderclap headache, and some patients may experience an isolated sentinel leak before aneurysmal rupture, three episodes within 4 days would be highly unusual for SAH. Normal results of head CT scans and lumbar puncture (LP) effectively exclude this diagnosis. RCVS is the second most frequent source of thunderclap headaches. Head CT and LP findings are both typically normal. Diagnosis is confirmed by documentation of multifocal constriction of intracranial vessels that normalizes within 3 months of onset. Brain magnetic resonance angiography or head CT angiography are the diagnostic procedures of choice. Predisposing factors include vasoactive drugs (such as sympathomimetic agents, triptans, cocaine, and cannabis) and antidepressants (such as sertraline). The headaches may be triggered by exertion, Valsalva maneuvers, emotion, or showering/bathing. Although some patients develop focal deficits, encephalopathy, or seizures, most have normal findings on clinical examination. Calcium channel blockers, such as verapamil and nimodipine, are the treatments of choice.

Digital subtraction angiography in patients with RCVS has been associated with transient neurologic deficits and is typically avoided.

Because glucocorticoids are associated with a worse clinical course in RCVS, methylprednisolone sodium succinate has no role in its management. This drug can be appropriate therapy for other headache disorders, such as giant cell arteritis, optic neuritis, cerebral vasculitis, or pituitary apoplexy, but none of these is compatible with the patient's clinical presentation and normal results on a head CT scan and LP.

Sumatriptan is an appropriate treatment for acute migraine headache but should be avoided in RCVS. Triptans may predispose patients to RCVS and potentially worsen cerebral vasospasm.

Valproic acid has been shown to be effective in the prevention of episodic migraine. The International Classification of Headache Disorders, third edition, (ICHD-3) criteria for all primary headaches, including migraine, include the requirement that headache is "not better accounted for by another ICHD-3 diagnosis." The clinical picture of recurrent thunderclap headache over a span of days or weeks is much more likely to represent RCVS than migraine.

KEY POINT

- Brain magnetic resonance angiography or head CT angiography are the diagnostic procedures of choice for reversible cerebral vasoconstriction syndrome, the second most frequent source of thunderclap headache.

Bibliography

Ducros A, Wolff V. The typical thunderclap headache of reversible cerebral vasoconstriction syndrome and its various triggers. Headache. 2016 Apr;56(4):657-73. Epub 2016 Mar 26. [PMID: 27015869] doi: 10.1111/head.12797

Item 11 Answer: A

H

Educational Objective: Treat a multiple sclerosis exacerbation.

This patient should receive high-dose oral prednisone, 1250 mg/d for 5 days. She is experiencing an acute exacerbation, or relapse, of multiple sclerosis (MS). Administration of high-dose glucocorticoids is the standard treatment for MS exacerbations. This treatment approach derives from the landmark Optic Neuritis Treatment Trial, in which high-dose intravenous methylprednisolone (1 g/d for 5 days) was compared to prednisone (1 mg/kg/d for 2 weeks) and placebo. Intravenous methylprednisolone was associated with a more rapid recovery of visual function. Subsequent studies have

H CONT.

shown that use of a bioequivalent oral high-dose regimen (such as oral prednisone, 1250 mg, or oral methylprednisolone, 1 g) is as efficacious as intravenous methylprednisolone and has no significant differences in adverse effects. Because of their ease of administration and reduced costs, high-dose oral regimens are beginning to replace intravenous methylprednisolone, although either approach is valid.

Low-dose oral prednisone, 1 mg/kg/d for 2 weeks, is inappropriate. In fact, low-dose oral prednisone was inferior to high-dose intravenous glucocorticoids and actually resulted in worse outcomes than placebo in the Optic Neuritis Treatment Trial. Although this dose of oral prednisone is used for some other neuroinflammatory conditions (such as Bell palsy), it potentially can harm patients with MS experiencing a flare and should be avoided.

A randomized control trial has documented that plasmapheresis may result in clinical improvement in patients with acute exacerbations of MS who do not respond to glucocorticoid therapy. Plasmapheresis is not considered primary, or first-line, therapy for patients with an acute relapse of MS.

The links between vitamin D deficiency and MS pathophysiology have been clearly established, with reduced levels of serum vitamin D predicting future accumulation of new lesions on MRI. Administration of vitamin D supplementation has been shown to provide additional disease activity control, with a recent trial finding less MRI activity in patients taking interferon plus vitamin D versus interferon alone. However, there is no role for vitamin D in the management of an acute relapse of MS. Chronic supplementation with vitamin D is reasonable for most patients with MS, especially if vitamin D levels are low.

KEY POINT

- Administration of high-dose glucocorticoids is the standard treatment for multiple sclerosis exacerbations.

Bibliography

Burton JM, O'Connor PW, Hohol M, Beyene J. Oral versus intravenous steroids for treatment of relapses in multiple sclerosis. Cochrane Database Syst Rev. 2012 Dec 12;12:CD006921. [PMID: 23235634]

Item 12 Answer: B

Educational Objective: Diagnose dystonic tremor.

This patient has a dystonic tremor, which occurs both at rest and with action and is characterized by associated dystonic posturing and the presence of a null point at which change in the position of the affected limb resolves the tremor. The null point is the position at which the trajectories of the forces caused by dystonic coactivation of agonist and antagonist muscles neutralize each other, which leads to resolution of the tremor. In addition, the action component of tremor has task specificity in that it is worse with use of scissors but spares the handwriting.

Cerebellar tremor is characterized by increasing tremor amplitude as the limb approaches the target (terminal intention tremor) and the presence of associated cerebellar symptoms. These features are absent in this patient.

Essential tremor is the most common movement disorder and often presents with a bilateral upper extremity postural and action tremor. It is not associated with dystonic features. Additional features include bilateral involvement and a positive family history. Amelioration of the tremor by ethanol is typical and did not occur in this patient.

Parkinsonian tremor is prominent at rest and can reemerge after a brief delay when the arms are held in an outstretched position. Although dystonia can be seen secondary to Parkinson disease, the absence of other associated features, especially the bradykinesia required for a diagnosis of Parkinson disease, excludes this diagnosis.

Rubral tremor is caused by focal injury to cerebellar outflow pathways and is characterized by a coarse tremor that is present at rest but most severe during action. This type of tremor has a prominent proximal component and interferes with various actions, such as feeding, typing, and writing, in a nonselective way. Also, MRIs of the brain reveal a focal causative lesion that is not present in this patient.

KEY POINT

- Dystonic tremor occurs both at rest and with action and is characterized by associated dystonic posturing and the presence of a null point at which a change in the position of the affected limb resolves the tremor.

Bibliography

Fasano A, Deuschl G. Therapeutic advances in tremor. Mov Disord. 2015;30:1557-65. [PMID: 26293405] doi:10.1002/mds.26383

Item 13 Answer: E

H

Educational Objective: Treat convulsive status epilepticus in a patient allergic to phenytoin.

The patient should now receive intravenous valproic acid. He is in generalized convulsive status epilepticus (CSE). A medical emergency that can lead to significant morbidity and mortality, CSE is defined as persistent tonic-clonic activity with impaired mental status that lasts longer than 5 minutes. Initial management of CSE requires rapidly assessing airways, breathing, and circulation; checking the blood glucose level; and administering thiamine with glucose, if needed. These steps should be performed simultaneously with initiation of drug treatment. According to a guideline from the American Epilepsy Society, intramuscular midazolam, intravenous (IV) lorazepam, and IV diazepam have been judged to be equivalent and are the first-line agents for the initial treatment of CSE. Phenytoin, a longer-acting antiseizure drug, should then be administered; if available, fosphenytoin, a prodrug of phenytoin, is preferable to phenytoin for initial treatment of CSE because it can be administered faster and does not carry the risk of thrombophlebitis or skin necrosis (purple glove syndrome) that is associated with phenytoin extravasation. Valproic acid is an alternative to phenytoin or fosphenytoin, particularly in patients with an allergy to phenytoin or

CONT.

primary generalized epilepsy. Therefore, intravenous valproic acid should be administered to this patient as a second line therapy.

CSE usually is diagnosed clinically. Obtaining an MRI of the brain is an unnecessary time-consuming process and would delay treatment. Once CSE is controlled, head CT usually is indicated because it takes less time and is more readily available in the acute setting.

Electroencephalography could eventually be considered, but, again, the diagnosis of CSE is primarily clinical, and treatment should not be postponed.

Lacosamide, which is available intravenously, sometimes is considered in the management of convulsive status epilepticus. However, evidence is insufficient to recommend it as part of the standard guidelines for initial treatment of generalized CSE, which makes it inappropriate for this patient.

KEY POINT

- According to current guidelines, valproic acid is an appropriate second-line therapy for convulsive status epilepticus for patients allergic to phenytoin.

Bibliography

Glauser T, Shinnar S, Gloss D, Alldredge B, Arya R, Bainbridge J, et al. Evidence-based guideline: treatment of convulsive status epilepticus in children and adults: report of the Guideline Committee of the American Epilepsy Society. Epilepsy Curr. 2016;16:48-61. [PMID: 26900382] doi: 10.5698/1535-7597-16.1.48

Item 14 Answer: B

Educational Objective: Treat depression as a cause of memory difficulties in an older patient.

This patient should undergo treatment for depression. Depression is common in older adults, although it is both underrecognized and undertreated. In these patients, depression can frequently masquerade as cognitive impairment or multiple somatic complaints, which often results in delayed diagnosis. The patient expresses concern about subjective cognitive changes. However, given his age, the fact that he recently assumed new responsibilities after losing his wife, the limited evidence of memory loss, and the normal findings on cognitive and neurologic examination, a significant cognitive disorder is not likely. His recent decreased appetite, problems falling asleep, and withdrawal from social activities suggest onset of a depressive disorder that is most likely associated with the loss of his wife. Depression is further suggested by the positive Geriatric Depression Scale (GDS) score of 9. The GDS has been validated in the older population. The GDS relies less on somatic symptoms and has a simplified yes-or-no format, which may be more conducive to screening those with possible cognitive impairment. Treatment of his depression with close follow-up evaluations is thus most advisable.

Because Alzheimer disease is an unlikely diagnosis in this patient and is unsupported by results of cognitive testing, treatment with an acetylcholinesterase inhibitor is premature and unwarranted at this point.

An MRI without contrast is similarly unwarranted in this patient who has normal scores on screening cognitive evaluation and lacks concerning findings in his history or examination findings.

Although often helpful in patients with cognitive impairment, a complete neuropsychological evaluation is unnecessary in this situation, given the normal findings of the screening examination. This patient's symptoms, including his memory difficulty, are most likely due to depression, and this reversible contributor should be treated first. If treatment results in no alleviation of the symptoms, then further testing can be pursued.

KEY POINT

- In older patients, depression can frequently masquerade as cognitive impairment; screening and treatment is appropriate in these patients.

Bibliography

Knopman DS, DeKosky ST, Cummings JL, Chui H, Corey-Bloom J, Relkin N, et al. Practice parameter: diagnosis of dementia (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 2001;56:1143-53. [PMID: 11342678]

Item 15 Answer: C

Educational Objective: Diagnose teratoma-associated anti-*N*-methyl-D-aspartate receptor antibody encephalitis.

This patient most likely has an ovarian teratoma. An autoimmune condition termed anti-*N*-methyl-D-aspartate receptor (anti-NMDAR) antibody encephalitis has emerged as an increasingly common cause of encephalitis. Anti-NMDAR antibody encephalitis is associated with ovarian teratomas in more than 50% of patients with the disease because of production of an antibody to a tumor protein that cross-reacts with neuronal tissue. The diagnosis is suggested by the presence of choreoathetosis, psychiatric symptoms, seizures, and autonomic instability and is confirmed by detection of anti-NMDAR antibody in serum. This patient has developed new-onset psychiatric disease and a movement disorder. These symptoms raise suspicion of paraneoplastic or autoimmune encephalitis, and testing confirms the presence of the anti-NMDAR antibody in the serum. Patients are evaluated with CT and/or transvaginal ultrasound. Treatment includes removal of the teratoma to eradicate the immune stimulus and immunosuppression with glucocorticoids or intravenous immune globulin.

Paraneoplastic syndromes associated with breast adenocarcinoma can present as ataxia, brainstem encephalitis, ophthalmoplegia, and parkinsonism. They are most often associated with anti-Ri and anti-glutamic acid decarboxylase antibodies rather than anti-NMDAR antibody.

Unlike small cell lung cancer, non-small cell lung cancer (NSCLC) typically is not associated with neurologic paraneoplastic syndromes. NSCLC, however, may be associated with other paraneoplastic syndromes, including hypercalcemia and hypertrophic osteoarthropathy.

H CONT.

Small cell lung cancer is associated with a host of neurologic paraneoplastic syndromes, including dementia, chorea, ataxia, brainstem encephalitis, and neuropathies, among others. The antibodies associated with these syndromes include anti-Hu, anti-LGI1 (voltage-gated potassium channel), and anti-CRMP5 antibodies but not the anti-NMDAR antibody.

KEY POINT

- Ovarian teratoma–associated anti–*N*-methyl-D-aspartate receptor antibody encephalitis is suggested by the presence of choreoathetosis, psychiatric symptoms, seizures, and autonomic instability.

Bibliography

Titulaer MJ, McCracken L, Gabilondo I, Armangué T, Glaser C, Iizuka T, et al. Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: an observational cohort study. Lancet Neurol. 2013;12:157-65. [PMID: 23290630] doi:10.1016/S1474-4422(12)70310-1

Item 16 Answer: C

Educational Objective: Prevent migraine.

This patient should be treated with metoprolol. Her headaches meet the criteria for episodic migraine without aura. Pharmacologic prevention should be considered for migraine occurring at a frequency of at least 5 days per month. According to guidelines, metoprolol, propranolol, timolol, divalproex sodium, and topiramate all have Level A evidence for prevention of episodic migraine, with atenolol, amitriptyline, and venlafaxine having level B evidence. Approximately a third of patients with episodic migraine meet criteria for pharmacologic prevention, yet only 3% to 13% receive this treatment. The goal of prevention is an at least 50% reduction in headache frequency; reductions in migraine intensity, disability, and cost are other established outcomes. Drug tapering or elimination should be considered after a period of 6 to 12 months of adequate control.

No data support the use of citalopram or other selective serotonin reuptake inhibitor antidepressants in migraine prevention.

Insufficient evidence about the effectiveness of gabapentin in migraine prevention is available; therefore, its use for this purpose is inappropriate.

Onabotulinum toxin A has an FDA indication for the prevention of chronic migraine but is not approved and has no established efficacy in the prevention of episodic migraine. Chronic migraine is defined as headache occurring 15 or more days per month with at least 8 days meeting full criteria for migraine or responding to migraine-specific medication.

Rizatriptan is an effective treatment option for acute migraine. However, this patient is responding well to an NSAID, and no adjustment in acute therapy is warranted. Escalation in headache frequency requires migraine-preventive measures.

KEY POINT

- Metoprolol, propranolol, timolol, divalproex sodium, and topiramate all have Level A evidence for prevention of episodic migraine and should be considered for migraine occurring at a frequency of at least 5 days per month.

Bibliography

Silberstein SD, Holland S, Freitag F, Dodick DW, Argoff C, Ashman E; Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society. Evidence-based guideline update: pharmacologic treatment for episodic migraine prevention in adults: report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society [erratum appears in Neurology. 2013 Feb 26;80(9):871]. Neurology. 2012 Apr 24;78(17):1337-45. [PMID: 22529202] doi:10.1212/WNL.0b013e3182535d20

Item 17 Answer: B

Educational Objective: Treat juvenile myoclonic epilepsy in a woman with childbearing potential.

Besides discontinuing the oral contraceptive, starting folic acid, and then tapering off valproic acid, this patient should begin taking levetiracetam for her juvenile myoclonic epilepsy (JME). This type of generalized epilepsy requires a history of myoclonic seizures for diagnosis but is also usually associated with generalized tonic-clonic seizures. In a woman with childbearing potential, levetiracetam and lamotrigine are the most appropriate treatment options because of their relatively low risk of teratogenicity. Levetiracetam is often preferred because lamotrigine can worsen myoclonus in some patients.

Valproic acid is strongly associated with neural tube defects and lower IQ in offspring and should be avoided in women with childbearing potential, unless absolutely necessary. In this patient, who has been seizure free for 10.5 years and has never taken another antiepileptic drug, replacing valproic acid with another medication should be attempted. In patients whose epilepsy is difficult to control with other medications, valproic acid may be continued during pregnancy.

Gabapentin and oxcarbazepine also have a relatively favorable profile in terms of lower fetal risk, but both are known to worsen generalized epilepsy and thus should be avoided in patients with JME.

Maternal topiramate use is associated with cleft lip/palate in offspring. This teratogenic drug should be avoided by women with childbearing potential.

JME most often requires lifelong treatment, even if patients have normal results on testing and are seizure free for many years. Therefore, providing this patient no additional treatment is inappropriate.

KEY POINT

- In a woman with childbearing potential, levetiracetam and lamotrigine are the most appropriate treatment options because of their relatively low risk of teratogenicity.

Bibliography

Crespel A, Gelisse P, Reed RC, Ferlazzo E, Jerney J, Schmitz B, et al. Management of juvenile myoclonic epilepsy. Epilepsy Behav. 2013;28 Suppl 1:S81-6. [PMID: 23756489] doi:10.1016/j.yebeh.2013.01.001

H Item 18 Answer: A

Educational Objective: Treat spinal cord metastases.

This patient should undergo decompressive surgery followed by radiation. This patient most likely has a metastatic extradural lesion from the prostate cancer that has resulted in cord compression. Spinal cord compression due to metastatic disease from most tumor types requires emergent use of high-dose glucocorticoids (dexamethasone, 20 mg) followed by maintenance glucocorticoids until definitive therapy with urgent surgical decompression followed by radiation is possible. Certain radiosensitive tumor types, such as leukemia, lymphoma, myeloma, and germ cell tumors, may not require initial surgical decompression and may be treated urgently with radiation therapy followed by chemotherapy. Surgical intervention sometimes is deferred in patients with a poor prognosis for long-term survival or with a low functional status. However, in appropriate patients, clinical trials have shown the superiority of surgical decompression followed by radiation compared with radiation alone in optimizing ambulation in patients younger than 65 years.

Laminectomy, in which the lamina (the back part of the vertebra covering the spinal canal) is removed to create more space, is not preferable to decompressive surgery, in which regions of the vertebra infiltrated by tumor are removed and reconstructed. In fact, radiation alone is superior to laminectomy in this patient because it would address the metastatic lesion.

Spinal angiography is appropriate to use in the diagnosis and treatment of a spinal dural arteriovenous fistula (AVF) or a spinal arteriovenous malformation (AVM) but not for a T8 vertebral body with invasion into the epidural space. An AVF or an AVM would result in vascular-appearing lesions (usually associated with flow voids) on T2-weighted imaging.

KEY POINT

- Spinal cord compression from metastatic disease requires emergent use of high-dose glucocorticoids and urgent surgical decompression followed by radiation.

Bibliography

George R, Jeba J, Ramkumar G, Chacko AG, Tharyan P. Interventions for the treatment of metastatic extradural spinal cord compression in adults. Cochrane Database Syst Rev. 2015:CD006716. [PMID: 26337716] doi:10.1002/14651858.CD006716.pub3

H Item 19 Answer: A

Educational Objective: Diagnose Creutzfeldt-Jakob disease.

This patient most likely has Creutzfeldt-Jakob disease (CJD). CJD is the most common form of prion disease in humans, with most cases being sporadic. Iatrogenic transmission of CJD is possible and has resulted mainly from receipt of growth hormone prepared from cadaveric pituitaries and contaminated cadaveric dura mater allografts. Contaminated surgical instruments have also been documented to transmit CJD in rare instances. Sporadic CJD does not appear to be transmissible by blood. Brain MRIs typically show a pattern of increased intensity in the diffusion-weighted sequence in the basal ganglia and various cortical regions.

Periodic sharp wave complexes are often seen on electroencephalography. Elevated levels of tau and 14-3-3 proteins in the cerebrospinal fluid (CSF) also are typical but not necessary for diagnosis. Although rapidly progressive dementia has a broad differential diagnosis, CJD is very likely if it is accompanied by myoclonus, sleep problems, and other psychiatric symptoms. Progressive neurologic decline resulting in death occurs rapidly, typically within 6 to 12 months.

HIV encephalopathy is characterized by a subacute syndrome of cognitive and motor dysfunction. Although HIV screening is standard for rapid-onset dementia, the electroencephalographic and MRI findings are inconsistent with a diagnosis of acute HIV encephalopathy.

Lyme disease can be responsible for a seldom-reported inflammatory encephalomyelitis. The disease often mimics multiple sclerosis, with MRI abnormalities of the brain or spinal cord and abnormal CSF findings, including increased total immunoglobulin and oligoclonal bands. The patient's rapidly progressive dementia, myoclonus, psychiatric symptoms, and normal CSF findings are not compatible with this diagnosis.

Wernicke encephalopathy is an acute neuropsychiatric syndrome characterized by the triad of nystagmus and ophthalmoplegia, mental status changes, and ataxia. It is caused by thiamine deficiency, most often in patients who abuse alcohol, but can be seen in patients being treated for cancer, those with chronic vomiting or malnutrition, or those who have had gastrointestinal surgery, in particular bariatric surgery. The patient's findings are not compatible with Wernicke encephalopathy.

KEY POINT

- Creutzfeldt-Jakob disease is a transmissible prion-related disorder characterized by rapidly progressive dementia, myoclonus, sleep problems, and other psychiatric symptoms; typical imaging findings include an increased signal in the cortex and subcortical structures on diffusion-weighted MRI sequences.

Bibliography

Geschwind MD. Rapidly Progressive Dementia. Continuum (Minneap Minn). 2016;22:510-37. [PMID: 27042906] doi:10.1212/CON.0000000000000319

Item 20 Answer: A

Educational Objective: Evaluate a transient ischemic attack.

This patient should have carotid duplex ultrasonography. He most likely has had a transient ischemic attack (TIA) referable

to the left hemisphere and is at risk of ischemic stroke within the next 90 days, with the highest risk occurring within the first 2 days. Although his ABCD^2 score (based on patient Age, Blood pressure, Clinical presentation, Duration of symptoms, and presence of Diabetes mellitus) of 3 indicates a predicted stroke risk of 1.3% and the need for hospitalization and rapid evaluation, these scores are neither sensitive nor specific enough to identify patients at highest risk of stroke. Several studies have identified extracranial symptomatic internal carotid artery stenosis as an indicator of stroke risk of greater than 70% after TIA; this risk can be modified with carotid revascularization. Several modalities are available for imaging the internal carotid artery and identifying extracranial symptomatic stenosis, including duplex ultrasonography, CT angiography, and magnetic resonance angiography (MRA). Duplex ultrasonography has the benefit of being inexpensive, readily available, low risk, and noninvasive and thus is an appropriate early study. If the carotid duplex ultrasound shows high-grade stenosis, confirmation of this finding by CT angiography or MRA is required before surgical intervention. If the carotid duplex ultrasound is unrevealing, then additional vessel imaging of the neck is unnecessary.

CT angiography of the neck is more costly and less widely available than carotid duplex ultrasonography. Additionally, the radiation exposure makes CT angiography less desirable as an initial imaging test.

Brain MRI is not the initial test of choice because the presence or absence of a cerebral infarct will not immediately change medical management or affect the patient's stroke risk. Cerebral imaging with either CT or MRI eventually may be required in this patient but should occur after an evaluation of the internal carotid artery that may lead to hospitalization and surgical intervention.

In patients with risk factors for stroke after a TIA, transesophageal echocardiography is (TEE) is unlikely to immediately change management, is invasive, and has low yield for finding an embolic source of stroke in patients who are in sinus rhythm. TEE can be considered in certain patients with stroke if they are young and have no apparent risk factors for stroke or if unusual causes are suspected, such as cardiac tumor, patent foramen ovale, aortic arch atherosclerosis, or endocarditis.

KEY POINT

- In a patient with a transient ischemic attack, carotid duplex ultrasonography is an inexpensive, readily available, and noninvasive imaging modality for identifying high-grade stenosis and the possible need for surgery.

Bibliography

Yaghi S, Willey JZ, Khatri P. Minor ischemic stroke: Triaging, disposition, and outcome. Neurol Clin Pract. 2016;6:157-163. [PMID: 27104067]

Item 21 Answer: C

Educational Objective: Diagnose Huntington disease.

The most likely diagnosis is Huntington disease. His history of psychiatric disease, impulsivity, and substance abuse and clinical examination findings of executive dysfunction, dysarthria, incoordination, and ataxia are consistent with Huntington disease. His nonsuppressible flowing and variable movements are consistent with chorea, a major manifestation of Huntington disease. A positive family history is common in patients affected by this autosomal dominant disorder, but in its absence, a family history of associated conditions is suggestive. His father's prominent psychiatric disease may have led to suicide before onset of the motor features of Huntington disease; young onset parkinsonism is a common presentation in younger patients with the disease. Tetrabenazine and deutetrabenazine are the most appropriate treatments of chorea in this disorder.

Creutzfeldt-Jakob disease (CJD) is the most common form of prion disease in humans. Onset usually occurs in the seventh decade of life. The most prominent neurologic sign is disordered cognition. Typically, patients also have motor signs, such as ataxia or spasticity, vague sensory problems, or changes in visual perception. Myoclonus is common. Progressive neurologic decline resulting in death occurs rapidly, typically within 6 to 12 months. This patient's duration of symptoms is likely too long for CJD.

Behavioral-variant frontotemporal dementia (FTD) is associated with prominent changes in behavior, personality, or executive function. Apathy, diminished interest, loss of empathy, lack of initiative, increased emotionality, disinhibition, euphoria, impulsivity, changes in eating behaviors, hyperorality, and compulsiveness are the most common symptoms. Motor neuron disease, including amyotrophic lateral sclerosis, is seen in approximately 15% of patients preceding, simultaneous with, or after the diagnosis of FTD. Chorea is not typical.

The four cardinal signs of Parkinson disease are resting tremor, bradykinesia, cogwheel rigidity, and gait/postural impairment. Resting tremor is characteristically unilateral at onset and remains asymmetric. This patient's clinical features, including impulsivity, ataxia, hyperreflexia, and unprovoked chorea, are not consistent with Parkinson disease.

KEY POINT

- Huntington disease is an autosomal dominant disorder characterized by psychiatric disease, impulsivity, and clinical examination findings of executive dysfunction, dysarthria, incoordination, and ataxia; chorea is a major manifestation of Huntington disease.

Bibliography

Dayalu P, Albin RL. Huntington disease: pathogenesis and treatment. Neurol Clin. 2015;33:101-14. [PMID: 25432725] doi:10.1016/j.ncl.2014.09.003

Item 22 Answer: B

H

Educational Objective: Manage a mild traumatic brain injury.

This patient should have CT of the head without contrast. He sustained a mild traumatic brain injury (TBI), defined as head injury due to contact and/or acceleration or deceleration

H CONT.

forces, and now reports headache. Guidelines recommend imaging with noncontrast CT for patients exposed to mechanisms of injury perceived to be dangerous. These include falls from greater than 3 feet or 5 stairs, vehicular ejection, or vehicle-pedestrian motor vehicle collisions. Age greater than 60 years also is considered an indication for imaging, as are severe headache, vomiting, Glasgow Coma Scale score less than 15, focal deficit(s), posttraumatic seizure, coagulopathy, or persistent drowsiness or amnesia. Most patients with mild TBI will not require brain imaging.

Contrast administration with CT is helpful in the evaluation of malignant, vascular, and some inflammatory disorders of the nervous system. However, the addition of contrast to head CT adds nothing to the evaluation of acute head injury. Visualization of skull fracture and acute intracranial hemorrhage is best accomplished through noncontrasted head CT.

Hospital observation of patients with mild TBI may be indicated for those with intractable headache or vomiting, focal neurologic deficits, or persistent impairment of memory or consciousness but not for this patient with less severe symptoms. In all of these settings, however, patients should first undergo head CT to exclude intracranial hemorrhage. Hospital admission without imaging would be inappropriate for patients with TBI.

Intravenous prochlorperazine is indicated in the management of acute migraine in the emergency department. This patient describes neither nausea nor headache compatible with migraine.

KEY POINT

- Guidelines recommend imaging with noncontrast CT for patients with mild traumatic brain injury (TBI) who are exposed to dangerous mechanisms of injury, such as falls from greater than 3 feet or 5 stairs, vehicular ejection, or vehicle-pedestrian motor vehicle collisions; other indications for head CT in mild TBI include age older than 60 years, severe headache, vomiting, Glasgow Coma Scale score of less than 15, focal deficit(s), posttraumatic seizure, coagulopathy, or persistent drowsiness or amnesia.

Bibliography

Jagoda AS, Bazarian JJ, Bruns JJ, et al; American College of Emergency Physicians; Centers for Disease Control and Prevention. Clinical policy: neuroimaging and decision making in adult mild traumatic brain injury in the acute setting. Ann Emerg Med. 2008;52(6):714-48. [PMID: 19027497] doi: 10.1016/j.annemergmed.2008.08.021

Item 23 Answer: D

Educational Objective: Diagnose myasthenia gravis.

Myasthenia gravis can present with pronounced weakness of cervical or bulbar muscles. Fluctuation in weakness, with a fatigable pattern that worsens later in the day, suggests this neuromuscular junction disorder. In the setting of probable myasthenia gravis, seronegative status for acetylcholine receptor antibodies should trigger testing for muscle-specific kinase (MuSK) antibodies, which are positive in half of seronegative patients. Weakness of cervical extension, such as this patient exhibits, is a hallmark of MuSK antibody–positive myasthenia gravis. Although nerve conduction studies using a special protocol for repetitive stimulation can reveal a pattern of decrementing weakness in neuromuscular junction disorders, this protocol is not part of routine electromyography. Therefore, if suspicion for myasthenia gravis is high, a repetitive stimulation protocol should be specifically requested.

Although amyotrophic lateral sclerosis can present with prominent bulbar and cervical weakness, the fluctuating nature of the weakness, the absence of tongue weakness or fasciculations and of upper motor neuron signs, and the negative electromyography (EMG) findings make this an unlikely diagnosis.

Inclusion body myositis is a progressive inflammatory myopathy that can present with bulbar, forearm flexor, and quadriceps weakness. The absence of additional muscle involvement, the normal creatine kinase level, and the normal limb findings on needle EMG rule out this entity.

Multiple sclerosis (MS) can cause bulbar weakness secondary to central demyelination. Focal neck extensor weakness is atypical. The patient's history and normal MRI exclude MS.

Polymyositis also can present with head drop, but often proximal limb muscles are involved. In addition, a normal creatine kinase level and normal results on routine limb EMG rule out this entity.

KEY POINT

- In a patient with fluctuating weakness of the cervical muscles that worsens in the evening, myasthenia gravis should be suspected; weakness of cervical extension is a hallmark of muscle-specific kinase antibody–positive myasthenia gravis.

Bibliography

Sanders DB, Guptill JT. Myasthenia gravis and Lambert-Eaton myasthenic syndrome. Continuum (Minneap Minn). 2014;20:1413-25. [PMID: 25299290] doi:10.1212/01.CON.0000455873.30438.9b

Item 24 Answer: C

Educational Objective: Diagnose mild cognitive impairment.

The patient's symptoms of subjective cognitive problems, near-normal function, and objective cognitive impairment (score of 1/5 on the delayed recall section of the Montreal Cognitive Assessment) are most consistent with a diagnosis of mild cognitive impairment (MCI), amnestic type. MCI is a cognitive state between normal aging and dementia characterized by a decline in cognitive functioning that is greater than what is expected with normal aging but has not resulted in significant functional disability. The suggestive MRI evidence of minimal hippocampal atrophy is a biomarker conferring a risk of symptom progression. Given her objective

performance on cognitive tests and the noted MRI changes, the patient has an annual risk of developing Alzheimer disease of 5% to 15%.

In contrast to MCI, dementia is a progressive deterioration of cognitive function severe enough to impair occupational or social functioning. Alzheimer disease is the most common type of dementia (60%-80%). Whereas typical Alzheimer disease presents with the insidious development of recent memory loss, as this patient has experienced, she lacks the functional impairment that is a hallmark of dementia.

Multiple relationships between depression and cognitive impairment have been reported in the literature: late-life depression may lead to prodromal Alzheimer disease; depression may be a risk factor for future development of cognitive impairment, dementia, and Alzheimer disease; cerebrovascular disease can precipitate late-life depression; and cognitive impairment itself can lead to depression. More than half of patients with late-life major depression exhibit clinically significant cognitive impairment, most frequently affecting processing speed, executive function, and visuospatial ability. However, this patient's depression screening was negative, and thus depression is unlikely to account for her symptoms.

Normal aging can be associated with memory problems, but cognitive testing shows functioning within the normal range. In contrast, this patient's verbal learning and memory performance are 2 SDs below that of an age- and education-matched control population and are not consistent with normal aging.

KEY POINT

- Mild cognitive impairment is a cognitive state between normal aging and dementia characterized by a decline in cognitive functioning that is greater than what is expected with normal aging but has not resulted in significant functional disability.

Bibliography

Petersen RC. Clinical practice. Mild cognitive impairment. N Engl J Med. 2011;364:2227-34. [PMID: 21651394] doi:10.1056/NEJMcp0910237

Item 25 Answer: D

Educational Objective: Evaluate urinary symptoms in patients with multiple sclerosis.

This patient should undergo urodynamic testing. Her symptoms and history of multiple sclerosis (MS) suggest the presence of a neurogenic bladder. Given the mix of symptoms of urgency and frequency (symptoms of an overactive, spastic bladder) plus hesitancy and retention (symptoms of a hypotonic bladder or overactive sphincter), the patient has aspects of both hypertonic and hypotonic bladder. She also may have bladder sphincter dyssynergia, in which the contraction of the bladder wall is not properly timed with relaxation of the urinary sphincter. Management of complicated forms of neurogenic bladder involves proper diagnosis through urodynamic testing (which will guide medication choices), potential use of urinary catheterization, and monitoring of postvoid residuals while the patient is treated to avoid urinary retention. Involvement of a urologist is often required.

Dalfampridine has been shown to improve walking speed in patients with MS. Although the patient says that incontinence occurs when she is unable to get to the bathroom fast enough, use of this medication would not address the underlying cause of her urinary symptoms. Further, frequent urinary tract infections are a common adverse effect of this medication, and thus using it without first addressing her current urinary symptoms would be counterproductive.

Urinary frequency and urgency are more readily managed than other patterns of bladder dysfunction and are often amenable to abstinence from caffeine, timed voids, and anticholinergic medications, such as oxybutynin or tolterodine. Patients with urinary hesitancy or retention, such as this patient, should not be treated with anticholinergic agents because these medications can worsen retention and lead to predisposition to urinary tract infections. This patient with mixed bladder symptoms should be evaluated with urodynamic testing.

Solifenacin has been shown to reduce symptoms of overactive bladder in patients with MS. However, this patient's mixed bladder symptoms suggest that she is prone to urinary retention. Use of this medication without concurrent use of catheterization and monitoring of postvoid residuals would result in worsened urinary retention and predispose the patient to more frequent urinary tract infections and, possibly, bladder cancer.

KEY POINT

- In a patient with multiple sclerosis and mixed urinary symptoms that suggest both a hypertonic and a hypotonic bladder, urodynamic testing to guide medication choices is appropriate, as are the potential use of urinary catheterization and monitoring of postvoid residuals while the patient is treated.

Bibliography

Phé V, Chartier-Kastler E, Panicker JN. Management of neurogenic bladder in patients with multiple sclerosis. Nat Rev Urol. 2016;13:275-88. [PMID: 27030526] doi:10.1038/nrurol.2016.53

Item 26 Answer: D

H

Educational Objective: Treat pulmonary embolism in patients with primary brain tumors.

This patient should receive intravenous heparin. Venous thromboembolism (VTE) is a common complication in patients with brain tumors, occurring in up to 30% of patients with high-grade glioma. Risk of VTE is correlated with higher-grade malignancies and is associated with release of the potent procoagulant tissue factor. Other factors, including immobilization and recent surgery, increase the risk. The risk of intracranial hemorrhage with the use of anticoagulants

H CONT

complicates the management of VTE in patients with brain tumor, including patients undergoing brain surgery. Although brain tumors have a risk of hemorrhage, therapeutic anticoagulation is generally considered safe. Intravenous heparin is the best choice for this patient because it has a short half-life and is reversible should hemorrhage occur. Although evidence does not support routine use of preanticoagulation neuroimaging to assess for hemorrhage, noncontrast head CT can be considered and is the most cost-effective test in this situation.

Apixaban is not indicated. Although non–vitamin K oral anticoagulants are a recommended therapy for VTE, evidence is insufficient to support their use in the setting of central nervous system tumors.

Inferior vena cava (IVC) filter placement is not indicated. IVC filters incur an increased risk of subsequent deep venous thrombosis and should be reserved for patients with an absolute contraindication to anticoagulation. The presence of a primary brain tumor and recent biopsy do not absolutely preclude anticoagulation.

Alteplase, a tissue plasminogen activator, is contraindicated in most CNS tumors. This class of drugs can be considered in low-risk tumors, such as meningioma, but not high-risk tumors, such as glioblastoma multiforme.

Subcutaneous low-molecular-weight heparin (LMWH) is an effective treatment for VTE but should be avoided in this patient because of her kidney dysfunction. LMWH also lacks an effective reversal agent and has a prolonged duration of action, making it a less optimal choice in a patient at increased risk of bleeding.

KEY POINT

- In patients with glioblastoma multiforme and pulmonary embolism, anticoagulation with heparin is the most appropriate treatment.

Bibliography

Jo JT, Schiff D, Perry JR. Thrombosis in brain tumors. Semin Thromb Hemost. 2014;40:325-31. [PMID: 24599439] doi:10.1055/s-0034-1370791

Item 27 Answer: D

Educational Objective: Diagnose POEMS syndrome.

The most likely diagnosis is POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes). POEMS syndrome is characterized by the presence of a monoclonal plasma cell disorder, peripheral neuropathy, and one or more of the following: osteosclerotic myeloma, Castleman disease (angiofollicular lymph node hyperplasia), elevated serum vascular endothelial growth factor, organomegaly, endocrinopathy, edema, typical skin changes, and papilledema. His clinical presentation, including splenomegaly, skin lesions (hyperpigmentation and angiomas), endocrine disease (hypothyroidism), peripheral neuropathy, and λ monoclonal gammopathy support the diagnosis of POEMS syndrome. POEMS syndrome is typically secondary to an underlying cancer; identification and treatment of the underlying cancer leads to improvement of the neuropathy.

Amyotrophic lateral sclerosis (ALS) is characterized by upper motor neuron signs (such as hyperreflexia, spasticity, and an extensor plantar response) coexistent with lower motor neuron findings (such as atrophy and fasciculation). Sensory deficits are characteristically absent, and sensory nerve conduction studies are often normal in ALS. These findings are not consistent with this patient's presentation.

The classic presentation of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is generalized areflexia and progressive or relapsing symmetric sensory and motor neuropathy. CIDP resembles POEMS syndrome in its neurologic manifestations, but the presence of monoclonal gammopathy, splenomegaly, and skin changes makes this diagnosis unlikely.

Mitochondrial myopathy can present with significant variability and may cause fatigue, myalgia, ophthalmoplegia, and various extramuscular manifestations. Mitochondrial myopathies should be suspected in the presence of multiorgan involvement and maternal transmission. In this patient, the presence of sensory deficits and neuropathic findings on needle electromyography are not consistent with a myopathy.

KEY POINT

- POEMS syndrome is characterized by the presence of a monoclonal plasma cell disorder, peripheral neuropathy, and one or more of the following: osteosclerotic myeloma, Castleman disease (angiofollicular lymph node hyperplasia), elevated serum vascular endothelial growth factor, organomegaly, endocrinopathy, edema, typical skin changes, and papilledema.

Bibliography

Rison RA, Beydoun SR. Paraproteinemic neuropathy: a practical review. BMC Neurol. 2016;16:13. [PMID: 26821540] doi:10.1186/s12883-016-0532-4

Item 28 Answer: C

Educational Objective: Diagnose focal seizures.

The patient is experiencing focal seizures with altered awareness (formerly known as complex partial seizures or focal dyscognitive seizures). These seizures typically are infrequent, are associated with "warning" symptoms (aura, which may consist of an epigastric rising sensation or a feeling of déjà vu), last more than 30 seconds, have associated mouth or limb automatisms (semipurposeful repetitive movements), and are followed by confusion and/or exhaustion. Patients who experience this type of seizure often have no memory of the episode itself.

Absence seizures may also present with staring and confusion but typically are more frequent (occurring multiple times per day), last less than 15 seconds, and are associated with immediate recovery, to the point that patients and witnesses may not realize a seizure has occurred. Absence seizures are most characteristic of childhood absence epilepsy, which typically resolves by puberty but also can occur in adults with idiopathic generalized epilepsy syndromes.

Atonic seizures involve the abrupt loss of muscle tone and typically are associated with falling down and a brief loss of consciousness lasting only a few seconds. Atonic seizures are one cause of "drop attacks" in which the patient will suddenly, and without warning symptoms, drop to the ground. Individuals with drop attacks can get themselves up and typically will deny loss of consciousness. Other causes of drop attacks include cataplexy, vertebrobasilar transient ischemic attack, and vestibular pathologies. The patient's seizures do not match the description of atonic seizures.

Myoclonic seizures generally consist of a single jerk of the entire body, usually last less than 1 second, and are associated with retained awareness and no postictal confusion. In contrast, this patient's seizures last at least 45 seconds and are characterized by staring, chewing motions, repetitive grabbing of her clothes, and a 20-minute postseizure period of exhaustion and sleepiness.

KEY POINT

- Focal seizures with altered awareness typically are infrequent, are associated with warning symptoms (aura), last more than 30 seconds, have associated mouth or limb automatisms (semipurposeful repetitive movements), and are followed by confusion and/or exhaustion.

Bibliography

Dobrin S. Seizures and epilepsy in adolescents and adults. Dis Mon. 2012:58:708-29. [PMID: 23149523] doi:10.1016/j.disamonth.2012.08.011

Item 29 Answer: B

Educational Objective: Diagnose idiopathic brachial plexopathy.

Idiopathic brachial plexopathy (also known as neuralgic amyotrophy and Parsonage-Turner syndrome) is characterized by subacute severe pain followed by resolution of pain and progressive weakness and atrophy involving the shoulder girdle and upper extremity muscles. This syndrome often is triggered by a preceding event, such an infection or surgery. In this patient, motor and sensory involvement in the territory of multiple nerves and roots is consistent with a process involving the brachial plexus. Imaging rules out a pathologic process at the level of the cervical spine. An iatrogenic traumatic plexopathy caused by surgery is unlikely, given the absence of weakness immediately after the procedure and the abdominal location of the procedure.

Although compressive polyradiculopathy secondary to degenerative spinal disease can simulate plexopathy, with a presentation consisting of mixed motor, sensory, and pain symptoms in multiple nerve root distributions, negative cervical imaging rules out this entity in this patient.

Lambert-Eaton syndrome is associated with neuromuscular junction dysfunction. Sensory deficits, prominent pain, and focal weakness are atypical.

Statins can cause a toxic myopathy, but sensory deficits are not expected findings in myopathies, and asymmetry also is atypical. Moreover, in this patient, rapid weakness appeared after resolution of pain, whereas in statin myopathy, pain often persists along with muscle necrosis-induced weakness.

KEY POINT

- Idiopathic brachial plexopathy is characterized by subacute severe pain followed by resolution of pain and progressive weakness and atrophy involving the shoulder girdle and upper extremity muscles; this syndrome often is triggered by a preceding event, such as an infection or surgery.

Bibliography

Van Eijk JJ, Groothuis JT, Van Alfen N. Neuralgic amyotrophy: an update on diagnosis, pathophysiology, and treatment. Muscle Nerve. 2016;53:337-50. [PMID: 26662794] doi:10.1002/mus.25008

Item 30 Answer: B

Educational Objective: Treat Tourette syndrome.

This patient should be treated with clonidine. The suppressible stereotyped neck movements and premonitory sensory cues are consistent with motor tics, and the history of other motor (eye rolling) and vocal (throat clearing) tics, childhood onset, duration of greater than 1 year, and comorbidity of obsessive-compulsive disorder (OCD) are consistent with the diagnosis of Tourette syndrome. Clonidine is a first-line agent used to treat Tourette syndrome. Anti-tic medications should be considered when tics interfere with education, daily function, or work. Other first-line medications include guanfacine, topiramate, and the dopamine-depleter agent tetrabenazine. Second-line treatments include antipsychotic agents (such as haloperidol), but their benefit should be weighed against risk of tardive dyskinesia.

Although botulinum toxin can be considered as an off-label option in the treatment of severe refractory cervical tics, this patient has not yet tried medication to control her tics. Botulinum toxin also is indicated in the treatment of cervical dystonia, but this disorder is not consistent with her clinical findings of suppressibility and the absence of sustained motor activity.

Treatment of mild tics includes reassurance, treatment of psychiatric comorbidities (such as the sertraline she already takes for OCD), and cognitive behavioral therapy to teach patients about tic diversion techniques (such as the foot taps she initiates after sensory premonitory cues). Given that this patient's symptoms have persisted, pharmacologic therapy for Tourette syndrome is appropriate.

Haloperidol should not be considered before a trial of first-line anti-tic medications is attempted. Clonidine appears to be better tolerated than antidopaminergic drugs, such as haloperidol or risperidone. Additionally, the tardive dyskinesia that can result from neuroleptic agents may take months to years to resolve after discontinuation of the culprit drug.

KEY POINT

- First-line agents used to treat Tourette syndrome when the associated tics interfere with education, daily function, or work are clonidine, guanfacine, topiramate, and tetrabenazine.

Bibliography

Kurlan RM. Treatment of Tourette syndrome. Neurotherapeutics. 2014; 11:161-5. [PMID: 24043501] doi:10.1007/s13311-013-0215-4

Item 31 Answer: B

Educational Objective: Treat migraine with aura.

This patient should be treated with sumatriptan. He has a history of episodic migraine with typical aura that is no longer responsive to appropriate NSAIDs. Guidelines recommend the use of triptans in patients with moderate to severe migraine for whom NSAID therapies are not effective. Triptans (5-hydroxytryptamine receptor 1B [5-HT1B] and 5-hydroxytryptamine receptor 1D [5-HT1D] agonists) are migraine-specific agents with a direct impact on the trigeminovascular activation associated with migraine attacks. Activation of the 5-HT1B receptor reverses vasodilation. Binding to the 5-HT1D receptors on trigeminal nerve terminals blocks release of vasoactive and inflammatory mediators, such as calcitonin gene-related peptide. This second action is likely more important in the interruption of nociceptive transmission. Unless medication overuse headache is a concern, patients should be advised to treat at the first sign of pain. Because migraine intensity is highly variable, occasional attacks that are less responsive to medication are to be expected. Contraindications include coronary, cerebral, or peripheral vascular disease; uncontrolled hypertension; and migraine with brainstem or hemiplegic auras.

Guidelines recommend against the use of opioid agents, such as hydrocodone, in migraine management. Concerns include the potential for dependence or addiction and, more importantly, an increased risk of transformation from episodic to chronic migraine. In patients with migraine, opioids are associated with a 44% increase in risk of headache progression over 1 year and butalbital compounds with a 70% increase. Both drug classes should be used cautiously and only when more appropriate acute therapies are contraindicated.

Level A evidence exists for migraine prevention with topiramate. Because this patient has only two episodes of migraine per month, prophylactic medication is not indicated.

Verapamil has no established benefit in the acute treatment or prevention of migraine.

KEY POINT

- For patients with a history of episodic migraine with typical aura that no longer responds to appropriate NSAIDs, guidelines recommend the use of triptans.

Bibliography

Marmura MJ, Silberstein SD, Schwedt TJ. The acute treatment of migraine in adults: the American Headache Society evidence assessment of migraine pharmacotherapies. Headache. 2015;55(1):3-20. [PMID: 25600718] doi: 10.1111/head.12499

Item 32 Answer: B

H

Educational Objective: Diagnose convulsive syncope.

The patient most likely had an episode of convulsive syncope. Syncope is nontraumatic, complete transient loss of consciousness and loss of postural tone. Onset is abrupt and recovery is spontaneous, rapid, and complete. Neurally mediated syncope, the most common type of syncope, generally occurs with standing and is associated with a prodrome of nausea, lightheadedness, and warmth. It may follow cough, urination, defecation, pain, or laughing. This patient's tunnel vision, palpitations, short duration of loss of consciousness (<1 minute), and immediate and complete neurologic recovery is typical of syncope. Movements and shaking (in this instance, nonepileptic myoclonus) are common with syncope. In fact, syncope without any movements is the exception rather than the rule.

Atonic seizures can be associated with falling and brief loss of consciousness with decreased tone, but their duration is much briefer (a few seconds only) than that of syncope, and they usually do not have warning symptoms, such as tunnel vision or palpitations.

Generalized tonic-clonic seizures have increased tone at the onset (tonic phase), followed by rhythmic, synchronous jerking of all limbs (clonic phase), typically for more than 1 minute. These seizures are followed by confusion, lethargy, and (sometimes) combativeness. This patient's seizure, especially her normal neurologic state after regaining consciousness, does not match this description.

Myoclonic seizures are very brief, typically lasting less than 1 second, and usually involve synchronous limb jerking (all limbs shaking together at the same time). The duration of this patient's seizure and her asynchronous limb jerking are not consistent with myoclonic seizure.

Tonic seizures may involve brief loss of consciousness and falling, but there is no associated aura (prodrome or warning symptoms). Additionally, patients generally have increased tone that leads to the fall.

KEY POINT

- Convulsive syncope is a seizure type typically associated with tunnel vision, palpitations, short duration of loss of consciousness (<1 minute), movements and shaking, and immediate and complete neurologic recovery.

Bibliography

Lempert T, Bauer M, Schmidt D. Syncope: a videometric analysis of 56 episodes of transient cerebral hypoxia. Ann Neurol. 1994;36:233-7. [PMID: 8053660] doi: 10.1002/ana.410360217

Answers and Critiques

Item 33 Answer: D

Educational Objective: Evaluate for stroke-related sleep-disordered breathing with polysomnography.

This patient should undergo polysomnography. Sleep-disordered breathing is highly prevalent in patients with any form of stroke and is a leading cause of fatigue, headaches, and difficult-to-control hypertension in these patients. Given her recent stroke and elevated BMI, she is at particularly high risk for sleep-disordered breathing, which is best detected by polysomnography. Measurement tools, such as the Epworth Sleepiness Scale, also may help in patients with stroke but have not been well validated in this population. Treatment of sleep-disordered breathing can improve this patient's energy level, fatigue, and blood pressure.

Discontinuation of atorvastatin would be reasonable only if the patient were experiencing significant adverse effects, such as myalgia, rhabdomyolysis, or persistently elevated liver transaminase levels. Atorvastatin is effective in reducing the risk of recurrent ischemic stroke and is a key component of secondary risk reduction in this patient. Fatigue may be a side effect of atorvastatin but would not prompt discontinuation of the medication.

Fluoxetine should not be initiated in this patient, who already is taking another antidepressant medication and has no symptoms of depression other than fatigue. Although fluoxetine has been studied as an agent to promote motor recovery independent of its effect on depression in the acute stroke setting, the current evidence supporting this indication is lacking.

An MRI of the brain may be indicated if there is concern for a specific intracranial structural process, such as a new stroke or an underlying intracranial mass. These processes, however, are usually associated with specific neurologic symptoms or focal neurologic findings on examination. Fatigue is a nonspecific symptom that is not attributable to a specific region of the brain and is unlikely to be the sole clinical manifestation of a new stroke or mass.

KEY POINT

- Sleep-disordered breathing is highly prevalent in patients with any form of stroke, and the best diagnostic test is polysomnography.

Bibliography

Kernan WN, Ovbiagele B, Black HR, Bravata DM, Chimowitz MI, Ezekowitz MD, et al; American Heart Association Stroke Council, Council on Cardiovascular and Stroke Nursing, Council on Clinical Cardiology, and Council on Peripheral Vascular Disease. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2014;45:2160-236. [PMID: 24788967] doi:10.1161/STR.0000000000000024

Item 34 Answer: B

Educational Objective: Treat multiple sclerosis in a patient with hepatic disease.

This patient should receive glatiramer acetate. He has newly diagnosed multiple sclerosis (MS) and should begin a disease-modifying therapy. Definitive treatment of MS relies less on addressing relapses as they occur than on preventing relapse occurrence (and the associated accrual of disability) in the first place. This prevention is achieved with MS disease-modifying therapies, a series of immunomodulatory or immunosuppressive medications that have been shown to reduce the risk of relapse, disability progression, and new lesion formation on MRI. Several disease-modifying therapies have been approved by the FDA for use in relapsing-remitting MS, each differing in their route of administration, mechanism of action, and potential adverse effects. Generally, most physicians recommend self-injection medications (one of the interferon beta preparations or glatiramer acetate) as first-line agents, given their favorable risk profiles. Glatiramer acetate, a copolymer of four amino acids, is administered daily or several times weekly by subcutaneous injection. Glatiramer acetate and high-dose interferon beta formulations exhibit similar reductions in relapse rates compared with placebo and are equivalent in head-to-head studies. In choosing which therapy is most appropriate to recommend, the clinician should consider all comorbid conditions. Given the patient's history of liver disease, the most appropriate treatment is glatiramer acetate. This medication has no known adverse effects on liver function.

Liver dysfunction is a potential adverse effect of fingolimod, the interferon beta preparations, and natalizumab. Therefore, none of these drugs would be the best choice for this patient. Additionally, natalizumab is recommended for patients who have not responded to previous disease-modifying therapy. Because this patient has not yet been treated for his MS, use of natalizumab as a first-line agent would be inappropriate.

KEY POINT

- Interferon beta preparations or glatiramer acetate are considered first-line agents for relapsing-remitting multiple sclerosis given their favorable risk profiles; glatiramer acetate is preferred in patients with liver disease.

Bibliography

Wingerchuk DM, Weinshenker BG. Disease modifying therapies for relapsing multiple sclerosis. BMJ. 2016;354:i3518. [PMID: 27549763] doi:10.1136/bmj.i3518

Item 35 Answer: A

Educational Objective: Diagnose amyotrophic lateral sclerosis.

This patient most likely has amyotrophic lateral sclerosis (ALS). Diagnosis requires fulfillment of positive diagnostic criteria and exclusion of mimics. Positive diagnostic criteria for ALS include the presence of clinical upper (hyperreflexia, Hoffman sign, clonus) and lower (atrophy, fasciculation, weakness) motor neuron signs and electromyographic lower motor neuron signs in two (probable ALS) or more (definitive ALS) body regions (upper and lower limbs,

paraspinal, bulbar). Because hyperthyroidism can lead to a combination of upper and lower motor neuron findings that may mimic ALS, it must be excluded before diagnosis. Other important mimics include structural brain and cervical spinal lesions, vitamin B_{12} and copper deficiency, Lyme disease, and hyperparathyroidism.

Charcot-Marie Tooth (CMT) disease is an inherited neuropathy arising from mutations in several genes encoding for myelin formation, structure, and function. The two most common forms are demyelinating (CMT1) and axonal (CMT2). Both share the clinical features of numbness, distal extremity weakness, unsteady gait, areflexia, high arches, hammer toes, and atrophy of distal extremity muscles and foreleg muscles ("stork leg" deformity). This patient's findings are not consistent with CMT disease.

Granulomatosis with polyangiitis is an antineutrophil cytoplasmic antibody-associated vasculitis. Areas most commonly affected by the vasculitis include the airways, lung parenchyma, kidneys, skin, eyes, and nervous system. The vasculitic neuropathy can present as mononeuropathy multiplex and are associated with focal or multifocal weakness. However, these entities are associated with pain and sensory deficits and not with upper motor neuron signs.

The Miller Fisher variant of Guillain Barré syndrome typically presents with subacute ataxia, areflexia, and ophthalmoplegia, with or without diffuse weakness. Antibodies to GQ1b (a ganglioside component of nerve) are present in more than 85% of patients. The patient's findings are not compatible with the Miller Fisher variant.

KEY POINT

- Amyotrophic lateral sclerosis is characterized by upper motor neuron signs (hyperreflexia, spasticity, and an extensor plantar response) coexistent with lower motor neuron findings (atrophy and fasciculation); sensory deficits are characteristically absent.

Bibliography

Kiernan MC, Vucic S, Cheah BC, Turner MR, Eisen A, Hardiman O, et al. Amyotrophic lateral sclerosis. Lancet. 2011;377:942-55. [PMID: 21296405] doi:10.1016/S0140-6736(10)61156-7.

H

Item 36 Answer: B

Educational Objective: Diagnose cavernous sinus thrombosis.

This patient has right cavernous sinus thrombosis. Painful ophthalmoplegia affecting multiple nerves involved with extraocular movement indicates a pathologic process in the superior orbital fissure or cavernous sinus. Proptosis and chemosis are typical because of marked venous congestion. Thrombosis of the cavernous sinus most commonly arises from contiguous spread of infection, most likely from nasal, sinus, and dental sites. *Staphylococcus aureus* is the most common organism and is found in 70% of affected patients. Progression to bilateral involvement of the cavernous sinuses may be seen within 1 to 2 days of presentation. Brain MRI is more sensitive than head CT in confirming the diagnosis; magnetic resonance venography also is frequently helpful. Lumbar puncture is required to exclude meningeal involvement. This condition is life-threatening and requires immediate administration of antibiotics and consideration of surgical drainage.

Dissection of the carotid artery can present with orbital pain, partial Horner syndrome (ptosis and miosis only), and ipsilateral signs of cerebral or retinal ischemia. Ptosis with Horner syndrome is partial, whereas that seen with oculomotor nerve palsy is complete. Ophthalmoplegia would be highly unusual and proptosis and chemosis unexpected in carotid artery dissection.

Aneurysms of the posterior communicating artery may expand and present with ipsilateral third nerve palsy but not fourth or sixth nerve palsies. Even without aneurysmal rupture, aneurysmal expansion can provoke ipsilateral or global headache. A fixed dilated pupil, ptosis, and inability to elevate or adduct the globe are noted. Diabetic third nerve palsy may present in a similar fashion but typically spares the pupil.

Vertebral artery dissection often presents with occipital and neck pain and posterior fossa symptoms, such as dysarthria, dysphagia, ataxia, and hemifield visual loss. Ophthalmoplegia, chemosis, and proptosis are not features of this type of dissection.

KEY POINT

- Painful ophthalmoplegia affecting multiple nerves involved with extraocular movement indicates a pathologic process in the superior orbital fissure or cavernous sinus.

Bibliography

Sparaco M, Feleppa M, Bigal M. Cerebral venous thrombosis and headache - a case-series. Headache. 2015 Jun;55(6):806-14. doi: 10.1111/head.12599 [PubMed 26084237] doi:10.1111/head.12599

Item 37 Answer: A

H

Educational Objective: Treat symptomatic carotid artery stenosis.

Carotid endarterectomy is the most appropriate next step in management. This patient has an ischemic stroke due to symptomatic extracranial internal carotid artery stenosis, which is associated with a high short-term risk of recurrent stroke despite best medical therapy. Guidelines recommend carotid endarterectomy for patients with symptomatic carotid artery stenosis within 2 weeks of transient ischemic attack or nondisabling stroke. The procedure is safe and reduces the risk of ischemic stroke. The choice of revascularization procedure is largely driven by medical comorbidities and by the expertise of locally available surgeons. However, a consistent finding has been a higher risk of perioperative stroke with stenting. In a clinical trial that enrolled symptomatic patients with carotid stenosis in Europe, endarterectomy was associated with a lower risk of recurrent stroke risk than was stenting.

H CONT.

Carotid stenting may be considered in patients with significant cardiac comorbidities that would preclude surgery under general anesthesia because of safety considerations; this patient has no such comorbidities. Patients should be counseled that stenting is associated with a higher risk of perioperative stroke, according to randomized clinical trials of symptomatic patients.

Diagnostic angiography is not routinely indicated to confirm the degree of stenosis before carotid revascularization, given the associated risk of vessel injury. Additionally, sufficient information is available from both the magnetic resonance angiogram and the carotid duplex ultrasound.

A 30-day period of outpatient telemetry is not required to diagnose the stroke subtype in this patient with established high-grade stenosis in the carotid artery. Evaluation for occult atrial fibrillation is recommended for patients in whom the cause of stroke has not been identified, especially if an embolic cause (suggested by infarcts involving the brain surface or in the distribution of more than one cerebral artery) is suspected.

KEY POINT

- Carotid endarterectomy within 2 weeks of transient ischemic attack or nondisabling stroke is safe and reduces the risk of ischemic stroke in patients with symptomatic carotid artery stenosis.

Bibliography

Kernan WN, Ovbiagele B, Black HR, Bravata DM, Chimowitz MI, Ezekowitz MD, et al; American Heart Association Stroke Council, Council on Cardiovascular and Stroke Nursing, Council on Clinical Cardiology, and Council on Peripheral Vascular Disease. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2014;45:2160-236. [PMID: 24788967] doi:10.1161/STR.0000000000000024

Item 38 Answer: C

Educational Objective: Diagnose normal pressure hydrocephalus.

This patient most likely has normal pressure hydrocephalus (NPH) and should undergo lumbar puncture with removal of a large volume of cerebrospinal fluid (CSF) and subsequent measurement of CSF opening pressure. Because NPH is reversible, detecting it early is essential. The triad of gait changes, urinary incontinence, and cognitive impairment is most characteristic of NPH, with gait impairment being the most prominent feature. The MRI shows ventricular dilation typical of normal pressure hydrocephalus. The diagnosis is suggested by an expansion of the entire ventricular system in the absence of sulcal atrophy or an obstruction. A timed gait evaluation performed just before CSF removal and again before 60 minutes have passed since removal is appropriate to confirm the diagnosis. If gait improves after CSF removal, then NPH likely is present and reversal is possible.

Amyloid PET scanning is approved for clinical use in patients with suspected Alzheimer disease. The most prominent early symptom of Alzheimer disease is memory disturbance, not gait disturbance or urinary incontinence. More importantly, however, this imaging test would delay the diagnosis of NPH, a potentially reversible cause of his symptoms.

Although a fluorodeoxyglucose PET scan can be used for pattern recognition of certain dementias, it is a nonspecific test and is unlikely to definitively establish the diagnosis in this patient.

Neuropsychological testing is most helpful in patients with mild symptoms of cognitive impairment, especially in localizing these symptoms. It also can help establish or exclude malingering as the reason for the symptoms. It likely would have limited utility for this patient who had good results on the memory portion of the Mini–Mental State Examination and whose other symptoms are gait impairment and urinary incontinence.

KEY POINT

- In patients with normal pressure hydrocephalus (NPH), lumbar puncture with removal of a large volume of cerebrospinal fluid (CSF) and subsequent measurement of CSF opening pressure can help confirm the diagnosis and determine if the NPH is reversible.

Bibliography

Halperin JJ, Kurlan R, Schwalb JM, Cusimano MD, Gronseth G, Gloss D. Practice guideline: Idiopathic normal pressure hydrocephalus: response to shunting and predictors of response: report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. Neurology. 2015;85:2063-71. [PMID: 26644048] doi:10.1212/WNL.0000000000002193

Item 39 Answer: A

H

Educational Objective: Diagnose autoimmune limbic encephalitis.

This patient most likely has autoimmune limbic encephalitis. New-onset status epilepticus in a previously healthy person suggests the presence of a neurologic autoimmune disorder. This patient has a rapidly progressive neurologic syndrome that is most consistent with autoimmune encephalitis, with antibodies directed against the voltage-gated potassium channel receptor complex (the most common target being the LGI1 antibody). This condition is marked by the presence of hyponatremia, myoclonus, and limbic encephalitis (amnesia, temporal lobe seizures, and confusion). Although many neurologic autoimmune disorders are paraneoplastic, primary autoimmune disorders with no accompanying cancer may occur.

Lyme disease with neurologic involvement typically presents with meningitis or brainstem encephalitis (multiple cranial nerve palsies and confusion) in a patient with a history of rash and arthralgia. Chronic indolent disease may involve cognitive symptoms, but they are typically not acutely progressive, as they are in this patient.

Progressive multifocal leukoencephalopathy typically presents with subacute neurologic symptoms that are focal

H CONT.

(unilateral weakness or numbness, aphasia, cranial nerve palsies) in an immunocompromised patient, with characteristic white matter abnormalities on MRI.

Rapidly progressive dementia, such as Creutzfeldt-Jakob disease, sometimes presents with symptoms similar to this patient's but usually is not accompanied by hyponatremia or focal seizures.

KEY POINT

- The presence of new-onset status epilepticus and progressive confusion in a previously healthy patient strongly suggests a diagnosis of autoimmune limbic encephalitis.

Bibliography

Shin YW, Lee ST, Shin JW, Moon J, Lim JA, Byun JI, et al. VGKC-complex/LGI1-antibody encephalitis: clinical manifestations and response to immunotherapy. J Neuroimmunol. 2013;265:75-81. [PMID: 24176648] doi:10.1016/j.jneuroim.2013.10.005

Item 40 Answer: C

Educational Objective: Evaluate cognitive and functional decline in a patient with depression.

This patient should undergo neuropsychological testing. She has treatment-refractory depression but also cognitive impairment and some functional deficits. Given the progression of the cognitive symptoms, additional diagnostic studies should be pursued to evaluate for cognitive impairment independent of that associated with depression. More than half of patients with late-life major depression exhibit clinically significant cognitive impairment, most frequently affecting processing speed, executive function, and visuospatial ability. Notably, late-life depression may be a prodromal feature of Alzheimer disease. A history should be obtained from the patient and someone well acquainted with the patient who can provide information on current daily functioning relative to premorbid functioning. A tool for identifying and assessing the severity of depression is the Patient Health Questionnaire (PHQ)-9. A score of 5 to 9 indicates mild depression, 10 to 14 moderate depression, 15 to 19 moderately severe depression, and 20 or higher severe depression. In a patient with possible depression-related cognitive and functional decline, a trial of antidepressant therapy is an appropriate first step. Psychotherapy (cognitive-behavioral therapy, psychodynamic therapy, and interpersonal therapy) and psychopharmacology, alone or in combination, are mainstays of treatment and can prove synergistic. Patients who do not respond to full-dose antidepressant monotherapy for 6 weeks may respond to a different antidepressant drug, either from the same or a different class, or the addition of a second antidepressant drug. If the patient does not respond to an adequate trial of therapy, other diagnoses should be considered. Because this patient has not responded to two different antidepressants, the addition of mirtazapine is unlikely to be helpful.

Neuropsychological testing can be useful in identifying a pattern or degree of cognitive impairment that is not typical of depression-related cognitive impairment. When results of neuropsychological testing are more consistent with Alzheimer disease than depression, additional diagnostic studies, such as 18F-fluorodeoxyglucose PET, could be pursued, as could a trial of cognitive enhancers (such as acetylcholinesterase inhibitors).

Although some Alzheimer disease-specific biomarkers can be detected by cerebrospinal fluid (CSF) analysis, abnormal Aβ42 peptide levels are often seen in an older population (30%-50%) in the absence of cognitive impairment. These CSF studies are most helpful in younger patients to discriminate normal from abnormal findings.

A normal head CT scan and normal MRI of the brain do not rule out an underlying neurodegenerative process, particularly if a disease is in its mild stages, and are thus inappropriate in a patient with probable depression as the cause of her symptoms.

KEY POINT

- In a patient with treatment-refractory depression who also has cognitive and functional decline, neuropsychological testing can be useful in identifying a pattern or degree of cognitive impairment that is not typical of depression-related cognitive impairment.

Bibliography

Hashem AH, Gomaa MA, Sadek MN, Khalaf OO. Late versus early onset depression in elderly patients: Vascular risk and cognitive impairment. Curr Aging Sci. 2017. [PMID: 28382870] doi:10.2174/1874609810666170404105634

Item 41 Answer: D

Educational Objective: Evaluate medically intractable epilepsy.

This patient is having ongoing focal seizures with altered awareness (formerly known as complex partial seizures) because of temporal lobe epilepsy despite taking two antiepileptic drugs and should be referred to an epilepsy center for monitoring by video electroencephalography (EEG). Because his epilepsy is medically intractable, he may be a candidate for epilepsy surgery. Video EEG is the first step in determining candidacy for surgery by confirming that the seizures seen on video EEG match the location of abnormal findings on MRI. Temporal lobectomy leads to seizure freedom in 60% to 70% of patients with temporal lobe epilepsy not helped by medication and is the best option for treating this patient.

Although levetiracetam and topiramate are reasonable options for treating this seizure type, and topiramate has the added benefit of migraine prophylaxis, the chance of seizure freedom from an additional drug is only approximately 5% to 10%. Additionally, this patient's migraines are already well controlled, so a prophylactic agent is not required.

Use of a vagus nerve stimulator is a palliative measure, is unlikely to result in freedom from seizures, and should be offered only if resection is not an option.

KEY POINT

- Video electroencephalography is first step in determining candidacy for epilepsy surgery in patients with medically intractable epilepsy.

Bibliography

Nair DR. Management of drug resistant epilepsy. Continuum (Minneap Minn). 2016;22:157-72. [PMID: 26844735] doi:10.1212/CON.0000000000000297

Item 42 Answer: C

Educational Objective: Treat an unruptured intracranial aneurysm.

This patient should be referred for surgical intervention. She has an intracranial aneurysm in the posterior circulation (posterior communicating artery) that is unruptured but now has several features consistent with a high risk of subarachnoid hemorrhage (SAH): size equal to or greater than 7 millimeters, rapid growth, and a cranial nerve deficit, which in this patient is compression of the oculomotor nerve (cranial nerve III) on the right. Although neurosurgical intervention (with clipping or coiling, depending on local expertise) has a potential risk of adverse events, the risk of SAH without surgery is greater. A diagnostic angiogram is likely to be required for operative planning and can be obtained in conjunction with a planned coiling procedure.

The patient's blood pressure is already within the appropriate target of less than 140/80 mm Hg. Given the high risk of rupture, further control of blood pressure (with an agent such as lisinopril) at this point is unwarranted and unlikely to be effective.

Carotid artery dissection is typically recognized by the presence of unilateral pain of the head, neck, or face; partial Horner syndrome (ptosis, miosis); and cerebral or retinal ischemia. Less than one third of patients will have all three components. The patient has no headache or other features on examination that are consistent with an internal carotid artery dissection. The examination is instead consistent with oculomotor nerve (cranial nerve III) palsy. If internal carotid artery dissection were suspected, a magnetic resonance angiogram (MRA) of the neck would be an appropriate next step. It is not indicated in this patient.

A repeat MRA of the brain in 6 months also is inappropriate. This patient has now met several criteria for aneurysm surgery. Additional screening to document further changes in the size of the aneurysm will change nothing, and delaying surgery runs the risk of rupture.

KEY POINT

- Surgical treatment with clipping or endovascular coiling can be considered in patients with symptomatic aneurysms or aneurysms of 7 millimeters or greater in the posterior circulation (posterior communicating and basilar arteries).

Bibliography

Thompson BG, Brown RD Jr, Amin-Hanjani S, Broderick JP, Cockroft KM, Connolly ES Jr, et al; American Heart Association Stroke Council, Council on Cardiovascular and Stroke Nursing, and Council on Epidemiology and Prevention. Guidelines for the Management of Patients With Unruptured Intracranial Aneurysms: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke. 2015;46:2368-400. [PMID: 26089327] doi:10.1161/STR.0000000000000070

Item 43 Answer: D

Educational Objective: Treat psychosis in Parkinson disease.

The dopamine agonist pramipexole should be discontinued in this patient with Parkinson disease psychosis. Dopamine agonists, such as pramipexole, can be used as adjuvant therapy to limit the total dose of levodopa. Dopamine agonists are associated with higher risk of specific adverse effects, including impulse control disorder, punding, sleep attacks, ankle edema, and confusion, that may limit their use, especially in older patients. Impulse control disorder is the increased tendency for compulsive behaviors, such as excessive gambling, shopping, or hypersexuality. Punding is a complex prolonged, purposeless, and stereotyped behavior (such as collecting, sorting, cataloguing, or assembling and disassembling common objects). Sleep attacks involve falling asleep without warning. Medication-induced psychosis, especially visual hallucinations, triggered by dopaminergic medications also is a potential complication of Parkinson disease. All patients with Parkinson disease and psychosis should be evaluated for systemic triggers (such as infection and metabolic disturbance) and major depression. Reducing the dose of levodopa also can be considered after removal of the dopamine agonist, but this step may not be possible because of worsening of motor symptoms (as may occur in this patient given the recurrence of rigidity and slowness before each dose of medication). The decision to treat psychosis with medication adjustments or discontinuation should be based on the presence of distress to patient and caregivers, lack of insight in the patient, and progressive frequency of psychosis.

Pimavanserin, a nondopaminergic atypical antipsychotic agent and selective serotonin 5-hydroxytryptamine receptor 2A inverse agonist, is the only FDA-approved medication for Parkinson psychosis. Quetiapine and clozapine also can be considered in this setting, but most other atypical antipsychotic agents (including aripiprazole, risperidone, and olanzapine) and all typical (first-generation) antipsychotic agents should be avoided. Atypical antipsychotic agents should be used only after discontinuation of any non-levodopa Parkinson medication and resolution of systemic triggers.

KEY POINT

- Dopamine agonists are associated with higher risk of specific adverse effects, including psychosis, impulse control disorder, punding, sleep attacks, ankle edema, and confusion, that may limit their use, especially in older patients with Parkinson disease.

Bibliography

Samudra N, Patel N, Womack KB, Khemani P, Chitnis S. Psychosis in Parkinson disease: A review of etiology, phenomenology, and management. Drugs Aging. 2016;33:855-63. [PMID: 27830568]

H

Item 44 Answer: A

Educational Objective: Diagnose a subarachnoid hemorrhage.

The patient should undergo lumbar puncture. He has had a new thunderclap headache (severe headache that reaches maximum intensity within 1 minute) that has lasted 12 hours. Although a head CT scan without contrast was normal, an aneurysmal subarachnoid hemorrhage (SAH) is not always evident on CT scans and still needs to be excluded as a diagnosis. Several features of the patient's headache suggest aneurysmal SAH, including the sudden onset, nuchal rigidity, and pupillary dilation of the left eye. The latter finding can be seen with a posterior communicating artery aneurysm as it exerts pressure on the outer portion of the oculomotor nerve (cranial nerve III). Only examination of the cerebrospinal fluid (CSF) can effectively determine if this patient has such a hemorrhage. This test has a higher yield 12 hours or longer after headache onset when erythrocyte breakdown products will produce a yellow color (xanthochromia). Before then, the presence of erythrocytes can make it difficult to distinguish a traumatic lumbar puncture from an SAH. Examination of the CSF also allows for the evaluation of other potential causes, such as meningitis, although meningitis is unlikely in this patient, given the absence of fever and sudden onset of symptoms.

Magnetic resonance angiography is helpful in evaluating a carotid artery dissection, but the patient's examination findings are not consistent with this diagnosis. Clinically, carotid artery dissection is recognized by the presence of unilateral pain of the head, neck, or face; partial Horner syndrome (ptosis, miosis); and cerebral or retinal ischemia. However, less than one third of patients will have all three components. This patient has a global headache and an enlarged pupil consistent a compressive process involving the oculomotor nerve (cranial nerve III) and not Horner syndrome.

MRI is neither sensitive nor specific enough to definitively diagnose SAH. Furthermore, MRI is time consuming and not always available.

Given the patient's abnormal neurologic findings, performing no further testing to find the cause of his symptoms is inappropriate.

KEY POINT

- In a patient with a thunderclap headache and normal findings on a CT scan of the head, lumbar puncture should be performed next.

Bibliography

Thompson BG, Brown RD Jr, Amin-Hanjani S, Broderick JP, Cockroft KM, Connolly ES Jr, et al; American Heart Association Stroke Council, Council on Cardiovascular and Stroke Nursing, and Council on Epidemiology and Prevention. Guidelines for the management of patients with unruptured intracranial aneurysms: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2015;46:2368-400. [PMID: 26089327] doi:10.1161/STR.0000000000000070

Item 45 Answer: D

Educational Objective: Diagnose primary central nervous system lymphoma with vitreous fluid sampling.

This patient should undergo vitreous fluid sampling. He most likely has primary central nervous system lymphoma (PCNSL). PCNSL is a non-Hodgkin lymphoma that can affect any part of the central nervous system but commonly presents as a focal supratentorial lesion. Although PCNSL is commonly seen in patients with HIV infection, PCNSL is increasing in incidence among older, immunocompetent patients. An association with Epstein-Barr virus has been noted. Pathologic analysis, usually of a brain biopsy specimen, is required to make a diagnosis of PCNSL. Diffuse large B-cell lymphoma is typical. Cerebrospinal fluid (CSF) cytology can be diagnostic in 10% of patients, although repeated samples often are necessary. Ocular involvement in the vitreous or retina may be seen in 10% to 20% of patients and can be detected with a slit-lamp examination and confirmed by vitreous fluid sampling. In this patient, vitreous fluid collection with cytologic analysis may obviate the need for more invasive and potentially risky testing, such as brain biopsy. Despite being chemo- and radiosensitive, PCNSL typically recurs and has a generally poor prognosis.

Because the lesion is in the brainstem, brain biopsy can result in significant neurologic injury and is considered a high-risk procedure. Brain biopsy should be considered only if other tests have been unrevealing, including cytologic analysis of vitreous fluid.

When PCNSL is suspected, glucocorticoids should be avoided until the diagnosis is confirmed because they are lymphocytotoxic and can result in false-negative histopathologic or cytopathologic results. Although this patient has hydrocephalus, herniation and brain edema are not present, and thus glucocorticoid therapy may be delayed while the diagnostic evaluation is completed.

Lumbar puncture is contraindicated in a patient with mass effect and hydrocephalus because it may precipitate herniation. If mass effect with hydrocephalus were not present, CSF sampling would be a reasonable step because lymphomatous cells may often be present in the CSF and would establish the diagnosis of PCNSL.

KEY POINT

- Slit-lamp examination and vitreous fluid collection with cytologic analysis should be considered in patients with biopsy-inaccessible lesions who have suspected primary central nervous system lymphoma.

Bibliography

Hoang-Xuan K, Bessell E, Bromberg J, Hottinger AF, Preusser M, et al; European Association for Neuro-Oncology Task Force on Primary CNS Lymphoma. Diagnosis and treatment of primary CNS lymphoma in immunocompetent patients: guidelines from the European Association

for Neuro-Oncology. Lancet Oncol. 2015 Jul;16(7):e322-32. doi: 10.1016/S1470-2045(15)00076-5. [PMID: 26149884]

Item 46 Answer: D

Educational Objective: Manage periodic limb movements of sleep.

This patient most likely has periodic limb movements of sleep, a disorder characterized by periodic leg kicks, often with a stereotyped triple-flexion phenomenology that repeats periodically during sleep. This condition can occur in otherwise healthy persons or be associated with sleep disorders, such as restless legs syndrome, sleep apnea, narcolepsy, and others. If another sleep disorder is present, treatment targeting the associated disorder also improves the periodic limb movements. If no associated sleep disorder is present (as is suggested in this patient by history and polysomnographic findings), treatment is only necessary if limb movements cause sleep fragmentation (brief arousals that occur during a sleep period). In the absence of such issues, no further testing or treatment is recommended.

Clonazepam often is used to treat rapid eye movement (REM) sleep behavior disorder, a condition associated with loss of the muscle paralysis normally experienced during the REM dream phase of sleep and typically characterized by dream enactment behavior with complex movements and vocalizations.

Electroencephalography (EEG) is indicated if nocturnal epilepsy is suspected. Nocturnal epilepsy is a major entity in the differential diagnosis of sleep-related movement disorders. However, this patient's stereotyped periodic movements are classic for periodic limb movements of sleep, and EEG is unnecessary.

Restless legs syndrome (RLS) is a common movement disorder characterized by discomforting sensations in the legs at rest or when falling asleep, an urge to move the legs, and immediate relief after moving the legs or walking. Patients with RLS should be screened for iron deficiency and receive iron supplements in the presence of deficiency or even low-normal serum ferritin levels. This patient does not have symptoms of RLS, such as sensory abnormalities or the urge to move.

KEY POINT

- The disorder periodic limb movements of sleep is characterized by periodic leg kicks that often exhibit a stereotyped triple-flexion phenomenology repeating periodically during sleep; if no associated sleep disorder is present, reassurance is the best management.

Bibliography

Aurora RN, Kristo DA, Bista SR, Rowley JA, Zak RS, Casey KR, et al; American Academy of Sleep Medicine. The treatment of restless legs syndrome and periodic limb movement disorder in adults--an update for 2012: practice parameters with an evidence-based systematic review and meta-analyses: an American Academy of Sleep Medicine Clinical Practice Guideline. Sleep. 2012;35:1039-62. [PMID: 22851801] doi:10.5665/sleep.1988

Item 47 Answer: A

H

Educational Objective: Diagnose epidural hematoma.

The patient has an epidural hematoma. This head injury most commonly results from a fracture of the temporal bone and subsequent laceration of the ipsilateral middle meningeal artery. Only 20% to 30% of these hematomas occur in other locations, and most follow trauma; spontaneous hemorrhages are rare. An epidural hematoma develops between the inner table of the skull and the dura mater. Lateral extension is prevented by dual attachments at the skull sutures; expansion occurs inwardly towards the brain parenchyma. Appearance on a head CT scan is biconvex or "lenticular." After a lucid interval, neurologic deterioration is rapid. Peak expansion of the hematoma occurs 6 to 8 hours after initial formation. Severe headache, nausea with vomiting, and eventual impairment in consciousness progress quickly. Ipsilateral compression of the occulomotor nerve (cranial nerve III) indicates potential uncal herniation. Subsequent ipsilateral midbrain compression results in contralateral upper motor neuron findings. Emergent surgical evacuation is required for those with anisocoria, a Glasgow Coma Scale (GCS) score of less than 9, or a hematoma volume greater than 30 mL.

Lobar hemorrhages are collections of blood within the brain parenchyma. Common causes are hypertension, anticoagulation, cerebral amyloid angiopathy, and aneurysmal or arteriovenous malformation rupture. Hemorrhage into areas of ischemic infarction or into tumors of primary central nervous system or metastatic origin also may be seen. Mass effect (from the hemorrhage) and the surrounding area of edema lead to a variety of neurologic presentations, some of which may require surgical evacuation.

Subarachnoid hemorrhage can result from trauma or, more commonly, rupture of an intracranial cerebral artery aneurysm. This hemorrhage is not confined by anatomic landmarks and typically spreads throughout the subarachnoid space.

Subdural hematomas are collections of blood between the brain and the dura mater. Most involve rupture of veins bridging the subarachnoid space. Because of cerebral atrophy and stretching of these veins, older patients are particularly vulnerable. Subdural hematomas can occur spontaneously or as a result of cranial trauma, and presentations range from acute to chronic. Those with acute subdural hematoma are at high mortality risk and require urgent surgical evacuation. GCS scores of less than 9, pupillary asymmetry, and hematomas greater than 10 mm in thickness are indications for emergent surgery.

KEY POINT

- Typical symptoms of epidural hematoma include severe headache, nausea with vomiting, and eventual impairment in consciousness with neurologic deterioration; emergent surgical evacuation is required when anisocoria, a Glasgow Coma Scale score of less than 9, or a hematoma volume greater than 30 mL is present.

Bibliography

Rincon S, Gupta R, Ptak T. Imaging of head trauma. Handb Clin Neurol. 2016;135:447-77. [PubMed: 27432678] doi: 10.1016/B978-0-444-53485-9.00022-2

Item 48 Answer: C

Educational Objective: Diagnose metabolic myopathy.

This patient has metabolic myopathy consistent with McArdle disease (glycogen storage disease V). This diagnosis is supported by a history of exercise intolerance associated with myalgia, "mild" weakness, and myoglobinuria and by laboratory evidence of chronic kidney disease (elevated serum creatinine level secondary to myoglobinuria). McArdle disease is caused by myophosphorylase deficiency and may be underdiagnosed because of the variability and intermittent nature of its symptoms. Patients with McArdle disease often do not have any muscle weakness or atrophy at baseline evaluation but may develop transient "mild" weakness after exertion. They can protect against severe exercise intolerance by eating a carbohydrate-rich diet before exercise; they also often describe a characteristic "second-wind" phenomenon by which a brief break taken after onset of cramping and fatigue allows for a higher level of exercise tolerance with much less difficulty.

Acute intermittent porphyria (AIP) is characterized by acute attacks of abdominal pain and vomiting and by central, peripheral, sensory, motor, autonomic, and enteric nervous system abnormalities. Patients may have episodes of reddish-brown urine (porphobilin and porphyrins) during an acute attack. AIP does not have a myopathic presentation and is not associated with intermittent exercise intolerance or "second-wind" phenomenon.

Limb-girdle muscular dystrophies are associated with baseline muscle atrophy and weakness and not with crises of exercise intolerance.

Myotonic dystrophy is unlikely in the absence of myotonia (delayed muscle relaxation), fixed muscle weakness, stiffness, and multiorgan involvement. Crises of exercise intolerance and myoglobinuria are not typical in myotonic dystrophy.

Symmetric painless proximal weakness of the arms and legs is the classic feature of polymyositis. Onset is acute or subacute, with disease progressing over weeks. A prolonged clinical course without baseline weakness and a history of exercise intolerance is not consistent with polymyositis.

KEY POINT

- McArdle disease is a metabolic myopathy associated with exercise intolerance, cramping, myalgia, mild weakness, "second-wind" phenomenon, and myoglobinuria.

Bibliography

Adler M, Shieh PB. Metabolic myopathies. Semin Neurol. 2015;35:385-97. [PMID: 26502762] doi:10.1055/s-0035-1558973

Item 49 Answer: C

Educational Objective: Diagnose dementia with Lewy bodies.

Rapid eye movement (REM) sleep behavior disorder commonly occurs in dementia with Lewy bodies (DLB) and can help distinguish DLB from Alzheimer disease and other cognitive disorders. This patient has cognitive and other symptoms suggestive of mild DLB. All the synucleinopathies (Parkinson disease, Parkinson disease dementia, and DLB) have a much higher rate of REM sleep behavioral sleep disorder than other neurologic and neurodegenerative diseases. REM sleep behavior disorder is characterized by the acting out of dreams secondary to loss of normal muscle paralysis during the dream phase of sleep. Symptoms may range from hand gestures to violent thrashing, punching, and kicking that may result in harm to self or bed partner. Patients also may have severe sensitivity to neuroleptic medications, which is more common in DLB than in other dementing illnesses.

Delusions occur in both Alzheimer disease (especially the later stages) and DLB; frank hallucinations are more typical of DLB. Therefore, the presence of delusions is unlikely to help distinguish Alzheimer disease from DLB.

Depression is a common symptom in most neurodegenerative dementia syndromes; it occurs in as many as 40% to 60% of patients with Alzheimer disease at some point of their disease. Its presence in this patient would not help establish a diagnosis.

Repeated falls can occur in DLB but also in vascular cognitive impairment, normal pressure hydrocephalus, and the later stages of Alzheimer disease. Therefore, this finding is unlikely to help in establishing a diagnosis in this patient.

KEY POINT

- Rapid eye movement sleep behavior disorder commonly occurs in dementia with Lewy bodies (DLB) and can help distinguish DLB from Alzheimer disease and other cognitive disorders.

Bibliography

Walker Z, Possin KL, Boeve BF, Aarsland D. Lewy body dementias. Lancet. 2015;386:1683-97. [PMID: 26595642] doi:10.1016/S0140-6736(15)00462-6

Item 50 Answer: B

H

Educational Objective: Treat acute intracerebral hemorrhage.

This patient should receive intravenous nicardipine. She has an acute intracerebral hemorrhage whose location suggests hypertension as the cause. Systolic blood pressure on emergent physical examination is greater than 180 mm Hg; this means she is at high risk for hematoma expansion. The systolic blood pressure should thus be lowered to a target of 140 mm Hg with a rapidly acting intravenous agent, such as intravenous nicardipine. A recently completed trial that compared systolic blood pressure targets of 120 mm Hg and 140 mm Hg noted increased adverse renal events in the treatment

H CONT.

arm with lower blood pressure. Whatever intravenous antihypertensive agent is chosen, it should be possible to taper its dose quickly if systolic blood pressure becomes too low.

Hematoma evacuation is an inappropriate treatment because the patient's intracerebral hemorrhage is not near the cortical surface, and the clinical and imaging findings show no evidence of elevated intracranial pressure (ICP) or cerebral herniation. If she were to have neurologic decline, repeat head CT would be appropriate to evaluate for hematoma expansion. Candidates for surgical evacuation of an intracerebral hematoma include those with evidence of elevated ICP or a cerebellar hemorrhage greater than 3 centimeters in size.

Nitroprusside is not a first-line blood pressure treatment for patients with acute hemorrhagic stroke, given its potential for increasing ICP.

There is no evidence that platelet transfusion reverses the coagulopathy associated with antiplatelet agents or prevents hematoma expansion. Platelet transfusion also carries the risk of coronary stent thrombosis, volume overload, and transfusion-related reactions.

KEY POINT

- Patients who have intracerebral hemorrhage without elevated intracranial pressure whose systolic blood pressure is greater than 180 mm Hg should be treated with an intravenous antihypertensive agent, such as nicardipine, to a target blood pressure of 140 mm Hg.

Bibliography

Hemphill JC 3rd, Greenberg SM, Anderson CS, Becker K, Bendok BR, Cushman M, et al; American Heart Association Stroke Council. Guidelines for the management of spontaneous intracerebral hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2015;46:2032-60. [PMID: 26022637] doi:10.1161/STR.0000000000000069

Item 51 Answer: E

Educational Objective: Prevent cluster headache.

This patient should be treated with verapamil. His history is compatible with the diagnosis of cluster headache. Cluster headache is the most common of the trigeminal autonomic cephalalgias (TACs). The term "cluster" is derived from this disorder's characteristic short cycles of headache activity (weeks) interrupted by long periods of complete remission (month or years). Male sex and tobacco use are two potential risk factors. Alcohol is a commonly reported trigger during an active cycle. Episodes are common nocturnally and may occur seasonally. Attack duration is between 15 and 180 minutes. Pain is almost always unilateral and localized near the temple or orbit. Ipsilateral autonomic symptoms, such as tearing, ptosis, nasal congestion, and rhinorrhea, are characteristic. Attacks may occur one to eight times daily for several weeks or months. Brain MRI should be performed initially to exclude structural lesions mimicking cluster headache. Oxygen inhalation and subcutaneous sumatriptan are first-line therapies for acute cluster headache. The patient should be counseled to stop smoking. Verapamil is the preventive medication of choice.

Carbamazepine is the treatment of choice for trigeminal neuralgia, which most often occurs in patients older than 50 years, but has no effect on cluster headache or any of the TACs. Periorbital location of pain would be atypical for trigeminal neuralgia, as would an attack duration beyond seconds. Ipsilateral autonomic symptoms are also generally absent.

Fexofenadine, a second-generation antihistamine, has no established benefit in cluster headache. This patient has no history of allergic rhinitis or other conditions that would respond to an antihistamine.

Several indomethacin-responsive headache syndromes have been identified, but cluster headache is not among them. Chronic paroxysmal hemicrania is a TAC that responds to indomethacin. Episodes of this condition last only 3 to 20 minutes and can recur up to 40 times daily. The diagnosis also requires concomitant ipsilateral autonomic findings, such as tearing, nasal congestion, or rhinorrhea.

Propranolol is an effective migraine preventive therapy but has no benefit for cluster headache. Migraine may present with severe periorbital headache with nausea and photophobia and occasionally with autonomic features. Unlike cluster headache, which typically lasts 15 to 180 minutes, migraine by definition extends 4 to 72 hours without treatment.

KEY POINT

- Cluster headache, the most common of the trigeminal autonomic cephalalgias, is best prevented with verapamil.

Bibliography

Pareja J, Alvarez M. The usual treatment of trigeminal autonomic cephalalgias. Headache. 2013 Oct;53(9):1401-14. [PMID: 24090529] doi:10.1111/head.12193

Item 52 Answer: D

Educational Objective: Diagnose familial amyloidosis.

The most likely diagnosis is familial amyloidosis. His progressive sensory, motor, and autonomic axonal polyneuropathy; bilateral carpal tunnel syndrome; and family history of neuropathy and cardiac disease suggest familial amyloidosis. This disorder is diagnosed by detection of a transthyretin gene (*TTR*) mutation. Affected patients often have multiorgan involvement (diseases of the eye [glaucoma] and the neurologic, gastrointestinal, cardiac, and urinary systems), but there is wide phenotypic variation leading to delayed diagnosis. Therefore, a high level of clinical suspicion of amyloidosis is necessary in the presence of relentless progression of neuropathy, autonomic dysfunction, and positive family history of typical symptoms.

This patient has no evidence of upper motor neuron disease on clinical examination and exhibits prominent sensory and autonomic neuropathy, which are inconsistent with amyotrophic lateral sclerosis.

In this patient, the electromyographic (EMG) findings, positive family history, absence of upper motor neuron findings, and diffuse dysautonomia are inconsistent with a cervical myelopathy.

This patient's EMG findings are consistent with an axonal neuropathy, not a demyelinating neuropathy such as chronic inflammatory demyelinating polyradiculoneuropathy.

West Nile virus, which typically has an acute or subacute (not chronic) course, can cause a flaccid motor myelopathy that does not involve sensory and autonomic small fiber neurons.

KEY POINT

- Familial amyloidosis is characterized by predominantly sensory and motor peripheral neuropathy and/or autonomic neuropathy; it is diagnosed by detecting a mutation of the transthyretin gene.

Bibliography

Adams D, Lozeron P, Lacroix C. Amyloid neuropathies. Curr Opin Neurol. 2012;25:564-72. [PMID: 22941262] doi:10.1097/WCO.0b013e328357bdf6

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Item 53 Answer: A

Educational Objective: Diagnose nonconvulsive status epilepticus.

The patient should undergo continuous (24-hour) electroencephalography (EEG). He has fluctuating mental status of unknown origin in the setting of a critical illness, sepsis, and multiorgan dysfunction. These findings raise suspicion of nonconvulsive status epilepticus (NCSE), which is intermittent electrical seizure activity without clinically evident seizure activity. A 20-minute EEG usually is inadequately sensitive to capture seizures, particularly if they are occurring intermittently. NCSE also is increasingly diagnosed in critically ill comatose or stuporous patients with acute neurologic or medical conditions who have not had a convulsive seizure. Similar to NCSE following CSE, NCSE in critically ill populations also is associated with increased morbidity and mortality and requires prompt attention and intervention. The diagnostic test of choice is continuous (24-hour) EEG monitoring. Most critically ill patients with nonconvulsive seizures have their first detectable seizure with EEG monitoring within 24 hours of initiating the recording, but an additional 12% have detectable seizures with 48 hours of continuous monitoring. Cefepime has been known to cause encephalopathy, coma, and status epilepticus in patients with or without epilepsy, especially those with acute kidney injury, and its use should raise the clinician's suspicion of NCSE.

Empiric treatment with fosphenytoin or lorazepam is generally not recommended until the diagnosis of NCSE or intermittent nonconvulsive seizures is confirmed by EEG. This approach differs from the treatment of generalized convulsive status epilepticus, which is diagnosed clinically and, optimally, treated without delay.

Providing no treatment is inadequate as the next step in management for this patient with altered mental status, a fluctuating level of consciousness, and other abnormalities on neurologic and laboratory testing. The diagnosis of NCSE first must be established (or excluded).

KEY POINT

- Nonconvulsive status epilepticus should be suspected in patients with critical illness who develop altered mental status; the diagnosis is confirmed with continuous (24-hour) electroencephalography.

Bibliography

Herman ST, Abend NS, Bleck TP, Chapman KE, Drislane FW, Emerson RG, et al; Critical Care Continuous EEG Task Force of the American Clinical Neurophysiology Society. Consensus statement on continuous EEG in critically ill adults and children, part I: indications. J Clin Neurophysiol. 2015;32:87-95. [PMID: 25626778] doi:10.1097/WNP.0000000000000166

Item 54 Answer: E

Educational Objective: Diagnose subacute combined degeneration due to vitamin B_{12} deficiency.

This patient's serum level of vitamin B_{12} should be measured. His examination findings are consistent with a myelopathy localizing to both the posterior columns and the corticospinal tracts of the spinal cord, and neuroimaging confirms the diagnosis. Common entities causing this pattern of weakness and sensory deficits are vitamin B_{12} deficiency, copper deficiency, and neurosyphilis. When these symptoms occur as a consequence of vitamin B_{12} or copper deficiency, the neurologic syndrome is termed subacute combined degeneration. This patient's previous chronic abuse of nitrous oxide has resulted in a functional B_{12} deficiency that is due to inactivation of the vitamin. In patients who abuse nitrous oxide, the B_{12} level also is often low or low-normal, with elevated methylmalonic acid and homocysteine levels. Not all patients with neurologic abnormalities will have anemia or macrocytosis.

Although low 25-hydroxyvitamin D levels have been associated with several conditions, including increased risk for autoimmune disease, this vitamin deficiency itself is not a cause of myelopathy.

Similarly, thiamine deficiency is associated with Wernicke-Korsakoff syndrome (nystagmus, ophthalmoplegia, ataxia, and confusion) but not with myelopathy. Wernicke encephalopathy most commonly occurs in persons with alcoholism but also has been reported in patients who have undergone bariatric surgery, have had a prolonged period of fasting, have had repeated episodes of vomiting, or have been on prolonged parenteral nutrition without adequate vitamin supplementation.

Vitamin A deficiency can cause blindness and hypervitaminosis and has been associated with benign idiopathic intracranial hypertension. Vitamin A deficiency is rarely seen in the United States but is the most common vitamin deficiency worldwide. When it does occur in resource-rich countries, it typically is associated with conditions causing fat malabsorption, such as pancreatic insufficiency, celiac disease, or certain forms of bariatric surgery. Alterations in vitamin A level do not result in myelopathy.

Vitamin B_6 deficiency is not common but may be associated with drugs that interfere with its metabolism, including isoniazid, hydralazine, carbidopa, and levodopa. The most common manifestations are stomatitis, glossitis, cheilosis, confusion, and depression. Both deficiency and toxicity of this nutrient can cause peripheral neuropathy. The upper motor neuron signs evident on physical examination of this patient, however, rule out a peripheral neuropathy.

KEY POINT

- Subacute combined degeneration is a myelopathy manifesting as dysfunction of the corticospinal tracts and dorsal columns that is caused by vitamin B_{12} and copper deficiencies.

Bibliography

Briani C, Dalla Torre C, Citton V, Manara R, Pompanin S, Binotto G, et al. Cobalamin deficiency: clinical picture and radiological findings. Nutrients. 2013;5:4521-39. [PMID: 24248213] doi:10.3390/nu5114521

Item 55 Answer: A

Educational Objective: Treat impaired mobility in multiple sclerosis.

This patient should be given dalfampridine. She has multiple sclerosis (MS) and had a relapse more than 1 year ago that resulted in poor recovery of left leg function, which is likely now permanent. Maintenance of mobility in patients with MS is essential for maintaining overall quality of life, and maintenance of an active, healthy lifestyle can help stave off future disability. Physical and occupational therapy is useful to ensure gait safety and improve walking ability and endurance. Assistive aids, such as braces, canes, walkers, and electrostimulatory walk-assist devices, can be useful for many patients. Two recent phase III studies found that dalfampridine, a voltage-gated potassium channel antagonist, significantly improved timed 25-foot walking speeds in patients with multiple sclerosis and gait impairment. This medication theoretically helps boost conductance through demyelinated axonal pathways, which may be of most benefit for long axons, such as those providing motor signals to the legs. As a consequence of this method of action, however, dalfampridine has the rare adverse effect of seizures and should not be used in patients with kidney impairment, given the reduced clearance of the drug and resultant potentially higher rate of seizures.

Pseudobulbar affect, a less common symptomatic manifestation of MS, can act as a significant impediment to social interaction in patients with MS. This symptom manifests as uncontrolled fits of laughter or crying that occur without distinct or appropriate triggers. A successful trial of the combination agent dextromethorphan-quinidine has led to FDA approval of the use of this pharmacotherapy for pseudobulbar affect in MS. It is not effective for improving or maintaining ambulation.

Gabapentin's most frequent use in MS is to treat neuropathic pain, which this patient currently is not experiencing. There is no evidence that this medication benefits impaired mobility.

Memantine frequently is used in mild to severe Alzheimer disease to boost cognition but has not been shown to benefit cognitive dysfunction or to increase mobility in MS patients. In fact, one small study found transient worsening of MS symptoms in those taking memantine.

Modafinil also is inappropriate. This drug is frequently used to treat MS-related fatigue but has no impact on muscle strength or walking ability.

KEY POINT

- In patients with multiple sclerosis and impaired mobility, dalfampridine is the most appropriate medication.

Bibliography

Goodman AD, Brown TR, Edwards KR, Krupp LB, Schapiro RT, Cohen R, et al; MSF204 Investigators. A phase 3 trial of extended release oral dalfampridine in multiple sclerosis. Ann Neurol. 2010;68:494-502. [PMID: 20976768] doi:10.1002/ana.22240

Item 56 Answer: A

Educational Objective: Diagnose diabetic mononeuropathy.

This patient most likely has diabetic mononeuropathy. He has an elevated hemoglobin A_{1c} value that is consistent with a diagnosis of diabetes mellitus and has no evidence of herpes zoster infection. Truncal diabetic mononeuropathy presents with acute or subacute pain and paresthesia in a dermatomal pattern in the thoracic or abdominal region. The area affected may be unilateral or cross the midline. Associated weakness of abdominal wall muscles can also be present and is detected by the presence of apparent abdominal swelling in the absence of palpable organomegaly. The differential diagnosis for this condition includes truncal radiculopathy caused by varicella zoster infection and thoracic myelopathy caused by demyelinating disease.

Paraproteinemic neuropathy can present as a symmetric distal sensory neuropathy or as sensorimotor, multifocal motor, and cranial neuropathies. The normal results of serum electrophoresis and serum free light chain measurement rules out this diagnosis.

Uremic neuropathy is similar to other neuropathies caused by metabolic disruptions and is associated with distal symmetric polyneuropathy. Asymmetric truncal neuropathy is not a typical presentation. Also, uremic neuropathy is often associated with a more severe degree of kidney injury than is present in this patient.

Vitamin B_{12} deficiency can cause myeloneuropathy, distal symmetric neuropathy, and cranial neuropathy but typically does not present as truncal mononeuropathy.

KEY POINT

- Acute or subacute pain and paresthesia in a dermatomal pattern in the thoracic or abdominal region in a patient with diabetes mellitus and no evidence of herpes zoster is most likely due to diabetic mononeuropathy.

Bibliography

Pasnoor M, Dimachkie MM, Barohn RJ. Diabetic neuropathy part 2: proximal and asymmetric phenotypes. Neurol Clin. 2013;31:447-62. [PMID: 23642718] doi:10.1016/j.ncl.2013.02.003

H

Item 57 Answer: C

Educational Objective: Diagnose spinal cord compression.

This patient should undergo emergent MRI of the lumbosacral spine. His history and clinical findings suggest acute (or subacute) compression of the lower spinal cord–most likely a cauda equina syndrome–given the finding of saddle anesthesia and the absence of a sensory spinal level on physical examination. Given the elevated INR, the most likely diagnosis is a spinal epidural hematoma compressing the lumbosacral spine. MRI is the most appropriate test to localize the injury and determine its cause, both of which are necessary to make an immediate treatment plan. Of note, an MRI of the thoracic spine is not appropriate for this patient; although compression of the thoracic spine could cause an acute myelopathy, it would be unlikely to produce saddle anesthesia in the sacral pattern noted, and the lack of a thoracic spine sensory level on physical examination makes this localization unlikely. Given the suspected hemorrhagic cause of cord compression, noncontrast CT could be an alternative imaging modality in this patient.

Surgical decompression will likely be required to treat nerve root compression due to a probable hematoma. In this patient, management of the bleeding diathesis by correcting the INR also will be necessary. Glucocorticoids have no role in treating spinal cord compression caused by a hematoma. Several trials have shown a benefit of high-dose intravenous glucocorticoids administered within the first 8 hours of traumatic spinal cord injury and in the management of metastatic spinal cord compression.

A CT myelogram would be inappropriate for this patient. Although the myelogram may show compression of the cord, it does not always reveal the cause. Furthermore, this test is difficult to obtain on an emergency basis, given the interventional nature of the procedure, and cannot be used in patients with contrast dye allergies or impaired kidney function. CT myelography is useful when MRI is not feasible (as in patients with implantable devices).

A radiograph of the lumbosacral spine is unlikely to reveal an epidural hematoma or cord compression. This test would be most appropriate in traumatic injury of the spine to investigate for fracture.

KEY POINT

- In a patient with suspected compression of the lower spinal cord, emergent MRI of the lumbosacral spine is the most appropriate test both to localize the injury and to determine its cause.

Bibliography

Kelley BC, Arnold PM, Anderson KK. Spinal emergencies. J Neurosurg Sci. 2012;56:113-29. [PMID: 22617174]

Item 58 Answer: C

H

Educational Objective: Diagnose idiopathic intracranial hypertension.

This patient should have a lumbar puncture. The clinical picture is compatible with idiopathic intracranial hypertension (IIH), and lumbar puncture is required to confirm the diagnosis. Although most presentations of IIH occur in the context of obesity in women of child-bearing age, several other risk factors have been identified. Exposure to minocycline or other members of the tetracycline class of antibiotics has been linked to the development of IIH. Retinoic acid, estrogen and progesterone supplements, and glucocorticoids are other drugs implicated as causes of this disorder. Headaches, vision changes, and intracranial noises are the most common presenting symptoms. Visual blurring, diplopia, and brief episodic dimming (obscurations) also are common, and papilledema is characteristic; abducens nerve (cranial nerve VI) palsy occurs occasionally. Cerebrospinal fluid (CSF) analysis typically shows an elevated opening pressure (>250 mm H_2O) with normal CSF composition. The treatment of choice is acetazolamide.

Amitriptyline is the preventive medication of choice for chronic tension-type headache (CTTH). Although the headache described in this patient is similar to that of CTTH, the presence of vision changes and intracranial noises would be atypical, and abducens nerve palsy is incompatible with that diagnosis.

Of the indomethacin-responsive headache syndromes, only hemicrania continua is possible in a patient with daily headache. However, the bilateral location of the headache pain, the absence of cranial autonomic features, and the presence of papilledema and abducens nerve palsy are incompatible with that diagnosis.

Magnetic resonance angiography is indicated in cases of suspected intracranial or cervical arterial disease. Although occulomotor nerve (cranial nerve III) palsy is common with an aneurysm of the posterior communicating artery, isolated abducens nerve palsy from vascular lesions is unusual. Carotid or vertebral dissections may result in Horner syndrome or, less commonly, ophthalmoplegia but not papilledema.

Temporal artery biopsy would be indicated in cases of suspected giant cell arteritis, which most commonly presents after age 50 years. Despite classic involvement of the temporal artery, pain may occur in various head locations. Amaurosis and jaw claudication are common associated features. Although cranial nerve palsies occasionally are noted, papilledema is not.

KEY POINT

- In a patient with suspected idiopathic intracranial hypertension, lumbar puncture is required to confirm the diagnosis.

Bibliography

Markey KA, Mollan SP, Jensen RH, Sinclair AJ. Understanding idiopathic intracranial hypertension: mechanisms, management, and future directions. Lancet Neurol. 2016 Jan;15(1):78-91. Epub 2015 Dec 8. [PMID: 26700907] doi:10.1016/S1474-4422(15)00298-7

Item 59 Answer: E

Educational Objective: Treat asymptomatic extracranial carotid artery stenosis.

This patient with 60% to 80% stenosis of the left internal carotid artery should receive no further treatment or intervention. The patient's LDL cholesterol level indicates that his atherogenic dyslipidemia is adequately treated with pravastatin, a moderate-intensity statin. Although there is some evidence suggesting that his 10-year risk for a major cardiovascular event is high enough to warrant switching to a high-dose, high-intensity statin, there are no specific guidelines recommending such a change. Asymptomatic carotid artery stenosis was not included in the definition of atherosclerotic cardiovascular disease used in the latest dyslipidemia treatment targets. Data are insufficient among patients with asymptomatic disease to recommend a specific therapy beyond treatment with a statin; there is currently no consensus on which statin and what dose to use.

Carotid endarterectomy or stenting is not the best treatment for this patient. The patient has asymptomatic internal carotid artery stenosis of 60% to 80%; the risk of stroke with best medical therapy is very low. Carotid revascularization with either endarterectomy or stenting, on the other hand, has a higher risk of adverse effects, including stroke, and its absolute risk reduction of stroke in asymptomatic patients is small, particularly among patients with stenosis of 80% or less. According to previous studies, predictors of stroke with asymptomatic internal carotid artery stenosis include greater than 80% stenosis, asymptomatic infarcts on brain imaging, an abnormal transcranial Doppler ultrasound study, or rapid progression. Carotid revascularization should be considered in patients at low risk for perioperative cardiovascular morbidity who have greater than 80% stenosis only in the context of a clinical trial.

Magnetic resonance angiography (MRA) of the neck is inappropriate because an additional diagnostic test is unlikely to change medical management. The accuracy of MRA without contrast versus carotid ultrasound is likely similar, but neck MRA is associated with patient discomfort and a higher cost.

Because there is no clear evidence that clopidogrel is superior to aspirin for the primary prevention of stroke in the setting of asymptomatic internal carotid artery stenosis, replacing this patient's aspirin with clopidogrel is unwarranted.

KEY POINT

- Statin therapy is indicated for asymptomatic carotid stenosis of 60% to 80%.

Bibliography

Marquardt L, Geraghty OC, Mehta Z, Rothwell PM. Low risk of ipsilateral stroke in patients with asymptomatic carotid stenosis on best medical treatment: A prospective, population based study. Stroke 2010 Jan; 41:e11-7. [PMID: 19926843]

Item 60 Answer: B

Educational Objective: Manage Guillain-Barré syndrome.

This patient with Guillain-Barré syndrome (GBS) who exhibits improvement after an initial course of plasma exchange should be discharged to rehabilitation. A diagnosis of GBS, an acute inflammatory demyelinating polyradiculoneuropathy, is supported by prodromal systemic infection, ascending weakness, radicular symptoms, cerebrospinal fluid albumin-ocytologic dissociation (elevated protein, normal leukocyte count), demyelinating changes (reduced conduction velocity) on a nerve conduction study, and areflexia. GBS is a monophasic disease with weakness reaching its nadir in less than 4 weeks. Given that this patient has already passed the nadir of weakness and is stable from a respiratory and autonomic standpoint, she should be transferred to a rehabilitation center. Rates of full recovery can be slow, but 80% of patients resume ambulation by 6 months.

In a patient with GBS who is already extubated and whose motor strength has improved by 50%, continued monitoring in the hospital is unnecessary and would not be cost-effective high value care. Additionally, early initiation of an active rehabilitation program would reduce the risk of secondary weakness caused by decompensation.

Repeating plasma exchange is indicated in GBS only if symptoms get worse after initial improvement or stabilization. This patient has experienced no deterioration.

Treatment with intravenous glucocorticoids is contraindicated in GBS and may worsen the clinical outcome.

Although intravenous immune globulin (IVIG) has the same efficacy as plasma exchange in shortening the time to recovery and reducing the duration of ventilation in GBS, serial treatment with IVIG after plasma exchange is not superior to either treatment alone and is not recommended. An exception would be if symptoms deteriorate after initial improvement or stabilization.

KEY POINT

- A hospitalized patient with Guillain-Barré syndrome who exhibits improvement after an initial course of plasma exchange should be discharged to rehabilitation.

Bibliography

Willison HJ, Jacobs BC, van Doorn PA. Guillain-Barré syndrome. Lancet. 2016;388:717-27. [PMID: 26948435] doi:10.1016/S0140-6736(16)00339-1

Item 61 Answer: B

Educational Objective: Avoid antiepileptic medications that can accelerate bone loss in patients with osteoporosis.

Lamotrigine is the most appropriate antiepileptic drug (AED) to treat this patient's focal seizures. Carbamazepine, phenytoin, and phenobarbital are all inducers of the cytochrome p450 system; these drugs increase breakdown of vitamin D, which results in increased parathyroid hormone levels, and

thus cause bone loss and osteoporosis. Valproic acid also is associated with bone loss, although the mechanism of this effect is unclear. Lamotrigine and other AEDs that do not induce the P450 system, such as levetiracetam, have no recognized effect on bone turnover; therefore, of the choices listed, lamotrigine is the most appropriate AED to use in a patient with established osteoporosis.

All patients on chronic AED therapy with phenytoin, carbamazepine, phenobarbital or valproic acid should undergo initial bone densitometry testing after 5 years of therapy, regardless of age, sex, or menopausal status. Those especially at risk are nonambulatory and physically inactive patients with epilepsy who have a non–weight-bearing status. Screening should be repeated, depending on the results, but not more frequently than every 2 years.

Patients with AED-associated osteoporosis should be assessed for adequate intake of calcium and vitamin D, with initiation of supplementation if intake is inadequate or if low levels of 25-hydroxyvitamin D are noted. Otherwise, treatment for osteoporosis associated with AEDs is the same as for osteoporosis in general and usually involves administration of a bisphosphonate, such as alendronate.

KEY POINT

- Lamotrigine does not have the potential to cause or worsen osteoporosis in patients with epilepsy.

Bibliography

Schmidt D. Starting, choosing, changing, and discontinuing drug treatment for epilepsy patients. Neurol Clin. 2016 May;34(2) (2016): 363-81, viii. Epub 2016 Mar 5. [PMID: 27086984] doi:10.1016/j.ncl.2015.11.007

H

Item 62 Answer: C

Educational Objective: Treat subarachnoid hemorrhage with nimodipine.

This patient should receive nimodipine. She has an aneurysmal subarachnoid hemorrhage (SAH) and is at high risk for neurologic decline from cerebral vasospasm. The risk of vasospasm is greatest 5 to 10 days after SAH onset. Nimodipine is indicted for all nonhypotensive patients with SAH and is associated with improved neurologic outcomes and survival. Because nimodipine may not directly reduce the vasospasm, additional monitoring with repeat neurologic examinations and transcranial Doppler ultrasonography is indicated in a specialized ICU. The presence of vasospasm is suggested by worsening findings on neurologic examination and can be confirmed with CT angiography or catheter angiography, with the latter test having the additional benefit of providing endovascular therapy.

Glucocorticoids, such as dexamethasone, are not routinely indicated for any stroke subtype and are ineffective in reducing intracranial pressure in that setting. One randomized study of 95 patients with aneurysmal SAH treated with 3 days of methylprednisolone showed improved 1-year functional outcomes in patients. However, the preponderance of evidence does not support glucocorticoid treatment for SAH.

Magnesium sulfate therapy has been used to prevent vasospasm following SAH, but randomized trials have not shown improved clinical outcomes. A 2013 systematic review and meta-analysis concluded that while intravenous magnesium reduced delayed cerebral ischemia, there was no improvement in clinical neurologic outcomes.

Nitroglycerin is not an appropriate treatment for this patient. Given the risk of cerebral vasospasm, blood pressure often is allowed to remain elevated in such patients. If her blood pressure were to require treatment, nitroglycerin would be inappropriate because it can increase cerebral venous volume and intracranial pressure, which is a concern in patients with SAH.

Verapamil is a calcium channel blocker, as is nimodipine, but verapamil has not been shown to improve outcomes in patients with SAH or vasospasm.

KEY POINT

- Nimodipine is indicated for all nonhypotensive patients with subarachnoid hemorrhage and is associated with improved neurologic outcomes and survival.

Bibliography

Hemphill JC 3rd, Greenberg SM, Anderson CS, Becker K, Bendok BR, Cushman M, et al; American Heart Association Stroke Council. Guidelines for the management of spontaneous intracerebral hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2015;46:2032-60. [PMID: 26022637] doi:10.1161/STR.0000000000000069

Item 63 Answer: B

Educational Objective: Screen a patient with Parkinson disease for risk of falling backward.

This patient's risk of falling backward is best determined by the pull test, which is the most sensitive predictor of risk of backward falls in Parkinson disease. During this test of postural stability, the examiner throws the patient off base by pulling backward on the shoulders; the test is considered positive if the patient topples into the examiner's arms or takes more than two corrective steps. Backward falls are often related to loss of postural reflexes and resultant postural instability. Additional factors, including insufficient control of motor symptoms, dyskinesia, and orthostatic hypotension, also can contribute to falls in Parkinson disease. In this patient, history and gait assessment did not reveal any interference with balance caused by freezing of gait or lower body dyskinesia, and he had no symptoms or findings suggestive of orthostatic hypotension.

The head impulse (or thrust) test involves asking the patient to keep eyes focused on a distant object; the examiner then suddenly turns the head approximately 20 degrees. Patients with a normal vestibuloocular reflex remain focused on the object. An abnormal response, indicating a peripheral vestibular lesion, is movement of the eyes off the target followed by jerking of the eyes back to the target (corrective saccade). In this patient, the absence of vertigo and dizziness makes a vestibular cause less likely and testing unnecessary.

The Dix-Hallpike test is another bedside test for assessment of peripheral vestibular pathology and is most helpful in the presence of vertigo, which is absent here.

A positive Romberg test, defined as severe unsteadiness elicited by eye closure in a patient standing comfortably, indicates impairment of large sensory pathways at the spinal-cord or peripheral nerve level. The absence of abnormal findings on sensory and reflex examinations makes a sensory ataxia less likely in this patient.

Tandem gait, in which a patient walks on a straight line, may be intact in the early phase of Parkinson disease. An impaired tandem gait, however, can indicate cerebellar or sensory ataxia or other causes of imbalance but is not a sensitive or specific predictor of backward falls.

KEY POINT

- The pull test is the most sensitive predictor of the risk of backward falls in Parkinson disease.

Bibliography

Canning CG, Paul SS, Nieuwboer A. Prevention of falls in Parkinson's disease: a review of fall risk factors and the role of physical interventions. Neurodegener Dis Manag. 2014;4:203-21. [PMID: 25095816] doi:10.2217/nmt.14.22

Item 64 Answer: C

Educational Objective: Diagnose primary stabbing headache.

This patient most likely has a primary stabbing headache (also known as an "ice pick" headache). The condition is characterized by transient localized stabs of head pain that occur spontaneously in the absence of organic disease and typically last seconds, with some lingering for 1 to 2 minutes; a less-localized dull ache or soreness lasting minutes may follow. The frequency of primary stabbing headache averages less than one per day in most patients, but headache attacks also can occur in series. Periods of activity and remission are common. Pain can occur anywhere on the head, including the eye, but the face is often spared. Primary stabbing headache is more common among those with a history of migraine. No cranial autonomic symptoms are reported. Indomethacin may be helpful during cycles of repeated occurrences but is rarely necessary.

Cluster headache is characterized by episodes of severe pain localized to the periorbital or temporal area with associated ipsilateral cranial autonomic features. Attacks of cluster headache may last 15 to 180 minutes and recur one to eight times daily over a span of weeks to months; the shorter duration distinguishes cluster headache from migraine. Many of the attacks are nocturnal, and some may be provoked by alcohol ingestion. The brief duration, parietal location, and absence of autonomic features in this case make cluster headache unlikely.

A new daily persistent headache is one with an identifiable and remembered onset. Pain becomes continuous and unremitting within 24 hours, a quality absent in this patient. The pain lacks many characteristic features, but the most common phenotype is similar to that of chronic tension-type headache. This disorder has no known treatment.

This patient's pain is occurring in an extratrigeminal location incompatible with the diagnosis of trigeminal neuralgia.

Of note, hemicrania continua is characterized by continuous head discomfort isolated and "locked" to one side. Some patients experience brief intense exacerbations of head pain that may be sharp and similar to that of primary stabbing headache. The condition, however, is known to display ipsilateral autonomic features not present in this patient, such as conjunctival injection, lacrimation, nasal congestion, rhinorrhea, forehead and facial sweating, miosis, and ptosis (and/or eyelid edema). An ipsilateral foreign body sensation in the eye is common. This headache is absolutely sensitive to indomethacin.

KEY POINT

- Primary stabbing headache is characterized by transient localized stabs of head pain that occur spontaneously in the absence of organic disease and typically last seconds; this headache is common among those with a history of migraine.

Bibliography

Chua AL, Nahas S. Ice pick headache. Curr Pain Headache Rep. 2016 May;20(5):30. [PMID: 27038969] doi:10.1007/s11916-016-0559-7

Item 65 Answer: A

Educational Objective: Treat focal seizures in an older patient with multiple comorbidities.

This patient should be treated with lamotrigine. He has a history of focal seizures with altered awareness (formerly known as complex partial seizures) and also has had a generalized tonic-clonic seizure. Only a few antiepileptic drugs (AEDs) (namely, lamotrigine, levetiracetam, topiramate, valproic acid, and zonisamide) are considered broad-spectrum agents and can be used to treat both generalized and partial epilepsy syndromes. Other narrow-spectrum AEDs (such as carbamazepine, gabapentin, oxcarbazepine, phenobarbital, phenytoin, and pregabalin) have the potential to exacerbate seizures in patients with generalized epilepsy. Lamotrigine is the most appropriate treatment because of the good evidence of its safety and effectiveness in epilepsy with focal seizures, especially in older patients, and is effective in generalized seizures. Lamotrigine is unlikely to cause cognitive dysfunction and does not affect blood counts, the liver, the kidney, or electrolytes. Although lamotrigine is associated with Stevens-Johnson syndrome, the drug can be titrated slowly to minimize risk; this patient's seizures are infrequent enough to allow for a 6- to 8-week titration. Although all the other drugs listed are likely effective in controlling seizures, lamotrigine also has a lower risk of adverse effects.

Oxcarbazepine is known to cause hyponatremia, especially in older patients taking thiazide diuretics, and thus should be avoided in this patient.

Phenytoin can lead to dizziness, ataxia, tremor, peripheral neuropathy, cerebellar atrophy, and agranulocytosis. Additionally, it has a narrow therapeutic window that is difficult to maintain, especially in older patients who are usually more sensitive to its zero-order pharmacokinetics at higher doses (constant absorption rate independent of concentration).

Kidney stones and cognitive impairment can be exacerbated by topiramate. The drug should be avoided in this patient with mild cognitive impairment and nephrolithiasis.

Valproic acid can cause tremor, cognitive dysfunction (including parkinsonism-associated dementia in older persons), and thrombocytopenia and thus is inappropriate for this patient.

KEY POINT

- Lamotrigine is the most appropriate treatment for epilepsy with focal seizure in older patients because of strong evidence of its safety and effectiveness.

Bibliography

Motika PV, Spencer DC. Treatment of epilepsy in the elderly. Curr Neurol Neurosci Rep. 2016;16:96. [PMID: 27628963] doi:10.1007/s11910-016-0696-8

Item 66 Answer: C

Educational Objective: Diagnose frontotemporal dementia.

This patient's age, gender, history, and cognitive evaluation findings all support a diagnosis of behavioral variant frontotemporal dementia (FTD). FTD typically involves an alteration in personality and behavior that develops years before the onset of cognitive impairment; altered behaviors typically manifest as obsessive-compulsive tendencies, impulsivity, apathy, impaired judgment, emotional coldness, disinhibition, excessive spending, and excessive eating, particularly of high-caloric, nonnutritional foods. Amyotrophic lateral sclerosis, the major form of motor neuron disease, is found in 20% to 30% of patients diagnosed with behavioral variant FTD. The presence of motor neuron disease generally portends a much more rapid progression of FTD but is exceptionally rare in other neurodegenerative disorders.

Classically, Alzheimer disease presents with the insidious development of recent memory loss. Forgetfulness of the details of recent events predominates early in the disease course. Aphasia is frequently seen early and is initially characterized by word finding difficulties. Visuospatial dysfunction also is common and often presents as episodes of becoming lost in familiar environments or problems in assembling objects (constructional apraxia). Executive dysfunction may manifest as impairment of problem solving abilities, judgment, and multitasking. Obsessive-compulsive tendencies, impulsivity, apathy, impaired judgment, emotional coldness, disinhibition, and excessive eating are not typical of Alzheimer disease.

Core features of dementia with Lewy bodies are fluctuating cognition, recurrent visual hallucinations, and parkinsonism. Cognitive fluctuations include variations in both attention and level of arousal and can vary hour to hour, day to day, or week to week. These features are not present in this patient.

Cognitive impairments in Parkinson disease are subcortical, which implies that they primarily involve slow processing speed, impaired short-term memory, and attention deficits with relative sparing of cortical functions, such as language and declarative memory. Dopamine agonists are associated with higher risk of specific adverse effects, including impulse control disorder, punding (repetition of complex motor behaviors), sleep attacks, hallucinations, and confusion, but are not seen in untreated Parkinson disease.

KEY POINT

- Frontotemporal dementia typically involves an alteration in personality and behavior that develops years before the onset of cognitive impairment.

Bibliography

Bang J, Spina S, Miller BL. Frontotemporal dementia. Lancet. 2015;386:1672-82. [PMID: 26595641] doi:10.1016/S0140-6736(15)00461-4

Item 67 Answer: B

Educational Objective: Diagnose multiple system atrophy.

The combination of parkinsonism, cerebellar ataxia, dysautonomia, and early postural instability and falls in this patient is most consistent with multiple system atrophy, a Parkinson plus syndrome. Typical autonomic deficits include orthostatic hypotension and urinary symptoms. Anosmia and acting out of dreams during sleep are suggestive of multiple system atrophy and Parkinson disease but not of progressive supranuclear palsy. A trial with levodopa may provide limited or partial benefit for this patient.

Corticobasal degeneration usually presents with markedly asymmetric parkinsonism and frequently is associated with dystonia, myoclonus, cortical sensory deficits, prominent cognitive dysfunction, and apraxia (impaired motor planning). MRI typically shows asymmetric posterior parietal and frontal cortical atrophy. The absence of these features makes this diagnosis less likely.

Many features of this patient's disorder are expected in idiopathic Parkinson disease, but the early prominent imbalance, recurrent falls, and cerebellar findings are atypical.

Given her early prominent postural instability, progressive supranuclear palsy is the main differential diagnosis in this patient. However, she does not have the characteristic impairment in vertical extraocular movements (supranuclear gaze palsy) that is typical. Additionally, the cerebellar features, asymmetric tremor, anosmia, and rapid eye

movement sleep behavior disorder are more typical of multiple system atrophy than progressive supranuclear palsy.

Patients with vascular parkinsonism have sudden or step-wise onset of symptoms and exhibit disproportionate involvement of the lower extremities. The involvement of the upper body, gradual course, nonmotor symptoms, and brain MRI findings in this patient make this diagnosis unlikely.

KEY POINT

- The combination of parkinsonism, cerebellar ataxia, dysautonomia, and early postural instability characterizes multiple system atrophy, a Parkinson-plus syndrome.

Bibliography

Aerts MB, Esselink RA, Post B, van de Warrenburg BP, Bloem BR. Improving the diagnostic accuracy in parkinsonism: a three-pronged approach. Pract Neurol. 2012;12:77-87. [PMID: 22450452] doi:10.1136/practneurol-2011-000132

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Item 68 Answer: B

Educational Objective: Manage an acute stroke treated with thrombolysis.

This patient should have CT angiography of the head. She has an acute ischemic stroke and was appropriately treated within 3 hours of symptom onset with intravenous recombinant tissue plasminogen activator (alteplase). The neurologic examination was consistent with an acute occlusion of the left intracranial internal carotid artery or middle cerebral artery. The patient's atrial fibrillation and subtherapeutic INR make a cardioembolic stroke subtype likely. Patients with an ischemic stroke and large-vessel occlusion have low recanalization rates with intravenous thrombolysis, and recently completed clinical trials have shown a clinical benefit from the addition of endovascular therapy, such as embolectomy, among carefully selected patients. The first step in patient selection requires the presence of a large vessel occlusion on vessel imaging, which is most quickly seen with CT angiography.

Because this patient already has received intravenous alteplase, all antithrombotics need to be held for at least 24 hours after a head CT shows no hemorrhage to prevent hemorrhagic conversion. In patients who do not receive thrombolysis, aspirin can reduce the risk of recurrent stroke within the first 2 weeks when administered within 48 hours of ischemic stroke onset.

Intravenous labetalol should not be administered to this patient. Her blood pressure does not meet the postthrombolytic treatment threshold (180/105 mm Hg). If clinical or radiographic evidence of hemorrhage is seen after treatment, lisinopril can be initiated.

MRI the area of infarction is not necessary for planning the next treatment steps. Furthermore, obtaining an MRI is time consuming and may lengthen the duration of time before an embolectomy can be performed. In acute ischemic stroke embolectomy trials, the greatest benefit occurred the faster treatment was initiated.

KEY POINT

- CT angiography of the head is the most appropriate test to determine candidacy for endovascular therapy in patients with a cardioembolic stroke who have undergone thrombolysis.

Bibliography

Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, et al; American Heart Association Stroke Council. 2018 Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2018 Mar;49(3):e46-e110. [Epub 2018 Jan 24] [PMID: 29367334] doi:10.1161/STR.0000000000000158

Item 69 Answer: C

H

Educational Objective: Treat brain herniation.

This patient should receive intravenous dexamethasone. He has a primary brain tumor (most likely, a high-grade glioma) that has expanded and led to brainstem compression, as suggested by the focal ocular and limb examination findings. The subsequent development of fixed, dilated pupils in the presence of acute coma indicates brainstem herniation. His elevated blood pressure, irregular respirations, and bradycardia (Cushing triad) are typical of elevated intracranial pressure, which can be caused by herniation. His condition represents a neurologic emergency and requires immediate treatment with intravenous glucocorticoids. Dexamethasone is the preferred agent because of its lack of mineralocorticoid effects. Although glucocorticoids are generally avoided when lymphoma is suspected, the presence of brain herniation is an exception because death is likely if the herniation is not treated.

While considering more definitive treatment options, such as surgical decompression or resection, other temporizing, immediate measures also should be taken, including elevation of the head of the bed to 30 degrees, artificial hyperventilation, and (possibly) osmotic diuresis with mannitol or hypertonic saline. Because artificial respiratory alkalosis will lower intracranial pressure, herniation is an indication for emergent intubation, even in the absence of respiratory compromise. Although surgical resection is the definitive treatment for many gliomas, treatment of herniation takes precedence because of its associated mortality, and other temporizing measures, including glucocorticoid administration, are needed to stabilize the patient for necessary emergent CT to confirm the herniation and assess for its cause (for example, stroke, tumor, or hemorrhage).

Brain MRI is appropriate to further characterize the lesion and help in planning for biopsy or resection, but treatment for herniation should not be delayed while awaiting MRI results. In an emergency situation, CT is preferred because it is can be performed more rapidly and is more widely available.

Brain biopsy may be necessary eventually. However, administration of glucocorticoids is the most appropriate first step because they can be administered immediately and may be lifesaving.

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Antiepileptic drugs (AEDs), such as levetiracetam, may be considered if the patient develops seizures or needs perioperative prophylaxis, but their administration is not a first priority in this patient because AEDs have no effect on herniation, which is an immediate threat to life.

KEY POINT

- Brain herniation in a patient with a malignant primary brain tumor should be emergently treated with a glucocorticoid, particularly dexamethasone.

Bibliography

Stevens RD, Shoykhet M, Cadena R. Emergency neurological life support: intracranial hypertension and herniation. Neurocrit Care. 2015;23 Suppl 2:S76-82. [PMID: 26438459] doi:10.1007/s12028-015-0168-z

H

Item 70 Answer: D

Educational Objective: Avoid using antibiotics that lower seizure threshold in patients with epilepsy.

Given his history of epilepsy, this patient should receive an injection of piperacillin-tazobactam as treatment of his hospital-acquired pneumonia. This drug has the lowest risk of triggering seizures of the drugs listed. Although all four choices may trigger seizures, piperacillin-tazobactam and non-fourth-generation cephalosporins have the weakest association with triggering seizures in patients with epilepsy (class IV evidence that seizure association is not well established in patients with epilepsy or past seizures).

Cefepime and carbapenems (such as imipenem) have class III evidence of triggering seizures in patients with epilepsy. In addition, cefepime has been known to cause encephalopathy, coma, and status epilepticus in patients with or without epilepsy, especially those with acute kidney injury.

There is class IV evidence that fluoroquinolones (such as levofloxacin) and fourth-generation cephalosporins lower the seizure threshold, including in patients with epilepsy.

KEY POINT

- Although evidence is limited, carbapenems, fluoroquinolones, and fourth-generation cephalosporins may lower the seizure threshold and thus should be avoided in patients with epilepsy.

Bibliography

Sutter R, Rüegg S, Tschudin-Sutter S. Seizures as adverse events of antibiotic drugs: A systematic review. Neurology. 2015;85:1332-41. [PMID: 26400582] doi:10.1212/WNL.0000000000002023

Item 71 Answer: B

Educational Objective: Diagnose migraine.

The patient's headaches meet the diagnostic criteria for migraine. The International Classification of Headache Disorders (third edition [beta version]) (ICHD-3) criteria require at least five episodes lasting 4 to 72 hours when untreated (or unsuccessfully treated) for this diagnosis. Pain should exhibit two of the following four characteristics: unilateral location, throbbing nature, moderate to severe intensity, and worsening with physical activity. Associated features must include either nausea or a combination of photophobia and phonophobia. Neurologic symptoms reflective of aura are described by 30% of patients with migraine. There must be no evidence of a secondary pathologic cause of the headache. Patients with chronic migraine may report milder attacks meeting tension-type headache criteria with at least some attacks meeting full migraine criteria. This patient described 8- to 12-hour severe attacks aggravated by activity with associated combined photophobia and phonophobia; her neurologic examination findings are normal. Neuroimaging is unnecessary in typical migraine presentations such as hers.

Medication overuse headache may result from overtreatment with acute medication in patients with underlying migraine or tension-type headache. Use of triptans, ergot alkaloids, opioids, or combination analgesics for 10 or more days per month or simple analgesics for 15 or more days per month constitutes medication overuse. Naproxen sodium used 8 days per month does not constitute medication overuse.

Over 90% of self- and clinician-diagnosed "sinus" headaches fulfill criteria for migraine. Acute rhinosinusitis may cause discomfort in the head or face, but headache is late in the disease course and typically a minor feature. Correlation of chronic or recurrent headaches with sinonasal pathology is without solid evidence. Weekly episodes of headache without nasal or sinus symptoms have no origins in the sinus cavities.

Episodic tension-type headache (TTH) is characterized by attacks of a nondisabling headache that lacks the typical features of migraine. Episodes may last from 30 minutes to 1 week. The pain of TTH typically is not severe or aggravated by routine physical activity. Photophobia or phonophobia may be present, but not both, according to ICHD-3 criteria. Mild nausea sometimes is noted with chronic TTH (≥15 days/mo) but not episodic TTH (<15 days/mo). Moderate to severe nausea and aura are not found with either TTH subtype.

KEY POINT

- The diagnosis of migraine requires at least five episodes lasting 4 to 72 hours when untreated (or unsuccessfully treated), with pain exhibiting two of the following characteristics: unilateral location, throbbing nature, moderate to severe intensity, and worsening with physical activity; associated features must include either nausea or a combination of photophobia and phonophobia.

Bibliography

MacGregor EA. Migraine. Ann Intern Med. 2017;166:ITC49-ITC64 [PMID: 28384749]

H

Item 72 Answer: B

Educational Objective: Treat ischemic stroke with antiplatelet agents.

This patient should be treated with aspirin. She most likely has a cardioembolic stroke related to atrial fibrillation. She is beyond the treatment window for intravenous thrombolysis and is not a candidate for intra-arterial therapy because of the location of the lesion in the posterior circulation and already demonstrated infarction. Therefore, medical therapy is indicated for preventing recurrent stroke. Only aspirin and heparinoids have been studied for their effectiveness in the acute stroke setting, and only aspirin has been shown to reduce the risk of stroke at 2 weeks. Therefore, aspirin monotherapy is a reasonable first-line antiplatelet regimen for secondary stroke prevention in the acute setting. For stable patients with small strokes, long-term warfarin therapy is typically administered 24 hours after hospitalization to reduce the risk of hemorrhagic transformation. Hemorrhagic transformation is more likely to occur in larger infarcts (those involving more than one third of hemispheric volume) and in infarcts with a cardioembolic cause. Warfarin is often withheld for 2 weeks in the setting of large strokes, strokes that have undergone hemorrhagic transformation, or uncontrolled hypertension.

The use of novel oral anticoagulants, including apixaban, has not been established as effective in the acute setting after a stroke. Apixaban may be a reasonable long-term option for stroke prevention at hospital discharge.

Clopidogrel has not been studied as monotherapy for acute ischemic stroke and is currently not recommended.

Intravenous heparin is not effective in reducing the risk of recurrent stroke within the acute hospitalization period in patients with all stroke subtypes, including ischemic strokes with a cardioembolic cause. Intravenous heparin can be considered in patients with a high short-term risk of recurrent ischemic stroke, such as those with mechanical heart valves, but the benefit of this approach must be weighed against the risk of hemorrhagic conversion.

KEY POINT

- In the absence of thrombolytic therapy for cardioembolic stroke, short-term therapy with aspirin reduces the risk of stroke at 2 weeks.

Bibliography

Kernan WN, Ovbiagele B, Black HR, Bravata DM, Chimowitz MI, Ezekowitz MD, et al; American Heart Association Stroke Council, Council on Cardiovascular and Stroke Nursing, Council on Clinical Cardiology, and Council on Peripheral Vascular Disease. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2014 Jul;45(7):2160-236. [PMID: 24788967] doi:10.1161/STR.0000000000000024

Item 73 Answer: C

Educational Objective: Manage mild traumatic brain injury in an athlete.

The patient should undergo neuropsychological testing. She sustained a mild closed head injury with typical symptoms of a concussion. Loss of consciousness established the presence of mild traumatic brain injury (TBI). Headache, nausea, dizziness, and cognitive dysfunction are all typical symptoms of postconcussion syndrome. Guidelines recommend initial screening with a symptom checklist and a neurologic examination, including assessments of cognition and balance. Guidelines also recommend head CT in those with suspected hemorrhage. Neuropsychological testing provides an additional objective and more sensitive measure of cognitive function and should be part of a comprehensive TBI management strategy for patients with persistent symptoms.

Amantadine has been shown to be useful in the management of severe traumatic brain injuries. Data suggest that treatment with amantadine can accelerate functional recovery among patients in vegetative or minimally conscious states after a TBI and can effectively accelerate the pace of recovery of cognitively mediated behaviors compared with placebo. However, there is insufficient evidence to recommend amantadine in cases of mild TBI.

A brain MRI is not indicated in this patient, who has shown symptomatic improvement in the 2 weeks since injury and now has normal neurologic examination findings. Further neuroimaging is unnecessary.

Return to play before complete recovery may increase the risk of recurrent injury. Concussion symptoms should have resolved completely before the patient resumes exercise. A return-to-play program should then involve a stepwise increase in physical activity, with monitoring for recurrence of symptoms. Guidelines recommend that a patient be asymptomatic without medication both at rest and when subjected to physical exertion. The presence of continued cognitive symptoms in this patient makes return to play inappropriate at this time.

KEY POINT

- Besides initial screening with a symptom checklist and a neurologic examination, including assessments of cognition and balance, neuropsychological testing should be part of a comprehensive mild traumatic brain injury management strategy for patients with persistent symptoms.

Bibliography

Wasserman EB, Kerr ZY, Zuckerman SL, Covassin T. Epidemiology of sports-related concussions in National Collegiate Athletic Association athletes from 2009-2010 to 2013-2014: symptom prevalence, symptom resolution time, and return-to-play time. Am J Sports Med. 2016 Jan;44(1):226-33. [PMID: 26546304] doi:10.1177/0363546515610537

Item 74 Answer: B

Educational Objective: Treat cognitive impairment in a patient with vascular cognitive impairment.

The most appropriate medication for this patient's cognitive impairment is the acetylcholinesterase inhibitor donepezil. Given her history of multiple strokes, pseudobulbar affect (a neurologic disorder characterized by involuntary outbursts of laughing and/or crying that are out of proportion to the

emotions being experienced), prominent gait problems, and asymmetric neurologic findings, she most likely has vascular cognitive impairment. Treatment of vascular cognitive impairment should focus on identifying and treating cerebrovascular risk factors, such as smoking, diabetes mellitus, hyperlipidemia, hypertension, ischemic heart disease, atrial fibrillation, and hypercoagulable states. Although not yet FDA approved as treatment of vascular cognitive impairment, acetylcholinesterase inhibitors have shown modest benefit in clinical trials and are generally recommended for this type of dementia.

Citalopram and other selective serotonin reuptake inhibitors are appropriate to treat the pseudobulbar symptoms exhibited by this patient but are unlikely to improve her cognitive deficits.

Ginkgo biloba has not been found to be more effective for dementia than placebo in controlled trials. Because this herbal supplement also is associated with increased bleeding, it is contraindicated in patients taking anticoagulant or antiplatelet agents.

Methylphenidate has been shown to be effective in treating the severe apathy often associated with vascular cognitive impairment. This patient has no evidence of apathy. In addition, this agent can raise blood pressure and is inappropriate for this patient with hypertension.

KEY POINT

- Treatment of vascular cognitive impairment should focus on identifying and treating cerebrovascular risk factors; off-label use of acetylcholinesterase inhibitors has shown modest benefit in clinical trials and thus is generally recommended for this condition.

Bibliography

Ritter A, Pillai JA. Treatment of vascular cognitive impairment. Curr Treat Options Neurol. 2015;17:367. [PMID: 26094078] doi:10.1007/s11940-015-0367-0

Item 75 Answer: D

Educational Objective: Treat immune-mediated necrotizing myopathy.

This patient, whose progressive muscle weakness has persisted after discontinuation of simvastatin and who has biopsy evidence of necrotizing myopathy without inflammation, should be treated with a glucocorticoid, such as prednisone. He most likely has immune-mediated necrotizing myopathy. This condition can be triggered by previous exposure to statins but is distinguished from more common statin-induced toxic myopathies by progression of muscle necrosis and weakness after removal of the statin. The presence of antibodies to hydroxymethylglutaryl coenzyme A reductase is disease specific and can further support the diagnosis because these antibodies are absent in patients with nonnecrotizing statin myopathy or in those without myopathy who take statins. Treatment with a glucocorticoid or other immunosuppressive agents can reverse the myopathy. In patients who have fully recovered from a previous episode of nonnecrotizing myopathy caused by a lipophilic statin, such as simvastatin, resumption of treatment with a hydrophilic statin, such as pravastatin, may be considered.

Although glucocorticoid-sparing immunosuppressive medications, such as azathioprine, are sometimes used as second-line therapy in other inflammatory myopathies (for example, polymyositis), evidence is limited with these agents in immune-mediated necrotizing myopathy. In addition, azathioprine has a delayed mechanism of action and is not immediately effective. Glucocorticoids are much more effective as first-line therapy.

Continued clinical monitoring is indicated in nonnecrotic statin myopathy, in which symptoms gradually improve in the absence of the causative agent. Progressive weakness and ongoing necrosis on biopsy should prompt suspicion of immune-mediated necrotizing myopathy, which requires immunosuppressive therapy.

The benefit of coenzyme Q10 as a protective agent against statin-induced myopathy remains controversial. No evidence suggests that coenzyme Q10 supplementation is effective against immune-mediated necrotizing myopathy.

KEY POINT

- Immune-mediated necrotizing myopathy is a form of statin myopathy that is associated with antibodies to hydroxymethylglutaryl coenzyme A reductase and biopsy evidence of muscle necrosis without inflammation; treatment with a glucocorticoid or other immunosuppressive agents can reverse the myopathy.

Bibliography

Mohassel P, Mammen AL. Statin-associated autoimmune myopathy and anti-HMGCR autoantibodies. Muscle Nerve. 2013;48:477-83. [PMID: 23519993] doi:10.1002/mus.23854

Item 76 Answer: B

Educational Objective: Manage intracranial hypotension.

This patient has intracranial hypotension and should undergo placement of an epidural blood patch (EBP). Spontaneous intracranial hypotension classically presents with an orthostatic headache. The interval between postural change and headache development is highly variable. When the headache duration is weeks to months, the orthostatic component may fade completely. Presentation may be thunderclap (maximum onset within 1 minute) or subacute. Intracranial hypotension is the result of cerebrospinal fluid (CSF) leakage that can arise as a result of lumbar puncture, surgery, or trauma or can occur spontaneously. Associated features include tinnitus, diplopia, neck pain, nausea, photophobia, and phonophobia. Clinical examination findings are typically normal but occasionally reveal a "falsely localizing" abducens nerve (cranial nerve VI) palsy. Female sex, middle age, and connective tissue disorders are risk factors. Brain MRI with contrast is abnormal in 80% of affected patients, with possible findings of diffuse

nonnodular pachymeningeal enhancement, cerebellar tonsillar abnormalities, and subdural fluid collections.

Use of an EBP is the initial treatment of choice. Patients who do not respond to this treatment should undergo CT myelography for potential detection of the precise site of cerebrospinal fluid (CSF) leakage. Subsequent treatments may include a repeat EBP or surgical repair of the identified site.

Acetazolamide is indicated in patients with intracranial hypertension but relatively contraindicated in cases of intracranial hypotension.

A diagnosis of intracranial hypotension can be confirmed by a CSF opening pressure of less than 60 mm H_2O, but lumbar puncture would introduce another site of potential CSF leakage. In the presence of patient history and brain MRI abnormalities that are typical for intracranial hypotension, lumbar puncture is unnecessary and should be avoided.

Small subdural fluid collections are commonly seen in patients with intracranial hypotension and do not require surgical evacuation. Typical indications for surgical management include an acute subdural hematoma measuring greater than 10 mm in thickness, a Glasgow Coma Scale score less than 9, and pupillary asymmetry or fixation.

KEY POINT

- Placement of an epidural blood patch is the initial treatment of choice for patients with intracranial hypotension; CT myelography is appropriate for those who do not respond to this treatment.

Bibliography

Hoffmann J, Goadsby PJ. Update on intracranial hypertension and hypotension. Curr Opin Neurol. 2013;26(3):240-7. [PMID: 23594732] doi:10.1097/WCO.0b013e328360eccc

H

Item 77 Answer: D

Educational Objective: Diagnose multiple sclerosis.

This patient should undergo MRI of the brain. She has signs and symptoms consistent with an episode of inflammatory transverse myelitis. Although idiopathic transverse myelitis can occur, the most common cause of a transverse myelitis event is multiple sclerosis (MS). MRI of the brain should be routinely performed in patients with new onset transverse myelitis to evaluate for lesions consistent with MS, such as those located in periventricular, juxtacortical (or cortical), and infratentorial white matter. If these lesions are present, MS should be diagnosed if they fulfill the diagnostic criteria for dissemination in space and in time.

No MS-specific diagnostic biomarkers are available. Initial studies championed myelin basic protein as a potential marker of MS disease activity, but subsequent evidence found that this biomarker is not associated with MS disease activity and is not useful to confirm a diagnosis of MS.

Lumbar puncture to determine the presence of oligoclonal bands is not warranted. Although lumbar puncture sometimes is appropriate in the evaluation of MS, the presence or absence of oligoclonal bands is not part of multiple sclerosis diagnostic criteria because of poor sensitivity and specificity for the disease. Approximately 10% to 15% of patients with MS have normal cerebrospinal fluid on testing; additionally, oligoclonal bands are sometimes elevated in other inflammatory conditions. For these reasons, if MRI confirms the diagnosis of MS, CSF testing is unnecessary.

The erythrocyte sedimentation rate may be elevated in patients with inflammatory transverse myelitis. However, the test is nonspecific and would not lead to a diagnosis of the cause of this patient's myelitis, such as MS.

Detection of a subclinical lesion in a site remote from the region of clinical dysfunction supports a diagnosis of multifocal MS. Evoked potentials also may help define the anatomic site of the lesion in tracts not easily visualized by imaging (for example, optic nerves, dorsal columns). Evoked potential testing is reserved for situations in which the diagnosis of MS is equivocal. The best initial test remains a brain MRI.

KEY POINT

- Because multiple sclerosis (MS) is the most common cause of transverse myelitis, MRI of the brain should be performed in patients with new-onset transverse myelitis to evaluate for MS lesions.

Bibliography

Thompson AJ, Banwell BL, Barkhof F, Carroll WM, Coetzee T, Comi G, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurol. 2017. [Epub ahead of print] [PMID: 29275977] doi:10.1016/S1474-4422(17)30470-2

Item 78 Answer: A

H

Educational Objective: Prevent venous thromboembolism after a hemorrhagic stroke.

This patient should begin receiving low-molecular-weight heparin. He has severe hemiparesis. Two poststroke CT scans obtained 48 hours apart show no evidence of active bleeding. The hemiparesis places him at high risk of deep venous thrombosis (DVT), which is the leading complication of hospitalization for stroke. DVT is found in 11% of immobile patients at 1 week after stroke and pulmonary embolism in about 1% of patients with stroke. Prophylaxis with low-molecular-weight heparin can be started 48 hours after hemorrhagic stroke in patients with no evidence of active bleeding on imaging. Before that time, DVT prophylaxis is possible with external sequential compression devices.

Administering warfarin without heparin is not adequate for immediate and short-term prevention of DVT because the anticoagulant effect of warfarin is delayed for 36 to 72 hours. Because of the immediacy of its action, heparin is preferred.

A randomized trial of thigh-high graduated compression stockings showed no benefit in preventing venous thromboembolism in patients with all types of stroke and

H CONT.

substantial leg weakness. Skin breaks, ulcers, blisters, and skin necrosis were significantly more common in patients wearing stockings.

Aspirin should not be resumed in this patient who has no immediate indication for use of antiplatelet agents, such as an acute myocardial infarction or a history of vascular stents. There is no evidence that aspirin is effective prophylaxis for DVT in hospitalized patients. Aspirin can be resumed in patients with intracerebral hemorrhage caused by hypertension 2 to 4 weeks after stroke onset if the hematoma has resolved on imaging and there is an appropriate high-risk indication.

KEY POINT

- Prophylactic heparin can be started 48 hours after a hemorrhagic stroke to prevent development of deep venous thrombosis as long as there is no evidence of active bleeding on neuroimaging

Bibliography

Hemphill JC 3rd, Greenberg SM, Anderson CS, Becker K, Bendok BR, Cushman M, et al; American Heart Association Stroke Council. Guidelines for the management of spontaneous intracerebral hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2015;46:2032-60. [PMID: 26022637] doi:10.1161/STR.0000000000000069

Item 79 Answer: D

Educational Objective: Treat chronic cervical stenosis.

This patient should have physical therapy. Spinal cord compression can result from acute or chronic causes. Evaluation and confirmation of suspected acute spinal cord compression with appropriate neuroimaging studies should occur in an urgent manner. Immediate treatment may be necessary to prevent severe and irreversible neurologic injury. Patients with chronic spinal stenosis due to osteoarthritic degenerative spinal disease frequently have chronic myelopathic symptoms, most often involving the cervical and lumbar spines. This patient has chronic symptoms of cervical stenosis due to multilevel disc disease. Most patients with chronic cervical and lumbar stenosis respond well to conservative measures, such as physical therapy and pain control. However, those with symptoms of more moderate to severe disease who also have signs of myelopathy on examination, such as progressive leg weakness, spasticity, distal numbness, and bladder impairment, may require surgical intervention. The lack of these findings in this patient supports the use of conservative measures, such as physical therapy.

Gabapentin can be useful in patients with neuropathic pain. This patient, however, has none of the typical symptoms of neuropathic pain, such as burning, electrical, or frostbite-like sensations.

Immobilization of the neck in hard (or soft) cervical collar would be an unnecessary and excessive restriction for someone with chronic cervical stenosis, especially in light of potential adverse effects. A hard cervical collar most commonly is used for cervical spine stabilization after trauma, surgery, and fractures or dislocations. It would be excessive in this patient whose clinical examination and imaging findings show no true cord compression or spinal instability.

Although some patients with spinal stenosis will eventually require neurosurgical intervention, outcomes for multilevel disc disease are generally poor, and this approach should be used only after conservative measures have been exhausted. The finding of signal abnormality within the cord may correlate with the severity of compressive myelopathy. Multiple levels of signal abnormality may be a more significant finding than single-level changes. The lack of clear cord compression on examination or signal-intensity changes on MRI indicates that this patient does not need emergent surgery.

KEY POINT

- Most patients with chronic cervical and lumbar stenosis respond well to conservative measures, such as physical therapy and pain control.

Bibliography

Rhee JM, Shamji MF, Erwin WM, Bransford RJ, Yoon ST, Smith JS, et al. Nonoperative management of cervical myelopathy: a systematic review. Spine (Phila Pa 1976). 2013;38:S55-67. [PMID: 23963006] doi:10.1097/BRS.0b013e3182a7f41d

Item 80 Answer: C

Educational Objective: Treat a patient with Alzheimer disease and sick sinus syndrome with memantine.

This patient should receive memantine. She has probable Alzheimer disease, moderate stage, given the degree of functional impairment she exhibits and her Mini-Mental State Examination score. The treatment of Alzheimer dementia is multifactorial and is symptom targeted. Both cholinesterase inhibitors (such as donepezil) and the *N*-methyl-D-aspartate receptor antagonist memantine are approved for treatment of moderate stages of Alzheimer disease. The cholinesterase inhibitors exert their effect by inhibiting the enzymes responsible for breaking down acetylcholine, thereby increasing the levels of acetylcholine in the neuronal synapse. No clinically significant difference in effectiveness has been shown between the cholinesterase inhibitors. Relative contraindications for their use include (but are not limited to) sick sinus syndrome, left bundle branch block, uncontrolled asthma, angle-closure glaucoma, and ulcer disease. Memantine is believed to reduce glutamate-mediated neurotoxicity in the central nervous system, is not associated with adverse cardiovascular effects, and thus is the most appropriate treatment for this patient.

Benzodiazepines (such as alprazolam) and antipsychotic agents (such as risperidone) should be used only in very limited circumstances in patients with Alzheimer disease who have severe psychosis and anxiety. At this point in her disease course, this patient has neither.

In patients with mild to moderate Alzheimer disease, donepezil and other acetylcholinesterase inhibitors have had

modest benefits in improving cognitive performance without clear improvements in daily functioning. Because of this patient's cardiac history, donepezil is not an appropriate medication.

Selective serotonin reuptake inhibitors (such as paroxetine) can be helpful for improving mood and treating psychiatric and behavioral symptoms of dementia. This patient's symptoms are mild at this time, do not warrant use of this drug class, and should be treated with behavioral management.

KEY POINT

- Relative contraindications for the use of cholinesterase inhibitors in the treatment of dementia include sick sinus syndrome, left bundle branch block, uncontrolled asthma, angle-closure glaucoma, and ulcer disease.

Bibliography

Molano JRI, Bratt R, Shatz R. Treatment and management of dementia due to Alzheimer's disease. Curr Treat Options Neurol. 2015 Aug;17(8):363. doi: 10.1007/s11940-015-0363-4

Item 81 Answer: B

Educational Objective: Diagnose a secondary headache.

This patient should have a brain MRI. His development of a new headache after age 50 years, use of an anticoagulant, and progressive headache pattern are all red flags indicating a potential secondary headache condition. Other red flags for secondary headache include first or worst headache, abrupt-onset or thunderclap attack, episode associated with neurologic symptoms lasting more than 1 hour, alterations in consciousness, abnormal physical examination findings, and onset after exertion, sex, or Valsalva maneuvers. Brain MRI is the most appropriate diagnostic study for patients with a suspected secondary headache and should be performed before additional testing is considered.

Amitriptyline is the treatment of choice for prevention of chronic tension-type headache. Diagnosis of this condition, however, first requires exclusion of a secondary headache. Although features of the patient's clinical presentation may suggest a tension-type headache syndrome, the presence of red flags makes brain neuroimaging a priority.

Neck pain is a nonspecific feature common to many primary and secondary headache syndromes. Its presence does not necessarily indicate a primary pathologic abnormality in the cervical region. Neurologic examination findings do not suggest cervical radiculopathy or myelopathy and thus an MRI of the cervical spine is not indicated.

Head CT is indicated in the assessment of acute severe headache in an emergent setting. In these situations, intracranial hemorrhage often is suspected and is well-visualized by a noncontrast CT scan. Given its greater sensitivity and safety, brain MRI is recommended in the evaluation of subacute or chronic headache requiring imaging.

Temporal artery biopsy is helpful in the evaluation of suspected giant cell arteritis. Most patients with this disorder are older than 50 years. Erythrocyte sedimentation rate and C-reactive protein level are frequently elevated. Brain MRI and reversal of anticoagulation are both indicated before temporal artery biopsy.

KEY POINT

- Brain MRI is the most appropriate diagnostic study for patients with a suspected secondary headache and should be performed before additional testing is considered.

Bibliography

Nye BL, Ward TN. Clinic and emergency room evaluation and testing of headache. Headache. 2015 Oct;55(9):1301-8. [PMID: 26422648] doi: 10.1111/head.12648

Item 82 Answer: B

Educational Objective: Monitor for adverse effects of multiple sclerosis treatment.

This patient should now have regular ophthalmologic examinations. Fingolimod is a once-daily pill that results in sequestration of activated lymphocytes in lymph nodes. Fingolimod reduces relapse rates by approximately half over 2 years compared with placebo and also reduces the risk of disability progression and accumulation of new MRI lesions. In clinical trials of fingolimod as treatment of multiple sclerosis (MS), the medication was found to confer a 0.5% risk of macular edema. This adverse effect is reversible and typically resolves after discontinuation of the drug. If unrecognized, however, macular edema can result in permanent visual deficits. Therefore, regular macular examinations (that is, visual evaluation or measurement through optical coherence tomography) are recommended for patients taking this medication. Fingolimod also requires first-dose monitoring because of the first-dose bradycardia that occurs in most patients and should not be used in patients with heart block.

There have been rare reports of patients who take fingolimod as a disease-modifying therapy for MS developing progressive multifocal leukoencephalopathy (PML). However, no evidence suggests that serum antibodies to the JC virus are a useful tool for predicting this adverse effect of the drug. Extensive data do support serum testing to predict the risk of PML in patients with MS who take natalizumab, in whom PML is much more common. The overall risk is approximately 1 in 1000 but is significantly higher in patients who have previous exposure to immunosuppressant agents or chemotherapy and those who have elevated serum titers of antibodies against the JC virus. Stratification of risk by treatment history and JC virus antibody testing is thus an important step before initiating natalizumab.

Kidney complications have not been associated with fingolimod use, which makes serum creatine measurement every 6 months unnecessary.

Tuberculosis has not been reported as an adverse effect of fingolimod. Although the risk of opportunistic infections may be increased with use of this drug, tuberculin skin testing is not recommended specifically, and given this patient's office-based occupation, she has no specific expected exposures that would require such testing.

KEY POINT

- In patients with multiple sclerosis who take fingolimod as a disease-modifying therapy, regular ophthalmic examinations are necessary because of the increased risk of macular edema with this medication.

Bibliography

Jain N, Bhatti MT. Fingolimod-associated macular edema: incidence, detection, and management. Neurology. 2012;78:672-80. [PMID: 22371414] doi:10.1212/WNL.0b013e318248deea

Item 83 Answer: D

Educational Objective: Diagnose primary progressive aphasia.

The most likely diagnosis is language-variant frontotemporal dementia, also known as primary progressive aphasia (PPA). Frontotemporal dementia (FTD) comprises two distinct clinical syndromes. The first, behavioral-variant FTD, is associated with prominent changes in behavior, personality, or executive function. The second, PPA, is associated with prominent and early changes in language function and is further subclassified according to the pattern of language impairment: semantic (or fluent) aphasia, nonfluent (agrammatic) aphasia, and logopenic aphasia. Semantic aphasia, as demonstrated by this patient, is characterized by early prominent difficulty with language comprehension. Nonfluent aphasia is recognized by changes in language production. Logopenic aphasia describes hesitant but grammatically correct speech. Although language decline is common in many dementia syndromes, in PPA it is the symptom noted first, and language is often the only cognitive domain affected for years before the development of additional cognitive deterioration. Structural brain imaging typically reveals asymmetric involvement of the left temporal lobe (which controls language in most patients), as shown (*arrow*).

Persistent forgetfulness is the hallmark of Alzheimer disease, beginning with objects, appointments, names, and other apparently trivial items. As the disease progresses, memories are lost, and problems with word-finding ability become apparent.

The most prominent feature of behavioral-variant FTD is an alteration in personality and behavior that typically develops years before the onset of cognitive impairment. Apathy, diminished interest, loss of empathy, lack of initiative, increased emotionality, disinhibition, euphoria, impulsivity, changes in eating behaviors, and compulsiveness are the most common symptoms reported by families.

Patients with dementia with Lewy bodies may demonstrate a pattern of cognitive impairment with psychiatric features of personality change, apathy, depression, and psychosis. Abnormal dream enactment behavior during rapid-eye movement (REM) sleep in which patients fight or call out in their sleep (REM sleep behavior disorder) may precede the onset of cognitive decline or motor symptoms by years.

KEY POINT

- Primary progressive aphasia is a language-predominant neurodegenerative dementia in which language is often the only cognitive domain affected for years before the development of additional cognitive deterioration; structural brain imaging often shows asymmetric involvement of the left temporal lobe.

Bibliography

Mesulam MM, Rogalski EJ, Wieneke C, Hurley RS, Geula C, Bigio EH, et al. Primary progressive aphasia and the evolving neurology of the language network. Nat Rev Neurol. 2014;10:554-69. [PMID: 25179257] doi:10.1038/nrneurol.2014.159

Item 84 Answer: C

Educational Objective: Diagnose a medication-induced movement disorder.

This patient has tardive dyskinesia. Involuntary choreiform movements, most often involving the face and hands, can be an adverse effect of long-term exposure to dopamine-blocking agents, including neuroleptic agents and chronic antiemetic medications, such as metoclopramide. Removal of the causative medication is key to treatment, but symptoms of tardive dyskinesia can take months to resolve or may become permanent. A longer duration and higher dose of the causative medication, older age, and female sex carry a higher risk of permanent dyskinesia. The risk of tardive dyskinesia should be discussed with patients before starting chronic dopamine-blocking agents. Pharmacologic treatment of tardive dyskinesia is often unsatisfactory, but options include clonazepam, tetrabenazine, valbenazine, anticholinergic agents, and clozapine. The persistence of involuntary movements 6 months after removal of metoclopramide is most consistent with tardive dyskinesia. The initial symptoms of shuffling gait and pill-rolling tremor were likely due to neuroleptic-induced parkinsonism, a distinct movement disorder

that, unlike tardive dyskinesia, is reversible with discontinuation of the causative dopamine-blocking agent.

Akathisia and dystonic reaction are both caused by exposure to dopamine-blocking agents of the neuroleptic or antiemetic class; these disorders occur acutely and do not account for the persistent symptoms described. Akathisia is a movement disorder characterized by a feeling of restlessness and an overwhelming need to be in motion manifested as pacing, rocking from foot to foot, lifting the feet as if marching in place, and crossing and uncrossing the legs; this patient does not have a need to move, and her symptoms are more limited than what is typically seen with akathisia. Acute dystonic reaction consists of sustained, frequently painful muscle contractions that can cause abnormal twisting postures, repetitive movements, and difficulty speaking. It may be limited to the head and neck, but the choreiform appearance of movements and their persistence months after removal of the offending medication make it an unlikely cause in this patient.

Withdrawal emergent syndrome is characterized by dyskinesia starting after sudden withdrawal of a dopamine-blocking agent; the disorder usually is managed by reinstitution of the causative agent (or another agent from same class) and a subsequent slow taper over few months. In this patient, the presence of dyskinesia before the offending medication was removed and its persistence for 6 months after removal is not consistent with withdrawal emergent syndrome.

KEY POINT

- Tardive dyskinesia can be caused by exposure to dopamine-blocking agents, such as neuroleptic and antiemetic agents, and may persist for more than 6 months after removal of the offending medication or become permanent.

Bibliography

Caroff SN, Campbell EC. Drug-induced extrapyramidal syndromes: implications for contemporary practice. Psychiatr Clin North Am. 2016;39:391-411. [PMID: 27514296] doi:10.1016/j.psc.2016.04.003

Item 85 Answer: C

Educational Objective: Treat a hemorrhagic stroke with an ACE inhibitor.

The patient had an intracerebral hemorrhage in the thalamus due to hypertension. Given his age and hypertension, the hemorrhage is unlikely to have had a secondary cause. During acute hospitalization for an intracerebral hemorrhage, lowering the blood pressure acutely is recommended, although achieving systolic blood pressure levels of less than 140 mm Hg is associated with increased adverse events. After the initial hospitalization, however, the risk of recurrent ischemic and hemorrhagic stroke remains increased if the blood pressure is higher than 130/80 mm Hg, according to secondary prevention trials of stroke examining the effectiveness of ACE inhibitors. There is no contraindication to starting an ACE inhibitor, such as lisinopril, which reduces the risk of ischemic and hemorrhagic stroke regardless of blood pressure levels.

Aspirin is an inappropriate treatment for this patient who has no clear indications for secondary prevention of ischemic stroke or other ischemic cardiovascular disease events. If a patient were to require an antiplatelet agent in the setting of known atherosclerotic disease (for example), aspirin can be safely started 30 days after an initial hemorrhagic stroke if the original event was due to hypertension and the blood pressure is well controlled.

The patient does not require fluoxetine because currently there is no evidence of clinical depression. Low-dose fluoxetine was shown to be better than placebo at improving motor function after stroke, but only when the drug was administered during the acute hospitalization. In the chronic setting, fluoxetine has not been shown to improve stroke recovery, and several reports suggest a potential increase in the risk of hemorrhage with selective serotonin reuptake inhibitors.

Rosuvastatin is not appropriate as treatment for this patient, whose serum LDL cholesterol level is not elevated, who has no evidence of atherosclerotic disease or diabetes mellitus, and whose 10-year atherosclerotic risk is less than 7.5%.

KEY POINT

- After the acute phase of stroke, patients with hypertension should be treated with antihypertensive therapy to reduce the risk of recurrent stroke.

Bibliography

Hemphill JC 3rd, Greenberg SM, Anderson CS, Becker K, Bendok BR, Cushman M, et al; American Heart Association Stroke Council. Guidelines for the management of spontaneous intracerebral hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2015;46:2032-60. [PMID: 26022637] doi:10.1161/STR.0000000000000069

Item 86 Answer: C

Educational Objective: Treat Bell palsy.

Oral prednisone should be given to this patient with Bell palsy within 72 hours of symptom onset to expedite the speed and rate of full recovery. Clinical history and examination findings in this patient are classic for Bell palsy, and thus no initial imaging or laboratory testing is indicated. Unilateral facial weakness involving both upper and lower parts of the face is characteristic of peripheral facial nerve (cranial nerve VII) involvement and distinguishes this condition from a central nervous system process (such as stroke), which typically spares the upper facial muscles because of bilateral innervation. Associated features of classic Bell palsy include alteration in taste (due to involvement of the chorda tympani) and hyperacusis (intolerance of loud noise due to involvement of stapedius muscle); other common features are ipsilateral sensory paresthesia and pain without objective sensory loss. Because this patient does not have subjective or objective

hearing loss or any other involvement beyond a unilateral facial nerve, initial brain imaging is not indicated.

Neither brain MRI nor intracranial magnetic resonance angiography is indicated in this patient. Sudden painless paralysis of a unilateral facial nerve is unlikely to be caused by aneurysmal compression or bleeding. These imaging tests might be appropriate if the patient had a thunderclap headache (maximum onset of pain within minutes of symptom onset), a slow progressive course of facial weakness, or progressive myoclonic hemifacial spasms.

The effectiveness of oral antiviral therapy, such as valacyclovir, in the treatment of Bell palsy is controversial. Currently, no available evidence suggests that adding antiviral therapy improves prognosis.

KEY POINT

- Oral prednisone administered within 72 hours of symptom onset expedites the speed and rate of full recovery in patients with Bell palsy.

Bibliography

Glass GE, Tzafetta K. Bell's palsy: a summary of current evidence and referral algorithm. Fam Pract. 2014;31:631-42. [PMID: 25208543] doi:10.1093/fampra/cmu058

Item 87 Answer: B

Educational Objective: Treat trigeminal neuralgia.

The patient should receive carbamazepine. She has paroxysmal facial pain typical of trigeminal neuralgia. Episodes of this disorder consist of sharp or shock like pain and have a duration of less than 1 second to 120 seconds, with variable frequency. The maxillary and mandibular branches of the trigeminal nerve (cranial nerve V) are affected in 95% of affected patients. Attacks may be spontaneous or triggered by innocuous stimuli. Autonomic features are rare. Incidence increases with advanced age. Multiple sclerosis (MS) is present in 5% of patients with trigeminal neuralgia and is a common cause in patients younger than 50 years. Demyelinating plaques in the pontine entry of the trigeminal root may be seen. Carbamazepine is the treatment of choice; management with this agent requires serum monitoring for hyponatremia and agranulocytosis.

Acetazolamide is indicated for idiopathic intracranial hypertension (IIH). Headaches associated with this condition are phenotypically similar to tension-type headache or migraine and not to the pain of neuralgia. This patient lacks both significant risk factors for and the papilledema typical of IIH. Her afferent pupillary defect is secondary to MS.

Indomethacin is the preferred treatment for chronic paroxysmal hemicrania (CPH). As with the other trigeminal autonomic cephalalgias, CPH pain mainly involves the ophthalmic branch of the trigeminal nerve, resulting in pain localized to the orbital, supraorbital, or temporal regions. Episodes of CPH last 2 to 30 minutes and recur as many as 40 times per day. Ipsilateral cranial autonomic features are present. Attacks may be precipitated by cervical spine rotation or compression, but facial stimulation is not provocative. Response to indomethacin is absolute.

Lamotrigine is the treatment of choice for short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT), although this type of headache is largely refractory to medical management. Similarly to trigeminal neuralgia, episodes last 1 to 600 seconds and may recur more than 100 times daily. Unlike trigeminal neuralgia, attacks of SUNCT involve the ophthalmic branch of the trigeminal nerve and include the ipsilateral autonomic features of conjunctival injection and tearing.

KEY POINT

- Carbamazepine is the treatment of choice for trigeminal neuralgia; management with this agent requires serum monitoring for hyponatremia and agranulocytosis.

Bibliography

Maarbjerg S, Gozalov A, Olesen J, Bendtsen L. Trigeminal neuralgia–a prospective systematic study of clinical characteristics in 158 patients. Headache. 2014 Nov-Dec;54(10):1574-82. [PMID: 25231219.] doi: 10.1111/head.12441

Item 88 Answer: D

H

Educational Objective: Treat glucocorticoid-refractory idiopathic transverse myelitis.

This patient is exhibiting signs and symptoms consistent with idiopathic transverse myelitis (TM). Idiopathic TM is a monophasic inflammatory and demyelinating myelopathy affecting a portion of the spinal cord. Affected patients frequently experience a subacute onset of weakness, sensory changes, and bowel or bladder dysfunction, which is sometimes preceded by back pain or a thoracic banding sensation. Diagnostic criteria for idiopathic TM require the presence of clinical features of the syndrome, evidence of inflammation (either leukocytosis in the cerebrospinal fluid or contrast enhancement on MRI), and exclusion of other potential causes. First-line treatment for this disorder is administration of high-dose intravenous glucocorticoids. A 5-day course of high-dose methylprednisolone, however, had no beneficial effect on this patient's symptoms. The most appropriate next step is plasma exchange therapy, which has been shown to improve outcomes in patients with idiopathic transverse myelitis that is refractory to glucocorticoids.

The symptoms experienced by this patient are unlikely to be the result of tuberculosis. Tuberculosis can cause central nervous system infection and inflammation, but when it does, it most often involves the meninges, which are not affected in this patient, and spinal fluid analysis frequently shows a low glucose level and a mononuclear pleocytosis. The acute onset of symptoms also is highly unusual for tuberculosis.

Although this patient will benefit from inpatient rehabilitation, it should be delayed until all of the other treatment options have been exhausted. Transfer to rehabilitation

H CONT.

without initiation of plasma exchange would not provide the patient with the best chance for recovery.

Intravenous immune globulin therapy has not been shown to provide benefit in glucocorticoid-refractory transverse myelitis and thus would be inappropriate treatment for this patient.

KEY POINT

- In a patient with signs and symptoms of idiopathic transverse myelitis in whom first-line treatment with a high-dose intravenous glucocorticoid has been ineffective, plasma exchange therapy is the most appropriate next step in treatment.

Bibliography

Scott TF, Frohman EM, De Seze J, Gronseth GS, Weinshenker BG; Therapeutics and Technology Assessment Subcommittee of American Academy of Neurology. Evidence-based guideline: clinical evaluation and treatment of transverse myelitis: report of the therapeutics and technology assessment subcommittee of the American Academy of Neurology. Neurology. 2011;77:2128-34. [PMID: 22156988] doi:10.1212/WNL.0b013e31823dc535

Item 89 Answer: D

Educational Objective: Evaluate for vitamin D deficiency in patients with multiple sclerosis.

This patient's serum 25-hydroxyvitamin D level should be measured to determine if she has vitamin D deficiency. The response to disease-modifying therapy is monitored with clinical evaluation and often with periodic MRI studies. Although she is clinically stable, the MRI shows possible new disease activity. Accumulating evidence suggests that disease activity in multiple sclerosis (MS) is highly correlated with serum vitamin D levels, with less frequent relapses and MRI lesion development in patients with high vitamin D levels. Furthermore, administration of vitamin D supplementation has now been shown to provide additional control of disease activity, with a recent trial finding less MRI activity in patients taking interferon plus vitamin D versus interferon alone. This patient is not taking any vitamin D supplementation, which may make her more prone to exacerbations. Supplementation would be indicated if she demonstrates deficiency on serologic testing.

The addition of dalfampridine to this patient's regimen would have no benefit at this time. Although this medication has shown efficacy in improving ambulatory function in some patients with MS, it has no immunologic, disease-modifying effect. Because this patient has no ambulation difficulty and is experiencing an inflammatory disease breakthrough, addition of dalfampridine would be an inappropriate choice.

Glatiramer acetate is a copolymer of four amino acids that, among other mechanisms of action, may bind major histocompatibility complex molecules and induce a shift in the immune response away from autoimmunity. Glatiramer acetate also has been shown to reduce the relapse rate by approximately one third compared with placebo and appears equivalent to the beta interferons in head to head studies. However, clinical trial evidence has shown that combining glatiramer acetate with an interferon beta provides no added benefit to what either drug achieves alone.

Lumbar puncture to obtain cerebrospinal fluid for JC virus testing is not appropriate. Reactivation of the JC virus in the brain can result in progressive multifocal leukoencephalopathy (PML), an adverse effect of some immunosuppressive medications and chemotherapy. PML, however, is not a known adverse effect of the interferon beta preparations, and the changes on this patient's MRI are not indicative of PML. Thus, performance of this invasive test is not indicated.

KEY POINT

- Adjuvant therapy with vitamin D supplementation in patients with relapsing-remitting multiple sclerosis provides additional disease activity control.

Bibliography

Soilu-Hänninen M, Aivo J, Lindström BM, Elovaara I, Sumelahti ML, Färkkilä M, et al. A randomised, double blind, placebo controlled trial with vitamin D3 as an add on treatment to interferon β-1b in patients with multiple sclerosis. J Neurol Neurosurg Psychiatry. 2012;83:565-71. [PMID: 22362918] doi:10.1136/jnnp-2011-301876

Item 90 Answer: A

Educational Objective: Identify Alzheimer disease as the cause of mild cognitive impairment.

Cerebrospinal fluid (CSF) analysis is likely to provide the most specific information about whether Alzheimer disease is the cause of this patient's mild cognitive impairment (MCI). This test can measure levels of soluble Aβ42 peptide and soluble tau protein, which can help identify a specific pattern consistent with a diagnosis of Alzheimer disease, namely, decreased Aβ42 and increased tau and p-tau levels. In a patient with MCI, these levels have a greater than 80% sensitivity and specificity in identifying Alzheimer disease as the cause of cognitive symptoms. With the emphasis of clinical trials targeting the earliest stages of Alzheimer disease, the use of CSF biomarkers can assist in the diagnosis and prognosis of the underlying cause of MCI and in identifying patients who could qualify for clinical trials.

Electroencephalography (EEG) detects electrical activity in the brain and is most useful in the diagnosis of epilepsy, although it also can help diagnose sleep disorders, encephalopathy, coma, and brain death. Because EEG provides only nonspecific information about brain function, it is not helpful in detecting the presence of Alzheimer disease.

Fluorodeoxyglucose (FDG) PET provides information on the metabolic function of the brain and can help identify patterns of neuronal impairment. However, these findings are not exclusive to Alzheimer disease. Any information FDG PET provides about brain function is similarly nonspecific.

MRI can provide information on hippocampal atrophy and the presence of enlarged ventricles and cerebrovascular disease. However, these features are seen in both Alzheimer disease and other unrelated syndromes. Likewise, the information MRI provides about brain structure and size is not specific to Alzheimer disease.

Serum apolipoprotein E (*ApoE*) allele testing provides no useful information for diagnosing cognitive disorders. *ApoE* is a gene that can indicate a patient's risk for Alzheimer dementia but adds little to the prediction of progression of symptoms from MCI.

KEY POINT

- In a patient with mild cognitive impairment, decreased Aβ42 peptide and increased tau protein and p-tau levels in the cerebrospinal spinal fluid have a greater than 80% sensitivity and specificity in identifying Alzheimer disease as the cause.

Bibliography

Blennow K, Zetterberg H. Cerebrospinal fluid biomarkers for Alzheimer's disease. J Alzheimers Dis. 2009;18:413-7. [PMID: 19661632] doi:10.3233/JAD-2009-1177

H

Item 91 Answer: D

Educational Objective: Treat blood pressure after thrombolysis.

This patient requires no further treatment of his blood pressure at this time. He has had an acute ischemic stroke and was treated appropriately with recombinant tissue plasminogen activator (alteplase). His posttreatment blood pressure is less than 180/105 mm Hg, which is less than the guideline threshold for initiating antihypertensive therapy. Given the presence of internal carotid artery stenosis, expansion of the infarct is possible if the blood pressure is significantly lowered. Blood pressure lowering may be appropriate in patients with symptomatic intracerebral hemorrhage after thrombolysis, but this diagnosis is unlikely in this patient whose physical examination findings after thrombolysis are stable.

Amlodipine is inappropriate as treatment because this patient's blood pressure does not need to be lowered acutely after thrombolysis. Home antihypertensive agents thus should be held for most patients with acute ischemic stroke for at least 48 hours unless evidence of end-organ damage exists.

Clopidogrel is an antithrombotic agent and thus is contraindicated in this patient who has just received thrombolytic therapy. In patients with a transient ischemic attack or minor stroke, aspirin in combination with clopidogrel for 21 days may reduce the risk of recurrent stroke, although confirmatory trials are required.

Intravenous nitroprusside also is inappropriate treatment in this patient who does not require acute lowering of blood pressure. Additionally, nitroprusside is not the medication of first choice in patients with acute stroke because of its potential to increase intracranial pressure.

KEY POINT

- After thrombolytic therapy for acute stroke, antihypertensive treatment is not necessary if blood pressure is less than 180/105 mm Hg and there are no symptoms of intracerebral hemorrhage.

Bibliography

Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, et al; American Heart Association Stroke Council. 2018 Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2018 Mar;49(3):e46-e110. [Epub 2018 Jan 24] [PMID: 29367334] doi:10.1161/STR.0000000000000158

Item 92 Answer: D

Educational Objective: Diagnose secondary progressive multiple sclerosis, with progression and activity.

This patient's clinical course at this time can best be described as secondary progressive multiple sclerosis (MS), with progression and activity. His initial relapsing event of optic neuritis initially would have been diagnosed as relapsing-remitting MS. However, over the past 3 years, the patient has had a slow progressive decline in multiple neurologic symptoms without any clear exacerbations, which is the hallmark of progression in MS. Given the initial relapsing course followed by at least 2 years of disability progression without relapses, the patient's disease would now be considered secondary progressive. Recent revisions to clinical course descriptions in MS have been made to acknowledge that the clinical course in MS is not static and should be redefined constantly. Furthermore, these revised course descriptions have acknowledged the fact that relapses can occur in patients who otherwise have progressive MS and that MRI changes should be seen as a sign of relapsing activity in MS. In summary, clinical relapses or MRI evidence of new or enlarging lesions define "activity," whereas the gradual accumulation of neurologic deficits independent of relapses defines "progression." In light of this patient's recent gradual decline in neurologic function (progression) and MRI changes (activity), his disease status is best described as secondary progressive with progression and activity. If, at a later time, the patient exhibits a pattern of no new neurologic deficits, experiences no relapses, and has no new lesions on MRI, his disease status can then be described as secondary progressive without progression or activity.

The patient's initial symptoms involved an acute demyelinating event (optic neuritis), with signs of disability progression coming later. He is not among the 15% of patients with MS who never experience a relapse but instead have progressive disability accumulation from the time of disease onset; these patients have primary progressive MS. Therefore, it would be inaccurate to describe the current status of this patient's MS as primary progressive.

Although this patient's initial clinical course was relapsing, the progressive decline with absence of improvement in the past 3 years indicates a transition to progressive MS. The clinical course of his MS thus cannot be described as relapsing remitting, with activity.

KEY POINT

- The three core phenotypes of multiple sclerosis can be modified by the presence of activity (clinical relapse or new/enlarging MRI lesion); primary and secondary progressive multiple sclerosis can be further modified as "progressive" if there is ongoing accumulation of neurologic deficits independent of clinical relapses.

Bibliography

Lublin FD, Reingold SC, Cohen JA, Cutter GR, Sorensen PS, Thompson AJ, et al. Defining the clinical course of multiple sclerosis: the 2013 revisions. Neurology. 2014;83:278-86. [PMID: 24871874] doi:10.1212/WNL.0000000000000560

Item 93 Answer: B

Educational Objective: Treat generalized epilepsy in a patient with psychiatric disease.

This patient should receive lamotrigine instead of valproic acid to control his seizures. No single antiepileptic drug (AED) is recommended for the initial treatment of epilepsy. Approximately 50% of patients with this disorder will respond to the first AED administered. Choosing an AED for an individual patient depends on several factors, including his or her epilepsy syndrome, age, sex, and comorbid medical conditions and the drug's adverse effect profile and cost. Lamotrigine is commonly prescribed in women with childbearing potential and is also a good option for older patients or those who have depression or other mood disorders. This patient has generalized epilepsy that is not controlled with valproic acid. Lamotrigine is the most appropriate medication to use instead, not only because of its effectiveness as treatment for generalized tonic-clonic seizures, but also because of its mood-stabilizing effects. Lamotrigine is FDA approved for maintenance treatment of bipolar I disorder, and clinical trials have demonstrated its efficacy in the treatment of depersonalization/derealization disorder.

Ethosuximide is used only to treat absence seizures, not other types of generalized seizures. Therefore, the medication is inappropriate for this patient with tonic-clonic seizures.

Although often used as a first line treatment of generalized epilepsy, levetiracetam can worsen depression and should be avoided in this patient who has depression with psychotic features.

Topiramate also is not appropriate for this patient because it can cause or worsen psychosis.

KEY POINT

- In a patient with generalized epilepsy and psychiatric disease, lamotrigine is an appropriate medication to use not only because of its effectiveness as treatment for generalized tonic-clonic seizures, but also because of its mood-stabilizing effects.

Bibliography

Thigpen J, Miller SE, Pond BB. Behavioral side effects of antiepileptic drugs. US Pharm. 2013;38(11):HS15-HS20.

Item 94 Answer: D

Educational Objective: Diagnose myoclonus.

This patient's clinical history and clinical examination findings are most consistent with myoclonus. Myoclonus consists of rapid, nonsuppressible, shock-like, jerky movements that can result from metabolic, endocrine, toxic, infectious, epileptic, autoimmune, and other causes. Posthypoxic myoclonus (Lance-Adams syndrome) occurs in patients with a history of hypoxic brain injury (suggested in this patient by his previous cardiopulmonary arrest) and is characterized by prominent action-induced myoclonus that impairs ambulation because of a combination of positive (rapid jerky movements) and negative (lapses in muscle tone) myoclonus. Other examples of negative myoclonus include hiccups and asterixis.

Ataxia is associated with wide-based gait, incoordination, and dysmetria. However, rapid shock-like movements and brief lapses of muscle tone are not features of ataxia. Ataxia is a hallmark of cerebellar damage and can be seen in posthypoxic settings.

Chorea consists of random, nonrepetitive, flowing, dance-like movements, unlike the abnormal movements exhibited by this patient. Choreiform movements are not rapid or shock-like.

Dystonia involves sustained muscle contractions leading to stereotyped and directional twisting and posturing movements that are absent in this patient.

An orthostatic tremor is a high-frequency, rhythmic tremor that emerges in the legs only during standing and resolves with sitting or ambulation. This does not describe the patient's movements, which are nonrhythmic and jerky.

KEY POINT

- Posthypoxic myoclonus, which occurs in patients with a history of hypoxic brain injury, is characterized by prominent action-induced myoclonus that impairs ambulation because of a combination of positive (rapid jerky movements) and negative (lapses in muscle tone) myoclonus.

Bibliography

Mills K, Mari Z. An update and review of the treatment of myoclonus. Curr Neurol Neurosci Rep. 2015;15:512. [PMID: 25398378] doi:10.1007/s11910-014-0512-2

Item 95 Answer: D

Educational Objective: Evaluate a patient who has minor cognitive difficulties and daytime sleepiness with polysomnography.

This patient should have polysomnography. He has minor symptoms of cognitive impairment, such as memory lapses and calculation difficulties at work. To exclude a slowly progressive dementia and identify any potentially reversible causes of his symptoms, the patient's examination should consist of a neurologic examination, including a cognitive screening evaluation, and evaluation for depression, sleep disorders, alcohol abuse, and family history of dementia. The patient does not use alcohol and has no family history of dementia. His score on the Montreal Cognitive Assessment is borderline abnormal, which would be unlikely if Alzheimer disease or another progressive dementia were the cause of his symptoms, and several depression scales provide no evidence of depression. Because depression and a primary neurodegenerative disorder are unlikely in this patient, additional diagnostic testing is necessary. His hypertension, obesity, and self-reported daytime sleepiness are consistent with a diagnosis of obstructive sleep apnea (OSA). Other neuropsychiatric symptoms of OSA include mood alterations, difficulty concentrating, and problems completing tasks at school or the workplace. Objective testing is required for the diagnosis of OSA.

The traditional gold standard of in-laboratory, technician-attended polysomnography is being replaced by portable technology designed for use by the unaccompanied patient and is referred to as out-of-center sleep testing (OCST). This portable testing is typically limited to measurement of oronasal airflow, chest wall excursion, body position, and pulse oximetry, whereas in-laboratory polysomnography also measures brain waves (electroencephalography), muscle activity (electromyography), and heart rhythm (electrocardiography) and occurs in the presence of a technician in case of technical difficulties. OCST performs comparably to polysomnography in patients without comorbid cardiopulmonary disease who have a high pretest probability of moderate to severe OSA.

Given the patient's normal findings on neurologic examination and relatively minor neurologic symptoms, cerebrospinal fluid analysis, fluorodeoxyglucose PET scanning, and mild structural brain imaging with MRI are likely to be of low yield.

KEY POINT

- Polysomnography should be performed in a patient with minor symptoms of cognitive impairment and self-reported daytime sleepiness who scores normally on cognitive and depression assessments.

Bibliography

Gagnon K, Baril AA, Gagnon JF, Fortin M, Décary A, Lafond C, et al. Cognitive impairment in obstructive sleep apnea. Pathol Biol (Paris). 2014;62:233-40. [PMID: 25070768] doi:10.1016/j.patbio.2014.05.015

Item 96 Answer: A

Educational Objective: Treat cognitive dysfunction in multiple sclerosis.

This patient should be referred for cognitive rehabilitation therapy. Cognitive dysfunction occurs in at least 50% of patients with multiple sclerosis (MS). The most common deficits involve short-term memory, processing speed, and executive function. Cognitive disability has a significant effect on the employability of patients with MS and can reduce their overall quality of life. To this point, however, no pharmaceutical agent has been shown to improve these symptoms in patients with MS. In contrast, cognitive rehabilitation approaches, such as the development of accommodative strategies and training with challenging cognitive tasks, have shown this benefit and should be pursued in this patient.

Depression also is a common symptom in patients with MS, and the suicide rate is elevated in these patients compared with patients who have depression for other reasons. The depression that occurs in MS is likely multifactorial, involving the emotional response to dealing with a chronic disease, the consequences of demyelinating lesions and inflammatory cytokines, and the adverse effects of treatments (such as the interferon beta formulations). Clinicians should be vigilant for signs of depression and have a low threshold for initiating antidepressants and offering referrals to psychiatry. This patient has not had any severe worsening of depression. Therefore, increasing the dosage of the selective serotonin reuptake inhibitor fluoxetine is unlikely to improve any cognitive deficits.

In trials of their effectiveness in improving cognitive deficits in MS, donepezil, memantine, and methylphenidate have shown no benefit. Donepezil has shown modest benefits in cognitive performance in patients with mild to moderate Alzheimer disease, and memantine has shown a similar benefit in patients with moderate to severe Alzheimer disease. Methylphenidate is a central nervous system stimulant used in the treatment of attention-deficit/hyperactivity disorder and narcolepsy.

KEY POINT

- Cognitive rehabilitation approaches, such as the development of accommodative strategies and training with challenging cognitive tasks, have been shown to improve symptoms of cognitive deficits in patients with multiple sclerosis.

Bibliography

Benedict RH, Zivadinov R. Risk factors for and management of cognitive dysfunction in multiple sclerosis. Nat Rev Neurol. 2011;7:332-42. [PMID: 21556031] doi:10.1038/nrneurol.2011.61

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6 (A) (B) (C) (D) (E)	51 (A) (B) (C) (D) (E)	96 (A) (B) (C) (D) (E)	141 (A) (B) (C) (D) (E)
7 (A) (B) (C) (D) (E)	52 (A) (B) (C) (D) (E)	97 (A) (B) (C) (D) (E)	142 (A) (B) (C) (D) (E)
8 (A) (B) (C) (D) (E)	53 (A) (B) (C) (D) (E)	98 (A) (B) (C) (D) (E)	143 (A) (B) (C) (D) (E)
9 (A) (B) (C) (D) (E)	54 (A) (B) (C) (D) (E)	99 (A) (B) (C) (D) (E)	144 (A) (B) (C) (D) (E)
10 (A) (B) (C) (D) (E)	55 (A) (B) (C) (D) (E)	100 (A) (B) (C) (D) (E)	145 (A) (B) (C) (D) (E)
11 (A) (B) (C) (D) (E)	56 (A) (B) (C) (D) (E)	101 (A) (B) (C) (D) (E)	146 (A) (B) (C) (D) (E)
12 (A) (B) (C) (D) (E)	57 (A) (B) (C) (D) (E)	102 (A) (B) (C) (D) (E)	147 (A) (B) (C) (D) (E)
13 (A) (B) (C) (D) (E)	58 (A) (B) (C) (D) (E)	103 (A) (B) (C) (D) (E)	148 (A) (B) (C) (D) (E)
14 (A) (B) (C) (D) (E)	59 (A) (B) (C) (D) (E)	104 (A) (B) (C) (D) (E)	149 (A) (B) (C) (D) (E)
15 (A) (B) (C) (D) (E)	60 (A) (B) (C) (D) (E)	105 (A) (B) (C) (D) (E)	150 (A) (B) (C) (D) (E)
16 (A) (B) (C) (D) (E)	61 (A) (B) (C) (D) (E)	106 (A) (B) (C) (D) (E)	151 (A) (B) (C) (D) (E)
17 (A) (B) (C) (D) (E)	62 (A) (B) (C) (D) (E)	107 (A) (B) (C) (D) (E)	152 (A) (B) (C) (D) (E)
18 (A) (B) (C) (D) (E)	63 (A) (B) (C) (D) (E)	108 (A) (B) (C) (D) (E)	153 (A) (B) (C) (D) (E)
19 (A) (B) (C) (D) (E)	64 (A) (B) (C) (D) (E)	109 (A) (B) (C) (D) (E)	154 (A) (B) (C) (D) (E)
20 (A) (B) (C) (D) (E)	65 (A) (B) (C) (D) (E)	110 (A) (B) (C) (D) (E)	155 (A) (B) (C) (D) (E)
21 (A) (B) (C) (D) (E)	66 (A) (B) (C) (D) (E)	111 (A) (B) (C) (D) (E)	156 (A) (B) (C) (D) (E)
22 (A) (B) (C) (D) (E)	67 (A) (B) (C) (D) (E)	112 (A) (B) (C) (D) (E)	157 (A) (B) (C) (D) (E)
23 (A) (B) (C) (D) (E)	68 (A) (B) (C) (D) (E)	113 (A) (B) (C) (D) (E)	158 (A) (B) (C) (D) (E)
24 (A) (B) (C) (D) (E)	69 (A) (B) (C) (D) (E)	114 (A) (B) (C) (D) (E)	159 (A) (B) (C) (D) (E)
25 (A) (B) (C) (D) (E)	70 (A) (B) (C) (D) (E)	115 (A) (B) (C) (D) (E)	160 (A) (B) (C) (D) (E)
26 (A) (B) (C) (D) (E)	71 (A) (B) (C) (D) (E)	116 (A) (B) (C) (D) (E)	161 (A) (B) (C) (D) (E)
27 (A) (B) (C) (D) (E)	72 (A) (B) (C) (D) (E)	117 (A) (B) (C) (D) (E)	162 (A) (B) (C) (D) (E)
28 (A) (B) (C) (D) (E)	73 (A) (B) (C) (D) (E)	118 (A) (B) (C) (D) (E)	163 (A) (B) (C) (D) (E)
29 (A) (B) (C) (D) (E)	74 (A) (B) (C) (D) (E)	119 (A) (B) (C) (D) (E)	164 (A) (B) (C) (D) (E)
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34 (A) (B) (C) (D) (E)	79 (A) (B) (C) (D) (E)	124 (A) (B) (C) (D) (E)	169 (A) (B) (C) (D) (E)
35 (A) (B) (C) (D) (E)	80 (A) (B) (C) (D) (E)	125 (A) (B) (C) (D) (E)	170 (A) (B) (C) (D) (E)
36 (A) (B) (C) (D) (E)	81 (A) (B) (C) (D) (E)	126 (A) (B) (C) (D) (E)	171 (A) (B) (C) (D) (E)
37 (A) (B) (C) (D) (E)	82 (A) (B) (C) (D) (E)	127 (A) (B) (C) (D) (E)	172 (A) (B) (C) (D) (E)
38 (A) (B) (C) (D) (E)	83 (A) (B) (C) (D) (E)	128 (A) (B) (C) (D) (E)	173 (A) (B) (C) (D) (E)
39 (A) (B) (C) (D) (E)	84 (A) (B) (C) (D) (E)	129 (A) (B) (C) (D) (E)	174 (A) (B) (C) (D) (E)
40 (A) (B) (C) (D) (E)	85 (A) (B) (C) (D) (E)	130 (A) (B) (C) (D) (E)	175 (A) (B) (C) (D) (E)
41 (A) (B) (C) (D) (E)	86 (A) (B) (C) (D) (E)	131 (A) (B) (C) (D) (E)	176 (A) (B) (C) (D) (E)
42 (A) (B) (C) (D) (E)	87 (A) (B) (C) (D) (E)	132 (A) (B) (C) (D) (E)	177 (A) (B) (C) (D) (E)
43 (A) (B) (C) (D) (E)	88 (A) (B) (C) (D) (E)	133 (A) (B) (C) (D) (E)	178 (A) (B) (C) (D) (E)
44 (A) (B) (C) (D) (E)	89 (A) (B) (C) (D) (E)	134 (A) (B) (C) (D) (E)	179 (A) (B) (C) (D) (E)
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Rheumatology High Value Care Recommendations

The American College of Physicians, in collaboration with multiple other organizations, is engaged in a worldwide initiative to promote the practice of High Value Care (HVC). The goals of the HVC initiative are to improve health care outcomes by providing care of proven benefit and reducing costs by avoiding unnecessary and even harmful interventions. The initiative comprises several programs that integrate the important concept of health care value (balancing clinical benefit with costs and harms) for a given intervention into a broad range of educational materials to address the needs of trainees, practicing physicians, and patients.

HVC content has been integrated into MKSAP 18 in several important ways. MKSAP 18 includes HVC-identified key points in the text, HVC-focused multiple choice questions, and, for subscribers to MKSAP Digital, an HVC custom quiz. From the text and questions, we have generated the following list of HVC recommendations that meet the definition below of high value care and bring us closer to our goal of improving patient outcomes while conserving finite resources.

High Value Care Recommendation: A recommendation to choose diagnostic and management strategies for patients in specific clinical situations that balance clinical benefit with cost and harms with the goal of improving patient outcomes.

Below are the High Value Care Recommendations for the Rheumatology section of MKSAP 18.

- An accurate history and a thorough musculoskeletal examination can avoid unnecessary testing.
- Do not obtain antinuclear antibody testing for patients with nonspecific symptoms and a normal clinical examination.
- Do not obtain antinuclear antibody subserology testing without a strong clinical suspicion of an underlying connective tissue disease.
- Plain radiography is usually the first-line imaging test performed in the evaluation of rheumatologic diseases.
- Ultrasonography is an inexpensive means to assess soft-tissue abnormalities, assess disease activity, and assist with tendon or joint injections.
- Acetaminophen is not beneficial for osteoarthritis and lower back pain, even at high doses.
- Topical NSAIDs are beneficial for patients at high risk for toxicity from oral NSAIDs (see Item 20).
- The most useful laboratory studies to aid in the diagnosis of rheumatoid arthritis are rheumatoid factor and anti-cyclic citrullinated peptide antibodies.
- Weight loss can lower the risk for developing osteoarthritis (see Item 78).
- Laboratory testing is usually not necessary to diagnose osteoarthritis.
- A muscle strengthening program is part of the management plan for knee osteoarthritis (see Item 73).
- Arthroscopic surgery is generally not indicated for knee osteoarthritis unless there is a mechanical disorder.
- Nonpharmacologic therapy (education, exercise, psychosocial support) remains a cornerstone of treatment for fibromyalgia.
- Plain radiography of the sacroiliac joints is the first imaging test in patients with suspected ankylosing spondylitis (see Item 94).
- HLA-B27 cannot independently confirm or exclude a diagnosis of spondylitis.
- Antibiotics are not usually effective in treating reactive arthritis.
- Löfgren syndrome (a triad of bilateral hilar lymphadenopathy, erythema nodosum, and migratory polyarthralgia) is highly specific for sarcoidosis, obviating the need for tissue biopsy.
- Plain radiography is the initial radiographic study of choice for osteonecrosis, and MRI is indicated when plain radiographs are normal (see Item 81).

Rheumatology

Approach to the Patient with Rheumatologic Disease

Inflammatory Versus Noninflammatory Pain

The differentiation between inflammatory and noninflammatory signs and symptoms is central to the evaluation of patients with musculoskeletal pain. Autoimmune conditions typically present with inflammation, whereas mechanical or degenerative disorders are characteristically noninflammatory. The cardinal signs of inflammation are pain, erythema, swelling, and warmth; with the exception of pain, noninflammatory conditions usually lack these features. Importantly, patients may simultaneously experience more than one type of pain. **Table 1** compares the features of inflammatory and noninflammatory pain.

The Musculoskeletal Examination

An accurate history and a thorough musculoskeletal physical examination are essential to diagnose and differentiate inflammatory and noninflammatory symptoms and can help to avoid unnecessary testing. Musculoskeletal pain may be articular, periarticular, or referred. Pain with passive range of motion suggests an articular condition, whereas pain with active range of motion suggests a periarticular condition.

See MKSAP 18 General Internal Medicine for more information.

KEY POINTS

- Inflammatory symptoms include pain, erythema, swelling, and warmth; with the exception of pain, noninflammatory conditions usually lack these features.
- An accurate history and a thorough musculoskeletal physical examination are essential to diagnose and differentiate inflammatory and noninflammatory symptoms and can help to avoid unnecessary testing. HVC

Arthritis

H

Monoarthritis

Monoarthritis involves a single joint and is classified as acute or chronic. Acute monoarthritis can be noninflammatory (for example, trauma, hemarthrosis, or internal derangement) or inflammatory (for example, crystal induced or infectious). Evaluation for infectious arthritis should be guided by the clinical presentation and examination, but suspicion should always be high. Joint aspiration is usually the most effective means of diagnosing the underlying cause.

Chronic inflammatory monoarthritis (>26 weeks) can be caused by chronic infection (for example, mycobacterial, fungal, or *Borrelia burgdorferi*) or by autoimmune rheumatologic disease. Synovial fluid analysis will confirm inflammation but may be inadequate for diagnosis; assessment for systemic disease (serologies and other laboratory studies) and, in some cases, synovial biopsy may be required.

Chronic noninflammatory monoarthritis is usually caused by osteoarthritis.

TABLE 1. Features of Inflammatory Versus Noninflammatory Pain

Feature	Inflammatory Pain	Noninflammatory Pain
Physical examination findings	Erythema; warmth; soft-tissue swelling; joint effusions; reduced ROM is frequent	Minimal or no warmth; no soft-tissue swelling; bony enlargement and joint effusions may occur in osteoarthritis; reduced ROM may occur
Morning stiffness	>60 min; worsens with immobility	<30 min
Constitutional symptoms	Fever; fatigue; malaise	Generally absent
Synovial fluid	Leukocyte count >2000/µL (2.0×10^9/L), predominantly neutrophils in acute inflammation and monocytes in chronic inflammation	Leukocyte count between 200-2000/µL ($0.2\text{-}2.0 \times 10^9$/L), predominantly monocytes
Other laboratory findings	Elevated inflammatory markers (ESR, CRP); anemia of chronic disease	Inflammatory markers usually normal or minimally elevated

CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; ROM = range of motion.

H CONT.

Oligoarthritis

Oligoarthritis involves two to four joints, typically in an asymmetric pattern. Acute inflammatory oligoarthritis may be caused by gonorrhea or rheumatic fever. Chronic inflammatory oligoarthritis can be caused by autoimmune conditions such as spondyloarthritis.

Chronic noninflammatory oligoarthritis is usually caused by osteoarthritis.

Polyarthritis

Polyarthritis involves five or more joints. In many cases, it involves the small joints of the hands and/or feet. Acute polyarthritis (<6 weeks in duration) can be caused by viral infections (for example, parvovirus B19, HIV, hepatitis B virus, or rubella) or may be an early manifestation of a chronic inflammatory polyarthritis (>6 weeks in duration) such as rheumatoid arthritis, systemic lupus erythematosus, or psoriatic arthritis.

Soft-Tissue Abnormalities

Common nonarticular sources of musculoskeletal symptoms are the soft tissues (tendons, ligaments, and bursae) around or away from the joints. Isolated tendon and/or ligament involvement is usually suggestive of noninflammatory disorders such as mechanical injury/irritation, overuse, or degeneration (for example, rotator cuff disorders or tennis elbow). Disorders of widespread musculoskeletal pain (such as fibromyalgia) also have symptoms localizing to these structures.

The enthesis is a complex structure at the site of the insertion of a tendon or ligament onto the bone. Inflammation of the enthesis (enthesitis) is highly suggestive of spondyloarthritis. When enthesitis is particularly severe, the inflammation may extend along the associated tendon and local ligaments, resulting in dactylitis ("sausage digits").

See MKSAP 18 General Internal Medicine for more information. H

KEY POINTS

- HVC Joint aspiration is usually the most effective means of diagnosing the underlying cause of acute monoarthritis.
- Chronic inflammatory arthritis can be caused by autoimmune diseases, whereas chronic noninflammatory arthritis is usually caused by osteoarthritis.
- Isolated tendon and/or ligament involvement is usually suggestive of noninflammatory disorders such as mechanical injury/irritation, overuse, or degeneration.
- Inflammation of the enthesis (enthesitis) is highly suggestive of spondyloarthritis.

H

Extra-Articular Manifestations of Rheumatologic Disease

Constitutional Symptoms

Fever, morning stiffness, and fatigue occur in numerous rheumatologic conditions. Fever is usually low grade but may be high and spiking in some conditions (for example, adult-onset Still disease and autoinflammatory diseases). Morning stiffness lasting more than 60 minutes is most commonly described in rheumatoid arthritis but also occurs in other forms of inflammatory arthritis. Significant and even disabling fatigue is a prominent feature of fibromyalgia and chronic fatigue syndrome.

Skin Involvement

Skin involvement is common in rheumatologic conditions and may go unnoticed by the patient (**Table 2**). Skin involvement may also occur as an adverse effect of medications used to treat rheumatologic conditions, including skin infections secondary to immunosuppressive therapy.

Eye Involvement

Eye involvement in different rheumatologic diseases usually follows fairly distinct patterns, and the location and type of involvement can help narrow the differential diagnosis (**Table 3**). If not quickly recognized and treated, certain forms of eye involvement can have devastating consequences, including permanent loss of vision.

Internal Organ Involvement

Rheumatologic diseases frequently affect internal organs, with different diseases tending to follow characteristic patterns (**Table 4**). H

KEY POINT

- Rheumatologic disease can cause constitutional symptoms and extra-articular manifestations affecting the skin, eyes, and internal organs.

Laboratory Studies

Laboratory studies are useful for diagnosing rheumatologic diseases, identifying the extent/severity of involvement, evaluating disease activity, and monitoring therapeutic responses. Because of limited specificity, these tests should always be interpreted in the context of the clinical history and physical examination and should be used with great caution, if at all, in the setting of low pretest probability.

Tests That Measure Inflammation

Erythrocyte Sedimentation Rate

The erythrocyte sedimentation rate (ESR) measures the fall of erythrocytes (mm/h) through anticoagulated plasma. Erythrocytes tend to be negatively charged on their surfaces, leading to repulsion and a prolonged ESR. Fibrinogen and other acute phase reactants neutralize the erythrocytes' surface charges, promoting their ability to settle at a faster rate. Elevated fibrinogen levels and high ESRs are seen in many rheumatologic diseases, as well as in nonrheumatologic inflammatory conditions such as chronic infections and malignancies. The normal ESR increases with age and is usually higher in women. A well-accepted rule of thumb is to

TABLE 2. Dermatologic Manifestations of Rheumatologic Disease

Rheumatologic Disease	Dermatologic Manifestations
Systemic lupus erythematosus	Butterfly (malar) rash; photosensitive rash; discoid lupus erythematosus; subacute cutaneous lupus erythematosus; oral ulcerations (on the tongue/hard palate; usually painless); alopecia; lupus panniculitis (painful, indurated subcutaneous swelling with overlying erythema of the skin)
Dermatomyositis	Gottron papules (erythematous plaques on extensor surfaces of MCP and PIP joints); photodistributed poikiloderma, including shawl sign (over the back and shoulders) and V sign (over the posterior neck/back or neck/upper chest); heliotrope rash (violaceous rash on the upper eyelids); mechanic's hands (hyperkeratotic, fissured skin on the palmar and lateral aspects of fingers); nailfold capillary abnormalities; holster sign (poikilodermic rash along lateral thigh); can occur in the absence of myositis (amyopathic dermatomyositis)
Systemic sclerosis	Skin thickening and hardening; nailfold capillary changes
Vasculitis	Palpable purpura; cutaneous nodules; ulcers; necrosis
Behçet syndrome	Painful oral and genital ulcers; erythema nodosum; acne/folliculitis; pathergy (skin inflammation/ulceration from minor trauma)
Sarcoidosis	Erythema nodosum; infiltrated plaques; maculopapular and papular lesions; nodules; soft infiltrates of the nose (lupus pernio); on blanching with a glass slide, sarcoid skin lesions reveal "apple jelly" discoloration
Psoriatic arthritis	Plaque psoriasis typically on extensor surfaces, umbilicus, gluteal fold, scalp, and behind ears; pustular psoriasis on palms and soles; nail pitting; onychodystrophy
Reactive arthritis	Keratoderma blennorrhagicum (psoriasiform rash on soles, toes, palms); circinate balanitis (psoriasiform rash on penis)
Adult-onset Still disease	Evanescent, salmon-colored rash on trunk and proximal extremities
Rheumatic fever (secondary to streptococcal infection)	Erythema marginatum (annular pink to red nonpruritic rash with central clearing)
Lyme disease	Erythema chronicum migrans (slowly expanding, often annual lesion with central clearing)

MCP = metacarpophalangeal; PIP = proximal interphalangeal.

TABLE 3. Ocular Manifestations of Systemic Inflammatory Disease

Systemic Inflammatory Disease	Ocular Manifestations
Ankylosing spondylitis, reactive arthritis, and inflammatory bowel disease (anterior chamber); sarcoidosis and Behçet syndrome (anterior and/or posterior chamber); granulomatosis with polyangiitis (posterior chamber)	Uveitis (inflammation of the anterior and/or posterior chamber and/or retina)
Rheumatoid arthritis; spondyloarthritis; systemic vasculitis	Episcleritis
Rheumatoid arthritis; relapsing polychondritis; inflammatory bowel disease; systemic vasculitis	Scleritis
Systemic vasculitis; antiphospholipid syndrome	Retinal ischemia
Sjögren syndrome	Dryness of the eyes (keratoconjunctivitis sicca)
Giant cell arteritis	Anterior/posterior ischemic optic neuropathy; central retinal artery occlusion; loss of vision
Sarcoidosis; granulomatosis with polyangiitis	Exophthalmos/retrobulbar inflammatory infiltrate
Reactive arthritis	Conjunctivitis

adjust the upper limit of normal as age in years divided by 2 for men and (age in years + 10)/2 for women.

In addition to inflammatory conditions, elevated ESRs can be seen in pregnancy, diabetes mellitus, and end-stage kidney disease. Due to rheostatic properties, anemia and macrocytosis are also associated with an increased ESR. An excessively low ESR can occur in low fibrinogen states such as liver or heart failure and in conditions promoting rouleaux formation (for example, polycythemia vera). Sickle cell disease and microcytosis (including spherocytosis) may also lower ESR.

A markedly elevated ESR (>100 mm/h) should alert physicians to conditions such as giant cell arteritis, multiple myeloma, metastatic cancer, or other overwhelming inflammatory states (infection or autoimmune disease).

TABLE 4. Internal Organ Involvement in Rheumatologic Disease

Organ	Disease	Type of Involvement
Heart		
	Kawasaki disease	Coronary artery vasculitis
	Systemic sclerosis	Arrhythmia; myocardial fibrosis
	SLE	Pericarditis; valvular disease; myocarditis
	RA	Pericarditis; myocarditis
	Rheumatic fever; antiphospholipid syndrome	Valvular disease
	GCA	Aortic aneurysm/dissection; aortitis; large-vessel obstruction
Lung		
	RA	Serositis; ILD; rheumatoid nodules
	SLE; CTDs; Henoch-Schönlein purpura	Serositis; pneumonitis; pulmonary hemorrhage from vasculitis
	AAV	Pulmonary hemorrhage; cavitary nodules
	Diffuse cutaneous systemic sclerosis	ILD; pulmonary hypertension
	Limited cutaneous systemic sclerosis	Pulmonary hypertension
	Antiphospholipid syndrome	Pulmonary embolism
	Sarcoidosis	Hilar lymphadenopathy; ILD
	Goodpasture syndrome	Pulmonary hemorrhage
Kidney		
	SLE; CTDs; AAV; systemic vasculitis (except PAN)	Glomerulonephritis
	PAN	Renal artery vasculitis; pseudoaneurysms
	Antiphospholipid syndrome	Renal infarct; renal vein thrombosis
	Sjögren syndrome	Acute interstitial nephritis/renal tubular acidosis
	Goodpasture syndrome	Glomerulonephritis
Gastrointestinal System		
	PAN	Mesenteric vasculitis
	Henoch-Schönlein purpura	Intestinal vasculitis and ulcerations
	Diffuse and limited cutaneous systemic sclerosis	Esophageal and small bowel hypomotility
	Behçet syndrome	Mucosal ulcerations
	Familial Mediterranean fever	Peritonitis
Nervous System		
	SLE; CTDs; AAV; systemic vasculitis	Mononeuritis multiplex; peripheral neuropathy
	PACNS	CNS vasculitis

AAV = ANCA-associated vasculitis; CNS = central nervous system; CTD = connective tissue disease; GCA = giant cell arteritis; ILD = interstitial lung disease; PACNS = primary angiitis of the central nervous system; PAN = polyarteritis nodosa; RA = rheumatoid arthritis; SLE = systemic lupus erythematosus.

C-Reactive Protein

C-reactive protein (CRP) is produced by the liver mainly in response to interleukin-6 generated by leukocytes during the inflammatory state. CRP levels and ESR usually follow a common pattern, but CRP is often more rapidly responsive to changes in inflammation. In rheumatologic conditions, CRP is typically elevated 2 to 10 times the normal level; a higher level (especially >10 mg/dL [100 mg/L]) should prompt consideration of an alternative diagnosis such as infection. CRP is thought to be a better marker than ESR in measuring inflammation in spondyloarthritis. In contrast, in some patients with systemic lupus erythematosus (SLE), the CRP may remain normal despite active disease. CRP can be elevated in obesity, and a low CRP can occur with the use of certain antibiotics and interleukin-6 blockers.

Complement

The complement system is an essential part of the immune response, promoting vasodilation, attracting leukocytes, and assisting in the lysis of opsonized bacteria during humoral immunity.

Complement components are acute phase reactants and rise in many inflammatory states. However, in response to immune complex formation diseases (SLE and cryoglobulinemic and urticarial vasculitis) and certain other states, complement cascades are activated, and complement levels fall due to excessive consumption. Paradoxically, genetic deficiency of early complement components may increase the risk for lupus-like autoimmune diseases.

C3 and C4 are the commonly measured complement components. The CH50 assay should not be performed routinely due to cost and limited utility.

Autoantibody Tests

Rheumatologic diseases are commonly associated with autoantibodies, but their presence does not equate with the diagnosis of an underlying condition because they lack specificity and may be seen in other conditions and healthy persons. In commercial laboratories, autoantibody testing has been automated using enzyme-linked immunosorbent assay in a sequential algorithm, which may simplify physician assessment but tends to have reduced sensitivity and specificity.

Rheumatoid factor is an IgM antibody directed against the Fc portion of IgG immunoglobulin. Although characteristically associated with rheumatoid arthritis (RA), rheumatoid factor is present in fewer than 70% of patients with RA and is common in several other diseases. Anti-cyclic citrullinated peptide antibodies are more specific for RA but less sensitive. The presence of both autoantibodies together increases the likelihood of RA.

Antinuclear antibodies (ANA) are directed against nuclear antigens and are traditionally associated with SLE. About one third of the healthy population has a low-titer (1:40) ANA, and 3% to 5% have a titer of 1:160 or more. ANA can also be seen in other autoimmune conditions, infection, and malignancy, and it may be drug induced. An isolated positive ANA with nonspecific symptoms and normal clinical examination does not establish the diagnosis of a connective tissue disease.

A higher titer of ANA is more often associated with an underlying rheumatologic disease, although not always SLE. However, almost all patients with SLE (>95%) have a positive ANA. ANA titer does not correlate with disease activity and should not be used for activity assessment.

ANA specificity or subserology testing (that is, testing for antibodies to specific nuclear components such as DNA or centromeres) should be reserved for patients with a positive ANA and a clinical syndrome suggestive of an underlying connective tissue disease. ANA subserology testing should not be routinely performed, even in the setting of a positive ANA, without a strong clinical suspicion of underlying connective tissue disease.

Table 5 provides details on these and other autoantibodies and their associations with specific conditions.

KEY POINTS

- Erythrocyte sedimentation rate and C-reactive protein (CRP) levels usually follow a common pattern, but CRP is often more rapidly responsive to changes in inflammation.
- An isolated positive antinuclear antibody with nonspecific symptoms and normal clinical examination does not establish the diagnosis of a connective tissue disease. **HVC**
- Antinuclear antibody (ANA) subserology testing should not be routinely performed, even in the setting of a positive ANA, without strong clinical suspicion of an underlying connective tissue disease. **HVC**

Imaging Studies

Radiography

H

Plain radiography is an essential modality in the evaluation of many rheumatologic diseases and can assess and differentiate inflammatory arthritis, osteoarthritis, and crystal arthropathies (**Table 6**). Plain radiography has limitations because it gives a two-dimensional picture of three-dimensional structures, is limited in its ability to visualize soft tissues, and may not detect early or small erosive changes. Despite these limitations, plain radiography is usually the first imaging test ordered in the evaluation of rheumatologic diseases because it is readily available, is inexpensive, exposes patients to only a low level of ionizing radiation, and is useful in monitoring arthritis progression.

CT

CT provides multiple views and orientations from a single study but is more useful for bony abnormalities than for soft-tissue inflammation or fluid collections. CT is more sensitive for detecting bone erosions than plain radiographs or MRI. However, CT is more expensive than plain radiography and exposes the patient to more radiation.

MRI

MRI is the most sensitive routine radiologic technique for detecting soft-tissue abnormalities, inflammation, and fluid collections but is less effective than CT in demonstrating bony abnormalities or erosions. MRI is sensitive for detecting early spine and sacroiliac joint inflammation and may be indicated for the evaluation of suspected spondyloarthritis if plain radiographs are negative. MRI does not expose patients to radiation but is associated with high cost, limited availability, and possible patient intolerance due to claustrophobia or body habitus. The American College of Rheumatology Choosing Wisely list recommends against routine MRI of the peripheral joints to monitor RA due to inadequate data supporting its use. **H**

Ultrasonography

The use of ultrasonography to evaluate patients with rheumatologic diseases has expanded dramatically in the past 10 years.

TABLE 5. Autoantibodies in Rheumatologic Disease

Autoantibody	Rheumatologic Disease	Sensitivity/Specificity	Comments
ANA	SLE; also SSc, Sjögren, MCTD	SLE: >95% sensitivity, poor specificity; indirect IFA is the most appropriate methodology	Does not correlate with disease activity
Anti-double-stranded DNA	SLE	SLE: 50%-60% sensitivity, >95% specificity; *Crithidia* IFA or Farr assays more specific than ELISA	Found in more severe disease, especially kidney disease; antibody levels commonly follow disease activity and are useful to monitor
Anti-Smith	SLE	SLE: 30% sensitivity, 99% specificity	Most specific test for SLE; does not correlate with disease activity
Anti-U1-RNP	MCTD; SLE	High sensitivity for MCTD	High titer seen in MCTD (>1:10,000); does not correlate with disease activity
Anti-Ro/SSA; anti-La/SSB	Sjögren; SLE; RA; SSc	Sjögren: 70% sensitivity; SLE: 20% sensitivity	Sicca symptoms; in SLE, associated with photosensitive rash; offspring of mothers who are positive for anti-Ro/SSA or anti-La/SSB are at increased risk for neonatal lupus erythematosus (rash and congenital heart block)
Antiribosomal P	SLE	15% sensitivity	Associated with CNS lupus and lupus hepatitis
Anti-Scl-70 (antitopoisomerase-1)	DcSSc	10%-30% sensitivity	Seen more often in patients with DcSSc who have pulmonary fibrosis
Anticentromere	LcSSc (CREST)	10%-30% sensitivity	Patients with LcSSc with this antibody are more likely to develop pulmonary arterial hypertension
c-ANCA (antiproteinase-3)	GPA	90% sensitivity when disease is active; high specificity in classic presentations	Correlation with disease activity is unclear
p-ANCA (antimyeloperoxidase)	MPA; EGPA	MPA: 80% sensitivity; EGPA: 60% sensitivity; less specific than c-ANCA	Atypical p-ANCA (antimyeloperoxidase negative) can be seen in inflammatory bowel disease and with positive ANA
Anti-Jo-1	Polymyositis	20%-30% sensitivity	Associated with antisynthetase syndrome, including lung inflammation
Rheumatoid factor	RA; Sjögren; cryoglobulinemia	RA: 70% sensitivity; limited specificity, especially in patients without a classic disease presentation	RF is common in multiple other diseases (e.g., hepatitis C, endocarditis, SLE); 30% with RA are RF negative but may become positive later in RA course
Anti-cyclic citrullinated peptide	RA	RA: 70% sensitivity; 95% specificity	Can be positive in RF-negative RA patients; often present before RF becomes positive; associated with erosions; predicts disease progression in undifferentiated arthritis
Antihistone	DILE	95% sensitivity; poor specificity	Also seen in primary SLE
Cryoglobulins	Vasculitis; hepatitis C; myeloma; SLE; RA	Type II or III cryoglobulins seen in cryoglobulinemic vasculitis	May be present in connective tissue diseases in the absence of vasculitis

ANA = antinuclear antibodies; CNS = central nervous system; CREST = calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia; DcSSc = diffuse cutaneous systemic sclerosis; DILE = drug-induced lupus erythematosus; EGPA = eosinophilic granulomatosis with polyangiitis; ELISA = enzyme-linked immunosorbent assay; GPA = granulomatosis with polyangiitis; IFA = immunofluorescence assay; LcSSc = limited cutaneous systemic sclerosis; MCTD = mixed connective tissue disease; MPA = microscopic polyangiitis; RA = rheumatoid arthritis; RF = rheumatoid factor; RNP = ribonucleoprotein; SLE = systemic lupus erythematosus; SSc = systemic sclerosis.

Ultrasonography is relatively inexpensive, can scan across three-dimensional structures, and can provide real-time data in the clinic without exposure to ionizing radiation. It can assess soft-tissue abnormalities, including synovitis, tendonitis, bursitis, and effusions; assess disease activity using Doppler; and assist with tendon or joint injections. However, it is operator dependent, and training/practice is needed to achieve competence.

KEY POINTS

- Plain radiography is usually the first imaging test ordered in the evaluation of rheumatologic diseases because it is readily available, is inexpensive, exposes patients to only a low level of ionizing radiation, and is useful in monitoring arthritis progression. HVC

(Continued)

TABLE 6. Radiographic Findings of Common Rheumatologic Diseases

Rheumatologic Disease	Radiographic Findings
Rheumatoid arthritis	Bony erosions; periarticular osteopenia; subluxations; soft-tissue swelling; MCP, PIP, and wrist involvement
Osteoarthritis	Asymmetric joint-space narrowing; osteophytes; subchondral sclerosis and cystic changes; degenerative disk disease with collapse of disks; degenerative joint disease with facet joint osteophytes; spondylolisthesis (anterior/posterior misalignment of the spine); kyphosis
Diffuse idiopathic skeletal hyperostosis	Calcification of the anterior longitudinal ligament; bridging horizontal syndesmophytes; usually seen in the thoracic spine and more prominent on the right side of the spine
Ankylosing spondylitis	Sacroiliitis; squaring of the vertebral bodies; bridging vertical syndesmophytes; shiny corners; ankylosis does not skip vertebrae
Psoriatic arthritis	Destructive arthritis with erosions and osteophytes; DIP involvement is common; pencil-in-cup deformity on hand radiograph; arthritis mutilans; syndesmophytes
Gout	Punched-out erosions with sclerotic borders and overhanging edges; periarticular soft-tissue swelling with calcifications in tophaceous deposits
Calcium pyrophosphate deposition	Chondrocalcinosis, most commonly of the knees, shoulders, wrists, pubic symphysis; osteoarthritis, including in locations atypical for primary osteoarthritis (MCPs, wrists, shoulders)

DIP = distal interphalangeal; MCP = metacarpophalangeal; PIP = proximal interphalangeal.

KEY POINTS *(continued)*

- HVC • CT is more sensitive for detecting bony abnormalities or erosions than plain radiographs or MRI, whereas MRI is the most sensitive routine radiologic technique for detecting soft-tissue abnormalities, inflammation, and fluid collections.
- HVC • Ultrasonography is an inexpensive means to assess soft-tissue abnormalities, assess disease activity, and assist with tendon or joint injections, but it is operator dependent.

H Joint Aspiration

Joint aspiration and synovial fluid analysis are essential for discriminating between inflammatory and noninflammatory effusions or for distinguishing between infectious arthritis and acute crystal arthropathies. In the evaluation of any monoarthritis or when infection is being considered, joint aspiration should be performed to diagnose the underlying cause. Aspirated synovial fluid should be sent for leukocyte count, Gram stain, and cultures, as well as evaluation for crystals under polarized light. See **Table 7** for more information.

There is no absolute cutoff of synovial fluid leukocyte counts for ruling out infectious arthritis; however, counts greater than 50,000/µL (50×10^9/L) with polymorphonuclear cell predominance have a high likelihood of infection. Counts less than 2000/µL (2.0×10^9/L) are usually associated with noninflammatory etiologies. Notably, crystals can coexist with infection, and their presence does not rule out infection if suspicion is high. H

Tissue Biopsy

When appropriate, tissue biopsy of involved organs can be helpful in diagnosing numerous rheumatologic conditions such as vasculitis (lung, kidney, or temporal artery biopsy) and SLE (skin biopsy). Tissue biopsy may also help assess disease

TABLE 7. Synovial Fluid Analysis

	Normal	Noninflammatory	Inflammatory	Crystal Induced	Infectious	Hemorrhagic
Appearance	Clear/yellow/ transparent	Clear/yellow/ transparent	Yellow/white/ translucent/ opaque	Yellow/white/ translucent/ opaque	Yellow/white/ opaque	Red/opaque
Leukocyte count	<200/µL (0.2×10^9/L)	200-2000/µL ($0.2\text{-}2.0 \times 10^9$/L)	2000-20,000/µL ($2.0\text{-}20 \times 10^9$/L) (may be higher)	10,000-50,000/µL ($10\text{-}50 \times 10^9$/L) (may be higher)	>50,000/µL (50×10^9/L) (may be lower)	—
Other studies	Negative Gram stain; negative culture	Negative Gram stain; negative culture	Negative Gram stain; negative culture	Negative Gram stain; positive crystals[a]	Positive Gram stain[b]; positive culture[c]	Negative Gram stain; negative culture

[a]Crystal description: Urate crystals are needle shaped and bright. Viewed under polarized light, they are negatively birefringent; they appear yellow when parallel to the axis of the polarized field and blue when perpendicular to the axis. Calcium pyrophosphate crystals are rhomboid, pale, and weakly (not as vividly) positively birefringent; they appear blue when parallel to the axis and yellow when perpendicular.

[b]Gram stain sensitivity for infection is approximately 30% to 50%.

[c]Nearly all cultures are positive except for infection caused by *Neisseria gonorrhoeae*, which may be positive in 50% or fewer cases.

activity (for example, kidney biopsy in SLE). The benefits should be appropriately balanced with possible risks of the procedure.

KEY POINTS

- Synovial fluid leukocyte counts greater than 50,000/µL (50×10^9/L) with polymorphonuclear cell predominance have a high likelihood of infection; counts less than 2000/µL (2.0×10^9/L) are usually associated with noninflammatory etiologies.
- Tissue biopsy of involved organs can be helpful in diagnosing numerous rheumatologic conditions and in assessing disease activity in some conditions.

Principles of Therapeutics

Overview

This section reviews the indications for use, mechanisms of action, major toxicities, and monitoring requirements of medications used in rheumatologic disease. Drug applications in specific disease states are elaborated upon in their respective sections.

Anti-Inflammatory Agents

Glucocorticoids

Glucocorticoids are effective in many rheumatologic diseases, including rheumatoid arthritis (RA), acute crystal arthropathy, systemic vasculitis, polymyalgia rheumatica, systemic lupus erythematosus (SLE), inflammatory myopathies, and autoinflammatory diseases. Advantages include rapid onset of action, ease of use, low cost, and universal availability; in many disease states, they are disease modifying and sometimes lifesaving.

Glucocorticoids have numerous adverse effects, which are more likely to occur with higher doses and longer treatment. These include osteoporosis, immunosuppression, skin fragility, glaucoma, cataracts, weight gain, diabetes mellitus, hypertension, psychomotor agitation, osteonecrosis, and hypothalamic-pituitary-adrenal axis suppression.

Patients anticipated to be taking ≥2.5-mg prednisone for ≥3 months should be risk-assessed for glucocorticoid-induced osteoporosis and appropriately managed. Those who are at moderate or high risk for osteoporotic fractures and placed on chronic glucocorticoid therapy should begin oral bisphosphonates.

NSAIDs

NSAIDs prevent prostaglandin production by inhibiting the two isoforms of cyclooxygenase (COX), COX-1 and COX-2. COX-2 is an inducible enzyme typically expressed in inflammatory milieus, whereas COX-1 is constitutively expressed and helps maintain organismal homeostasis. Nearly all available COX inhibitors are nonselective (inhibit both isoenzymes), down-regulating prostaglandin production in inflammatory states and interfering with housekeeping functions of prostanoids (for example, renal blood flow and gut mucosal integrity maintenance) (**Table 8**). Nonselective COX inhibitors also inhibit thromboxane A_2, inhibiting platelet function and promoting bleeding.

Although they alleviate symptoms, COX inhibitors are not disease modifying, with the apparent exception of ankylosing spondylitis. Major concerns surrounding all COX inhibitors include increased risk for gastrointestinal bleeding (particularly in those already at risk) and adverse cardiovascular events; therefore, they should be prescribed at the lowest dose for the shortest time possible. COX inhibitors should generally be avoided in patients on concomitant anticoagulation.

Selective COX-2 inhibitors were developed to spare COX-1 and reduce gastrointestinal risk; although effective for this purpose, the most selective COX-2 inhibitors were found to increase the risk of cardiovascular events and were removed from the market.

NSAIDs vary with regard to kinetics, COX-1/2 selectivity, and other features, and carry somewhat different degrees of risk; having experience with several different NSAIDs is potentially beneficial in clinical practice.

Topical NSAIDs such as diclofenac are available by prescription for arthritis and pose a lower risk for systemic side effects than oral NSAIDs. They may be preferred for patients at high risk for toxicity from oral NSAIDs and/or for those ≥75 years of age. However, they are often expensive.

TABLE 8. Potential Toxicities of NSAID Use

Category	Toxicity
Cardiovascular	Myocardial infarction; exacerbation of heart failure
Hemostatic	Platelet dysfunction
Gastrointestinal	Dyspepsia; reflux; peptic ulcer disease; gastrointestinal bleeding
Obstetric/Gynecologic	Bleeding; delayed labor; premature ductus arteriosus closure
Pulmonary	Asthma exacerbation
Renal	Hypertension; decreased glomerular filtration; increased salt and water retention; increased renin production; uncommonly, allergic interstitial nephritis or acute tubular necrosis

Colchicine

Colchicine inhibits microtubules and impairs neutrophil function. It is most commonly employed for gout and acute calcium pyrophosphate crystal arthritis (pseudogout). It is also used to treat hypersensitivity vasculitis and familial Mediterranean fever.

Gastrointestinal side effects (particularly diarrhea) are common. With overdose, severe (even fatal) myelosuppression can occur. Dosing must be adjusted for kidney disease. When given chronically, colchicine can rarely cause neuromuscular toxicity, particularly if coadministered with statin drugs. Concomitant administration of strong CYP3A4 inhibitors (for example, clarithromycin) that reduce the hepatic catabolism of colchicine should be avoided.

KEY POINTS

- Although effective inflammatory agents in many rheumatologic diseases, glucocorticoids have numerous adverse side effects, including osteoporosis, immunosuppression, skin fragility, glaucoma, cataracts, weight gain, diabetes mellitus, hypertension, psychomotor agitation, osteonecrosis, and hypothalamic-pituitary-adrenal axis suppression.
- Because of the increased risk for gastrointestinal bleeding and adverse cardiovascular events, cyclooxygenase inhibitors should be prescribed at the lowest dose for the shortest time possible.

Analgesics and Pain Pathway Modulators

Acetaminophen

The efficacy of acetaminophen for osteoarthritis and lower back pain is increasingly questioned, with recent controlled trials and meta-analyses demonstrating no benefit from the drug, even at high doses (3000-4000 mg/d).

Tramadol

Tramadol is a mixed opioid analgesic and weak serotonin-norepinephrine reuptake inhibitor; potential for addiction is lower than for traditional opioids, which are generally avoided in rheumatologic treatment.

Duloxetine

Duloxetine is a serotonin-norepinephrine reuptake inhibitor that is FDA approved for the management of chronic musculoskeletal pain and fibromyalgia. Duloxetine provides modest pain relief for knee osteoarthritis, chronic lower back pain, and fibromyalgia. Patients must be slowly weaned off the drug when discontinuing to avoid withdrawal symptoms.

Gabapentinoids

Gabapentinoids (gabapentin and pregabalin) inhibit voltage-gated calcium channels, reducing pain signaling. Pregabalin is FDA approved for fibromyalgia. Common side effects (dizziness, disequilibrium, somnolence, weight gain, peripheral edema, cognitive difficulties) may limit its utility, and discontinuation is sometimes warranted. Gabapentin also modestly improves fibromyalgia symptoms, with a similar side-effect profile.

KEY POINT

- The efficacy of acetaminophen for osteoarthritis and lower back pain is increasingly questioned, with recent controlled trials and meta-analyses demonstrating no benefit from the drug, even at high doses. **HVC**

Disease-Modifying Antirheumatic Drugs

Nonbiologic Disease-Modifying Antirheumatic Drugs

Table 9 summarizes the mechanisms of action, indications, and common monitoring parameters of various nonbiologic disease-modifying antirheumatic drugs (DMARDs). See Medications and Pregnancy for information on these drugs in pregnancy.

Methotrexate

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Methotrexate is a first-line medication for treating RA and other autoimmune diseases. Once-weekly dosing is generally between 10 to 25 mg and can be given orally or subcutaneously. At doses above 15 mg, parenteral administration is more reliable but much more expensive.

Potential side effects include headaches, fatigue, and nausea (particularly around the time of weekly dosing). Hepatotoxicity and cytopenias can occur (especially macrocytic anemia), and dose adjustment is required with kidney disease. Methotrexate should be avoided in patients with significant hepatic or kidney disease. Folic acid supplements minimize toxicity while preserving efficacy. Limiting alcohol intake is recommended. H

Hydroxychloroquine

Hydroxychloroquine is an immunomodulator that is widely used in SLE, in which it decreases mortality and the likelihood of developing nephritis. It is rarely sufficient as single-drug therapy for RA but is useful as an adjunctive therapy.

Sulfasalazine

Sulfasalazine is used to treat RA and nonaxial psoriatic arthritis, but use has decreased because of the relative effectiveness of methotrexate and leflunomide. It is now most frequently used as part of combination DMARD therapy for RA and in women considering pregnancy. Serious side effects include blood dyscrasias, hepatitis, and hypersensitivity reactions. Because of its benefit for inflammatory bowel disease (IBD), it may constitute a useful strategy for patients with IBD-associated arthritis.

TABLE 9. Nonbiologic Disease-Modifying Antirheumatic Drugs

Agent	Mechanism	Indications	Common Monitoring Parameters
Methotrexate	Low dose: anti-inflammatory agent via up-regulation of adenosine A_{2A} signaling High dose: antimetabolite/folate antagonist used in neoplastic disease	RA; psoriasis; psoriatic arthritis; IBD; SLE (arthritis only); reactive arthritis; DM; PM; vasculitis	Baseline: chest radiography, hepatitis screening, CBC, LCTs, serum creatinine Thereafter: CBC, LCTs, serum creatinine after the first month, then approximately every 2-3 months[a]
Hydroxychloroquine	Uncertain; appears to involve stabilization of lysosomal vacuoles, leading to inhibition of antigen processing and/or inhibition of Toll-like receptor activation	SLE; RA	Baseline: CBC, LCTs, serum creatinine Retinal examinations at baseline and annual examination after 5 years of therapy to evaluate for retinopathy
Sulfasalazine	Unknown; the prodrug is broken down into 5-amino salicylic acid (active metabolite in the gastrointestinal tract) and sulfapyridine (exerts systemic action)	RA; SpA; IBD	Baseline: CBC, LCTs, serum creatinine Thereafter: CBC, LCTs, serum creatinine every 3-6 months
Leflunomide	Inhibits the mitochondrial enzyme dihydroorotate dehydrogenase to block pyrimidine synthesis (decreasing lymphocyte production); antiproliferative	RA	Baseline: hepatitis screening, CBC, LCTs, serum creatinine Thereafter: CBC, LCTs, serum creatinine after 4 weeks, then every 3 months
Azathioprine	A prodrug of 6-mercaptopurine; purine analogue; inhibits DNA synthesis essential for proliferating T- and B-lymphocytes	SLE; DM; PM; vasculitis; IBD	Baseline: CBC, LCTs, serum creatinine Thereafter: CBC, LCTs, serum creatinine every 3 months[a]
Cyclophosphamide	Alkylating agent; blocks DNA synthesis and causes cell death, especially of T cells	Severe and life-threatening disease in SLE, DM, PM, and vasculitis; may be used when other agents fail	Close monitoring clinically and measuring CBC, chemistries, LCTs, urinalysis every 4-8 weeks
Mycophenolate mofetil	Active metabolite (mycophenolic acid) inhibits purine synthesis; preferentially inhibits T- and B-lymphocytes	SLE (especially lupus nephritis); vasculitis (maintenance therapy); DM; PM; SSc	Baseline: CBC, LCTs, serum creatinine Thereafter: CBC, LCTs, serum creatinine after 4 weeks and then every 3 months[a]
Cyclosporine	Inhibits calcineurin (a transcription activating factor); preferentially targets T cells	SLE; psoriasis; RA	Baseline: CBC, LCTs, serum creatinine Thereafter: CBC, LCTs, serum creatinine every 2-3 months[a]
Tofacitinib	Janus kinase inhibitor	RA	Baseline: CBC, LCTs, creatinine, lipid panel Thereafter: CBC, LCTs, creatinine every 8 weeks, lipids after 8 weeks and then every 6 months
Apremilast	Inhibits phosphodiesterase 4	Psoriasis; psoriatic arthritis	Baseline: weight Thereafter: weight, neuropsychiatric effects

CBC = complete blood count; DM = dermatomyositis; IBD = inflammatory bowel disease; LCTs = liver chemistry tests; PM = polymyositis; RA = rheumatoid arthritis; SLE = systemic lupus erythematosus; SpA = spondyloarthritis; SSc = systemic sclerosis.

[a]Recommended monitoring interval is for a stable dose but may be shorter after initiation or in the case of abnormal results and must be individualized to the patient's risk of toxicity.

Leflunomide

Leflunomide is FDA approved for rheumatoid and psoriatic arthritis, with comparable efficacy to methotrexate. Patients must be monitored for hepatotoxicity and myelosuppression. Other common side effects include nausea, headaches, rash, diarrhea, and transaminitis. An uncommon side effect is peripheral neuropathy, but it is usually self-limited if the drug is discontinued. The active metabolite of leflunomide (teriflunomide) has a half-life of nearly 3 weeks; therefore, when the drug needs to be eliminated quickly, an 11-day cholestyramine washout is necessary.

Azathioprine

Azathioprine is an immunosuppressant used in various inflammatory diseases. Concomitant use with xanthine oxidase inhibitors (allopurinol, febuxostat) is contraindicated. Azathioprine's primary toxicity is myelosuppression. Thiopurine methyltransferase enzyme testing allows for identification of patients with decreased or absent enzyme activity at high myelosuppression risk.

Cyclophosphamide

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Cyclophosphamide is a powerful immunosuppressant with a rapid onset of action (days to weeks). It treats vasculitis,

H CONT.

life-threatening complications of SLE, and interstitial lung disease. Cyclophosphamide has largely been displaced by newer and safer drugs for first-line treatment of ANCA-associated vasculitis and lupus nephritis (rituximab and mycophenolate mofetil, respectively) but is still used in severe cases or when these agents fail. Serious potential side effects include severe immunosuppression, leukopenia, hemorrhagic cystitis, and ovarian failure, as well as long-term risk for bladder cancer, leukemia, and lymphoma. H

Mycophenolate Mofetil

Mycophenolate mofetil is currently the first-line agent for lupus nephritis and may be effective for systemic sclerosis and associated interstitial lung disease. Gastrointestinal side effects are common, particularly diarrhea. Myelosuppression may occur.

Calcineurin Inhibitors

Calcineurin inhibitors include cyclosporine and tacrolimus. Although cyclosporine is now rarely used in rheumatology, one of its most common side effects is hyperuricemia, and cyclosporine-induced gout is an important consideration in patients taking the drug who present with acute monoarthritis. There is currently renewed interest in tacrolimus as a possible alternative therapy for lupus nephritis.

Tofacitinib

Tofacitinib is an oral agent that inhibits Janus kinase (JAK) signaling. Tofacitinib is FDA approved for RA and has efficacy equal to biologic DMARDs. Risks include hyperlipidemia, hepatotoxicity, and leukopenia.

Apremilast

Apremilast is modestly effective for psoriasis and psoriatic arthritis. It does not cause immunosuppression or myelosuppression. However, apremilast is less efficacious than biologic DMARDs and has a slow onset of action, and its effect on progression of erosive damage is unknown. Adverse events include gastrointestinal side effects (mainly nausea and diarrhea) and weight loss. It should be used with caution in patients with a history of depression.

KEY POINTS

- Methotrexate is a first-line medication for treating rheumatoid arthritis and other autoimmune diseases.
- Hydroxychloroquine is widely used in systemic lupus erythematosus, in which it decreases mortality and the likelihood of developing nephritis.
- Cyclophosphamide has been largely displaced by newer drugs for first-line treatment of ANCA-associated vasculitis and lupus nephritis but is still used in severe cases or when other agents fail.
- The oral agent tofacitinib is FDA approved for rheumatoid arthritis and has efficacy equal to biologic agents.

Biologic Disease-Modifying Antirheumatic Drugs

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Biologic DMARDs are highly specific, parenterally administered, protein-based agents with extracellular targets (specific proinflammatory cytokines, cytokine receptors, or clusters of differentiation cell surface molecules on immune cells; **Figure 1**). The end of the generic name of a biologic agent indicates what type of molecule it is: *-mab* indicates monoclonal antibody; *-kin* indicates an interleukin-type substance; *-ra* is for a receptor antagonist; and *-cept* is for receptor molecules.

Table 10 and **Table 11** summarize the structures, targets, indications, and common monitoring parameters of various biologic DMARDs. See Medications and Pregnancy for information on these drugs in pregnancy. Biologic DMARDs increase the risk for infection to variable degrees. Targeted screening is therefore necessary before initiation (see Vaccination and Screening in Immunosuppression).

The cost of biologic agents is significant and may be a barrier to access.

Tumor Necrosis Factor α Inhibitors

Tumor necrosis factor (TNF)-α inhibitors are large protein-based molecules that require parenteral administration (see Table 10). They are widely used for treating RA, psoriasis, psoriatic arthritis, and ankylosing spondylitis, and are also approved for several nonrheumatologic diseases.

TNF-α inhibitors are generally well tolerated, with increased risk for infection the primary safety concern. They pose a particularly high risk for reactivation of tuberculosis, so all patients being considered for TNF-α inhibitor therapy need to be screened and receive appropriate prophylaxis. TNF-α inhibitors do not appear to increase the risk of new cancers, aside from nonmelanoma and possibly melanoma skin cancer; the risk for malignant recurrence is unclear. These agents may also exacerbate heart failure and rarely provoke a demyelinating condition. Over time, TNF-α inhibitors may often lose efficacy owing to formation of anti-drug antibodies.

Other Biologic Disease-Modifying Antirheumatic Drugs

Multiple biologic DMARDs with additional extracellular and cell-surface targets have been approved by the FDA in the past decade. Most of these agents are started after one or two TNF-α inhibitors have failed. See Table 11 for more information. H

Biosimilars

Biosimilar agents are "copycat" versions of brand-name biologic medications. The drugs are not exact replicas (hence the term "biosimilar" rather than "generic"); therefore, they must go through phase III testing to garner regulatory approval. In 2016, the FDA approved three biosimilar anti-TNF agents.

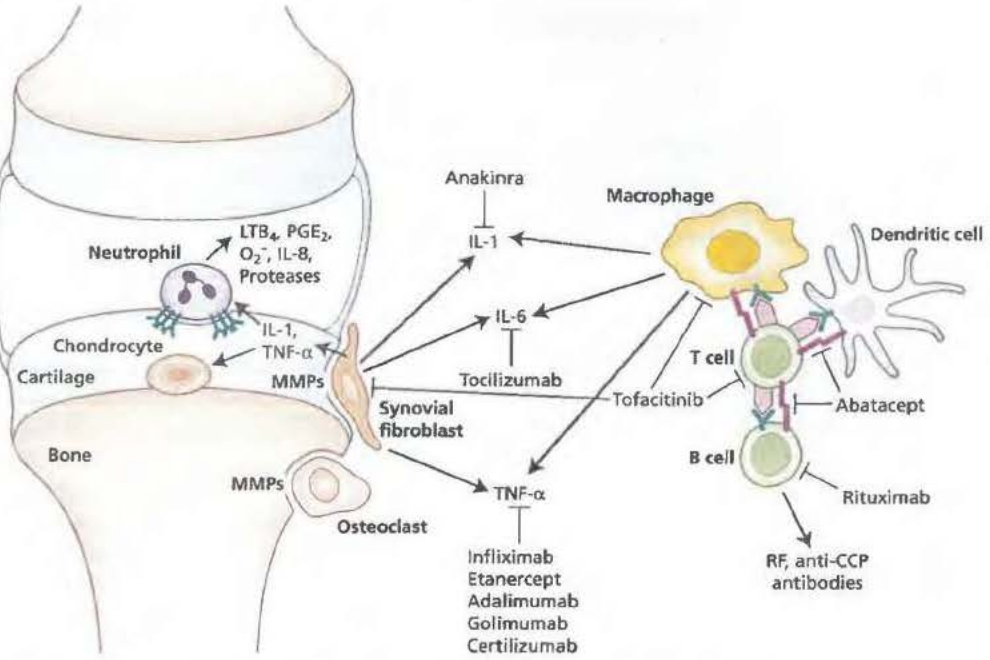

FIGURE 1. The inflammatory cascade in rheumatoid arthritis (RA). Dendritic cells, macrophages, and B cells present inciting antigens to T cells. Macrophages secrete multiple cytokines, including ILs and TNF-α, which are also secreted by activated synovial fibroblasts. The activated fibroblasts secrete matrix metalloproteinases (MMPs) and other enzymes that contribute to the degradation of articular cartilage and activate neutrophils, which mediate joint damage through proteases and other enzymes. Activated osteoclasts additionally secrete MMPs that contribute to marginal erosions of bone. ILs, TNF-α, T cells, and B cells may all be targeted for inhibition by the various disease-modifying antirheumatic drugs useful in RA. CCP = cyclic citrullinated peptide; IL = interleukin; LTB_4 = leukotriene B_4; MMP = matrix metalloproteinase; O_2 = oxygen; PGE_2 = prostaglandin E_2; RF = rheumatoid factor; TNF = tumor necrosis factor.

TABLE 10. Tumor Necrosis Factor α Inhibitors[a]

Agent	Agent Structure	Indications
Adalimumab	Humanized monoclonal antibody	RA; psoriatic arthritis; ankylosing spondylitis; IBD
Etanercept	Fusion protein made of two p75 TNF-α receptors linked to IgG Fc segment	RA; psoriatic arthritis; ankylosing spondylitis
Certolizumab pegol	Fab' segment of humanized monoclonal antibody attached to polyethylene glycol strands	RA; psoriatic arthritis; ankylosing spondylitis
Golimumab	Humanized monoclonal antibody	RA; psoriatic arthritis; ankylosing spondylitis
Infliximab	Chimeric (mouse-human) monoclonal antibody	RA; psoriatic arthritis; ankylosing spondylitis; IBD

IBD = inflammatory bowel disease; RA = rheumatoid arthritis; TNF = tumor necrosis factor.

[a]Common monitoring parameters for TNF-α inhibitors include tuberculosis, fungal, and other infections as well as complete blood count, serum creatinine, and liver chemistry tests at baseline and thereafter every 3 to 6 months.

KEY POINTS

- All biologic agents increase the risk for infection; therefore, targeted screening is necessary before initiation.
- Tumor necrosis factor α inhibitors are widely used for treating rheumatoid arthritis, psoriasis, psoriatic arthritis, and ankylosing spondylitis; they are also approved for treating some nonrheumatologic diseases.
- HVC Non–tumor necrosis factor (TNF)-α biologic agents are usually started after one or two TNF-α inhibitors have failed.

Urate-Lowering Therapy

Allopurinol

Allopurinol is the most commonly used urate-lowering agent. It competitively inhibits the enzyme xanthine oxidase, blocking the conversion of hypoxanthine (a breakdown product of purines) to uric acid. Allopurinol is metabolized to oxypurinol, which also inhibits xanthine oxidase. Allopurinol is FDA approved for doses up to 800 mg/d. According to the American College of Rheumatology, allopurinol should be initiated at 100 mg/d and titrated in 100-mg increments as needed, and

TABLE 11. Other Biologic Disease-Modifying Antirheumatic Drugs[a]

Agent	Agent Structure	Target	Indications	Comments
Abatacept	Soluble CTLA4 receptor/IgG Fc segment chimera	CD80/CD86; blocks T-cell costimulation	RA	Preferred for those with history of severe infection; relatively contraindicated in COPD
Rituximab	Chimeric (mouse-human) monoclonal antibody	$CD20^+$ B cells	RA; ANCA-associated vasculitis; occasionally for SLE (off-label); hyper-IgG4 syndrome	Given as an intravenous infusion over several hours; has a higher risk of infusion reactions than other biologic DMARDs; can cause hypogammaglobulinemia
Tocilizumab	Humanized monoclonal antibody	IL-6 receptor	RA; JIA; Castleman disease; GCA	Can cause transaminitis, hyperlipidemia, leukopenia, thrombocytopenia; avoid in those with history of diverticulitis because of an attendant risk of bowel perforation
Belimumab	Human monoclonal antibody	BLyS/BAFF	SLE	Phase III trials showed a small but statistically significant improvement versus standard therapy alone, with a glucocorticoid-sparing effect
Ustekinumab	Human monoclonal antibody	IL-12/IL-23	Psoriasis; psoriatic arthritis	Injectable; less robust effect than other biologic DMARDs
Secukinumab	Human monoclonal antibody	IL-17a	Psoriatic arthritis; ankylosing spondylitis	Phase III trials suggest equal efficacy to TNF-α inhibitors; can cause flares of IBD
Anakinra	Recombinant receptor antagonist	IL-1β receptor	RA; CAPS[b]; AOSD (off-label); acute gouty arthritis (off-label)	Rarely used in RA because efficacy is inferior to other biologic DMARDs; reversible neutropenia can develop
Canakinumab	Human monoclonal antibody	IL-1β	CAPS[b]	Newer, more expensive IL-1 inhibitor
Rilonacept	Dual IL-1β receptors chimerically attached to IgG Fc segment	IL-1	CAPS[b]; refractory gout	Newer, more expensive IL-1 inhibitor

AOSD = adult-onset Still disease; BAFF = B-cell-activating factor; BLyS = B-lymphocyte stimulator; CAPS = cryopyrin-associated periodic syndromes; DMARD = disease-modifying antirheumatic drug; GCA = giant cell arteritis; IBD = inflammatory bowel disease; IL = interleukin; JIA = juvenile idiopathic arthritis; RA = rheumatoid arthritis; SLE = systemic lupus erythematosus; TNF = tumor necrosis factor.

[a]Prior to initiating any biologic, tuberculosis screening must be performed. Complete blood counts should be performed every 3 to 6 months for all biologics, and aspartate aminotransferase/alanine aminotransferase and a lipid panel should be checked every 2 to 3 months for tocilizumab.

[b]The cryopyrin-associated periodic syndromes (CAPS) include familial cold autoinflammatory syndrome, Muckle-Wells syndrome, and neonatal-onset multisystem inflammatory disease (chronic infantile neurologic, cutaneous, articular syndrome).

for those with stage 4 or 5 chronic kidney disease, allopurinol should be initiated at 50 mg/d and titrated in 50-mg increments as needed.

H The biggest risk the drug poses is DRESS (drug reaction with eosinophilia and systemic symptoms) syndrome, a rare reaction that usually occurs in the presence of chronic kidney disease and diuretic use and has a high mortality rate (see MKSAP 18 Dermatology). A recently discovered DRESS risk factor is the HLA-B*5801 allele, which is more common in persons of Han Chinese, Thai, and Korean descent. Screening for HLA-B*5801 in high-risk populations is recommended before initiating therapy. Xanthine oxidase inhibitors cannot be coadministered with purine analogues (such as azathioprine). H

Febuxostat

Febuxostat is a noncompetitive xanthine oxidase inhibitor. As with allopurinol, transaminitis rarely occurs, and liver enzymes should be monitored. Concomitant use with purine analogues is contraindicated. Incidence of DRESS syndrome is rare.

Uricosuric Agents

Probenecid is an organic acid transport inhibitor that decreases renal reuptake of uric acid. Probenecid is uncommonly used because of limited efficacy, as well as inconvenience and limitations on use.

Lesinurad is a recently approved, highly potent inhibitor of renal uric acid reuptake targeting the urate transporter URAT1. It is approved only for combination use with febuxostat or allopurinol. Lesinurad can rarely cause renal toxicity and should not be given to those with an estimated creatinine clearance less than 45 mL/min.

Pegloticase

Unlike most other mammals, humans lack a functioning uricase to break down uric acid. Pegloticase is a recombinant, nonhuman, infusible pegylated uricase that is highly effective at lowering serum urate. Pegloticase is reserved for severe and/or refractory gout. Because of its extreme potency, mobilization flares of gout are common, and prophylaxis against acute gouty attacks is required. Pegloticase is administered

intravenously every 2 weeks; if the pre-infusion serum urate increases to more than 6.0 mg/dL (0.35 mmol/L) on two occasions, it is likely that antibodies have formed, and the drug should be discontinued to prevent infusion reactions.

KEY POINTS

- Allopurinol is the most commonly used urate-lowering agent; the biggest risk the drug poses is DRESS (drug reaction with eosinophilia and systemic symptoms) syndrome, which has a high mortality rate.
- Concomitant use of xanthine oxidase inhibitors (allopurinol or febuxostat) with purine analogues is contraindicated.

Medications and Pregnancy

Some rheumatologic medications can have adverse effects on pregnancy. See **Table 12** for a discussion of these agents and their relative risks.

KEY POINTS

- Methotrexate is highly teratogenic and abortifacient; it must be discontinued at least 3 months before pregnancy.
- Hydroxychloroquine is relatively safe in pregnancy and should not be discontinued if it is needed.
- Leflunomide is extremely teratogenic and must not be used before or during pregnancy; upon discontinuation, cholestyramine administration is required to remove the drug from the body in all women of childbearing potential and specifically in those wishing to become pregnant.

Vaccination and Screening in Immunosuppression

Patients should be updated with vaccinations before initiating biologic DMARD regimens. Vaccine response may be diminished once on treatment, and patients on some immunosuppressants (including all biologic DMARDs and tofacitinib) should not receive live attenuated vaccines (such as for herpes zoster, live attenuated influenza, and yellow fever) because of risk for viral activity in an immunocompromised host. Despite diminished efficacy, patients already on a biologic DMARD should receive any non-live vaccines that are indicated as per standard of care. Patients receiving traditional oral DMARDs (for example, hydroxychloroquine, methotrexate, and sulfasalazine) may receive any and all vaccines as needed.

Before initiating immunosuppressive therapy, the following screening is recommended:

- Tuberculosis screening with tuberculin skin testing or interferon-γ release assay, particularly for patients initiating biologic DMARDs
- Hepatitis B and C serologies (for biologic DMARDs and drugs that can cause hepatotoxicity)
- HIV screening

Patients with latent or active tuberculosis, active hepatitis B, or untreated HIV infection require initiation of appropriate therapy before initiating immunosuppression. Repeat screening for tuberculosis should be performed annually if there are risk factors for ongoing tuberculosis exposure.

KEY POINTS

- Vaccinations should be updated before initiating biologic disease-modifying antirheumatic drug regimens.
- Screening (and therapy if needed) for tuberculosis, hepatitis B and C serologies, and HIV is appropriate before initiating immunosuppressive therapy.

Nonpharmacologic and Nontraditional Management

Because rheumatologic diseases frequently affect the musculoskeletal system, nonpharmacologic measures are often employed to address pain not eliminated by medications. These measures include physical therapy, occupational therapy, surgery, weight reduction, psychosocial support, and self-management programs. Many patients turn to complementary and alternative medicine as adjuncts to traditional medical interventions.

Physical and Occupational Therapy

The physical therapist can aid the primary care provider in assessing a patient's aerobic fitness and conditioning as well as the patient's ability to carry out activities of daily living. Pain and functional limitation can be addressed through manual therapy, assistive devices, joint protection techniques, and thermal treatments. A targeted exercise program can be initiated, and adapting the program for home use is critical. Tendinitis, bursitis, many forms of arthritis, and chronic soft tissue pain due to overuse, injury, and chronic pain syndromes (such as fibromyalgia) are among the diagnoses appropriate for physical therapy referral.

Occupational therapists assess upper extremity functioning, including the ability to perform self-care and job-related tasks. Braces and splints may be provided for painful or unstable joints. An ergonomic evaluation of the workstation may accompany instruction in improved body mechanics and avoidance of repetitive trauma.

Complementary and Alternative Medicine

Nontraditional options for symptom management are employed by about one third of patients overall and up to 90% of patients with chronic pain, including arthritis and rheumatologic diseases. Commonly used over-the-counter supplements include fish oil, vitamins, glucosamine, and chondroitin. Providers should ask about supplement use because

TABLE 12. Rheumatologic Medications and Pregnancy[a]	
Medication/Class	**Comments**
Anti-Inflammatory Agents	
NSAIDs	May impede implantation and may be associated with a small increased risk of miscarriage when used before 20 weeks' gestation. Use of NSAIDs after 30 weeks' gestation can lead to premature closure of the ductus arteriosus.
Glucocorticoids	When taken in the first trimester, can increase the risk of fetal cleft palate, and can raise the risk of maternal gestational diabetes throughout the pregnancy.
	Useful in the management of active autoimmune disease in pregnancy. Non-fluorinated glucocorticoids (e.g., prednisone, prednisolone, methylprednisolone) have limited ability to cross the placenta and are preferred, except when treating the fetus (e.g., neonatal lupus erythematosus).
Colchicine	Should be used only if the potential benefit justifies the potential risk to the fetus.
Analgesics	
Acetaminophen	Generally considered safe at standard dosing, but does cross the placenta.
Opiates	Some opiates/opioids cross the placenta; may cause fetal opioid withdrawal at birth.
Tramadol	Should be used only if the potential benefit justifies the potential risk to the fetus; postmarketing reports suggest the possibility of neonatal seizures, withdrawal syndrome, and stillbirth.
Topical agents	Topical use may limit serum levels; individual agents should be reviewed for pregnancy impact prior to use.
Nonbiologic DMARDs	
Methotrexate	Highly teratogenic and abortifacient; must be discontinued at least 3 months before pregnancy.
Hydroxychloroquine	Relatively safe in pregnancy and should not be discontinued if needed.
Sulfasalazine	Relatively safe during pregnancy.
Leflunomide	Extremely teratogenic; must not be used before/during pregnancy; upon discontinuation, cholestyramine administration is required to remove the drug from the body in all women of childbearing potential and specifically in those wishing to become pregnant; should be followed up with measurement of leflunomide and its metabolite levels to ensure removal of the drug.
Azathioprine	Routine use in pregnancy is not recommended; however, azathioprine may be safer than some other DMARDs and may be used if an immunosuppressive agent is imperative.
Cyclophosphamide	Not used in pregnancy unless absolutely necessary.
Mycophenolate mofetil	Teratogenic; should not be used in pregnancy; discontinue for 3 months before attempting pregnancy.
Cyclosporine	May be used in pregnancy only if benefits outweigh the risks.
Tofacitinib	May be teratogenic at high doses.
Biologic DMARDs	
TNF-α inhibitors	Accumulating retrospective data suggest low risk in pregnancy, but evidence is limited; can be continued if absolutely needed; different agents may have different considerations regarding crossing the placenta.
Ustekinumab; anakinra; secukinumab	Should be used only if the potential benefit justifies the undefined risk to the fetus.
Abatacept; belimumab; canakinumab; rilonacept; rituximab; tocilizumab	Should be used only if the potential benefit justifies the potential risk to the fetus.
Urate-Lowering Therapy (rarely needed in premenopausal women)	
Allopurinol	Should be used only if the potential benefit justifies the potential risk to the fetus.
Febuxostat	Should be used only if the potential benefit justifies the potential risk to the fetus.
Probenecid	No current evidence for adverse impact on pregnancy.
Pegloticase	Should be used only if the potential benefit justifies the potential risk to the fetus.

DMARD = disease-modifying antirheumatic drug; TNF = tumor necrosis factor.

[a]See MKSAP 18 General Internal Medicine for information on the FDA pregnancy categories.

patients rarely volunteer this information. Significant drug interactions may occur; for example, some herbal preparations can interact with anticoagulants.

Mind-body interventions such as tai chi, meditation, and yoga can improve psychological well-being, strength, balance, and pain level. Chiropractic and osteopathic manipulation as well as massage remain popular. Randomized controlled trials support the use of tai chi for arthritis; smaller trials suggest benefit from meditation techniques, yoga, massage, and manipulative medicine for various musculoskeletal problems.

Role of Surgery

Surgical procedures such as carpal tunnel release or rotator cuff tendon repair can address conditions that arise from repetitive trauma, injury, and degenerative changes in the soft tissue. Synovectomy of inflammatory pannus is occasionally employed when a single or limited number of joints in patients with RA do not respond to medications. Total joint arthroplasty, particularly of the knee or hip, can reduce or eliminate pain and restore function in patients with an inadequate response to medication and physical or occupational therapy.

KEY POINT

- Nonpharmacologic measures used in rheumatologic diseases include physical or occupational therapy, surgery, weight reduction, psychosocial support, and self-management programs.

Rheumatoid Arthritis

Pathophysiology and Risk Factors

Rheumatoid arthritis (RA) is a systemic autoimmune disease characterized by a chronic inflammatory polyarthritis affecting large and small joints with a predilection for the small joints of the hands and feet. RA has a prevalence of 0.5% to 1% in the general population, with some specific populations having rates as high as 7%.

Genetic Factors

Genes provide 60% of the risk for RA. Among some 100 genetic loci currently recognized as associated with RA risk, the most important is the class II HLA group, especially HLA-D alleles. These risk alleles code for the shared epitope, a five amino acid sequence that binds and presents citrullinated peptide antigens important in the pathophysiology of RA. Because citrulline is an amino acid that does not normally occur in humans, citrullinated proteins are immunogenic, especially in people who also have the shared epitope.

Citrulline is formed by the action of the enzyme peptidylarginine deiminase (PADI), which is found at sites of inflammation and serves to deiminate arginine to form citrullinated peptides. Many of the genes associated with RA modify immune responses to provide a milieu for the development of autoantibodies.

Environmental Factors

Environmental factors provide 40% of the risk for RA. One of the most provocative environmental factors is smoking. Smoking can lead to lung inflammation, which activates enzymes such as PADI, and may promote citrullination. Patients who smoke and are at risk for RA because of family history must be counseled about smoking cessation.

Infectious Agents

A potential risk factor for the development of RA is periodontal disease. *Porphyromonas gingivalis*, a bacterium associated with periodontitis, produces PADI enzymes and provides a potential link to citrullinated peptide formation. Other infectious agents implicated include mycoplasma, Epstein-Barr virus, and parvovirus B19. However, a direct infectious cause of RA has not been identified. There is also interest in the role of the intestinal microbiome in RA. Gut dysbiosis has been postulated to promote early RA, possibly by activating proinflammatory lymphocytes.

Hormones

Women are two to three times as likely as men to develop RA. The role of estrogen and other gender-specific factors is incompletely understood but appears to promote a proinflammatory and/or proautoimmune milieu. Estrogen receptors are present on synovial fibroblasts and may lead to the production of cartilage-damaging metalloproteases. Stimulation of estrogen receptors on macrophages can increase tumor necrosis factor α production, a key RA inflammatory cytokine.

KEY POINT

- Potential risk factors for rheumatoid arthritis include genetic and environmental factors, infectious agents, and hormones; genes provide 60% of the risk.

Diagnosis

The 2010 American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) classification criteria for RA are more sensitive but less specific than the prior 1987 criteria and emphasize early diagnosis and treatment to prevent the permanent consequences of chronic inflammation (**Table 13**).

Clinical Manifestations

RA is a chronic disorder, and onset of symptoms is usually gradual. Patients with RA typically report joint pain and inflammatory symptoms, including swelling and morning stiffness often lasting several hours. Stiffness is generally worse with rest but alleviated by ongoing activity. Joint swelling (softness or bogginess of the affected joint) is palpable on joint examination.

TABLE 13. The 2010 American College of Rheumatology/European League Against Rheumatism Classification Criteria for Rheumatoid Arthritis

Criteria	Score[a]
Joint Involvement[b]	
1 large joint (shoulders, elbows, hips, knees, ankles)	0
2-10 large joints	1
1-3 small joints (MCPs, PIPs, wrists, 2-5 MTPs)	2
4-10 small joints	3
More than 10 small joints	5
Serology	
Negative RF or anti-CCP antibodies	0
Low-positive RF or anti-CCP antibodies (under 3 times the upper limit of normal)	2
High-level RF or anti-CCP antibodies (above 3 times the upper limit of normal)	3
Acute Phase Reactants	
Normal CRP or ESR	0
Abnormal CRP or ESR	1
Duration	
Less than 6 weeks	0
More than 6 weeks	1

CCP = cyclic citrullinated peptide; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; MCP = metacarpophalangeal; MTP = metatarsophalangeal; PIP = proximal interphalangeal; RF = rheumatoid factor.

[a]Six points needed for classification as rheumatoid arthritis.

[b]At least one joint with definite clinical synovitis that is not better explained by another disease.

From Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO 3rd, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum. 2010 Sep;62(9):2569-81. doi: 10.1002/art.27584. [PMID: 20872595] Copyright 2010, American College of Rheumatology. Adapted with permission from John Wiley & Sons, Inc.

H The pattern of joint involvement is useful for diagnosing RA. RA characteristically affects the metacarpophalangeal joints, metatarsophalangeal joints, and proximal interphalangeal joints of the hands and feet but spares the distal interphalangeal joints of both the upper and lower extremities (**Figure 2** and **Figure 3**). Wrists, elbows, shoulders, hips, knees, and ankles also can be involved. RA affects joints symmetrically (that is, joints on both sides of the body are generally involved), but severity may be asymmetric. RA may occasionally present as persistent involvement in a single joint. RA spares the thoracic and lumbar spine but affects the cervical spine, especially the C1-C2 (atlantoaxial) articulation. See **Table 14** for more information. H

FIGURE 2. Early rheumatoid arthritis of the hands, with swelling in the third and fourth proximal interphalangeal joints.

FIGURE 3. Severe rheumatoid arthritis of the hands, with ulnar deviation and subluxation at the metacarpophalangeal joints on both sides.

Laboratory Studies

The most useful laboratory studies to aid in the diagnosis of RA are rheumatoid factor and anti–cyclic citrullinated peptide (CCP) antibodies. Rheumatoid factor is found in approximately 70% of patients with RA and may be present at the time of disease onset. Because other diseases can be associated with rheumatoid factor, its specificity for RA is somewhat limited. Anti-CCP antibodies are also present in 70% of patients with RA but have a specificity of 95%. Anti-CCP antibodies are also more predictive than rheumatoid factor for erosive disease.

Approximately 10% to 20% of patients diagnosed with RA are seronegative (that is, neither rheumatoid factor nor anti-CCP antibodies is positive). Although categorized as having RA, these patients have somewhat different genetics and risk factors and generally have a better prognosis than those with seropositive RA.

TABLE 14. Consequences of Persistent Inflammation on Joints and Supporting Structures

Joint Area	Implications
C1-C2 articulation and transverse ligament	Laxity of the transverse ligament results in increased posterior motion of the dens on C2; with neck flexion, the dens can impact the midbrain and other vital neurologic structures
Shoulder and rotator cuff tendons	Restricted range of motion of the glenohumeral joint and rotator cuff tears
Elbow joint	Elbow contractures and difficulty with hand pronation and supination
Wrist carpal joints and finger tendons	Restricted range of motion of wrist; carpal tunnel syndrome; rupture of finger extensor tendons, especially the fourth and fifth
MCPs and surrounding structures	Ulnar deviation and subluxation of MCPs
PIPs and surrounding structures	Swan neck or boutonniere deformity due to inflammatory disruption of periarticular support structures
Hip joint	Axial migration of the femoral head in the acetabulum (protrusio acetabuli)
Knee joint	Tricompartmental joint-space narrowing
Ankle and mid-foot joints and tendons	Restricted range of motion of ankle; progressive pronated flat foot deformity
MTPs and surrounding structures	Fibular deviation of MTPs; cock-up deformities; skin ulceration underneath subluxed MTP heads

MCP = metacarpophalangeal; MTP = metatarsophalangeal; PIP = proximal interphalangeal.

Erythrocyte sedimentation rate and C-reactive protein are elevated in 75% of patients with RA and can be used to monitor treatment response. The systemic inflammation inherent to RA is commonly reflected by an anemia of inflammation and modest thrombocytosis.

Imaging Studies

Plain radiography of the hands and/or feet is a standard imaging study for RA and can aid in diagnosis and assessing progression, although early radiographs may be normal. Radiographic changes include periarticular osteopenia, marginal erosions, and joint-space narrowing (**Figure 4** and **Figure 5**). Radiography of the cervical spine with flexion/extension views is appropriate if C1-C2 subluxation is suspected.

MRI and ultrasonography are more sensitive than plain radiography and may have utility in following disease, assessing risk of progression, and determining response to therapy. Ultrasonography is becoming a standard tool for detecting joint fluid, synovial tissue thickening, early erosions, and increased vascularity. MRI is used for measuring bone marrow edema, synovitis, and erosions; it is also specifically indicated if atlantoaxial involvement is suspected.

FIGURE 4. Radiograph showing advanced rheumatoid arthritis in the hand. There is ulnar deviation at the metacarpophalangeal joints; marginal erosions most prominently at the second through fourth metacarpophalangeal joints and the second and third proximal interphalangeal joints (*arrows*); and joint-space narrowing at the wrist, metacarpophalangeal, and proximal interphalangeal joints, which also represents erosive disease. Note the loss of the ulnar styloid (*arrowhead*), another common sign of bony erosion in rheumatoid arthritis.

KEY POINTS

- Clinical manifestations of classic rheumatoid arthritis typically include pain, swelling, and prolonged morning stiffness in symmetric small joints.
- The most useful laboratory studies to aid in the diagnosis of rheumatoid arthritis (RA) are rheumatoid factor and anti-cyclic citrullinated peptide (CCP) antibodies; anti-CCP antibodies have a specificity of 95% for RA. HVC
- Plain radiography of the hands and/or feet is a standard imaging study for rheumatoid arthritis; radiographic changes include periarticular osteopenia, marginal erosions, and joint-space narrowing, although early radiographs may be normal. HVC

Complications and Extra-Articular Manifestations

Joints

RA joint damage is a consequence of the development of synovitis within the joint. The synovial lining, normally only a few

FIGURE 5. Radiograph of rheumatoid arthritis in the foot showing marginal erosions and joint-space narrowing at the third, fourth, and fifth metatarsophalangeal joints (*arrows*). Erosion at the fifth metatarsophalangeal joint is often the first radiographic sign of rheumatoid arthritis foot involvement.

cells thick, becomes significantly expanded and produces cartilage-damaging metalloproteases. Receptor activator of nuclear factor kappa B ligand (RANKL), produced by inflammatory cells, activates osteoclasts to erode bone. The metalloproteases and activated osteoclasts result in various irreversible changes to the joints (see Table 14).

Skin

The most common RA skin changes are rheumatoid nodules, present in up to 30% of patients. Nodules typically occur in the olecranon region and can be confused with gouty tophi, but can also occur over the hand and feet joints and even in the lungs. Nodulosis can rarely be induced by certain drugs (for example, methotrexate and leflunomide) but may respond to others (for example, hydroxychloroquine and colchicine). Patients with RA are also at an increased risk for neutrophilic dermatoses such as pyoderma gangrenosum or Sweet syndrome. Palpable purpura may result from small-vessel cutaneous vasculitis.

Eyes

The most common eye manifestation in RA is dry eye (keratoconjunctivitis sicca). It occurs in 10% to 15% of patients and can be severe. Most of these patients also have dry mouth and are classified as having secondary Sjögren syndrome. Less common (1%) are episcleritis (inflammation of the superficial scleral vessels) and scleritis (inflammation of deep scleral vessels). RA is one of the most common diseases associated with scleritis, which can be vision-threatening and lead to thinning of the sclera and perforation. Keratitis (corneal inflammation) can occur, which is ulcerative and occurs at the periphery of the cornea; severe keratitis is known as corneal melt. Both scleritis and keratitis require immediate referral to an ophthalmologist.

Lungs

H

Air trapping reflecting small airway disease occurs in up to 50% of patients with RA. Pleural disease occurs in up to 5%; pleural effusions are exudative and can be large. RA pleural effusions are characterized by low glucose and pH (mimicking bacterial or tubercular infection and malignancy) and low complement levels, as well as elevated levels of total protein, rheumatoid factor, and lactate dehydrogenase. Inflammatory cells in the RA effusion are characteristically mononuclear; a neutrophil-predominant effusion suggests infection. Interstitial lung disease contributes to excess mortality in RA and may develop in 50% of patients, but clinically significant disease is seen in 10%. Bronchiectasis and bronchiolitis occur, and the bronchiolitis can be obliterative/constrictive. Upper airway involvement from cricoarytenoid arthritis occurs rarely; symptoms include hoarseness, sore throat, dysphagia, and stridor. Cricoarytenoid arthritis can pose problems for endotracheal intubation.

Heart

Atherosclerotic heart disease remains the major cause of excess death in patients with RA, although recent data suggest that cardiovascular disease risk may be decreasing toward that of the general population. Nonetheless, patients with RA should be considered at high cardiovascular risk for purposes of perioperative evaluation, and cardiovascular disease risk factors such as dyslipidemia and hypertension should be addressed. Clinically significant pericarditis is rare. Granulomatous myocarditis, valvular disease (mainly mitral), conduction block, and aortitis are reported to occur in RA but are very rare.

Hematologic

Anemia of inflammation is the most common RA hematologic abnormality. Felty syndrome consists of neutropenia and splenomegaly and occurs in patients with long-standing, severe, seropositive RA. These patients are at risk for serious bacterial infection, lower extremity ulceration, lymphoma, and vasculitis. With current treatment, Felty syndrome has become rare.

H CONT.

Patients with RA can also have a large granular lymphocyte syndrome that can progress to large granular lymphocyte leukemia. Findings overlap with Felty syndrome and include neutropenia, anemia, thrombocytopenia, splenomegaly, and recurrent infections. Patients with RA are at increased risk for lymphomas (particularly large B-cell lymphomas), and risk is correlated with disease activity. H

Blood Vessels

A small-vessel cutaneous vasculitis occurs in a small percentage of patients with RA, leading to palpable purpura or periungual infarcts. A very rare, larger-vessel vasculitis similar to polyarteritis nodosa can affect multiple organ systems; prior to current therapy, it had a 5-year mortality of 30% to 50%.

KEY POINT

- Extra-articular manifestations and complications of rheumatoid arthritis include rheumatoid nodules, rheumatoid vasculitis, dry eye, small airway disease, interstitial lung disease, pleural effusions, and anemia of inflammation.

Management

See Principles of Therapeutics for details on the uses, mechanisms of action, major toxicities, and/or monitoring requirements of the medications used in RA.

General Considerations

The 2015 ACR RA treatment guidelines (https://www.rheumatology.org/Practice-Quality/Clinical-Support/Clinical-Practice-Guidelines/Rheumatoid-Arthritis) advocate for early diagnosis and aggressive early therapy of RA to prevent irreversible cartilage and bone damage. The 2010 ACR RA classification criteria emphasize sensitivity to permit early diagnosis and institution of disease-modifying therapy (see Table 13). A key treatment goal is to treat to target, with the target being achievement of remission or low disease activity. Disease activity assessment involves making a measured determination using combinations of numbers of tender and swollen joints (typically utilizing 28 joints that exclude the feet), patient and physician impressions of disease activity, and, in some activity scoring systems, measurement of the erythrocyte sedimentation rate or C-reactive protein. These parameters are combined into a composite score, thus assigning a disease activity ranging from remission, to low, moderate, or high. The Clinical Disease Activity Index (CDAI) and Disease Activity Score 28 (DAS28) are two commonly used instruments to assess disease activity and response to treatment. Treating to target in RA results in less radiographic damage, reduced cardiovascular risk, and increased work productivity compared with conventional care.

The 2015 ACR RA treatment guidelines can assist in making initial treatment decisions in early RA. Treatment is typically advanced at 12-week intervals with the goal of reaching remission or low disease activity as rapidly as possible. Patients who remain in remission or a low disease activity state for 6 months or longer may be able to reduce treatment intensity. Treatment decisions for established RA are more complex. An initial approach to the treatment of both early and established RA is outlined in **Figure 6**.

Disease-Modifying Antirheumatic Drugs

Nonbiologic Disease-Modifying Antirheumatic Drugs

Methotrexate is the anchor drug in RA, used in both monotherapy and combination therapy. It can be titrated to doses as high as 25 mg per week in partial responders; the treating physician should generally maximize methotrexate dosing before adding other agents. At doses greater than 15 mg weekly, methotrexate oral absorption approaches its effective limit; switching to subcutaneous administration allows for higher serum drug levels. Folic acid supplements minimize toxicity without diminishing efficacy. Of patients with RA taking methotrexate alone, 30% to 50% achieve remission or low disease activity.

Sulfasalazine, leflunomide, and hydroxychloroquine also can be used as monotherapy agents in RA. Leflunomide may

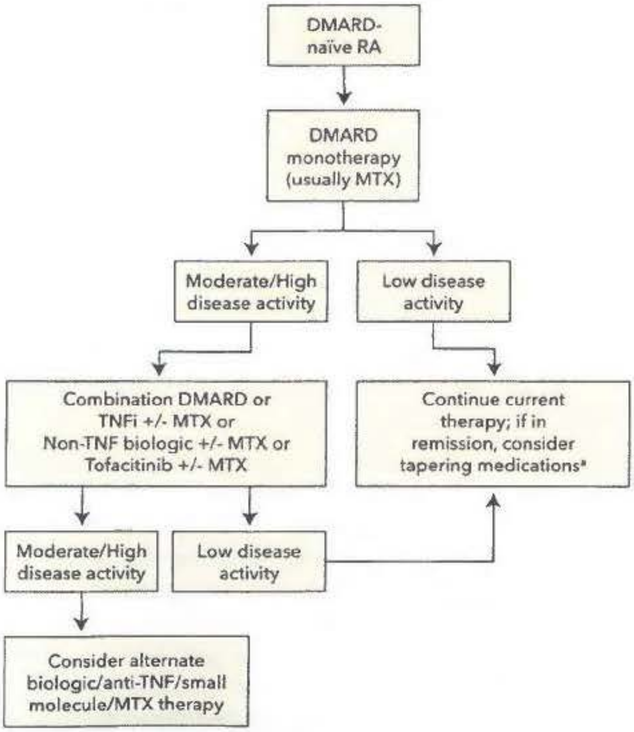

FIGURE 6. A simplified algorithm presenting an initial approach to the treatment of both early and established rheumatoid arthritis (RA). All patients with RA should receive a disease-modifying antirheumatic drug initially and be advanced to more aggressive and/or combination therapy as needed to control disease. Disease activity should be assessed, wherever possible, using a formal, validated, and consistent disease activity index. Refer to the American College of Rheumatology RA treatment guidelines for more complex algorithms accounting for differences between agents and patient-specific complexities. DMARD = disease-modifying antirheumatic drug; MTX = methotrexate; RA = rheumatoid arthritis; TNFi = tumor necrosis factor inhibitor.

[a]Do not discontinue all RA treatments.

be useful in those who cannot tolerate methotrexate. Hydroxychloroquine is the least potent agent but can be used in very early disease when the disease activity score is low. It is also used as part of triple therapy (methotrexate, sulfasalazine, and hydroxychloroquine). Data suggest that triple therapy is comparable to methotrexate combined with a tumor necrosis factor α inhibitor, except in the area of radiographic progression.

Biologic Disease-Modifying Antirheumatic Drugs

Biologic DMARDs can be used as monotherapy but are typically added to methotrexate when moderate to high disease activity persists. Tumor necrosis factor (TNF)-α inhibitors are the most frequently used biologic DMARDs; these agents have a relatively rapid onset of action and demonstrate synergy with methotrexate. The combination of methotrexate and a TNF-α inhibitor has also been shown to have a "disconnect effect," meaning that even patients with continued clinical disease activity may demonstrate little to no damage to cartilage and bone. This effect also has been shown with rituximab or tocilizumab in combination with methotrexate. Other biologic DMARDs used in RA include abatacept (a selective T-cell costimulation modulator) and tofacitinib (a small-molecule Janus kinase inhibitor).

Until better data are available to guide therapeutic decisions, choice of a biologic DMARD remains empiric and based on patient characteristics, including what agents should be avoided due to patient comorbidity (for example, avoiding abatacept in a patient with COPD).

NSAIDs

NSAIDs were once the mainstay of therapy of RA. These agents are not disease modifying and do not prevent joint damage. They are used primarily to control symptoms while waiting for the full effect of DMARDs to be realized or in patients with postinflammatory osteoarthritis.

Glucocorticoids

Unlike NSAIDs, glucocorticoids may have a disease-modifying effect. A recent study tested 10 mg/d of prednisone versus placebo for 2 years in combination with methotrexate; the prednisone group had no more side effects than the placebo group but gained better control of disease activity, used less methotrexate, needed fewer additional medications, and had less radiographic damage. Low-dose prednisone (5-10 mg/d) can be used to rapidly improve RA symptoms while waiting for long-term medications to become effective, or they can be used short term for disease flares. Long-term therapy with glucocorticoids, however, may be associated with substantial adverse effects including osteoporosis, diabetes mellitus, and infection.

Surgery

Surgical therapy has become much less common in RA with current treatment strategies. However, some patients may require a synovectomy for a single persistently swollen joint, carpal tunnel release, repair of a ruptured tendon, total joint replacement (shoulder, metacarpophalangeal joints, hip, knee, or ankle), or joint fusion for a painful damaged joint (wrist or ankle). See MKSAP 18 General Internal Medicine for a discussion of perioperative RA medication management.

KEY POINTS

- In rheumatoid arthritis, treating to target of remission or low disease activity results in less radiographic damage, reduced cardiovascular risk, and increased work productivity compared with conventional care.
- Methotrexate is the anchor drug in rheumatoid arthritis; it is used as monotherapy and as a component of combination therapy. **HVC**
- Tumor necrosis factor α inhibitors are the most frequently used biologics to treat rheumatoid arthritis; they have a relatively rapid onset of action and demonstrate synergy with methotrexate.
- In rheumatoid arthritis, NSAIDs are not disease modifying and do not prevent joint damage; they are used primarily to control symptoms while waiting for the full effect of disease-modifying antirheumatic drugs to be realized or in patients with postinflammatory osteoarthritis. **HVC**
- Low-dose prednisone can be used in rheumatoid arthritis to rapidly improve symptoms until long-term medications become effective, or they can be used short term for disease flares.

Pregnancy

There is an increased risk for developing RA in the first year after a first pregnancy. Breastfeeding may decrease this risk. For women with established RA, two thirds will go into remission or low disease activity during pregnancy, and one third will not improve or will get worse. Medication management is a major issue, and pregnancy plans should be discussed with any woman of childbearing age who will be placed on therapy. A discussion of RA medications in pregnancy is located in Principles of Therapeutics.

KEY POINT

- There is an increased risk for developing rheumatoid arthritis (RA) in the first year after a first pregnancy; for women with established RA, two thirds will go into remission or achieve low disease activity during pregnancy, whereas one third will not improve or will get worse.

Osteoarthritis

Pathophysiology

Osteoarthritis (OA) is a chronic progressive multifactorial disorder of maladaptive cellular repair responses to joint stress.

Previously deemed a "wear and tear" disease and an inevitable consequence of aging, OA is now recognized as a disorder driven by a complex interplay of genetics, joint injury, cell stress, extracellular matrix degradation, and inflammation. It affects all the tissues of the joint and is characterized by cartilage and meniscal degradation, subchondral bone changes (bone marrow lesions, subchondral sclerosis), and osteophyte formation. Other findings include synovial inflammation with hypertrophy and effusion as well as weakening of the periarticular muscle. Morphologic changes in cartilage reflect collagen and proteoglycan alterations driven by imbalanced anabolic and catabolic repair processes. In addition, inflammatory cytokines such as interleukin-1β and tumor necrosis factor α are produced in the synovium and cartilage; they drive joint tissue destruction and stimulate synthesis of additional inflammatory mediators.

Epidemiology and Risk Factors

OA is the most common form of arthritis worldwide and a leading cause of pain and disability, affecting approximately 30 million U.S. adults. OA is the leading cause of lower extremity disability among older adults, with an estimated lifetime risk for knee OA approaching 50%. Prevalence is projected to more than double by the year 2030, largely due to increasing obesity rates and aging of the population. Incidence and prevalence rates vary by joint and depend upon whether a clinical or radiographic definition is being applied. Recent efforts examining whether patients with OA are at increased risk for cardiovascular morbidity and all-cause mortality have been inconclusive, with positive associations appearing to relate more to functional decline and disability than to OA-specific pathologic processes.

Epidemiological risk factors for OA include age greater than 55, race/ethnicity, female sex, obesity, genetics, and occupations that include repetitive motions or physical labor. Age and female sex are strong nonmodifiable risk factors for OA of different sites. Obesity is the most important modifiable risk factor, especially for knee OA. Increased body mass is also a risk factor for hand OA, perhaps underscoring the systemic nature of the disease and a role for metabolic and/or inflammatory mechanisms in its pathogenesis. Single inherited conditions rarely predispose to OA; however, mutations in proteins involved in bone or articular cartilage structure or metabolism are possible risk factors.

Risk factors involving the joint itself include abnormal loading, injury, malalignment, and intrinsic cartilage or bone tissue defects. Injury may be acute (for example, anterior cruciate ligament tear) or may be more minor and repetitive (for example, physical labor or overuse); regardless of cause, injuries have been linked with the future development of OA of various sites. Hip dislocation, congenital dysplasia, femoroacetabular impingement, knee malalignment, and shape of the knee joint are also associated with incident OA.

Given its multifactorial etiology, an individual patient may develop OA as a consequence of one or more risk factors; how the interaction of these risk factors culminates in OA is complex and not fully understood.

KEY POINTS

- Osteoarthritis is a chronic progressive disorder characterized by cartilage and meniscal degradation, subchondral bone changes, and osteophyte formation.
- Risk factors for osteoarthritis include epidemiological factors (age, race/ethnicity, female sex, genetics, obesity) and joint-specific factors (malalignment, cartilage defects, joint injury).

Classification

Primary Osteoarthritis

The most common type of OA is primary OA, in which no identifiable proximal cause is recognized. Although almost any joint may be affected by OA, primary OA typically involves specific joints, including the distal interphalangeal (DIP) and proximal interphalangeal (PIP) finger joints, the first carpometacarpal joint at the base of the thumb, the hip and knee joints, and the cervical and lumbar spine.

Erosive Osteoarthritis

Erosive (inflammatory) OA is a subset of primary hand OA. Clinically, erosive OA mostly affects the DIP and PIP joints, is more inflammatory and painful than typical hand OA (with erythema and swelling), and is more common in women. Radiographs reveal diagnosis-defining central erosions (in contrast to marginal erosions seen in rheumatoid arthritis) with a "seagull" or "gull-wing" appearance in the finger joints (**Figure 7**); joint ankylosis (bony fusion) may also occur. Whether erosive OA comprises a separate disease entity or is part of the continuum of OA remains controversial.

Secondary Osteoarthritis

Secondary OA is historically defined in the presence of a predisposing disorder; however, an increasing number of risk factors are being identified for primary OA, thus blurring the lines between the primary and secondary forms of the disease. Pathologic changes, clinical presentations, symptoms, and management are indistinguishable between primary and secondary OA. When OA is observed in a joint not typically affected by primary OA, however, secondary causes should be entertained. Commonly recognized causes of secondary OA include a history of frank damage such as trauma, joint infection, or surgical repair (such as anterior cruciate ligament repair or meniscectomy); congenitally abnormal joints (for example, hip dysplasia); systemic metabolic, endocrine, and neuropathic disorders, particularly those that affect cartilage; and underlying inflammatory arthritis with accompanying damage (for example, rheumatoid or psoriatic arthritis) (**Table 15**).

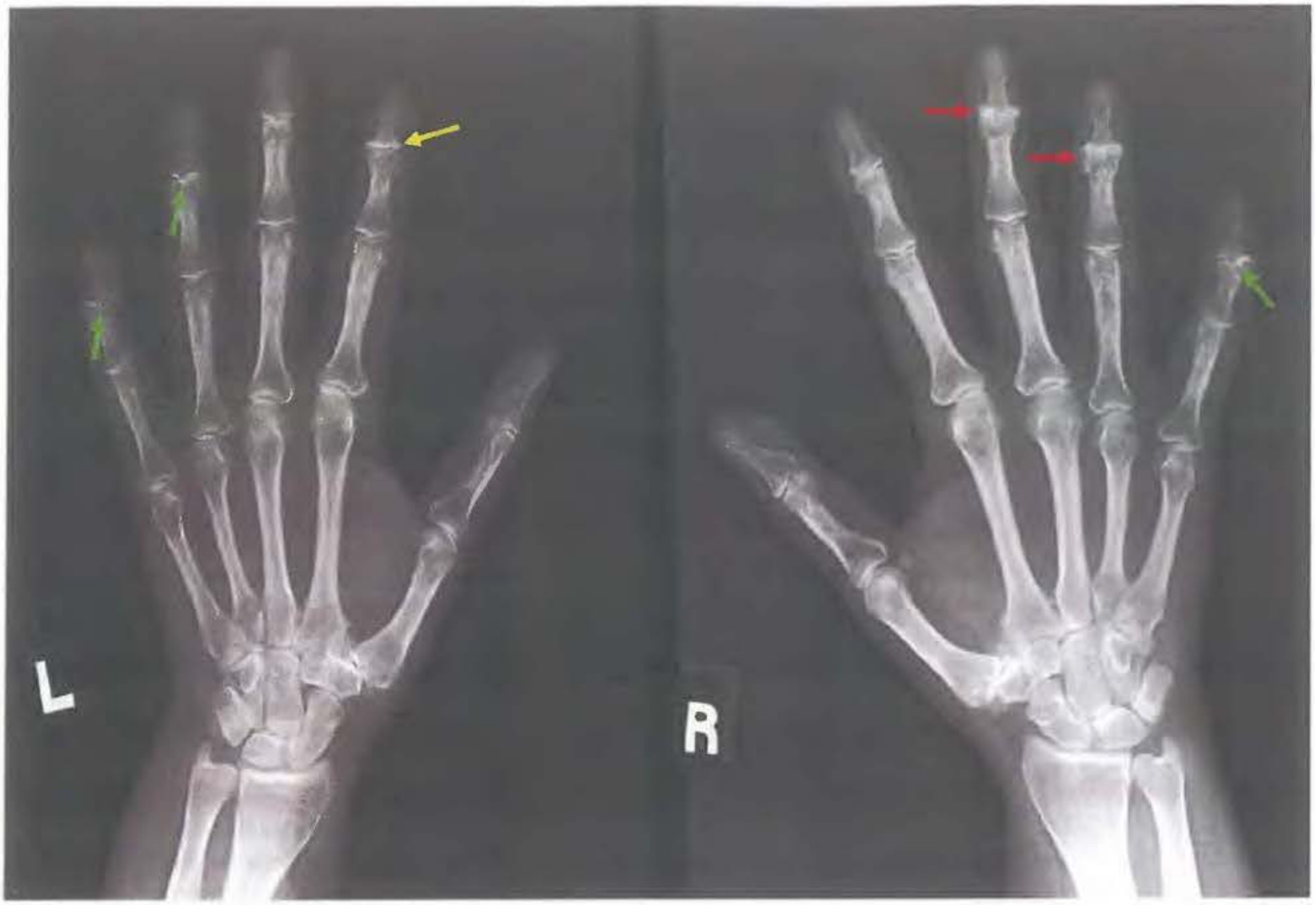

FIGURE 7. Plain radiographs showing erosive hand osteoarthritis (OA). Note the classic "gull-wing" appearance of the fourth and fifth distal interphalangeal (DIP) joints on the left and the fifth DIP joint on the right (*green arrows*), reflecting central erosion of cartilage on the proximal surface of the joint. Also seen is bony ankylosis, a feature of erosive OA, of the right fourth DIP joint and developing in the right third DIP joint (*red arrows*). Additionally, the left second DIP joint exhibits the findings of classic (nonerosive) hand OA (joint-space narrowing, subchondral sclerosis, and osteophytes without the "gull-wing" appearance) (*yellow arrow*).

TABLE 15. Secondary Causes of Osteoarthritis

Secondary Cause	Joint(s) Typically Involved
Hemochromatosis	Second/third MCP joints
Calcium pyrophosphate deposition	MCP joints; wrists; knees; hips; shoulders; atlanto-axial joint
Alkaptonuria/ochronosis	Spine; hips; knees
Acromegaly	Knees; shoulders; spine
Hyperparathyroidism	Wrists; MCP joints
Joint injury	Knees

MCP = metacarpophalangeal.

Diffuse Idiopathic Skeletal Hyperostosis

Diffuse idiopathic skeletal hyperostosis (DISH) is a noninflammatory condition characterized by calcification and ossification of spinal ligaments (especially the anterior longitudinal ligament) and entheses (tendon and ligament attachments to bone). Unlike OA, DISH is more common in men. DISH usually presents as back pain and stiffness, with the thoracic spine most often involved. Although spinal ligamentous ossification is also seen in ankylosing spondylitis, the spinal calcifications in DISH are more "flowing," wider and less vertically oriented than those seen with ankylosing spondylitis. There is additionally no involvement of the sacroiliac joints in DISH.

Radiographic changes characteristic of DISH include confluent ossification of at least four contiguous vertebral levels, usually on the right side of the spine (**Figure 8**). Patients with DISH have less involvement of the left side of the thoracic spine, perhaps secondary to the aorta serving as a mechanical barrier to the production of bony hyperostosis.

KEY POINTS

- The most common type of osteoarthritis (OA) is primary OA, in which no identifiable proximal cause is recognized.
- Erosive osteoarthritis (OA) mostly affects the distal interphalangeal and proximal interphalangeal joints, is more inflammatory and painful than typical hand OA (with erythema and swelling), and is more common in women.

(Continued)

FIGURE 8. Plain lumbar radiograph of a patient with diffuse idiopathic skeletal hyperostosis (DISH). Note the calcification at sites of tendinous and ligamentous insertion of the spine, taking the form of flowing ossification of multiple contiguous vertebrae (*arrows*). Also seen here is the typical extensive involvement of the right side of the spine and relative sparing of the left (calcification of the anterior longitudinal ligament is also common, but not readily observed in this view).

Courtesy of Soterios Gyftopoulos, MD, MSc.

KEY POINTS *(continued)*

- Commonly recognized causes of secondary osteoarthritis include a history of frank damage; congenitally abnormal joints; systemic metabolic, endocrine, and neuropathic disorders; and underlying inflammatory arthritis.
- Diffuse idiopathic skeletal hyperostosis is a noninflammatory condition characterized by calcification and ossification of spinal ligaments and entheses; radiographs usually show confluent "flowing" ossification of at least four contiguous vertebral levels, usually on the right side of the spine.

Diagnosis

Clinical Manifestations

OA diagnosis is based on history and physical examination; radiography is confirmatory but may not be necessary. In early OA, clinical findings may not be accompanied by radiographic changes; conversely, some patients with prominent radiographic changes may have minimal or no symptoms. Patients with OA are typically over 50 years of age; diagnosis at an earlier age should prompt inquiry into a history of prior joint damage, endocrine or metabolic disorders, or a genetic proclivity for early disease.

Joints most commonly affected are the hands (DIPs and PIPs) (**Figure 9**), feet (first metatarsophalangeal joint and mid foot), knees, hips, and spine, but the distribution is variable. Localized OA, in which a single joint is affected, is more often a consequence of injury or joint asymmetry and often occurs in weight-bearing joints (hip or knee). Generalized OA, which affects multiple joint groups (for example, hands, spine, knees, and hips), is more likely the result of a combination of genetic and environmental factors and may be more symmetric in distribution.

Patients with OA usually describe an insidious onset of intermittent symptoms, which become more persistent and severe over time. The most common symptom is joint pain that is exacerbated by activity and alleviated with rest. Patients also describe morning stiffness usually lasting less than 30 minutes, in contrast to the prolonged morning stiffness of inflammatory arthritis. A single joint may initially be involved with eventual involvement of multiple joints.

On joint examination, crepitus, decreased range of motion, bony enlargement, and sometimes effusion may be present. Patients with long-standing hand OA may have Heberden and Bouchard nodes (bony enlargement of the DIP and PIP joints, respectively) and squaring of the first carpometacarpal joint. Hip involvement typically manifests as groin pain and decreased range of motion, especially internal rotation. Knee symptoms include pain on walking, especially on stairs, and difficulty transferring from a seated to standing position. Spondylosis, or OA affecting the spine, can affect the vertebral bodies, facet joints, and neural foramina, and may lead to spinal stenosis.

Patients with OA generally do not have systemic features. Pain and structural changes, however, ultimately result in functional impairment, pain, disability, psychosocial isolation, and reduced quality of life.

Laboratory and Imaging Studies

Laboratory testing is usually not necessary for diagnosis of OA but is helpful if other causes of arthritis are being considered, such as crystal arthropathy, rheumatoid arthritis, psoriatic arthritis, or hemochromatosis (all of which can coexist with OA). Acute phase reactants should be normal in OA. Routine laboratory testing (complete blood count, kidney and hepatic function) are not necessary for diagnosing OA but may be important when considering pharmacologic therapy, especially in the elderly and those with comorbidities.

If effusion is present, evaluation for concurrent crystal arthritis, infections, or other inflammatory causes should be

FIGURE 9. Progression of hand osteoarthritis (OA). This image illustrates the progression from normal hand joints (*left*), to distal interphalangeal (DIP) joint bony hypertrophy (Heberden nodes) of hand OA (*middle*), to extensive hand OA findings of Heberden nodes and proximal interphalangeal (PIP) joint bony hypertrophy (Bouchard nodes) (*right*). The hand on the right also displays a gouty nodule (tophus) overlying the Heberden node on the second DIP joint, underlining the potential coexistence of these two arthropathies. White arrowheads = Heberden nodes; black arrows = Bouchard nodes; black asterisk = tophus.

considered, ideally by synovial fluid analysis. OA synovial fluid is typically clear in appearance and noninflammatory, with a leukocyte count $\leq 2000/\mu L$ ($2.0 \times 10^9/L$).

Although imaging is not necessary to make an OA diagnosis, it can be helpful to confirm the diagnosis, establish baseline severity, and exclude other diagnoses. Radiographic features of OA include asymmetric joint-space narrowing, subchondral sclerosis, osteophytes, and bone cysts; however, these changes may not be present in early disease. Even in established OA, symptoms may correlate poorly with imaging findings. Although MRI and ultrasonography can detect subtle OA changes at an earlier stage and are increasingly used in OA research, they are not needed for routine OA diagnosis. MRI may be indicated in the setting of symptoms suggestive of a concomitant mechanical disorder (joint catching, locking, instability), but incidental abnormalities such as meniscal tears are commonly seen on MRI in patients with OA and may prompt unnecessary surgical intervention.

Differential Diagnosis

Diagnosing OA may be problematic when OA is present in atypical joints, when an accurate history is difficult to obtain, or when a concurrent inflammatory arthropathy may be present. Calcium pyrophosphate deposition may occur in joints also typical for OA (hands or knees) but is associated with intermittent "flares," and radiographs show cartilage calcification (chondrocalcinosis). Gout and OA commonly co-associate, particularly in the DIP joints. Rheumatoid arthritis typically affects the hands, but unlike OA, the DIP joints are rarely affected, and signs and symptoms of chronic and persistent inflammation are seen. The presence of rheumatoid factor, anti-cyclic citrullinated peptide antibodies, and elevated inflammatory markers favors the diagnosis of rheumatoid arthritis but does not eliminate the possibility of concurrent OA. Psoriatic arthritis can involve the DIP joints, but also commonly includes prolonged morning stiffness, joint swelling, dactylitis, and a history of psoriasis. Synovial fluid analysis can also be helpful in distinguishing between OA and these inflammatory disorders.

Other conditions to consider when evaluating a patient for OA include nonarticular sources of pain such as bursitis and tendinitis. Hip pain that is not in the anterior groin but instead around the lateral hip and buttock may indicate trochanteric bursitis or lumbosacral radiculopathy. Similarly, knee pain may be secondary to pes anserine bursitis or iliotibial band syndrome rather than intra-articular pathology. The pes anserine bursa is located along the proximal medial aspect of the tibia; thus, pes anserine bursitis should be considered when there is spontaneous pain along the inner (inferomedial) aspect of the knee joint. Patients with iliotibial band syndrome typically present with pain at the lateral aspect of the knee, usually exacerbated by physical activity, such as walking up or down stairs, running, or cycling.

KEY POINTS

- The most common symptom of osteoarthritis is joint pain that is exacerbated by activity and alleviated with rest; morning stiffness usually lasts less than 30 minutes.
- Laboratory testing is usually not necessary to diagnose osteoarthritis but is helpful if other causes of arthritis are being considered, such as crystal arthropathy, rheumatoid arthritis, psoriatic arthritis, and hemochromatosis. **HVC**

(Continued)

KEY POINTS *(continued)*

- Radiographic features of osteoarthritis (OA) include asymmetric joint-space narrowing, subchondral sclerosis, osteophytes, and bone cysts; however, these changes may not be present in early disease, and symptoms may correlate poorly with imaging findings, even in established OA.

Management

To date, no agents have been FDA approved to prevent, delay, or remit the structural progression of disease in OA. Instead, current treatment is directed to the management of pain and disability. Evidence-based guidelines for OA management are available from the American College of Rheumatology (ACR), the Osteoarthritis Research Society International (OARSI), the European League Against Rheumatism (EULAR), and others; however, there is poor consensus among these guidelines. Nevertheless, there is agreement that optimal OA management requires a combination of nonpharmacologic and pharmacologic modalities. Patients with OA should receive individualized multidisciplinary treatment that takes into account their expectations, functional and activity levels, occupational and vocational needs, joints affected, severity of disease, and any coexisting medical problems.

Nonpharmacologic Therapy

The nonpharmacologic approach to OA starts with assessment of physical status, activities of daily living, health education, motivation, beliefs, and other biopsychosocial factors. An individualized management plan includes education on OA and joint protection, an exercise regimen, weight loss, proper footwear, and assistive devices as appropriate. Physical activity includes graduated aerobic exercise and strength training, with attention paid to strengthening periarticular structures and minimizing injury. Tai chi has also been shown to be as beneficial as physical therapy for knee OA pain. A recent study reports that the combination of diet and exercise is more effective at decreasing OA-related knee pain and dysfunction than either diet or exercise alone. Furthermore, a 2015 Cochrane review, which included 54 knee OA studies, concluded that land-based therapeutic exercise provides short-term benefit in terms of reduced knee pain and improved physical function that is sustained for at least 2 to 6 months after cessation of formal treatment.

Pharmacologic Therapy

In the absence of disease-modifying OA drugs, pharmacologic treatment is considered when symptoms are present and bothersome to the patient. Pharmacologic therapy for OA includes oral, topical, and intra-articular medications. Choice of treatment(s) depends upon individualized assessment, with particular attention to comorbidities, concomitant medications, and especially adverse effects of the treatments. See Principles of Therapeutics for details on the medications used in OA.

Oral and Topical Agents

Oral agents include acetaminophen, NSAIDs, duloxetine, and tramadol. Recent systematic reviews and meta-analyses suggest that acetaminophen provides no benefit for hip or knee OA. NSAIDs are efficacious in OA, but their side-effect profiles make sustained use problematic, especially in the elderly and those with comorbidities. If used, the proper choice of an NSAID, considering drug pharmacokinetics as well as gastrointestinal and cardiovascular effects, may improve tolerance and minimize risk. Duloxetine, a serotonin-norepinephrine reuptake inhibitor with central nervous system activity, has shown efficacy for knee OA pain, implicating the role of central sensitization in OA pain modulation. A 2018 randomized controlled trial demonstrated that opioids were not superior to nonopioid medications for improving pain-related function for chronic back pain or OA-related hip or knee pain; pain intensity was significantly improved in the nonopioid group. Tramadol may be useful in some patients who cannot take other analgesics, but has substantial adverse effects.

Topical NSAIDs are an alternative to oral NSAIDs and may be beneficial for those who should avoid or cannot tolerate oral NSAIDs, including those who are ≥75 years old, have a history of peptic ulcer disease, or have chronic kidney disease. However, topical NSAIDs are associated with more skin reactions and are more expensive than oral NSAIDs. Other topicals such as capsaicin, lidocaine, and methyl salicylate preparations may also be used as adjunctive measures, especially when NSAIDs are either ineffective or not tolerated.

The oral alternative therapies glucosamine and chondroitin sulfate are frequently used by patients; although they appear to be safe, the quality of evidence for their efficacy is poor.

Intra-Articular Injections

Patients with knee or hip OA who have inefficacy, intolerance, or contraindication to oral and topical therapies may benefit from intra-articular glucocorticoid or hyaluronic acid injections. There is no formal evidence for the utility of intra-articular therapy in joints other than the knee and hip.

Intra-articular glucocorticoids are efficacious in knee and hip OA and are supported by multiple treatment guidelines. Long-term harm has not been demonstrated; however, benefit is usually short term and usually wanes within 3 months. Injections can be administered repeatedly but are not usually given more often than every 3 months. A recent 2-year study has called the efficacy and long-term safety of intra-articular glucocorticoid injections into question, with possible negative effects on cartilage thickness, an outcome with unclear clinical meaning.

Patients with inadequate response to intra-articular glucocorticoids may benefit from intra-articular hyaluronic acid injection. The quality of trials assessing intra-articular hyaluronan efficacy is low, and the degree of benefit is unclear. Nonetheless, intra-articular hyaluronans are widely used, especially when other treatments have failed and surgery is not a feasible option. When benefit is seen, it is usually more

gradual and more persistent than that of intra-articular glucocorticoids.

Surgical Therapy

Surgery for OA is considered when nonpharmacologic and pharmacologic approaches fail to control pain or functional limitation. Multiple high-quality studies have shown that arthroscopic surgery for knee OA provides no better outcomes than conservative management unless there is joint buckling, instability, or locking or a concomitant and symptomatic mechanical disorder.

In contrast, total joint replacement is a "curative" option for those who have failed conservative therapies, providing pain relief and functional improvement. Overall, long-term outcomes are excellent, although hardware loosening and late infection may occur.

Recent studies suggest that for morbidly obese patients with knee OA, bariatric surgery may result in significant improvement in pain and function even without further OA management.

KEY POINTS

HVC
- Nonpharmacologic therapy for osteoarthritis includes education, an exercise regimen, weight loss, proper footwear, and assistive devices as appropriate.

HVC
- Recent systematic reviews and meta-analyses suggest that acetaminophen provides no benefit for hip or knee osteoarthritis; NSAIDs and duloxetine are efficacious.
- Pharmacologic therapy for osteoarthritis includes oral, topical, and intra-articular medications; choice of treatment(s) depends upon individualized assessment, with particular attention to comorbidities and concomitant medications.

HVC
- Arthroscopic surgery is not indicated in patients with osteoarthritis unless there is joint buckling, instability, or locking, or a concomitant and symptomatic mechanical disorder.
- Total joint replacement provides pain relief and functional improvement in patients with osteoarthritis who have failed conservative therapies.

Fibromyalgia

Epidemiology and Pathophysiology

Fibromyalgia is characterized by widespread pain, fatigue, disturbed sleep, and cognitive dysfunction. It is common (prevalence, 2%-3%), particularly among individuals of lower socioeconomic status and/or educational level. Prevalence increases with age, peaking around the seventh decade. The female-to-male ratio is approximately 3:1.

Early paradigms of fibromyalgia as an inflammatory or psychosomatic condition have yielded to an understanding of fibromyalgia as a disorder of pain processing. It is likely a form of "central sensitization," in which the pain centers of the brain and spinal cord are hyperresponsive. Allodynia (a heightened sensitivity to stimuli that are not normally painful) and hyperalgesia (an increased response to painful stimuli) are common. An additional characteristic feature is "wind-up," or temporal summation. When repeatedly exposed to a mildly uncomfortable stimulus, patients with fibromyalgia experience progressively additive pain, indicating that the stimuli are both persistent and inadequately damped.

The underlying changes seen in the neurologic system are complex. Ascending fibers from the dorsal root ganglia convey inappropriately strong or persistent signals to hypothalamic pain centers. Patients with fibromyalgia have higher cerebrospinal fluid levels of the pain-promoting neurotransmitters substance P and glutamate, along with sensitization of glutamate receptors. Concurrently, descending inhibitory pathways utilizing adrenergic neurotransmitters (serotonin, norepinephrine) are impaired. The resultant circuit of chronic pain is self-sustaining but may be amplified by both psychic distress and peripherally generated tissue pain (such as arthritic joint pain). Genetic influences are a focus of ongoing investigation.

Diagnosis

The characteristic clinical features of fibromyalgia are widespread chronic pain (including hypersensitivity to painful stimuli), fatigue, and sleep disorders (both disrupted and nonrestorative sleep). These are frequently accompanied by impaired cognitive function, mood disorders, and symptoms such as headache, gastrointestinal symptoms, and paresthesia. Although the diagnosis of fibromyalgia traditionally centered on the presence of specific tender points elicited on physical examination, tender point examination is subject to physician expertise (such as appropriate application of force). In addition, male patients report tender point pain less frequently than female patients, leading to possible underdiagnosis. The 2010 American College of Rheumatology Preliminary Diagnostic Criteria forgo physical examination to emphasize a careful characterization of symptoms (**Table 16**). Many physicians rely on these diagnostic criteria but perform tender point assessment as part of the examination.

Treatable alternative diagnoses that may provoke or be mistaken for fibromyalgia include hypothyroidism, hypoadrenalism, and depression.

Management

Optimal management of fibromyalgia requires a holistic approach, including education, exercise, and psychosocial support. Pharmacotherapy is often warranted, although nonpharmacologic measures remain a cornerstone of treatment.

TABLE 16. Comparison of the 1990 ACR Classification Criteria and the 2010 ACR Diagnostic Criteria for Fibromyalgia	
1990 ACR Classification Criteria	**2010 ACR Preliminary Diagnostic Criteria**
Widespread pain by self-report	Widespread pain by the Widespread Pain Index (WPI; 19-point scale) assessing the number of regions in which the patient has pain[a,b]
≥11 tender points on digital palpation or using a dolorimeter	Symptom severity by the Symptom Severity (SS) Scale (12-point scale) assessing 1) fatigue; 2) nonrestorative sleep; 3) cognitive symptoms[a,b]
	Duration of symptoms ≥3 months
	No other disorder explaining the pain

ACR = American College of Rheumatology.

[a]Fibromyalgia is diagnosed in the setting of WPI ≥7 plus SS score ≥5, or WPI ≥3 plus SS score ≥9.

[b]The Widespread Pain Index and the Symptom Severity Scale can be viewed at https://www.rheumatology.org/Portals/0/Files/2010%20Fibromyalgia%20Diagnostic%20Criteria_Excerpt.pdf.

Patients should be educated regarding the disease, with validation that the symptoms are real and that the painful areas are not injured and will not lose function. Aerobic exercise can improve well-being and function as well as reduce pain. Because patients initially experience postexercise pain that may threaten their willingness to continue, exercise must be introduced gradually and supported encouragingly. Strength training may also be helpful. Although the evidence base supporting their use is modest, alternative medicine approaches, including yoga, tai chi, acupuncture, and massage, may also help alleviate symptoms.

Patients with fibromyalgia should be assessed for psychosocial stressors and psychiatric illness, including a history of trauma. If present, referral for psychological care is mandatory, because psychic distress may both promote and result from fibromyalgia. Cognitive behavioral therapy has shown modest benefit in reducing pain, negative mood, and disability.

Choice of pharmacologic therapy is based on symptom profile, patient comorbidities, and medication side effects because few trials directly compare the efficacy of medications. Effective pharmacologic therapies target the underlying pathophysiology and inhibit the ascending pain pathways, enhance the descending inhibitory pathways to the dorsal roots, or inhibit release of the pain-promoting neurotransmitter glutamate.

The antiepileptic agents gabapentin and pregabalin (the latter FDA approved) inhibit $\alpha_2\delta$ calcium channels to inhibit glutamate release. They have been shown to improve quality of life and decrease pain.

Tricyclic antidepressants (TCAs) (such as amitriptyline) raise norepinephrine levels and have documented benefit, although efficacy may wane with time. TCAs induce drowsiness, with potential benefit for disordered sleep. The muscle relaxant cyclobenzaprine, another tricyclic, may be useful in patients with muscle spasms. Selective serotonin reuptake inhibitors have little benefit alone but may complement the activity of TCAs.

Among the more effective fibromyalgia therapies are the dual serotonin-norepinephrine reuptake inhibitors (SNRIs), including the FDA-approved agents duloxetine and milnacipran. They or a TCA may be particularly appropriate in the patient with concomitant depression.

Tramadol, which has a complex mechanism of action, has shown some benefit and may be considered as a second-line approach. Finally, in some cases, combination pharmacologic therapy may be helpful.

Evidence does not support the benefit of NSAIDs for fibromyalgia, and pure opioids should not be used.

Fibromyalgia is a chronic disease, and the patient and physician should understand that the benefit of treatment will likely be partial and palliative, rather than complete or curative. Nonetheless, proper treatment can help most patients manage and cope with their symptoms as well as maintain function and autonomy.

KEY POINTS

- The characteristic features of fibromyalgia are widespread chronic pain, fatigue, and sleep disorders, which are frequently accompanied by impaired cognitive function, mood disorders, and symptoms such as headache, gastrointestinal symptoms, and paresthesia.
- The diagnosis of fibromyalgia is no longer based upon physician examination findings but a careful characterization of symptoms using a validated scoring tool. **HVC**
- Nonpharmacologic therapy (education, exercise, psychosocial support) remains a cornerstone of treatment for fibromyalgia, although pharmacotherapy is often warranted. **HVC**

Spondyloarthritis

Overview

Spondyloarthritis refers to a group of arthritic disorders that tends to involve the spine and sacroiliac joints and share genetic, pathophysiologic, and clinical features. HLA-B27 is variably expressed but is more frequently present in this group

of patients than in the general population. Peripheral arthritis, enthesitis (inflammation of the insertion points of tendons and ligaments onto bone), inflammatory eye disease, psoriatic rashes, and gastrointestinal and genitourinary inflammation may occur in varying degrees.

Pathophysiology

Pathophysiologic processes involved in these disorders include T-cell activation and proliferation; elaboration of cytokines, particularly tumor necrosis factor (TNF)-α and the interleukins (IL)-1 and -23/17; and bony proliferation and destruction. Although the exact trigger for these processes is unknown, genetic and environmental factors are likely to play a role.

Genetic Factors

The most important genetic risk factor for spondyloarthritis is the presence of HLA-B27. The prevalence of HLA-B27 is high among Northern Europeans (about 6%) and low in Africans; accordingly, spondyloarthritis is seen with greater frequency in the former group. However, only 5% to 6% of those carrying HLA-B27 develop spondyloarthritis, and not all patients with spondyloarthritis are positive for HLA-B27. For these reasons, HLA-B27 should not be used as a screening test for these disorders, although its presence in a patient with a high pretest probability can support the diagnosis.

Several theories have been advanced to explain the relationship between HLA-B27 and the spectrum of disease observed. The arthritogenic peptide theory suggests that the presentation of an unknown peptide(s), perhaps of bacterial origin, activates cytotoxic T lymphocytes in the context of HLA-B27. Other theories propose that HLA-B27 molecules on antigen-presenting cells can either directly activate natural killer and T cells even in the absence of antigen or can induce a proinflammatory environment. Similarly, HLA-B27 expression on intestinal epithelium may interact with the gut microbiome to favor inflammation. Finally, tissue-specific chronic inflammation triggered by bacterial or mechanical stress may underlie a more autoinflammatory rather than autoimmune role for HLA-B27.

Other genes that have been identified as risk factors for spondyloarthritis include those associated with the TNF receptor signaling pathway as well as IL-1α and IL-23 receptor polymorphisms.

Environmental Factors

Considerable interest has focused on the role of the microbiome, particularly because gut inflammation is prevalent in many forms of spondyloarthritis. It is hypothesized that microbe-associated intestinal inflammation could cause loss of integrity of the bowel epithelium, permitting macrophage stimulation, increases in IL-23, and Th17 cell activation. However, specific causative pathogen exposure has not been identified except in some cases of reactive arthritis.

KEY POINTS

- Spondyloarthritis refers to a group of arthritic disorders that tends to involve the spine and sacroiliac joints and share genetic, pathophysiologic, and clinical features.
- The most important genetic risk factor for spondyloarthritis is the presence of HLA-B27; however, only 5% to 6% of patients carrying HLA-B27 develop spondyloarthritis, and not all patients with spondyloarthritis are positive for HLA-B27.

Classification

Spondyloarthritis is divided into five categories based on the predominant clinical features, although overlap of clinical features among these categories is common (**Table 17**):

1. Ankylosing spondylitis: Spinal involvement is the defining feature.
2. Psoriatic arthritis: Psoriasis co-occurs with spinal and/or peripheral arthritis.
3. Inflammatory bowel disease–associated arthritis: Clinically apparent intestinal inflammation is present along with spinal and/or peripheral arthritis.
4. Reactive arthritis: Inflammatory synovitis (primarily peripheral) occurs following specific gastrointestinal or genitourinary infections.
5. Undifferentiated spondyloarthritis: Spondylitis occurs in the absence of diagnostic features (including radiographic changes) that would permit diagnosis of one of the other categories of disease.

Clinical features common to all forms of spondyloarthritis are back pain, enthesitis, and dactylitis. Back pain is often the presenting symptom for spondyloarthritis, although spondyloarthritis only accounts for about 5% of chronic low back pain. Unlike most forms of back pain, the pain in spondyloarthritis is inflammatory and typically occurs in patients under the age of 40 years. It is characterized by an insidious onset, duration of more than 3 months, presence at rest and at night (waking the patient), morning stiffness lasting more than 30 minutes, and improvement with exercise. Enthesitis, or inflammation at the site where a ligament or tendon attaches to bone, presents as pain and tenderness in areas such as the Achilles tendon (**Figure 10**). Dactylitis ("sausage digits") is a diffuse fusiform swelling of the fingers or toes, consistent with tendon and ligament involvement beyond the points of insertion (**Figure 11**).

Although the categories listed here are extremely helpful in identifying and diagnosing disease, recently developed classification criteria emphasize the commonalities rather than the differences among the various forms of spondyloarthritis (for example, Assessment of SpondyloArthritis international Society [ASAS] criteria for peripheral and axial disease). Such criteria may permit diagnosis and treatment at an earlier stage

TABLE 17. Clinical Features of Spondyloarthritis

	Ankylosing Spondylitis	Psoriatic Arthritis	IBD-Associated Arthritis	Reactive Arthritis
Musculoskeletal				
Axial involvement	Axial involvement predominates; initially symmetrically involves the SI joints and lower spine, progressing cranially; does not skip regions	May occur at any level; may start in the cervical spine; may skip regions	May be asymptomatic but can follow a course similar to ankylosing spondylitis; SI involvement often asymmetric; axial arthritis does not parallel IBD activity	Less common than in other forms of spondyloarthritis
Peripheral involvement	Enthesitis; may have asymmetric large-joint oligoarthritis, including hips and shoulders; hip involvement can cause significant functional limitation; dactylitis uncommon	Five subtypes (symmetric polyarthritis; asymmetric oligoarthritis; DIP-predominant; spondyloarthritis; arthritis mutilans); also, enthesitis, dactylitis, and tenosynovitis	Acute polyarticular peripheral arthritis: especially knee; early; can parallel IBD activity Chronic polyarticular peripheral arthritis: of PIPs, MCPs, wrists, elbows, shoulders, knees, ankles, and MTPs; does not parallel IBD; dactylitis; enthesitis	Enthesitis and asymmetric large-joint oligoarthritis; usually self-limited; nonerosive; some patients experience recurrent or persistent arthritis; may develop features of other forms of spondyloarthritis
Dermatologic	Skin findings not characteristic, but psoriatic-like lesions may occasionally occur	Psoriasis typically precedes joint involvement; nail pitting; onychodystrophy	Pyoderma gangrenosum; erythema nodosum	Keratoderma blennorrhagicum (psoriasiform rash on soles, toes, palms); circinate balanitis (psoriasiform rash on penis)
Ophthalmologic	Anterior uveitis (unilateral, recurrent)	Conjunctivitis more common than anterior uveitis (can be bilateral, insidious, or chronic)	Anterior uveitis (can be bilateral, insidious, or chronic); conjunctivitis, keratitis, and episcleritis are rare	Conjunctivitis more common than anterior uveitis
Gastrointestinal	Asymptomatic intestinal ulcerations (rare)	—	Crohn disease; ulcerative colitis	Prior GI infection in some patients
Genitourinary	Urethritis (rare)	—	Nephrolithiasis	Prior GU infection in some patients; sterile urethritis; prostatitis; cervicitis; salpingitis
Cardiovascular	Aortic valve disease; aortitis; conduction abnormalities; CAD	Association with traditional CAD risk factors	Thromboembolism	—
Pulmonary	Restrictive lung disease from costovertebral rigidity; apical fibrosis (rare)	—	—	—
Bone quality	Falsely elevated bone mineral density from syndesmophytes; increased risk of spine fracture	Increased risk of fracture (multifactorial)	High risk for vitamin D deficiency, low bone density, and fracture	Localized osteopenia

CAD = coronary artery disease; DIP = distal interphalangeal; GI = gastrointestinal; GU = genitourinary; IBD = inflammatory bowel disease; MCP = metacarpophalangeal; MTP = metatarsophalangeal; PIP = proximal interphalangeal; SI = sacroiliac.

of disease before the unique features of the condition become well defined.

Ankylosing Spondylitis

Ankylosing spondylitis is a chronic inflammatory disease affecting the axial skeleton, entheses, and peripheral joints. In contrast to other forms of spondyloarthritis, sacroiliac joint involvement is considered an essential feature of ankylosing spondylitis. Ankylosing spondylitis has a strong familial predilection and the strongest association with HLA-B27 among the forms of spondyloarthritis, being present in up to 95% of patients. Although a male predominance of 2-3:1 has been described, women usually have milder and underappreciated disease; prevalence may actually be similar between genders. Disease can begin as early as adolescence, but peak age of diagnosis is between 20 and 30 years.

Symptoms of inflammatory back pain are most frequently the presenting complaint. Spinal involvement begins in the lumbar region and tends to ascend. Buttock pain may indicate sacroiliac joint involvement, which is characteristically bilateral. About one third of patients develop hip joint involvement and about one third develop peripheral arthritis elsewhere, often in the shoulders. Enthesitis most often manifests as Achilles tendinitis. Dactylitis occurs in fewer than 10% of patients.

FIGURE 10. Marked thickening of the distal right Achilles tendon and Achilles insertion on the calcaneus as the result of chronic Achilles tendinitis in a patient with psoriatic arthritis (normal contralateral Achilles insertion).

FIGURE 11. Diffuse swelling of the first and second toes of the left foot due to dactylitis in a patient with psoriatic arthritis resulting in a "sausage digit" appearance.

Physical examination, particularly in more advanced disease, can be highly characteristic. With active inflammation, tenderness over the sacroiliac joints is often the first sign of disease. Over time, marked reduction in spinal mobility can occur in all planes, and chest expansion becomes reduced. Flexion deformity at the neck and thoracic hyperkyphosis may lead to a hunched posture. A loss of lumbar lordosis and restricted range of motion in the hips may also be evident.

Extra-articular manifestations of ankylosing spondylitis are not uncommon (see Table 17). Cardiac and pulmonary manifestations, including aortic valve disease, cardiac conduction abnormalities, and restrictive lung disease, are more common in ankylosing spondylitis than other forms of spondyloarthritis. In addition, vertebral compression fractures may occur with little to no trauma as the disease progresses. The cervical spine is the most common site for fractures and can be associated with neurologic complications.

The course of ankylosing spondylitis is variable; progression may occur over many years. Markers of a poorer prognosis include a longer duration of disease, the presence of hip joint involvement, elevation of inflammatory markers, and the presence of radiographic changes in the spine. Mortality is increased in men and correlates with disease activity.

Psoriatic Arthritis

Psoriatic arthritis is an inflammatory joint disease associated with psoriasis. Estimates of the frequency of psoriatic arthritis among patients with psoriasis vary from 7% to 42%. Men and women are equally affected, and the usual age of onset is between 30 to 50 years. Psoriasis precedes or co-occurs with arthritis symptoms in about 90% of patients with psoriatic arthritis; less commonly, the rash may follow the arthritis, with a latency period as long as a decade. Skin involvement may be subtle, involving only areas such as the umbilicus, perineum, or gluteal cleft. There is no correlation between the extent of skin involvement and the severity of joint symptoms. In addition to skin lesions, nail pitting and onychodystrophy are seen; nail involvement is a risk factor for developing joint disease, particularly of the distal interphalangeal joints (**Figure 12**).

Five clinical subtypes of psoriatic arthritis, which may overlap, are recognized as follows: symmetric polyarthritis; asymmetric oligoarthritis; distal interphalangeal-predominant disease; spondyloarthritis; and arthritis mutilans. Arthritis mutilans represents the rare end stage of progressive, destructive arthritis in the small joints of the hands. It results in subluxation, ligamentous laxity, and telescope-like retraction of the fingers. Additional joints usually become involved over time.

Enthesitis, tenosynovitis, and dactylitis often occur. Common locations for enthesitis include the Achilles tendon (see Figure 10), the calcaneal insertion of the plantar fascia, and ligamentous insertions into the pelvic bones. Dactylitis typically involves one or two digits; the feet are more commonly affected than the hands (see Figure 11).

Symptomatic and radiographic spine involvement is unusual at disease onset but increased over long-term follow-up,

FIGURE 12. Dystrophic nail changes, including onycholysis and pitting, and inflammatory arthritic changes in the distal interphalangeal joints in a patient with psoriasis and psoriatic arthritis.

particularly in the cervical spine. The presence of sacroiliitis is associated with an increased likelihood for HLA-B27 positivity. In contrast to the almost universally bilateral sacroiliitis of ankylosing spondylitis, sacroiliitis is not always present in psoriatic arthritis and is more likely to be unilateral. Extra-articular manifestations are listed in Table 17.

Poor prognostic factors in psoriatic arthritis include the presence of polyarticular or erosive disease at the time of diagnosis. Patients additionally have an increased risk for cardiovascular disease.

Inflammatory Bowel Disease-Associated Arthritis

Inflammatory bowel disease (IBD), including Crohn disease and ulcerative colitis, may be associated with inflammatory arthritis in 6% to 46% of patients. Onset of arthritis may occur at any time in the course of the bowel disease.

IBD-associated arthritis occurs in three patterns:

1. Sacroiliitis/spondylitis: occurs in up to 26% of patients; 50% to 75% are positive for HLA-B27; men are more frequently affected than women; radiographic abnormalities of the sacroiliac joints may be seen in the absence of symptoms.
2. Acute polyarticular peripheral arthritis: self-limited; affects 5% of patients and occurs early in the course of IBD; the presence of arthritis is not as highly associated with HLA-B27 as in axial disease; the knee is most frequently involved; flares of joint symptoms may parallel exacerbations of bowel disease, but 90% resolve within 6 months.
3. Chronic polyarticular peripheral arthritis: affects less than 5% of patients; men and women are equally affected; the presence of arthritis is not as highly associated with HLA-B27 as in axial disease; the metacarpophalangeal joints, knees, ankles, elbows, shoulders, wrists, proximal interphalangeal, and metatarsophalangeal joints may be affected; flares of arthritis may recur repeatedly over years and last for months, but joint symptoms are unrelated to bowel disease activity.

See Table 17 for information on extra-articular manifestations.

Reactive Arthritis

Reactive arthritis is a rare cause of inflammatory arthritis that can occur following specific genitourinary and gastrointestinal infections, including *Chlamydia trachomatis* and *Ureaplasma urealyticum* in the urethra and *Campylobacter, Escherichia coli, Salmonella, Shigella,* and *Yersinia* in the intestine. Reactive arthritis occurs following 2% to 33% of cases of bacterial dysentery, with a higher incidence reported after single source outbreaks. About 90% of *Yersinia*-related cases occur in patients who are HLA-B27 positive, whereas only 30% to 50% of patients with reactive arthritis associated with other infectious agents are HLA-B27 positive.

Symptoms of inflammatory arthritis typically appear 2 to 3 weeks postinfection. Arthritis is asymmetric and may be monoarticular or oligoarticular; joints commonly affected include the knee, ankle, and wrist. Enthesitis is especially common; Achilles tendinitis and plantar fasciitis occur in up to 90% of cases. Dactylitis can also occur. The spine and sacroiliac joints are less commonly involved. In about half of patients, symptoms self-resolve within 6 months; most other cases self-resolve within 1 year, with a small proportion of cases converting to chronic disease. Extra-articular manifestations are described in Table 17. A subset of patients may demonstrate the "complete triad" of conjunctivitis, arthritis, and urethritis.

KEY POINTS

- Ankylosing spondylitis is a chronic inflammatory disease affecting the axial skeleton (including sacroiliac joints), entheses, and peripheral joints; HLA-B27 is present in up to 95% of patients.
- Psoriatic arthritis is an inflammatory joint disease associated with psoriasis, multiple possible joint patterns, enthesitis, tenosynovitis, and dactylitis.
- Inflammatory bowel disease-associated arthritis occurs in three patterns: sacroiliitis/spondylitis, acute polyarticular peripheral arthritis, and chronic polyarticular peripheral arthritis; only the acute polyarticular form is related to flares of bowel disease.
- Reactive arthritis can occur 2 to 3 weeks following specific gastrointestinal and genitourinary infections; an asymmetric monoarticular or oligoarticular arthritis, dactylitis, and enthesitis can occur.

Diagnosis

Laboratory Studies

Spondyloarthritis is considered seronegative because rheumatoid factor and other autoantibodies are typically absent. HLA-B27 is present in many patients, particularly those with ankylosing spondylitis and spinal involvement; however, it cannot independently confirm or exclude a diagnosis. With active disease, evidence of systemic inflammation may be diagnostically helpful, including elevations of erythrocyte sedimentation rate and C-reactive protein as well as normochromic, normocytic anemia. Each of these findings, however, is nonspecific and may be normal even in the presence of active disease. Several other laboratory findings are suggestive of the underlying disorder but are of limited utility diagnostically. Elevated IgA levels have been reported in patients with ankylosing spondylitis and psoriatic arthritis, consistent with increased mucosal immune activity. Serum alkaline phosphatase may be elevated in ankylosing spondylitis. Serum urate levels may be high in psoriatic arthritis, and these patients are at increased risk for co-occurrence of gout. Synovial fluid may show an elevated leukocyte count with a predominance of neutrophils.

In cases of suspected reactive arthritis, stool and urine cultures, genital swabs, nucleic acid amplification testing, and

rising serum antibody titers against the suspected causative organism can be helpful in establishing the diagnosis. Pathogens can generally not be cultured from joint fluid in these patients, and antecedent infection is verified in less than half of affected individuals.

Imaging Studies

Radiography of the sacroiliac joints is an essential part of the initial evaluation of patients being assessed for spondyloarthritis but may be normal early in the course of disease. Radiographic evidence of sacroiliitis includes pseudo-widening of the joints, erosions, sclerosis, and ankylosis. In the spine, bony proliferation between vertebral bodies can result in formation of syndesmophytes (bony bridges) that can lead to a "bamboo spine" appearance in 10% to 15% of affected patients with ankylosing spondylitis (**Figure 13**). Other changes in the spine include vertebral squaring, disk calcification, and vertebral and facet joint ankylosis. In psoriatic arthritis, the syndesmophytes are often described as less delicate, more "chunky," patchy, and asymmetric compared with those associated with ankylosing spondylitis.

Plain radiography of peripheral joints may aid in the diagnosis of spondyloarthritis, particularly when erosive and proliferative changes are present concurrently. Bony proliferative changes at entheseal sites may be seen in any spondyloarthritis. Features particularly characteristic of psoriatic arthritis include asymmetric distribution, distal interphalangeal joint involvement, osteolysis leading to pencil-in-cup deformity (**Figure 14**), and proliferative new bone formation along the shaft of metacarpal or metatarsal bones. There are no characteristic findings of reactive arthritis on plain radiographs.

Although plain radiography remains the cornerstone of radiographic diagnosis in spondyloarthritis, MRI is increasingly recognized as a useful diagnostic and prognostic modality. MRI is more sensitive for detecting early spine and sacroiliac joint inflammation and may be indicated in the evaluation of suspected spondyloarthritis if plain radiographs are negative. MRI can also detect inflammatory changes even in the absence of bony lesions. For example, the presence of bone marrow edema, although nonspecific, can suggest active inflammation in the sacroiliac joints. MRI can also detect soft-tissue abnormalities (such as bursitis and enthesitis), erosions, sclerosis, and ankylosis.

FIGURE 13. Spinal features of ankylosing spondylitis. *Left*, Sacroiliac erosive disease, characterized by areas of joint-space narrowing in some locations, apparent relative widening in others, and secondary bony sclerosis. Although the left sacroiliac joint is more severely involved, both sides are affected. *Right*, Delicate (gracile) syndesmophytes bridging lumbar vertebral bodies, leading to a "bamboo spine" appearance. Note that the syndesmophytes are "flowing" (contiguous without skipping any vertebral joints).

FIGURE 14. Radiograph showing pencil-in-cup deformity of the fifth metatarsal joint and ankylosis of the fourth metatarsal joint in a patient with psoriatic arthritis.

In older patients, the diagnostic specificity of radiographic evaluation for spondyloarthritis may decline. Other conditions such as osteitis condensans ilii, osteoarthritis, degenerative disk disease, and diffuse idiopathic skeletal hyperostosis (DISH) may cause sclerotic changes of the sacroiliac joints and osteophytes that may be difficult to distinguish from the syndesmophytes of ankylosing spondylitis. In particular, DISH typically causes multilevel bridging osteophytes. In ankylosing spondylitis, however, the bony bridges tend to be thinner and more vertically oriented than those seen in DISH.

KEY POINTS

- In patients with spondyloarthritis, rheumatoid factor and other autoantibodies are typically absent; HLA-B27 is positive in many patients, but it cannot independently confirm or exclude a diagnosis. HVC
- Markers of systemic inflammation such as erythrocyte sedimentation rate and C-reactive protein may be normal even in the presence of active spondyloarthritis.

(Continued)

KEY POINTS *(continued)*

- Radiography of the sacroiliac joints is essential in patients with suspected spondyloarthritis; radiographic evidence of sacroiliitis includes pseudo-widening of the joints, erosions, sclerosis, and ankylosis.
- HVC MRI is more sensitive for detecting early spine and sacroiliac joint inflammation and may be indicated in the evaluation of suspected spondyloarthritis if plain radiographs are negative.
- Radiographic changes in psoriatic arthritis can include asymmetric distribution, distal interphalangeal joint involvement, osteolysis leading to a pencil-in-cup deformity, and proliferative new bone formation along the shaft of metacarpal or metatarsal bones.

Management

General Considerations

Management goals in spondyloarthritis are to control pain and inflammation, preserve function, and prevent progressive structural damage, including spine and joint ankyloses (fusion). Patient education regarding the course, treatment, and prognosis of disease, as well as the importance of general health, avoiding smoking, and participating in regular exercise are critical components of the overall treatment program.

Ankylosing Spondylitis

NSAIDs are recommended as first-line treatment in ankylosing spondylitis and remain important in management throughout the course of disease. Patients with ankylosing spondylitis are more likely to respond to NSAIDs and to do so more rapidly and completely than patients with chronic low back pain from other causes. Several studies suggest that, in contrast to most forms of arthritis, continuous use of NSAIDs may help slow disease progression in ankylosing spondylitis. Oral glucocorticoids are not recommended, but intra-articular glucocorticoid injections, including in the sacroiliac joints, can help alleviate pain. Nonbiologic disease-modifying antirheumatic drugs (DMARDs) such as methotrexate have no efficacy in axial disease and limited efficacy in peripheral disease.

In patients with persistent symptoms on NSAID therapy, TNF-α inhibitors have efficacy in reducing signs and symptoms of ankylosing spondylitis, with about half of those treated improving by 50%. Whether TNF-α inhibitors can slow radiographic progression in ankylosing spondylitis remains an area of ongoing investigation. These agents are also effective in treating ankylosing spondylitis-associated anterior uveitis.

Physical therapy is the most important nonpharmacologic intervention in ankylosing spondylitis. The goals of therapy include improving pain and stiffness, maintaining range of motion, and reducing disability; transition to an ongoing daily exercise program is optimal.

Total hip arthroplasty can be highly effective in reducing pain and restoring function in the management of progressive hip involvement and may be indicated at an earlier age than in patients with osteoarthritis.

Psoriatic Arthritis

Treatment choices in psoriatic arthritis take into account the extent of both skin and joint involvement. NSAIDs may be effective for mild joint disease. Methotrexate is the most commonly used DMARD for psoriatic arthritis. Although benefit can be demonstrated in control of skin disease and joint pain, methotrexate has not been shown to reduce progression of joint damage. Sulfasalazine and leflunomide can also improve joint symptoms. Apremilast is modestly effective for psoriasis and psoriatic arthritis.

In more severe psoriatic arthritis, TNF-α inhibitors have been shown to have superior efficacy in the management of joint symptoms and to slow the progression of radiographic damage, including joint-space narrowing and erosions.

The biologic agents ustekinumab (anti-IL-12/23 antibody) and secukinumab (anti-IL-17A antibody) have also been approved for treating both psoriasis and psoriatic arthritis, and can improve dactylitis and enthesitis.

Inflammatory Bowel Disease-Associated Arthritis

Various pharmacologic agents may be useful in the treatment of both intestinal and peripheral arthritis related to Crohn disease and ulcerative colitis, including sulfasalazine, azathioprine, 6-mercaptopurine, methotrexate, glucocorticoids, and the TNF-α inhibitors infliximab and adalimumab. NSAIDs can provide symptomatic relief of arthritis symptoms but may occasionally exacerbate IBD.

Reactive Arthritis

Treatment of the antecedent infection is indicated in patients with reactive arthritis who have an identifiable cause. However, most patients present postinfection, and antibiotics are not usually effective in treating the arthritis. Most patients have self-limited disease, and short-term use of daily NSAIDs often improves symptoms until the condition resolves. If relief is incomplete, intra-articular glucocorticoid injections and oral glucocorticoids can be used. If symptoms persist beyond 3 to 6 months, the use of DMARDs such as sulfasalazine, methotrexate, or TNF-α inhibitors may be necessary for symptom control and to prevent joint erosion. Therapy is discontinued 3 to 6 months following disease remission.

KEY POINTS

- In ankylosing spondylitis, NSAIDs are recommended as first-line treatment and may help slow disease progression; physical therapy is the most important nonpharmacologic intervention. HVC

(Continued)

KEY POINTS *(continued)*

- In more severe psoriatic arthritis, tumor necrosis factor α inhibitors have been shown to have superior efficacy in the management of joint symptoms and to slow the progression of radiographic damage.
- Treatment options for both intestinal and peripheral arthritis related to Crohn disease and ulcerative colitis include sulfasalazine, azathioprine, 6-mercaptopurine, methotrexate, glucocorticoids, infliximab, and adalimumab.
- HVC Antibiotics are not usually effective in treating reactive arthritis, but short-term NSAIDs can be used to improve symptoms in this typically self-limited disease.

Systemic Lupus Erythematosus

Epidemiology and Pathophysiology

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease characterized by a heterogeneous constellation of organ involvement and the presence of antinuclear antibodies (ANA) and other autoantibodies.

In SLE, a complex and varying interaction of genes, environment, and random events leads to a breakdown of self-tolerance and autoimmunity. Defects in cellular apoptosis result in inadequate clearance of intracellular proteins, especially nuclear antigens, promoting the generation of self-directed T and B cells and the initiation/propagation of autoimmunity. Cytokine generation supports the autoreactivity, with type-1 interferons playing a major role. Autoantibodies may directly induce tissue damage or promote the formation of immune complexes that lead to complement activation and tissue inflammation and damage. Inheritance of SLE risk is polygenic, including major histocompatibility complex.

The risk of SLE developing in genetically predisposed individuals increases at puberty and peaks in the third decade. Approximately 90% of adult patients are women. The disease is more common, and perhaps more severe, in black, Asian, and Hispanic ethnicities.

KEY POINTS

- Systemic lupus erythematosus is a multisystem autoimmune disease characterized by a heterogeneous constellation of organ involvement and the presence of antinuclear antibodies and other autoantibodies.
- Approximately 90% of adult patients with systemic lupus erythematosus are women.

Clinical Manifestations

Mucocutaneous Involvement

Skin disease occurs in up to 90% patients with SLE and is classified as acute, subacute, or chronic.

Acute cutaneous lupus erythematosus (ACLE) presents as an erythematous, macular, patchy eruption, sometimes with desquamation. The facial eruption of ACLE (malar or butterfly rash) is characterized by erythema/edema over the cheeks and bridge of the nose, sparing the nasolabial folds; it occurs in about 50% of patients with SLE (**Figure 15**). Less characteristically, ACLE can also involve the neck, upper chest, and dorsum of the arms and hands; it affects the skin between the fingers but spares the knuckle pads. In some patients, a bullous eruption can occur. ACLE usually responds to therapy and heals without scarring or atrophy.

Subacute cutaneous lupus erythematosus (SCLE) is a photosensitive rash occurring especially on the arms, neck, and face (**Figure 16**). It consists of erythematous annular/polycyclic or patchy papulosquamous lesions, often with a fine scale, that may leave postinflammatory hypo- or hyperpigmentation. SCLE is associated with anti-Ro/SSA autoantibodies (prevalence >75%) and can occur in isolation or as a manifestation of underlying SLE.

Discoid lupus erythematosus (DLE) is the most common chronic cutaneous manifestation of SLE, occurring in 20% of patients (**Figure 17**). DLE presents as hypo- or hyperpigmented patches or plaques, with erythema during active disease, which may be variably atrophic or hyperkeratotic. Unlike ACLE and SCLE, DLE can cause scarring, atrophy, and permanent alopecia. DLE also occurs as an isolated finding in the absence of SLE. Isolated DLE is usually limited to the neck, face, and scalp, whereas discoid lesions in SLE are more diffusely distributed. Patients with isolated DLE tend to be ANA negative and usually do not progress to SLE. It is important to differentiate isolated DLE from DLE as a manifestation of

FIGURE 15. The facial eruption of acute cutaneous lupus erythematosus (malar or butterfly rash). This patient has fixed erythematous raised lesions over the malar eminences, the bridge of the nose with sparing of the nasolabial folds, and the chin.

FIGURE 16. Subacute cutaneous lupus erythematosus is characterized by erythematous, macular, or patchy skin lesions that are scaly and can evolve as (*A*) annular/polycyclic lesions or (*B*) papulosquamous plaques.

FIGURE 17. Discoid lupus erythematosus. This patient has hyperpigmented, raised patches with keratotic scaling and follicular plugging involving the malar and perioral areas as well as the bridge of the nose. Areas of atrophic scarring are also present.

underlying SLE when making therapeutic and prognostic decisions.

Painless oral or nasopharyngeal ulcerations occur in 5% of patients with SLE, with involvement of hard palate suggestive of the diagnosis. Rarely, DLE can be associated with painful ulcers. Nonscarring alopecia is a common feature of active SLE, with hair regrowth a sign of disease control. Raynaud phenomenon occurs frequently, reflecting arterial vasospasm of digital arteries.

See MKSAP 18 Dermatology for more information.

Musculoskeletal Involvement

Joints are affected in 90% of patients with SLE. The most common involvement is polyarthralgia, with frank arthritis occurring in 40%. Typical distribution is small peripheral joints, but large joints are also affected. In contrast to rheumatoid arthritis, SLE arthritis is nonerosive, but reducible subluxation of the digits, swan neck deformities, and ulnar deviation (Jaccoud arthropathy) can occur.

A serious complication of SLE is osteonecrosis, which most commonly affects the hips but can also involve other large joints, and should be suspected when there is otherwise unexplained pain and/or reduced range of motion. Chronic prednisone doses (>20 mg/d), severe/active SLE, and vasculitis are all associated with increased risk. MRI is the modality of choice for sensitive evaluation of early disease, with plain radiography useful to diagnose and follow later stages. Small lesions can improve and resolve spontaneously, but larger lesions usually lead to bony collapse and structural sequelae.

Myalgia and subjective weakness are common; frank myositis is rare. Assessment is complicated by the potential effect on muscle of antimalarials (rarely) and glucocorticoids (commonly), which must be differentiated from active SLE disease. Fibromyalgia is a common comorbidity (30%); symptoms may be similar to active SLE disease.

Kidney Involvement

H

Kidney disease occurs frequently among patients with SLE (70%) and was the major cause of SLE mortality prior to the advent of dialysis. Lupus nephritis can present with minimal laboratory abnormalities (non-nephrotic proteinuria, hematuria), frank nephritis (hypertension, lower extremity edema, active urine sediment, and elevated serum creatinine), and/or nephrosis (nephrotic-range proteinuria, dependent edema, and thrombosis). Untreated active disease may progress to kidney failure.

All patients with SLE should be regularly evaluated for kidney disease by assessing serum creatinine and urine for

H CONT.

protein and microscopic evaluation. Patients with significant abnormalities, including proteinuria greater than 500 mg/24 h or active urine sediment, should be urgently evaluated for active disease. Anti-double-stranded DNA antibody titers are a marker for risk, and complement consumption is a common phenomenon during active kidney disease.

Kidney biopsy defines both the histological subtype and the activity/chronicity of disease and is usually essential to make therapeutic decisions. Indications for kidney biopsy include an otherwise unexplained rise in serum creatinine, proteinuria greater than 1000 mg/24 h, proteinuria greater than 500 mg/24 h with hematuria, or an active urine sediment.

Patients who have SLE with hypercoagulable states (for example, nephrosis or antiphospholipid syndrome) may be at risk for renal artery or vein thrombosis.

See MKSAP 18 Nephrology for information on the classes and treatment of lupus nephritis. H

Neuropsychiatric Involvement

Neuropsychiatric systemic lupus erythematosus (NPSLE) may involve the central and/or peripheral nervous systems and has 19 defined manifestations. NPSLE prevalence is high (75%), with the most common manifestations being headache, mild cognitive dysfunction, and mood disorder. Peripheral neuropathy occurs in 10% to 14% of patients. Severe acute presentations, including seizures and psychosis, happen infrequently (<5%) but require aggressive symptomatic as well as disease-specific treatment.

H

Patients with suspected serious central NPSLE such as meningitis, stroke, and psychosis should undergo central nervous system imaging (CT, MRI, or PET) and cerebrospinal fluid analysis as appropriate. In some patients with severe disease, measurement of cerebrospinal fluid for NPSLE-associated autoantibodies (antineuronal, anti-*N*-methyl-D-aspartate receptor, antiribosomal P, and others) may be useful. For patients with suspected peripheral neuropathies, electromyography and nerve conduction studies should be performed. Neuropsychologic testing may help distinguish organic versus functional cognitive changes.

Cardiovascular Involvement

Asymptomatic pericarditis is the most frequent cardiac manifestation of SLE (40%). When symptomatic, features include chest pain, exudative effusion, and rarely tamponade or chronic constriction. Patients with SLE have a 2- to 10-fold increased prevalence of coronary artery disease (CAD), the most common cause of death among older patients. High SLE disease activity and prednisone doses greater than 10 mg/d are independent risk factors for future CAD.

Valvular abnormalities occurring in SLE include those associated with antiphospholipid syndrome (nonspecific thickening of the mitral and aortic valve leaflets, vegetations, regurgitation, and stenosis). Libman-Sacks endocarditis (noninfectious verrucous vegetations) preferentially affects the mitral valve and can cause embolic complications. Myocarditis occurs in 5% to 10% of patients with SLE and usually presents as insidious heart failure but can be acute. H

Pulmonary Involvement

Pulmonary involvement is common in SLE, with most patients presenting with pleuritis (45%-60%). Pleural effusions occur in approximately half of these patients and are typically exudative; fluid analysis may reveal a lymphocytic pleocytosis and mildly depressed glucose levels.

H

Parenchymal lung involvement occurs in less than 10% of patients with SLE. A nonspecific interstitial pneumonia pattern is most common, and evaluation centers on assessing SLE activity and excluding other causes of diffuse parenchymal lung disease. Two rare but potentially life-threatening complications of SLE lung disease are acute lupus pneumonitis (presenting as fever, cough, dyspnea, hypoxemia, pleuritic chest pain, and infiltrates) and diffuse alveolar hemorrhage (presenting with dyspnea, hypoxemia, diffuse alveolar infiltrates, a dropping hematocrit, and a high D_{LCO}). Both carry a high mortality rate (>50%); early recognition, rapid evaluation (CT and/or bronchoscopy with bronchoalveolar lavage or biopsy), and aggressive respiratory support combined with high-dose glucocorticoids and immunosuppression are required. With new pulmonary infiltrates, differentiation between these disorders and infection can be difficult, and antibiotics and immunosuppressive therapy are often administered simultaneously until the diagnosis is clear. H

Shrinking lung syndrome is a rare but characteristic syndrome consisting of pleuritic chest pain and dyspnea, with progressive decrease in lung volumes. The cause is uncertain, but pleuropulmonary disease and/or diaphragmatic dysfunction may contribute. Immunosuppression may reverse the process in some patients.

Hematologic Involvement

H

In patients with SLE, a normocytic, normochromic inflammatory anemia is common; autoimmune hemolytic anemia occurs in approximately 10% and correlates with SLE activity. Lymphopenia/leukopenia is also common but usually mild. Thrombocytopenia occurs in 30% to 50%, and approximately 10% of patients develop severe thrombocytopenia (<50,000/µL [50×10^9/L]) in isolation or in conjunction with hemolytic anemia.

The cytopenias in SLE may be caused by immune and nonimmune destructive mechanisms (including microangiopathy), medications, and kidney and liver disease. Moderate and severe or rapidly progressive cytopenias require prompt evaluation with serologic studies and/or bone marrow biopsy. An exact cause of cytopenias may be difficult to ascertain, and a trial of medication adjustment in concert with evaluation for other causes is often necessary.

Antiphospholipid antibodies/lupus anticoagulant (APLA/LAC) are frequently present in patients with SLE (about 40%) and may be associated with a false-positive rapid plasma reagin test for syphilis. Most patients are asymptomatic.

H CONT.

Thrombotic events occur in about 30% and are associated with moderate or high titer of the antibodies; these include venous and arterial thrombosis, miscarriage, stillbirth, livedo reticularis, and cardiac valve thickening/vegetations. The highest risk of thrombosis occurs in the presence of triple positivity for LAC, anti-β_2-glycoprotein I, and anticardiolipin antibodies. Patients with SLE are at increased risk for thrombotic events even in the absence of APLA.

See MKSAP 18 Hematology and Oncology for more information. H

Gastrointestinal Involvement

Gastrointestinal disease is a common (40%) and frequently underrecognized SLE manifestation. Serositis presents as abdominal pain, is usually associated with active disease, and improves with treatment. Mesenteric vasculitis, inflammation of the small and large bowel, pancreatitis, protein-losing enteropathy, and diffuse peritonitis are uncommon but may be severe and associated with cutaneous vasculitis. Patients with APLA can present with mesenteric thrombosis.

Noninfectious hepatitis can occur and is associated with the presence of antiribosomal P antibodies. Patients with SLE who have Raynaud phenomenon and anti-U1-ribonucleoprotein antibodies can develop esophageal disease and reflux.

Medications used to treat SLE (NSAIDs, prednisone, mycophenolate, azathioprine) also frequently affect the gastrointestinal system and may cause esophagitis, gastritis, pancreatitis, and other manifestations.

KEY POINTS

- The facial eruption of acute cutaneous lupus erythematosus (malar or butterfly rash) is characterized by erythema/edema over the cheeks and bridge of the nose, sparing the nasolabial folds.
- Polyarthralgia of the small peripheral joints is the most common joint manifestation in systemic lupus erythematosus; a nonerosive arthritis occurs in 40% of patients.
- All patients with systemic lupus erythematosus should be regularly evaluated for kidney disease by assessing serum creatinine and urine for protein and microscopic evaluation.
- The most common manifestations of neuropsychiatric systemic lupus erythematosus are headache, mild cognitive dysfunction, and mood disorder.
- Patients with systemic lupus erythematosus (SLE) have a 2- to 10-fold increased prevalence of coronary artery disease (CAD); high SLE disease activity and prednisone doses greater than 10 mg/d are independent risk factors for developing CAD.

Association with Malignancy

The greatest malignancy risk among patients with SLE is non-Hodgkin lymphoma, presumably due to chronic B-cell activation and/or medications (azathioprine or cyclophosphamide). Other hematologic malignancies, including Hodgkin lymphoma and leukemia, are also increased. Lung cancer rates are increased slightly compared with the general population, probably related to smoking. Cervical cancer risk is increased, likely due to immunosuppression and increased prevalence of human papillomavirus.

KEY POINT

- The greatest malignancy risk among patients with systemic lupus erythematosus is non-Hodgkin lymphoma.

Diagnosis

General Considerations

The diagnosis of SLE should be considered in any patient with unexplained symptoms affecting multiple organ systems or with any individual manifestation of SLE, especially in young women. At initial presentation, skin and joint manifestations are most common, along with constitutional symptoms (fever, weight loss, or severe fatigue). Patients with subjective complaints of fatigue, myalgia, and/or arthralgia, but lacking objective findings, most likely have an alternative diagnosis and should not be evaluated for SLE.

Classification criteria for SLE were developed by the American College of Rheumatology (ACR) in 1982 and revised in 1997; although intended for accruing homogenous SLE populations for research studies, they can also be used to suggest a clinical diagnosis of SLE (**Table 18**). In 2012, the Systemic Lupus International Collaborating Clinics (SLICC) proposed and validated alternative SLE classification criteria that are similar to the ACR criteria but require the following: 1) fulfillment of at least four criteria, with at least one clinical criterion and one immunologic criterion; or 2) biopsy-proven lupus nephritis as sufficient clinical criterion in the presence of ANA or anti-double-stranded DNA antibodies. When compared with the ACR classification criteria, the SLICC classification criteria are associated with fewer misclassifications and have greater sensitivity but less specificity.

Laboratory Studies

Initial evaluation for SLE includes routine laboratory testing to establish organ-specific involvement, including complete blood count, chemistry panel, and urinalysis with microscopy.

ANA should be obtained to screen for nuclear-directed autoantibodies. The most appropriate methodology for testing ANA is the indirect immunofluorescence assay, which is highly sensitive (95%) for SLE. ANA tests should be interpreted in the context of the probability of disease because ANA may be present in other autoimmune diseases, and low-titer positivity may be seen with aging and even in healthy individuals.

If ANA is positive, SLE-specific autoantibodies (anti-double-stranded DNA, anti-Smith, anti-U1-ribonucleoprotein, anti-Ro/SSA, and anti-La/SSB), as well as tests for other autoimmune diseases under consideration, should be obtained

TABLE 18. American College of Rheumatology Criteria for the Classification of Systemic Lupus Erythematosus

Criteria[a]	Definition
Malar rash	Fixed erythema, flat or raised, over the malar eminences
Discoid rash	Erythematous, circular, raised patches with keratotic scaling and follicular plugging; atrophic scarring may occur
Photosensitivity	Rash after exposure to ultraviolet light
Oral ulcers	Oral and nasopharyngeal ulcers (observed by physician)
Arthritis	Nonerosive arthritis of ≥2 peripheral joints, with tenderness, swelling, or effusion
Serositis	Sterile pleuritis, pericarditis, or peritonitis (documented by electrocardiogram, rub, or evidence of effusion or ascites)
Kidney disorder	Urinalysis: 3+ protein or urine protein >500 mg/24 h; cellular casts
Neurologic disorder	Seizures or psychosis (without other cause)
Hematologic disorder	Hemolytic anemia or leukopenia (<4000/µL [4.0×10^9/L]) or lymphopenia (<1500/µL [1.5×10^9/L]) or thrombocytopenia (<100,000/µL [100×10^9/L]) in the absence of offending drugs
Immunologic disorder	Anti-double-stranded DNA, anti-Smith, and/or antiphospholipid antibodies
ANA	An abnormal titer of ANA by immunofluorescence or an equivalent assay at any point in the absence of drugs known to induce ANA

ANA = antinuclear antibodies.

[a]Any combination of 4 or more of the 11 criteria, well documented at any time during a patient's history, makes it likely that the patient has systemic lupus erythematosus (specificity and sensitivity are 95% and 75%, respectively).

From Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum. 1997;40(9):1725. [PMID: 9324032] Copyright 1997, American College of Rheumatology. Adapted with permission from John Wiley & Sons, Inc.

to further characterize the disease (**Table 19**). A small percentage of patients with SLE are negative for ANA but positive for anti-Ro/SSA antibodies. A negative ANA plus a negative anti-Ro/SSA essentially rules out SLE.

H Disease activity markers (complements C3 and C4) should be assessed initially and regularly thereafter. Complement levels are reduced during SLE activity, reflecting immune complex formation and complement consumption. Anti-double-stranded DNA antibody levels may rise with SLE kidney disease activity. Other SLE autoantibodies, including the ANA test, do not reflect disease activity and need not be repeated. Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are variably associated with disease activity; some patients with SLE do not generate CRP during SLE flares, which may be helpful in distinguishing flares from infection. H

Differential Diagnosis

The differential diagnosis of SLE includes multisystem diseases, acute and chronic infections, medication effect, malignancies (particularly hematologic), and neurologic diseases (for example, multiple sclerosis). Multisystem autoimmune diseases (ANCA-associated vasculitis, rheumatoid arthritis, adult-onset Still disease, dermatomyositis, Sjögren syndrome, and mixed connective tissue disease) have overlapping features but may be distinguished through a careful assessment of their unique manifestations.

SLE should also be distinguished from undifferentiated connective tissue disease, which presents with milder symptoms and objective abnormalities that cannot be categorized or diagnosed as a specific connective tissue disease (see Mixed Connective Tissue Disease).

TABLE 19. Common Autoantibodies in Systemic Lupus Erythematosus

Autoantibody	Frequency in SLE	Comments
Antinuclear	>95%	Useful as an initial screening test; assesses multiple antigens simultaneously
Anti-double-stranded DNA	50%-60%	Found in more severe disease, especially kidney disease; antibody levels commonly follow disease activity and are useful to monitor
Anti-Ro/SSA	30%	Associated with photosensitive rashes, discoid lupus erythematosus, and neonatal lupus erythematosus; also common when secondary Sjögren syndrome is present
Anti-U1-ribonucleoprotein	35%	Associated with Raynaud phenomenon and esophageal dysmotility; also seen in MCTD
Anti-Smith	30%	Specific for SLE; often associated with more severe disease
Anti-La/SSB	20%	Common in Sjögren syndrome; less common in SLE and neonatal lupus erythematosus
Antiribosomal P	15%	Associated with CNS lupus and lupus hepatitis

CNS = central nervous system; MCTD = mixed connective tissue disease; SLE = systemic lupus erythematosus.

Certain medications can cause drug-induced lupus erythematosus (DILE), which mimics SLE (**Table 20**). The syndrome is usually mild with symptoms of malaise, fever, arthritis, and rash associated with a transient positive ANA and antihistone antibodies. Symptoms resolve after discontinuing the offending agent. Kidney and central nervous system disease are uncommon. Patients with SLE are at no more risk of DILE than the general population, and there is no contraindication to using medications associated with DILE in patients with SLE.

KEY POINTS

- Patients with systemic lupus erythematosus typically initially present with skin and joint manifestations, along with fever, weight loss, or severe fatigue.
- Initial evaluation for systemic lupus erythematosus includes antinuclear antibody testing as well as routine laboratory testing to establish organ-specific involvement, including complete blood count, chemistry panel, and urinalysis with microscopy.

(Continued)

KEY POINTS *(continued)*

- If antinuclear antibody testing is positive, autoantibodies specific to systemic lupus erythematosus (anti-double-stranded DNA, anti-Smith, anti-U1-ribonucleoprotein, anti-Ro/SSA, and anti-La/SSB) should be obtained to further characterize the disease.

Management

SLE management requires close monitoring of disease activity and frequent adjustment of therapy. Pharmacologic therapy is almost always required and is usually directed toward specific organ involvement (**Table 21**).

Hydroxychloroquine should be initiated in every patient who can tolerate it, because evidence suggests it reduces disease-associated damage, prevents disease flares, and improves kidney and overall survival. Hydroxychloroquine can be used alone for mild disease (especially skin and joints) and in combination with other agents in severe disease. In addition, hydroxychloroquine may reduce the risk of thrombosis, liver

TABLE 20. Medications Commonly Associated with Drug-Induced Lupus Erythematosus

Medication	Antibodies Detected	Comments
Procainamide	ANA (75%); antihistone	20% develop DILE; fever; arthritis; serositis
Hydralazine	ANA (20%); antihistone	5%-8% develop DILE; fever; arthritis; rare vasculitis and kidney disease
Minocycline	ANA; ANCA; anti-dsDNA rare	Arthritis; vasculitis; autoimmune hepatitis
Antithyroid drugs	ANA; ANCA; antihistone	Vasculitic rash; rare pulmonary and kidney disease
Statins	ANA; antihistone; anti-dsDNA	SLE, SCLE, dermatomyositis, and polymyositis all reported
Calcium channel blockers	ANA; anti-Ro/SSA; antihistone rare	SCLE
Thiazide diuretics	ANA; anti-Ro/SSA; antihistone rare	SCLE
ACE inhibitors	ANA; anti-Ro/SSA; antihistone rare	SCLE
TNF-α inhibitors	ANA (23%-57%); chromatin and anti-dsDNA common; antihistone rare	DILE most common with infliximab, uncommon for etanercept; SLE, SCLE, DLE all reported

ANA = antinuclear antibodies; DILE = drug-induced lupus erythematosus; DLE = discoid lupus erythematosus; dsDNA = double-stranded DNA; SCLE = subacute cutaneous lupus erythematosus; SLE = systemic lupus erythematosus; TNF = tumor necrosis factor.

TABLE 21. Medications Commonly Used to Treat Systemic Lupus Erythematosus

Medication	Common Uses in SLE	Important Side Effects
NSAIDs	Arthritis; pain; fever	Hypertension; GI bleeding; AKI
Prednisone	Used for all manifestations in varying doses	Hypertension; glucose intolerance; weight gain; infection; osteonecrosis
Hydroxychloroquine	Used in all patients; especially useful for skin involvement and to prevent disease flares	GI intolerance; rash; blurry vision; retinopathy; vacuolar myopathy
Mycophenolate mofetil	Moderate to severe disease; as effective as cyclophosphamide for remission induction for nephritis	Bone marrow suppression; elevation of liver enzymes; infection
Azathioprine	Moderate to severe disease	Bone marrow suppression; elevation of liver enzymes; hematologic malignancy
Cyclophosphamide	Severe organ or life-threatening disease	Bone marrow suppression; hemorrhagic cystitis; infection; malignancy; infertility
Belimumab	Add-on therapy for moderate to severe disease	Infusion reactions; infections

AKI = acute kidney injury; GI = gastrointestinal; SLE = systemic lupus erythematosus.

disease, and myocardial infarction; improve lipid profiles; and improve outcomes in high-risk pregnancies.

H Glucocorticoids are a mainstay of SLE management, particularly in acute disease. The glucocorticoid dose should be determined by the level of disease activity and organ systems threatened. For severe disease activity (including profound cytopenias, class III/IV nephritis, and NPSLE), high-dose glucocorticoids are recommended. For life- or organ-threatening disease (such as rapidly progressive glomerulonephritis or seizures), high-dose intravenous glucocorticoids are given followed by high-dose daily prednisone. After disease stability is achieved, glucocorticoids are tapered to the lowest effective dose, ideally to eventual discontinuation.

Immunosuppressive therapy is usually initiated concurrently with glucocorticoids to achieve and maintain disease control and to allow tapering of glucocorticoids. Intravenous cyclophosphamide is used as induction therapy for severe or refractory disease (for example, severe active nephritis, acute central nervous system lupus, diffuse alveolar hemorrhage, or myocarditis) followed by maintenance therapy with mycophenolate mofetil or azathioprine. Mycophenolate mofetil is currently the preferred oral agent for lupus nephritis and is as effective as cyclophosphamide for induction therapy. The biologic agent belimumab is FDA approved for patients with incomplete response to conventional treatments and has been shown to be useful in skin/joint involvement and moderate/severe disease. H

NSAIDs can be used as adjunct therapy for arthritis and pleuropericarditis, but are not disease modifying and may adversely affect kidney function and blood pressure.

See Principles of Therapeutics for information on SLE medication toxicities, monitoring parameters, and more. See MKSAP 18 Nephrology for details on the treatment of lupus nephritis.

KEY POINTS

HVC
- Hydroxychloroquine should be initiated in every patient with systemic lupus erythematosus who can tolerate it, because it can reduce disease-associated damage, prevent disease flares, and improve kidney and overall survival.
- Glucocorticoids are a mainstay of systemic lupus erythematosus management, particularly in acute disease; after disease stability is achieved, glucocorticoids are tapered to the lowest effective dose, ideally to eventual discontinuation.
- In systemic lupus erythematosus, immunosuppressive therapy is usually initiated concurrently with glucocorticoids to achieve and maintain disease control and to allow tapering of glucocorticoids.

Pregnancy and Childbirth Issues

SLE is associated with a five- to eightfold increase in miscarriage, stillbirth, premature delivery, and intrauterine growth retardation. Outcomes are worse in patients with active disease, nephritis, or anti-Ro/SSA and/or APLA antibodies. The best time to consider pregnancy is when SLE is quiescent, and conception should be considered only after at least 6 months of adequate disease control.

Proteinuria may increase during pregnancy in patients with SLE, making distinction between SLE and preeclampsia/eclampsia a challenge. Increases in anti-double-stranded DNA antibody levels, decreasing complement levels, or the development of active urine sediment suggests SLE as the cause. In contrast, serum urate levels are increased in preeclampsia but not during SLE flares.

Fetuses of women who have anti-Ro/SSA or anti-La/SSB antibodies are at risk for neonatal lupus erythematosus, which is characterized by rash and congenital heart block (CHB). Although the risk of CHB in the offspring of an anti-Ro/SSA-positive woman is only 2%, it is associated with significant fetal and neonatal morbidity and mortality. After a woman bears a child with neonatal lupus erythematosus, the risk of CHB is substantially increased (20%) in subsequent pregnancies. Hydroxychloroquine may reduce the overall risk.

Management of medications during SLE pregnancy is complicated. Hydroxychloroquine and low-dose glucocorticoids can be started during or continued throughout the pregnancy. Higher-dose glucocorticoids can be used to treat flare-ups or end-organ involvement. The preferred immunosuppressive agent for SLE during pregnancy is azathioprine, which should be used only if absolutely necessary. Belimumab, methotrexate, mycophenolate mofetil, and cyclophosphamide should be avoided. Cyclophosphamide is associated with age- and dose-dependent infertility. See Principles of Therapeutics for information on medications and pregnancy.

KEY POINTS

- Systemic lupus erythematosus is associated with a five- to eightfold increase in miscarriage, stillbirth, premature delivery, and intrauterine growth retardation.
- The best time to consider pregnancy is when systemic lupus erythematosus is quiescent, and conception should be considered only after at least 6 months of adequate disease control.
- Fetuses of women who have anti-Ro/SSA or anti-La/SSB antibodies are at risk for neonatal lupus erythematosus (rash and congenital heart block).
- Hydroxychloroquine and low-dose glucocorticoids can be started during or continued throughout the pregnancy.

Prognosis

The prognosis in SLE has improved significantly, and there is now a 90% 5-year survival rate. Early mortality is usually related to SLE disease and infections, and late mortality related to cardiovascular disease. Factors adversely affecting survival include myocarditis, nephritis, low socioeconomic status, male gender, and age over 50 years at diagnosis. SLE tends to

be a chronic waxing and waning disease with only 2% of patients achieving remission at 5 years.

KEY POINT

- Factors adversely affecting survival in systemic lupus erythematosus include myocarditis, nephritis, low socioeconomic status, male gender, and age over 50 years at diagnosis.

Sjögren Syndrome

Epidemiology and Pathophysiology

Sjögren syndrome is an autoimmune exocrinopathy affecting salivary and lacrimal glands. It is more prevalent in women and white persons and commonly presents in the fourth and fifth decades. Primary Sjögren syndrome occurs in isolation; secondary Sjögren syndrome occurs in the setting of other rheumatologic diseases, most commonly rheumatoid arthritis and systemic lupus erythematosus. Whereas the prevalence of primary Sjögren syndrome ranges from 0.5 to 5 patients per thousand, secondary Sjögren syndrome is common (10%-30%) among populations with predisposing rheumatologic conditions. Sjögren syndrome etiology remains unclear, although genetic associations include several HLA subtypes.

Clinical Manifestations

The most common presentation of Sjögren syndrome is sicca, consisting of dryness of the eyes (keratoconjunctivitis sicca) and mouth (xerostomia). Patients report gritty eyes or a foreign body sensation. Oral dryness can cause caries and difficulty eating unmoistened food. Symmetric parotid and lacrimal swelling is common, as is skin and vaginal dryness.

Extraglandular manifestations may also occur (**Table 22**). Arthralgia and arthritis are common; the joint distribution and presentation resemble rheumatoid arthritis but without bone erosions (Jaccoud arthropathy). Patients with Sjögren syndrome are at increased risk for non-Hodgkin lymphoma, presumably related to chronic lymphocyte activation.

TABLE 22. Extraglandular Clinical Manifestations of Sjögren Syndrome

Site/Organ	Manifestation/Frequency
General	Fatigue (70%), fever (6%)
Skin	Dry skin (xerosis), cutaneous vasculitis: 10%-16%
Joint	Arthralgia/arthritis: 36%
Lung	Interstitial pneumonitis: 5%-9%
Kidney	Interstitial nephritis, distal (type 1) renal tubular acidosis, glomerulonephritis: 5%-6%
Neurologic	Central nervous system (CNS): demyelinating disease, myelopathy, cranial nerve neuropathy
	Peripheral nervous system: small-fiber neuropathy, mononeuritis multiplex, peripheral neuropathy
	8%-27% for CNS and peripheral
Gastrointestinal	Autoimmune hepatitis, primary biliary cirrhosis: 3%-20%
Hematologic	Lymphoma, cytopenia: 2%
Other	Systemic vasculitis (7%), cryoglobulinemia (4%-12%), Raynaud phenomenon (16%), thyroid disease (10%-15%)

TABLE 23. American College of Rheumatology/European League Against Rheumatism Classification Criteria for Primary Sjögren Syndrome[a]

The presence of a subjective finding of Sjögren syndrome (e.g., sicca complaint) plus any combination of the following resulting in a score of ≥4:

Item	Score
Salivary gland biopsy with ≥1 foci of lymphocytic infiltrate/4 mm^2	3
Anti-Ro/SSA autoantibodies	3
Ocular staining score ≥5 in at least one eye	1
Schirmer test ≤5 mm/5 min in at least one eye	1
Unstimulated whole saliva flow rate ≤0.1 mL/min	1

[a]Exclusion criteria include prior head/neck radiation and history of active hepatitis C virus infection, AIDS, sarcoidosis, amyloidosis, graft-versus-host disease, and IgG4-related disease.

From Shiboski CH, Shiboski SC, Seror R, Criswell LA, Labetoulle M, Lietman TM, et al; International Sjögren's Syndrome Criteria Working Group. 2016 American College of Rheumatology/European League Against Rheumatism Classification Criteria for Primary Sjögren's Syndrome: A Consensus and Data-Driven Methodology Involving Three International Patient Cohorts. Arthritis Rheumatol. 2017 Jan;69(1):35-45. doi: 10.1002/art.39859. [PMID: 27785888]. Copyright 2016, American College of Rheumatology. Adapted with permission from John Wiley & Sons, Inc.

Diagnosis

A diagnosis of Sjögren syndrome is typically triggered by a complaint of sicca and requires objective confirmation of exocrinopathy along with demonstration of autoimmunity (**Table 23**). Dry eyes can be assessed using the Schirmer test, in which a strip of filter paper is placed under the lower eyelid and wetting is measured; less than 5 mm in 5 minutes indicates dryness. More formally, dryness and corneal damage are ascertained by slit-lamp examination by an ophthalmologist using fluorescein and lissamine green dyes. Dry mouth is assessed by direct examination, with dental caries and a lack of saliva suggesting the diagnosis. Measurement of salivary flow (sialography) is easily done but is less commonly performed. Salivary gland imaging with MRI or ultrasonography may assist in identifying characteristic abnormalities and provide additional support for the diagnosis.

Multiple autoantibodies may be present. Antinuclear antibodies and/or rheumatoid factor are often present at high titers; their coexpression is more suggestive of Sjögren syndrome than if only one is positive. The presence of anti-Ro/SSA autoantibodies is specific in the setting of primary Sjögren syndrome; their presence is less specific for secondary Sjögren syndrome because these antibodies are also common in systemic lupus erythematosus. The presence of anti-La/SSB autoantibodies is also characteristic of Sjögren syndrome, although these are not currently included in formal disease classification criteria. When initial evaluation is uninformative, a lip (minor salivary gland) biopsy should be considered. Characteristic histologic features include aggregate foci (>50 cells/aggregate) of CD4 T cells, B cells, and plasma cells surrounding secretory ducts.

The differential diagnosis of Sjögren syndrome typically relates to the presence of sicca and/or parotid and lacrimal enlargement. Sarcoidosis, IgG4-related disease, granulomatosis with polyangiitis, lymphoma, and viruses such as mumps, hepatitis C, and HIV may be associated with similar findings. Ocular and oral dryness may also occur with aging or in response to drugs such as anticholinergics.

Management

Management of sicca is centered on preservation of moisture and relief of symptoms. Eyes are treated with artificial tears and/or topical cyclosporine. The use of glasses with side panels to prevent surface drying may be helpful, as may be plugging of the lacrimal ducts to promote tear retention. For oral dryness, meticulous dental care is essential. Sugar-free candies can stimulate saliva flow. Artificial saliva may be used, but its effects may be too transient to be useful. Vaginal symptoms may be treated with topical lubricants or estrogen. Pharmacologic therapies include the muscarinic agonists pilocarpine and cevimeline, although these may not be well tolerated and are contraindicated in narrow-angle glaucoma.

Patients with extraglandular involvement are treated with immunosuppression. Evidence-based guidelines are limited, and decisions are often empiric. Options include hydroxychloroquine and methotrexate for arthritis, and cyclophosphamide and rituximab for severe or systemic central nervous system disease. Some of these agents may have benefit for sicca as well.

Prognosis

The prognosis for primary Sjögren syndrome is favorable, with no overall increase in mortality. Management of sicca reduces the risk of corneal damage or loss of teeth. In rare instances, end-organ involvement can be life-threatening. Secondary Sjögren syndrome may be associated with significant morbidity from the primary condition. An increased risk of lymphoma is present in both forms of the syndrome.

KEY POINTS

- Sjögren syndrome is an autoimmune exocrinopathy affecting salivary and lacrimal glands, with the most common presentation being sicca (dryness of the eyes and/or mouth).
- Patients with Sjögren syndrome are at increased risk for non-Hodgkin lymphoma.
- A diagnosis of Sjögren syndrome is typically triggered by a complaint of sicca and requires objective confirmation of exocrinopathy along with demonstration of autoimmunity.
- In patients with Sjögren syndrome, management of sicca is centered on preservation of moisture and relief of symptoms; extraglandular involvement is treated with immunosuppression.

Inflammatory Myopathies

Overview

The inflammatory myopathies include polymyositis (PM), dermatomyositis (DM), immune-mediated necrotizing myopathy (IMNM), and inclusion body myositis (IBM). Although the pathogenesis of these disorders is disparate, they all include immune-mediated muscle inflammation and destruction.

Evaluation of the Patient with Muscle Pain or Weakness

The differential diagnosis of muscle disease is broad and includes hereditary, environmental, infectious, and acquired muscle disease (**Table 24**). The inflammatory myopathies commonly present with symmetric proximal muscle weakness without substantial muscle pain or tenderness. Serum creatine kinase is almost universally elevated in the inflammatory myopathies and is a marker of muscle damage. The presence of pain or tenderness, however, should prompt considerations of other causes of myopathy. Muscle pain is more common with overexertion, muscle cramps, and injury. Muscle tenderness should prompt consideration of infectious, thyroid, or drug-induced myopathies. Medications and drugs are common causes of myopathy and should be considered in the differential diagnosis of the inflammatory myopathies (**Table 25**).

Weakness is often caused by conditions other than myopathy. Cardiopulmonary disease, malignancy, depression, and deconditioning frequently lead to generalized weakness. Although uncommon, primary neurologic disorders such as spinal muscle atrophies, amyotrophic lateral sclerosis, and myasthenia gravis may cause weakness. These diseases are distinguished by involvement of muscle groups other than the proximal muscles, nerve involvement on electromyography (EMG), and a normal serum creatine kinase. Finally, the presence of exercise-induced weakness may point to a metabolic etiology rather than an inflammatory myopathy.

TABLE 24. Differential Diagnosis of Myopathy

Myopathy	Common Examples	Comments
Inflammatory myopathies	Dermatomyositis (DM); polymyositis (PM); immune-mediated necrotizing myopathy (IMNM); inclusion body myositis (IBM)	DM and PM: acute-subacute onset, symmetric, proximal; DM: pathognomonic rash; IMNM: acute onset, symmetric, proximal; IBM: insidious onset, proximal and distal
Systemic rheumatologic disease	Systemic lupus erythematosus; systemic sclerosis; mixed connective tissue disease	Prominent extramuscular features typical of underlying disorder
Muscular dystrophies	Duchenne muscular dystrophy; Becker muscular dystrophy	Childhood onset; cardiomyopathy possible
Metabolic myopathies	Glycogen storage diseases; carnitine palmitoyltransferase deficiency	Exercise intolerance
Mitochondrial myopathies	Kearns-Sayre syndrome; Leigh syndrome	Variable age of presentation and features; isolated myopathy or with neurologic, multisystem disease
Endocrine disorders	Hypothyroidism; hyperthyroidism; adrenal insufficiency	Prominent myalgia
Infection induced	Bacterial: pyomyositis; viral: influenza; parasitic: trichinosis	Prominent myalgia; sometimes accompanied by fever

TABLE 25. Drug-Induced Myopathies

Drug	Time Course	Clinical Presentation
Alcohol	Increased with long-term use	Asymptomatic elevations of serum creatine kinase; chronic muscle atrophy; acute, severe rhabdomyolysis with kidney failure
Antimalarials	Can occur after prolonged use	Infrequent elevation of serum creatine kinase (30%); muscle weakness (50%); myopathic electromyogram findings (100%); cardiomyopathy can occur
Cocaine	Can occur after single use	Asymptomatic elevations of serum creatine kinase; acute, severe rhabdomyolysis with kidney failure
Colchicine	Usually months to years; increased risk with coadministration of cytochrome P450 inhibitors	Proximal muscle weakness with elevations of serum creatine kinase; mild sensory symptoms; reduced reflexes
Glucocorticoids	Increased with long-term use	Proximal muscle weakness in the absence of elevations of serum creatine kinase
Statins	Usually weeks to months but can occur at any time; increased risk with preexisting neuromuscular disease, hypothyroidism, kidney failure, and/or coadministration of cytochrome P450 inhibitors; may also trigger immune-mediated necrotizing myopathy	Elevations of serum creatine kinase with myalgia and weakness
Zidovudine	Variable; may be more common after long-term use	Elevations of serum creatine kinase with myalgia and weakness

Epidemiology and Pathophysiology of Inflammatory Myopathies

The annual incidence of inflammatory myopathies is between 2 and 10 cases per million. Two peaks of onset occur, with the first in childhood and the second in middle age. A female adult predominance is approximately 2:1 with the exception of IBM, which preferentially affects men.

Genetic factors contribute to the risk of inflammatory myopathies. The clearest association is with HLA DRB1*0301, but alleles vary in populations throughout the world. Except for IMNM, environmental factors have not been clearly implicated. Immune mechanisms that contribute include the presence of T lymphocytic infiltrates in muscle tissue and the expression of autoantibodies in many patients. T- and B-cell proliferation and activation, as well as increased cytokine and chemokine levels in muscle, also occur.

KEY POINTS

- The inflammatory myopathies commonly present with symmetric proximal muscle weakness without substantial muscle pain or tenderness; serum creatine kinase is almost universally elevated and is a marker of muscle damage.
- Muscle tenderness should prompt consideration of infectious, thyroid, or drug-induced myopathies.

Polymyositis

Clinical Manifestations

Muscle Involvement

The symptoms of PM usually progress slowly over months, although a more rapid onset may occur. Progressive, symmetric, proximal muscle weakness is the classic and dominant feature. Activities such as arising from a chair, stair climbing, and lifting objects above shoulder height are typically affected. Neck flexors are also commonly involved. Muscle pain and tenderness, if present, are mild. Muscle atrophy is a late manifestation. Weakness of respiratory muscles may also occur.

Cardiopulmonary Involvement

Interstitial lung disease, most commonly nonspecific interstitial pneumonitis, occurs in about 10% of patients with PM. It is particularly prominent in the subset of patients with antisynthetase syndrome (also seen in association with dermatomyositis). In addition to interstitial lung disease and myositis, antisynthetase syndrome is characterized by the presence of Raynaud phenomenon, nonerosive arthritis, and mechanic's hands, a dermatologic manifestation characterized by rough, cracked, scaly skin along the lateral aspects of the digits and palms with horizontal lines resembling the weathered hands of a laborer (See MKSAP 18 Dermatology). It can occasionally present as rapidly progressive respiratory failure. Antisynthetase syndrome is associated with autoantibodies against anti-aminoacyl-tRNA synthetases, most commonly anti-Jo-1 antibodies.

Cardiac involvement includes conduction system abnormalities that can result in arrhythmias and sudden death. Pericarditis can occur, and pericardial tamponade has been reported. Patients are also at increased risk for myocardial infarction and heart failure, which represent an important cause of morbidity and mortality in PM.

Gastrointestinal Involvement

The striated muscle of the upper two thirds of the esophagus can be affected by PM, leading to dysphagia, dysmotility, and increased risk of aspiration pneumonia.

Dermatomyositis

Clinical Manifestations

In DM, muscle involvement is clinically similar to PM but is almost universally accompanied by a unique constellation of skin findings.

Cutaneous Involvement

Cutaneous involvement of DM can be virtually pathognomic and serve as an indicator of response to therapy (**Table 26**). Most typical is the Gottron rash (Gottron papules and Gottron sign), erythematous to violaceous areas over the metacarpophalangeal and proximal interphalangeal joints (**Figure 18**). See MKSAP 18 Dermatology for more information.

Muscle Involvement

Similar to PM, the insidious onset of symmetric proximal muscle weakness is most common in DM. Some patients present initially with rash and develop weakness later.

A small percentage of patients may present with skin rash only and never develop muscle involvement (amyopathic DM). At least 6 months without evidence of muscle involvement is necessary before the diagnosis of amyopathic DM can be established.

Cardiopulmonary Involvement

Cardiopulmonary involvement is similar to that seen in PM, but interstitial lung disease is more common in DM (20%-25%). Arrhythmias, complete atrioventricular block, heart failure, myocardial infarction, and pericarditis have been reported.

Gastrointestinal Involvement

Gastrointestinal involvement in DM resembles that in PM.

Immune-Mediated Necrotizing Myopathy

IMNM occurs in a small subset of patients with inflammatory myopathy who demonstrate prominent myonecrosis on biopsy

TABLE 26. Cutaneous Manifestations of Dermatomyositis

Cutaneous Sign	Location	Clinical Appearance
Gottron rash (Gottron papules and Gottron sign)	Metacarpophalangeal and proximal interphalangeal joints; occasionally on distal interphalangeal joints, elbows, knees	Erythematous to violaceous papules; occasional scale; can ulcerate; atrophic scars may occur
Heliotrope rash	Eyelids	Subtle pink to deep purple or brown discoloration; may be associated with edema of eyelids or periorbital edema
V sign	V of neck	Erythematous to violaceous papules to patches
Shawl sign	Base of posterior neck to upper back	Erythematous to violaceous papules to patches
Fixed erythema	Malar area (may cross nasolabial folds); flanks of trunk	Erythematous to violaceous papules to patches
Nail area changes	Periungual area; cuticles	Periungual erythema; capillary dilatation and dropout; cuticular hypertrophy; cuticular infarcts
Mechanic's hands	Lateral aspects of digits and palms	Hyperkeratotic fissuring of the palmar and lateral surfaces of the fingers resembling the hands of a laborer

FIGURE 18. Gottron rash. Erythema and mild scaling are seen most prominently over the second and third metacarpophalangeal joints, and more subtle erythema is present over the proximal interphalangeal joints of both hands. The cracked and thickened skin on the lateral surfaces of the second digit bilaterally is consistent with mechanic's hands.

H CONT.

without the inflammatory changes typical of the other inflammatory myopathies. An immune-mediated mechanism is suggested by the presence of antibodies to signal recognition particles (SRPs) or 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. Although statin exposure may result in antibodies to HMG-CoA reductase and IMNM, most patients with statin-induced myopathies have processes other than IMNM (see Table 25).

Clinical Manifestations

Patients with IMNM experience severe, rapidly progressive weakness, very high serum creatine kinase levels, and few (if any) extramuscular manifestations.

Muscle Involvement

The characteristic symptom of IMNM is severe proximal muscle weakness, making it difficult to distinguish from PM and DM. Rapidity of onset may provide a clue. In patients with statin-triggered IMNM, the weakness may persist or progress even after statins are discontinued.

Other Organ Involvement

Cardiopulmonary involvement in IMNM is rare. Gastrointestinal involvement has not been reported. H

Inclusion Body Myositis

IBM is a uniformly insidious condition and is usually easily distinguishable from PM, DM, and IMNM because of its very slow onset and pattern of muscle involvement.

Clinical Manifestations

Muscle Involvement

Patients typically report a history of preexisting weakness averaging 5 years. Although proximal muscle involvement is present, distal muscle involvement also occurs, distinguishing it from PM and DM. Muscle distribution is typically symmetric, but asymmetry may occur. On physical examination, muscle weakness and atrophy are often present in the hip flexors, quadriceps, finger flexors, and forearm flexors. Serum creatine kinase levels are elevated but are lower than levels seen in PM and DM.

Gastrointestinal Involvement

Up to half of patients with IBM have cricopharyngeal muscle involvement, leading to dysphagia and increased risk of aspiration.

KEY POINTS

- Polymyositis and dermatomyositis are characterized by progressive, symmetric, proximal muscle weakness, leading to decline in physical function; dermatomyositis is further defined by cutaneous involvement.
- Gottron rash (Gottron papules and Gottron sign) is the characteristic rash of dermatomyositis, and is defined as erythematous to violaceous areas over the metacarpophalangeal and proximal interphalangeal joints.
- Immune-mediated necrotizing myopathy is characterized by severe, rapidly progressive proximal muscle weakness, very high serum creatine kinase levels, and few extramuscular manifestations.
- Inclusion body myositis is a uniformly insidious condition that involves both the proximal and distal muscles; although typically symmetric, muscle distribution may be asymmetric.

Inflammatory Myopathies and Malignancy

There is an association between risk of malignancy and DM (3- to 12-fold that of age-matched populations) as well as, to a lesser extent, PM. IMNM may occasionally be a paraneoplastic syndrome, but IBM is not strongly associated with malignancy. The risk of malignancy is greatest in the 3 years following the diagnosis of DM or PM. Common associated cancers are ovarian, lung, pancreas, stomach, colon, and lymphoma. Age- and sex-appropriate cancer screening is indicated at the time of diagnosis of DM or PM. Many experts advocate CT of the chest, abdomen, and pelvis, particularly in patients with DM.

KEY POINT

- Because of the malignancy risk associated with polymyositis and dermatomyositis, age- and sex-appropriate cancer screening is indicated at the time of diagnosis. HVC

Diagnosis

Muscle-Related Enzymes

H

Elevations of serum muscle enzymes are particularly useful in differentiating intrinsic muscle disease from neurologic causes

H CONT.

of weakness. Elevated serum creatine kinase levels are the most sensitive serum indicator of muscle pathology, and levels parallel the severity of involvement. Aldolase can occasionally be elevated when serum creatine kinase levels are normal. Serum aminotransferases and serum lactate dehydrogenase may also be elevated but are nonspecific. H

Autoantibodies

Various autoantibodies are used to help diagnose inflammatory myopathies. Some, such as antinuclear antibodies, lack specificity. Others, often termed *myositis-specific antibodies*, have more diagnostic and prognostic value (**Table 27**).

Imaging Studies

Although not required to diagnose inflammatory myopathies, MRI is potentially useful in identifying areas of muscle inflammation as an appropriate site for muscle biopsy. MRI is also helpful at identifying muscle atrophy; follow-up with MRI may provide a noninvasive technique to assess therapeutic efficacy.

Electromyography

EMG may show findings highly characteristic of active myositis, although no single finding is pathognomonic. The procedure, however, is invasive and uncomfortable. It may also be normal in the presence of active disease due to the patchy distribution of muscle inflammation (that is, sampling error).

Muscle Biopsy

Muscle biopsy is valuable in diagnosing inflammatory myopathies and for excluding metabolic myopathies, mitochondrial disease, and infection. In PM and DM, features include inflammatory cell infiltrates, muscle fiber necrosis, degeneration, and regeneration.

Muscle biopsy findings in IBM include mononuclear cell infiltrates with unique "rimmed" vacuoles without muscle cell necrosis; electron microscopy may show inclusion bodies.

Skin Biopsy

Skin biopsy is useful in diagnosing DM. Light microscopy findings include mild epidermal atrophy, vacuolar changes at the dermal-epidermal junction, perivascular lymphocytic infiltrates, and increased dermal mucin. However, these findings may be similar to those of systemic lupus erythematosus.

Diagnosis of amyopathic DM is made with skin biopsy confirmation of DM in the setting of at least 6 months of normal muscle strength, muscle enzymes, normal EMG, and, if performed, normal muscle biopsy.

KEY POINTS

- Elevated serum creatine kinase levels are the most sensitive serum indicator of muscle pathology, and levels parallel the severity of involvement.
- Antibodies against aminoacyl-tRNA synthetases, particularly anti-Jo-1 (anti-histidyl-tRNA synthetase antibodies), have been associated with antisynthetase syndrome (interstitial lung disease, Raynaud phenomenon, arthritis, and mechanic's hands).
- In patients with inflammatory myopathies, MRI can be helpful to locate a site for muscle biopsy, identify muscle atrophy, and assess therapeutic efficacy.
- Muscle biopsy is valuable in diagnosing inflammatory myopathies and for excluding metabolic myopathies, mitochondrial disease, and infection.

Management

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Glucocorticoids are the cornerstone of therapy for the inflammatory myopathies except for IBM. Prolonged exposure to high-dose glucocorticoids, particularly in the elderly, can be associated with the appearance of steroid-induced myopathy that may cause new proximal muscle weakness in a patient who had previously been improving; reduction in dose is appropriate management.

Additional immunosuppressives are often required to control inflammation or to serve as glucocorticoid-sparing agents; methotrexate and azathioprine are most frequently used. DM and PM are most responsive to immunosuppression, although DM is more responsive than PM. For patients with statin-induced IMNM, statin discontinuation is mandatory but not sufficient, and immunosuppressive treatment is required. IBM

TABLE 27. Autoantibodies in Inflammatory Myopathies

Autoantibody	Disease Association	Clinical Association
Antinuclear	DM; PM	Seen in up to 80%; nonspecific
Anti-aminoacyl-tRNA synthetase; most commonly anti-Jo-1 (anti-histidyl tRNA synthetase)	DM	Antisynthetase syndrome (ILD, Raynaud phenomenon, nonerosive arthritis, mechanic's hands)
Anti-cytoplasmic 5′-nucleotidase 1A	IBM	Insidious onset
Anti-HMG Co-A reductase	IMNM	Typically but not always in the setting of statin exposure; may also be seen in patients with statin exposure without IMNM
Anti-Mi 2	DM	Seen in up to 30%; associated with acute onset, typical rash
Anti-signal recognition protein	IMNM	Severe, treatment-resistant disease and myofiber necrosis but little to no inflammation on muscle biopsy

DM = dermatomyositis; IBM = inclusion body myositis; ILD = interstitial lung disease; IMNM = immune-mediated necrotizing myopathy; PM = polymyositis.

H CONT. usually does not respond to immunosuppression, and therapeutic trials should be undertaken only in selected patients and discontinued if benefit is not appreciated. Other immunosuppressives, including mycophenolate mofetil and rituximab, have been used in refractory DM, PM, and IMNM. Intravenous immunoglobulin may be a reasonable alternative in DM. H

Physical therapy may help maintain muscle function and should be used in all patients.

Prognosis

The prognosis in DM/PM varies from near-complete resolution to severe, treatment-resistant disease with marked functional impairment and early mortality. Prolonged symptoms prior to treatment, greater weakness at presentation, extensive multisystem disease, and the co-occurrence of malignancy confer a poorer prognosis. The degree of serum creatine kinase elevation is not predictive of outcome. Myositis-specific antibodies may have prognostic value. Patients with anti-Jo-1 antibodies have worse outcomes (due to interstitial lung disease), whereas those with anti-Mi-2 antibodies often respond completely, despite a rapidly progressive course of DM.

Patients with IMNM frequently respond well to statin discontinuation (if appropriate) and immunosuppression.

Given the lack of effective treatment, patients with IBM typically demonstrate a slow and gradual loss of function, with progression to wheelchair dependence within 10 to 15 years.

KEY POINTS

- Initial treatment for most inflammatory myopathies consists of glucocorticoids, with additional immunosuppressives (most commonly methotrexate and azathioprine) often required to control inflammation or serve as glucocorticoid-sparing agents.
- Inclusion body myositis often does not respond to immunosuppression, and therapeutic trials should be discontinued if benefit is not appreciated.
- In patients with dermatomyositis or polymyositis, prolonged symptoms prior to treatment, greater weakness at presentation, extensive multisystem disease, and the co-occurrence of malignancy confer a poorer prognosis.
- Patients with inclusion body myositis typically demonstrate a slow and gradual loss of function, with progression to wheelchair dependence within 10 to 15 years.

Systemic Sclerosis

Epidemiology and Pathophysiology

Systemic sclerosis (SSc) is a multiorgan disease characterized by fibrosis and vasculopathy. The skin is the principal target, but internal organs are also affected. SSc is relatively rare, with a prevalence of 275 cases per million, and an annual incidence of 19 cases per million. It is more common among women and black persons.

Vascular injury, vascular and visceral fibrosis, and innate and adaptive immune activation with autoantibody production play an interactive role in SSc. One of the earliest SSc manifestations is Raynaud phenomenon, suggesting that vascular injury precedes the fibrotic reaction. With vascular damage, the endothelial cells release endothelin-1, a potent vasoconstrictor that also induces vascular smooth muscle proliferation and fibroblast activation. Platelet activation occurs concurrently with subsequent release of growth factors that promote further vasoconstriction, fibroblast activation, and collagen production.

B-cell activation results in production of interleukin (IL)-6, which directly stimulates fibroblasts as well as various autoantibodies. The end result is increased collagen production and deposition by activated scleroderma fibroblasts, along with a progressive obliterative vasculopathy.

Classification

Although intended for research studies, the 2013 American College of Rheumatology/European League Against Rheumatism SSc classification criteria can be useful when a patient presents with features suggesting SSc (**Table 28**).

Classically, SSc is divided into three subtypes based on the extent of skin involvement: limited cutaneous systemic sclerosis (LcSSc), diffuse cutaneous systemic sclerosis (DcSSc), and systemic sclerosis sine scleroderma (internal organ involvement only). These subtypes have clinical and prognostic utility because specific long-term complications may be more likely in one subtype than another; however, overlap is common. Importantly, LcSSc is less commonly accompanied by fibrosis of internal organs, but is most commonly associated with pulmonary arterial hypertension and CREST (calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia) syndrome.

Various disorders may present with skin thickening and other manifestations that overlap with the findings of SSc; these conditions should be considered in the differential diagnosis of SSc (**Table 29**). Importantly, these conditions are not typically associated with Raynaud phenomenon, and the absence of Raynaud phenomenon in a patient with skin thickening makes SSc unlikely.

KEY POINTS

- Systemic sclerosis is a multiorgan disease characterized by fibrosis and vasculopathy; the skin is the principle target, with Raynaud phenomenon being one of the earliest manifestations.
- Systemic sclerosis is divided into three subtypes based on the extent of skin involvement: limited cutaneous systemic sclerosis, diffuse cutaneous systemic sclerosis, and systemic sclerosis sine scleroderma.

(Continued)

TABLE 28. American College of Rheumatology/European League Against Rheumatism Classification Criteria for Systemic Sclerosis

Manifestation	Additional Manifestations	Weight/Score[a]
Skin thickening of fingers of both hands extending proximal to the MCPs	—	9
Skin thickening of the fingers (count higher score only)	Puffy fingers	2
	Sclerodactyly of fingers distal to the MCPs but proximal to PIPs	4
Fingertip lesions	Digital tip ulcers	2
	Fingertip pitting scars	3
Telangiectasia	—	2
Abnormal nailfold capillaries	—	2
Pulmonary hypertension and/or interstitial lung disease (maximum score is 2)	Pulmonary hypertension	2
	Interstitial lung disease	2
Raynaud phenomenon	—	3
SSc-related autoantibodies (maximum score is 3)	Anticentromere	3
	Anti-Scl-70 (antitopoisomerase-1)	3
	Anti-RNA polymerase III	3

MCP = metacarpophalangeal; PIP = proximal interphalangeal; SSc = systemic sclerosis.

[a]A score of 9 or more equates to definite systemic sclerosis.

From van den Hoogen F, Khanna D, Fransen J, Johnson SR, Baron M, Tyndall A, et al. 2013 classification criteria for systemic sclerosis: an American College of Rheumatology/European League Against Rheumatism Collaborative Initiative. Ann Rheum Dis 2013;72:1747-55. doi: 10.1136/annrheumdis-2013-204424. [PMID: 24092682] Copyright 2013, American College of Rheumatology. Adapted with permission from BMJ Publishing Group Ltd.

KEY POINTS *(continued)*

- The absence of Raynaud phenomenon in a patient with skin thickening makes systemic sclerosis unlikely.

Clinical Manifestations and Diagnosis

The diagnosis of SSc is dependent on the presence of specific clinical findings and autoantibodies (present in 90%-95% of patients). In patients with clinical features suggestive of SSc, autoantibody testing should be done (**Table 30**).

Cutaneous Involvement

The skin is the most common organ involved in SSc, with the hands being universally affected. In LcSSc, the skin over the fingers/hands, face, and neck is typically affected. In DcSSc, skin involvement is more extensive and additionally includes the arms, trunk, and lower extremities.

The earliest skin manifestations are often diffusely swollen fingers/hands (sclerodactyly). Skin thickening, especially in LcSSc, may be subtle, and the inability to tent the skin over the fingers may be an important clue. With time, the skin becomes thickened, atrophic, and immobile; skin thickening around the joints can lead to contractures (**Figure 19**).

Vascular complications of the skin include digital infarcts, subungual infections, and ischemic skin ulceration. Another feature is poikiloderma, in which areas of hyperpigmentation mixed with hypopigmentation give the skin a salt-and-pepper appearance.

Facial involvement can lead to limitation of the oral aperture and difficulty eating. The face is also typically devoid of wrinkles, causing patients to sometimes look younger than their age.

Calcinosis occurs in approximately 25% of patients with SSc (**Figure 20**). Present in the hands, forearms, elbows, gluteal region, and iliac crest, these deposits can be seen/felt and are easily detected on radiograph.

Musculoskeletal Involvement

Joint involvement occurs in 12% to 65% of patients with SSc; it has a hand/wrist predominance and is one of the few forms of inflammatory arthritis that affects the distal interphalangeal joints. Between 1% and 5% of patients have a rheumatoid arthritis-SSc overlap, with positive anti-cyclic citrullinated antibodies and classic rheumatoid arthritis manifestations along with those of SSc.

Patients with SSc may develop acro-osteolysis, or resorption of the terminal bony tuft of fingers and less commonly the toes, with prevalence as high as 20% to 25% in more severe disease (**Figure 21**).

SSc-associated myositis occurs in 10% to 15% of patients. Myalgia and proximal muscle weakness are common symptoms. Serum creatine kinase and/or serum aldolase levels are

TABLE 29. Common Manifestations/Features of the Scleroderma Spectrum Disorders		
Disorder	**Manifestation/Feature**	**Comments**
Systemic Sclerosis		
Diffuse cutaneous systemic sclerosis (DcSSc)	Distal and proximal skin thickening (chest, abdomen, arms proximal to wrists); commonly has visceral organ involvement	Skin involvement is extensive and is commonly accompanied by internal organ fibrosis and ILD
Limited cutaneous systemic sclerosis (LcSSc)	Distal (face, neck, hands), but not proximal, skin thickening; typically not accompanied by internal organ fibrosis	More likely to develop PAH and Raynaud phenomenon early in the disease and more likely to display features of the CREST syndrome
Systemic sclerosis sine scleroderma	Fibrosing organ involvement without skin thickening	Difficult to diagnose; prognosis may be similar to LcSSc
Localized Scleroderma		
Morphea	Focal plaques of skin thickening, generally on the trunk	Systemic manifestations or Raynaud phenomenon is extremely rare
Linear scleroderma	Streaks/lines of thickened skin	Same as morphea
Scleroderma-like Conditions[a]		
Eosinophilic fasciitis	Orange peel induration (peau d'orange) of proximal extremities with sparing of hands and face; peripheral eosinophilia; skin retraction over the superficial veins may be more apparent with elevation of an affected limb	Full-thickness skin biopsy demonstrates lymphocytes, plasma cells, and eosinophils infiltrating the deep fascia; glucocorticoids are the mainstay of treatment
Nephrogenic systemic fibrosis	Secondary to gadolinium in patients with kidney disease; brawny, wood-like induration of extremities, sparing the digits	Skeletal muscle fibrosis with contractures and/or cardiac muscle involvement can occur, with cardiomyopathy and increased mortality; changes in use and formulation of gadolinium have reduced incidence
Scleredema	Indurated plaques/patches on back, shoulder girdle, and neck	Typically seen in long-standing diabetes mellitus
Scleromyxedema	Waxy, yellow-red papules over thickened skin of face, upper trunk, neck, and arms; deposition of mucin with large numbers of stellate fibroblasts in the dermis	Associated with paraproteinemia (IgGλ) and may therefore occur in the setting of multiple myeloma or AL amyloidosis; more frequent in men
Chronic graft-versus-host disease	Lichen planus-like skin lesions, or localized or generalized skin thickening	Occurs most commonly after hematopoietic stem cell transplantation; may occasionally be seen after blood transfusion in an immunocompromised host
Drug and toxin exposure	Can produce scleroderma-like tissue changes	Examples: bleomycin, docetaxel, pentazocine, L-tryptophan, organic solvents

CREST = calcinosis cutis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia; ILD = interstitial lung disease; PAH = pulmonary arterial hypertension.

[a]Scleroderma-like skin changes may also occur as a manifestation of systemic endocrine, kidney, or infiltrative disorders.

TABLE 30. Autoantibodies and Their Associations in Systemic Sclerosis		
Autoantibody	**Clinical Associations**	**Comments**
Antinuclear antibodies	DcSSc; LcSSc	Overall prevalence in SSc: 70%; not associated with specific manifestations
Anticentromere (kinetochore proteins)	LcSSc ± PAH	Overall prevalence in SSc up to 30%; highly associated (>90%) with CREST variant of LcSSc
Anti-Scl-70 (DNA topoisomerase-1)	DcSSc; ILD	Overall prevalence in SSc: up to 30%; highly associated with DcSSc
Anti-RNA polymerase III	DcSSc; scleroderma renal crisis	Useful in DcSSc with negative anti-Scl-70
Anti-U3-RNP (fibrillarin)	DcSSc; PAH; myositis	Associated with poor outcome; more common in black men
Anti-PM-Scl	Myositis	Associated with overlap syndrome and polymyositis
Anti-Ku	Myositis	Rare occurrence
Anti-Th/To	LcSSc; PAH	Rare occurrence

CREST= calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia; DcSSc = diffuse cutaneous systemic sclerosis; ILD = interstitial lung disease; LcSSc = limited cutaneous systemic sclerosis; PAH = pulmonary arterial hypertension; RNP = ribonucleoprotein; SSc= systemic sclerosis.

FIGURE 19. A 35-year-old woman with diffuse cutaneous systemic sclerosis. Note shortening of fingers and tight atrophic appearance of the skin. This patient is unable to make a full fist.

FIGURE 21. A posteroanterior radiograph of the hands in a patient with systemic sclerosis and acro-osteolysis. Note the destruction of the distal phalanges, particularly of the first and second digits, which will eventually result in clinical shortening of the affected digits.

FIGURE 20. Calcinosis seen in CREST (calcinosis cutis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia) syndrome in limited cutaneous systemic sclerosis. This patient has deposits of calcium in the subcutaneous tissues around the elbow. Calcinosis often occurs in the hands and forearms but can also affect other locations such as the trunk or lower extremities.

elevated, and electromyogram demonstrates myopathic changes. There is a strong association between SSc-associated myositis and myocardial involvement. The presence of anti-PM-Scl antibodies identifies a group of patients with an overlap between polymyositis and SSc. These patients usually have less skin and gastrointestinal involvement, but have more calcinosis and lung disease.

Tendon rubs can be felt or heard with a stethoscope because fibrosis affects tendons/tendons sheaths, leading to palpable and audible friction.

Vascular Involvement

Raynaud phenomenon occurs in approximately 95% of patients with SSc; it is the most common early manifestation of SSc, typically occurring years before other changes. Initially, Raynaud phenomenon is episodic, but with vascular fibrosis, the blood supply becomes permanently restricted. Approximately 80% of patients with the combination of Raynaud phenomenon, an SSc-associated autoantibody, and nailfold capillary changes in an SSc pattern (**Figure 22**), will develop SSc.

Digital ulcers occur in about 15% of patients with SSc, typically on the extensor surfaces and tips of the fingers and toes but also on the dorsum of hands and feet and even on the lower extremities. Vascular changes in the extremities may be indicative of involvement of the microcirculation of internal organs.

Gastrointestinal Involvement

Symptoms of esophageal dysmotility and reflux are common in all forms of SSc and may offer an early clue to the diagnosis when associated with other symptoms.

Approximately 80% of patients with SSc have involvement of the lower two thirds (smooth muscle portion) of the esophagus. Manifesting primarily as symptoms of dysmotility and/or gastroesophageal reflux disease, esophageal involvement is also associated with an increased risk of Barrett esophagus and adenocarcinoma.

Gastric symptoms also result mainly from dysmotility. Patients describe early satiety and may report nausea and

FIGURE 22. Capillary loops in systemic sclerosis. *Top*, Early changes with loss of capillary loop density (or drop out) with marked dilatation of the remaining capillary loops. *Bottom*, Late changes with extensive loss of capillary loops.

Courtesy of Mario Cutolo, MD.

vomiting as a result of delayed gastric emptying. Gastric antral vascular ectasia (GAVE), also known as watermelon stomach, is most common in patients with DcSSc and those with anti-RNA polymerase III antibodies. Bleeding ectasias can occasionally cause significant blood loss.

Small intestine bacterial overgrowth is common and can cause malabsorption and diarrhea. Diagnosis is established by hydrogen breath test, although an empiric trial of antibiotics is often utilized. Small intestine dysmotility can result in pseudo-obstruction. Large intestine dysmotility may lead to constipation, and vascular ectasia can occur in the large intestine (watermelon colon). Some patients may develop fecal incontinence.

Kidney Involvement

One of the most concerning manifestations of SSc is scleroderma renal crisis, which affects 5% of patients and was previously the chief cause of mortality. Risk factors include DcSSc, use of moderate- to high-dose glucocorticoids, and the presence of anti-RNA polymerase III antibodies. Patients characteristically present with manifestations of hypertensive emergency, including headache, encephalopathy, seizures, and hypertensive retinopathy. Rarely, a normotensive form of scleroderma renal crisis can occur.

Laboratory tests demonstrate microangiopathic hemolytic anemia with schistocytes on peripheral smear, thrombocytopenia, and proteinuria. Serum creatinine is typically elevated and may remain so for some time after controlling blood pressure. Abnormalities in the renin-angiotensin-aldosterone system and endothelin-1 contribute to the pathophysiology.

Lung Involvement

Lung involvement in SSc includes pleuritis and pleural effusions, interstitial lung disease (ILD), pulmonary arterial hypertension (PAH), bronchiolitis, pulmonary veno-occlusive disease, respiratory muscle weakness, and skin involvement of the trunk restricting chest wall movement. Patients are also at increased risk of lung cancer.

Significant ILD occurs in 50% of patients with DcSSc (85% of patients with anti-Scl-70 antibodies) and 35% of patients with LcSSc, and is the main cause of disease-associated mortality. The most common pathology pattern is nonspecific interstitial pneumonitis followed by usual interstitial pneumonitis. In patients with SSc, men are more likely than women to develop ILD, and black persons tend to have more severe disease. An abnormal FVC early in the disease course (first 5 years) is highly predictive of developing more severe disease, as is fibrosis of more than 20% of lung volume on baseline high-resolution CT scan. There is a strong association between ILD and GERD, but whether GERD contributes to ILD (through aspiration) is uncertain. ILD is common enough that all patients should undergo pulmonary function tests (PFTs) and high-resolution CT at the time of initial SSc diagnosis, and PFTs with DLCO should be repeated every 6 to 12 months for 5 years. A decline in the FVC of 10% or the DLCO of 15% within 12 months should raise concern for progression.

PAH has a prevalence of 10% in SSc. Patients present with exertional dyspnea, and with more advanced disease may have chest pain and edema as the right ventricle begins to fail. Patients with SSc should undergo echocardiography annually and more frequently for new or concerning symptoms. PFTs can provide a clue to underlying PAH; an FVC/DLCO ratio of ≥1.6 suggests the diagnosis. Right heart catheterization is required for accurate diagnosis.

Cardiac Involvement

Cardiac involvement with SSc is more common in men. Clinically significant pericarditis occurs in 10% of patients. Myocardial fibrosis is a more significant process caused by vascular vasospasm leading to myocardial ischemia and fibrosis. The result may be heart failure and arrhythmias. Mortality in those with myocardial fibrosis is quite high.

KEY POINTS

- The earliest skin manifestations of systemic sclerosis are often diffusely swollen fingers/hands (sclerodactyly); with time, the skin becomes thickened, atrophic, and immobile.
- Raynaud phenomenon is the most common early manifestation of systemic sclerosis.
- Symptoms of esophageal dysmotility and reflux are common in all forms of systemic sclerosis and may offer an early clue to the diagnosis when associated with other symptoms.

(Continued)

KEY POINTS *(continued)*

- Patients with scleroderma renal crisis characteristically present with manifestations of hypertensive emergency; risk factors include diffuse cutaneous systemic sclerosis, use of moderate- to high-dose glucocorticoids, and the presence of anti-RNA polymerase III antibodies.
- Lung involvement in systemic sclerosis includes pulmonary arterial hypertension and interstitial lung disease (ILD); ILD is currently the main cause of disease-associated mortality.

Management

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Table 31 outlines treatment options for manifestations of SSc.

TABLE 31. Treatment Options for Common Manifestations of Systemic Sclerosis

Manifestations	Treatment
Cutaneous manifestations	Methotrexate, mycophenolate, cyclophosphamide, and rituximab have been shown to improve skin scores; for pruritus, antihistamines can be tried; low-dose prednisone can also help; laser therapy can used for telangiectasias.
Musculoskeletal manifestations	NSAIDs, intra-articular or low-dose prednisone, hydroxychloroquine, or methotrexate can be used for arthralgia/arthritis; methotrexate, azathioprine, or mycophenolate can be used for significant myositis.
Raynaud phenomenon	Cold avoidance; gloves; central warmth
	Calcium channel blockers
	Sildenafil; losartan; prazosin
	Topical nitrates; low-dose aspirin
	Digital sympathectomy
Gastroesophageal reflux disease	Avoid eating close to bed time; head of bed elevation
	H_2 blockers; proton pump inhibitors
	Surgical fundoplication
Gastrointestinal dysmotility	Metoclopramide (avoid long-term use); domperidone (limited access program)
	Erythromycin; cisapride (limited access program)
Gastric antral vascular ectasia	Ablation laser therapy
Small intestine bacterial overgrowth	Rotating antibiotics
	If fat malabsorption, cholestyramine
Pseudo-obstruction	A promotility agent such as domperidone can be tried
	If resistant, octreotide may be useful
Constipation	Fiber; stool softeners
	Polyethylene glycol
Scleroderma renal crisis	ACE inhibitors (typically captopril)
	Dialysis
Interstitial lung disease	Mycophenolate mofetil
	Cyclophosphamide
	Lung transplantation
Pulmonary arterial hypertension	Supplemental oxygen; treat right-sided heart failure
	Prostanoids; endothelin receptor antagonists; phosphodiesterase-5 inhibitors; soluble guanylate cyclase inhibitors
	Combination therapy
	Lung transplantation

H CONT.

ACE inhibitors (typically captopril) can be lifesaving in patients with scleroderma renal crisis and should be titrated to control blood pressure. Dialysis may be needed temporarily. ACE inhibitor therapy should be continued in scleroderma renal crisis even in the presence of a rising serum creatinine and the need for dialysis, as late improvement may occur. In patients at high risk for developing scleroderma renal crisis, the prophylactic use of calcium channel blockers seems to offer some protection. However, prophylactic use of an ACE inhibitor has not been shown to offer protection and may increase mortality.

Cyclophosphamide can be used for stabilizing ILD, but the impact is modest and may not persist beyond 1 year. Recent evidence suggests that mycophenolate mofetil is as useful for stabilizing ILD as cyclophosphamide in SSc but with less toxicity. Mycophenolate mofetil can also be used for long-term therapy, making it the preferred agent for most patients with SSc-associated ILD.

Rituximab is a promising agent in SSc; in case series and one controlled trial, it has stabilized or slightly improved lung function and skin ulcers. Nintedanib (a tyrosine kinase inhibitor) and pirfenidone (a synthetic molecule) were recently approved by the FDA for treatment of idiopathic pulmonary fibrosis; results from clinical trials in SSc are pending. Autologous hematopoietic stem cell transplantation has been studied for several years in patients with severe SSc; one third to one half of patients had significant improvement in skin thickening and antibody status. However, cost and potential toxicity limit the utility of stem cell transplantation at present. H

KEY POINTS

- Treatment options for systemic sclerosis are mainly symptomatic and organ system specific.
- ACE inhibitors can be lifesaving in patients with scleroderma renal crisis and should be titrated to control blood pressure even in the presence of rising serum creatinine.

Pregnancy

Pregnant patients with SSc may experience hypertensive disease, preeclampsia, preterm delivery, and low birth weights. In general, pregnancy does not make SSc worse, and some features (for example, digital ulcers) may actually improve. Contraindications to pregnancy in patients with SSc include PAH and severe restrictive lung disease (FVC of <1 L); in the setting of PAH, the hemodynamic changes of pregnancy can put the mother at considerable risk. See Principles of Therapeutics for details on medications and pregnancy.

KEY POINT

- Pregnant patients with systemic sclerosis (SSc) may experience hypertensive disease, preeclampsia, preterm delivery, and low birth weights; contraindications to pregnancy in patients with SSc include pulmonary arterial hypertension and severe restrictive lung disease.

Mixed Connective Tissue Disease

Overview

Despite long-standing attempts to define rheumatologic diseases according to precise classification, some patients express only nonspecific, nondiagnostic signs and symptoms (undifferentiated connective tissue disease [UCTD]), whereas others experience features of more than one disease simultaneously (overlap syndromes). Mixed connective tissue disease (MCTD) is a specific overlap syndrome that includes clinical manifestations of at least two of the following: systemic lupus erythematosus (SLE), polymyositis, and systemic sclerosis. Positive anti-U1-ribonucleoprotein (RNP) antibodies are the primary laboratory feature.

See **Table 32** for a comparison of MCTD, UCTD, and overlap syndromes.

TABLE 32. Comparison of Mixed Connective Tissue Disease, Undifferentiated Connective Tissue Disease, and Overlap Syndrome

Condition	Typical Clinical Features	Diagnosis	Treatment
Mixed connective tissue disease	Raynaud phenomenon; arthritis; puffy fingers; sclerodactyly; serositis; esophageal dysmotility; myositis; interstitial lung disease; PAH	Positive anti-U1-RNP antibodies Fulfills criteria for at least two of the following: SSc, PM, and SLE	Disease/organ involvement specific Anti-inflammatories for symptoms; DMARDs and/or immunosuppressives for arthritis or other major organ disease Vasodilators for PAH and Raynaud phenomenon PPI for esophageal disease
Undifferentiated connective tissue disease	Variable; most common include Raynaud phenomenon, arthralgia, skin rash, cytopenia, and serositis	Insufficient criteria for any specific connective tissue disease	Same as mixed connective tissue disease
Overlap syndrome	Variable; will have features satisfying two distinct autoimmune diseases (such as SLE, RA, PM, and SSc)	Fulfills criteria for two distinct autoimmune diseases	Same as mixed connective tissue disease

DMARD = disease-modifying antirheumatic drug; PAH = pulmonary arterial hypertension; PM = polymyositis; PPI = proton pump inhibitor; RA = rheumatoid arthritis; RNP = ribonucleoprotein; SLE = systemic lupus erythematosus; SSc = systemic sclerosis.

Epidemiology and Pathophysiology

MCTD is rare, and 80% of patients are women. B-cell abnormalities and an association between anti-U1-RNP antibody titer and disease activity have been described.

Clinical Manifestations and Diagnosis

See Table 32 for details on the clinical manifestations and diagnosis of MCTD. Raynaud phenomenon is a particularly common feature. Pulmonary arterial hypertension is the major cause of death, but severe kidney disease is uncommon. Although antinuclear antibodies, rheumatoid factor, and anti-cyclic citrullinated peptide antibodies are often present, the presence of anti-double-stranded DNA or anti-Smith antibodies make SLE a more likely diagnosis.

Management

Treatment for MCTD is directed at the specific diseases and organ system involvement manifesting in the individual patient (see Table 32).

Prognosis

Prognosis of MCTD varies depending on the spectrum and severity of organ involvement. Patients with initially mild disease may develop new and more severe manifestations over decades, importantly including interstitial lung disease and pulmonary arterial hypertension. As with many other systemic inflammatory disorders, patients are at increased risk of atherosclerotic cardiovascular disease.

UCTD usually remains mild and stable but over time may evolve into a more specific autoimmune disorder, most commonly SLE.

KEY POINTS

- Mixed connective tissue disease includes clinical manifestations of at least two of the following diseases: systemic lupus erythematosus, polymyositis, and systemic sclerosis; anti-U1-ribonucleoprotein antibodies are typically present.
- Treatment for mixed connective tissue disease is directed at the specific diseases and organ systems involved.

Crystal Arthropathies

Gout

Epidemiology

Gout is characterized by intermittent painful inflammatory joint attacks, in response to crystals formed as a consequence of excessive levels of uric acid (hyperuricemia). Gout is increasingly common, with a U.S. prevalence of approximately 4%. Factors contributing to this increase include dietary changes, increasing obesity, and an aging population (the elderly account for the sharpest rise in gout over the past few decades). Nearly all patients with gout have comorbidities, including hypertension, coronary artery disease, hyperlipidemia, diabetes mellitus, and chronic kidney disease (CKD). Comorbidities frequently complicate treatment by posing relative contraindications for appropriate therapeutics (for example, CKD for NSAIDs or colchicine).

Men reach a steady-state serum urate level after puberty, whereas premenopausal women are generally protected from hyperuricemia by estrogenic effects. It is rare for premenopausal women to develop gout, whereas men usually have their first gout attack in the third to fifth decade.

Pathophysiology

Uric acid is the end product of purine metabolism, and about two thirds of urate production derives from cellular turnover of nucleic acids (purine bases); the remainder is derived from dietary purine intake. A small proportion of patients overproduce urate on an inherited metabolic basis. Unlike most mammals, humans do not express uricase, an enzyme that converts urate into highly soluble allantoin. Urate therefore accumulates and can precipitate as crystals in joints and other tissues if serum concentrations exceed the saturation point. At normal body temperature, the saturation point of urate is 6.8 mg/dL (0.40 mmol/L). At lower temperatures (for example, in the extremities), the saturation point is lower.

Nearly all urate is filtered at the glomerulus, but approximately 90% is reabsorbed in the proximal tubule; in most patients with gout, hereditary underexcretion of uric acid contributes to hyperuricemia (**Table 33**). Not all patients with hyperuricemia develop gout; about 20% of the U.S. population is hyperuricemic compared with the 4% prevalence of gout. The factors that lead to the development of gout in hyperuricemia are unclear, but degree of elevation in urate level is predictive. A serum urate level greater than 10 mg/dL (0.59 mmol/L) is associated with a 30% likelihood of an initial attack of gout within 5 years.

Acute gouty arthritis is triggered when tissue macrophages ingest uric acid crystals, leading to the generation of interleukin (IL)-1β. IL-1β is an inflammatory cytokine that causes local vasodilation, triggers production of other inflammatory cytokines (tumor necrosis factor α and IL-6), and both recruits and activates neutrophils. Complement activation on the surface of uric acid crystals also promotes neutrophil recruitment. Neutrophils are primarily responsible for the symptoms and signs of an acute gout attack.

Clinical Manifestations

Three requirements generally must be fulfilled for the onset of clinically apparent gout: 1) hyperuricemia, usually

TABLE 33. Causes of Hyperuricemia
Primary renal uric acid underexcretion (hereditary, renal tubular basis)
Chronic kidney disease of any cause (secondary uric acid underexcretion)
Uric acid overproduction due to primary defect in purine metabolism: PRPP synthetase overactivity; HPRT deficiency
Conditions of increased cell turnover leading to purine/urate generation: leukemia/lymphoma; psoriasis; hemolytic anemia; polycythemia vera
Drug-induced hyperuricemia (agents reducing renal glomerular filtration and/or tubular urate excretion): thiazide and loop diuretics; cyclosporine; low-dose salicylates; ethambutol; pyrazinamide; lead ingestion/toxicity
Diet-induced hyperuricemia (agents high in purines or inducing purine/urate biosynthesis): alcohol; shellfish; red meat; high-fructose corn syrup-sweetened beverages and foods; impact on serum urate generally is limited in the absence of other causes

HPRT = hypoxanthine-guanine phosphoribosyltransferase; PRPP = phosphoribosylpyrophosphate.

long-standing, 2) uric acid deposition in the joints and/or soft tissues, and 3) a reaction to phagocytosed crystals that leads to an acute inflammatory event.

Acute Gouty Arthritis

Initial acute gouty attacks are typically monoarticular, and ≥50% of first attacks in men involve the first metatarsophalangeal (MTP) joint of the great toe (podagra). Inflammatory states such as infection, surgery, and myocardial infarction can provoke gouty attacks, possibly through volume and pH changes. The hallmarks of an attack are pain, tenderness, swelling, redness, and warmth of the affected area. Attacks typically begin at night, and peak within 12 to 24 hours. The pain is often so exquisite that even the touch of a sheet on an affected toe is unbearable. Untreated, most gout attacks self-resolve within days to a few weeks, although with long-standing disease, attacks can persist for months. In men with established disease, attacks eventually affect joints other than the first MTPs, including the proximal feet, ankles, and knees, and later virtually any joint, including the spine. Postmenopausal women may present differently, with initial attacks often involving finger joints already affected by osteoarthritis. For those with more severe or long-standing disease, polyarticular attacks may occur. Soft tissues can also be involved, manifesting as acute bursitis, periarthritis, and gouty panniculitis and cellulitis, the last of which can be misdiagnosed as a refractory bacterial soft-tissue infection.

Intercritical Gout

Intercritical gout is the period between gout attacks. Early in the disease course, the intercritical period can be years, although most patients will have a second gout attack within 2 years. As the disease progresses, the intercritical period can progressively shorten. Even in the absence of acute arthritis, uric acid crystals still reside within joints and soft tissues, and low-grade inflammation persists in the absence of clinically apparent systemic disease.

Chronic Recurrent and Tophaceous Gout

Chronic recurrent gout and tophaceous gout result from a failure to recognize or adequately treat gout at an earlier stage.

In chronic recurrent gout, patients experience increasingly frequent and severe, and often polyarticular, arthritic attacks. These attacks may eventually evolve into a persistent chronic arthritis.

Other patients with long-standing disease develop tophaceous gout. Tophi are solid chalky white masses of uric acid, surrounded by inflammatory cells and a rind of fibrous tissue. They are located around joints and in soft tissues, with a predilection for the extensor surfaces of the elbows, the distal Achilles tendon, the fingers (usually from the proximal interphalangeal joints distally) (**Figure 23**), and the cartilaginous portions of the ears. The size ranges from millimeters to several centimeters in diameter. Tophi are deforming, can interfere with function, and directly erode bone. Ulceration of overlying skin can occur, and accompanying infection can be difficult to treat because tophi are avascular.

Diagnosis

A diagnosis of acute gout should be entertained in any patient with an acute monoarticular or oligoarticular arthritis. The differential diagnosis is listed in **Table 34**. Although designed primarily for research, gout classification criteria are available

FIGURE 23. Fingers of a patient with numerous bulky tophaceous deposits of monosodium uric acid crystals, a consequence of years of gout with uncontrolled hyperuricemia.

TABLE 34. Differential Diagnosis of Acute Gouty Arthritis

Condition	Comments
Infectious arthritis	Presentation may be identical to gout. Infectious arthritis is usually monoarticular but can be polyarticular. Onset may be less acute than gout. Gout and infectious arthritis can coexist.
Acute calcium pyrophosphate crystal arthritis (pseudogout)	Pseudogout is less likely to present in the great toe, but acute presentations may otherwise be identical to gout. Synovial fluid analysis can distinguish these entities. Gout and pseudogout can coexist.
Basic calcium phosphate deposition	Basic calcium phosphate deposition in articular cartilage and periarticular tissues. Because of their small size, basic calcium phosphate crystals are unlikely to be seen in synovial fluid on light microscopy except as aggregates stained with alizarin red.
Trauma	Trauma can lead to local pain and swelling, with or without a fracture, and can also trigger a gout attack.
Other forms of inflammatory arthritis (e.g., reactive arthritis, rheumatoid arthritis, psoriatic arthritis, acute rheumatic fever)	Clinical context, affected joints, and pattern of arthritis are all helpful in distinguishing these entities. Synovial fluid analysis is particularly important when there is diagnostic uncertainty.

H CONT.

for guidance, including as an online calculator (http://goutclassificationcalculator.auckland.ac.nz).

The gold standard for the diagnosis of acute gout is the identification of negatively birefringent, needle-like uric acid crystals within neutrophils in fluid obtained by arthrocentesis. Negatively birefringent means that under polarized light, the crystals appear yellow when parallel and blue when perpendicular to the polarizing axis. Arthrocentesis is not always completed when gout is suspected, but when infection is a concern, joint aspiration for Gram stain and culture is mandatory.

Findings that support an acute gout diagnosis include onset of symptoms over several hours, first MTP joint or midfoot/ankle involvement, and severe pain. The involved joint(s) are warm, red, swollen, and very tender. Low-grade fever may be present. Measuring serum urate at the time of attack is often done but may not be helpful, because levels may drop precipitously during periods of acute systemic inflammation (owing to the uricosuric effects of circulating cytokines). Nonetheless, an elevated serum urate level increases the likelihood of gout. Checking the serum urate 2 weeks after acute gout resolution gives a more accurate measure of baseline level. C-reactive protein and erythrocyte sedimentation rate are elevated but are nonspecific. Joint fluid will have an inflammatory leukocyte count (above 2000/µL [2.0×10^9/L] and occasionally >100,000/µL [100×10^9/L], with neutrophil predominance). Importantly, the diagnosis of acute gout, even when confirmed by the presence of intracellular crystals in synovial fluid, does not definitively rule out a concomitant infection.

Radiographs are not helpful in diagnosing acute gouty arthritis, but the characteristic radiographic changes of established disease (punched-out lesions with overhanging edges of cortical bone) may help confirm a history of previously unrecognized gout (**Figure 24**). Newer imaging modalities (ultrasonography and dual-energy CT) can demonstrate uric acid deposition in joints and are being studied for their possible role in acute diagnosis.

FIGURE 24. Periarticular bony erosions, appearing as punched-out bone lesions with disruption of bone cortex (overhanging edges), represent areas of tophaceous monosodium uric acid deposition and accompanying inflammation in a patient with severe, long-standing, inadequately treated gout.

Courtesy of Elaine Karis, MD.

Management

There are three components to treating gout: 1) treating acute attacks, 2) prophylaxis to prevent future attacks, and 3) urate-lowering therapy. See Principle of Therapeutics for details on the medications described in this section.

Treatment of Acute Gouty Arthritis

Treatment of acute gout focuses on anti-inflammatory therapy; colchicine, NSAIDs, and glucocorticoids are all reasonable options. Treatment choice should be determined by potential

H CONT.

drug interactions and patient comorbidities. The simplest is colchicine, 1.2 mg at the first symptoms of a gout attack, followed 1 hour later by a 0.6-mg dose. Colchicine is most effective when used early in attacks (<24 hours after onset) and is less useful when the attack is well established. High-dose NSAID therapy for 5 to 7 days is effective, as are glucocorticoids in any form—intra-articular injection, intramuscular depot injection (for example, depo-methylprednisolone, 40-80 mg), or an oral "burst" of prednisone (for example, 0.5 mg/kg/d, for 5 days).

Most gout attacks respond to a week or less of therapy, although more severe attacks may require a longer course of treatment. For patients with severe and refractory attacks, or with contraindications to other treatments, off-label use of IL-1 inhibitors (anakinra or canakinumab) can be considered. Gouty cellulitis, if present, should be treated as any other acute gout attack. H

Urate-Lowering Therapy

Guidelines conflict as to whether patients with gout should receive dietary counseling to reduce serum urate levels. If recommended, patients may limit intake of shellfish, oily fish, red meat, high-fructose foods, and alcohol. Overly strict diets that are unlikely to be complied with are not helpful, however. Weight loss (when appropriate) and increasing dairy intake may also lower serum urate levels. In patients with hypertension, agents other than diuretics should be used; losartan, for example, has mild uricosuric effects.

It is important to note that two recently published guidelines differ regarding the role of pharmacologic urate-lowering therapy in patients with gout. The 2016 American College of Physicians guideline (http://annals.org/aim/article/2578528/management-acute-recurrent-gout-clinical-practice-guideline-from-american-college) notes a lack of evidence supporting a specific target level for urate lowering; this guideline stresses discussing the risks and benefits of urate-lowering therapy with patients and suggests a "treat to avoid symptoms" approach without specifically considering the serum urate levels. The 2016 European League Against Rheumatism (EULAR) recommendations support a "treat-to-target" approach (consistent with the 2012 ACR gout guidelines), reducing the serum urate level to less than 6.0 mg/dL (0.35 mmol/L) in patients without tophi and less than 5.0 mg/dL (0.30 mmol/L) in patients with tophi. Both the ACR and EULAR recommend urate-lowering therapy for patients with gout plus any of the following: (1) ≥ stage 2 CKD; (2) ≥2 acute attacks per year; (3) one or more tophi; or (4) uric acid nephrolithiasis.

H

Contrary to prior practice, urate-lowering therapy can be initiated during an acute attack if adequate anti-inflammatory therapy is concurrently started; doing so may improve compliance in some patients.

Three classes of urate-lowering therapy are available: xanthine oxidase inhibitors (reduce urate production), uricosuric agents (decrease renal urate resorption), and pegloticase (a uricase). A xanthine oxidase inhibitor, either allopurinol or febuxostat, is the recommended first-line therapy. Allopurinol is FDA approved for doses up to 800 mg/d. According to the ACR, allopurinol should be initiated at 100 mg/d and titrated in 100-mg increments as needed, and for those with stage 4 or 5 CKD, allopurinol should be initiated at 50 mg/d and titrated in 50-mg increments as needed. An uncommon but serious complication of allopurinol is a hypersensitive rash that may progress to DRESS (drug reaction with eosinophilia and systemic symptoms) syndrome; the drug should therefore be discontinued in most (if not all) patients who develop a rash. Febuxostat is equally or more efficacious than allopurinol. It is less likely to cause hypersensitivity reactions than allopurinol and does not require dose adjustment in mild to moderate CKD, but is expensive. There appears to be an increased risk of heart-related death with febuxostat compared to allopurinol; FDA-mandated safety studies are ongoing.

The uricosuric agent probenecid is infrequently used because it is less effective than xanthine oxidase inhibitors and should be avoided in patients with CKD or nephrolithiasis. Combination therapy with a xanthine oxidase inhibitor and probenecid (or the incidentally uricosuric agents losartan and fenofibrate) may be more effective than a xanthine oxidase inhibitor alone. A more effective uricosuric agent, lesinurad, was recently FDA approved as add-on therapy to allopurinol or febuxostat; reversible kidney insufficiency may develop in some patients.

For patients with severe recurrent and/or tophaceous gout intolerant or resistant to standard therapies, pegloticase is an option. Infused every 2 weeks, pegloticase lowers serum urate to nearly zero, but 30% to 50% of patients develop antibodies to the drug within a month, rendering it ineffective and increasing the likelihood of infusion reactions. Pegloticase should be discontinued in any patient for whom it ceases to work. H

Prophylaxis

When initiating urate-lowering therapy, mobilization of uric acid crystals from the joints and soft tissues can provoke acute attacks. Accordingly, patients starting urate-lowering therapy should be placed on anti-inflammatory prophylaxis to prevent flares. For patients without tophi, the ACR recommends continuing prophylaxis for at least 6 months and 3 months after achieving the target serum urate level. In patients with tophi, prophylaxis should be continued for 6 months following achievement of the target serum urate level and resolution of tophi. Most patients tolerate colchicine, 0.6 mg (once or twice daily); for those who do not, low-dose NSAIDs or glucocorticoids are appropriate substitutes.

KEY POINTS

- The gold standard for the diagnosis of acute gout is the identification of negatively birefringent, needle-like uric acid crystals within neutrophils in fluid obtained by arthrocentesis.
- Colchicine, NSAIDs, and glucocorticoids are all reasonable options for treatment of acute gout; choice should be determined by potential drug interactions and patient comorbidities.

(Continued)

KEY POINTS *(continued)*

HVC
- The 2016 American College of Physicians guideline notes a lack of evidence supporting a specific target level for urate lowering; the guideline stresses discussing the risks and benefits of urate-lowering therapy with patients and suggests a "treat to avoid symptoms" approach without specifically considering the serum urate levels.
- The American College of Rheumatology and the European League Against Rheumatism both recommend a "treat-to-target" approach, reducing the serum urate level to less than 6.0 mg/dL (0.35 mmol/L) in patients without tophi and less than 5.0 mg/dL (0.30 mmol/L) in patients with tophi.
- Patients starting urate-lowering therapy should be placed on anti-inflammatory prophylaxis to prevent flares.

Calcium Pyrophosphate Deposition

Deposition of calcium pyrophosphate (CPP) crystals in and on cartilaginous surfaces can provoke acute inflammatory arthritis that is clinically similar to acute gout. Calcium pyrophosphate deposition (CPPD) is less well characterized than gout, but four subgroups are described: asymptomatic CPPD; acute CPP crystal arthritis; chronic CPP crystal inflammatory arthritis; and osteoarthritis with CPPD.

Epidemiology and Pathophysiology

CPPD primarily affects the elderly, and prior joint damage is a significant risk factor. The risk for cartilage calcification (chondrocalcinosis) doubles for every decade past 60 years, and nearly half of patients in their late 80s have CPPD. For younger patients with CPPD, consideration of contributory metabolic disease (hyperparathyroidism, hemochromatosis, hypophosphatasia, hypomagnesemia) is warranted.

The pathophysiology of CPPD is incompletely understood. Pyrophosphate produced by chondrocytes likely precipitates with calcium to form CPP crystals, which then activate inflammatory pathways resulting in an acute arthritic attack. CPPD may also drive osteoarthritis by inducing proinflammatory activity in chondrocytes and synovial fibroblasts, resulting in cartilage damage. Epidemiologic evidence suggests that cartilage calcification might play a role in osteoarthritis of the knees and wrists, but not at the hip.

Clinical Manifestations and Diagnosis

Asymptomatic Calcium Pyrophosphate Deposition

Asymptomatic CPPD occurs with radiographic changes in the absence of clinical symptoms. Cartilage calcification appears as a linear opacity below the surface of articular cartilage (**Figure 25**). It most commonly occurs in the knees, wrists (triangular fibrocartilage), pelvis (pubis symphysis), and metacarpophalangeal (MCP) joints, in descending order. Asymptomatic CPPD is common in the elderly and in osteoarthritic joints, and it may be a precursor of osteoarthritis with CPPD.

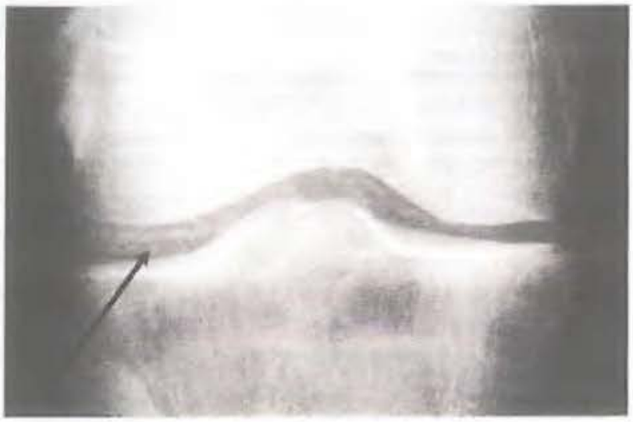

FIGURE 25. Cartilage calcification (chondrocalcinosis) of the knee. This radiograph shows linearly arranged calcific deposits in the articular cartilage (*arrow*).

Acute Calcium Pyrophosphate Crystal Arthritis

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Acute CPP crystal arthritis (pseudogout) typically presents as a monoarticular inflammatory arthritis, characterized by sudden onset of swelling, pain, loss of function, tenderness, and warmth of the affected joint, usually a knee or wrist. Similar to acute gout, attacks may be provoked by systemic insults such as major surgery or acute illness. Attacks are usually milder than those of gout, but if untreated can persist for months. Definitive diagnosis requires identification of CPP crystals (along with leukocytes) in synovial fluid; in contrast to uric acid crystals, the CPP crystals are rhomboid shaped and positively birefringent under polarized light. Radiographic evidence of cartilage calcification in elderly patients with acute monoarticular arthritis is suggestive but not diagnostic of acute CPP crystal arthritis. H

Chronic Calcium Pyrophosphate Arthropathy

Chronic calcium pyrophosphate arthropathy may be present as two patterns: (1) chronic calcium pyrophosphate (CPP) crystal inflammatory arthritis and (2) osteoarthritis with calcium pyrophosphate deposition (CPPD). Chronic CPP crystal inflammatory arthritis is a polyarthritis involving the wrists and MCP joints ("pseudo-rheumatoid arthritis"); it is rare and difficult to treat. Osteoarthritis with CPPD manifests as typical osteoarthritic findings involving joints not commonly associated with osteoarthritis (such as shoulders or MCP joints); radiographic CPPD often precedes the onset of osteoarthritis, suggesting a causal role for the CPP.

Management

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Because there is no known mechanism for dissolving or preventing the formation of articular CPP crystals, treatment aims at abrogating the inflammatory manifestations of the disease (**Table 35**). H

TABLE 35. Management of Calcium Pyrophosphate Deposition	
Clinical Presentation	**Treatment/Comments**
Cartilage calcification (chondrocalcinosis)	No specific treatment
Acute calcium pyrophosphate crystal arthritis (pseudogout)	Local treatment: joint aspiration, followed by intra-articular glucocorticoid injection, intramuscular glucocorticoid injection; joint immobilization; ice packs
	Systemic treatment: NSAIDs; colchicine; glucocorticoids (oral or parenteral)
	Prophylaxis if recurrent attacks (three or more annual attacks): low-dose colchicine or daily NSAIDs (with gastrointestinal protection)
Chronic calcium pyrophosphate crystal inflammatory arthritis	Low-dose colchicine or daily low-dose NSAIDs (with gastrointestinal protection); low-dose glucocorticoids
Osteoarthritis with calcium pyrophosphate deposition (CPPD)	Same treatment as osteoarthritis without CPPD (e.g., physical therapy; pain control; local glucocorticoids)

KEY POINTS

- Asymptomatic calcium pyrophosphate deposition is characterized by radiographic changes, including cartilage calcification (chondrocalcinosis), in the absence of clinical symptoms.
- The presentation of acute calcium pyrophosphate crystal arthritis (pseudogout) resembles gout; however, attacks are usually milder, and crystals are rhomboid shaped and positively birefringent under polarized light.
- Chronic calcium pyrophosphate crystal inflammatory arthritis often involves the wrists and metacarpophalangeal joints ("pseudo–rheumatoid arthritis").
- Osteoarthritis with calcium pyrophosphate deposition causes typical osteoarthritic findings involving joints not commonly associated with osteoarthritis (shoulders, metacarpophalangeal joints).

Basic Calcium Phosphate Deposition

Basic calcium phosphate (BCP) deposition occurs in the elderly and forms in the articular cartilage; in contrast to CPPD, BCP crystals also often deposit periarticularly. BCP is thought to rarely cause inflammatory arthritis and periarthritis, most classically manifesting in elderly women as "Milwaukee shoulder," an inflammatory periarthritis and arthritis of the shoulder, leading to progressive destruction of the rotator cuff and glenohumeral joint. Diagnosis is usually clinical; imaging of BCP crystals requires special stains and/or electron microscopy and is rarely performed.

KEY POINT

- Basic calcium phosphate deposition can rarely cause Milwaukee shoulder, an inflammatory arthritis and periarthritis of the shoulder occurring in elderly women that leads to progressive destruction of the rotator cuff and glenohumeral joint; diagnosis is usually clinical.

Infectious Arthritis

Diagnosis

H

Clinical Manifestations

Infectious arthritis typically presents with pain, swelling, warmth, and erythema of the affected joint, accompanied by fever and constitutional symptoms. Knee infection is common, but any joint may be affected. Previously damaged joints are at increased risk for involvement. Monoarthritis or new inflammation of a single joint in a patient with well-controlled inflammatory arthritis should prompt evaluation for infection.

Physical examination commonly shows functional loss of both active and passive range of motion in addition to signs of inflammation. Skin examination can reveal signs suggesting gonococcal infection (pustular skin lesions) or portals of entry (scratches, bites, or thorns).

Laboratory and Imaging Studies

In patients with suspected infectious arthritis, the most important diagnostic procedure is expeditious arthrocentesis. The synovial fluid should be sent for Gram stain, culture (bacterial and, when indicated, mycobacterial and/or fungal), leukocyte count, and crystal analysis. Synovial fluid levels of glucose, lactate dehydrogenase, and total protein do not aid in diagnosis and should not be obtained. Depending upon the clinical picture, the fluid may be sent for polymerase chain reaction to detect *Mycobacteria* or *Borrelia burgdorferi* DNA.

Bacterially infected synovial fluid is cloudy and less viscous than that seen in noninflammatory arthritis. Elevated synovial fluid leukocyte counts are typically greater than 50,000/µL (50×10^9/L) and often exceed 100,000/µL (100×10^9/L), with a polymorphonuclear cell predominance. Such high leukocyte counts may occur in other conditions (for example, crystal arthropathies) but should be presumed infectious until proven otherwise. Notably, the presence of crystals does not exclude the possibility of co-infection. Patients with gonococcal, mycobacterial, or fungal infections, injection drug users, or those who are immunocompromised may have lower synovial fluid leukocyte counts.

H CONT.

A positive Gram stain for bacteria should be considered definitive, but the sensitivity of the test is inadequate for a negative result to rule out infection when suspicion is high. Synovial fluid cultures are usually positive in bacterial infections unless antibiotics were administered prior to arthrocentesis. The peripheral blood leukocyte count, erythrocyte sedimentation rate, and C-reactive protein are often elevated; however, normal levels do not exclude the diagnosis, and elevated levels may occur in inflammatory arthritis and other conditions.

Blood cultures should always be drawn before antibiotic administration. When gonococcal arthritis is suspected, urogenital, rectal, and pharyngeal specimens should also be obtained for nucleic acid amplification testing.

Plain radiographs are usually normal early in the course of the infection, but baseline films are helpful to identify other diseases or contiguous osteomyelitis. Later radiographs (weeks to months) often show nonspecific changes. In advanced infection, periosteal reaction, marginal or central erosions, and subchondral bone destruction may be seen. Bony ankylosis is a late sequel. In joints that are difficult to evaluate clinically or have complex anatomic structures, ultrasonography, CT, and MRI can delineate the extent of the effusion and identify early bony changes. H

KEY POINTS

- Infectious arthritis typically presents with pain, swelling, warmth, and erythema of the affected joint, accompanied by fever and constitutional symptoms; monoarthritis or new inflammation of a single joint in a patient with well-controlled inflammatory arthritis should prompt evaluation for infection.
- Diagnosis of infectious arthritis is confirmed by arthrocentesis and evaluation of the synovial fluid for Gram stain, culture, leukocyte count, and crystal analysis.

Causes

See MKSAP 18 Infectious Disease for details on the specific infections and diseases discussed in this section.

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Infection with Gram-Positive Organisms

Bacterial arthritis is a medical emergency requiring immediate diagnosis and treatment. Risk factors include an immunocompromised state (including diabetes mellitus), injection drug use, joint surgery, and having a prosthetic joint. A recent "dirty" skin break may be a contributing factor. Infections occur very rarely after invasive procedures such as arthrocentesis or joint injection (**Table 36**). Most joint infections are monoarticular and derive from hematogenous seeding of synovium. Polyarticular infectious arthritis may occur in injection drug users, those with systemic inflammatory disorders such as rheumatoid arthritis, and in patients with overwhelming sepsis.

TABLE 36. Risk Factors for Infectious Arthritis in Adults

General Risk Factors
Age >80 years
Alcoholism
Cutaneous ulcers or skin infections
Diabetes mellitus
End-stage kidney disease
History of intra-articular glucocorticoid injection
Injection drug use
Low socioeconomic status
Malignancy
Patients receiving immunosuppressive agents
Preexisting arthritis or joint damage (e.g., rheumatoid arthritis or osteoarthritis)
Prosthetic joint or recent joint surgery
Sickle cell disease
Risk Factors for Gonococcal Arthritis
Younger, sexually active patients
Risk Factors for Lyme Arthritis
Travel or residence in an endemic area
Documented tick bite or erythema chronicum migrans
Risk Factors for Mycobacterial or Fungal Arthritis
Patients with HIV infection or other immunosuppression
Patients receiving tumor necrosis factor α inhibitors
Travel or residence in an endemic area
Risk Factors for Viral Arthritis
Chronic viral infection (HIV, hepatitis B, hepatitis C)
Exposure to infectious agent or vaccine (e.g., rubella)
Travel or residence in an endemic area
Exposure to affected children (parvovirus, rubella)

Approximately 75% of adult nongonococcal infectious arthritis is caused by gram-positive cocci, with *Staphylococcus aureus* being the most frequent microorganism in both native and prosthetic joints. *Staphylococcus epidermidis* infections occur more commonly in prosthetic than in native joints.

Infection with Gram-Negative Organisms

Disseminated Gonococcal Infection

Neisseria gonorrhoeae most typically occurs in younger, sexually active individuals. Disseminated infection occurs in 1% to 3% of patients infected with *N. gonorrhoeae*, with arthritis a common feature.

Disseminated gonococcal infection may present in one of two ways, although there may be overlap. The first is the arthritis-dermatitis syndrome, a triad of tenosynovitis, dermatitis (usually painless pustular or vesiculopustular lesions)

H CONT. (**Figure 26**), and polyarthralgia without frank arthritis. Fever, chills, and malaise are common. Inflammation of multiple tendons of the wrists, fingers, ankles, and toes distinguishes this syndrome from other forms of infectious arthritis. The second presentation is a purulent arthritis, usually without associated skin lesions or fever. Patients present with acute onset of mono- or oligoarthritis; the knees, wrists, and ankles are most commonly involved.

Patients with the arthritis-dermatitis syndrome are more likely to have positive blood cultures, whereas those with purulent arthritis are more likely to have positive synovial fluid cultures. Nucleic acid amplification testing should also be obtained on samples from genital, rectal, and pharyngeal sites.

Nongonococcal Gram-Negative Organisms

Aerobic gram-negative bacilli are the predominant cause of nongonococcal gram-negative joint infections. Predisposing factors include injection drug use, advanced age, and an immunocompromised state. *Pseudomonas aeruginosa* can be seen in infection related to injection drug use. Patients with sickle cell anemia may become infected with *Salmonella*. Gram-negative anaerobes account for only 5% to 7% of bacterial arthritis cases, most commonly in prosthetic joint infections and/or immunocompromised hosts.

Lyme Arthritis

Although arthralgia and myalgia often occur at the earlier stages of Lyme disease, Lyme arthritis is a late-stage manifestation. It is typically monoarticular or oligoarticular, most commonly in the knee. It should be suspected in patients who may have had untreated or incompletely treated Lyme disease, although not all patients will have a history compatible with prior Lyme disease. All patients with Lyme arthritis, however, should have positive enzyme-linked immunosorbent assay (ELISA) and Western blot serologies; this is the major means of establishing the diagnosis of Lyme arthritis. Additionally, *B. burgdorferi* DNA can be detected by polymerase chain reaction in synovial fluid.

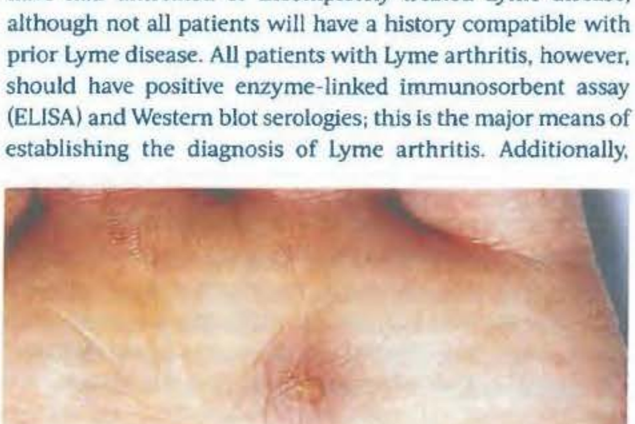

FIGURE 26. Disseminated gonococcal infection can present as a febrile arthritis-dermatitis syndrome with migratory polyarthralgia that may evolve to septic arthritis, tenosynovitis, and painless skin rash that may involve the palms and soles. Skin lesions can vary from maculopapular to pustular, often with a hemorrhagic component.

Mycobacterium tuberculosis

The most common musculoskeletal manifestation of tuberculosis is vertebral osteomyelitis (Pott's disease), usually resulting from the hematogenous spread of *Mycobacterium tuberculosis* into the cancellous bone tissue of the vertebral bodies. Patients usually have a primary pulmonary focus or extrapulmonary foci such as the lymph nodes. Predisposing factors for skeletal tuberculosis include previous tuberculosis infection, malnutrition, alcoholism, diabetes mellitus, and HIV infection. The onset of symptoms is commonly insidious, and disease progression is slow, sometimes resulting in delayed diagnosis.

Peripheral arthritis may also occur and typically presents with chronic pain in a single weight-bearing joint such as the knee, with only limited swelling. Concurrent pulmonary tuberculosis is present in a minority of these patients. Musculoskeletal tuberculosis infections are chronic and indolent; laboratory indicators of inflammation may be normal. Synovial fluid shows only nonspecific inflammation, and radiographic abnormalities may be delayed. Synovial biopsy is usually necessary for diagnosis because the yield of synovial fluid smear and culture is less than 50%.

Fungal Infections

Fungi are uncommon but important causes of bone and joint infections. Risk factors include immunosuppression and exposure to the fungi in endemic areas. Travel and immigration have broadened the risk of some fungal infections to non-endemic areas. Fungal joint infection may be indolent and more difficult to diagnose than other bone and joint infections. Fungal causes of osteomyelitis and arthritis include coccidioidomycosis, blastomycosis, cryptococcosis, candidiasis, and sporotrichosis. Fungal arthritis is usually a result of hematogenous dissemination but can occur after direct inoculation of the joint. Diagnosis of some fungal infections (for example, blastomycosis and sporotrichosis) can be made by synovial fluid examination and culture, whereas serologic testing and synovial biopsy may be needed for other organisms (such as *Coccidioides*). Synovial fluid leukocyte counts vary. H

Viral Infections

HIV

HIV infection is associated with several musculoskeletal disorders, including painful articular syndrome, HIV-associated arthritis, reactive arthritis, infectious arthritis, and diffuse infiltrative lymphocytosis syndrome (DILS). Painful articular syndrome consists of bone and joint pain, especially in the lower extremities in an asymmetric pattern, lasting less than 24 hours. HIV-associated arthritis is a nondestructive arthritis that involves joints of the lower extremity in an oligoarticular pattern and usually lasts less than 6 weeks. Reactive arthritis is the primary form of spondyloarthritis seen in patients with HIV infection and is likely due to a response to other sexually transmitted or enteric infections, rather than the HIV itself. Reactive

arthritis in HIV may take a chronic relapsing course and may be accompanied by enthesopathy and mucocutaneous manifestations. Psoriatic arthritis is not more common but is often more severe in patients with HIV infection, with disabling enthesitis and joint erosion as well as axial involvement including sacroiliitis. DILS is a rare condition that resembles Sjögren syndrome but with CD8 rather than CD4 cell infiltration.

Hepatitis

Hepatitis B virus infection causes a self-limited arthritis in up to 25% of infected patients during a prodromal stage prior to the onset of jaundice. Joint involvement can be sudden and severe, with a pattern that is usually symmetric, but can be migratory or additive. Hand and knee joints are most often affected; wrists, ankles, elbows, shoulders, and other large joints may be involved as well. Morning stiffness is common. Fusiform swelling of the small joints of the hand may be found on physical examination. Patients with chronic hepatitis B virus infection may have recurrent but self-limited polyarthralgia or polyarthritis; it is not known to progress or cause joint damage. Both hepatitis B and C virus infection may be accompanied by the presence of rheumatoid factor, which can cause diagnostic confusion.

Acute hepatitis C virus infection can cause acute-onset polyarthritis, including the small hand joints, wrists, shoulders, knees, and hips. One third of patients have an oligoarthritis. Chronic hepatitis C virus infection is often associated with circulating immune complexes, which may produce the clinical syndrome of mixed essential cryoglobulinemia (arthritis, glomerulonephritis, and vasculitis).

Parvovirus B19

Up to 60% of adults with parvovirus B19 experience arthritis. It often presents acutely, is symmetric and polyarticular, and typically involves the proximal small joints of the hands. Parvovirus B19 arthritis should be suspected when appropriate clinical features are present in someone who has exposure to children, such as teachers and caregivers. Acute parvovirus infection is diagnosed by detecting anti-parvovirus IgM antibodies in the serum. Anti-parvovirus IgG antibodies are highly prevalent in the general population and indicate prior infection. Joint symptoms may persist for weeks to months.

Rubella

Arthritis is uncommon in childhood rubella infection, but up to 60% of adults with rubella develop joint symptoms, mainly arthralgia. Joint involvement is usually symmetric and migratory, with resolution of most symptoms within 2 weeks. The small joints of the hands, wrists, elbows, ankles, and knees are most commonly affected. Tenosynovitis and carpal tunnel syndrome also occur. The pathogenesis of rubella arthritis is thought to be due to immune complexes and/or persistence of the virus in synovial cells or joint macrophages. Diagnosis is usually made by detection of IgM antirubella antibodies; the virus may also be cultured from the nasopharynx or joint tissues. Joint fluid findings are inflammatory.

Mosquito-Borne Viruses

Zika, dengue, and chikungunya viruses are transmitted by *Aedes* mosquitos in tropical areas. Zika also can be vertically and sexually transmitted, and localized transmission in the southern United States is now reported. All of these viruses can cause musculoskeletal symptoms in addition to fever, rash, and headache. In chikungunya, arthritis is a predominant feature; patients may experience synovial thickening and tenosynovitis, often involving the fingers and wrists. Zika may also manifest with a symmetric polyarthritis, whereas dengue tends to produce more arthralgia. The musculoskeletal symptoms of Zika and dengue tend to subside within a couple of weeks, whereas those of chikungunya usually continue longer, resembling rheumatoid arthritis (without rheumatoid factor or anti-cyclic citrullinated peptide antibodies) in some cases. Diagnosis of these mosquito-borne diseases is based on clinical features and serologic testing. Polymerase chain reaction testing on blood samples is also available.

Prosthetic Joint Infections

H

Bacterial infection complicates 1% to 3% of total knee and hip replacements; higher rates are seen in immunocompromised patients and those with rheumatoid arthritis. Infection with gram-positive organisms such as *S. aureus* is most common. Prosthetic joint infections are divided into early onset (<3 months after placement), delayed (3 to 24 months postsurgery), and late onset (>24 months after placement). Early and delayed infections are usually related to surgical contamination at the time of the implantation, whereas late infections result from hematogenous seeding of the joint. Early and late prosthetic joint infections typically present with pain, warmth, effusion, and fever. Peripheral leukocyte count and inflammatory markers are usually elevated. Delayed infections, however, may be more difficult to recognize because symptoms are less severe, and they are often caused by less virulent microorganisms such as coagulase-negative staphylococci and other skin organisms. H

KEY POINTS

- Approximately 75% of adult nongonococcal infectious arthritis is caused by gram-positive cocci, with *Staphylococcus aureus* being the most frequent microorganism in both native and prosthetic joints.
- Disseminated gonococcal infection may present as the arthritis-dermatitis syndrome (tenosynovitis, dermatitis, and polyarthralgia) or as a purulent arthritis with pain and swelling but usually without skin lesions or fever.
- Lyme arthritis is a late-stage manifestation of the disease and is typically monoarticular or oligoarticular, most commonly in the knee, and inflammatory; diagnosis should be suspected in patients who may have had untreated or incompletely treated Lyme disease.

(Continued)

KEY POINTS *(continued)*

- *Mycobacterium tuberculosis* arthritis typically presents as chronic pain in a single weight-bearing joint such as the knee, with only limited swelling; concurrent pulmonary tuberculosis is present in a minority of patients.
- Early and late prosthetic joint infections usually present with pain of the joint, warmth, effusion, and fever; delayed infections may be more difficult to recognize because they are often caused by less virulent microorganisms, and symptoms may be less severe.

Management

H

In patients with suspected infectious arthritis, blood and synovial cultures must be obtained before treatment, but empiric antibiotic therapy should be started while awaiting culture results (**Table 37**). In suspected bacterial arthritis, the initial antimicrobial coverage should be broad and account for host factors such as immunosuppression as well as likely causative microorganisms and regional antibiotic sensitivity data. Antibiotics should initially be given parenterally. Given the high prevalence of methicillin-resistant

TABLE 37. Infectious Arthritis Treatment Based on the Suspected Pathogen

Likely or Identified Pathogen	First-Line Therapy	Second-Line Therapy	Comments
Gram-Positive Cocci			
If MRSA is a concern (risk factors or known MRSA carrier)	Vancomycin	Clindamycin; daptomycin; linezolid	—
MSSA	Nafcillin or cefazolin	—	Narrow treatment to MSSA coverage based on sensitivity data.
Gram-Negative Bacilli			
Enteric gram-negative bacilli	Third generation cephalosporin (e.g., ceftriaxone or cefotaxime)	Fluoroquinolones	—
Pseudomonas aeruginosa	Ceftazidime; cefepime; piperacillin-tazobactam	Carbapenems; aztreonam; fluoroquinolones	—
Gram-Negative Cocci			
Neisseria gonorrhoeae	IV ceftriaxone for at least 7 days plus 1 gram of oral azithromycin x one dose	Fluoroquinolones (only if culture sensitivities confirm susceptibility)	In the absence of specific culture sensitivity data, "stepping down" to oral therapy of any type is no longer recommended due to increasing resistance of *N. gonorrhoeae* to commonly used oral agents.
Gram Stain Unavailable or Inconclusive			
Likely pathogen depends on patient risk factors: consider MRSA, and gram-negative organism if immunocompromised, at risk for gonococcal infection, or with joint trauma; also consider community patterns of infection.	Vancomycin, or vancomycin + third generation cephalosporin, or antipseudomonal antibiotic if pseudomonas suspected	—	Appropriate to start with broad antibiotic coverage and narrow coverage if culture data become available.
Borrelia burgdorferi (Lyme arthritis)	Oral doxycycline or amoxicillin × 28 days	—	If inadequate response or concurrent neurologic findings, IV ceftriaxone × 28 days.
Mycobacterium tuberculosis	3- to 4-drug treatment (e.g., isoniazid, pyrazinamide, rifampin, ethambutol, streptomycin)	—	Duration may vary from 6 months or longer depending on drug regimen (shorter treatment if rifampin is used).
Fungal infections	Amphotericin B, echinocandin, or azoles (fluconazole, itraconazole, voriconazole, posaconazole), depending on suspected organism or culture data	—	Prolonged treatment courses of several months may be needed; maintenance therapy may be required in high-risk patients.

IV = intravenous; MRSA = methicillin-resistant *Staphylococcus aureus*; MSSA = methicillin-sensitive *Staphylococcus aureus*.

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S. aureus, vancomycin is often initially used to cover gram-positive cocci. The duration of treatment depends on the causative organism and patient response, but usually lasts 2 to 4 weeks.

An infected joint must also be adequately drained. Needle aspiration is an acceptable approach and should be performed regularly (usually daily) as long as there is an effusion. Ultrasound guidance may improve the ability to fully drain the joint. Surgical drainage is an equally good alternative and is more immediately definitive. Additionally, surgical drainage is required for joints that are not easily accessible for needle aspiration (for example, sternoclavicular, sternomanubrial, shoulder, and hip joints), if there is evidence of soft-tissue extension of infection, or if the clinical response to antimicrobial therapy is inadequate. The goal of surgery is to remove all purulent material and nonviable tissue and, in some cases, to perform synovial biopsy or synovectomy.

Antibiotic treatment is recommended for all patients with Lyme arthritis. Approximately 90% of patients will respond to a 28-day course of oral doxycycline, amoxicillin, or cefuroxime axetil. Patients with incomplete responses may need treatment with a second course or a more aggressive drug regimen, usually intravenous ceftriaxone. Treatment beyond 1 month of ceftriaxone offers no benefit and should not be employed. Antibiotic-refractory Lyme arthritis occurs in ≤10% of patients, probably represents a progression to sterile autoimmune arthritis, and responds to synovectomy or treatment with disease-modifying antirheumatic drugs such as hydroxychloroquine or methotrexate.

Mycobacterial joint infections require at least 6 to 9 months of therapy. Treatment of arthritis associated with viral infections is largely supportive, although specific viral therapy is appropriate for HIV and hepatitis C infection; immunosuppressive therapy with glucocorticoids and rituximab may be needed in refractory hepatitis C–related disease or severe mixed cryoglobulinemia.

Treatment of prosthetic joint infections is challenging and requires early surgical consultation. Orthopedic implants serve as a nidus for microorganisms, and the avascularity of the infected hardware limits antibiotic penetrance. Many patients require removal of the orthopedic device as part of a two-stage procedure, with reimplantation of a new device after an appropriate course of intravenous antibiotics. H

KEY POINTS

- In patients with suspected infectious arthritis, blood and synovial cultures must be obtained before treatment, but empiric antibiotic therapy should be started while awaiting culture results.
- In addition to antibiotic therapy, an infected joint must also be adequately drained by needle aspiration or surgical drainage.
- Many patients with prosthetic joint infections require removal of the orthopedic device as part of a two-stage procedure, with reimplantation of a new device after an appropriate course of intravenous antibiotics.

Systemic Vasculitis

Overview

Vasculitis is inflammation of blood vessels, including the capillaries, arteries, and veins. Clinical manifestations result from tissue ischemia associated with the involved vessels. Vasculitis may be primary, secondary to an autoimmune disease, or triggered by other causes (**Table 38**). Mimics of vasculitis must also be considered in the differential diagnosis (**Table 39**). Primary autoimmune vasculitis disorders are discussed in this section.

TABLE 38. Causes of Secondary Vasculitis
Medications
Common causes: antimicrobial agents (e.g., minocycline, sulfadiazine); antithyroid agents (mostly propylthiouracil [80%-90%], methimazole, carbimazole, and benzylthiouracil [10%-20%]); other cardiovascular drugs (hydralazine); tumor necrosis factor α inhibitors
Rare causes: vaccines; antiepileptic agents; antiarrhythmic agents; diuretics; anticoagulants; antineoplastic agents; hematopoietic growth factors; NSAIDs; psychotropic drugs; sympathomimetic agents; allopurinol; interferon alfa; levamisole (associated with cocaine)
Infections
Hepatitis A, B, and C viruses; HIV; bacterial endocarditis; parvovirus B19
Neoplasms
Hairy cell leukemia (associated with polyarteritis nodosa); other hematologic and solid malignancies
Autoimmune Diseases
Systemic lupus erythematosus; rheumatoid arthritis; Sjögren syndrome; inflammatory myopathies; systemic sclerosis; relapsing polychondritis; inflammatory bowel disease; primary biliary cirrhosis

TABLE 39. Differential Diagnosis (Mimics) of Vasculitis

Disease	Comments
Infection (sepsis; endocarditis; hepatitis)	Rash and/or musculoskeletal symptoms can occur.
Drug toxicity/poisoning	Cocaine, amphetamines, ephedra alkaloids, and phenylpropanolamine may produce vasospasm, resulting in ischemia.
Coagulopathy	Thrombotic diseases (disseminated intravascular coagulation; antiphospholipid syndrome; thrombotic thrombocytopenic purpura) can produce ischemic symptoms.
Malignancy	Paraneoplastic vasculitis is rare. Any organ system may be affected, but the skin and nervous system are the most common. Vasculitic symptoms may precede, occur simultaneously with, or follow diagnosis of cancer. Lymphoma occasionally may involve the blood vessels and mimic vasculitis. Consider malignancy in patients with incomplete or no response to therapy for idiopathic vasculitis.
Atrial myxoma	Classic triad of symptoms is embolism, intracardiac obstruction leading to pulmonary congestion or heart failure, and constitutional symptoms (fatigue; weight loss; fever). Skin lesions can be identical to those seen in leukocytoclastic vasculitis. Atrial myxomas are rare but are the most common primary intracardiac tumors. Myxomas can also occur in other cardiac chambers.
Cholesterol emboli	Typically seen in patients with severe atherosclerosis. Embolization may occur after abdominal trauma, aortic surgery, or angiography. May also occur after heparin, warfarin, or thrombolytic therapy. Patients may have livedo reticularis, petechiae and purpuric lesions, and localized skin necrosis.

Large-Vessel Vasculitis

H

Giant Cell Arteritis

Epidemiology and Pathophysiology

Giant cell arteritis (GCA; temporal arteritis) affects patients over 50 years of age (peak incidence between 70 and 80 years). Most patients are women. GCA is more common in white persons; incidence ranges from 10 to 20/100,000 in Europe. An association with HLA-DRB*04 has been identified.

GCA is characterized by granulomatous inflammation of affected vessels with infiltration of lymphocytes, macrophages, and multinucleated giant cells. Involved vessels include the aorta, its major branches off the arch, and secondary branch vessels, including the external carotid, subclavian, axillary, temporal, ophthalmic, ciliary, occipital, and vertebral arteries. The level of vessel involved dictates the clinical symptoms.

Clinical Manifestations and Diagnosis

Common GCA symptoms include headache, scalp pain, and temporal artery tenderness. Symptoms are frequently unilateral but can be bilateral. Aching and fatigue with chewing (jaw claudication) indicates ischemia of the muscles of mastication. Fever, fatigue, and weight loss may be present. The most feared complication is ischemic optic neuropathy, which can cause amaurosis fugax and blindness. Because blindness is usually permanent, early recognition and treatment of any visual change are critical. Subcranial disease involving great vessels in the chest occurs in 25% of cases, resulting in upper extremity claudication. Severe but uncommon complications include aortic aneurysm and dissection. Dilation of the aortic root may cause aortic valve regurgitation and heart failure. Up to 50% of patients with GCA have polymyalgia rheumatica (PMR) that may occur before, concurrent with, or following diagnosis of GCA.

Physical examination may reveal scalp or temporal artery tenderness and induration, reduced pulses and bruits, or aortic regurgitation and heart failure. Laboratory findings may include elevated erythrocyte sedimentation rate (ESR) and/or C-reactive protein (CRP), but some have normal values. Nonspecific evidence of inflammation may include anemia and thrombocytosis.

GCA is suspected on the basis of the clinical presentation and is confirmed by temporal artery biopsy and/or imaging of great vessels. New or atypical headache, jaw claudication, or visual changes in a patient over the age of 50 years, especially with concurrent PMR, should raise suspicion. Temporal artery biopsy is diagnostic, but false-negative results are common; bilateral temporal artery biopsy can increase the yield. Importantly, temporal artery biopsy will remain abnormal for up to 2 weeks after initiation of glucocorticoids. Angiography is used to document and follow subcranial disease.

Management

Suspected GCA must be treated immediately to prevent visual loss. Prednisone, 1 mg/kg/d, is recommended. Intravenous pulse methylprednisolone for 3 days is used for acute visual loss, but established blindness is usually irreversible. Symptoms and inflammatory markers usually respond rapidly to glucocorticoids; lack of response should prompt reconsideration of the diagnosis. High-dose prednisone is maintained for 2 to 4 weeks; after symptoms resolve and inflammatory markers normalize, prednisone is tapered by 10% to 20% every 2 weeks. Once a dose of 10 mg/d is reached, the taper is slowed to 1 mg per month. Patients should be carefully monitored for

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symptom recurrence. ESR and/or CRP should be monitored monthly but should not be the sole indication for adjusting the glucocorticoid dose. Mild flares can be managed with increases of prednisone by 10% to 20% and a slower tapering schedule.

Based on limited data, daily low-dose aspirin may help to reduce the risk of blindness and is recommended for those without contraindication. Glucocorticoid-sparing immunosuppressives such as methotrexate are sometimes used, although little data support their efficacy. The IL-6 inhibitor tocilizumab was recently approved by the FDA for treatment of GCA.

The prognosis for properly treated GCA is good unless aortitis is present. GCA may recur. H

Polymyalgia Rheumatica

Epidemiology and Pathophysiology

Although not a vasculitis, polymyalgia rheumatica (PMR) is an inflammatory disorder that frequently accompanies GCA. PMR and GCA likely reflect the clinical spectrum of a single disease process, although PMR occurs 3 to 10 times more frequently. Up to 50% of patients presenting with GCA have PMR, and 20% of patients presenting with PMR have GCA symptoms on questioning.

Clinical Manifestations and Diagnosis

PMR is associated with pain and stiffness of the neck, shoulder, and hip girdle. Pain and stiffness are worse after immobility; 1 hour or more of morning stiffness is common. Inflammation is periarticular (bursitis and tenosynovitis). Synovitis in the hands and feet occasionally occurs. Constitutional symptoms and laboratory findings resemble GCA, but temporal artery biopsy should be performed only if GCA is suspected. Diagnosis of PMR is made clinically. Differential diagnosis includes myopathies, metabolic syndromes (thyroid and parathyroid), and musculoskeletal syndromes (capsulitis, cervical spondylosis, or calcium pyrophosphate deposition).

Management

PMR responds dramatically to low-dose prednisone (12.5-20 mg/d); lack of a rapid response should prompt consideration of alternate diagnoses. Prednisone taper is initiated 1 to 2 months after symptom resolution and requires months to years. Monitoring of recurrence is managed similarly to GCA. For relapses, recent guidelines for the management of PMR (developed by a collaborative effort of the American College of Rheumatology and the European League Against Rheumatism) recommend increasing the prednisone to the last pre-relapse dose at which the patient was doing well, followed by a gradual reduction within 4 to 8 weeks back to the relapse dose. Glucocorticoid-sparing therapies are the same as for GCA. Prognosis is good, although periodic recurrences are common.

Takayasu Arteritis

Epidemiology and Pathophysiology

Takayasu arteritis (TA) causes inflammation of the large vessels, most commonly the aorta, followed by the subclavian, common carotid, and renal arteries; the pulmonary arteries may also be involved. TA is rare (40/million in Japan and 4.7 to 8/million elsewhere). In contrast to GCA, TA predominantly affects younger women. Arterial lesions are often stenotic ("pulseless disease"), and one third contain aneurysms. Histopathology is similar to GCA.

Clinical Manifestations and Diagnosis

H

TA manifestations include carotodynia, limb claudication, reduced pulses, bruits, and blood pressure discrepancies between the arms. Heart failure related to aortic insufficiency or coronary artery disease may occur. Neurologic manifestations include transient ischemic attack, stroke, and mesenteric ischemia. As with GCA, laboratory studies are nonspecific and reveal anemia as well as elevated ESR and CRP. Angiogram may demonstrate arterial stenosis or aneurysm (**Figure 27**).

Management

Primary treatment of TA is high-dose glucocorticoids (1 mg/kg/d) with a slow taper. Glucocorticoid-sparing medications such as disease-modifying antirheumatic drugs are used but without clear evidence for efficacy. Angioplasty, graft placement, and bypass may be necessary but should be avoided during active inflammation. The leading cause of death is heart failure; stroke and cardiovascular disease also contribute to morbidity. The 10-year survival rate is 90%. H

FIGURE 27. Aortic angiogram from a patient with Takayasu arteritis. Note the high-grade stenosis of the proximal right subclavian artery (*white arrow*) as well as the left subclavian artery just below the origin of the left vertebral artery (*black arrow*). Incidentally noted is an anatomic variation with a common origin of the right brachiocephalic artery and the left common carotid artery.

KEY POINTS

- Giant cell arteritis should be suspected in a patient over the age of 50 years with new or atypical headache, jaw claudication, or visual changes.
- HVC Suspected giant cell arteritis should be treated immediately with prednisone because of the risk for visual loss; diagnosis is confirmed with temporal artery biopsy, as pathologic findings will persist for up to 2 weeks after initiation of prednisone.
- HVC Polymyalgia rheumatica is associated with pain and profound stiffness of the neck, shoulder, and hip girdle; it responds dramatically to low-dose prednisone.
- Takayasu arteritis occurs in younger women and causes inflammation of the aorta and other major noncranial vessels; manifestations include carotodynia, limb claudication, reduced pulses, bruits, and blood pressure discrepancies between the arms.

Medium-Vessel Vasculitis

Polyarteritis Nodosa

Epidemiology and Pathophysiology

Polyarteritis nodosa (PAN) is a rare systemic necrotizing vasculitis that affects medium and occasionally small arteries. Prevalence is 31/million but declining. PAN is more common in men than women. Average age of onset is 50 years.

Hepatitis B virus (HBV) infection has been strongly associated with PAN. However, the proportion of patients with HBV-associated PAN has declined from 36% to less than 5% since the advent of the HBV vaccine; thus, most contemporary cases are presumed autoimmune. Activated endothelial cells as well as increased interleukins, T cells, and macrophages have been identified as potential contributors to vessel damage.

Clinical Manifestations and Diagnosis

PAN most commonly affects the skin, neurologic, and musculoskeletal systems. It does not involve the lungs and rarely the heart. Kidney involvement is renovascular rather than glomerular. Cutaneous PAN is a variant confined to the skin. See **Table 40** for the clinical and laboratory findings of PAN.

The gold standard for diagnosis is focal segmental panmural necrotizing inflammation of a medium-sized vessel shown on biopsy. The biopsy is usually performed on an involved, easily accessible area, such as skin or a peripheral nerve/muscle. PAN may also be diagnosed on angiogram; mesenteric or renal arteries show characteristic aneurysms and stenosis, especially at branch points.

Management

H

Glucocorticoids and cyclophosphamide are indicated for severe organ-threatening disease; glucocorticoids and disease-modifying antirheumatic drugs are used for milder disease. HBV-associated PAN is treated with short-term glucocorticoids, antiviral medication, and plasmapheresis if necessary. The 5-year survival rate for treated PAN is 80%, and the relapse rate is 10% to 20%. H

Primary Angiitis of the Central Nervous System

Epidemiology and Pathophysiology

Primary angiitis of the central nervous system (PACNS) is a rare medium-vessel vasculitis of unknown cause that is confined to the central nervous system. Incidence is 2.4/100,000. Median age at onset is 50 years. There are three histologic

TABLE 40. Clinical Features of Polyarteritis Nodosa

Organ System	Symptoms	Frequency	Comments
Constitutional	Fever; malaise; weight loss	65%	—
Musculoskeletal	Arthralgia; myalgia	55%	—
Skin	Purpura; nodules; necrotic ulcers	50%-60%	—
Neurologic	Mononeuritis multiplex; peripheral neuropathy	79%	Wrist drop; foot drop
Kidney	Hypertension; hematuria; proteinuria	40%	Renal artery microaneurysms with tissue infarct/hematoma; no glomerulonephritis
Gastrointestinal	Mesenteric ischemia; intestinal perforation; pancreatitis; cholecystitis; appendicitis; gastrointestinal bleeding	38%	One third of gastrointestinal cases manifest as acute abdomen
Testicular	Orchitis	17%	Usually unilateral, due to testicular artery involvement
Other	Sensorineural hearing loss	Case reports	Bilateral; symmetric; sudden onset; rapidly progressive
Laboratory	Elevated erythrocyte sedimentation rate in 82%; elevated C-reactive protein; leukocytosis; anemia; thrombocytosis; increased liver chemistry tests in 33%	—	—

presentations, all with patchy distribution: granulomatous (58%), lymphocytic (28%), and necrotizing (14%).

H

Clinical Manifestations and Diagnosis

Patients with PACNS usually present with gradual and progressive symptoms of headache, cognitive impairment, neurologic deficits, transient ischemic attacks, and strokes. Laboratory studies are normal. Cerebrospinal fluid (CSF) is abnormal in 90%, with elevated protein, lymphocytic pleocytosis, and occasional oligoclonal bands. MRI shows nonspecific white and gray matter changes and infarcts. MR angiography and CT angiography have limited usefulness due to poor resolution. Cerebral angiogram may demonstrate vessel "beading" (alternating dilations and stenoses) but has limited sensitivity and specificity. Brain biopsy is the best test for diagnosis, but the patchy distribution of findings results in a 50% false-negative rate.

Evaluation centers on ruling out other conditions, including infection, malignancy, and reversible cerebral vasoconstriction syndrome. H

Management

PACNS is treated with high-dose glucocorticoids and cyclophosphamide. Patients often have permanent disability from neurologic damage, and the recurrence rate is 27%.

Kawasaki Disease

Kawasaki disease (KD) is a medium-vessel vasculitis that affects children and is very rare in adults. KD presents as fever, rash, cervical lymphadenopathy, conjunctival congestion, and mucositis. Coronary vessel vasculitis, aneurysm formation, and other cardiac complications (heart failure, pericarditis, arrhythmias) may develop. Treatment is with intravenous immunoglobulin and aspirin.

Many patients recover fully. However, coronary aneurysms may develop, and adults who had KD in childhood may suffer long-term cardiac sequelae. Chronic low-dose aspirin is indicated for coronary artery abnormalities. Clopidogrel may be added for cases with multiple aneurisms; warfarin prophylaxis is recommended for giant aneurysms.

KEY POINTS

- Polyarteritis nodosa most commonly affects the skin, neurologic, and musculoskeletal systems; the gold standard for diagnosis is focal segmental panmural necrotizing inflammation of a medium-sized vessel on biopsy.
- Patients with primary angiitis of the central nervous system usually present with gradual and progressive symptoms of headache, cognitive impairment, neurologic deficits, transient ischemic attacks, and strokes; treatment consists of high-dose glucocorticoids and cyclophosphamide.

(Continued)

KEY POINTS *(continued)*

- Kawasaki disease (KD) affects children; many patients recover fully, but coronary aneurysms may develop, and adults who had KD in childhood may suffer long-term cardiac sequelae.

Small-Vessel Vasculitis

ANCA-Associated Vasculitis

ANCA-associated vasculitis includes three diseases characterized by the presence of ANCA: granulomatosis with polyangiitis, microscopic polyangiitis, and eosinophilic granulomatosis with polyangiitis, along with ANCA-associated glomerulonephritis.

There are two types of vasculitis-associated ANCA: p-ANCA (perinuclear, directed against the neutrophil enzyme myeloperoxidase) and c-ANCA (cytoplasmic, directed against the neutrophil proteinase 3). Perinuclear and cytoplasmic refer to patterns of immunofluorescent staining; enzyme-linked immunosorbent assays are used to confirm antibody positivity.

ANCA may play a direct role in vessel damage by hyperactivating already primed neutrophils, leading to vessel endothelial inflammation and damage. The presence of granulomatous inflammation in some forms of ANCA-associated vasculitis suggests a role for cell-mediated immunity.

See **Table 41** for a comparison of the features of the three forms of ANCA-associated vasculitis.

See MKSAP 18 Nephrology for details on kidney involvement in ANCA-associated vasculitis.

Granulomatosis with Polyangiitis

Epidemiology and Pathophysiology

Granulomatosis with polyangiitis (GPA) is the most common ANCA-associated vasculitis, with an incidence of 7 to 12/million/year. It is more prevalent in Nordic countries and white persons. Typical age of onset is between 45 and 60 years.

Clinical Manifestations and Diagnosis

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GPA affects the upper and lower airways, kidneys, eyes, and ears. At least 50% of patients have constitutional symptoms. More than 95% of patients are ANCA positive, overwhelmingly (>90%) directed against proteinase 3 (anti-PR3 antibodies; c-ANCA).

GPA has two forms: systemic and localized. Systemic is more common, involves major organs, and is anti-PR3 positive. Localized has more granulomatous inflammation, has less vasculitis, and is less likely to be anti-PR3 positive. Patients in the localized group are more likely to be younger and female; have mainly ear, nose, and throat involvement; and be more prone to relapse. See Table 41 for GPA clinical features.

In the setting of a classic clinical presentation and positive c-ANCA/anti-PR3, diagnosis of GPA is straightforward. However, because of significant risks of treatment, biopsy of

TABLE 41. Clinical Features of ANCA-Associated Vasculitis Diseases

	Granulomatosis with Polyangiitis	Microscopic Polyangiitis	Eosinophilic Granulomatosis with Polyangiitis
ANCA	c-ANCA (antiproteinase-3 antibodies) (>95%)	p-ANCA (antimyeloperoxidase antibodies) (50%-75%)	p-ANCA (antimyeloperoxidase antibodies) (~50%)
Vascular Histology	Pauci-immune necrotizing granulomatous vasculitis	Pauci-immune nongranulomatous necrotizing vasculitis	Pauci-immune necrotizing granulomatous vasculitis with eosinophilic infiltration of vessel walls and tissues; extravascular granulomas
Cardiac	Pericarditis; myocarditis; conduction disorder (<10%)	—	Pericarditis; endomyocarditis; conduction disorder; heart failure (27%-47%)
Ears/Nose/Throat	Crusting; rhinorrhea; sinusitis; otitis media; chondritis of ears and nose with saddle nose deformity; septal perforation (70%-100%)	Sinusitis; sensorineural hearing loss (9%-30%)	Nasal polyps; rhinitis; sinusitis (prodromal)
Gastrointestinal	Ulceration; perforation (5%-11%)	Abdominal pain; bleeding (30%-58%)	Abdominal pain; bleeding
Kidney	Pauci-immune necrotizing glomerulonephritis (40%-100%)	Pauci-immune necrotizing glomerulonephritis (80%-100%)	Pauci-immune necrotizing glomerulonephritis (25%)
Lung	Alveolar hemorrhage; nodules; tracheal/subglottic stenosis (50%-90%)	Alveolar hemorrhage; pulmonary infiltrates; pulmonary fibrosis (25%-55%)	Asthma (prodromal, >90%); nodular opacities; infiltrates (25%-86%)
Ocular	Scleritis; episcleritis; retinal vasculitis; retro-orbital pseudotumor; dacryoadenitis (14%-60%)	—	—
Skin	Palpable purpura; nodules; pyoderma gangrenosum; mucosal ulcerations (10%-50%)	Palpable purpura; livedo reticularis; nodules; necrotic skin ulcers (30%-60%)	Palpable purpura; nodules (60%)
Neurologic	Mononeuritis multiplex, sensorimotor peripheral neuropathy (33%) Central nervous system involvement (pachymeningitis) (<5%)	Distal symmetric polyneuropathy; mononeuritis multiplex (37%-72%) Central nervous system pachymeningitis; cerebral hemorrhage; infarcts (<20%)	Sensorimotor peripheral neuropathy, mononeuritis multiplex (70%)

H CONT.

involved tissue is usually recommended. Histopathology of most tissues demonstrates pauci-immune necrotizing granulomatous vasculitis; pauci-immune necrotizing glomerulonephritis without granulomas is seen on kidney biopsy.

Management

For induction of remission in severe organ-threatening or life-threatening disease, treatment of GPA consists of high-dose glucocorticoids plus cyclophosphamide or rituximab, followed by maintenance therapy with azathioprine, mycophenolate mofetil, or rituximab for at least 12 to 24 months after stable remission has been achieved. Glucocorticoids alone are insufficient to control GPA. Patients with nonsevere forms of GPA (such as arthropathy or upper airway disease) without organ-threatening disease can be treated with glucocorticoids plus either methotrexate or mycophenolate mofetil; such patients should be carefully monitored for treatment failure or the development of renal or other organ-threatening disease, necessitating the more aggressive regimen. Using these approaches, GPA mortality has declined from 90% to around 10%.

Relapses are common (>50% 5 years after initial remission) and may respond better to rituximab than to cyclophosphamide.

Kidney failure and infection are the main causes of mortality. H

Microscopic Polyangiitis

Epidemiology and Pathophysiology

The incidence of microscopic polyangiitis (MPA) is estimated at 2.7 to 94/million/year in Europe and lower elsewhere. Average age at onset is between 50 to 60 years with a predilection of men over women (1.8:1). In contrast to GPA, ANCA are less prevalent (50%-75%) and tends to be directed against myeloperoxidase (MPO) rather than PR3.

Clinical Manifestations and Diagnosis

H

Like GPA, MPA characteristically affects the lungs and kidneys, along with other organ systems. See Table 41 for the clinical features of MPA. Diagnosis is suspected based upon typical clinical findings and positive ANCA, although negative ANCA

H CONT.

does not rule out the diagnosis. The diagnostic gold standard is a biopsy demonstrating nongranulomatous necrotizing pauci-immune vasculitis of small vessels or pauci-immune necrotizing crescentic glomerulonephritis in the kidney. Absence of granulomas distinguishes MPA from GPA.

Management

Like GPA, MPA treatment requires high-dose glucocorticoids plus either cyclophosphamide or rituximab, followed by maintenance therapy with azathioprine, mycophenolate mofetil, or rituximab. H

Prognosis is worse in the setting of pulmonary hemorrhage or rapidly progressive glomerulonephritis. Survival with treatment is 82% at 1 year and 76% at 5 years.

Eosinophilic Granulomatosis with Polyangiitis

Epidemiology and Pathophysiology

Eosinophilic granulomatosis with polyangiitis (EGPA) is the rarest ANCA-associated vasculitis, with an incidence of 0.11 to 2.66/million/year and a prevalence of 10 to 14/million (France). EGPA has no predisposition for gender or ethnicity. In addition to neutrophil activation, eosinophil infiltration, activation, and degranulation participate in the pathogenesis.

H

Clinical Manifestations and Diagnosis

The typical patient with EGPA has a history of asthma (96%-100%), nasal polyps, rhinitis, sinusitis, and/or atopy. A prodromal phase (months to years) consisting of arthralgia, myalgia, malaise, fever, and weight loss may occur. An eosinophilic phase with increased peripheral and tissue eosinophilia follows, with migratory pulmonary infiltrates and, less commonly, endomyocardial infiltration and gastrointestinal disease. The subsequent acute vasculitic phase includes mononeuritis multiplex or peripheral sensorimotor neuropathy (70%), kidney (25%), and skin involvement (60%). Paradoxically, the vasculitis phase is often associated with improvement of asthma. See Table 41 for the clinical features of EGPA.

Laboratory findings show peripheral eosinophilia of more than 10%, or more than 1500/µL (1.5×10^9/L). Only 50% of patients have a positive ANCA, mostly directed against MPO.

Diagnosis is based upon typical clinical findings, eosinophilia, and biopsy demonstrating fibrinoid necrosis and eosinophilic infiltration of vessel walls, as well as extravascular granuloma formation.

Management

In EGPA, glucocorticoids alone may be sufficient for mild disease without major organ involvement. With kidney, gastrointestinal, cardiac, or neurologic involvement, cyclophosphamide is indicated.

Mortality for EGPA is the lowest of all the forms of ANCA-associated vasculitis. The 5-year survival is 97%, and the relapse rate is 28%. H

KEY POINTS

- Granulomatosis with polyangiitis typically affects the upper and lower airways, kidneys, eyes, and ears; induction of remission in severe organ-threatening or life-threatening disease consists of high-dose glucocorticoids plus cyclophosphamide or rituximab, followed by maintenance therapy with azathioprine, mycophenolate mofetil, or rituximab.
- Microscopic polyangiitis commonly affects the lungs and kidneys; treatment requires high-dose glucocorticoids plus either cyclophosphamide or rituximab, followed by maintenance therapy with azathioprine, mycophenolate mofetil, or rituximab.
- Eosinophilic granulomatosis with polyangiitis is associated with asthma, nasal polyps, rhinitis, sinusitis, atopy, peripheral and tissue eosinophilia, migratory pulmonary infiltrates, and mononeuritis multiplex; treatment consists of glucocorticoids for mild disease, with cyclophosphamide added for more severe disease.

Immune Complex-Mediated Vasculitis

Immune complexes form from cross-linking of multiple antigens and antibodies. If not cleared, immune complexes deposit in tissue, leading to complement and neutrophil activation with inflammation and tissue damage. Although any tissue or organ may be affected, the classic finding is invariably in the skin. Inflammation and erythrocyte extravasation from involved vessels result in nonblanching palpable purpura, usually in dependent areas (**Figure 28**). Leukocytoclastic vasculitis refers to disintegration of nuclei (nuclear dust) of dead neutrophils along with fibrinoid necrosis of the vessel wall.

Cryoglobulinemic Vasculitis

Cryoglobulins can cause immune complex-mediated small-vessel vasculitis. There are three types of cryoglobulins;

FIGURE 28. Palpable purpura is the classic rash of any small-vessel, immune complex-mediated vasculitis. The lesions are nonblanching and represent extravasations of blood from damaged vessels. Purpuric lesions are typically more prominent on the lower extremities, a consequence of the superimposed effect of gravity on hydrostatic pressure.

discussion here is limited to types II and III ("mixed" types). Both are polyclonal, but type II cryoglobulins include a monoclonal IgM rheumatoid factor, whereas type III cryoglobulins include a polyclonal IgM rheumatoid factor. The ability of rheumatoid factor to directly bind other antibodies facilitates the formation of immune complexes even in the absence of persistent antigen. See MKSAP 18 Hematology and Oncology for details on cryoglobulins and the differentiation from cold agglutinin disease.

Epidemiology and Pathophysiology

Mixed cryoglobulinemia accounts for 85% to 90% of all cases; 90% of mixed cases are related to hepatitis C virus (HCV) infection, which can cause both type II and type III cryoglobulinemia. Autoimmune diseases such as systemic lupus erythematosus and Sjögren syndrome cause type III cryoglobulinemia. Onset is usually in the fifth decade, and women slightly outnumber men.

H

Clinical Manifestations and Diagnosis

Cutaneous symptoms (palpable purpura, Raynaud phenomenon, ulcers, necrosis, and livedo reticularis) predominate in 70% to 90% of patients with mixed cryoglobulinemia, but any organ may be involved. Peripheral neuropathy (60%), arthritis (40%), and glomerulonephritis (40%) are common. In addition to cryoglobulins, a low C4 complement and positive rheumatoid factor are present. A false-negative cryoglobulin result may occur if the serum sample is not maintained at 37.0 °C (98.6 °F) due to ex vivo cryoprecipitation at room temperature.

HCV infection associated with mixed cryoglobulinemia may go unrecognized for many years before the development of vasculitis. It is therefore important to test for HCV infection in patients with cryoglobulinemia.

Management

When possible, treatment of the underlying cause of cryoglobulinemia is the first priority. For HCV-related disease, antiviral medication is the primary therapy. For severe or refractory disease, the vasculitis must be independently addressed. Glucocorticoids and cyclophosphamide have been used in the past; plasmapheresis and rituximab (provided there is no hepatitis B virus infection) have demonstrated efficacy and may carry less toxicity. H

IgA Vasculitis

See MKSAP 18 Nephrology for information on IgA nephropathy and on kidney involvement in IgA vasculitis.

Epidemiology and Pathophysiology

IgA vasculitis (Henoch-Schönlein purpura) is a common vasculitis of childhood that occurs rarely in adults. Estimated incidence in adults is 14/million/year. Onset is often preceded by a viral or streptococcal upper respiratory infection.

H

Clinical Manifestations and Diagnosis

Patients with IgA vasculitis typically present with a palpable purpura in dependent areas. Gastrointestinal symptoms such as abdominal pain or bleeding (65%), arthritis and arthralgia (63%), and glomerulonephritis (40%) may be present. Although rare, life-threatening pulmonary hemorrhage may occur.

There are no specific laboratory tests for diagnosis; serum IgA may be elevated but is not sensitive or specific. Diagnosis is confirmed with biopsy. Skin biopsy demonstrates leukocytoclastic vasculitis with heavy deposits of IgA and complement on immunofluorescent staining. Renal histology is identical to IgA nephropathy.

Management

Although IgA vasculitis in children tends to be self-limited, adults are more likely to develop severe persistent disease, especially nephropathy, and may require glucocorticoids and cyclophosphamide. H

Hypersensitivity Vasculitis

Epidemiology and Pathophysiology

Hypersensitivity vasculitis is a small-vessel vasculitis mediated by immune complex deposition confined to the skin. It may be triggered by an antigen such as a drug or infection; in 50% of cases, the antigen is unknown.

Clinical Manifestations and Diagnosis

The most common presentation of hypersensitivity vasculitis is palpable purpura in dependent regions, developing 7 to 10 days after exposure to a triggering antigen; lesions appear in "crops" and resolve over a few weeks after the antigen is removed. Internal organs are unaffected. Skin biopsy with immunofluorescence demonstrates leukocytoclastic vasculitis without heavy IgA deposits. Evaluation should be guided by clinical signs and symptoms, and may only require a complete blood count, basic chemistries, and urinalysis.

Management

Removal of the antigen (if identified) and supportive care are usually sufficient. Resolution within a month is the rule. If symptoms persist or recur, anti-inflammatories, topical or low-dose systemic glucocorticoids, colchicine, or dapsone may be helpful.

KEY POINTS

- Mixed cryoglobulinemia is associated with cutaneous symptoms, peripheral neuropathy, arthritis, and glomerulonephritis, with 90% of cases related to hepatitis C virus infection; treatment of the underlying disorder causing cryoglobulinemia is required.
- IgA vasculitis (Henoch-Schönlein purpura) is characterized by palpable purpura and abdominal pain/bleeding and occurs mainly in children; adult disease is rare but more likely to be severe and/or persistent and to require glucocorticoids and cyclophosphamide.

(Continued)

KEY POINTS *(continued)*

- The most common presentation of hypersensitivity vasculitis is palpable purpura, developing 7 to 10 days after exposure to a triggering antigen; removal of the antigen and supportive care are usually sufficient management.

Other Rheumatologic Diseases

Behçet Syndrome

Behçet syndrome is a systemic disease associated with inflammatory infiltration of multiple organs, as well as small-vessel vasculitis and large-vessel vasculopathy. The characteristic clinical features are recurrent painful oral and genital mucosal ulcerations (**Figure 29**) and inflammatory eye disease (panuveitis, retinal vasculitis). A characteristic clinical finding is pathergy, an inflamed papular or pustular response to local skin injury that is clinically defined by similar lesions appearing 48 hours after skin prick with a sterile needle (**Figure 30**).

FIGURE 29. Recurrent, painful genital mucosal ulcerations are a characteristic clinical feature of Behçet syndrome. In women, they typically appear on the vulva, as shown, and may heal with disfiguring scaring.

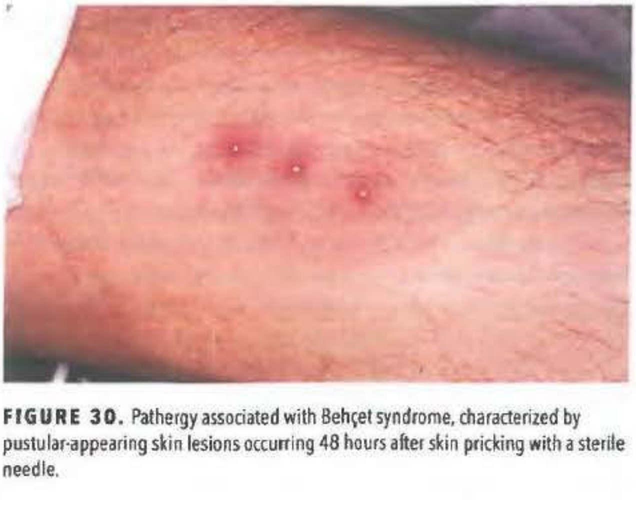

FIGURE 30. Pathergy associated with Behçet syndrome, characterized by pustular-appearing skin lesions occurring 48 hours after skin pricking with a sterile needle.

Other clinical manifestations include venous thrombosis that may affect the large veins, including the vena cava and the dural venous sinuses. Central nervous system (CNS) manifestations include brainstem lesions and aseptic meningitis; the most common CNS symptoms are headache and diplopia. Inflammatory arthritis (usually in the knees), skin lesions, and gastrointestinal inflammation/ulceration indistinguishable from inflammatory bowel disease also occur. Diagnostic criteria are listed in **Table 42**.

Behçet syndrome is most common in Asia, with the highest reported prevalence in Turkey; it is much less common in North America. It is slightly more prevalent in men than women, and men usually have more severe disease. HLA-B51 is strongly associated with the disease and is seen in patients with varied ethnicity.

Treatment for mild disease includes colchicine and low-dose glucocorticoids. The phosphodiesterase-4 inhibitor apremilast appears to be beneficial for oral ulcers. High-dose glucocorticoids and immunosuppressives such as cyclosporine and azathioprine are used for more severe disease. Interferon alfa and tumor necrosis factor (TNF)-α inhibitors may be used for refractory disease. Interleukin (IL)-1 and IL-6 inhibitors have been reported to be beneficial.

KEY POINT

- Behçet syndrome is characterized by recurrent painful oral and genital mucosal ulcerations, inflammatory eye disease, and pathergy.

Relapsing Polychondritis

Relapsing polychondritis (RP) is a rare autoimmune disease characterized by inflammation and damage of cartilaginous tissues. Anti-type II collagen antibodies have been identified, but a role in pathogenesis has not been established. RP can be primary or associated with other autoimmune diseases, particularly ANCA-associated vasculitis, Behçet syndrome, and antiphospholipid syndrome. Onset usually occurs between the ages of 40 and 50 years.

TABLE 42. International Criteria for Behçet Disease

Manifestations	Points[a]
Oral ulcers	2
Genital ulcers	2
Pathergy	1
Skin lesions (pseudofolliculitis; skin ulcers; erythema nodosum)	1
Eye lesions (anterior uveitis; posterior uveitis; retinal vasculitis)	2
Central nervous system lesions	1
Vascular lesions (arterial thrombosis; large vein thrombosis; phlebitis)	1

[a]Four or more points are needed for the diagnosis of Behçet syndrome.

Tissues affected include the cartilaginous portions of the external and middle ear (90%), nose (60%), tracheobronchial tree (50%), and joints (65%). Inflammation of noncartilaginous connective tissue also occurs, particularly uveitis and keratitis (65%). Cochlear and/or vestibular dysfunction may rarely occur (10%). Elevated inflammatory markers, anemia, antinuclear antibodies, and other autoantibodies are often observed but are nonspecific. Cartilage biopsy, which is necessary only with atypical presentations in which there is substantial diagnostic uncertainty, typically demonstrates inflammatory cell infiltration of the perichondrium. CT can demonstrate bronchial thickening, strictures, malacia, and air trapping.

Therapy is guided by organ involvement and disease severity. Mild disease may respond to NSAIDs, colchicine, or dapsone. Glucocorticoids and disease-modifying antirheumatic drugs (DMARDs) such as cyclosporine, azathioprine, or methotrexate are used for more severe disease. Biologic drugs such as TNF-α inhibitors have been reported as effective but not on a consistent basis. Surgery (stenting, dilation, extirpation, reconstruction) for airway lesions may be necessary.

KEY POINT

- Relapsing polychondritis is characterized by inflammation and damage of cartilaginous tissues; tissues most commonly affected include the cartilaginous portions of the external and middle ear, nose, tracheobronchial tree, and joints.

Adult-Onset Still Disease

H Adult-onset Still disease (AOSD) is a rare disorder that affects multiple organ systems. Symptoms and signs include daily high spiking fever, evanescent salmon-colored rash on the trunk and extremities, arthritis, lymphadenopathy, and leukocytosis. It is most commonly diagnosed in young adults (median age, 36 years) but has been described in older age groups. Some reports indicate a predilection for women. The cause is unknown, but AOSD appears to be a disease of autoinflammation rather than autoimmunity.

See **Table 43** for diagnostic criteria. Diagnosis is clinical, and other infectious, neoplastic, and rheumatologic diseases must be excluded. Rare complications include hemophagocytic lymphohistiocytosis, myocarditis, shock, multiple organ failure, disseminated intravascular coagulation, thrombotic microangiopathy, and fulminant hepatitis. H

Treatment includes NSAIDs, glucocorticoids, DMARDs such as methotrexate, and IL-1 inhibitors. TNF-α and IL-6 inhibitors may be beneficial, but more studies are needed to establish their efficacy. Most patients respond to therapy, and prognosis of AOSD with treatment is good.

KEY POINT

- Adult-onset Still disease is characterized by daily high spiking fever, evanescent salmon-colored rash, arthritis, lymphadenopathy, and leukocytosis.

TABLE 43. Yamaguchi Criteria for the Diagnosis of Adult-Onset Still Disease

Major Criteria[a]	Approximate Frequency
Daily spiking fever to 39.0 °C (102.2 °F)	99%
Arthralgia/arthritis >2 weeks	85%
Nonpruritic salmon-colored macular/maculopapular rash on trunk or extremities	85%
Leukocyte count >10,000/µL (10×10^9/L), >80% neutrophils	90%
Minor Criteria	**Approximate Frequency**
Sore throat	66%
Lymphadenopathy and/or splenomegaly	65%/50%
Elevated AST, ALT, or LDH	70%
Negative ANA and RF	—

ALT = alanine aminotransferase; ANA = antinuclear antibodies; AST = aspartate aminotransferase; LDH = lactate dehydrogenase; RF = rheumatoid factor.

[a]Diagnosis requires five criteria with at least two major criteria included.

Adapted with permission from Yamaguchi M, Ohta A, Tsunematsu T, Kasukawa R, Mizushima Y, Kashiwagi H, et al. Preliminary criteria for classification of adult Still's disease. J Rheumatol. 1992 Mar;19(3):424-30. [PMID: 1578458] Copyright 1992, the Journal of Rheumatology.

Autoinflammatory Diseases

Autoinflammatory diseases (periodic fever syndromes) are a category of rare monogenic conditions characterized by episodic and/or persistent inflammation in the absence of antigenically driven autoimmunity. Pathogenesis involves dysregulation of the innate immune system. The innate immune system represents a process separate and distinct from the antigen-based immune response modulated by lymphocytes. Rather than adaptively responding to antigens, the innate immune system responds to stimuli that it "innately knows" to mandate a response. Examples of such stimuli are "pathogen-associated molecular patterns" such as bacterial cell wall proteins and "damage-associated molecular patterns" or markers of cellular damage such as released uric acid. This process is largely regulated by "inflammasomes," large protein structures that recognize these stimuli. Autoinflammatory diseases involve inherited or spontaneous mutation of genes that encode for inflammasomes, including components of the IL-1β-activating inflammasome and the TNF-α receptor pathway.

See **Table 44** for the features and treatment of select autoinflammatory diseases.

KEY POINT

- Autoinflammatory diseases are characterized by episodic and/or persistent inflammation and involve inherited or spontaneous mutation of genes that encode for inflammasomes.

TABLE 44. Features and Treatment of Select Autoinflammatory Diseases

	FMF[a]	TRAPS	FCAS[b]	MWS[b]	NOMID/ CINCA[b]	Schnitzler Syndrome
Inheritance	AR	AD	AD	AD	AD	Acquired
Gene	*MEFV*	*TNFRSF1A*	*NLRP3*	*NLRP3*	*NLRP3*	Unknown
Protein	Pyrin	TNF receptor type 1	Cryopyrin	Cryopyrin	Cryopyrin	MGUS (hallmark but not proven causal)
Age at Onset	65% <10 years of age; 90% <20 years of age	50% <10 years of age; up to fifth decade	<1 year of age	Childhood	Neonatal period	Adult (51 ± 10 years)
Ethnicity	Mediterranean	All	European	European	All	Caucasian/European
Clinical Manifestations						
Attack Duration	12-72 h	Days to weeks	12-24 h	1-2 days	Continuous	Daily
Abdominal	Pain; serositis	Pain; serositis	Nausea	Pain	—	—
Pleuritis	Common	Common	—	Rare	Rare	—
Musculoskeletal	Monoarthritis of lower extremities	Large joints	Arthralgia	Arthralgia; oligoarthritis	Epiphyseal overgrowth; contractures	Arthralgia; arthritis; bone pain
Rash	Erysipeloid on lower legs	Migratory with underlying myalgia	Cold-induced; urticaria-like	Urticaria-like	Urticaria-like	Urticarial rash; neutrophilic
Other	High risk for amyloidosis	Conjunctivitis; periorbital edema	Conjunctivitis; headache; amyloidosis; sensorineural deafness	Sensorineural deafness; conjunctivitis; amyloidosis	Sensorineural deafness; aseptic meningitis; mental retardation; amyloidosis	Leukocytosis; lymphadenopathy; hepatospleno-megaly; MGUS (usually IgM kappa); may later develop Waldenstrom macroglobulinemia
Treatment	Colchicine	Glucocorticoids; TNF-α inhibitors	IL-1β inhibition	IL-1β inhibition	IL-1β inhibition	IL-1Ra or IL-1β inhibition

AD = autosomal dominant; AR = autosomal recessive; CINCA = chronic infantile neurologic, cutaneous, articular syndrome; FCAS = familial cold autoinflammatory syndrome; FMF = familial Mediterranean fever; IL = interleukin; IL-1Ra = interleukin-1 receptor antagonist; MGUS = monoclonal gammopathy of uncertain significance; MWS = Muckle-Wells syndrome; NOMID = neonatal-onset multisystem inflammatory disease; TNF = tumor necrosis factor; TRAPS = tumor necrosis factor receptor-associated periodic syndrome.

[a]FMF is the most common autoinflammatory disease.

[b]The cryopyrin-associated periodic syndromes (CAPS) include familial cold autoinflammatory syndrome, Muckle-Wells syndrome, and neonatal-onset multisystem inflammatory disease (chronic infantile neurologic, cutaneous, articular syndrome).

Sarcoidosis

Sarcoidosis is an inflammatory disease of unknown cause characterized by formation of noncaseating granulomas in multiple organs and tissues. Sarcoidosis most commonly affects the lungs, which is discussed in MKSAP 18 Pulmonary and Critical Care Medicine. Rheumatologic manifestations are discussed in this section.

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In patients with sarcoidosis, a periarthritis involving multiple joints may occur, typically affecting the ankles but also potentially the knees, wrists, and small joints of the hands and feet. Erosive damage, deformity, and dactylitis may develop. Bone involvement has been reported in 1% to 15% of patients; it most commonly accompanies multiorgan disease and is associated with a chronic disease course and poorer prognosis. Typical radiographic findings include cystic or sclerotic lesions and a lacy pattern of multiple lesions (**Figure 31**). Sarcoid myopathy is histologically present in 25% to 75% of patients but is symptomatic in only 0.5% to 5%. The most common clinical presentation is chronic proximal weakness with development of atrophy or contractures. Biopsy may show inflammatory muscle disease or destruction of muscle by granuloma formation. Glucocorticoids, DMARDs, and TNF-α inhibitors may be used to treat arthritis, bone disease, and myopathy.

Rarely, sarcoidosis can cause Heerfordt syndrome (uveoparotid fever), a combination of fever, uveitis, and parotitis with or without cranial nerve VII palsy. This can lead to sicca symptoms and can mimic Sjögren syndrome.

Löfgren syndrome is a sarcoidosis triad of bilateral hilar lymphadenopathy, erythema nodosum, and migratory

FIGURE 31. Hand radiograph showing the typical cystic lesions (*red arrow*) and a lacy pattern (*green arrow*) characteristic of sarcoidosis.

H CONT.

polyarthralgia. Fever is frequently present. When all three parts of the triad are present, there is a 95% diagnostic specificity for sarcoidosis, obviating the need for biopsy. Löfgren syndrome has a good prognosis and usually remits in 2 to 16 weeks. The goal of treatment is symptom reduction; NSAIDs are usually adequate, but low-dose glucocorticoids, colchicine, and hydroxychloroquine can all be helpful. H

KEY POINTS

- Rheumatologic manifestations of sarcoidosis include arthritis involving multiple joints that may develop erosive damage, deformity, and dactylitis; bone disease; and myopathy.

(Continued)

KEY POINTS *(continued)*

- Löfgren syndrome is a sarcoidosis triad of bilateral hilar lymphadenopathy, erythema nodosum, and migratory polyarthralgia; the presence of all three findings has a 95% diagnostic specificity for sarcoidosis. **HVC**

Genetic Diseases of Connective Tissue

Mutations in genes encoding for collagen, fibrillin, and other components of connective tissue can lead to poorly functional skin and integument. Common clinical findings include skin and joint laxity, skeletal fractures, and cardiovascular complications related to involvement of the aorta and cardiac valves. The three most common syndromes are Ehlers-Danlos syndrome (EDS), Marfan syndrome (MFS), and osteogenesis imperfecta (OI). See **Table 45** for a summary of clinical findings and management of these syndromes.

Vascular monitoring is necessary in MFS and several types of EDS. Patients with MFS should undergo echocardiography to assess the aortic root and ascending aorta at the time of diagnosis and at 6 months to ensure stability. Follow-up studies should be completed at least annually; MRI and/or CT are often used to further delineate risk. The best means of vascular surveillance in vascular EDS is unclear, and all patients should undergo expert consultation. See MKSAP 18 Cardiovascular Medicine for more information.

KEY POINTS

- Common clinical findings of genetic diseases of connective tissue include skin and joint laxity, skeletal fractures, and cardiovascular complications related to involvement of the aorta and cardiac valves.
- Regular vascular monitoring is required for patients with Marfan syndrome and several types of Ehlers-Danlos syndrome.

IgG4-Related Disease

Several previously ill-defined illnesses have been brought under the banner of IgG4-related disease (IgG4-RD) (**Table 46**). Most of these conditions are characterized by infiltration and tumefaction of the affected tissue with resultant organ enlargement, fibrosis, and dysfunction. Patients commonly present with a sentinel organ enlargement, but careful evaluation often reveals more extensive disease.

Currently, IgG4 is hypothesized not to be pathologic, but instead to act as a blocking antibody in patients with atopic disease, preventing allergens from interacting with IgE on mast cell surfaces. Consistent with this model, IgG4 elevations accompany loss of clinical responses to allergens in atopic individuals.

TABLE 45. Findings and Management of Genetic Diseases of Connective Tissue

	Ehlers-Danlos Syndrome				Marfan Syndrome	Osteogenesis Imperfecta
	Hypermobility	**Classic**	**Kyphoscoliotic**	**Vascular**		
Genetic Testing Available	Gene is unknown	*COL5A1*; *COL5A2*	*PLOD1*	*COL3A1*	*FBN1*	*COL*
Inheritance	AD	AD	AR	AD	AD	AD or AR
Clinical Findings						
Musculoskeletal	Joint laxity; joint instability; musculoskeletal pain; early osteoarthritis	Hypermobility; joint dislocations; pes planus	Hypermobility; progressive scoliosis; marfanoid habitus	Hypermobility; joint dislocations	Hypermobility; tall stature; dolichostenomelia[a]; arachnodactyly; pectus excavatum/carinatum; scoliosis	Bone fractures; short stature
Skin	Easy bruising; mild laxity	Smooth, velvety; easy bruising; hyperextensible; striae atrophicae (widened stretch marks)	Easy bruising; hyperextensible	Thin; translucent; easy bruising	Hyperextensible	—
Cardiovascular	No risk of organ rupture or dissection	Mitral/tricuspid valve prolapse; aortic root dilation (rare); arterial rupture (rare)	Medium-size arterial rupture; mitral/tricuspid valve prolapse	Arterial rupture; aneurysm; dissection	Aortic aneurysm/dissection; mitral valve prolapse	—
Other	—	Muscular hypotonia; delayed motor development	Muscular hypotonia; scleral fragility with risk of globe rupture; restrictive lung disease; recurrent pneumonia; heart failure	Organ rupture (uterus, bowel, rarely spleen, liver); pneumothorax; gingival recession	Myopia (most common feature [60%]); ectopia lentis; high arched palate; pneumothorax; blue sclerae	Dentinogenesis imperfecta[b]; hearing loss; blue sclerae
Management[c]	Joint protection; supportive care	Joint protection; echo/vascular monitoring; preconception counseling	Joint protection; echo/vascular monitoring; preconception counseling; physical therapy; bracing	Joint protection; echo/vascular monitoring; preconception counseling	Annual ophthalmic examination; periodic aortic arch imaging; β-blockers[d]; joint protection; pregnancy counseling/monitoring	Bisphosphonates; audiology assessments; joint and bone protection; dental evaluations

AD = autosomal dominant; AR = autosomal recessive.

[a]Dolichostenomelia describes when the extremities are disproportionately long for the size of the trunk.

[b]Dentinogenesis imperfecta is defined as discolored (blue/gray or yellow/brown), translucent, weak teeth prone to breakage.

[c]Genetic consultation is appropriate for all listed conditions.

[d]Slow rate of aortopathy.

Most patients with IgG4-RD are men over the age of 50 years; history of atopic disease is common. Clinical signs include painless enlargement of lymph nodes or the thyroid, parotid, or submandibular glands; proptosis with orbital pseudo-tumor; back or chest pain from aortic involvement; and abdominal pain from pancreatic or biliary tree disease. Systemic symptoms such as fever or weight loss are uncommon.

IgG4-RD can affect vascular structures directly, including the carotid, pulmonary, coronary, and iliac arteries as well as the aorta, in particular the thoracic aorta. The affected vessels can develop aneurysms, dissection, and stenosis. A periarteritis

TABLE 46. Select Conditions Associated with IgG4-Related Disease

Condition	Organ Involved
Hypertrophic pachymeningitis	Dura mater
Lymphocytic hypophysitis	Pituitary gland
Idiopathic orbital inflammatory disease	Periorbital often with involvement of the ocular adnexal tissues
Mikulicz disease	Parotid glands
Dacryoadenitis	Lacrimal glands
Küttner tumor	Submandibular glands
Riedel thyroiditis	Thyroid
Inflammatory aortitis/ vasculitis	Aorta/arteries
Autoimmune pancreatitis	Pancreas
Ormond disease (retroperitoneal fibrosis)	Periaortic mass
Tubulointerstitial nephropathy	Kidneys
Sclerosing cholangitis	Biliary tract

primarily affecting the infrarenal aorta in conjunction with retroperitoneal fibrosis may also develop.

Diagnosis is by tissue biopsy, which demonstrates a dense lymphoplasmacytic infiltrate, CD4-positive T cells and plasma cells in germinal centers, IgG4-staining plasma cells, storiform fibrosis, obliterative phlebitis or arteritis, and tissue eosinophilia.

IgG4 levels are elevated in the serum in 70% to 80% of patients; therefore, a normal serum level does not rule out the disease. A ratio of the IgG4 level to total IgG of more than 8% is suggestive of the diagnosis. PET scan can identify involvement that is not clinically apparent and can be used to document response.

Initial treatment is prednisone, 0.5-0.6 mg/kg/d, for 2 to 4 weeks with a slow taper over 3 to 6 months; some experts advocate subsequent low-dose (5 mg/d) therapy for several years. Rituximab has shown significant benefit and appears to affect IgG4 production more than other IgG subtypes. Methotrexate may be a useful agent to maintain remission in patients treated with prednisone or rituximab. Azathioprine and mycophenolate mofetil have also been used as glucocorticoid-sparing agents. Treatment response may be influenced by the amount of fibrosis present prior to therapy initiation.

See MKSAP 18 Gastroenterology and Hepatology for information on IgG4-related pancreatitis.

KEY POINT

- The conditions comprising IgG4-related disease are characterized by infiltration and tumefaction of the affected tissue with resultant organ enlargement, fibrosis, and dysfunction; diagnosis is by tissue biopsy.

Bibliography

Approach to the Patient with Rheumatologic Disease

Brown AK. How to interpret plain radiographs in clinical practice. Best Pract Res Clin Rheumatol. 2013;27:249-69. [PMID: 23731934] doi:10.1016/j.berh.2013.03.004

Castro C, Gourley M. Diagnostic testing and interpretation of tests for autoimmunity. J Allergy Clin Immunol. 2010;125:S238-47. [PMID: 20061009] doi:10.1016/j.jaci.2009.09.041

Colglazier CL, Sutej PG. Laboratory testing in the rheumatic diseases: a practical review. South Med J. 2005;98:185-91. [PMID: 15759949]

Courtney P, Doherty M. Joint aspiration and injection and synovial fluid analysis. Best Pract Res Clin Rheumatol. 2013 Apr;27(2):137-69. [PMID: 23731929]

Iagnocco A, Ceccarelli F, Perricone C, Gattamelata A, Finucci A, Ricci F, et al. The use of musculoskeletal ultrasound in a rheumatology outpatient clinic. Med Ultrason. 2014;16:332-5. [PMID: 25463887]

Man A, Shojania K, Phoon C, Pal J, de Badyn MH, Pi D, et al. An evaluation of autoimmune antibody testing patterns in a Canadian health region and an evaluation of a laboratory algorithm aimed at reducing unnecessary testing. Clin Rheumatol. 2013;32:601-8. [PMID: 23292519] doi:10.1007/s10067-012-2141-y

Qaseem A, Alguire P, Dallas P, Feinberg LE, Fitzgerald FT, Horwitch C, et al. Appropriate use of screening and diagnostic tests to foster high-value, cost-conscious care. Ann Intern Med. 2012;156:147-9. [PMID: 22250146] doi:10.7326/0003-4819-156-2-201201170-00011

Yazdany J, Schmajuk G, Robbins M, Daikh D, Beall A, Yelin E, et al; American College of Rheumatology Core Membership Group. Choosing wisely: the American College of Rheumatology's top 5 list of things physicians and patients should question. Arthritis Care Res (Hoboken). 2013;65:329-39. [PMID: 23436818] doi:10.1002/acr.21930

Principles of Therapeutics

Cheng L, Xiong Y, Qin CZ, Zhang W, Chen XP, Li J, et al. HLA-B*58:01 is strongly associated with allopurinol-induced severe cutaneous adverse reactions in Han Chinese patients: a multicentre retrospective case-control clinical study [Letter]. Br J Dermatol. 2015;173:555-8. [PMID: 26104483] doi:10.1111/bjd.13688

da Costa BR, Reichenbach S, Keller N, Nartey L, Wandel S, Jüni P, et al. Effectiveness of non-steroidal anti-inflammatory drugs for the treatment of pain in knee and hip osteoarthritis: a network meta-analysis. Lancet. 2017;390:e21-e33. [PMID: 28699595] doi:10.1016/S0140-6736(17)31744-0

Hochberg MC, Altman RD, April KT, Benkhalti M, Guyatt G, McGowan J, et al; American College of Rheumatology. American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. Arthritis Care Res (Hoboken). 2012;64:465-74. [PMID: 22563589]

Hwang YG, Saag K. The safety of low-dose glucocorticoids in rheumatic diseases: results from observational studies. Neuroimmunomodulation. 2015;22:72-82. [PMID: 25228230] doi:10.1159/000362727

Kavanaugh A, Mease PJ, Gomez-Reino JJ, Adebajo AO, Wollenhaupt J, Gladman DD, et al. Treatment of psoriatic arthritis in a phase 3 randomised, placebo-controlled trial with apremilast, an oral phosphodiesterase 4 inhibitor. Ann Rheum Dis. 2014;73:1020-6. [PMID: 24595547] doi:10.1136/annrheumdis-2013-205056

Kroon FP, van der Burg LR, Ramiro S, Landewé RB, Buchbinder R, Falzon L, et al. Non-steroidal anti-inflammatory drugs (NSAIDs) for axial spondyloarthritis (ankylosing spondylitis and non-radiographic axial spondyloarthritis). Cochrane Database Syst Rev. 2015:CD010952. [PMID: 26186173] doi:10.1002/14651858.CD010952.pub2

McGrory BJ, Weber KL, Jevsevar DS, Sevarino K. Surgical management of osteoarthritis of the knee: evidence-based guideline. J Am Acad Orthop Surg. 2016;24:e87-93. [PMID: 27355286] doi:10.5435/JAAOS-D-16-00159

McInnes IB, Mease PJ, Kirkham B, Kavanaugh A, Ritchlin CT, Rahman P, et al; FUTURE 2 Study Group. Secukinumab, a human anti-interleukin-17A monoclonal antibody, in patients with psoriatic arthritis (FUTURE 2): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2015;386:1137-46. [PMID: 26135703] doi:10.1016/S0140-6736(15)61134-5

Mielenz TJ, Xiao C, Callahan LF. Self-management of arthritis symptoms by complementary and alternative medicine movement therapies. J Altern Complement Med. 2016;22:404-7. [PMID: 27058260] doi:10.1089/acm.2015.0222

Mok CC, Ying KY, Yim CW, Siu YP, Tong KH, To CH, et al. Tacrolimus versus mycophenolate mofetil for induction therapy of lupus nephritis: a randomised controlled trial and long-term follow-up. Ann Rheum Dis. 2016;75:30-6. [PMID: 25550339] doi:10.1136/annrheumdis-2014-206456

Omair MA, Alahmadi A, Johnson SR. Safety and effectiveness of mycophenolate in systemic sclerosis. A systematic review. PLoS One. 2015;10:e0124205. [PMID: 25933090] doi:10.1371/journal.pone.0124205

Singh JA, Saag KG, Bridges SL Jr, Akl EA, Bannuru RR, Sullivan MC, et al. 2015 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. Arthritis Rheumatol. 2016;68:1-26. [PMID: 26545940] doi:10.1002/art.39480

van der Goes MC, Jacobs JW, Bijlsma JW. The value of glucocorticoid co-therapy in different rheumatic diseases-positive and adverse effects. Arthritis Res Ther. 2014:16 Suppl 2:S2. [PMID: 25608693] doi:10.1186/ar4686

Wang C, Schmid CH, Iversen MD, Harvey WF, Fielding RA, Driban JB, et al. Comparative effectiveness of tai chi versus physical therapy for knee osteoarthritis: a randomized trial. Ann Intern Med. 2016;165:77-86. [PMID: 27183035] doi:10.7326/M15-2143

Rheumatoid Arthritis

Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO 3rd, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum. 2010;62:2569-81. [PMID: 20872595] doi:10.1002/art.27584

Bakker MF, Jacobs JW, Welsing PM, Verstappen SM, Tekstra J, Ton E, et al; Utrecht Rheumatoid Arthritis Cohort Study Group. Low-dose prednisone inclusion in a methotrexate-based, tight control strategy for early rheumatoid arthritis: a randomized trial. Ann Intern Med. 2012;156:329-39. [PMID: 22393128] doi:10.7326/0003-4819-156 5-201203060-00004

Moreland LW, O'Dell JR, Paulus HE, Curtis JR, Bathon JM, St Clair EW, et al; TEAR Investigators. A randomized comparative effectiveness study of oral triple therapy versus etanercept plus methotrexate in early aggressive rheumatoid arthritis: the treatment of Early Aggressive Rheumatoid Arthritis Trial. Arthritis Rheum. 2012;64:2824-35. [PMID: 22508468] doi:10.1002/art.34498

Scher JU, Littman DR, Abramson SB. Microbiome in Inflammatory Arthritis and Human Rheumatic Diseases. Arthritis Rheumatol. 2016;68:35-45. [PMID: 26331579] doi:10.1002/art.39259

Schiff MH, Jaffe JS, Freundlich B. Head-to-head, randomised, crossover study of oral versus subcutaneous methotrexate in patients with rheumatoid arthritis: drug-exposure limitations of oral methotrexate at doses ~15 mg may be overcome with subcutaneous administration. Ann Rheum Dis. 2014;73:1549-51. [PMID: 24728329] doi:10.1136/annrheumdis-2014-205228

Singh JA, Saag KG, Bridges SL Jr, Akl EA, Bannuru RR, Sullivan MC, et al. 2015 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. Arthritis Rheumatol. 2016;68:1-26. [PMID: 26545940] doi:10.1002/art.39480

Smolen JS, Aletaha D, McInnes IB. Rheumatoid arthritis. Lancet. 2016;388:2023-2038. [PMID: 27156434] doi:10.1016/S0140-6736(16)30173-8

Soubrier M, Barber Chamoux N, Tatar Z, Couderc M, Dubost JJ, Mathieu S. Cardiovascular risk in rheumatoid arthritis. Joint Bone Spine. 2014;81:298-302. [PMID: 24880190] doi:10.1016/j.jbspin.2014.01.009

Stoffer MA, Schoels MM, Smolen JS, Aletaha D, Breedveld FC, Burmester G, et al. Evidence for treating rheumatoid arthritis to target: results of a systematic literature search update. Ann Rheum Dis. 2016:75:16-22. [PMID: 25990290] doi:10.1136/annrheumdis-2015-207526

Osteoarthritis

Bannuru RR, Schmid CH, Kent DM, Vaysbrot EE, Wong JB, McAlindon TE. Comparative effectiveness of pharmacologic interventions for knee osteoarthritis: a systematic review and network meta-analysis. Ann Intern Med. 2015;162:46-54. [PMID: 25560713] doi:10.7326/M14-1231

da Costa BR, Reichenbach S, Keller N, Nartey L, Wandel S, Jüni P, et al. Effectiveness of non-steroidal anti-inflammatory drugs for the treatment of pain in knee and hip osteoarthritis: a network meta-analysis. Lancet. 2017;390:e21-e33. [PMID: 28699595] doi:10.1016/S0140-6736(17)31744-0

Derry S, Moore RA, Rabbie R. Topical NSAIDs for chronic musculoskeletal pain in adults. Cochrane Database Syst Rev. 2012:CD007400. [PMID: 22972108] doi:10.1002/14651858.CD007400.pub2

Fernandes L, Hagen KB, Bijlsma JW, Andreassen O, Christensen P, Conaghan PG, et al; European League Against Rheumatism (EULAR). EULAR recommendations for the non-pharmacological core management of hip and knee osteoarthritis. Ann Rheum Dis. 2013;72:1125 35. [PMID: 23595142] doi:10.1136/annrheumdis-2012-202745

Fransen M, McConnell S, Harmer AR, Van der Esch M, Simic M, Bennell KL. Exercise for osteoarthritis of the knee. Cochrane Database Syst Rev. 2015;1:CD004376. [PMID: 25569281] doi:10.1002/14651858.CD004376.pub3

Hochberg MC, Altman RD, April KT, Benkhalti M, Guyatt G, McGowan J, et al; American College of Rheumatology. American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. Arthritis Care Res (Hoboken). 2012;64:465-74. [PMID: 22563589]

McAlindon TE, Bannuru RR, Sullivan MC, Arden NK, Berenbaum F, Bierma-Zeinstra SM, et al. OARSI guidelines for the non-surgical management of knee osteoarthritis. Osteoarthritis Cartilage. 2014;22:363-88. [PMID: 24462672] doi:10.1016/j.joca.2014.01.003

McAlindon TE, LaValley MP, Harvey WF, Price LL, Driban JB, Zhang M, et al. Effect of intra-articular triamcinolone vs saline on knee cartilage volume and pain in patients with knee osteoarthritis: a randomized clinical trial. JAMA. 2017:317:1967-1975. [PMID: 28510679] doi:10.1001/jama.2017.5283

Machado GC, Maher CG, Ferreira PH, Pinheiro MB, Lin CW, Day RO, et al. Efficacy and safety of paracetamol for spinal pain and osteoarthritis: systematic review and meta-analysis of randomised placebo controlled trials. BMJ. 2015:350:h1225. [PMID: 25828856] doi:10.1136/bmj.h1225

Messier SP, Mihalko SL, Legault C, Miller GD, Nicklas BJ, DeVita P, et al. Effects of intensive diet and exercise on knee joint loads, inflammation, and clinical outcomes among overweight and obese adults with knee osteoarthritis: the IDEA randomized clinical trial. JAMA. 2013;310:1263-73. [PMID: 24065013] doi:10.1001/jama.2013.277669

Siemieniuk RAC, Harris IA, Agoritsas T, Poolman RW, Brignardello-Petersen R, Van de Velde S, et al. Arthroscopic surgery for degenerative knee arthritis and meniscal tears: a clinical practice guideline. BMJ. 2017:357:j1982. [PMID: 28490431] doi:10.1136/bmj.j1982

Thorlund JB, Juhl CB, Roos EM, Lohmander LS. Arthroscopic surgery for degenerative knee: systematic review and meta-analysis of benefits and harms. BMJ. 2015;350:h2747. [PMID: 26080045] doi:10.1136/bmj.h2747

Wang C, Schmid CH, Iversen MD, Harvey WF, Fielding RA, Driban JB, et al. Comparative effectiveness of tai chi versus physical therapy for knee osteoarthritis: a randomized trial. Ann Intern Med. 2016;165:77-86. [PMID: 27183035] doi:10.7326/M15-2143

Fibromyalgia

Adams EH, McElroy HJ, Udall M, Masters ET, Mann RM, Schaefer CP, et al. Progression of fibromyalgia: results from a 2-year observational fibromyalgia and chronic pain study in the US. J Pain Res. 2016:9:325-36. [PMID: 27330325] doi:10.2147/JPR.S100043

Bernardy K, Klose P, Busch AJ, Choy EH, Häuser W. Cognitive behavioural therapies for fibromyalgia. Cochrane Database Syst Rev. 2013:CD009796. [PMID: 24018611] doi:10.1002/14651858.CD009796.pub2

Clauw DJ. Fibromyalgia: a clinical review. JAMA. 2014;311:1547-55. [PMID: 24737367] doi:10.1001/jama.2014.3266

Macfarlane GJ, Kronisch C, Dean LE, Atzeni F, Häuser W, Fluß E, et al. EULAR revised recommendations for the management of fibromyalgia. Ann Rheum Dis. 2017:76:318-328. [PMID: 27377815] doi:10.1136/annrheumdis-2016-209724

Queiroz LP. Worldwide epidemiology of fibromyalgia. Curr Pain Headache Rep. 2013;17:356. [PMID: 23801009] doi:10.1007/s11916-013-0356-5

Wolfe F, Clauw DJ, Fitzcharles MA, Goldenberg DL, Katz RS, Mease P, et al. The American College of Rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity. Arthritis Care Res (Hoboken). 2010:62:600-10. [PMID: 20461783] doi:10.1002/acr.20140

Spondyloarthritis

Asquith M, Rosenbaum JT. The interaction between host genetics and the microbiome in the pathogenesis of spondyloarthropathies. Curr Opin Rheumatol. 2016;28:405-12. [PMID: 27152700] doi:10.1097/BOR.0000000000000299

Coates LC, Kavanaugh A, Mease PJ, Soriano ER, Laura Acosta-Felquer M, Armstrong AW, et al. Group for Research and Assessment of Psoriasis and Psoriatic Arthritis 2015 treatment recommendations for psoriatic arthritis. Arthritis Rheumatol. 2016:68:1060-71. [PMID: 26749174] doi:10.1002/art.39573

Colia R, Corrado A, Cantatore FP. Rheumatologic and extraintestinal manifestations of inflammatory bowel diseases. Ann Med. 2016;48:577-585. [PMID: 27310096]

Gossec L, Smolen JS, Ramiro S, de Wit M, Cutolo M, Dougados M, et al. European League Against Rheumatism (EULAR) recommendations for the management of psoriatic arthritis with pharmacological therapies: 2015 update. Ann Rheum Dis. 2016;75:499-510. [PMID: 26644232] doi:10.1136/annrheumdis-2015-208337

Husni ME. Comorbidities in psoriatic arthritis. Rheum Dis Clin North Am. 2015:41:677 98. [PMID: 26476226] doi:10.1016/j.rdc.2015.07.008

Bibliography

Mease PJ. Biologic therapy for psoriatic arthritis. Rheum Dis Clin North Am. 2015;41:723-38. [PMID: 26476229] doi:10.1016/j.rdc.2015.07.010

Napolitano M, Caso F, Scarpa R, Megna M, Patrì A, Balato N, et al. Psoriatic arthritis and psoriasis: differential diagnosis. Clin Rheumatol. 2016;35:1893-1901. [PMID: 27156076] doi:10.1007/s10067-016-3295-9

Sieper J, Poddubnyy D. New evidence on the management of spondyloarthritis. Nat Rev Rheumatol. 2016;12:282-95. [PMID: 27052489] doi:10.1038/nrrheum.2016.42

Soriano ER. Management of psoriatic arthritis: traditional disease-modifying rheumatic agents and targeted small molecules. Rheum Dis Clin North Am. 2015;41:711-22. [PMID: 26476228] doi:10.1016/j.rdc.2015.07.012

Stolwijk C, van Onna M, Boonen A, van Tubergen A. Global prevalence of spondyloarthritis: a systematic review and meta-regression analysis. Arthritis Care Res (Hoboken). 2016;68:1320-31. [PMID: 26713432] doi:10.1002/acr.22831

Taurog JD, Chhabra A, Colbert RA. Ankylosing spondylitis and axial spondyloarthritis. N Engl J Med. 2016;374:2563-74. [PMID: 27355535] doi:10.1056/NEJMra1406182

Ward MM, Deodhar A, Akl EA, Lui A, Ermann J, Gensler LS, et al. American College of Rheumatology/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network 2015 recommendations for the treatment of ankylosing spondylitis and nonradiographic axial spondyloarthritis. Arthritis Rheumatol. 2016;68:282-98. [PMID: 26401991] doi:10.1002/art.39298

Systemic Lupus Erythematosus

Abeles AM, Abeles M. The clinical utility of a positive antinuclear antibody test result. Am J Med. 2013;126:342-8. [PMID: 23395534] doi:10.1016/j.amjmed.2012.09.014

Dooley MA, Jayne D, Ginzler EM, Isenberg D, Olsen NJ, Wofsy D, et al; ALMS Group. Mycophenolate versus azathioprine as maintenance therapy for lupus nephritis. N Engl J Med. 2011;365:1886-95. [PMID: 22087680] doi:10.1056/NEJMoa1014460

Hahn BH, McMahon MA, Wilkinson A, Wallace WD, Daikh DI, Fitzgerald JD, et al; American College of Rheumatology. American College of Rheumatology guidelines for screening, treatment, and management of lupus nephritis. Arthritis Care Res (Hoboken). 2012;64:797-808. [PMID: 22556106] doi:10.1002/acr.21664

Haliloglu S, Carlioglu A, Akdeniz D, Karaaslan Y, Kosar A. Fibromyalgia in patients with other rheumatic diseases: prevalence and relationship with disease activity. Rheumatol Int. 2014;34:1275-80. [PMID: 24589726] doi:10.1007/s00296-014-2972-8

Lazzaroni MG, Dall'Ara F, Fredi M, Nalli C, Reggia R, Lojacono A, et al. A comprehensive review of the clinical approach to pregnancy and systemic lupus erythematosus. J Autoimmun. 2016;74:106-117. [PMID: 27377453] doi:10.1016/j.jaut.2016.06.016

Miner JJ, Kim AH. Cardiac manifestations of systemic lupus erythematosus. Rheum Dis Clin North Am. 2014;40:51-60. [PMID: 24268009] doi:10.1016/j.rdc.2013.10.003

Petri M, Orbai AM, Alarcón GS, Gordon C, Merrill JT, Fortin PR, et al. Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus. Arthritis Rheum. 2012;64:2677-86. [PMID: 22553077] doi:10.1002/art.34473

Singh JA, Hossain A, Kotb A, Oliveira A, Mudano AS, Grossman J, et al. Treatments for lupus nephritis: a systematic review and network metaanalysis. J Rheumatol. 2016;43:1801-1815. [PMID: 27585688]

van Vollenhoven RF, Mosca M, Bertsias G, Isenberg D, Kuhn A, Lerstrøm K, et al. Treat-to-target in systemic lupus erythematosus: recommendations from an international task force. Ann Rheum Dis. 2014;73:958-67. [PMID: 24739325] doi:10.1136/annrheumdis-2013-205139

Sjögren Syndrome

Carsons SE, Vivino FB, Parke A, Carteron N, Sankar V, Brasington R, et al. Treatment guidelines for rheumatologic manifestations of Sjögren's syndrome: use of biologic agents, management of fatigue, and inflammatory musculoskeletal pain. Arthritis Care Res (Hoboken). 2017;69:517-527. [PMID: 27390247] doi:10.1002/acr.22968

Foulks GN, Forstot SL, Donshik PC, et al. Clinical guidelines for management of dry eye associated with Sjögren disease. Ocul Surf. 2015 Apr;13(2):118-32. [PMID: 25881996]

Shiboski CH, Shiboski SC, Seror R, Criswell LA, Labetoulle M, Lietman TM, et al; International Sjögren's Syndrome Criteria Working Group. 2016 American College of Rheumatology/European League Against Rheumatism classification criteria for primary Sjögren's syndrome: a consensus and data-driven methodology involving three international patient cohorts. Ann Rheum Dis. 2017;76:9-16. [PMID: 27789466] doi:10.1136/annrheumdis-2016-210571

Vivino FB, Carsons SE, Foulks G, Daniels TE, Parke A, Brennan MT, et al. New treatment guidelines for Sjögren's disease. Rheum Dis Clin North Am. 2016;42:531-51. [PMID: 27431353] doi:10.1016/j.rdc.2016.03.010

Inflammatory Myopathies

Basharat P, Christopher-Stine L. Immune-mediated necrotizing myopathy: update on diagnosis and management. Curr Rheumatol Rep. 2015;17:72. [PMID: 26515574] doi:10.1007/s11926-015-0548-6

Lundberg IE, Miller FW, Tjärnlund A, Bottai M. Diagnosis and classification of idiopathic inflammatory myopathies. J Intern Med. 2016;280:39-51. [PMID: 27320359] doi:10.1111/joim.12524

Mahler M, Miller FW, Fritzler MJ. Idiopathic inflammatory myopathies and the anti-synthetase syndrome: a comprehensive review. Autoimmun Rev. 2014;13:367-71. [PMID: 24424190] doi:10.1016/j.autrev.2014.01.022

Mammen AL. Necrotizing myopathies: beyond statins. Curr Opin Rheumatol. 2014;26:679-83. [PMID: 25203117] doi:10.1097/BOR.0000000000000106

Mammen AL. Statin-associated autoimmune myopathy. N Engl J Med. 2016;374:664-9. [PMID: 26886523] doi:10.1056/NEJMra1515161

Needham M, Mastaglia FL. Sporadic inclusion body myositis: a review of recent clinical advances and current approaches to diagnosis and treatment. Clin Neurophysiol. 2016;127:1764-73. [PMID: 26778717] doi:10.1016/j.clinph.2015.12.011

Qiang JK, Kim WB, Baibergenova A, Alhusayen R. Risk of malignancy in dermatomyositis and polymyositis. J Cutan Med Surg. 2017;21:131-136. [PMID: 27534779] doi:10.1177/1203475416665601

Tieu J, Lundberg IE, Limaye V. Idiopathic inflammatory myositis. Best Pract Res Clin Rheumatol. 2016;30:149-68. [PMID: 27421222] doi:10.1016/j.berh.2016.04.007

Systemic Sclerosis

Cappelli L, Wigley FM. Management of Raynaud phenomenon and digital ulcers in scleroderma. Rheum Dis Clin North Am. 2015;41:419-38. [PMID: 26210127] doi:10.1016/j.rdc.2015.04.005

Hudson M. Scleroderma renal crisis. Curr Opin Rheumatol. 2015;27:549-54. [PMID: 26352732] doi:10.1097/BOR.0000000000000221

Marder W, Littlejohn EA, Somers EC. Pregnancy and autoimmune connective tissue diseases. Best Pract Res Clin Rheumatol. 2016;30:63-80. [PMID: 27421217] doi:10.1016/j.berh.2016.05.002

McCray CJ, Mayes MD. Update on systemic sclerosis. Curr Allergy Asthma Rep. 2015;15:25. [PMID: 26139334] doi:10.1007/s11882-015-0526-0

Silver KC, Silver RM. Management of systemic-sclerosis-associated interstitial lung disease. Rheum Dis Clin North Am. 2015;41:439-57. [PMID: 26210128] doi:10.1016/j.rdc.2015.04.006

Valenzuela A, Nandagopal S, Steen VD, Chung L. Monitoring and diagnostic approaches for pulmonary arterial hypertension in patients with systemic sclerosis. Rheum Dis Clin North Am. 2015;41:489-506. [PMID: 26210131] doi:10.1016/j.rdc.2015.04.009

van den Hoogen F, Khanna D, Fransen J, Johnson SR, Baron M, Tyndall A, et al. 2013 classification criteria for systemic sclerosis: an American college of rheumatology/European league against rheumatism collaborative initiative. Ann Rheum Dis. 2013;72:1747-55. [PMID: 24092682] doi:10.1136/annrheumdis-2013-204424

Mixed Connective Tissue Disease

Mosca M, Tani C, Vagnani S, Carli L, Bombardieri S. The diagnosis and classification of undifferentiated connective tissue diseases. J Autoimmun. 2014;48-49:50-2. [PMID: 24518855] doi:10.1016/j.jaut.2014.01.019

Tani C, Carli L, Vagnani S, Talarico R, Baldini C, Mosca M, et al. The diagnosis and classification of mixed connective tissue disease. J Autoimmun. 2014;48-49:46-9. [PMID: 24461387] doi:10.1016/j.jaut.2014.01.008

Crystal Arthropathies

Abhishek A. Calcium pyrophosphate deposition disease: a review of epidemiologic findings. Curr Opin Rheumatol. 2016;28:133-9. [PMID: 26626724] doi:10.1097/BOR.0000000000000246

Hill EM, Sky K, Sit M, Collamer A, Higgs J. Does starting allopurinol prolong acute treated gout? A randomized clinical trial. J Clin Rheumatol. 2015;21:120-5. [PMID: 25807090] doi:10.1097/RHU.0000000000000235

Khanna PP, Gladue HS, Singh MK, FitzGerald JD, Bae S, Prakash S, et al. Treatment of acute gout: a systematic review. Semin Arthritis Rheum. 2014;44:31-8. [PMID: 24650777] doi:10.1016/j.semarthrit.2014.02.003

Lipsky PE, Calabrese LH, Kavanaugh A, Sundy JS, Wright D, Wolfson M, et al. Pegloticase immunogenicity: the relationship between efficacy and antibody development in patients treated for refractory chronic gout. Arthritis Res Ther. 2014;16:R60. [PMID: 24588936] doi:10.1186/ar4497

Neogi T, Jansen TL, Dalbeth N, Fransen J, Schumacher HR, Berendsen D, et al. 2015 Gout Classification Criteria: an American College of Rheumatology/ European League Against Rheumatism collaborative initiative. Arthritis Rheumatol. 2015;67:2557-68. [PMID: 26352873] doi:10.1002/art.39254

Qaseem A, Harris RP, Forciea MA; Clinical Guidelines Committee of the American College of Physicians. Management of Acute and Recurrent Gout: A Clinical Practice Guideline From the American College of Physicians. Ann Intern Med. 2017;166:58-68. [PMID: 27802508]doi:10.7326/M16-0570

Richette P, Doherty M, Pascual E, Barskova V, Becce F, Castañeda-Sanabria J, et al. 2016 updated EULAR evidence-based recommendations for the management of gout. Ann Rheum Dis. 2017;76:29-42. [PMID: 27457514] doi:10.1136/annrheumdis-2016-209707

Rosenthal AK, Ryan LM. Calcium Pyrophosphate Deposition Disease. N Engl J Med. 2016;374:2575-84. [PMID: 27355536] doi:10.1056/NEJMra1511117

van Durme CM, Wechalekar MD, Buchbinder R, Schlesinger N, van der Heijde D, Landewé RB. Non-steroidal anti-inflammatory drugs for acute gout. Cochrane Database Syst Rev. 2014:CD010120. [PMID: 25225849] doi:10.1002/14651858.CD010120.pub2

Infectious Arthritis

Arvikar SL, Steere AC. Diagnosis and treatment of Lyme arthritis. Infect Dis Clin North Am. 2015;29:269-80. [PMID: 25999223] doi:10.1016/j.idc.2015.02.004

Kapadia BH, Berg RA, Daley JA, Fritz J, Bhave A, Mont MA. Periprosthetic joint infection. Lancet. 2016;387:386-394. [PMID: 26135702] doi:10.1016/S0140-6736(14)61798-0

Osmon DR, Berbari EF, Berendt AR, Lew D, Zimmerli W, Steckelberg JM, et al; Infectious Diseases Society of America. Diagnosis and management of prosthetic joint infection: clinical practice guidelines by the Infectious Diseases Society of America. Clin Infect Dis. 2013;56:e1-e25. [PMID: 23223583] doi:10.1093/cid/cis803

Sharff KA, Richards EP, Townes JM. Clinical management of septic arthritis. Curr Rheumatol Rep. 2013;15:332. [PMID: 23591823] doi:10.1007/s11926-013-0332-4

Wang DA, Tambyah PA. Septic arthritis in immunocompetent and immunosuppressed hosts. Best Pract Res Clin Rheumatol. 2015;29:275-89. [PMID: 26362744] doi:10.1016/j.berh.2015.05.008

Systemic Vasculitis

Cacoub P, Comarmond C, Domont F, Savey L, Saadoun D. Cryoglobulinemia vasculitis. Am J Med. 2015;128:950-5. [PMID: 25837517] doi:10.1016/j.amjmed.2015.02.017

Comarmond C, Cacoub P. Granulomatosis with polyangiitis (Wegener): clinical aspects and treatment. Autoimmun Rev. 2014;13:1121-5. [PMID: 25149391] doi:10.1016/j.autrev.2014.08.017

de Souza AW, de Carvalho JF. Diagnostic and classification criteria of Takayasu arteritis. J Autoimmun. 2014;48-49:79-83. [PMID: 24461381] doi:10.1016/j.jaut.2014.01.012

De Virgilio A, Greco A, Magliulo G, Gallo A, Ruoppolo G, Conte M, et al. Polyarteritis nodosa: a contemporary overview. Autoimmun Rev. 2016;15:564-70. [PMID: 26884100] doi:10.1016/j.autrev.2016.02.015

Dejaco C, Singh YP, Perel P, Hutchings A, Camellino D, Mackie S, et al; European League Against Rheumatism. 2015 Recommendations for the management of polymyalgia rheumatica: a European League Against Rheumatism/American College of Rheumatology collaborative initiative. Ann Rheum Dis. 2015;74:1799-807. [PMID: 26359488] doi:10.1136/annrheumdis-2015-207492

Greco A, De Virgilio A, Rizzo MI, Gallo A, Magliulo G, Fusconi M, et al. Microscopic polyangiitis: advances in diagnostic and therapeutic approaches. Autoimmun Rev. 2015;14:837-44. [PMID: 25992801] doi:10.1016/j.autrev.2015.05.005

Greco A, Rizzo MI, De Virgilio A, Gallo A, Fusconi M, Ruoppolo G, et al. Churg-Strauss syndrome. Autoimmun Rev. 2015;14:341-8. [PMID: 25500434] doi:10.1016/j.autrev.2014.12.004

Micheletti RG, Werth VP. Small vessel vasculitis of the skin. Rheum Dis Clin North Am. 2015;41:21-32, vii. [PMID: 25399937] doi:10.1016/j.rdc.2014.09.006

Patel RM, Shulman ST. Kawasaki disease: a comprehensive review of treatment options. J Clin Pharm Ther. 2015;40:620-5. [PMID: 26547265] doi:10.1111/jcpt.12334

Rodriguez-Pla A, Monach PA. Primary angiitis of the central nervous system in adults and children. Rheum Dis Clin North Am. 2015:41:47-62, viii. [PMID: 25399939] doi:10.1016/j.rdc.2014.09.004

Stone JH, Tuckwell K, Dimonaco S, Klearman M, Aringer M, Blockmans D, et al. Trial of tocilizumab in giant-cell arteritis. N Engl J Med. 2017;377:317-328. [PMID: 28745999] doi:10.1056/NEJMoa1613849

Weyand CM, Goronzy JJ. Giant-cell arteritis and polymyalgia rheumatica [Letter]. N Engl J Med. 2014;371:1653. [PMID: 25337759] doi:10.1056/NEJMc1409206

Yates M, Watts RA, Bajema IM, Cid MC, Crestani B, Hauser T, et al. EULAR/ERA-EDTA recommendations for the management of ANCA-associated vasculitis. Ann Rheum Dis. 2016;75:1583-94. [PMID: 27338776] doi:10.1136/annrheumdis-2016-209133

Other Rheumatologic Diseases

Gerfaud-Valentin M, Jamilloux Y, Iwaz J, Sève P. Adult-onset Still's disease. Autoimmun Rev. 2014;13:708-22. [PMID: 24657513] doi:10.1016/j.autrev.2014.01.058

International Team for the Revision of the International Criteria for Behçet's Disease (ITR-ICBD). The International Criteria for Behçet's Disease (ICBD): a collaborative study of 27 countries on the sensitivity and specificity of the new criteria. J Eur Acad Dermatol Venereol. 2014;28:338-47. [PMID: 23441863] doi:10.1111/jdv.12107

Kobak S. Sarcoidosis: a rheumatologist's perspective. Ther Adv Musculoskelet Dis. 2015;7:196-205. [PMID: 26425148] doi:10.1177/1759720X15591310

Mahajan VS, Mattoo H, Deshpande V, Pillai SS, Stone JH. IgG4-related disease. Annu Rev Pathol. 2014;9:315-47. [PMID: 24111912] doi:10.1146/annurev-pathol-012513-104708

O'Regan A, Berman JS. Sarcoidosis. Ann Intern Med. 2012;156:ITC5-1, ITC5-2, ITC5-3, ITC5-4, ITC5-5, ITC5-6, ITC5-7, ITC5-8, ITC5-9, ITC5-10, ITC5-11, ITC5-12, ITC5-13, ITC5-14, ITC5-15; quiz ITC5-16. [PMID: 22547486] doi:10.7326/0003-4819-156-9-201205010-01005

Perugino CA, Wallace ZS, Meyersohn N, Oliveira G, Stone JR, Stone JH. Large vessel involvement by IgG4-related disease. Medicine (Baltimore). 2016;95:e3344. [PMID: 27428181] doi:10.1097/MD.0000000000003344

Rubartelli A. Autoinflammatory diseases. Immunol Lett. 2014;161:226-30. [PMID: 24452074] doi:10.1016/j.imlet.2013.12.013

Russo RA, Brogan PA. Monogenic autoinflammatory diseases. Rheumatology (Oxford). 2014;53:1927-39. [PMID: 24831056] doi:10.1093/rheumatology/keu170

Vitale A, Sota J, Rigante D, Lopalco G, Molinaro F, Messina M, et al. Relapsing polychondritis: an update on pathogenesis, clinical features, diagnostic tools, and therapeutic perspectives. Curr Rheumatol Rep. 2016;18:3. [PMID: 26711694] doi:10.1007/s11926-015-0549-5

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Directions

Each of the numbered items is followed by lettered answers. Select the ***ONE*** *lettered answer that is* ***BEST*** *in each case.*

Item 1

A 72-year-old man is evaluated in the emergency department after falling when his leg gave way as he tried to arise from bed. He has left hip pain, with the inability to stand and pain at rest. He was recently diagnosed with lymphoma, for which he is receiving chemotherapy. History is significant for a left hip replacement 7 years ago for osteoarthritis. His chemotherapy regimen consists of rituximab plus hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone.

On physical examination, temperature is 38.2 °C (100.8 °F); other vital signs are normal. The right upper chest is implanted with a venous access port. Warmth and tenderness around the left hip are noted. Pain in the groin is noted. There is limitation of motion in all directions on both active and passive range of motion of the left hip. There are no other joint abnormalities.

Laboratory studies show an erythrocyte sedimentation rate of 73 mm/h, a leukocyte count of 13,400/µL (13.4×10^9/L), and a serum urate level of 8.2 mg/dL (0.48 mmol/L).

Left hip radiographs show periprosthetic lucency.

Which of the following is the most likely diagnosis?

(A) Gout flare
(B) Hemarthrosis
(C) Hip dislocation
(D) Prosthetic joint infection

Item 2

A 55-year-old man is hospitalized for acute respiratory failure requiring intubation and mechanical ventilation. He also has increasing leg swelling with nonhealing skin ulcers on the legs for the past 4 weeks, and pain with swelling of the bilateral wrists and finger joints for the past 6 weeks. He quit smoking 15 years ago. History is otherwise unremarkable. Prior to hospitalization he was taking no medications.

On physical examination, temperature is 37.2 °C (99.0 °F), blood pressure is 150/95 mm Hg, pulse rate is 110/min, respiration rate is 20/min (ventilator set rate, 14/min), and oxygen saturation is 92% on FIO_2 of 40%. There is blood in the endotracheal tube. Lung crackles are heard bilaterally. Swelling of the wrists, metacarpophalangeal joints, and proximal interphalangeal joints is noted. Two necrotic ulcers on the left leg and one necrotic ulcer on the right leg are present. There is 2+ pitting edema of the legs.

Laboratory studies show normal C3, C4, and rheumatoid factor; negative antinuclear antibodies; positive ANCA with a perinuclear pattern; and 3+ protein on urinalysis. Blood and sputum cultures are negative.

Chest radiograph shows diffuse bilateral infiltrates.

Biopsy of a skin ulcer shows nongranulomatous, necrotizing small-vessel vasculitis with immunofluorescence negative for immune complexes.

Which of the following is the most likely diagnosis?

(A) Granulomatosis with polyangiitis
(B) IgA vasculitis
(C) Microscopic polyangiitis
(D) Rheumatoid vasculitis
(E) Thromboangiitis obliterans

Item 3

A 78-year-old woman is evaluated for a 2-year history of gout with progressively more frequent and severe attacks. She currently has pain and swelling in the right second finger. History is also significant for hypertension, chronic kidney disease, nephrolithiasis, and type 2 diabetes mellitus. Medications are lisinopril, furosemide, metformin, and the maximal dose of febuxostat; she is allergic to allopurinol.

On physical examination, vital signs are normal. The joint findings are shown.

Laboratory studies show an erythrocyte sedimentation rate of 76 mm/h, a serum creatinine level of 1.5 mg/dL (132.6 µmol/L), and a serum urate level of 6.3 mg/dL (0.37 mmol/L).

Which of the following is the most appropriate treatment?

(A) Add probenecid
(B) Stop febuxostat; begin pegloticase infusions
(C) Stop lisinopril; begin losartan
(D) Continue current treatment

Item 4

A 30-year-old man is evaluated for arthritis. Three weeks ago he noticed the abrupt onset of dysuria without a discharge. Two weeks later, he developed the acute onset of warmth, pain, and swelling in the left knee. Two days later, pain and swelling developed over the left heel. He also noted the onset of stinging and redness of the right eye. He takes no medications. The dysuria and eye symptoms have since resolved.

On physical examination, vital signs are normal. A moderate effusion of the left knee is present with warmth and pain with range of motion. Diffuse swelling, warmth, erythema, and tenderness are present at the insertion of the left Achilles tendon at the calcaneus. There is no rash.

Radiographs of the left knee show a joint effusion, no bony abnormalities, and normal joint space.

Aspiration of the left knee is performed; synovial fluid analysis shows a leukocyte count of 5000/µL (5.0×10^9/L) with 65% neutrophils and 35% mononuclear cells, negative Gram stain and cultures, and no crystals.

Which of the following is the most appropriate diagnostic test to perform next?

(A) *Chlamydia* nucleic acid amplification urine testing
(B) C-reactive protein
(C) HLA-B27
(D) Interferon-gamma release assay

Item 5

A 32-year-old woman is evaluated for a 15-year history of low back pain. The pain is worse with rest, improves with movement, and can awaken her during the night. Family history is notable for three paternal uncles with back problems. She takes naproxen twice daily with some relief.

On physical examination, vital signs are normal. Joint examination does not reveal any warmth, erythema, or swelling. Tenderness over the sacroiliac joints bilaterally and reduction in the range of motion of the lumbar spine are noted.

Laboratory studies are notable for an erythrocyte sedimentation rate of 27 mm/h.

A plain anteroposterior radiograph of the pelvis shows fusion of the sacroiliac joints.

Which of the following is the most appropriate diagnostic test to perform next?

(A) ANCA
(B) Anti–cyclic citrullinated peptide antibodies
(C) Antinuclear antibodies
(D) HLA-B27 antigen
(E) No additional testing

Item 6

H

A 43-year-old man is evaluated in the emergency department for gastrointestinal bleeding. He reports loose, dark stools of 2 weeks' duration. He has an 8-year history of diffuse cutaneous systemic sclerosis (DcSSc) complicated by Raynaud phenomenon and gastroesophageal reflux disease. He does not drink alcohol or take NSAIDs. His only medication is omeprazole.

On physical examination, temperature is normal, blood pressure is 100/60 mm Hg, pulse rate is 80/min, respiration rate is 16/min, and oxygen saturation is 94% breathing ambient air. Skin changes associated with DcSSc are noted from the hands to the elbows in the upper extremities and from the feet to the knees in the lower extremities. The abdomen is nontender to palpation. The remainder of the physical examination is normal.

Laboratory studies show a normal chemistry panel and a hematocrit level of 26%.

Upper gastrointestinal endoscopy demonstrates linear ectatic vessels resembling the stripes found on a watermelon that arise from the pylorus. There is no evidence of a hiatal hernia or other abnormal findings.

Which of the following is the most likely diagnosis?

(A) Cameron lesions
(B) Dieulafoy lesions
(C) Gastric antral vascular ectasia
(D) Portal hypertensive gastropathy

Item 7

H

A 76-year-old man is evaluated for fever and a swollen, painful left knee. He was hospitalized 7 days ago for heart failure and appropriately treated. However, he developed fevers up to 38.0 °C (100.4 °F). On examination, lungs were clear to auscultation. The left knee was hot and swollen; 60 mL of turbid fluid was drained from the knee. Gram stain of the synovial fluid was negative; microscopy revealed needle-shaped intracellular crystals. Gout was diagnosed and the knee was drained again, followed by an injection of 80 mg of methylprednisolone, without improvement. Intravenous methylprednisolone, 60 mg/d for 3 days, did not improve the knee or the fevers. History is also significant for hypertension and gout. Other medications are furosemide, lisinopril, metoprolol, subcutaneous heparin, and morphine as needed.

On physical examination today, temperature is 38.0 °C (100.4 °F), blood pressure is 148/92 mm Hg, pulse rate is 116/min, and oxygen saturation is 97% on ambient air. The left knee is warm, swollen, and tender.

Blood, urine, and synovial fluid cultures are negative.

Which of the following is the most appropriate treatment for the knee?

(A) Anakinra
(B) Colchicine
(C) Ibuprofen
(D) Vancomycin

Item 8

A 55-year-old woman is evaluated for an 18-month history of increasingly severe knee pain with the inability to arise when seated on the floor. She does not have pain at rest or nocturnal pain. Medications are celecoxib and omeprazole.

On physical examination, vital signs are normal. Bony hypertrophy of both knees is present. There is no warmth, erythema, or swelling of the joints.

Plain anteroposterior knee radiographs show medial joint space narrowing, peaking of the tibial spines, and osteophytes; there are no erosions or osteopenia.

Which of the following is the most appropriate management?

(A) Glucosamine supplements
(B) Knee replacement surgery
(C) Physical therapy
(D) Prednisone

Item 9

A 25-year-old man is evaluated for the gradual onset of bilateral low back pain without radiation to the lower extremities daily, with increasing severity over the past year. The pain now awakens him during the night 2 to 3 times per week, with morning stiffness lasting more than an hour. He has improvement with exercise and no improvement at rest. He takes ibuprofen with some improvement.

On physical examination, vital signs are normal. Limited lateral bending bilaterally and a reduction in forward flexion at the lumbar spine are noted. The remainder of the examination is normal.

An anteroposterior plain radiograph of the pelvis and sacroiliac joints is unremarkable.

Which of the following is the most appropriate diagnostic test to perform next?

(A) Bone scan
(B) CT of the lumbar spine
(C) MRI of the sacroiliac joints
(D) Radiography of the hip joints

Item 10

A 75-year-old man is evaluated for a 5-year history of hand joint pain and morning stiffness lasting a few minutes. He walks about a mile every day and plays tennis 3 days a week; however, the pain has started to limit him from gripping a tennis racket. He also has noticed fatigue for the past 6 months. He reports no other constitutional symptoms, shortness of breath, or rash. History is also significant for hypertension and diet-controlled type 2 diabetes mellitus. Medications are losartan, acetaminophen as needed, and aspirin, 81 mg/d.

On physical examination, vital signs are normal. Bony enlargement of multiple proximal and distal interphalangeal joints of the hands is noted. The remainder of the physical examination is normal.

Laboratory studies show an erythrocyte sedimentation rate of 22 mm/h, a hematocrit level of 41%, and a C-reactive protein level of 0.9 mg/dL (9.0 mg/L).

Hand radiographs show joint-space narrowing and osteophytes of multiple proximal and distal interphalangeal joints, and similar changes are seen in both first carpometacarpal joints; there are no erosions.

Which of the following is the most appropriate next step in management?

(A) Anti-cyclic citrullinated peptide antibodies
(B) Antinuclear antibodies
(C) Rheumatoid factor
(D) Serum urate level
(E) No further testing

Item 11

A 47-year-old woman is evaluated for an onset over 2 to 3 weeks of low-grade, intermittent fever; blanching of the second and third right fingertips in response to cold exposure; cracking and peeling of the skin on the sides of the second digits and palms; and pain and swelling of the second and fourth proximal interphalangeal joints bilaterally. She does not take any medications.

On physical examination, temperature is 37.6 °C (99.7 °F), pulse rate is 95/min, and respiration rate is 20/min; blood pressure and oxygen saturation are normal. The tips of the digits are cool without discoloration. Erythema of the malar area, forehead, and chin is present. Pulmonary examination reveals crackles at the lung bases. There is no weakness.

Skin findings are shown.

Laboratory studies:

Creatine kinase	115 U/L
Antinuclear antibodies	Titer: 1:1280
Anti-double-stranded DNA antibodies	Negative
Anti-Jo-1 antibodies	Positive
Anti-Smith antibodies	Negative

Which of the following is the most likely diagnosis?

(A) Antisynthetase syndrome
(B) Sjögren syndrome
(C) Systemic lupus erythematosus
(D) Systemic sclerosis

Item 12

A 33-year-old woman is evaluated for concerns about the development of rheumatoid arthritis (RA). She has some mild joint discomfort in the hands at the end of the day. She is a software engineer and has been smoking five cigarettes per day for the past 2 years. She takes no medications. Her identical twin sister was recently diagnosed with seropositive RA, and her maternal grandmother had RA.

On physical examination, vital signs are normal. There is no swelling or tenderness in the joints of the hands, wrists, elbows, knees, or feet.

Which of the following is the most appropriate preventive measure for this patient at risk for developing RA?

(A) Avoid food/drinks containing high-fructose corn syrup
(B) Begin hydroxychloroquine
(C) Begin probiotics
(D) Smoking cessation

H

Item 13

A 26-year-old man is hospitalized for a 1-week history of dry cough and progressive shortness of breath. He has a 2-year history of systemic lupus erythematosus (SLE); disease manifestations have been pleuropericarditis, polyarthritis, leukopenia, and nephritis. He currently reports no fever, sputum production, or hemoptysis, as well as no other SLE manifestations. His disease has been difficult to control and has needed multiple tapering doses of prednisone. He currently takes 15 mg/d of prednisone; other medications are hydroxychloroquine and azathioprine.

On physical examination, temperature is 36.4 °C (97.6 °F), blood pressure is 150/100 mm Hg, pulse rate is 98/min, respiration rate is 30/min, and oxygen saturation is 84% breathing ambient air. Diffuse crackles are heard on auscultation of the chest. Diffuse tenderness and swelling of multiple small joints of the hands are present. The remainder of the physical examination is normal.

Laboratory studies:

Erythrocyte sedimentation rate	68 mm/h
Hematocrit	42%
Leukocyte count	5500/µL (5.5×10^9/L) with normal differential
Complements (C3 and C4)	Low
C-reactive protein	Normal
Creatinine	0.6 mg/dL (53 µmol/L)
Procalcitonin	Normal

Chest radiograph and CT scan of the chest show diffuse infiltrates in both lungs with ground glass opacities in multiple lobes. Bronchoalveolar lavage shows only increased leukocytes with lymphocytic predominance. Cultures are pending.

Which of the following is the most likely diagnosis?

(A) Acute lupus pneumonitis
(B) Acute pulmonary hypertension
(C) Community-acquired pneumonia
(D) Diffuse alveolar hemorrhage
(E) Shrinking lung syndrome

Item 14

A 45-year-old woman is evaluated for a 4-month history of diarrhea and a 4.5-kg (10-lb) weight loss. She reports explosive episodes of loose stools that follow most meals. There is a feeling of bloating and pain with the episodes. She has a 10-year history of diffuse cutaneous systemic sclerosis (DcSSc) complicated by Raynaud phenomenon with occasional digital ulceration and gastroesophageal reflux disease. Her only medication is omeprazole.

On physical examination, vital signs are normal. BMI is 21. Skin changes associated with DcSSc involve the arms, forearms, and hands. The abdominal examination reveals active and loud bowel sounds but is otherwise unremarkable.

Which of the following is the most likely diagnosis?

(A) Carcinoid syndrome
(B) Chronic mesenteric ischemia
(C) Irritable bowel syndrome
(D) Small intestinal bacterial overgrowth

Item 15

A 50-year-old man is evaluated for a left lower extremity ulcer. He has a 15-year history of worsening arthritis for which he has never been evaluated. He takes ibuprofen as needed.

On physical examination, vital signs are normal. The spleen tip is palpable. There is swelling of multiple small joints at the hands, knees, and metatarsophalangeal (MTP) joints. There is ulnar deviation and subluxation of the metacarpophalangeal joints. Subcutaneous nodules are present at the elbows bilaterally. There is a 2- × 2-cm shallow ulcer at the medial left lower extremity just above the ankle.

Laboratory studies:

Hematocrit	33%
Leukocyte count	2100/µL (2.1×10^9/L), with 900 neutrophils
Platelet count	276,000/µL (276×10^9/L)
Urinalysis	Normal

Which of the following is the most likely diagnosis?

(A) AA amyloidosis
(B) Felty syndrome
(C) Sarcoidosis
(D) Systemic lupus erythematosus

H

Item 16

A 49-year-old man is evaluated a 3-month history of right knee swelling without significant pain. He does a lot of physical activity as a park ranger in Michigan but does not recall trauma. He likes to walk for exercise and does not have significant pain when he walks. He has only minimal discomfort in the knee and stiffness when he squats. He reports no swelling or pain in other joints and no fever, rash, or other symptoms. He takes no medications.

On physical examination, vital signs are normal. Examination of the right knee shows a large effusion without erythema, but with minimal warmth and tenderness; full range of active motion is noted. The remainder of the musculoskeletal and physical examination is normal.

Knee radiographs confirm a large joint effusion in the right knee; no other abnormalities are seen.

Which of the following tests is most likely to confirm the diagnosis?

(A) HLA-B27 haplotype testing
(B) MRI of the right knee
(C) Serologic testing for *Borrelia burgdorferi*
(D) Synovial fluid analysis for crystals

H

Item 17

A 55-year-old man is evaluated in the emergency department for a 1-month history of low back pain and lower extremity swelling during the past 2 weeks. History is

H CONT.

significant for a goiter that was surgically removed 5 years ago; pathology revealed extensive fibrosis. He takes levothyroxine.

On physical examination, temperature is normal, blood pressure is 165/90 mm Hg, pulse rate is 88/min, and respiration rate is 18/min. A surgical scar over the anterior neck is noted. There is 2+ lower extremity edema to the mid calf bilaterally. The remainder of the examination is normal.

Laboratory studies show a hematocrit level of 34%, a serum creatinine level of 2.1 mg/dL (185.6 µmol/L), and a normal urinalysis.

Abdominal ultrasound shows bilateral hydronephrosis. Noncontrast CT of the abdomen and pelvis shows a soft-tissue mass surrounding the infrarenal aorta without any significant lymphadenopathy; the ureters are encased within the mass.

Which of the following is the most likely diagnosis?

(A) Germ cell tumor
(B) IgG4-associated retroperitoneal fibrosis
(C) Lymphoma
(D) Malignant peritoneal mesothelioma

Item 18

A 42-year-old woman is evaluated during a follow-up visit for Raynaud phenomenon of 6 months' duration. She also has gastroesophageal reflux disease. Her only medication is ranitidine.

On physical examination, vital signs are normal. There is no sclerodactyly or digital pitting at the fingertips. The remainder of the physical examination is normal.

Laboratory studies are significant for positive antinuclear antibodies (titer: 1:640) in a centromere pattern, with a strongly positive anticentromere B antibody level.

The nailfold capillaries are shown.

Which of the following is the most likely diagnosis?

(A) Dermatomyositis
(B) Limited cutaneous systemic sclerosis
(C) Mixed connective tissue disease
(D) Systemic lupus erythematosus

Item 19

A 65-year-old man is evaluated for a 1-month history of progressive malaise, myalgia, a 3.6-kg (8.0-lb) weight loss, and numbness and weakness of the right foot; left testicular pain for 1 week; and a painful rash on his legs for 2 days. He was diagnosed 2 months ago with hypertension, for which he takes hydrochlorothiazide.

On physical examination, temperature is 37.2 °C (99.0 °F), and blood pressure is 165/90 mm Hg. The left testicle is tender. Small necrotic ulcers are noted on the legs. Numbness of the right lateral ankle and calf is noted, as well as weakness of right foot plantar flexion.

Laboratory studies:

Erythrocyte sedimentation rate	100 mm/h
Hemoglobin	10 g/dL (100 g/L)
Leukocyte count	13,000/µL (13×10^9/L)
Platelet count	430,000/µL (430×10^9/L)
Creatinine	1.7 mg/dL (150.3 µmol/L)
ANCA	Negative
Urinalysis	Normal

Renal angiogram shows microaneurysms of the renal arteries. A deep skin biopsy (deep dermis and subcutis) shows panmural inflammation with necrosis of a medium-sized artery.

Which of the following is the most likely diagnosis?

(A) Giant cell arteritis
(B) IgA vasculitis
(C) Microscopic polyangiitis
(D) Polyarteritis nodosa

Item 20

An 85-year-old woman is evaluated for left knee pain of moderate intensity that occurs with ambulation and at night. Acetaminophen provides no relief. History is significant for coronary artery disease, hypertension, and stage 3 chronic kidney disease. Medications are aspirin, lisinopril, metoprolol, and vitamin D.

On physical examination, blood pressure is 152/88 mm Hg; other vital signs are normal. The left knee demonstrates crepitus and decreased passive range of motion; a small effusion is present, and there is no warmth or tenderness.

Joint aspiration of the left knee shows a leukocyte count of 1100/µL (1.1×10^9/L).

Which of the following is the most appropriate treatment for long-term symptom control?

(A) Intra-articular glucocorticoid injections
(B) Low-dose prednisone
(C) Naproxen
(D) Oxycodone
(E) Topical diclofenac

Item 21

A 79-year-old man is evaluated for a 2-month history of progressive malaise and weakness, aching bilateral shoulders and hips, and stiffness for 2 hours in the morning and after immobility. He recently noted aching in his jaw when chewing. He also reports new left-sided headaches. Last

week he had an episode of diplopia lasting 1 minute. He has hypertension, for which he takes hydrochlorothiazide.

On physical examination, vital signs are normal. Tenderness and slight swelling over the left temple are present. Painful and limited range of motion of both hips and shoulders is noted. The remainder of the examination is unremarkable.

Laboratory studies show an erythrocyte sedimentation rate of 85 mm/h.

Which of the following is the most appropriate initial management?

(A) CT of the head
(B) Low-dose aspirin
(C) Methotrexate
(D) Prednisone
(E) Temporal artery biopsy

Item 22

A 67-year-old man is evaluated for a 1-year history of weakness, with increased tripping on curbs and difficulty with handwriting, which is not as neat as in the past. He reports no muscle cramping. He takes no medications.

On physical examination, vital signs are normal. There is no rash. There is symmetric weakness of the forearm and thigh muscles. Reduced grip strength and reduced wrist and finger flexion are noted. Reflexes are normal. There is atrophy of the muscles of the forearms and interosseous muscles of the right hand greater than the left. There are no fasciculations.

Laboratory studies show a serum creatine kinase level of 1150 U/L and a normal thyroid-stimulating hormone level; antinuclear and anti-Jo-1 antibody testing is negative.

Electromyogram and nerve conduction studies show myopathic changes in the proximal and distal muscles of the extremities, as well as some neurogenic changes.

Which of the following is the most likely diagnosis?

(A) Amyotrophic lateral sclerosis
(B) Inclusion body myositis
(C) Mitochondrial myopathy
(D) Polymyositis

Item 23

A 66-year-old woman is evaluated after developing five dental caries over the past year. She cannot eat crackers without accompanying water. She has lost two teeth due to caries. She also reports scratchy and itchy eyes for 2 years and intermittent joint pain, particularly of the small hand joints, for 1 year. She takes ibuprofen as needed for the joint pain, which provides relief.

On physical examination, vital signs are normal. Two molars are missing, and there is no salivary pooling below the tongue. Bilateral parotid and lacrimal enlargement is present. Mild tenderness without swelling of the second through fourth metacarpophalangeal joints bilaterally is noted.

Laboratory studies show positive rheumatoid factor, high-titer antinuclear antibodies, and high-titer anti-Ro/SSA antibodies.

A Schirmer test for ocular wetting is diminished at 3 mm. Chest radiograph is normal. Radiographs of the hands show no erosions.

Which of the following is the most appropriate treatment at this time?

(A) Artificial tears and sugar-free candies
(B) Methotrexate
(C) Pilocarpine
(D) Rituximab
(E) Topical ophthalmic NSAID drops

Item 24

A 45-year-old woman is evaluated for a 2-day history of deep boring pain in the right eye. She also describes eye redness and photophobia but no recent trauma to the eye. She has a 10-year history of rheumatoid arthritis, treated with etanercept.

On physical examination, vital signs are normal. Diffuse right eye redness is noted, and there is pain on extra-ocular movement testing. Gentle pressure over the eye with the lid closed results in pain. There is no scleromalacia in either eye. There is diminished visual acuity of the right eye. Limited range of motion of the right wrist is noted. There is no swelling of the joints of the upper or lower extremities.

Which of the following is the most likely diagnosis?

(A) Conjunctivitis
(B) Episcleritis
(C) Scleritis
(D) Subconjunctival hemorrhage

Item 25

H

A 26-year-old woman is evaluated in the emergency department for an acute onset of fatigue, chills, and joint pain in the fingers of the left hand, left wrist, and right ankle during the past 3 days. There is no travel history. She is currently taking ibuprofen for her symptoms; she also takes an oral contraceptive pill.

On physical examination, temperature is 39.0 °C (102.2 °F), blood pressure is 114/72 mm Hg, and pulse rate is 106/min. Fusiform enlargement of the second and fourth digits of the left hand with pain on extension is noted. Tenosynovitis over the dorsum of the left wrist and at the right ankle is present.

A painless lesion on the palm is shown (see top of next page).

Which of the following is the most likely diagnosis?

(A) Chikungunya infection
(B) Disseminated gonococcal infection
(C) Reactive arthritis
(D) Sarcoidosis

ITEM 25

Item 26

A 32-year-old woman is evaluated for a recent episode of transient left monocular blindness. She noted dimness of vision in the left eye that came on suddenly and persisted for 15 minutes and then resolved completely. She had no accompanying headache or other symptoms. She has an 8-year history of systemic lupus erythematosus, which initially manifested as photosensitivity, discoid rash, and arthritis. She has responded well to treatment and has been doing well without active disease for the past year. History is significant for recurrent first trimester pregnancy loss attributed to positive antiphospholipid and anticardiolipin antibodies. Medications are hydroxychloroquine, prednisone, aspirin, and a daily multivitamin.

On physical examination, vital signs are normal. Cardiac rhythm is normal. A 2/6 holosystolic murmur is heard at the apex with radiation toward the axilla. Temporal and carotid artery pulsations are normal; there is no scalp tenderness or vascular bruits. The remainder of the physical examination, including ophthalmologic examination, is normal.

Which of the following is the most likely cause of her visual symptom?

(A) Bacterial endocarditis

(B) Carotid artery stenosis

(C) Giant cell arteritis

(D) Libman-Sacks endocarditis

Item 27

A 73-year-old woman is hospitalized for symptoms of heart failure, with progression occurring over the past 2 weeks. She also reports a 6-week history of arm aching that is worse with lifting and reaching, hip aching, morning stiffness, fever, and malaise. She reports no headache or jaw claudication.

On physical examination, temperature is 37.5 °C (99.5 °F), blood pressure is normal but systolic pressure is 16 mm Hg less on the right arm than the left arm, pulse rate is 90/min, respiration rate is 20/min, and oxygen saturation is 93% breathing ambient air. There is no rash. There is no temporal tenderness. A bruit is heard over the right supraclavicular fossa. The right radial pulse is reduced. A diastolic decrescendo murmur is heard in the upper right sternal border. Bibasilar crackles are heard. Painful range of motion is noted in the shoulders and hips. No joint swelling is present.

Transthoracic echocardiogram shows aortic valve regurgitation with normal leaflets, dilated aortic root, and dilated left ventricle.

Which of the following is the most likely diagnosis?

(A) Kawasaki disease

(B) Polyarteritis nodosa

(C) Subcranial giant cell arteritis

(D) Takayasu arteritis

Item 28

A 43-year-old woman is evaluated for a 3-day history of left knee pain and swelling. Similar episodes have occurred in either knee as well as the left wrist during the past 2 years. She also reports a sense of generalized weakness, and has experienced constipation and vague abdominal discomfort during the past year. Because of her constipation, her thyroid-stimulating hormone level was recently measured and found to be normal. She takes no medications.

On physical examination, vital signs are normal. The left knee is warm with a moderate- to large-sized effusion, and decreased range of motion is noted. Proximal muscle strength is normal.

Radiographs show a thin white line at the chondral surfaces of both knees and at the pubic symphysis.

Joint aspiration of the left knee shows a leukocyte count of 35,000/µL (35×10^9/L), with 90% neutrophils; polarizing microscopy shows numerous positively birefringent rhomboid crystals within neutrophils.

Which of the following laboratory studies will most likely identify the cause of this patient's symptoms?

(A) Anti–cyclic citrullinated peptide antibodies

(B) Serum calcium

(C) Serum creatine kinase

(D) Serum urate

Item 29

A 66-year-old man is hospitalized for progressive dyspnea for the past 10 days. He was diagnosed with granulomatosis with polyangiitis 5 years ago; at that time, cyclophosphamide was initiated, with resolution of all symptoms. He was subsequently switched to maintenance azathioprine therapy. Today he was started on intravenous methylprednisolone.

On physical examination, temperature is 37.8 °C (100.0 °F), blood pressure is 140/85 mm Hg, pulse rate is 100/min, respiration rate is 25/min, and oxygen saturation

H CONT.

is 90% on 2 L of oxygen by nasal cannula. Bilateral crackles are heard in the lower lung fields.

Laboratory studies:

Erythrocyte sedimentation rate	90 mm/h
Hemoglobin	12 g/dL (120 g/L)
Leukocyte count with differential	Normal
Platelet count	450,000 (450×10^9/L)
ANCA	Positive with a cytoplasmic pattern and a titer of 1:160; positive proteinase 3 antibodies
Urinalysis	Normal

Chest radiograph shows hazy opacification and a few nodules in the mid and lower lung zones. Sputum and bronchoalveolar lavage, Gram stain, and cultures are negative. Blood cultures are negative.

In addition to discontinuing azathioprine, which of the following is the most appropriate treatment?

(A) Cyclophosphamide
(B) Etanercept
(C) Methotrexate
(D) Rituximab

Item 30

A 47-year-old woman is evaluated for a 6-month history of disequilibrium. She often feels "dizzy" and "off-balance," which has led to several falls. She does not experience vertigo. She has a 10-year history of fibromyalgia, and has experienced a 60% improvement in pain and function with graded aerobic exercise, duloxetine, and pregabalin.

On a focused physical examination, vital signs are normal. Neurologic examination, including strength testing, sensory examination (light touch, proprioception), tandem walking, and Romberg testing, is normal.

Laboratory studies show normal serum folate, thyroid-stimulating hormone, and vitamin B_{12} levels; hemoglobin A_{1c} level is 5.0%.

Which of the following is the most appropriate next step in management?

(A) Discontinue duloxetine
(B) Discontinue pregabalin
(C) Measure methylmalonic acid and homocysteine levels
(D) Order an MRI of the brain
(E) Schedule vestibular rehabilitation

Item 31

A 75-year-old woman is evaluated for a 2-week history of gradually increasing pain in both shoulders and hips; the pain radiates down both arms to the elbows and down both hamstrings to the knees. She reports no headache, jaw claudication, or vision changes. She was diagnosed with polymyalgia rheumatica 3 months ago. She started prednisone, 15 mg/d, with immediate and complete relief of symptoms; prednisone was weaned from 15 to 10 mg/d 2 months ago, then to 8 mg/d (current dose) 1 month ago. She remained asymptomatic until 2 weeks ago. She says that her current symptoms are just as bad as when she was first diagnosed.

On physical examination, vital signs are normal; blood pressure is identical in both arms. There is no temporal tenderness or induration. Painful range of motion of both shoulders and hips is noted.

Which of the following is the most appropriate management?

(A) Prednisone, 10 mg/d
(B) Prednisone, 30 mg/d
(C) Prednisone, 60 mg/d
(D) Prednisone, 20 mg/d, and methotrexate

Item 32

H

A 50-year-old woman is hospitalized for right arm weakness and altered mental status. Over the past 4 months, she has had gradual onset of headaches that have progressively worsened, and her family reports that the patient has had cognitive problems over the past 1 to 2 weeks. Today she developed right arm weakness. She has no other pertinent history and takes no medications.

On physical examination, the patient is not oriented to place or date. Vital signs are normal. The patient has 4+/5 strength of the right upper extremity and achieves 16 of 30 points on the Mini-Mental State Examination; the remainder of the neurologic examination is normal.

Laboratory studies show a normal erythrocyte sedimentation rate, complete blood count with differential, and comprehensive metabolic panel; a negative ANCA; and a negative urinalysis.

Cerebrospinal fluid analysis shows a leukocyte count of 12/µL (12×10^6/L; all lymphocytes) and a protein level of 70 mg/dL (700 mg/L); Gram stain and cultures are negative.

MRI of the brain shows diffuse nonspecific white matter changes and a low attenuation area in the right frontal lobe. Cerebral angiogram demonstrates multiple areas of vessel dilation and stenosis. Brain biopsy shows granulomatous vessel inflammation.

In addition to high-dose glucocorticoids, which of the following is the most appropriate management?

(A) Adalimumab
(B) Cyclophosphamide
(C) Methotrexate
(D) Rituximab

Item 33

A 27-year-old woman is evaluated for a sudden onset of joint pain and significant stiffness in her fingers, wrists, knees, and ankles for the past 3 days. She had a brief fever with muscle aches a few days ago and a faint, pink rash on her arms and legs at the same time. She reports no other symptoms. She takes no medications. She works at a daycare.

On physical examination, temperature is 37.2 °C (99.0 °F); other vital signs are normal. There are no rashes, hair loss, or oral ulcers. There is mild warmth and tenderness

of the first through fifth proximal interphalangeal and metacarpophalangeal joints bilaterally as well as the wrists. Warmth and tenderness of the knees and ankles are also noted, with pain on range of motion.

Which of the following will most likely confirm the diagnosis?

(A) Antinuclear antibodies
(B) HIV testing
(C) Parvovirus B19 testing
(D) Rheumatoid factor

Item 34

A 36-year-old woman is evaluated for a 2-month history of morning stiffness in the hands, wrists, knees, and feet lasting 90 minutes. She recently noted difficulty making a fist in the morning and feels like she is walking on pebbles when she first gets out of bed. She feels better after a hot shower and activity. Her only medication is ibuprofen, which is helpful.

On physical examination, vital signs are normal. There is tenderness and swelling of the second, third, and fifth metacarpophalangeal joints bilaterally, the second through fourth proximal interphalangeal joints of both hands, the right wrist, the left knee, and the second through fifth metatarsophalangeal joints bilaterally. The remainder of the examination is normal.

Which of the following is the most appropriate diagnostic test to perform next?

(A) Anti-cyclic citrullinated peptide antibodies
(B) HLA-B27
(C) Parvovirus IgG antibodies
(D) Serum urate
(E) Thyroid-stimulating hormone

Item 35

A 73-year-old woman is evaluated for a 10-year history of osteoarthritis affecting multiple joints over the years, including the distal joints of her fingers, bases of the thumbs, knees, and cervical and lower lumbar spines. She has chronic daily pain in at least one joint. She has tried nonpharmacologic measures, and she had minimal benefit from intra-articular glucocorticoid and hyaluronic acid injections to her knees. She was recently diagnosed with peptic ulcer disease. History is also significant for coronary artery disease, diabetes mellitus, and hypertension. Medications are enalapril, carvedilol, metformin, atorvastatin, pantoprazole, and low-dose aspirin.

On physical examination, vital signs are normal. Heberden nodes and squaring of the bilateral carpometacarpal joints are present. Crepitus and limited extension of the cervical spine are noted. Bilateral knee varus deformity and bony enlargement are present, with crepitus on range of motion.

Which of the following is the most appropriate treatment?

(A) Duloxetine
(B) Gabapentin
(C) Ibuprofen
(D) Topical capsaicin

Item 36

A 35-year-old woman is hospitalized for left-sided pleuritic chest pain and dyspnea that began 1 day ago. Four weeks ago, she began to experience fever once or twice a day, pharyngitis, intermittent rash on the trunk and proximal extremities that occurs with the fever, severe joint pain, and myalgia. She gave birth 10 weeks ago to a healthy female infant.

On physical examination, temperature is 39.0 °C (102.2 °F), pulse rate is 90/min, and respiration rate is 22/min. Enlarged cervical lymph nodes, hepatomegaly, and splenomegaly are present. A pleural friction rub is heard. A pink maculopapular rash is present on the trunk. Tenderness and swelling of the wrists, knees, and ankles are noted.

Laboratory studies:	
Erythrocyte sedimentation rate	90 mm/h
Hemoglobin	10 g/dL (100 g/L)
Leukocyte count	20,000/µL (20×10^9/L), 90% neutrophils
Alanine aminotransferase	80 U/L
Aspartate aminotransferase	70 U/L
Ferritin	6000 ng/mL (6000 µg/L)
Urinalysis	Normal

Chest radiograph shows a small left-sided pleural effusion.

Which of the following is the most likely diagnosis?

(A) Adult-onset Still disease
(B) Cryoglobulinemic vasculitis
(C) Lymphoma
(D) Microscopic polyangiitis
(E) Systemic lupus erythematosus

Item 37

A 49-year-old woman is evaluated for recently worsening joint symptoms. She has a 13-year history of Crohn disease characterized by four to six stools daily and mild crampy abdominal pain. She also has a 1-year history of arthritis. She currently has pain in the left knee, right ankle, and two joints of the right foot; diffuse swelling involving the left third toe; and 30 minutes of morning stiffness. She has been treated with various NSAIDs, which seem to worsen her bowel disease. She has tried, in succession, azathioprine, mesalamine, and methotrexate without notable improvement in her symptoms. She currently is taking methotrexate.

On physical examination, vital signs are normal. The left knee has a small effusion. Dactylitis of the left third toe is present. The right ankle and the right second and third metatarsophalangeal joints are tender to palpation.

Which of the following is the most appropriate long-term treatment?

(A) Adalimumab
(B) Intra-articular glucocorticoid injections
(C) Prednisone
(D) Rituximab

Item 38

A 64-year-old man is evaluated for a 9-month history of a swollen and painful right knee without trauma or injury. The knee has been drained twice; synovial fluid leukocyte counts were between 15,000/μL to 20,000/μL ($15\text{-}20 \times 10^9/L$), predominantly lymphocytes. All stains and cultures have been negative. He also reports a low-grade fever in the evening. He has no history of skin rash or tick bites. He had a positive tuberculin skin test 20 years ago and was treated with isoniazid for an unknown duration. He takes no medications.

On physical examination, vital signs are normal. The right knee is tender and has a moderate effusion, with reduced passive range of motion. The remainder of the physical examination is normal.

Laboratory studies show an erythrocyte sedimentation rate of 48 mm/h and negative Lyme disease serologies.

Chest radiograph shows three small calcified granulomas in the left upper lobe. Plain radiograph of the right knee shows joint space narrowing, osteopenia, and small sinus tracts.

Which of the following is the most appropriate diagnostic test to perform next?

(A) Angiotensin-converting enzyme level
(B) CT of the chest
(C) HLA-B27 testing
(D) Synovial biopsy

Item 39

A 59-year-old woman is evaluated for a 5-year history of bilateral hand pain and stiffness of several hand joints, with enlargement and crookedness developing at some of the hand joints over the past few years. The stiffness is present in the morning and lasts about 30 minutes. One area of enlargement, at the right fourth distal interphalangeal (DIP) joint, has occasionally become abruptly swollen, red, and tender, and is currently inflamed. Family history is significant for deformed and painful, arthritic hand joints in her mother.

On physical examination, vital signs are normal. There are no rashes or nail changes. Grossly deformed digits on both hands with bony enlargement and deviation at the right second, left second and third, and bilateral fourth DIP joints are noted. A tender, erythematous bony nodule is present over the right fourth DIP joint. Significant squaring of the right carpometacarpal joint is also present. The remainder of the musculoskeletal examination is normal.

Laboratory studies show normal erythrocyte sedimentation rate, C-reactive protein, serum urate, rheumatoid factor, and anti-cyclic citrullinated peptide antibodies.

A hand radiograph is shown (see top of next column).

Which of the following is the most likely diagnosis?

(A) Erosive osteoarthritis
(B) Gout
(C) Psoriatic arthritis
(D) Rheumatoid arthritis

ITEM 39

Item 40

A 21-year-old woman is evaluated for a 2-week history of worsening rash and arthritis as well as intermittent low-grade fever. She has a 5-year history of systemic lupus erythematosus (SLE). She has been doing well without active disease for the past 3 years and has been compliant with hydroxychloroquine.

On physical examination, temperature is 37.8 °C (100.0 °F), and blood pressure is 150/86 mm Hg; other vital signs are normal. A malar rash is present. Diffuse tenderness and swelling of multiple small joints of the hands are present. New dependent edema is present.

Laboratory studies show low C3 and C4 complement levels, a serum creatinine level of 1.8 mg/dL (159.1 μmol/L), a urine protein-creatinine ratio of 3200 mg/g, and active urine sediment on microscopic examination.

Which of the following laboratory studies should be done next?

(A) Anti-double-stranded DNA antibodies
(B) Antinuclear antibodies
(C) Anti-Ro/SSA and anti-La/SSB antibodies
(D) Anti-Smith antibodies
(E) Anti-U1-ribonucleoprotein antibodies

Item 41

A 64-year-old woman is evaluated for worsening leg weakness. She was evaluated 2 weeks ago for a 3-week history of lower extremity weakness; laboratory studies showed a serum creatine kinase level of 23,000 U/L. History is notable for hypercholesterolemia treated with lovastatin, which was discontinued at the initial visit.

On physical examination, vital signs are normal. There is no rash. Examination shows 3/5 strength of the quadriceps and hamstrings (4/5 strength 2 weeks ago); 4/5 strength in the deltoids, biceps, and triceps; and 5/5

H CONT.

strength of the neck flexors, neck extensors, and distal upper and lower extremities. The remainder of the examination is normal.

Current laboratory studies show an erythrocyte sedimentation rate of 25 mm/h and a serum creatine kinase level of 20,876 U/L.

In addition to a muscle biopsy, which of the following is most likely to establish the diagnosis?

(A) Anti-cyclic citrullinated peptide antibodies
(B) Anti-cytosolic 5'-nucleotidase 1A antibodies
(C) Anti-histidyl tRNA synthetase antibodies
(D) Anti-HMG Co-A reductase antibodies

Item 42

A 32-year-old woman is evaluated for a 2-year history of dry eyes and dry mouth. She wakes up in the morning with a feeling like something is in her eyes. She cannot eat dry foods without consuming large amounts of water. She has noticed a change in the shape of her face; it has gotten more round. She previously saw an ophthalmologist who found abnormal ocular surface staining consistent with dry eyes. She uses artificial tears as needed.

On physical examination, vital signs are normal. There is no pooled saliva under the tongue. Bilateral parotid and lacrimal enlargement is present. The remainder of the examination is normal.

Antinuclear antibodies, anti-Ro/SSA antibodies, and rheumatoid factor are negative. Screening for HIV and hepatitis B and C is negative. Serum IgG levels are normal.

Chest radiograph is normal.

Which of the following is the most appropriate diagnostic test to perform next?

(A) CT of the chest
(B) Lip biopsy
(C) Parotid biopsy
(D) Schirmer test
(E) Sialography

Item 43

A 67-year-old woman is evaluated for a 3-year history of severe rheumatoid arthritis. She had an inadequate response to methotrexate and low-dose prednisone. She responded well to the addition of infliximab, but eventually the drug lost effect and she required a change in biologic therapy. She has done well with tocilizumab and methotrexate over the past year. She notes several months of prominent fatigue. History is also significant for type 2 diabetes mellitus, hypertension, and hyperlipidemia. Current medications are methotrexate, folic acid, tocilizumab, basal insulin, lisinopril, metoprolol, atorvastatin, ibuprofen, and omeprazole.

On physical examination, vital signs are normal. Joint examination reveals no swollen or tender joints. The remainder of the physical examination is normal.

Laboratory studies:

Hemoglobin	9.3 g/dL (93 g/L)
Leukocyte count	5600/µL (5.6×10^9/L)
Mean corpuscular volume	111 fL
Platelet count	330,000/µL (330×10^9/L)

Which of the following is the most likely cause of the anemia?

(A) Inflammation
(B) Iron deficiency
(C) Methotrexate
(D) Tocilizumab

Item 44

H

A 55-year-old man is evaluated for a swollen and painful right knee of 2 days' duration. One week ago, he injured both knees when he fell on the concrete pavement. He previously had two episodes of acute gout affecting the right first toe. He takes no medications.

On physical examination, temperature is 38.1 °C (100.6 °F); other vital signs are normal. There are superficial scrapes on the front of both knees. The right knee is swollen and tender and has a moderate effusion with redness; restriction of both passive and active range of motion due to pain is noted. The remainder of the examination is normal.

Plain radiograph of the right knee shows mild joint-space narrowing, an effusion, and soft-tissue swelling.

Which of the following is most likely to establish the diagnosis?

(A) Aspiration of the right knee
(B) Blood cultures
(C) Erythrocyte sedimentation rate
(D) MRI of the right knee

Item 45

A 65-year-old woman is evaluated during a follow-up visit for giant cell arteritis. Prior to confirmation of the diagnosis she was started on 60 mg of prednisone daily and low-dose aspirin. The diagnosis was subsequently confirmed with a temporal artery biopsy. She is otherwise healthy and takes no additional medications.

On physical examination, vital signs are normal. There is a healing incision over the right temporal artery.

Dual-energy x-ray absorptiometry (DEXA) was performed 6 months ago. Based upon the results of the Fracture Risk Assessment Tool, the patient was classified as medium risk (10%-20%) for a major osteoporotic fracture in the next 10 years.

Which of the following is the most appropriate next step in management?

(A) Begin alendronate
(B) Begin teriparatide
(C) Repeat DEXA
(D) No additional testing or therapy

Item 46

A 48-year-old woman is evaluated for 3 months of progressive exertional dyspnea. She was diagnosed with limited cutaneous systemic sclerosis 4 years ago. She also has Raynaud phenomenon and gastroesophageal reflux disease. Medications are nifedipine and omeprazole.

On physical examination, vital signs are normal. Oxygen saturation is 95% at rest, breathing ambient air. Scattered telangiectasias are present on the face, nose, and hands. Sclerodactyly at the fingers and tightness of the skin at the neck are noted. There is increased intensity of the pulmonic sound and a widened split S_2 on cardiac examination. Lungs are clear to auscultation.

Electrocardiogram and chest radiograph are normal.

Which of the following is the most likely cause of her symptom?

(A) Interstitial lung disease
(B) Myocardial fibrosis
(C) Pulmonary arterial hypertension
(D) Venous thromboembolic disease

Item 47

A 67-year-old man is evaluated for a 5-year history of right knee pain, with morning stiffness lasting 20 minutes.

On physical examination, vital signs are normal. Limitation of flexion and extension of the right knee is noted, with bony enlargement and tenderness to palpation along the medial and lateral joint lines. Crepitus is noted upon range of motion of the right knee. Bony enlargement of a few proximal interphalangeal and distal interphalangeal joints on both hands is present.

Which of the following is the most appropriate initial imaging study?

(A) CT
(B) MRI
(C) Radiography
(D) Ultrasonography

Item 48

A 50-year-old woman is evaluated for a 1-month history of pain around the lower part of the inner left knee. The pain is aggravated by ascending stairs and rising from a seated position. She has a history of knee osteoarthritis, for which she takes acetaminophen. Her new pain is different in location and intensity compared with her prior pain. She has no other pertinent personal or family history.

On physical examination, vital signs are normal. Tenderness to palpation and slight swelling over the proximal medial tibia about 6 cm below the anteromedial joint margin of the knee are noted. Examination of the knee shows no crepitus, minimal pain along the medial joint line, and no pain on valgus stress; anterior and posterior drawer signs are negative.

Which of the following is the most likely diagnosis?

(A) Medial collateral ligament tear
(B) Meniscal tear
(C) Pes anserine bursitis
(D) Quadriceps tendonitis

Item 49

A 48-year-old woman is evaluated for a 2-month history of increased dyspnea, wheezing, and nonproductive cough. She also reports intermittent pain and swelling in the wrists and knees for the past 6 months. She was diagnosed with scleritis of the left eye 1 month ago that improved with glucocorticoid drops. She also had two episodes of right pinna pain, redness, and swelling. Medications are prednisolone acetate ophthalmic and ibuprofen as needed for joint pain.

On physical examination, vital signs are normal. There is no rash. Sclerae are normal. Hearing is normal. The trachea is tender. On lung auscultation, wheezing is heard in both lung fields with no crackles or rubs. Swelling of the wrists and knees is present.

The ear findings are shown.

Laboratory studies show an erythrocyte sedimentation rate of 60 mm/h and a normal complete blood count with differential except for a hemoglobin level of 11 g/dL (110 g/L).

Chest radiograph is normal. CT of the chest reveals bronchial thickening with strictures; there is air trapping distal to the strictures.

Which of the following is the most likely diagnosis?

(A) Cogan syndrome
(B) Polyarteritis nodosa
(C) Relapsing polychondritis
(D) Systemic lupus erythematosus

Item 50

A 28-year-old woman requests a referral to an obstetrician. She has been attempting to conceive, and her menstrual period is now 3 weeks late. Her home pregnancy test was positive. She has a 2-year history of seropositive rheumatoid arthritis. Her only medication is hydroxychloroquine; methotrexate was stopped 4 months ago in anticipation of conception.

On physical examination, vital signs are normal. Swelling of the second and third metacarpophalangeal joints of the right hand is noted.

Pregnancy test is positive.

Which of the following is the most appropriate treatment at this time?

(A) Add etanercept
(B) Add leflunomide
(C) Discontinue hydroxychloroquine
(D) No change in therapy

Item 51

A 68-year-old man is evaluated in the emergency department for a 4-week history of severe lower left leg pain, swelling, and redness. The pain is localized to the shin and ankle. He was previously diagnosed with cellulitis, but no improvement was seen with sequential courses of cephalexin and clindamycin. History is also significant for gout and atrial fibrillation. Medications are allopurinol, colchicine, and apixaban.

On physical examination, vital signs are normal. The left lower shin is erythematous, warm, and tender to palpation; the erythema is not sharply demarcated. The left ankle is swollen, warm, and tender. There is no ulceration or skin breakdown over lower legs or feet. Solid masses at the extensor surfaces of both elbows are present.

Laboratory studies show an erythrocyte sedimentation rate of 90 mm/h and a serum urate level of 6.8 mg/dL (0.40 mmol/L). Blood cultures performed 1 week ago were negative.

Plain radiographs of the left shin and ankle show no changes suggestive of osteomyelitis.

Aspiration of the left ankle yields no fluid.

Which of the following is the most appropriate next step in management?

(A) Indomethacin
(B) Intravenous clindamycin
(C) MRI of the lower leg
(D) Prednisone
(E) Surgical debridement

Item 52

A 47-year-old woman is evaluated during a follow-up visit for a 2-year history of symptoms diagnosed 4 months ago as fibromyalgia. She reports ongoing widespread pain, fatigue, and difficulty concentrating. She does not have trouble falling asleep, but her sleep is nonrestorative. She was seen 3 months ago, and was given duloxetine and instructed to exercise. The medication produced a modest benefit, but she continues to have difficulty working as a housekeeper. She can only exercise to a limited extent without experiencing disabling pain for the next several days. On a 9-point pain scale, her pain was formerly an 8; after initiation of duloxetine, it decreased to a 5.

On physical examination, vital signs are normal. There is tenderness between the shoulder blades and at the occiput, trapezius, elbows, and hips bilaterally. There is no joint swelling.

Which of the following is the most appropriate treatment?

(A) Add meloxicam
(B) Add pregabalin
(C) Discontinue duloxetine; start gabapentin
(D) Discontinue duloxetine; start sertraline

Item 53

A 44-year-old woman is evaluated for recent-onset dyspnea on exertion and a nonproductive cough. She has a 1-year history of diffuse cutaneous systemic sclerosis. She takes no medications.

On physical examination, vital signs are normal. Oxygen saturation is 96% breathing ambient air. Skin thickening is noted on the face, neck, anterior chest, upper extremities to the mid forearm bilaterally, and lower extremities to the mid calf bilaterally. Heart examination is normal. There are fine crackles at the bases of both lungs on auscultation.

Anti-Scl-70 antibodies are strongly positive.

Pulmonary function tests:

	Today	6 Months Ago
FVC	85% of predicted	96% of predicted
D_{LCO}	65% of predicted	75% of predicted

High-resolution CT scan of the chest shows lower lobe ground-glass opacities in a pattern consistent with nonspecific interstitial pneumonitis.

Which of the following is the most appropriate treatment?

(A) Cyclophosphamide
(B) High-dose glucocorticoids
(C) Methotrexate
(D) Mycophenolate mofetil

Item 54

A 30-year-old woman is evaluated for a 3-month history of pain and swelling of the proximal interphalangeal (PIP) joints. She has difficulty performing tasks such as gripping or typing. Naproxen provides minimal relief.

On physical examination, vital signs are normal. There are no rashes or oral ulcers. Swelling and tenderness of the PIP joints bilaterally are noted. Pain occurs with flexion of the fingers. There is blanching coloration of the fingers and cyanosis at the fingertips. Nailfold examination shows a few dilated capillary loops. There are no cardiopulmonary friction rubs. The remainder of the examination is normal.

Laboratory studies performed 1 month ago showed the following: a positive antinuclear antibody titer of 1:320 with a speckled pattern; negative anti-double-stranded DNA antibodies, anti-Smith antibodies, anti-U1-ribonucleoprotein antibodies, anti-Ro/SSA antibodies, anti-La/SSB antibodies, anti-cyclic citrullinated peptide antibodies, and rheumatoid factor; and normal complete blood count with differential, serum creatinine, and urinalysis.

Radiographs of the hands are normal.

Which of the following is the most appropriate management?

(A) Add hydroxychloroquine
(B) Discontinue naproxen; begin ibuprofen
(C) Obtain plain radiography of the feet
(D) Repeat anti-double-stranded DNA antibodies
(E) Repeat antinuclear antibodies

Item 55

A 78-year-old woman is evaluated for knee pain that occurs when walking, ascending and descending stairs, and getting up from a seated position. She was diagnosed with bilateral knee osteoarthritis 10 years ago. She has tried acetaminophen, up to 3000 mg/d in divided doses, without significant relief.

Previous examinations have documented bony hypertrophy and crepitus on range of motion of the knees with weakness of the quadriceps.

She is scheduled to begin physical therapy. Topical diclofenac is prescribed.

The patient should be warned about which of the following possible side effects?

(A) Eye and mucous membrane irritation
(B) Localized lipoatrophy
(C) Localized skin hypopigmentation
(D) Localized skin rash

Item 56

A 78-year-old woman is evaluated for a 2-week history of pain and swelling in the left wrist. In the past year, she experienced two similar episodes, one in the left knee and one in the left wrist, each resolving after 3 weeks.

On physical examination, the patient appears well. Vital signs are normal. The left wrist is swollen, warm, and tender, with decreased range of motion.

Laboratory studies show an erythrocyte sedimentation rate of 53 mm/h and a serum urate level of 3.8 mg/dL (0.22 mmol/L).

A plain radiograph of the left wrist is shown.

Which of the following is the most likely diagnosis?

(A) Acute calcium pyrophosphate crystal arthritis
(B) Gout
(C) Infectious arthritis
(D) Palindromic rheumatism

Item 57

A 48-year-old man is evaluated for a 3-week history of slowly progressive dyspnea on exertion, left-sided chest pain, and fever. He has a 20-year history of anti-cyclic citrullinated peptide antibody-positive rheumatoid arthritis. Prior to starting a tumor necrosis factor α inhibitor, his tuberculin skin test was nonreactive. Medications are methotrexate, etanercept, and folic acid. Despite these medications, he has morning stiffness for 1 hour and has swelling of the joints in his hands, wrists, and feet.

On physical examination, temperature is 37.8 °C (100 °F), blood pressure is 148/84 mm Hg, pulse rate is 100/min, and respiration rate is 24/min. Breath sounds are absent at the right base, with dullness on percussion. Joint changes typical of rheumatoid arthritis are present, along with swelling and tenderness of eight joints. The remainder of the examination is normal.

Chest radiograph shows a moderate right-sided pleural effusion.

Pleural fluid analysis following a thoracentesis shows a leukocyte count of 3500/µL (3.5×10^9/L) with 4% neutrophils, 87% lymphocytes, and 9% monocytes; a pleural fluid glucose level of 6.0 mg/dL (0.3 mmol/L); a pH of 7.2; and a pleural fluid lactate dehydrogenase level of 900 U/L. A pleural fluid adenosine deaminase measurement is low, at 30 U/L.

Which of the following is the most likely cause of the pleural effusion?

(A) Malignancy
(B) Parapneumonic effusion
(C) Rheumatoid pleuritis
(D) Tuberculosis

Item 58

A 36-year-old woman is hospitalized for acute kidney injury and hypertension. She has an 18-month history of diffuse cutaneous systemic sclerosis. She was well and taking no medications prior to hospitalization.

On physical examination, temperature is 36.6 °C (97.8 °F), blood pressure is 240/130 mm Hg, pulse rate is 100/min, and respiration rate is 18/min. Cardiac examination reveals a prominent S_4. Pulmonary auscultation reveals bibasilar crackles. Cutaneous examination reveals sclerodactyly of both hands as well as skin induration of the forearms and anterior chest.

Laboratory studies:

Hemoglobin	8.0 g/dL (80 g/L)
Platelet count	90,000/µL (90×10^9/L)
Creatinine	4.9 mg/dL (433.1 µmol/L)
Urinalysis	2+ protein; a few hyaline casts

H CONT. Peripheral blood smear shows schistocytes and decreased platelets.

Which of the following is the most likely diagnosis?

(A) Disseminated intravascular coagulation
(B) Hemolytic uremic syndrome
(C) Scleroderma renal crisis
(D) Thrombotic thrombocytopenic purpura

H

Item 59

A 31-year-old man is evaluated in the emergency department for fever and red, painful eyes. He reports a 1-month history of intermittent painful oral and genital ulcers, knee pain, and fever, and 1 week of bilateral eye redness, pain, and photophobia.

On physical examination, temperature is 38.3 °C (101.0 °F), and pulse rate is 100/min. Slit lamp examination reveals white cells in the anterior chambers of both eyes. There are aphthous ulcers on the tongue and one aphthous ulcer on the scrotum. Swelling and warmth are noted in both knees. The heart, lung, abdominal, and neurologic examinations are normal.

Which of the following is the most likely diagnosis?

(A) Behçet syndrome
(B) Crohn disease
(C) Sarcoidosis
(D) Systemic lupus erythematosus

Item 60

An 82-year-old woman is evaluated for a 3-year history of chronic discomfort and stiffness in the hands, wrists, and shoulders. Some of these joints intermittently become acutely swollen and warm. She currently has 3 days of severe left wrist pain and swelling. She previously had been diagnosed with seronegative rheumatoid arthritis; there was no improvement with sulfasalazine or intravenous infliximab, both of which were discontinued. Short courses of prednisone have alleviated the acute attacks of arthritis. History is also significant for hypertension and stage 3 chronic kidney disease. Medications are hydrochlorothiazide, metoprolol, and losartan.

On physical examination, vital signs are normal. Decreased range of motion of both wrists and a few metacarpophalangeal (MCP) joints is noted, and shoulder abduction is limited to 90 degrees passively. The left wrist is swollen and tender. There are no subcutaneous nodules at the elbows, hands, or heels.

Laboratory studies:

Erythrocyte sedimentation rate	51 mm/h
Urate	4.3 mg/dL (0.25 mmol/L)
Rheumatoid factor	15 U/mL (15 kU/L)
Anti-cyclic citrullinated peptide antibodies	Negative

Radiographs show osteoarthritic changes at the second through fourth MCP joints bilaterally, both wrists, and glenohumeral joints. Chondrocalcinosis is seen in the knees and both wrists. There are no periarticular erosions in the wrists or hands.

Which of the following is the most appropriate treatment?

(A) Adalimumab
(B) Allopurinol
(C) Low-dose prednisone
(D) Methotrexate
(E) NSAID therapy

Item 61

H

A 63-year-old man is evaluated for a 2-month history of progressive lower extremity weakness. He reports increased difficulty arising from a chair, climbing stairs, and reaching overhead. He was diagnosed with polymyositis 6 months ago; prednisone and azathioprine were initiated at that time, with clinical improvement. He currently takes prednisone, 20 mg/d, and azathioprine, 100 mg/d.

On physical examination, vital signs are normal. The patient cannot arise from the chair without using his arms to push off and can squat only by using his hands to hold on to the chair. He has cushingoid features and scattered ecchymoses on the forearms. There is no rash.

Laboratory studies show a serum creatine kinase level of 160 U/L.

Which of the following is the most appropriate management?

(A) Order electromyography
(B) Order muscle biopsy
(C) Reduce azathioprine dose
(D) Reduce prednisone dose

Item 62

A 26-year-old woman is evaluated for a 4-week history of progressive dyspnea on exertion. She has experienced malaise and myalgia for the past 6 months, noting that her arms ache when she does physical activity with them. She was previously healthy. She reports no rashes, headache or jaw claudication, gastrointestinal symptoms, or neurologic symptoms.

On physical examination, blood pressure is 120/60 mm Hg in the right arm and 95/50 in the left arm, pulse rate is 80/min, and respiration rate is 18/min. There is no rash. A reduced radial pulse in the left upper extremity is noted. A grade 2/6 decrescendo diastolic murmur at the left sternal border is heard. The lungs are clear. There is no synovitis. Strength is normal.

Laboratory studies:

Complete blood count	Normal, except for anemia
Erythrocyte sedimentation rate	90 mm/h
Hemoglobin	10 g/dL (100 g/L)
Creatinine	Normal
Antinuclear antibodies	Negative
Urinalysis	Negative

Transthoracic echocardiogram shows mild to moderate aortic valve regurgitation, dilated aortic root, normal valve

leaflets, left ventricle dilation, and normal left ventricular ejection fraction.

Which of the following is the most likely diagnosis?

(A) Giant cell arteritis
(B) IgA vasculitis
(C) Kawasaki disease
(D) Polyarteritis nodosa
(E) Takayasu arteritis

Item 63

A 25-year-old woman is evaluated for a 2-month history of joint pain and swelling involving the hands, knees, and feet.

On physical examination, vital signs are normal. Swelling is noted at the second and third metacarpophalangeal joints of both hands, the left wrist, both knees, and the second through fifth metatarsophalangeal joints of both feet.

Laboratory studies are positive for rheumatoid factor and anti-cyclic citrullinated peptide antibodies.

Radiographs of the hands and feet are normal.

In addition to methotrexate and short-term prednisone, which of the following should be initiated?

(A) Folic acid
(B) Niacin
(C) Thiamine
(D) Vitamin C

H

Item 64

A 55-year-old man is evaluated for a 3-week history of progressive joint pain, swelling of the ankles, and occasional dry cough. He also reports a 2-day history of low-grade fever and painful red lumps on his shins. He has no other significant history and takes no medications.

On physical examination, temperature is 37.8 °C (100.0 °F): other vital signs are normal. The chest is clear to auscultation. Swelling and warmth of the ankles are noted. There are three raised, erythematous, and indurated subcutaneous nodules on the right anterior shin and one on the left anterior shin.

Laboratory studies show a normal complete blood count and an erythrocyte sedimentation rate of 70 mm/h.

Chest radiograph shows bilateral hilar adenopathy but is otherwise normal.

Which of the following is the most appropriate management?

(A) Biopsy of the hilar node
(B) Biopsy of a shin lesion
(C) Rheumatoid factor testing
(D) Synovial fluid cultures
(E) No further testing

H

Item 65

A 30-year-old woman is evaluated in the emergency department for worsening abdominal pain over past 2 days as well as a rash starting in the feet and spreading up to the thighs and buttocks. She feels generally achy in the joints and muscles. She reports no diarrhea, vomiting, or nausea. She was previously healthy. She takes no medications.

On physical examination, vital signs are normal. A palpable purpuric rash is noted on the feet, legs, and buttocks. There is peri-umbilical tenderness to palpation.

Stool is positive for occult blood.

Laboratory studies:

Complete blood count with differential	Normal
Erythrocyte sedimentation rate	70 mm/h
Antinuclear antibodies	Negative
ANCA	Negative
Urinalysis	Normal

CT of the abdomen shows a short segment of small bowel thickening and edema.

Which of the following is the most appropriate test to establish the diagnosis?

(A) Kidney biopsy
(B) Mesenteric angiography
(C) Serum IgA levels
(D) Skin biopsy with immunofluorescence

Item 66

A 53-year-old man is evaluated for a 5-year history of recurrent gout attacks involving the base of the great toes, mid feet, and ankles. Episodes are becoming more frequent and severe. History is also significant for hypertension and stage 3 chronic kidney disease. Medications are lisinopril and metoprolol. The patient is of Thai descent.

On physical examination, vital signs are normal. There are no tophi or swollen joints.

Laboratory studies show a serum urate level of 9.2 mg/dL (0.54 mmol/L).

Which of the following is the most appropriate next step in management?

(A) Begin allopurinol
(B) Begin probenecid
(C) Measure antinuclear antibodies
(D) Order HLA-B*5801 allele testing

Item 67

A 45-year-old man is evaluated for a 3-month history of swollen and painful hands and toes of both feet, without trauma or injury. He also has morning stiffness of the small joints of the hands and feet lasting 2 hours. He takes no medications.

On physical examination, vital signs are normal. Diffuse tenderness and swelling are noted in the third and fourth toes of the right foot, fourth toe of the left foot, and third and fourth digits of the left hand. The remainder of the joint examination is normal.

The appearance of the hand digits is shown (see top of next page).

Plain radiographs of the feet show joint-space narrowing and soft-tissue swelling of the digits without erosions.

ITEM 67

Which of the following disorders is most likely to be associated with this patient's presentation?

(A) Infectious arthritis
(B) Rheumatoid arthritis
(C) Spondyloarthritis
(D) Systemic lupus erythematosus

H

Item 68

A 54-year-old man is evaluated for a 5-month history of mid lower back pain. The pain radiates from the center of his back to his flanks and abdomen. He has intermittent numbness in the areas of the pain. He also reports a 2.3-kg (5-lb) weight loss over the past 3 months. He emigrated from India to the United States 20 years ago and travels to India yearly. He has tried ibuprofen for the pain without relief and takes no other medications.

On physical examination, temperature is 38.2 °C (100.8 °F); other vital signs are normal. Examination of the spine reveals kyphosis, tenderness to palpation, and paraspinal muscle tightness around T10. Decreased sensation to light touch along the T10 dermatome is noted.

Chest radiograph shows calcified granuloma in the right upper lobe. Thoracic spine radiograph shows marked kyphosis and erosive changes and collapse of the anterior portions of the T10 and T11 vertebral bodies, destruction of the T10-11 disk space, and surrounding fusiform paravertebral swelling.

Which of the following is the most likely diagnosis?

(A) Herniated intervertebral disk
(B) Multiple myeloma
(C) Osteoporosis
(D) Tuberculous vertebral osteomyelitis

Item 69

A 43-year-old man is evaluated for knee, hip, shoulder, and arm stiffness, worsening over the past year. He also has pain in the arms, legs, neck, and torso, both on and between the joints. He states that his discomfort is continuous. He also reports chronic fatigue, lack of sleep, a band-like headache, and difficulty concentrating. He also has intermittent constipation and diarrhea. He takes acetaminophen and ibuprofen as needed for pain without much benefit.

On physical examination, the patient appears tired and anxious, with no acute distress. Vital signs are normal. He has minimal tenderness on palpation of multiple muscle groups. Full range of motion of all joints without crepitus is noted. There is no joint swelling or rash.

Laboratory studies, including complete blood count, erythrocyte sedimentation rate, serum creatine kinase, and thyroid-stimulating hormone, are within normal limits.

Which of the following is the most likely diagnosis?

(A) Fibromyalgia
(B) Hypothyroidism
(C) Osteoarthritis
(D) Rheumatoid arthritis

Item 70

H

A 25-year-old woman is hospitalized for a 4-week history of swelling of the legs, weight gain, and shortness of breath on exertion. She was diagnosed with systemic lupus erythematosus 1 year ago when she presented with polyarthritis, rash, and alopecia. She was initially treated with hydroxychloroquine and prednisone with a good response.

On physical examination, blood pressure is 142/96 mm Hg; other vital signs are normal. There is pitting edema of the lower extremities extending to the knees. The remainder of the physical examination is normal.

Laboratory studies:

Erythrocyte sedimentation rate	68 mm/h
Hematocrit	38%
Complements (C3 and C4)	Low
Creatinine	1.0 mg/dL (88.4 µmol/L)
Anti-Smith antibodies	Positive
Anti-double-stranded DNA antibodies	Positive
Urinalysis	3+ protein; no erythrocytes; no leukocytes; no casts
Urine protein	6000 mg/24 h

The patient is started on prednisone, along with diuretics and an ACE inhibitor.

Kidney biopsy results show class V (membranous) lupus nephritis with absent chronicity and mild activity.

Which of the following is the most appropriate treatment of the kidney disease?

(A) Adalimumab
(B) Belimumab
(C) Cyclophosphamide
(D) Methotrexate
(E) Mycophenolate mofetil

Item 71

A 45-year-old woman is evaluated for increased pain and swelling in her left knee and right ankle. She has a 5-year history of psoriatic arthritis and psoriasis treated with methotrexate, which previously improved her joint and skin symptoms. She also takes folic acid.

On physical examination, vital signs are normal. There is an erythematous, flaky patch on the left elbow. Nail pitting is present. The left knee has a moderate effusion and is warm without erythema, with discomfort on range of motion. The right ankle is swollen anteriorly, with discomfort on range of motion in flexion and extension.

Laboratory studies show an erythrocyte sedimentation rate of 30 mm/h.

Plain radiographs of the left knee show mild medial and lateral joint space narrowing.

Aspiration of the left knee shows a leukocyte count of 7500/µL (7.5×10^9/L), with 50% neutrophils.

Which of the following is the most efficacious medication to add to this patient's treatment regimen?

(A) Abatacept
(B) Hydroxychloroquine
(C) Infliximab
(D) Rituximab

Item 72

A 24-year-old man is evaluated for increasing left buttock pain that worsens over the course of the day. It is improved by exercise and does not improve with rest. The pain had a gradual onset 1 year ago without a clear precipitant. At that time, radiographs were unremarkable, and physical therapy provided no benefit. He has stopped exercising because of the increasing discomfort. Family history includes ankylosing spondylitis in his father. The patient takes no medications.

On physical examination, vital signs are normal. Normal range of motion of the lumbar spine is noted. There is no reduction in lateral bending and no limitation of cervical spine motion in any plane. There are no warm, erythematous, or swollen joints.

Laboratory studies show the presence of HLA-B27; normal complete blood count and C-reactive protein; and negative rheumatoid factor and anti-cyclic citrullinated peptide antibodies.

Radiographs of the lumbar spine are normal.

Which of the following is the most appropriate treatment?

(A) Diclofenac
(B) Etanercept
(C) Methotrexate
(D) Sulfasalazine

Item 73

A 58-year-old man is evaluated for a 3-year history of left knee stiffness, which was intermittent but has become more persistent in the past 4 months. He reports no daily pain but has knee stiffness for 10 minutes in the morning and when he sits for an extended period of time. He reports no swelling and no knee buckling or locking. History is significant for gastroesophageal reflux disease and peptic ulcer disease diagnosed 6 months ago now treated with omeprazole. He prefers not to take medications for his knee symptoms.

On physical examination, vital signs are normal. BMI is 24. Crepitus and medial joint line tenderness to palpation are noted. There is no redness, effusion, or signs of knee instability.

Left knee radiograph shows mild medial joint space narrowing and spiking of the tibial spines.

Which of the following is the most appropriate management?

(A) Ibuprofen
(B) Intra-articular glucocorticoids
(C) Left knee MRI
(D) Physical therapy

Item 74

A 21-year-old woman is evaluated for an 8-week history of fatigue and low-grade fever. Last week she developed a facial rash. She takes a multivitamin.

On physical examination, vital signs are normal. The remainder of the examination is normal.

The appearance of the face is shown.

Which of the following is the most likely diagnosis for the rash?

(A) Acute cutaneous lupus erythematosus
(B) Erysipelas
(C) Rosacea
(D) Seborrheic dermatitis
(E) Subacute cutaneous lupus erythematosus

Item 75

H

A 53-year-old woman is evaluated for intermittent sensory loss in the hands and an occasional shock-like sensation from the neck down the back with neck flexion. She has not noted any weakness. She has a 15-year history of

H

CONT.

rheumatoid arthritis. Medications are methotrexate, etanercept, and folic acid.

On physical examination, vital signs are normal. Ulnar deviation of the metacarpophalangeal joints on both hands is present without active synovitis. Neck flexion triggers her symptoms. There is no muscle atrophy at the hands. Tinel and Phalen signs at the wrist are negative. Reflexes, strength, and sensation of the upper and lower extremities are normal.

Which of the following is the most appropriate diagnostic test to perform next?

(A) Electrodiagnostic studies of the upper extremities
(B) Flexion/extension radiography of the cervical spine
(C) Serum vitamin B_{12} level
(D) Thyroid-stimulating hormone level

H

Item 76

A 36-year-old woman is brought to the emergency department by her family for mental status changes. For the past 2 days, the family has noticed forgetfulness, confusion, and alteration of personality. She has a 5-year history of systemic lupus erythematosus (SLE), which has been quiescent. One week ago, she developed fatigue, a diffuse erythematous rash, and polyarthritis. There is no history of focal deficits, seizures, or neck stiffness. She does not have a fever. History is also significant for hypertension. Medications are losartan, hydroxychloroquine, prednisone, 5 mg/d, and a daily multivitamin.

On physical examination, the patient is alert, awake, and follows commands but is not oriented to place and time. She is afebrile, and vital signs are normal. Neurologic examination other than mental status is normal, with no motor or sensory deficits. There is no neck stiffness. The remainder of the examination is normal.

Laboratory studies:

Erythrocyte sedimentation rate	42 mm/h
Complements (C3 and C4)	Low
C-reactive protein	0.2 mg/dL (2.0 mg/L)
Creatinine	1.4 mg/dL (123.8 µmol/L)
Antinuclear antibodies	Titer: 1:320
Cerebrospinal fluid analysis	Normal cell count and glucose; protein, 85 mg/dL (850 mg/L)

CT scan of the brain is normal. MRI with MR angiogram of the brain shows multiple small punctate white matter changes in periventricular areas. There is no evidence of vasculitis or blood vessel narrowing.

Which of the following is the most likely diagnosis?

(A) Acute bacterial meningitis
(B) Neuropsychiatric systemic lupus erythematosus
(C) Status epilepticus
(D) Steroid-induced psychosis

Item 77

An 18-year-old man is seen for a physical examination required to join the ice hockey team at his university. He was diagnosed with Kawasaki disease at age 5 years; he does not recall how or if he was treated for the disease. He has medical records from his pediatrician who has provided ongoing care until now.

Physical examination, including vital signs, is normal.

Which of the following disease complications is most important in determining the nature of his sports evaluation and prognosis?

(A) Bundle branch block
(B) Coronary artery aneurysm
(C) Myocarditis
(D) Pericarditis

Item 78

A 38-year-old woman seeks advice regarding preventative measures for developing osteoarthritis. One year ago, she started an exercise regimen of running approximately 20 miles per week. She has no joint pain when running. History is significant for polycystic ovary syndrome. Family history is notable for both parents having knee replacements for osteoarthritis. Her only medication is an oral contraceptive.

On physical examination, vital signs are normal. BMI is 31. Musculoskeletal examination is normal.

Which of the following is the most appropriate preventive measure for this patient?

(A) Begin chondroitin sulfate supplements
(B) Begin vitamin D
(C) Recommend weight loss
(D) Stop running

Item 79

H

A 32-year-old woman is evaluated in the emergency department for a 2-day history of headache and vomiting. She was diagnosed with Raynaud phenomenon 1 year ago and gastroesophageal reflux disease 6 months ago. Her only medication is omeprazole.

On physical examination, temperature is 38.0 °C (100.4 °F), blood pressure is 240/140 mm Hg, pulse rate is 88/min, respiration rate is 16/min, and oxygen saturation is 96% breathing ambient air. Skin findings are digital pitting at the ends of the fingers, thickening of the skin over the fingers and dorsum of the hands, and thickening with poikilodermic changes over the skin of the anterior chest.

Laboratory studies:

Hematocrit	32%
Platelet count	75,000/µL (75×10^9/L)
Creatinine	1.5 mg/dL (132.6 µmol/L)
Urinalysis	2+ protein; no blood

Peripheral blood smear shows diminished platelet numbers and schistocytes.

Which of the following is the most appropriate treatment?

(A) Captopril
(B) Cyclophosphamide
(C) Methylprednisolone
(D) Nitroprusside

Item 80

A 32-year-old woman is evaluated during a follow-up visit for a 3-month history of arthralgia affecting the hands, wrists, knees, and feet. At her initial visit 3 weeks ago, joint examination demonstrated nine tender and six swollen joints; prednisone, 10 mg/d, was initiated at that time. She now reports some benefit from the prednisone for morning stiffness and joint pain. Family history is notable for her mother with seropositive erosive rheumatoid arthritis.

Laboratory studies from 3 weeks ago showed an erythrocyte sedimentation rate of 38 mm/h, and high levels of rheumatoid factor and anti–cyclic citrullinated peptide antibodies.

On physical examination today, vital signs are normal. The second and third proximal interphalangeal joints on the right hand and the second metacarpophalangeal joint on the left hand are tender and swollen. Her clinical disease activity index score is 12, indicating moderate disease activity.

Radiographs of the hands and feet are normal.

Which of the following is the most appropriate treatment at this time?

(A) Increase prednisone
(B) Initiate ibuprofen
(C) Initiate methotrexate
(D) Initiate mycophenolate mofetil

Item 81

A 34-year-old woman is evaluated for a 6-month history of gradually increasing pain in the left groin with some radiation to the left buttock, particularly with stair climbing. She has a 2-year history of lupus nephritis. Medications are hydroxychloroquine, mycophenolate mofetil, and prednisone.

On physical examination, vital signs are normal. Musculoskeletal examination reveals weakness of the left hip flexors. Decreased passive range of motion of the left hip in both external and internal rotation with pain is noted.

Which of the following is the most appropriate initial test to evaluate the patient's hip pain?

(A) Dual-energy x-ray absorptiometry
(B) MRI of the left hip
(C) Plain radiography of the left hip
(D) Ultrasonography

H Item 82

A 65-year-old man is evaluated in the emergency department for left knee pain and swelling of 10 days' duration. He reports no other joint pain. He has a 15-year history of rheumatoid arthritis, which has been well controlled with methotrexate and adalimumab. He began taking over-the-counter naproxen 8 days ago, without improvement.

On physical examination, temperature is 38.1 °C (100.6 °F), blood pressure is 106/68 mm Hg, and pulse rate is 97/min. The left knee is erythematous, warm, and tender to touch, with a large effusion; range of motion is limited, especially flexion. Examination of the other joints is normal.

Laboratory studies show an erythrocyte sedimentation rate of 53 mm/h and a leukocyte count of 12,000/µL (12×10^9/L).

Which of the following is the most appropriate next step in management?

(A) Perform arthrocentesis
(B) Start colchicine
(C) Start prednisone
(D) Start sulfasalazine

Item 83

A 52-year-old man is evaluated for an episodic rash on the legs for the past month; diffuse arthralgia and Raynaud phenomenon for 2 months; and burning pain and tingling of the feet for 3 months. He has a remote history of intravenous drug use. He takes no medications.

On physical examination, vital signs are normal. Cyanosis of the fingertips is noted. There is no sclerodactyly, dilated capillary loops of fingernail beds, or digital pitting. Palpable purpura is present on the lower legs. Reduced sensation to pinprick of the soles of the feet is noted. The remainder of the examination is normal.

Laboratory studies:

Erythrocyte sedimentation rate	70 mm/h
C3	Normal
C4	Low
Rheumatoid factor	Positive
Antinuclear antibodies	Negative
Cryoglobulins	Positive
Urinalysis	1+ blood; 2+ protein

Chest radiograph is normal. Skin biopsy shows leukocytoclastic vasculitis.

Which of the following is the most appropriate test to perform next?

(A) Anticentromere antibodies
(B) Anti-cyclic citrullinated peptide antibodies
(C) Anti-Jo-1 antibodies
(D) Anti-U1-ribonucleoprotein antibodies
(E) Hepatitis C antibodies

Item 84

A 30-year-old man is evaluated for a 7-year history of intermittent pain and swelling in multiple fingers and toes, along with 1 hour of morning stiffness. History is notable for an episode of swelling of the left second toe 2 years ago. He has been treated with multiple NSAIDs over the years, with ibuprofen being the most efficacious.

On physical examination, vital signs are normal. Mild soft-tissue swelling of the fourth and fifth distal interphalangeal (DIP) joints bilaterally is present. Tenderness is present with metacarpophalangeal joint squeeze on the left. There is no rash.

The patient's nail findings are shown (see top of next page).

ITEM 84

Laboratory studies show a serum urate level of 6.7 mg/dL (0.40 mmol/L); rheumatoid factor and anti-cyclic citrullinated peptide antibodies are negative.

Plain radiographs of the hands show pencil-in-cup deformities of the DIP joints of the third and fourth digits bilaterally; there is no periarticular osteopenia.

Which of the following is the most likely diagnosis?

(A) Gouty arthritis
(B) Psoriatic arthritis
(C) Reactive arthritis
(D) Rheumatoid arthritis

H

Item 85

A 32-year-old woman is evaluated for an 8-week history of fatigue and low-grade fever. She also reports swelling and tenderness of the hand joints, along with morning stiffness lasting 2 hours. Over the past 2 weeks, she has been taking naproxen with relief. Last week, she developed swelling of the legs and gained 4.5 kg (10 lb).

On physical examination, blood pressure is 152/96 mm Hg; other vital signs are normal. A malar rash is present. Active tenderness and swelling of multiple joints of the hands are noted. There is pitting edema of the lower extremities. The remainder of the physical examination is normal.

Laboratory studies:

Erythrocyte sedimentation rate	88 mm/h
Hematocrit	38%
Complements (C3, C4)	Low
Creatinine	1.1 mg/dL (97.2 µmol/L)
Antinuclear antibodies	Titer: 1:320
Anti-Smith antibodies	Positive
Anti-double-stranded DNA antibodies	Positive
Urinalysis	3+ protein; no erythrocytes; no leukocytes; no casts
Urine protein	4000 mg/24 h

Which of the following tests is most appropriate to perform next to assess this patient's kidney disease?

(A) Antiphospholipid antibodies
(B) CT of the abdomen and pelvis
(C) Kidney biopsy
(D) Renal arteriography
(E) Serum and urine protein electrophoresis

Item 86

A 71-year-old woman is evaluated for a 3-year history of rheumatoid arthritis. She reports burning and tingling sensations in her feet and legs that are worse at night, without exacerbation with position or activity. She has not noted back pain, lower extremity weakness, or bowel or bladder dysfunction. Medications are methotrexate, hydroxychloroquine, low-dose prednisone, and folic acid. Her rheumatoid arthritis was moderately active 6 months ago, at which time leflunomide was added with good response.

On physical examination, vital signs are normal. Decreased sensation to light touch and vibration is limited to the feet. Joint examination reveals one tender and two swollen metacarpophalangeal joints. Strength testing is intact throughout, and reflexes are intact. There are no skin rashes or lesions.

Laboratory studies show normal complete blood count, serum creatinine, blood glucose, and hemoglobin A_{1c} values.

Which of the following is the most appropriate next step in management?

(A) Begin gabapentin
(B) Increase prednisone
(C) Stop leflunomide
(D) Stop methotrexate

Item 87

An 83-year-old woman is evaluated for a 15-year history of gout. Attacks were initially limited to the first metatarsophalangeal joints and occurred once or twice a year. She now has recurrent attacks, occurring every 3 months. Her feet, ankles, knees, wrists, elbows, and hands have been affected. Attacks last for 1 to 2 weeks and have been treated with NSAIDs. History is also significant for recurrent nephrolithiasis, stage 3 chronic kidney disease, and hypertension. Medications are allopurinol, 400 mg/d; colchicine, 0.6 mg/d; and lisinopril. She tolerates her medications well.

On physical examination, vital signs are normal. There are palpable masses at the olecranon processes and white nodules on a few distal and proximal interphalangeal joints of both hands.

Laboratory studies show a serum creatinine level of 1.0 mg/dL (88.4 µmol/L) and a serum urate level of 5.8 mg/dL (0.34 mmol/L).

Which of the following is the most appropriate next step in management?

(A) Add probenecid
(B) Discontinue allopurinol; begin pegloticase infusions
(C) Increase allopurinol
(D) Increase colchicine

Item 88

A 40-year-old woman is evaluated for a 12-year history of inflammatory arthritis, puffy fingers, Raynaud phenomenon, serositis, and gastroesophageal reflux disease.

On physical examination, vital signs are normal. The fingers are puffy, and cyanosis of the fingertips is noted. Cardiac examination is normal. The lungs are clear. There is no friction rub heard on examination.

Laboratory studies show positive anti-U1-ribonucleoprotein antibodies.

Which of the following complications of this patient's disease is a major cause of early mortality?

(A) Central nervous system vasculitis
(B) Pericarditis
(C) Pulmonary arterial hypertension
(D) Rapidly progressive glomerulonephritis

Item 89

A 75-year-old woman is evaluated for a 15-year history of right knee pain, which recently has become more constant, with morning stiffness lasting 15 minutes. She participates in a home exercise program. Her knee pain persists despite treatment with acetaminophen. She could not tolerate topical capsaicin or diclofenac. History is also significant for atrial fibrillation and hypertension. Medications are dabigatran and diltiazem. She would like to improve her knee pain, because she is going on vacation in 2 weeks and will be walking a lot.

On physical examination, vital signs are normal. Examination of the right knee reveals crepitus upon movement, bony hypertrophy presenting as varus deformity, and no effusion or warmth.

Weight-bearing knee radiographs show moderate medial joint space narrowing, osteophytes at the medial femoral and tibial joint margins, and subchondral sclerosis at the medial tibia.

Which of the following is the most appropriate treatment?

(A) Alendronate
(B) Arthroscopic debridement and lavage
(C) Intra-articular glucocorticoid injection
(D) Pregabalin
(E) Tramadol

Item 90

A 26-year-old woman is evaluated for a rash on her scalp and polyarthritis associated with systemic lupus erythematosus (SLE). She was diagnosed with SLE 8 years ago with an initial presentation of photosensitivity, malar and discoid rashes, pleuropericarditis, and arthritis. She was initially treated with hydroxychloroquine, azathioprine, and glucocorticoids with a good response, but she has had intermittent flare-ups of arthritis and rash. She developed lupus nephritis 3 years ago and had a 6-month course of cyclophosphamide followed by mycophenolate mofetil (MMF). She is currently on MMF, hydroxychloroquine, and prednisone but continues to have joint and skin disease. Methotrexate and leflunomide were tried, but she was not able to tolerate them. Her kidney disease is well controlled without any active nephritis.

On physical examination, vital signs are normal. Several hyperkeratotic, dyspigmented, discoid plaques are present on the scalp. Multiple joints of the hands are tender and swollen. The remainder of the examination is normal.

Laboratory studies:

Erythrocyte sedimentation rate	56 mm/h
Hematocrit	38%
Complements (C3, C4)	Low
Creatinine	1.5 mg/dL (132.6 µmol/L)
Anti-double-stranded DNA antibodies	Elevated
Urinalysis	Normal

Chest radiograph is normal.

Which of the following is the most appropriate therapeutic option to consider in this patient?

(A) Abatacept
(B) Adalimumab
(C) Belimumab
(D) Secukinumab

Item 91

A 74-year-old man is evaluated for pain and stiffness in the mid and lower spine that has progressively worsened over the past 10 years. The pain is worse with physical activity. He notes recent difficulty when bending to pick something up from the floor. He takes no medications.

On physical examination, vital signs are normal. No rash or nail changes are seen. Limited range of motion and pain on motion of thoracic and lumbar spine are noted. There is no peripheral joint swelling or tenderness and no sacroiliac tenderness. The FABER test of the hip is normal.

Laboratory studies show a normal erythrocyte sedimentation rate.

Thoracolumbar spine radiographs reveal bridging ossification on the right side along the anterolateral aspects of the vertebral bodies of T9-L2. Radiographs of the sacroiliac joints are normal.

Which of the following is the most likely diagnosis?

(A) Ankylosing spondylitis
(B) Calcium pyrophosphate deposition disease
(C) Diffuse idiopathic skeletal hyperostosis
(D) Psoriatic arthritis

Item 92

H

A 78-year-old man is evaluated in the emergency department. Five days ago he was diagnosed with community-acquired pneumonia at an urgent care center for which he was prescribed clarithromycin. Yesterday he developed generalized weakness and diarrhea. History is also significant for hypertension and gout. He has a history of allopurinol-induced drug rash. Current medications are lisinopril, colchicine, clarithromycin, and febuxostat.

H CONT.

On physical examination, temperature is 36.9 °C (98.4 °F), blood pressure is 104/60 mm Hg, pulse rate is 112/min, respiration rate is 18/min, and oxygen saturation is 98% breathing ambient air. There is no rash. The oropharynx appears dry. The chest is clear to auscultation. Tophi are noted at the olecranon processes. There are no swollen or tender joints. Neurologic examination is normal.

Laboratory studies:

Absolute neutrophil count	1300/µL (1.3×10^9/L)
Hemoglobin	9.8 g/dL (98 g/L)
Leukocyte count	2700/µL (2.7×10^9/L)
Platelet count	96,000/µL (96×10^9/L)
Reticulocyte count (corrected)	1.2%
Creatine kinase	8433 U/L
Creatinine	1.7 mg/dL (150.1 µmol/L)
Urinalysis	4+ blood; 0-1 erythrocytes/hpf; 0-2 leukocytes/hpf

There are no schistocytes seen on peripheral blood smear.

Which of the following is the most appropriate next step in management?

(A) Begin high-dose glucocorticoids
(B) Begin plasma exchange
(C) Stop colchicine and clarithromycin
(D) Stop febuxostat

Item 93

A 33-year-old woman is evaluated for a 4-week history of recurrent worsening joint pain and a new rash on the chest and upper back. She reports sun exposure from spending time at the beach. She has no other symptoms. She has no other medical problems and takes no medications.

On physical examination, vital signs are normal. Diffuse tenderness of multiple small joints of the hands is noted. The remainder of the examination is normal.

The appearance of the rash is shown.

Which of the following is the most likely diagnosis for the rash?

(A) Acute cutaneous lupus erythematosus
(B) Dermatomyositis
(C) Discoid lupus erythematous
(D) Subacute cutaneous lupus erythematous

Item 94

A 49-year-old man is evaluated for a 10-year history of intermittent low back pain with 30 to 60 minutes of morning stiffness, both of which improve with exercise. The back pain can awaken him from sleep. He also reports occasional pain in the neck, shoulder blades, and buttocks on one side or the other. History is notable for anterior uveitis diagnosed more than 30 years ago, the symptoms of which recurred every 3 to 4 years but have been subsequently controlled by topical glucocorticoids. Current medications are as-needed NSAIDs and ophthalmic glucocorticoid drops.

On physical examination, vital signs are normal. Lumbar spine range of motion is restricted for forward flexion. There are no warm, erythematous, or swollen joints. There is no spinal or sacroiliac tenderness. Conjunctivae are without injection.

Which of the following is the most appropriate test to perform next?

(A) Bone scan
(B) CT of the sacroiliac joints
(C) MRI of the lumbar spine
(D) Radiography of the sacroiliac joints

Item 95

A 48-year-old man is evaluated during a routine follow-up visit for gout diagnosed 2 months ago, at which time he started allopurinol and colchicine. Since then, he has had three acute attacks separately involving the left wrist, right knee, and left foot. He has no current joint pain. He also reports having diarrhea two to three times daily over the past 6 weeks. History is also significant for type 2 diabetes mellitus, for which he takes insulin.

On physical examination, vital signs are normal. Musculoskeletal examination is normal.

Laboratory studies show a serum creatinine level of 0.8 mg/dL (70.7 µmol/L) and a serum urate level of 5.5 mg/dL (0.32 mmol/L).

Which of the following is the most appropriate next step to decrease the frequency of gout attacks?

(A) Add prednisone
(B) Add probenecid
(C) Discontinue colchicine; begin meloxicam
(D) Increase allopurinol
(E) Increase colchicine

Item 96

A 28-year-old woman is evaluated for a 3-week history of isolated left groin pain. The pain is worse with weight bearing. She has a 10-year history of systemic lupus

erythematosus (SLE) and lupus nephritis. She has also received high-dose glucocorticoids multiple times in the past 10 years. She is currently doing well without any active SLE manifestations. Medications are hydroxychloroquine and low-dose prednisone.

On physical examination, vital signs are normal. The left groin has slight discomfort with hip movement and weight bearing but is nontender. There is no active synovitis. The remainder of the examination is normal.

Pelvic and hip radiographs are normal.

Which of the following is the most appropriate test to perform next in this patient?

(A) CT of the hip
(B) MRI of the hip
(C) Radionuclide bone scan
(D) Single photon emission CT

Answers and Critiques

Item 1 Answer: D

Educational Objective: Diagnose prosthetic joint infection.

Prosthetic joint infection is the most likely diagnosis. This patient has a prosthetic hip and is currently undergoing chemotherapy. Malignancy and immunosuppression are risk factors for prosthetic joint infection, and this patient also has a central venous catheter that increases his risk for bacteremia. The elevated leukocyte count and erythrocyte sedimentation rate, along with periprosthetic lucency on radiographs, are all suggestive of prosthetic joint infection. Prosthetic joint infections are divided into early onset (<3 months after placement), delayed (3 to 24 months postsurgery), and late onset (>24 months after placement). Early and delayed infections are usually related to surgical contamination at the time of the implantation, whereas late infections result from hematogenous seeding of the joint. Early and late prosthetic joint infections typically present with pain, warmth, effusion, and fever. *Staphylococcus aureus* is a leading causative agent in prosthetic joint infections; treatment involves prompt intravenous antibiotics and sometimes removal of the prosthesis.

Gout flare may also cause joint pain and loss of mobility, as well as fever, elevated leukocyte count, and inflammatory markers. However, this patient has no prior history of gout, and the hip is an uncommon place for a gout flare, especially an initial flare. Most initial gout flares affect the foot and/or ankle joints.

Hemarthrosis causes bleeding into a joint and is characterized by pain, swelling, warmth, and impaired mobility. It is diagnosed by synovial fluid aspiration. This patient does not have a history or findings suggestive of a bleeding diathesis to put him at risk for a traumatic hemarthrosis.

A patient with hip dislocation may present in a similar manner as one with prosthetic joint infection, namely pain and difficulty moving the joint; however, a dislocation would be evident on radiographs.

KEY POINT

- Both early and late prosthetic joint infections are typically characterized by pain, warmth, effusion, and fever; treatment involves prompt intravenous antibiotics and possible removal of the prosthesis.

Bibliography

Osmon DR, Berbari EF, Berendt AR, Lew D, Zimmerli W, Steckelberg JM, et al; Infectious Diseases Society of America. Diagnosis and management of prosthetic joint infection: clinical practice guidelines by the Infectious Diseases Society of America. Clin Infect Dis. 2013;56:e1-e25. [PMID: 23223583] doi:10.1093/cid/cis803

Item 2 Answer: C

Educational Objective: Diagnose microscopic polyangiitis.

The most likely diagnosis is microscopic polyangiitis (MPA), which characteristically affects the lungs and kidneys, along with other organ systems. Diagnosis is suspected based upon typical clinical findings and positive ANCA. The diagnostic gold standard is a biopsy demonstrating nongranulomatous necrotizing pauci-immune vasculitis of small vessels or pauci-immune necrotizing crescentic glomerulonephritis in the kidney. This patient has pulmonary hemorrhage, pauci-immune small-vessel necrotizing vasculitis of the skin, proteinuria, inflammatory arthritis, and a positive p-ANCA (directed against myeloperoxidase)—all consistent with the diagnosis of MPA.

Granulomatosis with polyangiitis (GPA) can cause the same lung, skin, joint, and kidney findings but is usually associated with a positive c-ANCA (directed against proteinase-3). Furthermore, GPA causes granulomatous inflammation; absence of granulomas distinguishes MPA from GPA.

IgA vasculitis (Henoch-Schönlein purpura) can affect lungs, skin, joints, and kidneys but it is an immune complex-mediated vasculitis with deposition of IgA containing immune complexes identified on biopsy, which is not present in this patient.

Rheumatoid vasculitis usually occurs in long-standing disease with positive rheumatoid factor and is immune complex mediated, none of which is present in this patient.

Thromboangiitis obliterans is a smoking-related vasculopathy affecting small to medium vessels with inflammation and thrombosis of vessels in upper and lower limbs, leading to reduced pulses and gangrenous ulcers. This diagnosis is unlikely because this patient no longer smokes, and has involvement of internal organs in addition to the legs.

KEY POINT

- The diagnostic gold standard of microscopic polyangiitis is a biopsy demonstrating nongranulomatous necrotizing pauci-immune vasculitis of small vessels or pauci-immune necrotizing crescentic glomerulonephritis in the kidney.

Bibliography

Kallenberg CG. The diagnosis and classification of microscopic polyangiitis. J Autoimmun. 2014;48-49:90-3. [PMID: 24461388] doi:10.1016/j.jaut.2014.01.023

Item 3 Answer: B

Educational Objective: Treat severe tophaceous gout.

In addition to stopping febuxostat, the most appropriate treatment is pegloticase infusions. This patient has severe recurrent and tophaceous gout that has been resistant to

standard therapies, including febuxostat. Pegloticase is an intravenously administered porcine-derived uricase (infused every 2 weeks), which reduces serum urate to nearly zero within hours of administration. If anti-drug antibodies do not form, tophi may resolve over the course of months. Other urate-lowering therapies should be discontinued with initiation of pegloticase because they can mask the development of antibodies that manifest as rising serum urate levels. Patients starting pegloticase should be placed on prophylaxis to prevent acute gout attacks; colchicine, prednisone, or NSAIDs are appropriate. In this case, glucocorticoids and NSAIDs should be avoided because of the concomitant type 2 diabetes mellitus and chronic kidney disease; therefore, low-dose colchicine is the appropriate prophylactic agent.

It is important to note that two recently published guidelines differ regarding the role of pharmacologic urate-lowering therapy in patients with gout. The 2016 American College of Physicians guideline (http://annals.org/aim/article/2578528/management-acute-recurrent-gout-clinical-practice-guideline-from-american-college) notes a lack of evidence supporting a specific target level for urate lowering; this guideline stresses discussing the risks and benefits of urate-lowering therapy with patients and suggests a "treat to avoid symptoms" approach without specifically considering the serum urate levels. The 2016 European League Against Rheumatism (EULAR) recommendations support a "treat-to-target" approach (consistent with the 2012 ACR gout guidelines), reducing the serum urate level to less than 6.0 mg/dL (0.35 mmol/L) in patients without tophi and less than 5.0 mg/dL (0.30 mmol/L) in patients with tophi. The patient's serum urate level is 6.3 mg/dL (0.37 mmol/L) on febuxostat therapy, and she continues to have symptoms; therefore, escalation of treatment is appropriate according to both the ACP and EULAR guidelines.

Probenecid is not appropriate for those with an estimated glomerular filtration rate of less than 60 mL/min/1.73 m^2 or with a history of kidney stones; this patient has both.

Losartan has a modest uricosuric effect, but not significant enough that it would be recommended in a patient with severe tophaceous gout, especially one who remains symptomatic with an elevated serum urate level despite febuxostat therapy.

KEY POINT

- Pegloticase may be considered for patients with severe recurrent and/or tophaceous gout that is intolerant or resistant to standard therapies.

Bibliography

Sundy JS, Baraf HS, Yood RA, Edwards NL, Gutierrez-Urena SR, Treadwell EL, et al. Efficacy and tolerability of pegloticase for the treatment of chronic gout in patients refractory to conventional treatment: two randomized controlled trials. JAMA. 2011;306:711-20. [PMID: 21846852] doi:10.1001/jama.2011.1169

Item 4 Answer: A

Educational Objective: Diagnose reactive arthritis.

The most appropriate diagnostic test to perform next is nucleic acid amplification urine testing for chlamydia. *Chlamydia trachomatis* is the most common agent causing urethritis that is associated with reactive arthritis. This patient has the triad of conjunctivitis, urethritis, and arthritis seen in a subset of patients with chlamydial reactive arthritis. Typically, affected men experience dysuria and note a urethral discharge, although less frequently than in arthritis related to gonococcal infection. Gonococcal arthritis, however, is not associated with conjunctivitis and is often accompanied by vesicopustular skin lesions and tenosynovitis. Reactive arthritis typically occurs 3 to 6 weeks after the infectious trigger, with a latency range of 2 weeks to 6 months. In a significant minority of cases, the triggering infection may go unrecognized. Although infection has usually resolved by the time of arthritis onset in patients with reactive arthritis, nucleic acid amplification urine testing for *C. trachomatis* should be performed because some individuals may have asymptomatic persistent infection or carriage of this organism.

C-reactive protein would not be of value in establishing the diagnosis. The patient has an acute inflammatory process in the joints based on his history, physical examination, and synovial fluid analysis. C-reactive protein would not lend further diagnostic information.

HLA-B27 antigen may be present in those with reactive arthritis, but it has little diagnostic specificity in this disorder. The presence of HLA-B27 antigen would neither rule in nor rule out reactive arthritis.

The interferon-gamma release assay can indicate prior exposure to tuberculosis. The clinical picture in this scenario is not that of tuberculous arthritis, which tends to be monoarticular, most frequently affects the hip, has a course that is subacute with progressive pain and loss of function over weeks to months, and is not often associated with features of inflammatory synovitis on physical examination (warmth, erythema).

KEY POINT

- Nucleic acid amplification urine testing is the appropriate diagnostic test for suspected chlamydial reactive arthritis.

Bibliography

Carter JD, Hudson AP. Recent advances and future directions in understanding and treating Chlamydia-induced reactive arthritis. Expert Rev Clin Immunol. 2017;13:197-206. [PMID: 27627462] doi:10.1080/1744666X.2017.1233816

Item 5 Answer: E

Educational Objective: Diagnose ankylosing spondylitis.

No additional tests are necessary. Different criteria have been proposed for the diagnosis of ankylosing spondylitis. Common requirements include the presence of inflammatory back pain for 3 or more months in a person younger than age 45 years, limited lumbar spine motion, elevated inflammatory markers, and evidence of bilateral sacroiliitis on imaging. The patient has a long history of inflammatory back pain (improves with exercise, worsens with sleep or inactivity), loss of range of motion of the lumbar spine, and radiographs showing fusion of the sacroiliac joints, one of

the typical features of ankylosing spondylitis. It is important to establish the diagnosis of ankylosing spondylitis to assess the risk of further joint fusion and deformity in this patient.

ANCA is present in some forms of medium-vessel vasculitis. In the absence of cutaneous or internal organ manifestations suggestive of vasculitis (sinus, pulmonary, kidney, cutaneous, and ophthalmologic abnormalities), it is not appropriate as the next step in this patient's evaluation.

Anti-cyclic citrullinated peptide antibodies have specificity for the diagnosis of rheumatoid arthritis and are appropriately ordered when patients present with bilaterally symmetric inflammatory arthritis of the small joints of the hands. These antibodies will not establish the diagnosis of ankylosing spondylitis.

Testing for antinuclear antibodies should be carried out when there is suspicion for the presence of systemic lupus erythematosus. This patient does not have rash, sun sensitivity, alopecia, oral ulcers, pleuropericarditis, kidney disease, or laboratory abnormalities that would raise suspicion for lupus.

The presence of HLA-B27 antigen is not a diagnostic criterion for ankylosing spondylitis. However, such testing may be particularly helpful in patients with inflammatory back pain and other manifestations of ankylosing spondylitis but without evidence of sacroiliitis on imaging.

KEY POINT

- A diagnosis of ankylosing spondylitis can be made in a patient younger than age 45 years with symptoms of inflammatory back pain for 3 months or more and bilateral sacroiliitis on imaging.

Bibliography

Taurog JD, Chhabra A, Colbert RA. Ankylosing spondylitis and axial spondyloarthritis. N Engl J Med. 2016;374:2563-74. [PMID: 27355535] doi:10.1056/NEJMra1406182

H

Item 6 Answer: C

Educational Objective: Diagnose gastric antral vascular ectasia associated with diffuse cutaneous systemic sclerosis.

The most likely diagnosis is gastric antral vascular ectasia (GAVE) associated with systemic sclerosis. GAVE is the proliferation of blood vessels typically in the antrum of the stomach; on endoscopy, it has the appearance of watermelon stripes (watermelon stomach). Approximately 60% of patients with GAVE have an underlying autoimmune disease; the remainder have portal hypertension secondary to hepatic cirrhosis. GAVE can be a source of both acute and chronic gastrointestinal bleeding. First-line therapy is argon plasma coagulation or laser coagulation.

Cameron lesions are erosions found on the crest of gastric folds within a large hiatal hernia and are thought to be caused by mechanical trauma as the hiatal hernia slides up and down. Up to 5% of patients with known hiatal hernias may have Cameron lesions. There is no evidence of a hiatal hernia, making this diagnosis unlikely.

Dieulafoy lesions are submucosal arterioles that intermittently protrude through the mucosa and cause hemorrhage. Dieulafoy lesions are of unknown etiology and account for about 2% of all causes of acute upper gastrointestinal bleeding and are located in the proximal stomach along the lesser curvature. When bleeding they appear as an isolated pumping arteriole in the absence of a mass or ulcer. The patient's findings do not match those of Dieulafoy lesions.

Portal hypertensive gastropathy (PHG) commonly occurs with advanced cirrhosis and has a characteristic mosaic appearance on endoscopy, most often seen in the body and fundus. It can be confused with GAVE. This patient has no history of cirrhosis or findings to suggest chronic liver disease, making PHG an unlikely diagnosis.

KEY POINT

- Patients with diffuse cutaneous systemic sclerosis are at risk for acute and chronic gastrointestinal bleeding secondary to gastric antral vascular ectasia.

Bibliography

Fuccio L, Mussetto A, Laterza L, Eusebi LH, Bazzoli F. Diagnosis and management of gastric antral vascular ectasia. World J Gastrointest Endosc. 2013;5:6-13. [PMID: 23330048] doi:10.4253/wjge.v5.i1.6

Item 7 Answer: A

H

Educational Objective: Treat refractory acute gout.

Anakinra is the most appropriate treatment for this patient's knee. He has a persistent fever due to a severe acute gouty attack. Synovial fluid analysis permits definitive diagnosis and can rule out other conditions. Under polarized light, monosodium urate crystals are needle shaped and negatively birefringent. Whereas extracellular crystals confirm a chronic gout diagnosis, crystals within neutrophils define active, gout-induced inflammation. Even in the setting of acute gout, Gram stain and cultures must be obtained to exclude infection because acute gout and joint infection occasionally coexist. This patient has not responded favorably to glucocorticoid therapy, which characterizes some severe acute episodes. In a case such as this, an interleukin-1 inhibitor such as anakinra should be provided as a reliable (although expensive) off-label treatment.

Colchicine is unlikely to be effective for an established attack of greater than 12 to 24 hours' duration. It is also unlikely to be useful when intravenous and intra-articular glucocorticoids have been ineffective.

The absence of a response to intra-articular or intravenous glucocorticoids necessitates an alternative treatment; however, NSAIDs would not be as effective as the two previously provided failed alternatives. Additionally, NSAIDs have numerous side effects that might be even more likely to occur during critical illness, and they are relatively contraindicated in a patient with heart failure.

H CONT.

Blood, urine, and synovial fluid cultures have all been negative, the pneumonia is resolving, and there is no clinical evidence of infection. Vancomycin for methicillin-resistant staphylococcus is unnecessary.

KEY POINT

- For patients with severe and refractory gouty attacks or with contraindications to other treatments, off-label use of interleukin-1 inhibitors (anakinra or canakinumab) can be considered.

Bibliography

Thueringer JT, Doll NK, Gertner E. Anakinra for the treatment of acute severe gout in critically ill patients. Semin Arthritis Rheum. 2015;45:81-5. [PMID: 25795473] doi:10.1016/j.semarthrit.2015.02.006

Item 8 Answer: C

Educational Objective: Treat osteoarthritis with physical therapy.

Physical therapy is appropriate for this patient whose history, physical examination, and radiographic findings are consistent with the diagnosis of osteoarthritis (OA). Physical therapy is an effective intervention for the management of pain and reduced functioning due to OA, with numerous guidelines supporting exercise as an appropriate intervention for all patients with OA. Evidence is most robust for knee OA. Many patients become sedentary due to their symptoms, and physical therapy is often a useful starting point to transition patients to participation in a regular exercise program. Physical therapy can be prescribed at any point in the course of the disease instead of medication, as a supplement to medication that does not adequately reduce pain, or prior to surgery to increase strength and potentially influence surgical outcomes.

Glucosamine supplements are the most widely used over-the-counter products worldwide for OA. Many randomized controlled trials have found that pain, function, and radiographic progression improve overall at a level equivalent to the effects of placebo in patients taking glucosamine.

Knee replacement surgery is effective for treatment of pain and disability but is not appropriate in a patient who has not been through a trial of physical therapy, particularly a patient who is not regularly exercising. Assessment of the ability to carry out activities of daily living, as well as occupational and recreational activities, will be important in the decision to seek surgery, and a physical therapist can be particularly helpful to the primary care provider in carrying out this assessment. Considerations for surgical referral include the presence of pain at rest or pain that awakens the patient in the middle of the night, both of which are less likely to respond to analgesics, exercise, or physical modalities.

Prednisone is an oral glucocorticoid that can be used as an adjunctive medication in the treatment of some forms of inflammatory arthritis. However, insufficient evidence exists to support the use of oral glucocorticoids in the treatment of OA.

KEY POINT

- Physical therapy can be prescribed at any point in the course of osteoarthritis instead of medication, as a supplement to medication that does not adequately reduce pain, or prior to surgery to increase strength and potentially influence surgical outcomes.

Bibliography

Hochberg MC, Altman RD, April KT, Benkhalti M, Guyatt G, McGowan J, et al; American College of Rheumatology. American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. Arthritis Care Res (Hoboken). 2012;64:465-74. [PMID: 22563589]

Item 9 Answer: C

Educational Objective: Diagnose ankylosing spondylitis using MRI.

The most appropriate diagnostic test to perform next is MRI of the sacroiliac joints. This patient has symptoms suggestive of back pain due to inflammation, including young age of onset, gradual onset, pain during the night, morning stiffness, improvement with motion, no history of trauma, and no improvement with rest. A single anteroposterior pelvis plain radiograph to view the sacroiliac joints is an appropriate first diagnostic step in this setting, which may reveal joint space widening (early) or narrowing (late), erosions, sclerosis, and ankylosis, and can establish the diagnosis of ankylosing spondylitis. However, plain radiographs may be normal early in the course of disease, as seen in this patient. MRI of the sacroiliac joints can then be utilized, which is more sensitive for detecting early spine and sacroiliac joint inflammation. The finding of bone marrow edema on STIR or T2-weighted images with fat suppression is not specific for ankylosing spondylitis but does suggest active inflammation, particularly if found in characteristic periarticular and subchondral locations. MRI can also identify soft-tissue evidence of inflammation in the entheses, bursae, and tendons, as well as subtle structural abnormalities.

Bone scan is sensitive for the detection of osteoblast activity and is the study of choice for detecting bone metastases from various forms of cancer. However, bone scan is not used in the diagnosis of any form of inflammatory arthritis because it lacks specificity.

CT of the lumbar spine can be useful in the diagnosis of ankylosing spondylitis when radiography of the sacroiliac joints is normal. However, it is not routinely used in the evaluation of patients for arthritis due to the high dose of radiation required.

Hip pathology frequently results in anterior groin pain and would be unlikely to cause back pain. Therefore, radiography of the hip joints is not likely to aid in the diagnosis and is not indicated for this patient.

KEY POINT

- MRI is more sensitive than radiography for detecting early spine and sacroiliac joint inflammation and may be indicated in the evaluation of suspected spondyloarthritis if radiographs are normal.

Bibliography

Sieper J, Poddubnyy D. Axial spondyloarthritis. Lancet. 2017. [PMID: 28110981] doi:10.1016/S0140-6736(16)31591-4

Item 10 Answer: E

Educational Objective: Avoid serologic testing in patients with low pretest probability of connective tissue disease.

No further testing is currently needed in this 75-year-old man with no clinical findings suggestive of a connective tissue disease. His symptoms of hand joint pain are noninflammatory (pain with use, no warmth or swelling, and only minimal morning stiffness), and the distribution and findings are consistent with a diagnosis of osteoarthritis. Furthermore, the radiographs confirm these findings and do not show changes consistent with an inflammatory rheumatologic disorder (such as erosive joint disease seen in rheumatoid arthritis and psoriatic arthritis, or tophi seen in gout). Therefore, no further testing is indicated.

Positive antinuclear antibodies (ANA) in a patient with nonspecific symptoms are difficult to interpret. As with all tests, the positive predictive value of ANA rests upon the pretest probability of disease. In the presence of 0 or 1 clinical manifestations of systemic lupus erythematosus (SLE), a positive ANA is associated with a very low posttest probability of SLE. The American College of Rheumatology's Choosing Wisely list currently recommends against testing ANA and ANA subserologies without a clinical suspicion of immune-mediated disease. The clinical suspicion for a connective tissue disorder such as SLE or rheumatoid arthritis is low in this patient, and ANA, rheumatoid factor, or anti-cyclic citrullinated peptide antibodies should not be tested.

Osteoarthritis, psoriatic arthritis, and gout can involve distal interphalangeal joints. However, this patient does not have the rash seen in psoriatic arthritis or symptoms of crystal-induced arthritis such as recurrent acute attacks and/or tophaceous deposits. Serum urate levels are helpful in a patient with symptoms suggestive of gout but are unlikely to helpful here.

KEY POINT

- The positive predictive value of antinuclear antibody (ANA) tests is determined by the pretest probability of disease; in the presence of 0 or 1 clinical manifestations of systemic lupus erythematosus (SLE), a positive ANA is associated with a very low posttest probability of SLE.

Bibliography

Yazdany J, Schmajuk G, Robbins M, Daikh D, Beall A, Yelin E, et al; American College of Rheumatology Core Membership Group. Choosing wisely: the American College of Rheumatology's top 5 list of things physicians and patients should question. Arthritis Care Res (Hoboken). 2013;65:329-39. [PMID: 23436818] doi:10.1002/acr.21930

Item 11 Answer: A

Educational Objective: Diagnose antisynthetase syndrome.

The most likely diagnosis is antisynthetase syndrome, which is characterized by interstitial lung disease, myositis, Raynaud phenomenon, nonerosive inflammatory arthritis, constitutional findings such as low-grade fever, and mechanic's hands. Mechanic's hands is a dermatologic manifestation unique to antisynthetase syndrome and is characterized by hyperkeratotic skin along the ulnar aspect of the thumb and radial aspects of the digits, most commonly on the index and middle fingers, and involvement of the palms. Unlike eczema, there is no pruritus, vesicles, or hand dominance. Antisynthetase syndrome can occur in patients with dermatomyositis or polymyositis; about one third of patients with dermatomyositis belong to this subset characterized by a relatively abrupt onset and features. Antinuclear antibodies (ANA) are often positive in patients with antisynthetase syndrome, but anti-aminoacyl-tRNA synthetases antibodies, including the subset anti-Jo-1 antibodies, are more specific for the diagnosis.

In patients with Sjögren syndrome, constitutional findings and inflammatory arthritis are common, but Raynaud phenomenon is less so. Rash and mechanic's hands are not characteristics. Furthermore, dry eyes and dry mouth are the most common presenting symptoms, along with positive anti-Ro/SSA and anti-La/SSB antibodies.

Fever, Raynaud phenomenon, rash, inflammatory arthritis, and positive ANA are seen in systemic lupus erythematosus. However, an abrupt onset rarely occurs, mechanic's hands are not a feature, and anti-Jo-1 antibodies are not characteristic.

In patients with systemic sclerosis, fever and inflammatory arthritis are far less likely. Furthermore, although Raynaud phenomenon is very common in systemic sclerosis, the findings of either localized or diffuse skin tightening and thickening, including sclerodactyly, are absent in this patient. Mechanic's hands is not a feature of systemic sclerosis, and anti-Jo-1 antibodies are not characteristic.

KEY POINT

- Antisynthetase syndrome is characterized by interstitial lung disease, myositis, Raynaud phenomenon, nonerosive inflammatory arthritis, constitutional findings such as low-grade fever, and mechanic's hands; anti-aminoacyl-tRNA synthetases antibodies, such as anti-Jo-1, are highly suggestive of the diagnosis.

Bibliography

Lega JC, Fabien N, Reynaud Q, Durieu I, Durupt S, Dutertre M, et al. The clinical phenotype associated with myositis-specific and associated autoantibodies: a meta-analysis revisiting the so-called antisynthetase syndrome. Autoimmun Rev. 2014;13:883-91. [PMID: 24704867] doi:10.1016/j.autrev.2014.03.004

Item 12 Answer: D

Educational Objective: Prevent rheumatoid arthritis with smoking cessation.

The most preventive measure for this patient at risk for developing rheumatoid arthritis (RA) is smoking cessation. Smoking has been definitively identified as a risk factor for the development of RA, especially in genetically susceptible individuals. This woman has a strong family history of RA,

including an identical twin sister who was recently diagnosed. Smoking increases the risk for RA 2 to 21 times depending on the presence of one or two copies of the shared epitope in the HLA makeup of the individual. Data suggest that if she stops smoking now, the risk for developing RA will decline each year that she does not smoke and will eventually be 30% lower than if she continued to smoke, but will not reach the level of someone who has never smoked for up to 20 years. There is additional evidence that if she stops smoking now and does develop RA, future mortality will be favorably affected, as will her disease activity. Smoking stimulates the production of enzymes that modify arginine to citrulline, and the modified proteins containing citrulline are targets for the immune system in susceptible individuals. This patient's hand symptoms seem more mechanical in nature (that is, end of the day) rather than inflammatory (prolonged morning stiffness).

High-fructose corn syrup has been identified as a possible risk factor for hyperuricemia and gout but not RA.

The use of hydroxychloroquine to prevent the development of RA in susceptible individuals is unproven. A clinical trial will soon evaluate the impact of hydroxychloroquine in patients positive for anti-cyclic citrullinated peptide antibodies, but it is premature to recommend this intervention without supporting evidence.

To date, probiotics have not been shown to modify risk for RA.

KEY POINT

- Smoking is a risk factor for the development of rheumatoid arthritis, especially in genetically susceptible individuals; all patients should be counseled to quit smoking.

Bibliography

Di Giuseppe D, Orsini N, Alfredsson L, Askling J, Wolk A. Cigarette smoking and smoking cessation in relation to risk of rheumatoid arthritis in women. Arthritis Res Ther. 2013;15:R56. [PMID: 23607815] doi:10.1186/ar4218

H

Item 13 Answer: A

Educational Objective: Diagnose acute lupus pneumonitis.

Acute lupus pneumonitis is the most likely diagnosis in this patient who has difficult-to-control systemic lupus erythematosus (SLE) requiring aggressive therapy with prednisone and azathioprine. Lupus pneumonitis is a rare but severe presentation of SLE characterized by shortness of breath, hypoxia, and diffuse pulmonary infiltrates. Other major entities in the differential diagnosis include infection and diffuse alveolar hemorrhage. He has clear evidence of active SLE with polyarthritis, a high erythrocyte sedimentation rate, hypocomplementemia, and diffuse pulmonary infiltrates on radiologic studies, as well as lymphocytic predominance on bronchoalveolar lavage. These findings are very suggestive of lupus pneumonitis. It usually requires rapid and aggressive therapy with glucocorticoids and/or immunosuppressive agents.

Pulmonary hypertension does not present with diffuse infiltrates with ground glass opacities, as seen in this patient, and it cannot explain the bronchoalveolar lavage findings.

This patient has no fever or sputum production, and testing shows a normal leukocyte count and differential, normal C-reactive protein (CRP), and normal procalcitonin, making infection less likely. CRP is a marker of inflammation, and levels are significantly increased in bacterial pneumonia but frequently normal or only slightly elevated in SLE flares. Procalcitonin is produced by cells as a response to bacterial toxins, which result in serum procalcitonin elevations in bacterial infections.

The patient reports no hemoptysis, and lack of anemia and absence of erythrocytes on bronchoalveolar lavage exclude a diagnosis of diffuse alveolar hemorrhage.

Shrinking lung syndrome presents with chronic insidious shortness of breath with low lung volumes possibly related to diaphragmatic dysfunction. This patient's acute presentation and diffuse infiltrates on imaging is not consistent with this syndrome.

KEY POINT

- Lupus pneumonitis is a rare but severe presentation of systemic lupus erythematosus characterized by shortness of breath, hypoxia, and diffuse pulmonary infiltrates.

Bibliography

Mittoo S, Fell CD. Pulmonary manifestations of systemic lupus erythematosus. Semin Respir Crit Care Med. 2014;35:249-54. [PMID: 24668539] doi:10.1055/s-0034-1371537

Item 14 Answer: D

Educational Objective: Diagnose small intestinal bacterial overgrowth associated with systemic sclerosis.

The most likely diagnosis is small intestinal bacterial overgrowth (SIBO) associated with systemic sclerosis (SSc). More than 70% of patients with SSc have clinical gastrointestinal involvement. Gastrointestinal motility is compromised in 40% to 90% of patients with systemic sclerosis, especially those with diffuse disease. Because of the decrease in motility of the small bowel, bacterial overgrowth occurs and leads to the symptoms described in this patient history, including diarrhea, bloating, and pain, and can lead to malabsorption. Patients with SSc can also develop chronic pancreatic insufficiency and develop symptoms similar to SIBO, which must be considered in the differential diagnosis. Diagnosis of SIBO can be confirmed with glucose hydrogen breath testing or jejunal aspirate cultures. Treatment is with rotating antibodies to try to reduce the overgrowth using agents with both aerobic and anaerobic coverage. Probiotics may have some benefit in such patients. It is important to screen such patients for nutritional deficiencies.

Carcinoid tumors are neuroendocrine tumors arising from the aerodigestive tract. Although most neuroendocrine tumors are hormonally nonfunctioning, a few produce serotonin and are responsible for the clinical manifestations of the carcinoid syndrome characterized by diarrhea and facial flushing. The diarrhea associated with the carcinoid syndrome is secretory, and symptoms are not confined to periods of food intake; nocturnal diarrhea is a clinical hallmark.

Chronic mesenteric ischemia is almost always associated with atherosclerotic disease. Symptoms consist of postprandial pain within 60 minutes after meals, which results in fear of eating and weight loss. It is not associated with postprandial bloating or explosive diarrhea.

Irritable bowel syndrome is a symptom complex characterized by abdominal pain and altered bowel habits. Diagnosis is established by fulfilling specific diagnostic criteria, including recurrent abdominal pain or discomfort at least 3 days per month in the last 3 months associated with two or more of the following: improvement with defecation; onset associated with a change in frequency of stool; and onset associated with a change in form (appearance) of stool. The presence of "red flags" such as anemia, fever, or weight loss strongly suggests the presence of an alternative diagnosis.

KEY POINT

- In patients with systemic sclerosis, gastrointestinal dysmotility can result in small intestinal bacterial overgrowth with resultant chronic diarrhea and malabsorption.

Bibliography

Gyger G, Baron M. Systemic sclerosis: gastrointestinal disease and its management. Rheum Dis Clin North Am. 2015;41:459-73. [PMID: 26210129] doi:10.1016/j.rdc.2015.04.007

Item 15 Answer: B

Educational Objective: Diagnose Felty syndrome.

The most likely diagnosis is Felty syndrome, which consists of the triad of long-standing aggressive rheumatoid arthritis (RA), neutropenia, and splenomegaly. Patients with Felty syndrome are almost always seropositive. This patient has the typical findings of long-standing RA, including involvement of multiple small joints of the hands and feet, joint subluxation, and subcutaneous nodules. Felty syndrome is associated with the risk for serious infections, lower extremity ulcers, lymphoma, and vasculitis. Treatment of Felty syndrome consists of more aggressive therapy for the underlying RA.

AA amyloid results from accumulation of the AA protein, an acute phase reactant seen in chronic inflammatory diseases. Although AA amyloidosis can be associated with hepatosplenomegaly, the most common organ involved in AA amyloidosis is the kidney and is evidenced by heavy proteinuria. Hematologic abnormalities may include anemia as the result of chronic kidney disease and thrombocytopenia secondary to splenomegaly, but neutropenia is unusual. AA amyloidosis cannot account for this patient's joint findings or lower extremity ulcer.

Sarcoidosis most commonly affects the lungs. Severe sarcoidosis can uncommonly be associated with a chronic arthritis that is typically polyarticular, involving the shoulders, hands, wrists, knees, and ankles, and often coexists with lung and cutaneous sarcoidosis. An entire digit may be affected, leading to dactylitis. Sarcoidosis can also be associated with slightly tender subcutaneous nodules of the upper extremities and (rarely) splenomegaly. Sarcoidosis does not cause leukopenia or cutaneous ulcers and is an unlikely cause of this patient's findings.

Joint involvement occurs in 90% of patients with systemic lupus erythematosus (SLE), with inflammatory polyarthralgia the most common presentation. Frank arthritis occurs in 40% of patients with SLE. Both small and large joints can be affected. Persistent periarticular inflammation can damage soft-tissue structures that support joints, resulting in reducible subluxation of the digits, swan neck deformities, and ulnar deviation (Jaccoud arthropathy). All three bone marrow cell lines can be affected in SLE. Leukopenia occurs in 50% of patients, with lymphopenia predominating. Subcutaneous nodules are not usually found in SLE. In addition, up to 90% of patients with SLE have skin (acute, subacute, or chronic lupus) or mucous membrane involvement. The presence of splenomegaly and subcutaneous nodules and absence of skin rash argue against the diagnosis of SLE. In addition, serologies would help distinguish RA from SLE.

KEY POINT

- Felty syndrome consists of the triad of long-standing aggressive rheumatoid arthritis, neutropenia, and splenomegaly and is associated with the risk for serious infections, lower extremity ulcers, lymphoma, and vasculitis.

Bibliography

Owlia MB, Newman K, Akhtari M. Felty's syndrome, insights and updates. Open Rheumatol J. 2014 Dec 31; 8:129-36. [PMCID: PMC4296472] doi: 10.2174/1874312901408010129.

Item 16 Answer: C

H

Educational Objective: Diagnose Lyme arthritis.

The most likely diagnosis is Lyme arthritis, which can be confirmed by serologic testing for detection of *Borrelia burgdorferi*-specific antibodies using a two-tiered approach: enzyme-linked immunosorbent assay (ELISA) followed by Western blot. This patient is a park ranger in an area endemic for Lyme disease, thus the diagnosis should be strongly suspected, especially given a monoarthritis of the knee that is not overly painful, which is typical for Lyme arthritis. Lyme arthritis is a late manifestation of Lyme disease; after the first month of infection, at least 5/10 bands should be present on Western blot testing for IgG antibodies to different *B. burgdorferi* proteins. It is not uncommon for patients to be unaware of or experience manifestations of early stages of disease, such as erythema migrans or constitutional symptoms.

Positive HLA-B27 haplotype may be seen in patients who have spondyloarthritis such as ankylosing spondylitis, psoriatic arthritis, or reactive arthritis. Although these conditions commonly involve the peripheral joints, including the knees, the arthritis is usually painful and oligoarticular, not monoarticular. Additionally, inflammatory symptoms such as morning stiffness are prominent.

H CONT.

MRI of the knee can be useful to diagnose meniscal, ligamentous, and other soft-tissue abnormalities, as well as synovitis and effusion. It is particularly useful to localize knee pathology in the clinical setting of trauma, which has not occurred in this patient. Degenerative meniscal tears due to knee osteoarthritis may be seen on MRI, without a clinical history of trauma, but this patient does not have clinical or radiographic symptoms/signs of osteoarthritis.

In crystal arthropathies, metabolic abnormalities promote the formation and deposition of crystals that stimulate inflammation. Symptoms are typically of an acute painful arthritis, which is not present in this patient. Synovial fluid analysis for crystals is therefore not indicated.

KEY POINT

- Chronic monoarticular arthritis with a large effusion and stiffness but minimal pain is characteristic of Lyme arthritis; diagnosis is made by serologic testing (enzyme-linked immunosorbent assay followed, if positive, by Western blot).

Bibliography

Arvikar SL, Steere AC. Diagnosis and treatment of Lyme arthritis. Infect Dis Clin North Am. 2015;29:269-80. [PMID: 25999223] doi:10.1016/j.idc.2015.02.004

H

Item 17 Answer: B

Educational Objective: Diagnose IgG4-associated retroperitoneal fibrosis.

The most likely diagnosis is IgG4-associated retroperitoneal fibrosis. Most of the conditions that are under the banner of IgG4-related disease (IgG4-RD) are characterized by IgG4-producing plasma cell infiltration and tumefaction of the affected tissue with resultant organ enlargement, fibrosis, and dysfunction. Patients commonly present with a sentinel organ enlargement, but careful evaluation often reveals more extensive disease. Clinical signs include painless enlargement of lymph nodes or the thyroid, parotid, or submandibular glands; proptosis with orbital pseudo-tumor; back or chest pain from aortic involvement; and abdominal pain from pancreatic or biliary tree disease. This patient presents with a classic picture of retroperitoneal fibrosis with back pain and kidney failure from the periaortic mass that is large enough to encase the ureters resulting in obstructive uropathy and kidney injury. In a recent study, almost 60% of patients with retroperitoneal fibrosis were found to have IgG4-RD. Some patients present with an inflammatory aortitis as well. The patient's history of a fibrotic thyroid gland is also a feature of IgG4-RD.

Young men with germ cell tumor can present with bulky retroperitoneal or mediastinal lymphadenopathy. A testicular mass may not always be present. Similarly, involvement of retroperitoneal, mesenteric, and pelvic nodes is common in many types of non-Hodgkin lymphoma and can lead to urinary tract obstruction. It is uncommon for either of these conditions to present as a retroperitoneal mass in the absence of lymphadenopathy, and neither germ cell tumor nor lymphoma can account for the fibrous goiter.

Mesothelioma is a highly lethal disease that most commonly involves the pleura but also the peritoneum. The most frequently noted symptoms are abdominal pain, weight loss, and increase in abdominal girth due to ascites. Malignant peritoneal mesothelioma does not present as a retroperitoneal mass and does not cause urinary obstruction or a fibrous thyroid goiter.

KEY POINT

- IgG4-related disease is characterized by IgG4-producing plasma cell infiltration and tumefaction of the affected tissue with resultant organ enlargement, fibrosis, and dysfunction.

Bibliography

Khosroshahi A, Carruthers MN, Stone JH, Shinagare S, Sainani N, Hasserjian RP, et al. Rethinking Ormond's disease: "idiopathic" retroperitoneal fibrosis in the era of IgG4-related disease. Medicine (Baltimore). 2013;92:82-91. [PMID: 23429355] doi:10.1097/MD.0b013e318289610f

Item 18 Answer: B

Educational Objective: Diagnose limited cutaneous systemic sclerosis.

The most likely diagnosis is limited cutaneous systemic sclerosis (LcSSc). This patient has Raynaud phenomenon and abnormal nailfold capillary changes that suggest that the Raynaud disease is part of the features of an underlying connective tissue disease. Raynaud phenomenon (sequential white, blue, and red color changes in the digits precipitated by cold or stress) occurs in almost all patients with systemic sclerosis (SSc). Raynaud phenomenon in LcSSc is initially transient and reversible; later, structural changes develop within small blood vessels, resulting in permanently impaired flow that produces acrocyanosis, digital pitting, and/or ulcerations. Office-based examination of the nailfold capillaries of patients with SSc using a dermatoscope or ophthalmoscope reveals both capillary destruction and dilated capillary loops, which can distinguish SSc from primary Raynaud. Early changes in nailfold capillaries in the setting of a connective tissue disease include dilatation. In the scleroderma spectrum disorders, nailfolds can demonstrate capillary dropout and then more disorganized loops as the vasculopathy progresses. Elevated antinuclear antibodies in a centromere pattern occur in 20% to 40% of patients with SSc and have a 90% specificity for the disease, and in particular for LcSSc. The presence of anticentromere antibodies also increases the risk for developing pulmonary arterial hypertension (PAH). This patient will need to be monitored for progression, including PAH screening.

Anticentromere B antibodies are not seen in patients with dermatomyositis or mixed connective tissue disease, neither of which is the likely diagnosis in this patient. The pathognomonic cutaneous features of dermatomyositis are the heliotrope rash and Gottron papules, which are absent

in this patient, as is another key feature, proximal muscle weakness.

Mixed connective tissue disease (MCTD) is an overlap syndrome that includes features of systemic lupus erythematosus (SLE), SSc, and/or polymyositis in the presence of anti-U1-ribonucleoprotein antibodies. More than 50% of patients with MCTD have hand edema and synovitis at disease onset, which is not present in this patient.

Anticentromere B antibodies are rarely seen in SLE (4% or less), and this patient does not have any findings associated with this disorder. SLE should be considered in any patient who presents with unexplained multisystem disease. The most common early SLE manifestations include constitutional symptoms (fever, weight loss, or severe fatigue), arthralgia/arthritis, and skin disease, all of which are absent in this patient.

KEY POINT

- Elevated antinuclear antibodies in a centromere pattern have a 90% specificity for systemic sclerosis, and in particular for limited cutaneous systemic sclerosis.

Bibliography

Mehra S, Walker J, Patterson K, Fritzler MJ. Autoantibodies in systemic sclerosis. Autoimmun Rev. 2013;12:340-54. [PMID: 22743034] doi:10.1016/j.autrev.2012.05.011

Item 19 Answer: D

Educational Objective: Diagnose polyarteritis nodosa.

The most likely diagnosis is polyarteritis nodosa (PAN), a vasculitis affecting medium-sized arteries. This entity may occur in the setting of chronic hepatitis B virus infection, HIV infection, and hairy cell leukemia. The most common symptoms are constitutional, including fever, malaise, and weight loss, and neurologic symptoms such as mononeuritis multiplex. Skin rashes, including purpura and necrotic ulcers, occur in more than half of patients. Kidney involvement manifests as hypertension due to renal artery vasculitis with renal infarction, not glomerulonephritis. Orchitis, an uncommon manifestation, is usually unilateral and due to testicular artery involvement. Mesenteric vasculitis may cause abdominal pain, perforation, and bleeding. This patient has all of these findings except for mesenteric involvement. Diagnosis of PAN is best established by demonstrating necrotizing arteritis in biopsy specimens or finding characteristic medium-sized artery aneurysms and stenoses on imaging studies of the mesenteric or renal arteries. This patient's renal angiogram confirms the presence of vasculitis and skin biopsy confirms medium-vessel vasculitis, consistent with the diagnosis of PAN.

Giant cell arteritis causes myalgia and elevated erythrocyte sedimentation rate but involves large vessels usually in the head and neck area or great vessels of the chest, not medium-sized vessels. Furthermore, it usually does not involve nerves or kidneys.

IgA vasculitis can cause testicular involvement, mononeuritis, and rash (palpable purpura), but it affects small vessels and causes glomerulonephritis rather than renovascular involvement.

Microscopic polyangiitis (MPA) is an ANCA-associated vasculitis affecting small vessels. It can cause neurologic involvement and skin rash, but kidney involvement is due to glomerulonephritis rather than renal artery vasculitis. Furthermore, MPA is associated with a positive ANCA with perinuclear pattern, directed against myeloperoxidase. This patient does not have a positive ANCA or glomerulonephritis, making MPA an unlikely diagnosis.

KEY POINT

- Polyarteritis nodosa is a vasculitis affecting medium-sized arteries and is characterized by constitutional and neurologic symptoms, skin rashes, and kidney involvement that is renovascular rather than glomerular in origin.

Bibliography

De Virgilio A, Greco A, Magliulo G, Gallo A, Ruoppolo G, Conte M, et al. Polyarteritis nodosa: a contemporary overview. Autoimmun Rev. 2016;15:564-70. [PMID: 26884100] doi:10.1016/j.autrev.2016.02.015

Item 20 Answer: E

Educational Objective: Treat osteoarthritis in an elderly patient using a topical NSAID.

Topical diclofenac is the most appropriate treatment for long-term symptom control for this elderly patient with knee osteoarthritis (OA). Acetaminophen has not provided relief; furthermore, the efficacy of acetaminophen for OA is increasingly being questioned because recent controlled trials and meta-analyses demonstrated no benefit from the drug, even at high doses. NSAIDs are available in oral, topical, and intravenous forms. Due to efficacy and cost-effectiveness, oral preparations are usually first-line NSAID therapy in patients without contraindications to treatment. In OA, topical NSAIDs are considered to provide similar pain relief as oral medications with fewer gastrointestinal effects. Furthermore, the American College of Rheumatology currently recommends topical NSAIDs rather than oral NSAIDs for patients aged 75 years or older. However, they are associated with more skin reactions and are significantly more expensive than oral NSAIDs. This elderly woman with unilateral knee OA is an ideal candidate for topical NSAIDs–she has just one area of musculoskeletal pain and has several relative contraindications to oral NSAIDs (age, chronic kidney disease, coronary artery disease, and aspirin intake).

When a single symptomatic joint is present, injection directly into the joint may deliver medication to the affected site while minimizing the potential for systemic effects. Intra-articular injections may be used along with or in place of oral or topical analgesics. Intra-articular glucocorticoids are associated with short-term benefit with few side effects.

Glucocorticoid injection alone would not likely provide long-term benefit for this patient.

Low-dose oral prednisone is associated with modest reductions in short-term knee pain and may increase a 6-minute walk distance in older patients with moderate-to-severe knee OA. However, long-term use is associated with significant complications, including an increased risk for diabetes mellitus, osteoporosis, osteonecrosis, weight gain, fluid retention, hypertension, cardiovascular disease, striae and bruising, and glaucoma and cataracts.

Oral naproxen and other oral NSAIDs are relatively contraindicated given the patient's hypertension, chronic kidney disease, and coronary artery disease.

Traditional opiates may rarely be warranted to control pain in patients with OA who have not responded to other agents or are poor candidates for other interventions to treat painful joints, such as surgery. Opioid analgesics are inappropriate for this patient because other treatment options are available. In addition, opioids have limited effectiveness for chronic joint pain and are associated with substantial side effects in the elderly, especially increased fall risk, cognitive changes, and constipation.

KEY POINT

- Topical NSAIDs are beneficial for patients at high risk for toxicity from oral NSAIDs.

Bibliography

Rannou F, Pelletier JP, Martel-Pelletier J. Efficacy and safety of topical NSAIDs in the management of osteoarthritis: Evidence from real-life setting trials and surveys. Semin Arthritis Rheum. 2016;45:S18-21. [PMID: 26806189] doi:10.1016/j.semarthrit.2015.11.007

Item 21 Answer: D

Educational Objective: Treat giant cell arteritis.

The most appropriate treatment is prednisone, 60 mg/d. This patient has signs and symptoms of giant cell arteritis (GCA), including headache, jaw claudication, visual changes, and an elevated erythrocyte sedimentation rate, as well as symptoms of polymyalgia rheumatica (PMR). GCA is the most common primary vasculitis. Median age of onset is 70 years; GCA in patients under age 50 is rare. GCA characteristically affects the second- to fifth-order branches of the aorta. Affected arteries include the external carotids, temporal arteries, and ciliary and ophthalmic arteries. Subclavian and brachial arteries can be affected. Uncommonly, intracranial arteritis may occur. Up to 50% of patients with GCA have PMR that may occur prior to, concurrent with, or following diagnosis of GCA. It is imperative that high-dose prednisone be initiated without delay to prevent irreversible visual loss from GCA; some advocate intravenous pulse methylprednisolone for patients with significant visual changes. Prednisone should generally be administered for approximately 1 month (or until resolution of signs and symptoms), with subsequent dose reduction at a rate of about 10% every few weeks.

CT of the head would be helpful in assessing for stroke-induced vision changes, but this patient's clinical presentation is not that of stroke. Stroke cannot explain the patient's malaise, weakness, aching, and tenderness over the left temporal area.

There are insufficient data from randomized controlled trials to recommend daily low-dose aspirin to prevent GCA complications, and this therapy would be inappropriate without concomitant high-dose prednisone.

Methotrexate may be helpful as adjunctive therapy for GCA and PMR, especially for those patients who have relapses and are unable to taper glucocorticoids. It is not appropriate initial therapy for GCA, especially as it will not take effect for several weeks, and this patient requires immediate treatment to prevent vision loss.

Temporal artery biopsy is the gold standard for diagnosing GCA; at least 1 cm is required in order to reduce the false-negative rate because of skip lesions. However, glucocorticoid therapy should not be delayed in order to establish the diagnosis of GCA. If necessary, temporal artery biopsy can be obtained 1 to 2 weeks after glucocorticoids have been initiated, and will still reveal diagnostic abnormalities.

KEY POINT

- High-dose prednisone must be initiated immediately in patients with signs and symptoms that are highly suggestive of giant cell arteritis to prevent irreversible visual loss.

Bibliography

Buttgereit F, Dejaco C, Matteson EL, Dasgupta B. Polymyalgia rheumatica and giant cell arteritis: a systematic review. JAMA. 2016;315:2442-58. [PMID: 27299619] doi:10.1001/jama.2016.5444

Item 22 Answer: B

Educational Objective: Diagnose inclusion body myositis.

The most likely diagnosis is inclusion body myositis (IBM), an inflammatory myopathy that can involve both the proximal and distal muscles; although typically symmetric, muscle distribution may be asymmetric. Sporadic IBM is the most common muscle disease in elderly populations, is more common in men than women, and typically develops after age 50 years and does not appear to affect individuals younger than 45 years old. Serum creatine kinase levels are typically less than 10 to 12 times the upper limit of normal. Its insidious onset and distal muscle involvement help to distinguish IBM from the other inflammatory myopathies. The absence of rash helps to exclude dermatomyositis. Electromyogram may show myopathic, neurogenic, or mixed changes with both short and long duration motor unit potentials and spontaneous activity. Diagnosis of IBM is confirmed by muscle biopsy showing muscle fibers containing multiple rimmed vacuoles. Distinguishing IBM from polymyositis is important because IBM is usually not treated with immunosuppressive therapy and has an overall poor response to treatment.

Amyotrophic lateral sclerosis (ALS) is a progressive, neurodegenerative disease that can have an insidious

onset causing muscle weakness. Upper and lower motor neuron signs may be seen, including spasticity, abnormal gait, increased reflexes, and difficulty with coordination (including manipulation of small objects), tripping, and falling. Findings may initially be proximal or distal and asymmetric. ALS can be distinguished from IBM by the presence of fasciculations, and ALS does not raise serum creatine kinase levels.

Mitochondrial myopathy can present in childhood, adolescence, or young adulthood, and a family history of mitochondrial disease is often evident. When myopathy predominates, the patient generally presents with proximal muscle weakness. However, exercise intolerance, painful and sometimes severe muscle cramping, and eye symptoms such as ptosis and diplopia are common. Serum creatine kinase levels are usually within the normal range, but serum lactate levels may be elevated.

Polymyositis occurs more frequently in women than in men and has its age of onset before 50 more often than IBM. It generally presents with proximal, rather than distal, muscle weakness, and serum creatine kinase levels can be substantially higher than those seen in IBM, often greater than 10 to 50 times normal.

KEY POINT

- Inclusion body myositis (IBM) is an inflammatory myopathy that can involve both the proximal and distal muscles with typically symmetric muscle distribution; its insidious onset and distal muscle involvement help to distinguish IBM from the other inflammatory myopathies.

Bibliography

Needham M, Mastaglia FL. Sporadic inclusion body myositis: a review of recent clinical advances and current approaches to diagnosis and treatment. Clin Neurophysiol. 2016;127:1764-73. [PMID: 26778717] doi:10.1016/j.clinph.2015.12.011

Item 23 Answer: A

Educational Objective: Treat sicca symptoms associated with Sjögren syndrome.

Artificial tears and sugar-free candies are the most appropriate treatment at this time. This patient meets diagnostic criteria for Sjögren syndrome, with objective documentation of sicca in the presence of anti-Ro/SSA antibodies, antinuclear antibodies, and rheumatoid factor. Her dental carries and missing teeth are almost certainly due to her dry mouth, as evidenced by lack of salivary pooling below the tongue. She has arthralgia but no definite arthritis and, consistent with Sjögren joint involvement, no evidence of erosive joint disease on radiograph. The immediate treatment goal of sicca is the re-establishment of wetting of the eyes and mouth. For the eyes, topical application of artificial tears is usually the first strategy, potentially followed by addition of topical cyclosporine or lifitegrast if artificial tears prove insufficient. For oral dryness, sugar-free candy or chewing gum can help to increase saliva flow. Regular intake or rinsing with small sips of water is also recommended. Artificial saliva substitutes would be considered next if these approaches are insufficient.

Methotrexate is a nonbiologic disease-modifying antirheumatic drug occasionally used in Sjögren syndrome for arthritis. Because the patient's joint disease is unlikely to result in future bony damage and is responsive to ibuprofen, no additional arthritis management is needed at this time. There is no documented indication for methotrexate to treat sicca symptoms associated with Sjögren syndrome.

Pilocarpine is a muscarinic agonist that may stimulate saliva secretion. It is often poorly tolerated and would not be considered unless basic measures to treat oral dryness are insufficient.

Rituximab depletes B cells and has shown early promise for the management of Sjögren syndrome. Early studies suggest a possible benefit for treating sicca, but it is generally reserved for patients with systemic Sjögren complications or severe disease. At the present time, its use is not warranted in this patient.

Topical ophthalmic NSAID drops are absolutely contraindicated in Sjögren syndrome because they carry risk for severe corneal damage.

KEY POINT

- Initial management of Sjögren syndrome typically involves treatment of sicca symptoms by restoring moisture of the eyes and mouth.

Bibliography

Baer AN, Walitt B. Sjögren Syndrome and Other Causes of Sicca in Older Adults. Clin Geriatr Med. 2017;33:87-103. [PMID: 27886700] doi:10.1016/j.cger.2016.08.007

Item 24 Answer: C

Educational Objective: Diagnose scleritis in a patient with rheumatoid arthritis.

The most likely diagnosis is scleritis in this patient with rheumatoid arthritis (RA). RA is one of the most common diseases associated with scleritis. Typical features include eye pain, pain with gentle palpation of the globe, and photophobia. The deep scleral vessels are involved and may lead to scleromalacia, which is characterized by thinning of the sclera and is seen as a dark area in the white sclera. Scleromalacia may lead to perforation of the sclera called scleromalacia perforans. Scleritis can be vision-threatening and lead to blindness; it is therefore important to urgently refer the patient to an ophthalmologist for care.

Conjunctivitis also causes a red eye. Typically, the underlying vessels are visible, a discharge may be seen, and often there is mattering of the eye in the morning. The eye may feel irritated but there is no pain or loss of visual acuity. In general, conjunctivitis is a diagnosis of exclusion. The presence of pain and decreased visual acuity exclude conjunctivitis in this patient.

Episcleritis is an abrupt inflammation of the superficial vessels of the episclera, a thin membrane that lies just beneath the conjunctiva. The cause is often unclear; rarely, it is associated with systemic rheumatologic disease. Patients with episcleritis frequently present without pain or decreased visual acuity. On examination, the inflammation appears localized. White sclera can be seen between superficial dilated blood vessels. Episcleritis typically resolves spontaneously. The presence of pain, diffuse redness, and decreased visual acuity make episcleritis an unlikely diagnosis.

Subconjunctival hemorrhage is a common disorder and typically benign in origin. It is caused by painless bleeding into the superficial portion of the eye. Examination reveals a blotchy redness (from extravascular blood) that is typically confined to one area of the conjunctiva. Subconjunctival hemorrhage is painless and not associated with loss of vision. Most cases resolve within several weeks without intervention. The patient's findings are not compatible with subconjunctival hemorrhage.

KEY POINT

- Rheumatoid arthritis is one of the most common diseases associated with scleritis, which can be vision-threatening and lead to thinning of the sclera and perforation.

Bibliography

Artifoni M, Rothschild PR, Brézin A, Guillevin L, Puéchal X. Ocular inflammatory diseases associated with rheumatoid arthritis. Nat Rev Rheumatol. 2014;10:108-16. [PMID: 24323074] doi:10.1038/nrrheum.2013.185

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Item 25 Answer: B

Educational Objective: Diagnose disseminated gonococcal infection.

The most likely diagnosis is disseminated gonococcal infection (DGI). This patient has the arthritis-dermatitis syndrome of DGI due to *Neisseria gonorrhoeae*. This syndrome is characterized by a triad of tenosynovitis, dermatitis (usually painless pustular or vesiculopustular lesions), and polyarthralgia without frank arthritis. Fever, chills, and malaise are common. Inflammation of multiple tendons of the wrists, fingers, ankles, and toes distinguishes this syndrome from other forms of infectious arthritis. This presentation of DGI is associated with positive blood cultures and characteristic skin lesions. Diagnosis is established by blood and synovial fluid cultures, as well as pharynx, cervix, urethra, and rectum cultures, and/or nucleic acid amplification testing. Testing patients and their sexual partners for both gonorrhea and chlamydia is critical. Initial therapy for DGI is usually with ceftriaxone plus either azithromycin or doxycycline, and is rapidly effective.

Chikungunya virus is an alphavirus endemic to Asia and Africa, where it is transmitted by mosquito vectors; however, cases are increasingly seen in the United States secondary to travel to endemic countries. In addition to fever, maculopapular rash, and headache, patients may experience synovitis and tenosynovitis of the fingers and wrists that is usually symmetric and may resemble rheumatoid arthritis. The presence of a pustular rash and lack of travel to an endemic area makes this diagnosis unlikely.

Reactive arthritis is an acute, asymmetric arthritis that typically follows chlamydial urethritis or infectious gastroenteritis within 6 weeks. It mainly affects lower extremity joints. Enthesitis, particularly at the Achilles tendon, can also occur. Patients also often have conjunctivitis, circinate balanitis, or keratoderma blenorrhagicum. A pustular or vesiculopustular rash is not part of the reactive arthritis syndrome.

Acute sarcoid arthritis presents most often as part of Löfgren syndrome, which is characterized by the triad of hilar adenopathy, acute arthritis, and erythema nodosum. The acute polyarthritis is mostly oligoarticular, with symmetric involvement most commonly involving the ankles or other lower extremity joints. This is in contrast to DGI, which is usually asymmetric and involves the upper extremity joints. Sarcoidosis may involve the skin, but lesions may be papular, nodular, plaque-like, or indurated and deep.

KEY POINT

- The arthritis-dermatitis syndrome of disseminated gonococcal infection due to *Neisseria gonorrhoeae* is characterized by a triad of tenosynovitis, dermatitis, and polyarthralgia without frank arthritis; fever, chills, and malaise are common.

Bibliography

García-Arias M, Balsa A, Mola EM. Septic arthritis. Best Pract Res Clin Rheumatol. 2011;25:407-21. [PMID: 22100289] doi:10.1016/j.berh.2011.02.001

Item 26 Answer: D

H

Educational Objective: Diagnose Libman-Sacks endocarditis.

Libman-Sacks endocarditis (nonbacterial thrombotic endocarditis) is the most likely cause of this patient's transient monocular blindness. She has an 8-year history of systemic lupus erythematosus (SLE) and positive antiphospholipid antibodies (anticardiolipin antibodies plus lupus anticoagulant) with recurrent pregnancy loss. She meets the criteria for antiphospholipid syndrome. Patients who have SLE with positive antiphospholipid antibodies are at a high risk for developing valvular dysfunction/thickening, and in some cases manifesting as Libman-Sacks endocarditis. A recent study confirmed this significant association between valvular heart disease and antiphospholipid antibody positivity. It was also found that the highest risk was seen in double-positive antiphospholipid antibodies/lupus anticoagulant patients, as is the case in this patient. Libman-Sacks endocarditis may affect 11% or more of patients

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with SLE and has no relationship to disease activity. The condition is associated with large verrucous lesions near the edge of the valve, most often the mitral valve. Typical lesions consist of immune complexes, mononuclear cells, and fibrin and platelet thrombi. Libman-Sacks endocarditis is usually asymptomatic but can be responsible for numerous complications, including embolic stroke, or in this case a transient ischemic attack in the territory of the ophthalmic artery, peripheral emboli, and infective endocarditis.

Bacterial endocarditis can be a source of cardiogenic emboli, but 90% of patients with infective endocarditis have fever, and often other constitutional symptoms, which are absent in this patient.

Patients with SLE are prone to develop premature atherosclerosis (and can be a cause of stroke or transient ischemia attack), but this patient has no findings of atherosclerosis involving the carotid artery; furthermore, this diagnosis cannot account for the patient's heart murmur.

Transient monocular blindness can be a manifestation of giant cell arteritis, but this diagnosis is extremely rare in individuals less than 40 years old.

KEY POINT

- Patients with systemic lupus erythematosus and positive antiphospholipid antibodies are at a high risk for developing valvular dysfunction/thickening, in some cases manifesting as Libman Sacks endocarditis.

Bibliography

Vivero F, Gonzalez-Echavarri C, Ruiz-Estevez B, Maderuelo I, Ruiz-Irastorza G. Prevalence and predictors of valvular heart disease in patients with systemic lupus erythematosus. Autoimmun Rev. 2016;15:1134-1140. [PMID: 27639157] doi:10.1016/j.autrev.2016.09.007

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Item 27 Answer: C

Educational Objective: Diagnose subcranial giant cell arteritis.

The most likely diagnosis is giant cell arteritis (GCA), a large-vessel vasculitis that most commonly affects vessels in the head and neck area (cranial GCA), resulting in jaw claudication, headaches (from involvement of the superficial temporal artery), and visual changes (due to involvement of ophthalmic arteries). Polymyalgia rheumatica (PMR), although not a vasculitis, is an inflammatory disorder that frequently accompanies GCA. Symptoms of PMR (shoulder and hip girdle pain and stiffness) may precede, accompany, or follow the diagnosis of GCA, and may be the only symptom of silent or subclinical GCA. As in this case, GCA less commonly affects the great vessels of the chest (subcranial GCA), causing upper extremity claudication and/or aortitis, as seen in this patient. Aortitis may lead to aortic root dilation, aortic regurgitation, and heart failure, as seen in this patient; this manifestation is usually a late feature of GCA.

Kawasaki disease initially presents in childhood, affects medium-sized (coronary) vessels, and can lead to heart failure due to myocardial damage years after the inflammation from vasculitis has resolved. Kawasaki disease does not have an onset in late adulthood.

Polyarteritis nodosa is a medium-vessel vasculitis that rarely affects the heart, and when it does, involves coronary vessels, not large vessels; this patient has a large-vessel vasculitis affecting the aorta.

In Takayasu arteritis (TA), the affected arteries are primarily the aorta (ascending, descending thoracic, and abdominal aorta) and its major branches. In contrast to GCA, TA is rare (2 cases/million patient-years) and mainly affects young women (9:1 ratio) with a typical age at onset between 15 and 25 years. Histologically, the pathophysiologic processes of TA and GCA are similar, with infiltration of T cells, macrophages, and giant cells in the vessel wall. This patient's age effectively excludes TA as the cause of her symptoms.

KEY POINT

- Giant cell arteritis can affect the great vessels of the chest causing upper extremity claudication and/or aortitis; aortitis may lead to aortic root dilation, aortic regurgitation, and heart failure.

Bibliography

González-Gay MA, Pina T. Giant cell arteritis and polymyalgia rheumatica: an update. Curr Rheumatol Rep. 2015;17:6. [PMID: 25618572] doi:10.1007/s11926-014-0480-1

Item 28 Answer: B

Educational Objective: Diagnose a secondary cause of acute calcium pyrophosphate crystal arthritis.

A serum calcium measurement is most likely to identify the cause of this patient's symptoms. This young woman has recurrent attacks of acute calcium pyrophosphate (CPP) crystal arthritis (pseudogout). Clues to the diagnosis include acute and recurrent self-limited monoarticular arthritis, chondrocalcinosis on radiograph, and, most tellingly, identification of CPP crystals under polarizing microscopy. This condition usually affects the elderly; therefore, evidence of acute CPP crystal arthritis in a young person should always prompt an investigation for secondary causes. Secondary causes include hyperparathyroidism, hypothyroidism, hypophosphatasia, hypomagnesemia, and hemochromatosis. This patient has recent-onset signs and symptoms suggestive of hypercalcemia and hyperparathyroidism, including abdominal discomfort, constipation, and weakness. Therefore, measuring the serum calcium is appropriate (and serum parathyroid hormone, if hypercalcemia is present), because this patient appears to have CPP deposition due to hyperparathyroidism.

Anti-cyclic citrullinated peptide antibodies are useful in the diagnosis of rheumatoid arthritis (RA). RA

typically presents with the insidious onset of symmetric arthritis in the hands and feet along with morning stiffness. Monoarthritis is a rare presenting feature of RA, but it is usually followed by development of the symmetric arthritis.

Checking serum creatine kinase would not be a first-line test for this patient. Although muscle disease is associated with weakness, myositis would not account for many of the other manifestations, including the monoarticular arthritis, radiographic chondrocalcinosis, and synovial fluid crystals.

Serum urate would be an appropriate laboratory study to measure if gout was suspected, but the synovial fluid analysis is consistent with acute CPP crystal arthritis rather than gout, in which negatively birefringent crystals are seen. Gout also more typically affects the metatarsophalangeal joints, the mid foot, ankles, and knees, although the finger joints may be affected in postmenopausal women.

KEY POINT

- Evidence of acute calcium pyrophosphate crystal arthritis (pseudogout) in a young person should always prompt an investigation for secondary causes such as hyperparathyroidism, hypothyroidism, hypophosphatasia, hypomagnesemia, and hemochromatosis.

Bibliography

Rosenthal AK, Ryan LM. Calcium Pyrophosphate Deposition Disease. N Engl J Med. 2016;374:2575-84. [PMID: 27355536] doi:10.1056/NEJMra1511117

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Item 29 Answer: D

Educational Objective: Treat relapsed granulomatosis with polyangiitis.

Rituximab is the most appropriate treatment for this patient who has experienced a relapse of granulomatosis with polyangiitis (GPA), manifesting with pulmonary inflammation and nodules despite maintenance treatment with azathioprine. GPA is a rare systemic autoimmune disease of unknown cause that leads to vasculitis and granulomatosis of small- to medium-sized blood vessels. Without treatment, most patients die within 1 year. With treatment, most patients achieve remission within 6 months. Relapses of GPA are common, occurring in more than 50% of patients within 5 years, and may occur in different organs from the initial presentation. Both rituximab and cyclophosphamide are efficacious for initial induction therapy in patients with severe GPA. The choice of which therapy to use depends upon the individual patient presentation and comorbid conditions.

The RAVE (Rituximab versus Cyclophosphamide for ANCA-Associated Vasculitis) trial demonstrated that rituximab is superior to cyclophosphamide in the subgroup of patients with relapse. In this study, remission without prednisone at 6 months was observed in 67% of rituximab-treated patients compared with 42% of cyclophosphamide patients ($P = 0.01$; NNT = 4). Rituximab was also as effective as cyclophosphamide in the treatment of patients with kidney disease or alveolar hemorrhage. There were no significant differences between the treatment groups with respect to rates of adverse events.

In trials of etanercept treatment for GPA, patients manifested an increased risk for the development of solid malignancies, especially if they had previously been treated with cytotoxic drugs. Therefore, etanercept is not considered first-line treatment for GPA.

Methotrexate is inadequate as induction therapy for severe disease; it can be used alone either as maintenance therapy after induction, or for mild and limited disease.

KEY POINT

- Rituximab is appropriate treatment for patients who experience a relapse of granulomatosis with polyangiitis.

Bibliography

Comarmond C, Cacoub P. Granulomatosis with polyangiitis (Wegener): clinical aspects and treatment. Autoimmun Rev. 2014;13:1121-5. [PMID: 25149391] doi:10.1016/j.autrev.2014.08.017

Item 30 Answer: B

Educational Objective: Manage disequilibrium caused by pregabalin.

The most appropriate next step in management is to discontinue pregabalin. Disequilibrium is an unsteadiness, or sense of imbalance, with standing or walking. Patients may experience disequilibrium as a side effect of medication use. This patient has fibromyalgia, which is characterized by widespread pain, fatigue, disturbed sleep, and cognitive dysfunction. Education, exercise, and psychosocial support are cornerstones of treatment, although pharmacotherapy is often warranted. Pregabalin can be effective for patients with fibromyalgia, but use is often limited by side effects, including weight gain, peripheral edema, lethargy, and especially dizziness (31% of all patients in trials versus 9% on placebo). The patient has fallen several times; therefore, it is imperative to remove any possible offending agent, and pregabalin is the most likely culprit among her medications. Once the troubling side effects resolve off medication, restarting at a lower dose could be considered.

Duloxetine can cause dizziness but not nearly as frequently as pregabalin (10% of patients in controlled trials versus 6% on placebo). Because pregabalin is the more likely cause, it should be stopped first; if possible, only one variable should be changed at a time.

There is no need to measure methylmalonic acid and homocysteine levels in this patient. Although vitamin B_{12} deficiency can cause peripheral neuropathy, the normal B_{12} level and neurologic examination make this a very unlikely diagnosis.

Given the high likelihood that pregabalin is causing the dizziness as well as the normal neurologic examination, MRI of the brain is not indicated at this time. It would be most useful if a space-occupying lesion were suspected, but there are no neurologic symptoms or signs referable to the central nervous system. If the patient were to develop neurologic signs or if symptoms did not improve with discontinuation of the pregabalin, this decision would need to be reevaluated.

Vestibular rehabilitation may be appropriate as a means of adapting to long-lasting or permanent vestibular damage. It includes exercises and balance training intended to stabilize gait and decrease symptoms and falls. It is not an appropriate first step in this case, however, because drug discontinuation alone is likely to result in improvement of her symptoms.

KEY POINT

- Use of pregabalin is often limited by side effects, including weight gain, peripheral edema, lethargy, and dizziness; discontinuation may be needed to manage the side effects.

Bibliography

Derry S, Cording M, Wiffen PJ, Law S, Phillips T, Moore RA. Pregabalin for pain in fibromyalgia in adults. Cochrane Database Syst Rev. 2016;9:CD011790. [PMID: 27684492]

Item 31 Answer: A

Educational Objective: Treat relapsed polymyalgia rheumatica.

Prednisone, 10 mg/d, is the most appropriate treatment for this patient with a relapse of polymyalgia rheumatica (PMR) after her prednisone dose was weaned to 8 mg/d. Patients with PMR experience symmetric pain and stiffness in the shoulder, neck, and hip regions, typically without synovitis. PMR is a clinical diagnosis based on the characteristic symptoms in a patient older than 50 years and is supported by an elevated erythrocyte sedimentation rate and/or C-reactive protein. Recent guidelines for the management of PMR (developed by a collaborative effort of the American College of Rheumatology and the European League Against Rheumatism) recommend increasing the prednisone to the last pre-relapse dose at which the patient was doing well, followed by a gradual reduction within 4 to 8 weeks back to the relapse dose. This patient was asymptomatic on 10 mg/d, prior to reducing to her current relapse dose; therefore, an increase to 10 mg/d is appropriate. After the flare-up subsides, a slow taper of 1 mg every 4 weeks may be better tolerated then larger increments over 2- to 4-week periods.

Prednisone, 30 mg/d, would also help treat the flare-up, but this higher dose is probably unnecessary, and a lower dose should be attempted first.

Prednisone, 60 mg/d, is not a typical dose used for PMR, and in the absence of concomitant giant cell arteritis is not needed to treat a PMR flare-up.

Methotrexate can be added as a glucocorticoid-sparing agent for patients who cannot be successfully weaned off prednisone or who are experiencing significant glucocorticoid toxicity; this patient has only had one flare-up and may do well after a modest increase followed by a more gradual taper of prednisone, making the addition of methotrexate premature at this time.

KEY POINT

- A relapse of polymyalgia rheumatica should be treated with an increase in prednisone to the last pre-relapse dose at which the patient was doing well, followed by a gradual reduction within 4 to 8 weeks back to the relapse dose.

Bibliography

Dejaco C, Singh YP, Perel P, Hutchings A, Camellino D, Mackie S, et al; European League Against Rheumatism. 2015 Recommendations for the management of polymyalgia rheumatica: a European League Against Rheumatism/American College of Rheumatology collaborative initiative. Ann Rheum Dis. 2015;74:1799-807. [PMID: 26359488] doi:10.1136/annrheumdis-2015-207492

Item 32 Answer: B

H

Educational Objective: Treat primary angiitis of the central nervous system.

In addition to high-dose glucocorticoids, cyclophosphamide is the most appropriate treatment for this patient who has primary angiitis of the central nervous system. Patients typically present with gradual progressive neurologic symptoms such as headaches, cognitive impairment, and other neurologic deficits such as strokes. Laboratory studies, including erythrocyte sedimentation rate, are typically normal, but 90% of patients have abnormal cerebrospinal fluid with lymphocytic pleocytosis and elevated total protein. MRI, MR angiogram, or CT angiogram often demonstrates nonspecific findings; cerebral angiogram sometimes reveals beading, or alternating stenosis and dilation of vessels consistent with vasculitis. Brain biopsy is falsely negative in 50% of patients due to patchy distribution of abnormalities, but when positive will show granulomatous vasculitis. Due to the rarity of this vasculitis, treatment is based on expert opinion and retrospective studies. High-dose glucocorticoids and cyclophosphamide have been reported to be effective in inducing remission and, given the severity of this patient's presentation, is the most appropriate choice. Glucocorticoids could be weaned over 3 to 6 months or longer, depending upon patient response to treatment. Cyclophosphamide could be discontinued after 3 to 6 months, and a maintenance drug such as azathioprine or mycophenolate mofetil could be started.

Anecdotal reports indicate that rituximab and tumor necrosis factor α inhibitors (such as adalimumab) may be effective; however, until more reports and studies are available, these would not be the first choice of treatment.

Methotrexate is not indicated for this patient because it does not penetrate the central nervous system well and would not be effective.

KEY POINT

- Cyclophosphamide with high-dose glucocorticoids is appropriate treatment for primary angiitis of the central nervous system.

Bibliography

Rodriguez-Pla A, Monach PA. Primary angiitis of the central nervous system in adults and children. Rheum Dis Clin North Am. 2015;41:47-62, viii. [PMID: 25399939] doi:10.1016/j.rdc.2014.09.004

Item 33 Answer: C

Educational Objective: Diagnose parvovirus B19.

Parvovirus B19 testing will most likely confirm the diagnosis. Parvovirus B19, which causes the childhood condition known as fifth disease (erythema infectiosum), is a DNA virus with a tropism for erythrocyte precursors. Adults usually contract the virus from children; individuals at risk include daycare or school workers and parents. Infection may be asymptomatic or produce a flu-like illness. In adults, the rash may be absent or atypical. The arthritis begins acutely, with symmetric pain and stiffness of the small joints of the hands and feet, as well as wrists and knees, in a pattern often mimicking rheumatoid arthritis (RA). This arthritis typically lasts for several weeks before resolving. Circulating anti-parvovirus IgM antibodies provide evidence of active disease; IgG antibodies indicate prior infection and are found in many healthy persons. Treatment is supportive.

Antinuclear antibody testing may be appropriate if systemic lupus erythematosus (SLE) or other related autoimmune diseases are suspected. Although some features of parvovirus B19 may overlap with those of SLE (fever, arthritis, cytopenias), other features of SLE (rashes, other mucocutaneous abnormalities) are notably absent in this patient.

Although HIV testing may be part of the complete workup for this patient's arthritis, the patient's exposure to children and the resolved antecedent brief febrile illness with an evanescent rash make parvovirus B19 much more likely.

Only 50% of patients with RA have detectable rheumatoid factor at onset, increasing to 60% to 80% in established disease. Conversely, up to 20% of patients with RA lack rheumatoid factor. Although rheumatoid factor testing may be part of this patient's evaluation because she has findings resembling RA, diagnosis requires that symptoms be chronic, usually for at least 6 weeks. Additionally, RA usually does not follow a viral infection.

KEY POINT

- Parvovirus B19 infection should be suspected in patients with an acute onset of small-joint symmetric polyarthritis following a febrile illness with rash, who have exposure to children.

Bibliography

Young NS, Brown KE. Parvovirus B19. N Engl J Med. 2004;350:586-97. [PMID: 14762186]

Item 34 Answer: A

Educational Objective: Diagnose rheumatoid arthritis with anti-cyclic citrullinated peptide antibodies.

Anti-cyclic citrullinated peptide (CCP) antibody testing is appropriate. This patient has a symmetric inflammatory polyarthritis involving the small joints of the hands and feet, which is highly suggestive of rheumatoid arthritis (RA). Laboratory studies, including rheumatoid factor, anti-CCP antibodies, and inflammatory markers, can assist in confirming the diagnosis, with anti-CCP antibodies the most helpful. Anti-CCP antibodies have a sensitivity of 70%, similar to that of rheumatoid factor, but they have a much higher specificity than rheumatoid factor (95%) and are more predictive than rheumatoid factor for erosive disease, making this test very useful to diagnose RA. The dual presence of rheumatoid factor and anti-CCP antibodies makes a diagnosis of RA substantially more likely.

Spondyloarthritis disorders share an overlapping set of features, including inflammation of the axial skeleton, tendons, and entheses; tendon and enthesis calcification; and an association with HLA-B27 antigen. HLA-B27 testing can define a probability for spondyloarthritis but cannot independently confirm or exclude any specific diagnosis. This patient does not have any features besides peripheral arthritis to suggest spondyloarthritis.

Parvovirus can cause polyarthralgia/arthritis but is generally transient, lasting 3 weeks or less, and is often accompanied by a net-like rash on the extremities and low-grade fever. IgM serology would indicate a recent infection and has to be checked within 8 to 10 weeks of infection because it declines thereafter as IgG rises. An elevated IgG antibody would simply indicate a past infection with the virus. This patient's persistent joint findings lasting 8 weeks argue against parvovirus infection.

Serum urate is useful in the diagnosis of gout in patients with typical findings. Although chronic recurrent gout can be polyarticular, this patient does not have features that suggest underlying gout such as palpable tophaceous depositions, and gout is rare in women before menopause.

Hypothyroidism can cause fatigue and uncommonly cause arthralgia and joint stiffness but is not associated with the active synovitis seen in this patient. Therefore, measuring thyroid-stimulating hormone would not be indicated.

KEY POINT

- Anti-cyclic citrullinated antibody testing is beneficial in diagnosing rheumatoid arthritis.

Bibliography

Chang PY, Yang CT, Cheng CH, Yu KH. Diagnostic performance of anti-cyclic citrullinated peptide and rheumatoid factor in patients with rheumatoid arthritis. Int J Rheum Dis. 2016;19:880-6. [PMID: 25940989]

Item 35 Answer: A

Educational Objective: Treat osteoarthritis with duloxetine.

Duloxetine, a serotonin and norepinephrine reuptake inhibitor with central nervous system effects, is a good treatment option for this patient with generalized osteoarthritis (OA). Duloxetine is FDA approved for chronic musculoskeletal pain and has been shown to have analgesic efficacy for chronic low back pain and knee OA pain, implicating the role of central sensitization in OA pain modulation. This patient has already tried multiple nonpharmacologic measures, as well as intra-articular glucocorticoid and hyaluronic injections, all with insufficient symptomatic relief. Duloxetine is a reasonable choice given the patient's comorbidities and generalized musculoskeletal pain.

Gabapentin and pregabalin are more effective than placebo in the treatment of neuropathic pain conditions such as postherpetic neuralgia and diabetic neuropathy. These drugs are expensive and both are associated with dose-dependent dizziness and sedation. There is no evidence of their effectiveness specifically for chronic OA pain.

NSAIDs inhibit cyclooxygenase (COX) enzymes, blocking the generation of the lipid prostaglandin E_2 (PGE_2). PGE_2 stimulates inflammation, vasodilation, smooth muscle contraction, pain, and fever. However, PGE_2 also maintains gastric mucosa and promotes kidney sodium excretion and glomerular filtration. Other COX products include thromboxane A_2, a prothrombotic regulator of platelets, and prostacyclin, an antithrombotic and vasodilatory lipid. Because NSAIDs inhibit all of these, the consequences of COX inhibition are complex and accompanied by multiple potential side effects. Side-effect risk is increased in older patients and those with preexisting comorbidities. Therefore, ibuprofen is not an advisable choice in an elderly patient with peptic ulcer disease, hypertension, and heart disease.

Topical capsaicin may benefit localized OA (for example, knee only) but is impractical in this case given the multiple areas of involvement. Furthermore, duloxetine is more likely to be efficacious given how many treatments this patient has tried and failed.

KEY POINT

- Duloxetine is FDA approved for chronic musculoskeletal pain and has been shown to have analgesic efficacy for chronic low back pain and knee osteoarthritis pain.

Bibliography

McAlindon TE, Bannuru RR, Sullivan MC, Arden NK, Berenbaum F, Bierma-Zeinstra SM, et al. OARSI guidelines for the non-surgical management of knee osteoarthritis. Osteoarthritis Cartilage. 2014;22:363-88. [PMID: 24462672] doi:10.1016/j.joca.2014.01.003

Item 36 Answer: A

Educational Objective: Diagnose adult-onset Still disease.

The most likely diagnosis is adult-onset Still disease (AOSD), a systemic inflammatory disease of multiple organ systems. This patient displays the typical signs and symptoms of AOSD, with spiking fevers, pharyngitis, an evanescent salmon pink rash that occurs in conjunction with fever, adenopathy, hepatosplenomegaly with elevated liver enzymes, leukocytosis with neutrophil predominance, inflammatory arthritis, and myalgia. Patients with AOSD can also develop other manifestations such as serositis. Extremely high serum ferritin levels are a typical feature. AOSD may also be seen during pregnancy or in the postpartum period. The diagnosis is clinical, and other entities such as infection and malignancy must be excluded.

Cryoglobulinemic vasculitis can cause arthritis, rash, and fever and may be associated with liver abnormalities, particularly if it is related to hepatitis C virus. However, the rash of cryoglobulinemia is related to small-vessel vasculitis characterized by palpable purpura of the lower extremities. Other organs characteristically involved include peripheral nerves and the kidneys (glomerulonephritis). Cryoglobulinemia cannot explain the elevated serum ferritin level.

Lymphoma can cause arthralgia, fever, rash, lymphadenopathy, and organomegaly. Lymphoma would not explain the patient's pleural friction rub, arthritis, or elevated serum ferritin level.

Microscopic polyangiitis is a form of ANCA-associated vasculitis in which patients can develop fever, rash, arthritis, and pulmonary disease, but this patient's rash (pink, evanescent, involving the trunk) is not typical for vasculitis (palpable purpura, urticaria, livedo reticularis, nodules). In addition, kidney involvement is nearly ubiquitous in microscopic polyangiitis, and the normal urinalysis argues against this diagnosis.

Similarly, systemic lupus erythematosus (SLE) can cause the same symptoms, but the rash associated with SLE is unlike that of AOSD. The malar rash of acute cutaneous lupus erythematosus consists of bright erythematous patches over both cheeks and the nasal bridge, almost always sparing the nasolabial folds; the rash is unrelated to fever. In addition, SLE cannot explain the elevated ferritin level.

KEY POINT

- Adult-onset Still disease is characterized by spiking fever, an evanescent salmon-colored rash on the trunk and extremities that occurs in conjunction with fever, arthritis, lymphadenopathy, and leukocytosis; an extremely high serum ferritin level is characteristic.

Bibliography

Gerfaud-Valentin M, Jamilloux Y, Iwaz J, Sève P. Adult-onset Still's disease. Autoimmun Rev. 2014;13:708-22. [PMID: 24657513] doi:10.1016/j.autrev.2014.01.058

Item 37 Answer: A

Educational Objective: Treat inflammatory bowel disease-associated arthritis.

Adalimumab is the most appropriate treatment for this patient with inflammatory bowel disease-associated arthritis. Various

pharmacologic agents may be useful in the treatment of both intestinal manifestations and peripheral arthritis related to Crohn disease and ulcerative colitis, including sulfasalazine, azathioprine, 6-mercaptopurine, methotrexate, glucocorticoids, and certain tumor necrosis factor (TNF)-α inhibitors. Adalimumab, certolizumab pegol, golimumab, and infliximab are more effective than other TNF-α inhibitors in treating the combination of bowel and joint manifestations. This patient with Crohn disease has developed peripheral oligoarthritis and dactylitis ("sausage digit"). She also has symptomatic bowel disease. She is most likely to improve her bowel and joint disease by the addition of a TNF-α inhibitor.

Intra-articular glucocorticoid injections can be used to treat inflammatory arthritis. However, the duration of symptom relief can be short term, practical use is limited by the size and number of joints involved, and this therapy will have no effect on the patient's dactylitis or inflammatory bowel disease.

Glucocorticoids are effective for inducing but not maintaining remission in Crohn disease. Although prednisone could be used to improve the patient's joint and bowel symptoms on a short-term basis, it is unlikely to control her bowel and joint symptoms in the long term and is increasingly likely to be associated with significant side effects the longer it is used.

Rituximab depletes B cells and is used in combination with methotrexate to treat rheumatoid arthritis in patients who have not adequately responded to a TNF-α inhibitor. Rituximab is not indicated for this patient's arthritis or bowel disease and is not recommended.

KEY POINT

- Long-term treatment options for bowel and joint symptoms associated with inflammatory bowel disease include sulfasalazine, azathioprine, 6-mercaptopurine, methotrexate, and the tumor necrosis factor α inhibitors adalimumab, certolizumab pegol, golimumab, and infliximab.

Bibliography

Peluso R, Manguso F, Vitiello M, Iervolino S, Di Minno MN. Management of arthropathy in inflammatory bowel diseases. Ther Adv Chronic Dis. 2015;6:65-77. [PMID: 25729557] doi:10.1177/2040622314563929

Item 38 Answer: D

Educational Objective: Choose the most appropriate test to diagnose tuberculosis as the cause of chronic monoarthritis.

The most appropriate test to perform next is a synovial biopsy. This patient has persistent inflammatory swelling of the right knee, with synovial fluid leukocyte counts between 15,000 and 20,000/µL ($15-20 \times 10^9$/L). The differential diagnosis in this patient with chronic inflammatory monoarthritis includes mycobacterial, fungal, or *Borrelia burgdorferi* infection and other systemic rheumatologic diseases such as sarcoidosis. Frequently in these patients, synovial fluid analysis alone may be inadequate for diagnosis; serologies or other laboratory tests or synovial biopsy is required to establish the diagnosis. In this patient, a synovial biopsy is the most appropriate test to evaluate for all of the conditions in the differential diagnosis. The biggest concern here is *Mycobacterium tuberculosis* arthritis, given this patient's history of latent tuberculosis and a high risk due to advancing age.

Sarcoidosis is characterized by formation of noncaseating granulomas in multiple organs and tissues. These granulomas may increase angiotensin-converting enzyme levels. A history of latent tuberculosis, calcified granulomas in the upper lobe, and a chronically inflamed joint are more consistent with tuberculosis infection. In addition, the angiotensin-converting enzyme level is only 75% specific (25% of cases will be missed) and 90% specific (10% of positive results will be false positive), decreasing the usefulness of this test for sarcoidosis.

Multiple small pulmonary nodules (<5 mm) found incidentally in a patient without a known malignancy are likely to be nonmalignant. Like solitary pulmonary nodules, multiple pulmonary nodules may be further assessed with helical CT to better characterize their number, location, and morphology. However, in this patient, the previous history of tuberculosis, fever, and a chronic inflammatory monoarthritis strongly suggest tuberculosis, and a tissue diagnosis can be most easily established with synovial biopsy.

HLA-B27 testing may be useful in the evaluation of spondyloarthritis, which can present with chronic lower extremity inflammatory monoarthritis. However, this patient has no other findings of spondyloarthritis such as rash, bowel symptoms, or inflammatory back pain. Furthermore, HLA-B27 lacks specificity and is unlikely to yield the correct diagnosis.

KEY POINT

- Synovial fluid analysis can confirm inflammation but may be inadequate for diagnosis of a chronic inflammatory monoarthritis; synovial biopsy may be required.

Bibliography

Gerlag DM, Tak PP. How to perform and analyse synovial biopsies. Best Pract Res Clin Rheumatol. 2013;27:195-207. [PMID: 23731931] doi:10.1016/j.berh.2013.03.006

Item 39 Answer: A

Educational Objective: Diagnose erosive osteoarthritis.

Erosive osteoarthritis (OA) is the most likely diagnosis. Erosive OA is thought to be an aggressive subset of hand osteoarthritis that has periods of prominent inflammatory symptoms and characteristic erosive changes on imaging. Patients often experience pain, swelling, and joint deformities. Inflammatory damage to soft-tissue structures can result in deviation of the digits. Diagnosis is mostly based on the radiographic findings of articular surface erosions at the central portion of the joint. Erosions are often symmetric and occur mainly

in the distal interphalangeal (DIP) and, to a lesser extent, proximal interphalangeal (PIP) joints. Radiographs reveal a "gull-wing" deformity, resulting from marginal sclerosis and osteophytes on the distal side of the joints, whereas the proximal side is centrally eroded or collapsed and thinned. Women are affected more frequently than men. Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), rheumatoid factor, and anti-cyclic citrullinated peptide antibodies are usually normal, as seen in this patient. Heberden nodes and squaring at the carpometacarpal joint also support a diagnosis of erosive OA in this patient.

Although gout flares may be superimposed upon sites of nodal OA, the inflamed DIP joints in this patient are less likely to represent a gouty flare given the normal ESR, CRP, and urate levels. Moreover, radiographs of patients with tophaceous gout often show marginal and juxta-articular punched-out erosions, which are not seen in this patient.

Psoriatic arthritis may be symmetric and affect the hands, including the DIP joints, but the patient reports no personal history of psoriasis, does not indicate significant morning stiffness, has no rashes or nail pitting, and does not have the marginal erosions on radiograph that would support this diagnosis.

Although the patient has symmetric hand arthritis and fits the typical demographics of a patient with rheumatoid arthritis (RA), the predominance of DIP symptoms, the lack of prolonged morning stiffness, the laboratory studies negative for inflammatory markers and/or RA autoantibodies, and the typical "gull-wing" deformity on radiograph (rather than marginal erosions) do not support RA as the diagnosis.

KEY POINT

- Diagnosis of erosive hand osteoarthritis is based essentially on radiographic findings of articular surface erosions at the central portion of the joint; erosions are often symmetric and occur mainly in the distal interphalangeal joints.

Bibliography

Kloppenburg M, Kwok WY. Hand osteoarthritis–a heterogeneous disorder. Nat Rev Rheumatol. 2011;8:22-31. [PMID: 22105244] doi:10.1038/nrrheum.2011.170

H

Item 40 Answer: A

Educational Objective: Diagnose a systemic lupus erythematosus flare.

Measurement of the anti-double-stranded DNA antibodies will be most helpful in evaluating this patient with a systemic lupus erythematosus (SLE) flare. She has recent inflammatory swelling of multiple joints, malar eruption, hypertension, and new-onset edema. She also has an elevated urine protein-creatinine ratio, suggesting the presence of active lupus nephritis. In this situation, the measurement of inflammatory markers and other tests associated with SLE flares can be very useful in establishing a diagnosis and directing treatment. Elevation of the erythrocyte sedimentation rate, rising anti-double-stranded DNA antibody titer, and low complement levels reliably diagnose an SLE flare. Elevated C-reactive protein (CRP) is common in inflammatory states except in SLE, in which CRP levels do not rise during SLE flare-up (but do rise during an infectious episode). Complements are especially helpful in patients with SLE. Most inflammatory states are associated with increased complement levels except in certain immune complex–mediated diseases (SLE; cryoglobulinemic and urticarial vasculitis), where the levels decrease due to excessive consumption during active disease state. C3 and C4 are the commonly measured complements, and their levels decrease during the flare-up. An increase in the anti-double-stranded DNA antibody titer also indicates an SLE flare and has the best correlation with flare-up of lupus nephritis. A kidney biopsy to evaluate SLE kidney involvement should also be considered here.

Antinuclear antibody (ANA) testing is a useful screening tool for SLE but does not correlate with disease activity. Anti-Ro/SSA and anti-La/SSB antibodies correlate with SLE rashes and photosensitivity but do not correlate with disease activity. Anti-Smith antibodies are highly specific for the diagnosis of SLE but also do not correlate with disease activity. Anti-U1-ribonucleoprotein antibodies are found in patients with SLE and mixed connective tissue disease but do not correlate with disease activity.

KEY POINT

- Elevation of the erythrocyte sedimentation rate, rising anti-double-stranded DNA antibody titer, and low complement levels reliably diagnose a systemic lupus erythematosus flare.

Bibliography

Pisetsky DS. Anti-DNA antibodies–quintessential biomarkers of SLE. Nat Rev Rheumatol. 2016;12:102-10. [PMID: 26581343] doi:10.1038/nrrheum.2015.151

Item 41 Answer: D

H

Educational Objective: Diagnose immune-mediated necrotizing myopathy.

In addition to a muscle biopsy, anti-HMG Co-A reductase antibody testing is most likely to establish the diagnosis. A small number of patients taking statins develop immune-mediated necrotizing myopathy (IMNM), which can be easily confused with polymyositis. IMNM is thought to occur as a result of an immune response to HMGCR, the pharmacologic target of statins. IMNM can be a paraneoplastic phenomenon related to connective tissue disease, or drug related, most commonly statins. Statin use may initiate or worsen the syndrome. In patients taking statins, myositis may rapidly progress and persist despite drug discontinuation due to this abnormal immune response and is often associated with the production of anti-HMG Co-A reductase antibodies. The histologic finding of necrotic muscle fibers with only minimal inflammatory cells that do not invade the muscle fibers is characteristic of IMNM, and, given the patient's history of exposure to statins,

H CONT.

a muscle biopsy and determination of anti-HMG CO-A reductase antibodies will most likely establish the diagnosis. The condition may respond to immunosuppressive therapy.

Anti-cyclic citrullinated peptide antibodies are not seen in inflammatory myopathies; they have a relatively high specificity (>90%) for rheumatoid arthritis and may be useful in the differential diagnosis of early polyarticular inflammatory arthritis.

Anti-cytosolic 5′-nucleotidase 1A antibodies have been identified in about half of patients with inclusion body myositis. Strong reactivity for these antibodies has relatively high specificity for inclusion body myositis compared with other muscle diseases.

Anti-histidyl-tRNA synthetase antibodies, particularly the subset anti-Jo-1 antibodies, are associated with the presence of interstitial lung disease in patients with inflammatory myopathies and, in particular, with antisynthetase syndrome of interstitial lung disease, Raynaud phenomenon, inflammatory arthritis, and mechanic's hands.

KEY POINT

- In patients with immune-mediated necrotizing myopathy, myositis may persist despite statin discontinuation and is often associated with the production of anti-HMG Co-A reductase antibodies.

Bibliography

Musset L, Allenbach Y, Benveniste O, Boyer O, Bossuyt X, Bentow C, et al. Anti-HMGCR antibodies as a biomarker for immune-mediated necrotizing myopathies: a history of statins and experience from a large international multi-center study. Autoimmun Rev. 2016;15:983-93. [PMID: 27491568] doi:10.1016/j.autrev.2016.07.023

Item 42 Answer: B

Educational Objective: Diagnose Sjögren syndrome.

The most appropriate diagnostic test to perform next is a lip biopsy. This patient has parotid and lacrimal enlargement and sicca. The differential diagnosis of sicca with parotid/lacrimal enlargement includes Sjögren syndrome, sarcoidosis, IgG4-related disease, HIV-associated diffuse lymphocytic infiltrate syndrome, and others. The American College of Rheumatology/European League Against Rheumatism has proposed diagnostic criteria for Sjögren syndrome. The most heavily weighted criteria include focal lymphocytic sialadenitis in labial salivary gland biopsy and the presence of anti-Ro/SSA antibodies. The presence of both will establish the diagnosis. Alternatively, the diagnosis can be established with one of the two major criteria and an abnormal ocular staining score of ≥5, abnormal Schirmer test, or abnormal whole saliva flow test. In addition, entities in the differential diagnosis should be excluded. The patient meets the criteria for keratoconjunctivitis sicca, but because of the absence of anti-Ro/SSA antibodies, additional support is needed. A lip biopsy to assess minor salivary gland pathology is relatively noninvasive; it can provide evidence sufficient to meet the proposed diagnostic criteria and might assist in ruling out other entities in the differential diagnosis.

CT of the chest might identify findings to support an alternative diagnosis. For example, findings of hilar lymphadenopathy or pulmonary nodules might support a diagnosis of sarcoidosis. However, the yield would be low given the normal chest radiograph.

Like lip biopsy, parotid biopsy can provide evidence of Sjögren syndrome; however, it is more invasive and risks seventh cranial nerve damage. Its use is currently limited to special situations.

A Schirmer test could conveniently confirm dry eyes, but dry eyes have already been confirmed by a more rigorous and reproducible ophthalmologic examination.

Sialography can assess the extent of mouth dryness, but the diagnosis of sicca has already been sufficiently confirmed.

KEY POINT

- A lip biopsy should be considered in a patient with sicca and suspected Sjögren syndrome when initial serologic evaluation is uninformative.

Bibliography

Giovelli RA, Santos MC, Serrano ÉV, Valim V. Clinical characteristics and biopsy accuracy in suspected cases of Sjögren's syndrome referred to labial salivary gland biopsy. BMC Musculoskelet Disord. 2015;16:30. [PMID: 25887888] doi:10.1186/s12891-015-0482-9

Item 43 Answer: C

Educational Objective: Diagnose methotrexate-induced anemia.

The most likely diagnosis is methotrexate-induced anemia. Methotrexate can cause stomatitis, hepatic inflammation and fibrosis, and myelotoxicity, including megaloblastic anemia and pancytopenia. Folic acid supplementation is mandatory in all patients receiving methotrexate and can prevent the development of stomatitis and hepatotoxicity (as measured by elevated aminotransferase levels). Hematologic toxicity, however, can occur even with folic acid supplementation. In this patient, a rise in mean corpuscular volume (MCV) indicates a likely megaloblastic anemia, and methotrexate is the likely cause. Guidelines from the American College of Rheumatology recommend periodic monitoring of the complete blood count every 4 weeks during the first 3 months of therapy, every 8 to 12 weeks from 3 to 6 months, and every 8 to 12 weeks thereafter.

Inflammatory anemia (anemia of chronic disease) is a common manifestation of rheumatoid arthritis and is usually a mild, normocytic anemia. Most patients experience symptoms related to their underlying disease rather than the anemia. Inflammatory anemia would not present with this degree of anemia or macrocytosis.

Typical features of iron deficiency are identical to those of any symptomatic anemia but may be subtle owing to an insidious onset of the condition. Headache and pica (craving for typically undesirable items such as ice, dirt, clay, paper, and laundry starch) are frequently associated symptoms;

other less common symptoms include restless legs syndrome and hair loss. The hallmark of iron deficiency is a microcytic hypochromic anemia. However, this is usually only seen in advanced iron deficiency, and anemia tends to precede morphologic changes in the cells. The presence of macrocytosis makes iron deficiency unlikely.

Tocilizumab is not associated with a macrocytic anemia. Through its anti-inflammatory properties, it may decrease the likelihood of inflammatory-induced anemia in patients with rheumatoid arthritis.

KEY POINT

- Methotrexate use can result in a megaloblastic anemia or pancytopenia; periodic monitoring of the complete blood count is recommended.

Bibliography

Shea B, Swinden MV, Ghogomu ET, Ortiz Z, Katchamart W, Rader T, et al. Folic acid and folinic acid for reducing side effects in patients receiving methotrexate for rheumatoid arthritis. J Rheumatol. 2014;41:1049-60. [PMID: 24737913] doi:10.3899/jrheum.130738

H

Item 44 Answer: A

Educational Objective: Evaluate acute monoarthritis with joint aspiration.

Aspiration of the right knee is the most appropriate test to establish the diagnosis. This patient has isolated inflammatory swelling of the right knee. Synovial fluid aspiration is essential when evaluating for infection and crystal-related disease and can distinguish between inflammatory and noninflammatory conditions. The most useful tests of synovial fluid for infection are leukocyte count, stains, and cultures, as well as evaluation of synovial fluid for crystals under polarized light. Synovial fluid leukocyte counts less than 200/µL (0.2×10^9/L) are considered normal, between 200/µL and 2000/µL ($0.2\text{-}2.0 \times 10^9$/L) are associated with noninflammatory conditions, and greater than 2000/µL (2.0×10^9/L) are associated with inflammatory states. The higher the count is, the more inflammatory the fluid and the greater the suspicion for crystal-related or infectious disease. There is no absolute cutoff value that distinguishes infection from crystal-related disease, because some infections may have lower counts than expected and crystal-related disease may have counts greater than 100,000/µL (100×10^9/L). Thus, the proper application of synovial fluid leukocyte counts requires conservative interpretation. Generally, counts greater than 50,000/µL (50×10^9/L) should be managed as infectious until explicitly proven otherwise; if there is clinical suspicion for infection, fluid should be sent for stains and cultures even in the setting of counts less than 50,000/µL (50×10^9/L). Synovial fluid analysis can also confirm or rule out hemarthrosis, which can have a similar clinical presentation as in this case.

Blood cultures are appropriate in this patient but are only positive in 30% to 40% of patients with infectious arthritis and do not replace the need for arthrocentesis, which is the test most likely to establish the diagnosis.

The erythrocyte sedimentation rate (ESR) commonly indicates the presence of inflammation, and elevations are used to identify and monitor disease activity in rheumatologic diseases. However, obtaining an ESR will not provide additional information not already gleaned from the physical examination and will not establish a specific diagnosis.

MRI can detect soft-tissue abnormalities, inflammation, and fluid collections but is not the most appropriate next step to establish the cause of this patient's acute monoarthritis because it cannot distinguish between infection and acute gout.

KEY POINT

- Joint aspiration and synovial fluid analysis for Gram stain, cultures, and crystals are indicated to help diagnose the underlying cause of acute monoarthritis.

Bibliography

Becker JA, Daily JP, Pohlgeers KM. Acute monoarthritis: diagnosis in adults. Am Fam Physician. 2016;94:810-816. [PMID: 27929277]

Item 45 Answer: A

Educational Objective: Prevent glucocorticoid-induced osteoporosis.

This patient at risk for glucocorticoid-induced osteoporosis should begin alendronate. One of the many risks and side effects of chronic glucocorticoid therapy is osteoporosis. The Fracture Risk Assessment Tool (FRAX) calculator defines the 10-year fracture risk for patients with T-scores in the −1.0 to −2.5 range. The FRAX calculator (www.shef.ac.uk/FRAX) incorporates multiple risk factors, including sex, fracture history, femoral neck bone mineral density, glucocorticoid use, smoking, BMI, age, and alcohol intake to determine projected fracture risk. The American College of Rheumatology recommends that patients over the age of 40 years at moderate or high risk for osteoporotic fractures who are to be on at least 2.5 mg of prednisone daily for 3 months or more should begin prophylactic bisphosphonate therapy with alendronate, risedronate, or zoledronic acid. In patients on chronic glucocorticoid therapy, prophylactic bisphosphonate therapy significantly increases bone mineral density compared with placebo, and these patients also have fewer new vertebral fractures.

In patients at high risk for major osteoporotic fracture (10-year risk greater than 20% or a T score ≤−2.5 or a history of a fragility fracture) taking any dose of glucocorticoids for at least 1 month should receive prophylactic treatment (although these patients should be treated regardless of glucocorticoid therapy). Alendronate, risedronate, zoledronic acid, or teriparatide are therapeutic options. This patient is not in the high-risk category, and teriparatide is therefore not a recommended option.

Dual-energy x-ray absorptiometry (DEXA) is useful at the outset of chronic glucocorticoid therapy to risk-stratify patients and to provide baseline values. Although there is no consensus on the optimal frequency of monitoring bone

mineral density with DEXA, there is no role for repeating the study in less than 1 year.

Because of her prolonged need for prednisone and risk for osteoporotic fracture, no additional therapy would be inappropriate management for this patient.

KEY POINT

- Patients at moderate or high 10-year risk for a major osteoporotic fracture taking at least 2.5 mg of prednisone daily for 3 months or more should begin prophylactic bisphosphonate therapy.

Bibliography

Buckley L, Guyatt G, Fink HA, Cannon M, Grossman J, Hansen KE, et al. 2017 American College of Rheumatology Guideline for the Prevention and Treatment of Glucocorticoid-Induced Osteoporosis. Arthritis Care Res (Hoboken). 2017;69:1095-1110. [PMID: 28585410] doi:10.1002/acr.23279

Item 46 Answer: C

Educational Objective: Diagnose pulmonary arterial hypertension in a patient with limited cutaneous systemic sclerosis.

The most likely cause of her symptom is pulmonary arterial hypertension. Pulmonary vascular disease occurs in up to 40% of patients with systemic sclerosis. Vascular disease leading to pulmonary arterial hypertension may occur secondary to interstitial lung disease (typically in patients with diffuse cutaneous systemic sclerosis) or as an isolated process (typically in limited cutaneous systemic sclerosis). Patients are usually asymptomatic in early disease but later develop dyspnea on exertion and diminished exercise tolerance. Severe disease can lead to right-sided heart failure. This patient with limited cutaneous systemic sclerosis and progressive dyspnea has a normal chest radiograph and a normal pulmonary examination, but an increased pulmonic sound and a widened split of S_2 on cardiac examination compatible with pulmonary hypertension. Taken together, the most likely cause of the patient's progressive dyspnea is pulmonary arterial hypertension. Initial evaluation of this patient should proceed with pulmonary function tests and echocardiography.

Interstitial lung disease (ILD) usually develops subacutely with progressive fibrosis. Patients with diffuse cutaneous systemic sclerosis and anti-Scl-70 antibodies are at higher risk for developing ILD. The most common symptom of ILD is slowly progressive dyspnea, at first on exertion, but later at rest. Other symptoms include nonproductive cough, decreased exercise tolerance, and chest pain. Auscultation reveals "Velcro"-like inspiratory crackles, most prominent at the lung bases. This patient's symptom complex limited to exertional dyspnea and normal pulmonary examination and chest radiograph make this diagnosis less likely.

Cardiac involvement in systemic sclerosis may be due to cardiac fibrosis or coronary artery disease or secondarily due to systemic or pulmonary hypertension. Intrinsic cardiac fibrosis is uncommon and usually asymptomatic. Conduction disturbances and arrhythmias are common and probably relate to fibrosis of the conduction system. This uncommon complication is not the most likely cause of progressive exertional dyspnea in this patient.

There is an increased risk for venous thromboembolism in patients with systemic sclerosis, and risk is greatest during the first year after diagnosis. This patient's 3-month history of progressive exertional dyspnea is unlikely due to acute venous thromboembolic disease.

KEY POINT

- Patients with systemic sclerosis, especially those with limited disease, are at risk for pulmonary arterial hypertension.

Bibliography

Thakkar V, Lau EM. Connective tissue disease-related pulmonary arterial hypertension. Best Pract Res Clin Rheumatol. 2016;30:22-38. [PMID: 27421214] doi:10.1016/j.berh.2016.03.004

Item 47 Answer: C

Educational Objective: Select the most appropriate imaging study for probable osteoarthritis.

Radiography is the most appropriate initial imaging study. Radiography is used to assess inflammatory arthritis and osteoarthritis (OA). Radiography does not visualize soft tissues nearly as well as bone, and due to the two-dimensional nature of the images, not all bone findings are visible on every view. Radiography may not detect early or mild erosive arthritic changes. Despite these limitations, serial radiography can be useful for monitoring arthritis disease progression. Radiography is relatively inexpensive and readily available. Despite low levels of ionizing radiation, radiography is considered safe except for pregnant women. In this case, the most likely diagnosis is OA of the right knee. Weight-bearing views should be obtained to more accurately assess the knee joint on radiographs. Typical radiographic OA features are osteophytes, joint-space narrowing, subchondral sclerosis, and cysts. Erosions are uncommon unless the erosive OA subtype is present, which usually is more aggressive and inflammatory on clinical evaluation.

In contrast to radiography, CT permits multiple views and orientations from a single study. CT is more sensitive for detecting bony abnormalities, such as bone erosions, than radiography or MRI. CT is more expensive than radiography and exposes the patient to more radiation.

MRI is useful in detecting soft-tissue abnormalities, inflammation, and fluid collections, but is less effective than CT in demonstrating bony abnormalities and erosive changes. MRI is more sensitive than radiography in detecting early spine and sacroiliac joint inflammation. MRI is more expensive than radiography and CT and is generally ordered when assessment of soft-tissue imaging is required. Radiography is a better choice than MRI to detect typical changes of OA.

Ultrasonography can detect soft-tissue abnormalities such as synovitis, tendinitis, bursitis, and joint fluid, and Doppler can assess for increased tissue blood flow consistent with synovitis. Ultrasonography can diagnose and monitor disease, and can be used to guide arthrocentesis. Ultrasonography is relatively inexpensive, and there is no ionizing radiation. Because inflammatory disease or joint aspiration is not anticipated and radiography will be better able to detect bony changes of OA, ultrasonography is not indicated.

KEY POINT

- Radiography is typically used as the initial imaging modality to assess inflammatory arthritis and osteoarthritis.

Bibliography

Jacobson JA, Girish G, Jiang Y, Sabb BJ. Radiographic evaluation of arthritis: degenerative joint disease and variations. Radiology. 2008;248:737-47. [PMID: 18710973] doi:10.1148/radiol.2483062112

Item 48 Answer: C

Educational Objective: Diagnose pes anserine bursitis.

The most likely diagnosis is pes anserine bursitis, an inflammatory condition affecting the bursa at the insertion of the conjoined medial knee tendons into the anteromedial proximal tibia. This condition has been known to affect athletes but can also occur in those with concurrent knee osteoarthritis (usually in obese women) even without a history of trauma or overuse. The diagnosis of pes anserine bursitis is clinical, based on a history of increased medial knee pain worsened with climbing or descending stairs or rising from a seated position. Patients may also note morning pain and stiffness lasting more than 1 hour, and pain may worsen at night. Physical examination showing severe point tenderness at the insertion of the anserine tendon about 3 to 6 cm (2 in) below the medial joint line, often with local edema, supports the diagnosis. Relief with injection of a local anesthetic is also supportive.

A medial collateral ligament (MCL) tear may cause medial knee pain, which can also extend to where the MCL inserts on the anteromedial proximal tibia; however, an MCL injury is very painful and may cause difficulty ambulating. MCL injury is suspected when there is pain and/or laxity on valgus stress of the knee.

A meniscal tear could cause medial knee pain, but the pain is usually around the joint line; patients may also have unusual sensations in the knee such as clicking, locking, catching, or a sensation that the joint gives way. There are several provocative maneuvers on physical examination that may suggest a meniscal tear.

Quadriceps tendonitis occurs as a result of stress placed upon the quadriceps tendon, usually from sports-related activities. Pain can be felt at the lower part of the thigh, just above the patella. There may also be swelling around the quadriceps tendon.

KEY POINT

- Pes anserine bursitis is an inflammatory condition affecting the bursa at the insertion of the conjoined medial knee tendons into the anteromedial proximal tibia and should be considered when there is localized pain inferomedial to the knee joint.

Bibliography

Alvarez-Nemegyei J, Canoso JJ. Evidence-based soft tissue rheumatology IV: anserine bursitis. J Clin Rheumatol. 2004;10:205-6. [PMID: 17043509]

Item 49 Answer: C

Educational Objective: Diagnose relapsing polychondritis.

The most likely diagnosis is relapsing polychondritis (RP). RP is characterized by inflammation and damage of cartilaginous tissues; tissues most commonly affected include the cartilaginous portions of the external and middle ear, nose, tracheobronchial tree, and joints. Auricular involvement affects the helix but spares the earlobes. Nasal chondritis can result in collapse of the nasal bridge (saddle nose deformity), which can also be seen in trauma, granulomatosis with polyangiitis, cocaine use, congenital syphilis, and leprosy. Airway stenosis from tracheal ring involvement and aortitis/large-vessel vasculitis may occur and be life-threatening. RP is diagnosed by its typical clinical manifestations. Laboratory tests are nonspecific; acute phase reactants are elevated in 80%, and mild anemia is present in 44%. Patients with RP should undergo imaging (CT or MRI) to evaluate the large airways for inflammation/stenosis. This patient has a history of recurrent inflammation of the cartilage of the right ear, inflammatory eye disease, inflammatory arthritis, and bronchial strictures due to inflammation of bronchial cartilage, consistent with a diagnosis of RP.

Cogan syndrome (interstitial keratitis, with cochlear and vestibular dysfunction) is an unlikely diagnosis because the patient has neither vestibular nor cochlear findings.

Polyarteritis nodosa, a medium-vessel vasculitis, affects the mesenteric and renal arteries. Patients usually present with abdominal symptoms, neurologic involvement, and skin findings. Polyarteritis nodosa does not involve the eye or cartilage of the ear, nose, or airways, making this an unlikely diagnosis.

Besides the inflammatory arthritis, this patient has no typical symptoms or signs of systemic lupus erythematosus (SLE). In addition, SLE does not typically cause inflammation and destruction of cartilaginous structures.

KEY POINT

- Relapsing polychondritis is characterized by inflammation and damage of cartilaginous tissues; tissues most commonly affected include the cartilaginous portions of the external and middle ear, nose, tracheobronchial tree, and joints.

Bibliography

Vitale A, Sota J, Rigante D, Lopalco G, Molinaro F, Messina M, et al. Relapsing polychondritis: an update on pathogenesis, clinical features, diagnostic tools, and therapeutic perspectives. Curr Rheumatol Rep. 2016;18:3. [PMID: 26711694] doi:10.1007/s11926-015-0549-5

Item 50 Answer: D

Educational Objective: Treat rheumatoid arthritis during pregnancy.

No change in therapy is needed for this pregnant patient with rheumatoid arthritis (RA). For women with established RA, two thirds will go into remission or achieve low disease activity during pregnancy; however, one third will not improve or will get worse. Improvement may depend on an HLA-DQ mismatch between mother and child and/or other factors such as microchimerism (sharing of maternal cells with the fetus and vice versa). The benefit begins in the first trimester and continues throughout the pregnancy. Disease activity typically returns, often with a flare, after delivery. Medication management of a patient with RA is a major issue, and pregnancy plans should be discussed with any woman of childbearing age who will be placed on therapy. Hydroxychloroquine is an antimalarial medication that appears to inhibit antigen processing. It can be used to treat RA and other forms of inflammatory arthritis. Although its efficacy in arthritis is modest, its excellent side-effect profile makes it a useful adjunctive therapy. Hydroxychloroquine crosses the placenta; however, there does not appear to be fetal toxicity with doses used for the treatment of RA. This patient currently has minimal disease activity and is likely to improve during pregnancy; therefore, she requires no change in therapy.

Limited case studies suggest that use of tumor necrosis factor α inhibitors during pregnancy may be safe, but a relationship to rare birth defects has been raised. Different agents may have different potential to cross the placenta. Decisions regarding the use of any biologic agent in pregnancy should incorporate risk-benefit analysis. Etanercept could be used only if this patient has a significant flare of disease during pregnancy but is not needed at the current time.

Leflunomide is contraindicated in this patient; this medication is extremely teratogenic and must not be used before/during pregnancy. Pregnancy must be avoided until the drug is no longer detectable in the serum; cholestyramine may be used to hasten the elimination of leflunomide from the body.

Methotrexate was discontinued prior to attempted conception, which is highly appropriate. Methotrexate is highly teratogenic and abortifacient, and it must be discontinued at least 3 months before pregnancy.

KEY POINT

- Methotrexate and leflunomide are contraindicated in pregnant patients because these medications are highly teratogenic and must not be used before/during pregnancy; hydroxychloroquine can be safely used during pregnancy.

Bibliography

Ince-Askan H, Dolhain RJ. Pregnancy and rheumatoid arthritis. Best Pract Res Clin Rheumatol. 2015;29:580-96. [PMID: 26697768] doi:10.1016/j.berh.2015.07.001

Item 51 Answer: D

H

Educational Objective: Treat gouty cellulitis.

The most appropriate next step in management is treatment with prednisone. This patient has gouty cellulitis accompanying an attack of acute gouty arthritis of the ankle. This well-recognized manifestation is often misdiagnosed as bacterial cellulitis and treated (unsuccessfully) with antibiotics. Prednisone should resolve both the acute gouty arthritis and gouty cellulitis; a typical dose is 40 mg/d for 5 days.

NSAIDs such as indomethacin should be avoided in this patient who is anticoagulated with apixaban for atrial fibrillation.

Antibiotics such as intravenous clindamycin would be indicated for bacterial cellulitis, for which there is no evidence. There is not an expanding area of skin involvement, and two previous courses of antibiotics have not improved symptoms. Additionally, cellulitis would not explain the inflamed ankle joint. An infected joint with concomitant cellulitis is unlikely because of the protracted time course.

MRI of the lower leg would be appropriate to help define chronic osteomyelitis. This is unlikely, however, given the patient's lack of clear predisposing factors such as diabetes mellitus or an overlying skin ulcer, as well as normal plain radiographs after a month of symptoms.

Surgical debridement is the initial approach for necrotizing fasciitis. Necrotizing fasciitis, however, has a more fulminant course. It is unlikely in this afebrile, nontoxic-appearing patient with normal vital signs, whose symptoms have not significantly worsened during the past 4 weeks.

KEY POINT

- Prednisone is appropriate treatment for gouty cellulitis accompanying an attack of acute gouty arthritis.

Bibliography

Perez-Ruiz F, Castillo E, Chinchilla SP, Herrero-Beites AM. Clinical manifestations and diagnosis of gout. Rheum Dis Clin North Am. 2014;40:193-206. [PMID: 24703343] doi:10.1016/j.rdc.2014.01.003

Item 52 Answer: B

Educational Objective: Treat fibromyalgia.

The addition of pregabalin is the most appropriate treatment. This patient's current symptoms and history are consistent with her prior diagnosis of fibromyalgia. Patients with fibromyalgia typically benefit from validation of their symptoms by a physician because many patients have previously had their complaints disregarded by caregivers or family. In addition to psychological support and exercise, pharmacotherapy is a mainstay of fibromyalgia management. Three drugs are FDA approved for fibromyalgia: pregabalin, duloxetine, and

milnacipran. Each provides an average benefit of approximately 30% reduction in pain. The latter two agents can also address coexisting mood disorder. This patient has already been appropriately started on duloxetine, and has had significant but insufficient pain improvement. Because patients with fibromyalgia often benefit from combination therapy, the addition of a new treatment, acting through a complementary mechanism, is indicated now for this patient. In contrast to the dual serotonin-norepinephrine reuptake inhibitor duloxetine, which enhances the suppression of pain signals, pregabalin inhibits glutamate release to directly reduce the passage of pain signals from the dorsal root ganglion. The combination is frequently of benefit.

Meloxicam is a long-acting NSAID that has better gastrointestinal tolerability than some other NSAIDs. However, NSAIDs have not shown reliable benefit for fibromyalgia pain.

Gabapentin shares its mechanism of action with pregabalin; although its pharmacokinetics are less reliable than pregabalin, and it is not FDA approved for this indication, its use in fibromyalgia is accepted; however, the discontinuation of duloxetine would be inadvisable.

Although dual serotonin-norepinephrine reuptake inhibitors are beneficial in fibromyalgia, selective serotonin reuptake inhibitors such as sertraline have not shown any benefit when used as single agents.

KEY POINT

- Combination pharmacologic therapy that takes advantage of complementary mechanisms of action may be helpful in some patients with fibromyalgia.

Bibliography

Gilron I, Chaparro LE, Tu D, Holden RR, Milev R, Towheed T, et al. Combination of pregabalin with duloxetine for fibromyalgia: a randomized controlled trial. Pain. 2016;157:1532-40. [PMID: 26982602] doi:10.1097/j.pain.0000000000000558

Item 53 Answer: D

Educational Objective: Treat interstitial lung disease associated with diffuse cutaneous systemic sclerosis.

Mycophenolate mofetil is the most appropriate treatment for this patient who has interstitial lung disease (ILD) associated with diffuse cutaneous systemic sclerosis. In systemic sclerosis (SSc), significant ILD occurs in 50% of patients with diffuse disease and in 35% of those with limited disease. The presence of anti–Scl-70 (DNA topoisomerase-1) antibodies increases the risk for ILD. Cyclophosphamide has been used to improve and/or stabilize lung involvement in SSc, but its utility is limited because it can only be taken for a limited time and the positive results are lost in the year after stopping cyclophosphamide. Recently, mycophenolate mofetil has been shown to be as effective as cyclophosphamide and is a medication that can be used for many years. Data indicate that mycophenolate mofetil can improve FVC in 75% of patients with SSc-ILD who are able to take this medication for 2 years. It can also improve, similar to cyclophosphamide, the skin thickening associated with SSc in 71% of patients. This patient's FVC and D_{LCO} are down compared with previous determinations, and the high-resolution CT scan of the chest shows findings consistent with nonspecific interstitial pneumonitis. Therefore, treatment with mycophenolate mofetil is appropriate.

In head-to-head comparisons, cyclophosphamide was as effective as mycophenolate mofetil in improving respiratory function and dyspnea, but mycophenolate mofetil was better tolerated than cyclophosphamide based on a longer time to patient withdrawal and was associated with a better safety profile, including lower incidence of leukopenia and thrombocytopenia.

High-dose glucocorticoids are frequently used in patients with SSc-ILD; however, there is no clear evidence of their benefit, and their use may convey an increased risk for scleroderma renal crisis and should be avoided.

Methotrexate does not have the data to support its use in SSc-ILD and because it can cause pulmonary fibrosis, it is not a good choice for this patient.

KEY POINT

- Mycophenolate mofetil is an appropriate treatment option for patients who have interstitial lung disease associated with systemic sclerosis.

Bibliography

Tashkin DP, Roth MD, Clements PJ, Furst DE, Khanna D, Kleerup EC, et al; Sclerodema Lung Study II Investigators. Mycophenolate mofetil versus oral cyclophosphamide in scleroderma-related interstitial lung disease (SLS II): a randomised controlled, double-blind, parallel group trial. Lancet Respir Med. 2016;4:708-19. [PMID: 27469583] doi:10.1016/S2213-2600(16)30152-7

Item 54 Answer: A

Educational Objective: Treat undifferentiated connective tissue disease with hydroxychloroquine.

The addition of hydroxychloroquine is the most appropriate treatment for this patient's arthritis symptoms. This patient has undifferentiated connective tissue disease (UCTD), a term used to describe an autoimmune disease that has clinical manifestations of other specific connective tissue diseases, but not enough positive features to satisfy diagnostic or classification criteria for any one disease. She has Raynaud phenomenon, inflammatory arthritis, and positive antinuclear antibodies, but does not have enough clinical findings to establish a more specific diagnosis. Over time, her condition may evolve into a specific connective tissue disease, most commonly systemic lupus erythematosus. Management of UCTD is the same as other connective tissue diseases and is based on the manifestations of the individual patient. This patient has not responded to a trial of an NSAID and has impaired activities of daily living; thus, she is a candidate for hydroxychloroquine.

Discontinuing naproxen and starting ibuprofen is not indicated because ibuprofen is not necessarily more effective than naproxen.

Obtaining radiography of the feet in a patient without symptoms or physical findings in the feet is unlikely to show any abnormality and thus will not provide any useful diagnostic information.

Repeating anti-double-stranded DNA antibody testing is not appropriate because the results are unlikely to have changed over a 1-month period. Repeat testing could be considered in the future if the patient's clinical condition changes.

Repeating antinuclear antibody testing will not provide further insight into the diagnosis, and the titer does not correlate with disease activity.

KEY POINT

- Treatment of undifferentiated connective tissue disease is the same as other connective tissue diseases and is based on the manifestations of the individual patient.

Bibliography

Mosca M, Tani C, Carli L, Bombardieri S. Undifferentiated CTD: a wide spectrum of autoimmune diseases. Best Pract Res Clin Rheumatol. 2012;26:73-7. [PMID: 22424194] doi:10.1016/j.berh.2012.01.005

Item 55 Answer: D

Educational Objective: Recognize the most common side effect of a topical NSAID.

The patient should be warned about localized skin rash as a possible side effect of topical NSAIDs recently prescribed for her knee osteoarthritis (OA). Topical NSAIDs such as diclofenac (available as a solution, spray, gel, or patch) provide similar pain relief as oral medications with fewer gastrointestinal effects. The American College of Rheumatology currently recommends topical NSAIDs rather than oral NSAIDs for patients aged 75 years or older because topical NSAIDs are considered to provide similar OA pain relief as oral medications, with greater gastrointestinal safety and tolerability. However, there are slightly more skin reactions (rash, itch, and burning) than placebo (rate ratio, 1.14 [95% CI, 0.51-2.55]). Topical diclofenac 1% gel may be less prone to produce local skin reactions compared with the solution, but it may be slightly less effective in reducing pain.

Simple analgesics are neither anti-inflammatory nor disease modifying but can help relieve pain in patients with arthritis. Topical analgesics (such as capsaicin and lidocaine) may be useful and can limit systemic drug exposure when only a single area is painful. Topical capsaicin is safe to use in the treatment of OA, but it can be associated with local irritation of the eyes and mucous membranes when drug residue is transferred from the fingers to these areas.

Intra-articular glucocorticoids can reduce OA knee pain within days to weeks. When a joint effusion is present, glucocorticoid injections can be particularly helpful after drainage of the excessive joint fluid. Local side effects include skin hypopigmentation, subcutaneous tissue atrophy, and joint infection.

KEY POINT

- Topical NSAIDs are recommended to treat osteoarthritis in patients aged 75 years or older because they provide similar pain relief as oral medications with greater gastrointestinal safety and tolerability, but with an increased incidence of skin irritation and rash.

Bibliography

Lin J, Zhang W, Jones A, Doherty M. Efficacy of topical non-steroidal anti-inflammatory drugs in the treatment of osteoarthritis: meta-analysis of randomised controlled trials. BMJ. 2004;329:324. [PMID: 15286056]

Item 56 Answer: A

Educational Objective: Diagnose acute calcium pyrophosphate crystal arthritis.

The most likely diagnosis is acute calcium pyrophosphate (CPP) crystal arthritis (pseudogout). Acute CPP crystal arthritis occurs episodically and is generally a condition that occurs in the elderly. The most frequently involved joints are knees and wrists. An acute attack is characterized by pain, warmth, tenderness, and swelling; signs of systemic inflammation may be present but are not universal. Attacks can last for weeks to months (in general, longer than gout attacks). Acute CPP crystal arthritis usually occurs in patients with osteoarthritis of involved joints, and plain radiographs may demonstrate chondrocalcinosis, seen as a thin radiopaque line of CPP deposition at chondral surfaces (most easily appreciated in the knees, pubic symphysis, and wrists). Ideally, acute CPP crystal arthritis is definitively diagnosed by identifying positively refringent rhomboid-shaped CPP crystals from joint fluid. However, there is rarely fluid to drain from a wrist, and even when fluid is obtainable, CPP crystals can be difficult to identify.

Gout appears less likely than acute CPP crystal arthritis given the joints involved and the lengthy nature of the attacks. Initially, gout usually affects the metatarsophalangeal joints, the mid foot, ankles, and knees, although in postmenopausal women the finger joints may be affected (especially those with pre-existing osteoarthritis). Even without treatment, most gout attacks resolve within 10 to 14 days. Additionally, the low serum urate level makes gout less likely.

Infectious arthritis is highly unlikely in this patient because symptoms began 2 weeks ago, she otherwise appears well, and her radiographs demonstrate no joint destruction (which would be expected 2 weeks into an untreated joint infection). Additionally, she had two prior similar episodes, and infectious arthritis is not self-limited or recurrent.

Palindromic rheumatism is an uncommon arthritis that is often a precursor to rheumatoid arthritis and is characterized by acute episodes of monoarthritis that last from 24 to 72 hours; attacks migrate between different appendicular joints, especially the metacarpophalangeal and proximal interphalangeal joints. The prolonged symptoms and joints in this case do not fit the pattern of palindromic rheumatism.

KEY POINT

- Acute calcium pyrophosphate crystal arthritis (pseudogout) is characterized by the sudden onset of pain, warmth, tenderness, and swelling of the affected joint, usually a knee or wrist; attacks are typically longer than those of gout.

Bibliography

Rosenthal AK, Ryan LM. Calcium Pyrophosphate Deposition Disease. N Engl J Med. 2016;374:2575-84. [PMID: 27355536] doi:10.1056/NEJMra1511117

H

Item 57 Answer: C

Educational Objective: Diagnose rheumatoid arthritis–related pleural effusion.

Rheumatoid pleuritis is the most likely cause of this patient's pleural effusion. Pleuritis is the most common rheumatoid arthritis (RA) pulmonary manifestation but is frequently asymptomatic; exudative pleural effusions may occur. According to the Light criteria, this pleural fluid is an exudate based upon an elevated pleural fluid lactate dehydrogenase (LDH) concentration greater than two thirds the upper limit of normal for serum LDH. In rheumatoid effusions, pleural leukocyte count is typically less than 5000/µL (5.0×10^9/L), pleural fluid glucose is less than 60 mg/dL (3.33 mmol/L), and pH is less than 7.3. This exudative pleural effusion is compatible with rheumatoid pleurisy, malignancy, and tuberculosis pleurisy.

Malignancy is a possible diagnosis accounting for this patient's pleural effusion. However, extremely low pleural fluid glucose concentrations are found only in rheumatoid pleurisy and empyema. Glucose concentration of approximately 30 to 60 mg/dL (1.7-3.3 mmol/L) is more typical of malignancy. In addition, pleural fluid lymphocytosis, particularly with lymphocyte counts representing 85% or more of the total nucleated cells, is not commonly associated with malignancies other than lymphoma. When in doubt, a chest CT with contrast should be performed in patients with pleural effusion of indeterminate cause.

The low leukocyte count and lymphocytic predominance is not compatible with an acute parapneumonic effusion.

Tumor necrosis factor α inhibitors such as etanercept increase the risk for tuberculosis. However, a previous negative tuberculin skin test and low pleural fluid adenosine deaminase measurement (<40 U/L) effectively rule out this diagnosis.

KEY POINT

- Pleuritis is the most common rheumatoid arthritis pulmonary manifestation but is frequently asymptomatic; exudative pleural effusions may occur.

Bibliography

Kelly C, Iqbal K, Iman-Gutierrez L, Evans P, Manchegowda K. Lung involvement in inflammatory rheumatic diseases. Best Pract Res Clin Rheumatol. 2016 Oct;30(5):870-888. doi: 10.1016/j.berh.2016.10.004. [PMID: 27964793]

Item 58 Answer: C

H

Educational Objective: Diagnose scleroderma renal crisis.

The most likely diagnosis is scleroderma renal crisis (SRC) in this patient with systemic sclerosis. Kidney involvement is common in systemic sclerosis. Up to 50% of patients have mild proteinuria, elevation in the plasma creatinine concentration, and/or hypertension, but most do not progress to chronic kidney disease. The most striking and life-threatening manifestation of kidney disease is SRC. SRC occurs in 10% to 15% of patients, and is more frequent in diffuse cutaneous systemic sclerosis (DcSSc) and in patients with anti-RNA polymerase III antibodies. SRC tends to occur early in the disease course; if untreated, it carries a mortality rate approaching 90%. The typical presentation is acute kidney injury and severe hypertension, mild proteinuria, urinalysis with few cells or casts, microangiopathic hemolytic anemia, and thrombocytopenia. Some patients develop pulmonary edema and hypertensive encephalopathy. Occasionally, patients remain normotensive despite kidney dysfunction. ACE inhibitors significantly improve kidney survival and decrease mortality among patients with SRC, regardless of the serum creatinine level.

Disseminated intravascular coagulation (DIC) is characterized by abnormal activation of coagulation, generation of thrombin, consumption of clotting factors, and peripheral destruction of platelets. DIC may result from various causes, including sepsis, obstetric emergencies, acute leukemias (especially acute promyelocytic leukemia), severe burns, venoms, and shock. It is not associated with a hypertensive emergency or urgency.

Hemolytic uremic syndrome (HUS) is caused by some strains of *Escherichia coli*, including the O157:H7 strain that produces Shiga-like toxin that targets the vascular endothelium of the glomerulus, causing cell death, breakdown of the endothelium, hemorrhage, and activation of platelets and inflammatory pathways resulting in intravascular thrombosis and hemolysis. It manifests as microangiopathic hemolytic anemia, thrombocytopenia, and acute kidney injury in the setting of dysentery. The absence of dysentery in this patient makes HUS an unlikely diagnosis.

Thrombotic thrombocytopenic purpura is characterized by abnormal activation of platelets and endothelial cells, deposition of fibrin in the microvasculature, and peripheral destruction of erythrocytes and platelets. The diagnosis is clinical and requires the presence of thrombocytopenia and microangiopathic hemolytic anemia in the absence of other causes of these findings such as SRC. In this patient with systemic sclerosis, the diagnosis of SRC is much more likely.

KEY POINT

- The typical presentation of scleroderma renal crisis is acute kidney injury and severe hypertension, mild proteinuria, urinalysis with few cells or casts, microangiopathic hemolytic anemia, and thrombocytopenia.

Bibliography

Woodworth TG, Suliman YA, Furst DE, Clements P. Scleroderma renal crisis and renal involvement in systemic sclerosis. Nat Rev Nephrol. 2016;12:678-691. [PMID: 27641135] doi:10.1038/nrneph.2016.124

H

Item 59 Answer: A

Educational Objective: Diagnose Behçet syndrome.

The most likely diagnosis is Behçet syndrome, a systemic disease associated with inflammatory infiltration of multiple organs. The disease is characterized by recurrent painful oral and genital mucosal ulcerations, inflammatory eye disease (panuveitis, retinal vasculitis), and pathergy (an inflammatory response to skin prick with a sterile needle). Other clinical manifestations include venous thrombosis; central nervous system (CNS) manifestations such as brainstem lesions and aseptic meningitis, with the most common CNS symptoms being headache and diplopia; inflammatory arthritis (usually in the knees); skin lesions; and gastrointestinal inflammation/ulceration indistinguishable from inflammatory bowel disease. Behçet syndrome is most common in countries along the Silk Road and is more prevalent in men. The International Criteria for Behçet Disease are both sensitive and specific for the diagnosis and include the following weighted elements: genital aphthosis (2 points); ocular lesions (uveitis or retinal vasculitis) (2 points); oral aphthosis (1 point); skin lesions (pseudofolliculitis or erythema nodosum) (1 point); vascular lesions (superficial phlebitis, deep vein thrombosis, large vein thrombosis, arterial thrombosis, or aneurysm) (1 point); and pathergy (1 point). Three points are required to establish the diagnosis; this patient has 5 points.

Whereas Crohn disease can be associated with aphthous ulcers, uveitis, and peripheral arthritis, the lack of gastrointestinal symptoms make this an unlikely diagnosis.

Sarcoidosis can manifest as acute arthritis, bilateral hilar lymphadenopathy, and erythema nodosum, and a more chronic form of arthritis affects 1% to 4% of patients that may involve shoulders, hands, wrists, knees, and ankles. Uveitis is a common manifestation of sarcoidosis. Papular, nodular, and plaque-like skin lesions are common in sarcoidosis, but mucosal or genital ulcerations are not found.

Joint involvement occurs in 90% of patients with systemic lupus erythematosus (SLE), most commonly polyarthralgia, with frank arthritis involving both small and large peripheral joints found in 40% of patients. Bilateral knee inflammatory arthritis would be an unusual initial presentation for SLE. Oral ulcers can occur but are classically painless, and genital ulcers typically do not occur. Uveitis is one of the many ocular compilations of SLE but is relatively rare.

KEY POINT

- Behçet syndrome is characterized by recurrent painful oral and genital mucosal ulcerations, inflammatory eye disease, and pathergy.

Bibliography

International Team for the Revision of the International Criteria for Behçet's Disease (ITR-ICBD). The International Criteria for Behçet's Disease (ICBD): a collaborative study of 27 countries on the sensitivity and specificity of the new criteria. J Eur Acad Dermatol Venereol. 2014;28:338-47. [PMID: 23441863] doi:10.1111/jdv.12107

Item 60 Answer: C

Educational Objective: Treat chronic calcium pyrophosphate arthropathy.

Low-dose prednisone is the most appropriate treatment for this patient with chronic calcium pyrophosphate arthropathy, which may be present as two patterns: chronic calcium pyrophosphate (CPP) crystal inflammatory arthritis, and osteoarthritis with calcium pyrophosphate deposition (CPPD). Chronic CPP crystal inflammatory arthritis is a rare polyarthritis involving the wrists and metacarpophalangeal joints ("pseudo-rheumatoid arthritis"), with the absence of serologies associated with rheumatoid arthritis. The course may be marked by episodes of acute pseudogout, radiographic chondrocalcinosis, and lack of chronic inflammation on examination. Osteoarthritis with CPPD manifests as typical osteoarthritic findings involving joints not commonly associated with osteoarthritis (such as shoulders or metacarpophalangeal joints). Radiographic findings of osteoarthritis with CPPD (subchondral bone cysts, osteophytes, and subchondral sclerosis, consistent with osteoarthritis) often precede the onset of osteoarthritis. This patient presents with findings on examination and radiograph consistent with both patterns of chronic calcium pyrophosphate arthropathy. Treatment of chronic calcium pyrophosphate arthropathy can be difficult because there is a paucity of data. Options include low-dose glucocorticoids, low-dose colchicine, or NSAIDs to prevent inflammatory manifestations of the disease. For this patient, low-dose daily prednisone is appropriate.

Tumor necrosis factor (TNF)-α inhibitors have not been investigated as a treatment for chronic calcium pyrophosphate arthropathy, and beginning a TNF-α inhibitor such as adalimumab in not indicated. In this patient, the complete absence of response to one TNF-α inhibitor is another clue that rheumatoid arthritis was an incorrect diagnosis.

Allopurinol is a urate-lowering therapy, but calcium pyrophosphate deposition results from calcium pyrophosphate rather than uric acid deposition. The radiographic presence of chondrocalcinosis and osteoarthritic changes, as well as the absence of classic gouty erosions characterized by punched-out lesions with overhanging edges, argue against the diagnosis of chronic tophaceous gout. Finally, a low serum urate level and the absence of tophi also argue against the diagnosis of chronic tophaceous gout.

Methotrexate was recently found to be no better than placebo in a randomized trial for chronic calcium pyrophosphate arthropathy.

Although daily NSAID therapy can be a reasonable option, this patient is an elderly woman with hypertension

and chronic kidney disease, making NSAIDs relatively contraindicated.

KEY POINT

- Treatment options for chronic calcium pyrophosphate arthropathy include low-dose glucocorticoids, low-dose colchicine, or NSAIDs to prevent inflammatory manifestations of the disease.

Bibliography

Rosenthal AK, Ryan LM. Calcium Pyrophosphate Deposition Disease. N Engl J Med. 2016;374:2575-84. [PMID: 27355536] doi:10.1056/NEJMra1511117

H

Item 61 Answer: D

Educational Objective: Treat drug-induced myopathy.

The most appropriate management is reduction of the prednisone dose in this patient with drug-induced myopathy caused by glucocorticoids. Glucocorticoid myopathy is a common consequence of prolonged treatment with high-dose glucocorticoids, as seen in this patient treated for polymyositis. Distinguishing between glucocorticoid-induced myopathy and active inflammatory myopathy is important, particularly in older patients for whom long-term glucocorticoid side effects can be particularly debilitating. The history is suggestive of glucocorticoid myopathy when a patient has been started on high-dose glucocorticoids within a few months, has cushingoid features, and has normal serum creatine kinase levels. No single feature is diagnostic on electromyogram (EMG) or muscle biopsy. Weakness can often be addressed by reducing the glucocorticoid dose and following the patient over the next 3 to 4 weeks to assess for gains in strength. Colchicine and hydroxychloroquine are also implicated as a cause of drug-induced myopathy. Statins are a frequent cause of myalgia and/or asymptomatic serum creatine kinase elevations and, rarely, statin use can result in an immune-mediated necrotizing myopathy associated with antibodies to the enzyme HMG-CoA reductase.

An EMG could potentially reveal findings of low amplitude motor unit potentials or be normal in glucocorticoid myopathy. However, the initial clinical improvement and reduction in the muscle enzymes with reduction in glucocorticoid dose most strongly suggest drug-induced myopathy, and an EMG in this situation is unlikely to provide helpful results.

In glucocorticoid-induced myopathy, nonspecific atrophy of type IIb fibers without necrosis or inflammation can be seen that would help substantiate the diagnosis. However, muscle biopsy is an invasive procedure that is not indicated in a patient in whom initial clinical improvement and normalization of muscle enzyme levels has occurred, suggesting the diagnosis of glucocorticoid-induced myopathy.

Immunosuppressive therapy with azathioprine is used for glucocorticoid-resistant disease or glucocorticoid sparing. Reducing the azathioprine dose is not likely to be of diagnostic or therapeutic benefit because proximal muscle weakness is not an adverse effect of azathioprine.

KEY POINT

- Glucocorticoid myopathy should be suspected in a patient with recent initiation of high-dose glucocorticoids, cushingoid features, initial clinical improvement, and reduction in serum creatine kinase levels who has an increase in weakness with reduction in the glucocorticoid dose; treatment is appropriate dose reduction or discontinuation if possible.

Bibliography

Fasano S, Alves SC, Isenberg DA. Current pharmacological treatment of idiopathic inflammatory myopathies. Expert Rev Clin Pharmacol. 2016:1-12. [PMID: 26708717]

Item 62 Answer: E

Educational Objective: Diagnose Takayasu arteritis.

The most likely diagnosis is Takayasu arteritis, a rare granulomatous large-vessel vasculitis affecting the aorta and its major branches and pulmonary arteries. This disease predominantly affects females typically less than age 30 years and of Asian ancestry. Aneurysms and stenoses of large arteries cause symptoms of claudication in the extremities, discrepancies in blood pressure between the arms, and reduced pulses. Involvement of the aorta can lead to aortic insufficiency and heart failure. This rare complication is a leading cause of morbidity and mortality in patients with Takayasu arteritis. This patient has upper extremity claudication, reduced radial pulse, evidence of inflammation (elevated erythrocyte sedimentation rate, anemia) and new-onset aortic insufficiency with dilated aortic root, all consistent with the diagnosis of Takayasu arteritis.

Giant cell arteritis (GCA) is a large-vessel granulomatous vasculitis that can also affect the great vessels of the chest, leading to a similar presentation, but is unlikely given this patient's young age; GCA affects individuals over age 50 years.

IgA vasculitis is a small-vessel vasculitis mediated by immune complexes predominantly containing IgA. It does not involve the large vessels and almost always causes a rash, not seen in this patient.

Kawasaki disease is a medium-vessel vasculitis that begins in childhood, manifesting with a rash and other mucocutaneous findings. It can affect coronary vessels, leading to cardiac complications such as heart failure. This patient developed initial symptoms as an adult, and has no rash, making Kawasaki disease an unlikely diagnosis.

Polyarteritis nodosa (PAN) is a medium-vessel vasculitis that can affect multiple organ systems. Cardiac involvement as well as large-vessel involvement is not a typical manifestation of PAN, making this diagnosis unlikely.

KEY POINT

- Takayasu arteritis is a rare chronic granulomatous vasculitis seen in young Asian women that mainly affects the aorta and its major branches as well as the coronary and pulmonary arteries, resulting in claudication, cardiac ischemia, aortic or mitral regurgitation, aortic dissection, and renal artery stenosis.

Bibliography

de Souza AW, de Carvalho JF. Diagnostic and classification criteria of Takayasu arteritis. J Autoimmun. 2014;48-49:79-83. [PMID: 24461381] doi:10.1016/j.jaut.2014.01.012

Item 63 Answer: A

Educational Objective: Initiate folic acid in a patient with rheumatoid arthritis who is starting methotrexate.

In addition to methotrexate, folic acid, 1 mg/d, should be initiated in this patient with rheumatoid arthritis (RA). RA is characterized by a chronic inflammatory polyarthritis affecting large and small joints with a predilection for the small joints of the hands and feet. Patients with RA typically report joint pain and inflammatory symptoms, including swelling and morning stiffness often lasting several hours. Joint swelling (softness or bogginess of the affected joint) is palpable on joint examination. Glucocorticoids, such as prednisone, act rapidly to control inflammation and joint symptoms, and can be useful until slower-acting disease-modifying antirheumatic drugs (DMARDs) achieve full effect. DMARD treatment typically begins with weekly administration of methotrexate, which is the anchor drug in RA and is used in both monotherapy and combination therapy. Daily folic acid supplementation with 1 mg (or weekly folinic acid supplementation) has been found to reduce the mucosal, hematologic, hepatic, and gastrointestinal side effects of methotrexate. Folic acid supplementation also reduces discontinuation of methotrexate for any reason. Methotrexate blocks the cellular utilization of folic acid, and folate depletion is considered to be the cause of most of the side effects associated with methotrexate therapy. Supplementation with folic acid reduces the incidence of side effects without any loss of methotrexate efficacy in treating RA. Folic acid can be taken on the same day as methotrexate because folic acid and methotrexate enter the cell via different pathways. Folinic acid is the reduced form of folate and is typically reserved for patients who have not had a satisfactory response to folic acid. Folinic acid is considerably more expensive than folic acid, and proper timing and administration of folinic acid is complex.

Niacin, thiamine, and vitamin C have no known utility in treating RA or preventing methotrexate side effects.

KEY POINT

- Folic acid supplementation should be initiated in patients beginning therapy with methotrexate to reduce the risk of side effects and discontinuation of methotrexate.

Bibliography

Shea B, Swinden MV, Ghogomu ET, Ortiz Z, Katchamart W, Rader T, et al. Folic acid and folinic acid for reducing side effects in patients receiving methotrexate for rheumatoid arthritis. J Rheumatol. 2014;41:1049-60. [PMID: 24737913] doi:10.3899/jrheum.130738

Item 64 Answer: E

H

Educational Objective: Diagnose Löfgren syndrome.

No further testing is necessary. This patient has a triad of bihilar adenopathy, arthritis, and erythema nodosum, consistent with Löfgren syndrome, a common rheumatologic manifestation of sarcoidosis. Diagnostic specificity for sarcoidosis is 95% when all three parts of the triad are present, thus making further testing unnecessary. The most common joints involved are ankles, followed by knees and wrists. Löfgren syndrome has a good prognosis with disease remission within 2 to 16 weeks.

Biopsy of a hilar lymph node demonstrating noncaseating granulomas consistent with the diagnosis of sarcoidosis is unnecessary in this patient who clinically has Löfgren syndrome.

Biopsy of a shin lesion will demonstrate septal panniculitis without primary vasculitis that is consistent with erythema nodosum. The diagnosis of erythema nodosum is usually clinical, but biopsy may be helpful in patients with atypical presentations, such as lesions located in areas other than the anterior shins. In this case, biopsy will not add any further useful information.

Rheumatoid arthritis (RA) is a systemic autoimmune disorder that typically presents as a symmetric inflammatory polyarthritis. Characteristically affected joints include the proximal interphalangeal and metacarpophalangeal joints of the hands and feet and the wrists, but other joints can also be involved. Rheumatoid factor is ordered as part of the evaluation of RA but is unnecessary in a patient with acute arthritis, erythema nodosum, and hilar lymphadenopathy.

Synovial fluid analysis is likely to demonstrate inflammation but is not specific for sarcoidosis versus other rheumatologic diseases. Joint infection is unlikely in this patient with multiple swollen joints, rather than a single joint, and the presence of other findings specific for Löfgren syndrome.

KEY POINT

- The presence of acute arthritis, bilateral hilar lymphadenopathy, and erythema nodosum is 95% specific for Löfgren syndrome.

Bibliography

O'Regan A, Berman JS. Sarcoidosis. Ann Intern Med. 2012;156:ITC5-1, ITC5-2, ITC5-3, ITC5-4, ITC5-5, ITC5-6, ITC5-7, ITC5-8, ITC5-9, ITC5-10, ITC5-11, ITC5-12, ITC5-13, ITC5-14, ITC5-15; quiz ITC5-16. [PMID: 22547486] doi:10.7326/0003-4819-156-9-201205010-01005

Item 65 Answer: D

H

Educational Objective: Diagnose IgA vasculitis.

Skin biopsy with immunofluorescence is appropriate in this patient with purpura, abdominal pain, and arthralgia, which is the classic triad for IgA vasculitis (Henoch-Schönlein purpura).

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IgA vasculitis is the most common childhood vasculitis (incidence, 20/100,000) and tends to appear after upper respiratory infections. IgA vasculitis is rarer among adults. IgA vasculitis is an IgA immune complex-mediated small-vessel vasculitis that almost always affects the skin but frequently affects the bowel, leading to pain, bleeding, and occasionally intussusception; less commonly, it affects the kidneys and rarely causes pulmonary hemorrhage. Biopsy of the most accessible affected organ, in this case the skin, will establish the diagnosis by demonstrating leukocytoclastic vasculitis with predominance of IgA deposits on immunofluorescence. Furthermore, skin biopsy is easily obtainable and does not expose the patient to radiation or contrast agents or the risks of kidney biopsy. Kidney biopsy is reserved for patients in whom the diagnosis is uncertain or if there is clinical evidence of severe kidney involvement. Biopsy findings are characterized by IgA deposition in the mesangium on immunofluorescence microscopy that is identical to that in IgA nephropathy.

Mesenteric angiography may demonstrate reduced blood flow and possibly irregularities in small vessels consistent with vasculitis, but it will not establish the specific diagnosis of IgA-mediated vasculitis. With the exception of angiography, radiologic testing is not specific for vasculitis; the features of IgA vasculitis in the bowel such as edema from inflammation or poor blood supply may occur in other conditions such as infectious enterocolitis, inflammatory bowel disease, or ischemic bowel disease.

The diagnosis of IgA vasculitis is based on the clinical picture in both children and adults. Laboratory studies are nonspecific but confirm systemic inflammation. IgA levels are sometimes elevated in IgA vasculitis but are not sensitive or specific enough to establish the diagnosis.

KEY POINT

- The classic triad for IgA vasculitis (Henoch-Schönlein purpura) is purpura, abdominal pain, and arthralgia; diagnosis is established with biopsy of the affected organ.

Bibliography

Audemard-Verger A, Pillebout E, Guillevin L, Thervet E, Terrier B. IgA vasculitis (Henoch-Shönlein purpura) in adults: Diagnostic and therapeutic aspects. Autoimmun Rev. 2015;14:579-85. [PMID: 25688001] doi:10.1016/j.autrev.2015.02.003

Item 66 Answer: D

Educational Objective: Screen for the HLA-B*5801 allele in a patient at high risk for allopurinol hypersensitivity.

HLA-B*5801 allele testing is the most appropriate next step in management. This patient with gout is at high risk for allopurinol sensitivity. His risk factors include diuretic use, ethnicity (Thai descent), and chronic kidney disease. Patients of Thai, Han Chinese, and Korean descent have a higher likelihood of having the HLA-B*5801 allele, which confers a high risk for allopurinol sensitivity. Allopurinol hypersensitivity is characterized by DRESS (drug reaction, eosinophilia, and systemic symptoms) syndrome and can result in kidney failure and death; allopurinol should be discontinued at the first sign of a rash. The presence of the HLA-B*5801 allele is a contraindication to prescribing allopurinol; therefore, this patient should be screened before beginning urate-lowering therapy.

The absence of the HLA-B*5801 allele does not guarantee protection against allopurinol hypersensitivity. Febuxostat is a nonpurine, noncompetitive xanthine oxidase inhibitor, which is a viable alternative to allopurinol. It can be used in patients with mild to moderate chronic kidney disease and is safe to try after an adverse reaction or failure with allopurinol. Febuxostat is approximately 10 times more expensive than generic allopurinol.

Probenecid should be avoided in patients with chronic kidney disease, as the drug requires intact kidney function.

There is no suggestion of an antinuclear antibody (ANA)-related disease such as systemic lupus erythematosus, and testing for ANA should not be performed in patients with low pretest probability of disease. The presence of ANA does not correlate with the risk for drug hypersensitivity. Therefore, there is no indication for ANA testing.

KEY POINT

- Risk factors for allopurinol sensitivity include diuretic use, chronic kidney disease, and the presence of the HLA-B*5801 allele in certain Asian ethnic groups.

Bibliography

Saokaew S, Tassaneeyakul W, Maenthaisong R, Chaiyakunapruk N. Cost-effectiveness analysis of HLA-B*5801 testing in preventing allopurinol-induced SJS/TEN in Thai population. PLoS One. 2014;9:e94294. [PMID: 24732692] doi:10.1371/journal.pone.0094294

Item 67 Answer: C

Educational Objective: Diagnose spondyloarthritis in a patient with enthesitis.

Spondyloarthritis is the most likely diagnosis in this patient with enthesitis. Spondyloarthritis refers to a group of disorders that share an overlapping set of features, including inflammation of the axial skeleton, tendons, and entheses (insertion of tendon to bone); tendon and enthesis calcification; an association with HLA-B27; and mucocutaneous, gastrointestinal, and ocular inflammation. The four disorders of spondyloarthritis are ankylosing spondylitis, psoriatic arthritis, inflammatory bowel disease-associated arthritis, and reactive arthritis. The enthesis is a complex structure at the site of insertion of a tendon or ligament onto the bone. Inflammation of the enthesis (enthesitis) is highly suggestive of spondyloarthritis. When enthesitis is particularly severe, the inflammation may extend along the associated tendon and local ligaments, resulting in dactylitis ("sausage digits"). This patient has dactylitis, with diffuse inflammatory swelling of multiple digits, making spondyloarthritis the likely cause of this patient's presentation.

Infectious arthritis typically presents with pain, swelling, warmth, and erythema of a single joint, accompanied by fever and constitutional symptoms, and is not associated with enthesitis/dactylitis.

Rheumatoid arthritis is characterized by a chronic inflammatory polyarthritis affecting large and small joints with a predilection for the small joints of the hands and feet and is not associated with enthesitis/dactylitis.

System lupus erythematosus (SLE) should be considered in any patient who presents with unexplained multisystem disease. The most common early SLE manifestations include constitutional symptoms (fever, weight loss, or severe fatigue), arthralgia/arthritis, and skin disease. Joint involvement occurs in 90% of patients with SLE, with inflammatory polyarthralgia the most common presentation. SLE is unlikely due to the lack of rash or other clinical features; furthermore, it is not associated with enthesitis/dactylitis.

KEY POINT

- Enthesitis is highly suggestive of spondyloarthritis; when particularly severe, the inflammation may extend along the associated tendon and local ligaments, resulting in dactylitis ("sausage digits").

Bibliography

Ehrenfeld M. Spondyloarthropathies. Best Pract Res Clin Rheumatol. 2012;26:135-45. [PMID: 22424199] doi:10.1016/j.berh.2012.01.002

H

Item 68 Answer: D

Educational Objective: Diagnose tuberculous vertebral osteomyelitis.

The most likely diagnosis is tuberculous vertebral osteomyelitis (Pott's disease), the most common form of skeletal tuberculosis. Skeletal tuberculosis accounts for 10% to 35% of cases of extrapulmonary tuberculosis. Spinal involvement usually results from the hematogenous spread of *Mycobacterium tuberculosis* into the cancellous bone tissue of the vertebral bodies, from a primary pulmonary focus or extrapulmonary foci such as the lymph nodes. Predisposing factors for skeletal tuberculosis include previous tuberculosis infection, malnutrition, alcoholism, diabetes mellitus, and HIV infection. Delays in diagnosis are common because the onset of symptoms is insidious, and disease progression is slow. The duration of symptoms prior to diagnosis may range from weeks to years. The lower thoracic spine is the most frequently involved segment; common symptoms are back pain, fever, weight loss, and neurologic abnormalities. Paraplegia is the most devastating complication. Diagnosis is suggested by typical clinical presentation, along with evidence of past exposure to tuberculosis or concomitant visceral tuberculosis, and findings on neuroimaging modalities. Bone tissue or abscess samples from needle or surgical biopsy stained for acid-fast bacilli and/or positive cultures are most helpful in diagnosis.

Herniated intervertebral disk usually occurs in the lower lumbar spine (at L4-5 or L5-S1 levels) and typically causes pain and sometimes sensory symptoms radiating down the leg(s). This patient's constitutional symptoms of chills, weight loss, and low-grade fever, as well as image findings of erosion in the vertebral body and paravertebral swelling, are not consistent with herniated intervertebral disk.

Multiple myeloma is the most common primary malignant neoplasm of the skeletal system, and the vertebral column is a commonly affected site. The classic radiographic appearance includes multiple, small, well-circumscribed, lytic, punched-out, round lesions that can be found in the skull, pelvis, and spine on skeletal survey, not erosive changes as seen in this patient.

Osteoporosis with vertebral compression fracture may cause severe back pain and the thoracolumbar area is a common site, but patients do not typically experience neurologic or constitutional symptoms. Erosive changes with surrounding fusiform paravertebral swelling suggest another diagnosis.

KEY POINT

- In tuberculous vertebral osteomyelitis, the lower thoracic spine is the most frequently involved segment; common symptoms are back pain, fever, weight loss, and neurologic abnormalities.

Bibliography

Garg RK, Somvanshi DS. Spinal tuberculosis: a review. J Spinal Cord Med. 2011;34:440-54. [PMID: 22118251] doi:10.1179/2045772311Y.0000000023

Item 69 Answer: A

Educational Objective: Diagnose fibromyalgia in a man in the absence of discrete tender points.

The most likely diagnosis is fibromyalgia. The characteristic features of fibromyalgia are widespread chronic pain, fatigue, and sleep disorders, which are frequently accompanied by impaired cognitive function, mood disorders, and symptoms such as headache, gastrointestinal symptoms, and paresthesia. Although this patient initially appears to have specific joint symptoms, he is actually experiencing widespread (including nonarticular) pain. This widespread pain, together with poor/nonrestorative sleep, fatigue, and cognitive dysfunction (in this case, difficulty concentrating), is consistent with fibromyalgia. The absence of tender points is not relevant; men with fibromyalgia frequently do not experience tender points. Other features experienced by patients (bowel symptoms, anxiety/depression, low-grade fever, low-titer/borderline antinuclear antibodies) are not diagnostic of fibromyalgia but are consistent with its presence.

The clinical manifestations of hypothyroidism include fatigue, cold intolerance, constipation, weight gain, impaired concentration, dry skin, edema, depression, mood changes, muscle cramps, and myalgia. A normal thyroid-stimulating hormone level excludes hypothyroidism.

This patient's physical examination demonstrates full range of motion of the joints without crepitus, making

osteoarthritis less likely. Additionally, osteoarthritis cannot explain his diffuse body pain, difficulty sleeping, chronic fatigue, bowel symptoms, headache, and difficulty concentrating.

Rheumatoid arthritis (RA) is characterized by pain and swelling in multiple (>3) small joints of the hands and/or feet, along with morning stiffness lasting at least 1 hour. Initial symptoms often worsen gradually over weeks to months. RA frequently interferes with activities of daily living, including occupational and recreational activities. Constitutional symptoms such as increased fatigue and malaise are common. Depression and myalgia may occur and, less often, fever, anorexia, and weight loss. Physical examination reveals tenderness and swelling of the joints, sometimes with warmth and erythema; symmetric joint involvement is common. This patient lacks the synovitis characteristic of RA.

KEY POINT

- The characteristic features of fibromyalgia are widespread chronic pain, fatigue, and sleep disorders, which are frequently accompanied by impaired cognitive function, mood disorders, and symptoms such as headache, gastrointestinal symptoms, and paresthesia.

Bibliography

Clauw DJ. Fibromyalgia: a clinical review. JAMA. 2014;311:1547-55. [PMID: 24737367] doi:10.1001/jama.2014.3266

H

Item 70 Answer: E

Educational Objective: Treat class V (membranous) lupus nephritis.

Mycophenolate mofetil is the most appropriate treatment of this patient's kidney disease. Classification of lupus nephritis is based on findings by light microscopy, electron microscopy, and immunofluorescence. This patient with recently diagnosed systemic lupus erythematosus (SLE) now presents with proteinuria likely due to lupus nephritis (likely class V, membranous). Guidelines recommend aggressive therapy with immunosuppressives for significant kidney involvement. A number of immunosuppressive therapies are beneficial in the treatment of SLE nephritis, including mycophenolate mofetil, cyclophosphamide, azathioprine, and rituximab. In the treatment of isolated class V lupus nephritis, especially without kidney dysfunction, mycophenolate mofetil is the most appropriate initial immunosuppressive therapy based on the guideline recommendations. Importantly, mycophenolate mofetil is teratogenic and has been associated with fetal harm and death; it must be stopped 3 months before a planned pregnancy.

Adalimumab has not been shown to be effective in lupus nephritis and may potentially worsen the disease based on animal data.

Belimumab may be considered in patients with continued SLE activity after standard therapy has been tried and found to be ineffective. Its role in the treatment of lupus nephritis continues to evolve but is currently not well defined. Its use in this patient should not be considered before having tried standard therapy.

Cyclophosphamide may be considered in this patient and used appropriately in patients with lupus nephritis but is not an appropriate first choice due to a higher rate of side effects compared with mycophenolate mofetil, as well as its effect on reducing fertility and premature menopause. Cyclophosphamide is typically reserved for severe active nephritis to induce remission, followed by mycophenolate mofetil or possibly azathioprine as maintenance therapy.

Methotrexate is not effective in lupus nephritis and may be associated with toxicity in a patient with kidney disease.

KEY POINT

- Mycophenolate mofetil is the most appropriate initial immunosuppressive therapy in the treatment of isolated class V lupus nephritis, especially without kidney dysfunction.

Bibliography

Hahn BH, McMahon MA, Wilkinson A, Wallace WD, Daikh DI, Fitzgerald JD, et al; American College of Rheumatology. American College of Rheumatology guidelines for screening, treatment, and management of lupus nephritis. Arthritis Care Res (Hoboken). 2012;64:797-808. [PMID: 22556106] doi:10.1002/acr.21664

Item 71 Answer: C

Educational Objective: Treat psoriatic arthritis.

The most appropriate medication to add to this patient's treatment regimen is a tumor necrosis factor (TNF)-α inhibitor such as infliximab. In patients with psoriatic arthritis who have uncontrolled disease while taking methotrexate at a dose of 25 mg weekly, the addition of a TNF-α inhibitor is indicated. Randomized controlled trials have established the efficacy of the combination of methotrexate and TNF-α inhibitors for reducing symptoms, restoring function, and limiting joint damage. Other biologics shown to be effective include ustekinumab and secukinumab.

Abatacept is a biologic disease-modifying agent that targets the T-cell costimulation pathway and is used in the treatment of rheumatoid arthritis. A single randomized controlled trial has shown that abatacept could be efficacious in psoriatic arthritis. However, in a patient with psoriatic arthritis in whom a TNF-α inhibitor has not been used, abatacept is not the appropriate next choice in management due to limited experience in these patients.

Hydroxychloroquine is a long-acting anti-inflammatory medication that interferes with the innate immune system inflammatory response and is used to treat rheumatoid arthritis, systemic lupus erythematosus, and dermatomyositis. It has been reported to be associated with an increased incidence of severe cutaneous reactions in psoriasis and is not the best choice.

Rituximab is a monoclonal antibody that targets $CD20^+$ B cells used in the treatment of rheumatoid arthritis, vasculitis, and various malignancies. It has not been used in the treatment of psoriatic arthritis.

KEY POINT

- In recalcitrant psoriatic arthritis, the combination of methotrexate and a tumor necrosis factor α inhibitor has shown efficacy in managing joint symptoms and slowing the progression of radiographic damage, including joint space narrowing and erosions.

Bibliography

Elyoussfi S, Thomas BJ, Ciurtin C. Tailored treatment options for patients with psoriatic arthritis and psoriasis: review of established and new biologic and small molecule therapies. Rheumatol Int. 2016;36:603-12. [PMID: 26892034] doi:10.1007/s00296-016-3436-0

Item 72 Answer: A

Educational Objective: Treat ankylosing spondylitis with NSAIDs.

The most appropriate treatment is an NSAID such as diclofenac for this patient with ankylosing spondylitis, a chronic inflammatory disease affecting the axial skeleton (including sacroiliac joints), entheses, and peripheral joints. It has a strong familial predilection, the strongest association with HLA-B27 among the forms of spondyloarthritis, and a male predominance. This man's history is suggestive of ankylosing spondylitis, with symptoms of inflammatory back pain, the presence of HLA-B27, a family history of ankylosing spondylitis, and a change in his exercise routine. He is early in the course of his disease and has not developed plain radiographic or laboratory abnormalities. Continuous full-dose NSAIDs are first-line therapy and can help relieve pain and stiffness. Studies of continuous full-dose NSAIDs demonstrate symptomatic relief as well as reduced sacroiliac and spine inflammation as seen on MRI in some patients. In a young man with no medical comorbidities, they are associated with a low incidence of side effects. Patients with ankylosing spondylitis are more likely to respond to NSAIDs and do so more rapidly and completely than patients with chronic low back pain from other causes.

Results from most randomized controlled trials of methotrexate use in ankylosing spondylitis have shown no benefit, and it is therefore not appropriate in this patient.

A considerable amount of more recent data suggests that tumor necrosis factor (TNF)-α inhibitors can be particularly helpful in the management of symptoms of ankylosing spondylitis. However, NSAIDs remain first-line therapy. There is variability in the expression of disease, and some patients can be managed with complete symptom relief without immunosuppression. The efficacy of TNF-α inhibitors for symptom relief needs to be weighed against their cost, potential side effects, and the fact that these agents have not been definitively established to be disease modifying.

Sulfasalazine has historically been used in the treatment of ankylosing spondylitis, but its use as second-line therapy has declined as more effective agents, such as TNF-α inhibitors, have emerged. This patient's primary site of involvement is the spine, and many experts now relegate the use of sulfasalazine for treatment of the peripheral arthritis associated with ankylosing spondylitis and only if NSAIDs are ineffective and a TNF-α inhibitor is not available or affordable.

KEY POINT

- Continuous full-dose NSAIDs are first-line therapy for ankylosing spondylitis.

Bibliography

Taurog JD, Chhabra A, Colbert RA. Ankylosing Spondylitis and Axial Spondyloarthritis. N Engl J Med. 2016;374:2563-74. [PMID: 27355535] doi:10.1056/NEJMra1406182

Item 73 Answer: D

Educational Objective: Treat knee osteoarthritis with physical therapy and exercise.

Physical therapy and a graduated leg muscle strengthening exercise program are appropriate for this patient with knee osteoarthritis. For patients with osteoarthritis, an individualized management plan includes education on osteoarthritis and joint protection, an exercise regimen, weight loss, proper footwear, and assistive devices as appropriate. Physical activity includes graduated aerobic exercise and strength training, with attention paid to bolstering strengthening periarticular structures and minimizing injury. The patient's main symptom is stiffness, not pain, and he prefers nonpharmacologic therapy at this time, which is most appropriate from a management perspective as well. Muscle weakness is common in knee osteoarthritis, possibly related to disuse, and muscle strengthening has been associated with reduced pain and improved function. All treatment guidelines agree that a muscle strengthening exercise program should be part of the patient's management plan.

Because the patient has a history of peptic ulcer disease, ibuprofen is not advisable. He also chooses not to take medication for his knee symptoms, and it is unclear whether ibuprofen would help his main symptom of stiffness.

Intra-articular glucocorticoids are useful agents in knee osteoarthritis, particularly as second-line therapies. Similar to ibuprofen, it is unclear whether this treatment would help the patient with his stiffness.

A knee MRI is not indicated in a patient without knee buckling or locking or signs of instability, all of which may indicate an unstable meniscal tear that needs surgical management. Incidental meniscal tears are common MRI findings in the middle-aged population, and especially in patients with knee osteoarthritis. Studies have shown that patients with knee osteoarthritis and meniscal tears experience similar long-term improvements in pain and function with physical therapy compared with arthroscopic surgery, and that arthroscopic surgery may even pose higher harms.

KEY POINT

- Treatment guidelines recommend that a muscle strengthening exercise program should be part of the management plan for knee osteoarthritis.

Bibliography

McAlindon TE, Bannuru RR, Sullivan MC, Arden NK, Berenbaum F, Bierma-Zeinstra SM, et al. OARSI guidelines for the non-surgical management of knee osteoarthritis. Osteoarthritis Cartilage. 2014;22:363-88. [PMID: 24462672] doi:10.1016/j.joca.2014.01.003

Item 74 Answer: A

Educational Objective: Diagnose acute cutaneous lupus erythematosus.

This patient has acute cutaneous lupus erythematosus (ACLE) and most likely has systemic lupus erythematosus (SLE). The cutaneous manifestations of SLE are essential to recognize because skin findings are key diagnostic criteria. Because the subtypes of SLE are important to distinguish, the dermatologic examination is crucial. The malar (butterfly) rash of ACLE consists of bright erythematous patches over both cheeks and the nasal bridge, almost always sparing the nasolabial folds (in contrast to the more violaceous facial erythema of dermatomyositis, which often involves that crease). The malar rash of ACLE can occur simultaneously with other findings of SLE or may precede other symptoms of SLE by months or years. The rash can last a variable length of time from hours to weeks and typically recurs or worsens with sun exposure. Essentially all patients with ACLE have or will develop SLE; therefore, all patients should receive a thorough evaluation for systemic involvement.

Erysipelas is a superficial cellulitis involving the lymphatics that often presents as a violaceous-red, edematous, well-demarcated plaque on the face or lower extremities secondary to group A streptococci. Patients are extremely uncomfortable and often have systemic symptoms such as fever and malaise. When on the face, the presentation of erysipelas is not symmetrically distributed as it is with ACLE.

Rosacea often has inflammatory papules, small pustules, and telangiectasias, and tends to involve the nasolabial folds. These manifestations are rare to absent in SLE.

Seborrheic dermatitis is often characterized by a greasy scale and tends to involve the nasolabial folds, eyebrows, and scalp. None of these manifestations is present in this patient.

A less widely known subtype of cutaneous lupus is subacute cutaneous lupus erythematosus. The typical clinical eruption consists of circular or polycyclic scaly erythematous patches and papulosquamous plaques over the forearms, chest, or especially the upper back, in a V-shaped configuration. This pattern in not present in this patient.

KEY POINT

- The malar (butterfly) rash of acute cutaneous lupus erythematosus (ACLE) consists of bright erythematous patches over both cheeks and the nasal bridge, almost always sparing the nasolabial folds; essentially all patients with ACLE have or will develop systemic lupus erythematosus.

Bibliography

Okon LG, Werth VP. Cutaneous lupus erythematosus: diagnosis and treatment. Best Pract Res Clin Rheumatol. 2013;27:391-404. [PMID: 24238695] doi:10.1016/j.berh.2013.07.008

Item 75 Answer: B

H

Educational Objective: Diagnose C1-C2 subluxation in a patient with rheumatoid arthritis.

The most appropriate diagnostic test to perform next is radiography of the cervical spine with flexion/extension views. Patients with long-standing (generally 10 years or more) rheumatoid arthritis (RA) are at risk of developing C1-C2 subluxation. Inflammation from RA can lead to attenuation of the transverse ligament that normally limits the posterior motion of the odontoid process of the C2 vertebrae. Instability around the odontoid can impinge upon posterior structures, including the spinal cord and vertebral arteries. Common symptoms include a sensation of the head falling off, drop attacks, and painless paresthesia of the hands and feet; rarely, sudden death can occur. Initial imaging should be radiography of the cervical spine with flexion/extension views; if results are abnormal, MRI should then be performed. Consideration of surgery is necessary for patients with significant subluxation, especially if symptomatic. Patients with long-standing RA undergoing general anesthesia for any kind of surgery should have cervical spine radiography with flexion/extension views to assess for atlantoaxial subluxation, which can lead to neurologic compromise when the neck is extended during intubation.

Electromyography is the primary test used to diagnose lower motor neuron conditions such as focal neuropathies, polyneuropathies, motor neuron diseases, and myopathy. Nerve conduction studies are used to assess peripheral nerve system function and can classify peripheral nerve conduction abnormalities due to axonal degeneration, demyelination, and conduction block. In most clinical situations involving peripheral nerve or muscle disease, nerve conduction studies and electromyography are performed and interpreted at the same time. Electrodiagnostic studies are not helpful in a myelopathy as seen with C1-C2 subluxation.

The neurologic symptoms associated with vitamin B_{12} deficiency typically include paresthesia and ataxia, more often in the lower extremities. This patient has intermittent symptoms and no evidence of a peripheral neuropathy on examination. A normal complete blood count makes vitamin B_{12} deficiency less likely, although neurologic complications may occur without hematologic manifestations of deficiency.

Hypothyroidism can cause distal peripheral neuropathy (which is often painful) and carpal tunnel syndrome. The lack of painful paresthesias and a normal neurologic examination make hypothyroidism neuropathy an unlikely diagnosis.

KEY POINT

- Patients with long-standing rheumatoid arthritis are at risk for developing C1-C2 subluxation; symptoms include a sensation of the head falling off, drop attacks, and painless paresthesia of the hands and feet.

Bibliography

Del Grande M, Del Grande F, Carrino J, Bingham CO 3rd, Louie GH. Cervical spine involvement early in the course of rheumatoid arthritis. Semin Arthritis Rheum. 2014;43:738-44. [PMID: 24444595] doi:10.1016/j.semarthrit.2013.12.001

H

Item 76 Answer: B

Educational Objective: Diagnose neuropsychiatric systemic lupus erythematosus.

Neuropsychiatric systemic lupus erythematosus (NPSLE) is the most likely diagnosis in this patient with systemic lupus erythematosus (SLE). NPSLE prevalence is high in patients with SLE (75%) and may involve central and/or peripheral nervous systems, with the most common manifestations being headache, mild cognitive dysfunction, and mood disorder. Acute presentations, including seizures and psychosis, happen infrequently (<5%) but require aggressive symptomatic as well as disease-specific treatment. This patient has no sensory or motor deficits and presents with confusion, along with a nonfocal neurologic examination. She also shows signs of active SLE disease, including clinical evidence (fatigue, rash, arthritis) and laboratory findings (low complements and a high erythrocyte sedimentation rate). She has elevated protein in the cerebral spinal fluid (CSF), and radiologic studies show diffuse white matter changes. These findings suggest that NPSLE is the likely cause for the mental status changes/psychosis and aseptic meningitis.

This patient does not have acute bacterial meningitis because she lacks fever (seen in >75% of patients) and neck stiffness, and she has a normal cell count and glucose on CSF.

This patient's clinical presentation is not suggestive of seizures: she is alert and awake without involuntary movements, is following commands, and has no findings suggestive of ongoing seizure/status epilepticus.

Steroid-induced psychosis is seen in patients taking high doses of glucocorticoids (usually >1 mg/kg/d) and is very unusual at doses less than 20 mg/d. This patient's dose is only 5 mg/d, making steroid-induced psychosis unlikely.

KEY POINT

- Neuropsychiatric systemic lupus erythematosus prevalence is high in patients with systemic lupus erythematosus, with the most common manifestations being headache, mild cognitive dysfunction, and mood disorder; severe acute presentations, including seizures and psychosis, occur infrequently.

Bibliography

Popescu A, Kao AH. Neuropsychiatric systemic lupus erythematosus. Curr Neuropharmacol. 2011;9:449-57. [PMID: 22379459] doi:10.2174/157015911796557984

Item 77 Answer: B

Educational Objective: Predict long-term prognosis of Kawasaki disease.

A history of coronary artery aneurysm is the most important disease complication determining the patient's need for extensive evaluation and his long-term prognosis. Kawasaki disease (KD) is a medium-vessel vasculitis that affects children and is very rare in adults. KD presents as fever, rash, cervical lymphadenopathy, prominent nonexudative conjunctivitis, and oral mucosal and lip changes. Coronary vessel vasculitis, aneurysm formation, and other cardiac complications (such as heart failure, pericarditis, and arrhythmias) may develop. Up to 25% of untreated patients develop coronary artery aneurysms as long-term sequelae of KD; intravenous immunoglobulin (IVIG) treatment reduces the incidence of aneurysms, but 10% to 20% of patients do not respond. Estimates indicate that 4% to 8% of patients treated with IVIG will develop aneurysms. Thrombosis or stenosis of these aneurysms can lead to ischemia and myocardial infarction. It is important to identify and follow patients at risk for long-term cardiac complications of KD, because they may require preventive therapy with aspirin or other antithrombotic medications. With the exception of the complications related to the coronary arteries, most patients with KD completely recover from multisystem acute inflammation. Patients without abnormalities need no specific cardiology surveillance, but those with persistent coronary aneurysm may require periodic electrocardiography, echocardiography, and/or coronary artery imaging as part of a long-term surveillance program.

Recommendations about the nature and frequency of continued surveillance of patients recovering from KD, as well as physical activity restrictions, are provided by the American Heart Association and are based upon the coronary artery status of the patient. In the absence of coronary aneurysm, the available data suggest that the risk for coronary artery disease is low. For example, a large cohort study showed that among patients with KD, 5% had persistent coronary aneurysm, and long-term adverse cardiovascular events occurred in 8% with persistent coronary aneurysm versus 0% without persistent aneurysm. However, the nature and frequency of long-term surveillance are still unclear. An ongoing cohort study of Japanese children with a history of KD growing into adulthood will better inform the medical community on the best long-term surveillance and management plan.

A past history of bundle branch block, myocarditis, or pericarditis does not appear to be associated with the same risk for long-term cardiovascular events as does the presence of coronary aneurysm.

KEY POINT

- Persistent coronary artery aneurysm conveys the greatest risk for long-term cardiovascular events in survivors of childhood Kawasaki disease.

Bibliography

McCrindle BW, Rowley AH, Newburger JW, et al. Diagnosis, Treatment, and Long-Term Management of Kawasaki Disease: A Scientific Statement for Health Professionals From the American Heart Association. Circulation. 2017;135:e927-e999. [PMID: 28356445] doi:10.1161/CIR.0000000000000484

Item 78 Answer: C

Educational Objective: Prevent osteoarthritis with weight loss.

Recommending weight loss in order to lower the likelihood that she will develop osteoarthritis (OA) is the most appropriate

choice. Obesity is the strongest modifiable risk factor for OA incidence. Multiple studies have shown that higher BMI categories have proportionally higher risk of developing radiographic and symptomatic knee OA. A recent randomized clinical trial showed that a reduction of ≥5 kg or 5% of body weight over a 30-month period reduces the risk for the onset of radiographic knee OA in middle-aged overweight and obese women. Another recent study of obese and overweight patients found that subjects who lost weight over 48 months showed significantly lower knee cartilage degeneration, as assessed with MRI, compared with those whose weight was stable.

Chondroitin sulfate supplementation has not been studied to lower the risk for developing incident OA. There are promising but inconclusive data on whether chondroitin sulfate has a salutary effect on the progression of structural changes in established knee OA.

Limited studies have examined the association of vitamin D with incident OA, and available data thus far have not shown that low vitamin D confers a greater risk of incident OA. There is no evidence that vitamin D supplementation reduces the incidence of OA.

Suggesting that running will increase her risk of knee OA is not appropriate. Although not completely conclusive, the medical literature generally supports the idea that running does not contribute to the degeneration of articular cartilage in joints that are neuroanatomically normal. Some studies using advanced MRI techniques showed that moderate exercise in subjects at high risk for OA may be associated with favorable joint composition changes, which could have chondroprotective effects on the knee. Additionally, some studies suggest that quadriceps muscle weakness may be a risk for knee OA incidence. Nonetheless, there is a clear association with knee OA and antecedent knee injury, such as meniscal or cruciate ligament tears, so while stopping running may not be a beneficial recommendation, taking precaution to avoid injury would be prudent.

KEY POINT

- Obesity is the strongest modifiable risk factor for osteoarthritis incidence; weight loss can lower the risk for developing the disease.

Bibliography

Roos EM, Arden NK. Strategies for the prevention of knee osteoarthritis. Nat Rev Rheumatol. 2016;12:92-101. [PMID: 26439406] doi:10.1038/nrrheum.2015.135

H Item 79 Answer: A

Educational Objective: Treat scleroderma renal crisis.

The most appropriate treatment for this patient with scleroderma renal crisis is the ACE inhibitor captopril. This patient has features of systemic sclerosis (SSc), including a history of Raynaud phenomenon, gastroesophageal reflux disease, and skin changes typical of this disease. She also has features that occur in patients with scleroderma renal crisis, including hypertensive emergency, headache, microangiopathic hemolytic anemia (schistocytes on the peripheral blood smear), thrombocytopenia, elevated serum creatinine levels, and proteinuria. Approximately 75% of cases of scleroderma renal crisis occur in the first 4 years of SSc disease onset. Scleroderma renal crisis can be seen in both limited and diffuse forms of SSc but more often in those with rapidly progressive diffuse disease. Anti-RNA polymerase III antibodies serve as a marker for increased risk for scleroderma renal crisis as well as extensive skin disease. The use of ACE inhibitors has dropped the 1-year mortality of scleroderma renal crisis from 76% to 15%. The mechanism of action of ACE inhibitors is believed to be mitigation of the effect of interstitial fibrosis and vascular dysfunction in the glomerular arterial bed. Treatment with an ACE inhibitor (typically captopril) should be initiated promptly in SSc patients with even mild hypertension or otherwise unexplained elevations in serum creatinine levels or acute kidney injury. Angiotensin receptor blockers (ARBs) are an alternative for patients who cannot take ACE inhibitors, although ARBs are less effective for managing scleroderma renal crisis.

Cyclophosphamide is an immunosuppressive agent and not effective in scleroderma renal crisis.

Glucocorticoids, such as methylprednisolone, are implicated as potential risk factors for the development of scleroderma renal crisis and are not indicated for this patient.

In patients with hypertensive emergency, blood pressure must be lowered quickly with short-acting intravenous antihypertensive infusions to limit end-organ damage. Intravenous nitroprusside is often a first choice for patients with hypertensive emergencies. It can be titrated quickly to achieve blood pressure control. However, it does nothing to address the underlying physiological cause of scleroderma renal crisis and is inferior to ACE inhibitors on reducing mortality.

KEY POINT

- Features of scleroderma renal crisis include hypertensive emergency, headache, microangiopathic hemolytic anemia, thrombocytopenia, elevated serum creatinine levels, and proteinuria; treatment involves ACE inhibitors, typically captopril.

Bibliography

Woodworth TG, Suliman YA, Furst DE, Clements P. Scleroderma renal crisis and renal involvement in systemic sclerosis. Nat Rev Nephrol. 2016;12:678-691. [PMID: 27641135] doi:10.1038/nrneph.2016.124

Item 80 Answer: C

Educational Objective: Treat early rheumatoid arthritis with methotrexate.

The most appropriate treatment at this time is methotrexate. This patient has early rheumatoid arthritis (RA) with moderate disease activity measured by the clinical disease activity index (CDAI). Methotrexate is an anchor drug in RA and is the preferred initial monotherapy, as it both controls symptoms

and prevents joint damage. Clinical trials have demonstrated that 30% to 50% of patients treated with methotrexate monotherapy will show no disease progression as measured by hand and foot radiographs. Close dose titration (up to as high as 25 mg per week) based on her CDAI score is necessary, as is monitoring for the development of joint damage by radiography or ultrasonography. Ultrasonography is capable of identifying erosions earlier than radiography and can identify continued inflammation even in asymptomatic patients with no detectable synovitis on examination. If methotrexate alone does not lead to remission, a second disease-modifying treatment should be added.

Prednisone may improve symptoms and is disease modifying in conjunction with methotrexate, but long-term side effects (such as diabetes mellitus and osteoporosis) limit its usefulness as primary therapy in RA. Prednisone is primarily used as short-term therapy for disease flares and for temporary symptom control while waiting for long-term medications to become effective. Prednisone should be used at the lowest effective dose for the shortest period possible.

NSAIDs convey anti-inflammatory, analgesic, and antipyretic effects. As such, ibuprofen may address pain and swelling but is not considered disease modifying and will not slow the progression of disease. The major role for NSAIDs in the treatment of RA is for temporary symptom control while waiting for the effect of disease-modifying treatments such as methotrexate to be realized.

Although first-line therapy for lupus nephritis and potentially useful in systemic sclerosis, mycophenolate mofetil does not have a clearly defined role in the treatment of RA. A clinical trial of mycophenolate mofetil in RA showed no benefit compared with placebo.

KEY POINT

- In rheumatoid arthritis, methotrexate is an anchor drug and is the preferred initial monotherapy.

Bibliography

Singh JA, Saag KG, Bridges SL Jr, Akl EA, Bannuru RR, Sullivan MC, et al. 2015 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. Arthritis Rheumatol. 2016;68:1-26. [PMID: 26545940] doi:10.1002/art.39480

Item 81 Answer: C

Educational Objective: Diagnose glucocorticoid-induced osteonecrosis.

Plain radiography of the left hip is the most appropriate initial test for this patient with subacute hip pain. She has lupus nephritis that requires treatment with glucocorticoids. Both glucocorticoid treatment and systemic lupus erythematosus are risk factors for osteonecrosis, which causes death of an area of bone due to compromised blood supply. Other common risk factors include prior fracture or radiation exposure, excessive alcohol use, and sickle cell anemia. Osteonecrosis typically affects the ends of long bones, including the femoral head, humeral head, and distal femur. The involved area of bone collapses, often leading to rapidly progressive osteoarthritis. Patients with hip osteonecrosis present with groin pain (that is, true hip pain) occasionally radiating to the buttock, which worsens with ambulation; osteoarthritis can present in the same way, but would not be expected in a 34-year-old patient. Physical findings include reduced range of motion of the hip, altered gait, and pain with weight bearing. Plain radiography is the initial radiographic study of choice, although MRI is the gold standard for diagnosis and may be required if plain radiography is not diagnostic. Early radiographic findings include bone density changes, sclerosis, and, eventually, cyst formation. Subchondral radiolucency producing the "crescent sign" indicates subchondral collapse. End-stage disease is characterized by collapse of the femoral head, joint-space narrowing, and degenerative changes.

Dual-energy x-ray absorptiometry is useful to assess bone density in patients on chronic glucocorticoid therapy. Although it may establish the presence of osteoporosis, it cannot determine the cause of pain and has little role in the evaluation of acute symptoms such as hip pain.

MRI is the best method for detecting early bone edema caused by osteonecrosis when plain radiographs are normal. MRI is preferred for diagnostic use in patients with nondiagnostic plain radiographs. However, for end-stage disease, MRI is more expensive than plain radiography, and it may be unnecessary if plain radiography is diagnostic.

Ultrasonography can be used to evaluate for trochanteric bursitis as the cause of lateral hip pain but would not be useful to check for osteonecrosis.

KEY POINT

- Plain radiography is the initial radiographic study of choice for osteonecrosis, and MRI is the modality of choice for sensitive evaluation of early disease when plain radiographs are normal.

Bibliography

Weinstein RS. Glucocorticoid-induced osteonecrosis. Endocrine. 2012; 41:183-90. [PMID: 22169965] doi:10.1007/s12020-011-9580-0

Item 82 Answer: A

H

Educational Objective: Diagnose infectious arthritis.

Arthrocentesis followed by intravenous antibiotics is the appropriate next step in management of this immunocompromised patient with suspected infectious arthritis. This patient is immunosuppressed due to both his underlying rheumatoid arthritis (RA) and his medications. Additionally, other than the left knee, it appears that his arthritis is well controlled, raising concern for a cause other than a flare of his RA, including infectious arthritis. The hallmarks of a joint infection are warmth, erythema, pain, and swelling. The typical bacterial infectious arthritis develops over days. Joint infections are commonly limited to a single joint; the knee is the most common site, but the hip, wrist, and ankle are also commonly affected. Fever and rigors may occur but are not universally present (60% of patients); absence of fever

H CONT.

therefore does not exclude an infected joint. When infectious arthritis is suspected, the synovial fluid must be aspirated and assessed for leukocyte count, Gram stain, culture, and crystal analysis. Joint aspiration should be performed before initiating antibiotics whenever possible. Infectious arthritis must be expeditiously recognized and treated to prevent joint damage; therefore, intravenous antibiotics should be initiated right after arthrocentesis if the suspicion for infectious arthritis is high, as in this case. A synovial fluid leukocyte count of >50,000/µL (50×10^9/L), and especially ≥100,000/µL (100×10^9/L), strongly suggests an infectious process.

Colchicine is a useful medication for inflammatory arthritis caused by crystals composed of monosodium urate or calcium pyrophosphate. The lack of response to naproxen suggests that crystal-associated arthritis is an unlikely diagnosis. More importantly, infection must be ruled out with arthrocentesis before colchicine therapy is initiated.

Starting prednisone for a presumed RA flare would not be appropriate until infectious arthritis was ruled out by performing arthrocentesis and analyzing synovial fluid for leukocyte count and cultures. The elevated leukocyte count and erythrocyte sedimentation rate cannot differentiate whether the underlying cause of the patient's arthritis is infection or RA flare.

Adding sulfasalazine to the patient's medication regimen would only be appropriate if his RA was not well controlled (swelling, pain, and tenderness in multiple joints). Single joint involvement is highly suspicious of another diagnosis, particularly infection.

KEY POINT

- Arthrocentesis followed by intravenous antibiotics is appropriate for patients with suspected infectious arthritis.

Bibliography

Wang DA, Tambyah PA. Septic arthritis in immunocompetent and immunosuppressed hosts. Best Pract Res Clin Rheumatol. 2015;29:275-89. [PMID: 26362744] doi:10.1016/j.berh.2015.05.008

Item 83 Answer: E

Educational Objective: Diagnose hepatitis C virus–related cryoglobulinemic vasculitis.

Hepatitis C antibody testing is the most appropriate test to perform next in this patient who likely has cryoglobulinemic vasculitis. This patient has a small-vessel vasculitis documented on skin biopsy, along with Raynaud symptoms, arthralgia, sensory neuropathy, and abnormal urinalysis that may represent glomerulonephritis. The presence of cryoglobulins in this setting suggests cryoglobulinemic vasculitis; positive rheumatoid factor and low C4 are characteristic. Ninety percent of cases of mixed cryoglobulinemia are associated with hepatitis C virus infection; this infection may go unrecognized for many years before the development of vasculitis. It is important to assess for hepatitis C virus infection in an individual with cryoglobulinemia; treatment of the hepatitis C virus infection will also treat the cryoglobulinemia and the vasculitis.

In the absence of sclerodactyly, dilated capillary loops of fingernail beds, or digital pitting, the patient has no clinical features aside from Raynaud phenomenon to support a diagnosis of systemic sclerosis; therefore, anticentromere antibody testing is not indicated.

Similarly, the patient has no joint swelling on physical examination, making a diagnosis of rheumatoid arthritis much less likely; therefore, anti–cyclic citrullinated peptide antibody testing is not needed.

Anti-Jo-1 antibodies are found in patients with antisynthetase syndrome, which causes myositis and interstitial lung disease. This patient lacks these clinical features, as well as inflammatory arthritis and mechanic's hands (hyperkeratotic fissuring of the palmar and lateral surfaces of the fingers) that are often part of the syndrome. Therefore, he should not be tested for these antibodies.

Anti-U1-ribonucleoprotein antibodies is associated with systemic lupus erythematosus and mixed connective tissue disease, an overlap disease containing features of myositis, systemic sclerosis and lupus; however, the patient has negative antinuclear antibodies and aside from Raynaud phenomenon and joint pain has no other clinical features suggestive of these conditions.

KEY POINT

- Ninety percent of cases of mixed cryoglobulinemia are associated with hepatitis C virus infection; therefore, assessing for hepatitis C virus infection in an individual with cryoglobulinemia is indicated.

Bibliography

Cacoub P, Comarmond C, Domont F, Savey L, Saadoun D. Cryoglobulinemia vasculitis. Am J Med. 2015;128:950-5. [PMID: 25837517] doi:10.1016/j.amjmed.2015.02.017

Item 84 Answer: B

Educational Objective: Diagnose psoriatic arthritis.

The most likely diagnosis is psoriatic arthritis. Characteristic features of psoriatic arthritis include psoriasis, enthesitis, dactylitis ("sausage digits"), tenosynovitis, arthritis of the distal interphalangeal joints, asymmetric oligoarthritis, and spondylitis. This patient has an asymmetric, oligoarticular arthritis involving the small joints of the hands (particularly the distal joints) and feet, a history of dactylitis, negative autoantibodies, and new bone formation and pencil-in-cup deformities on radiographs, all of which are compatible with the diagnosis of psoriatic arthritis. Patients with a characteristic pattern of psoriatic joint involvement (especially distal interphalangeal arthritis and/or dactylitis), but without apparent psoriasis, should undergo a thorough examination for occult psoriatic skin changes (for example, scalp, umbilicus, gluteal cleft, genitals) and careful nail examination. Although the characteristic skin rash is absent, the patient did have psoriatic nail changes characterized by onycholysis, pitting, and trachyonychia (roughened surface).

Gout can occur as a monoarticular or oligoarticular inflammatory arthritis, most typically starting in the first metatarsophalangeal joint but, subsequently, involving joints in the upper and lower extremities. An increasingly polyarticular pattern, however, is not likely to be seen in a patient without kidney disease, without hyperuricemia, and without medication exposure that might be expected to increase the serum urate level.

Reactive arthritis is an inflammatory arthritis that occurs in the setting of a defined antecedent infection, usually of the genitourinary or gastrointestinal tract. These cases often present as an asymmetric oligoarthritis. Up to 50% of cases resolve by 6 months, but 20% of patients progress to chronic disease. This patient has arthritis lasting almost a decade in the setting of psoriasis and should not be attributed to reactive arthritis.

Rheumatoid arthritis is characterized by a symmetric polyarticular inflammatory arthritis involving the proximal interphalangeal and metacarpophalangeal joints in the hands and the analogous joints in the feet, and commonly affecting the wrists and ankles. Radiographic findings include periarticular osteopenia and marginal (near the edges of the joint) erosions. This patient does not have physical, radiographic, or laboratory findings (negative rheumatoid factor and anti–cyclic citrullinated peptide antibodies) to support this diagnosis.

KEY POINT

- Characteristic features of psoriatic arthritis include psoriasis, enthesitis, dactylitis, tenosynovitis, arthritis of the distal interphalangeal joints, asymmetric oligoarthritis, and spondylitis.

Bibliography

Raychaudhuri SP, Wilken R, Sukhov AC, Raychaudhuri SK, Maverakis E. Management of psoriatic arthritis: Early diagnosis, monitoring of disease severity and cutting edge therapies. J Autoimmun. 2017;76:21-37. [PMID: 27836567] doi:10.1016/j.jaut.2016.10.009

H

Item 85 Answer: C

Educational Objective: Evaluate kidney disease in systemic lupus erythematosus.

Kidney biopsy should be performed to assess this patient's kidney disease. Lupus nephritis occurs in up to 70% of patients with systemic lupus erythematosus (SLE); the presence of anti-double-stranded DNA antibodies is a marker for risk. This patient's symptoms and laboratory findings, including constitutional symptoms, inflammatory polyarthritis, a malar (butterfly) rash, positive autoantibodies (antinuclear, anti-Smith, and anti-double-stranded DNA antibodies), hypocomplementemia, and proteinuria, are suggestive of SLE. She likely has the nephrotic syndrome due to lupus nephritis, and further evaluation is needed. Kidney disease is frequent in SLE and can be seen in 10% to 30% of patients at initial presentation. There are six different pathologic classes of kidney involvement in SLE with significant prognostic and therapeutic implications. Kidney biopsy is the diagnostic test of choice to assess and categorize the kidney disease and should be performed in most cases. Indications for kidney biopsy are as follows: increasing serum creatinine without explanation, proteinuria >1000 mg/24 h, proteinuria >500 mg/24 h with hematuria, and proteinuria >500 mg/24 h with cellular casts.

Testing for antiphospholipid antibodies is appropriate to complete this patient's evaluation but will not help to further assess her kidney disease.

CT of the abdomen and pelvis may reveal masses or retroperitoneal obstruction but is unlikely to be helpful in diagnosing the cause of the nephrotic syndrome. Renal vein thrombosis can present with proteinuria but cannot account for this patient's rash, polyarthritis, or hypocomplementemia.

Renal arteriography should be performed in patients with medium-vessel vasculitis such as polyarteritis nodosa. This patient has SLE, and the vasculitis in SLE is small-vessel immune complex-mediated, in which arteriogram is usually normal and would unnecessarily expose the patient to nephrotoxic dye.

Serum and urine protein electrophoresis can assess a myeloproliferative disorder, which is not suspected in this patient with rash, polyarthritis, and the nephrotic syndrome.

KEY POINT

- Kidney biopsy is the diagnostic test of choice to assess and categorize kidney disease in patients with systemic lupus erythematosus and is usually essential to make therapeutic decisions.

Bibliography

Almaani S, Meara A, Rovin BH. Update on lupus nephritis. Clin J Am Soc Nephrol. 2016. [PMID: 27821390]

Item 86 Answer: C

Educational Objective: Manage neuropathic side effects of leflunomide.

The most appropriate next step in management is to stop leflunomide. Leflunomide inhibits lymphocyte activation by blocking the pyrimidine synthesis pathway. It is approved to treat rheumatoid arthritis (RA), in which its efficacy is comparable to methotrexate. Common toxicities include gastrointestinal upset, diarrhea, aminotransferase elevations, cytopenias, infection, and teratogenesis. An uncommon side effect is peripheral neuropathy, which is usually axonal and may include sensory, motor, or mixed findings. The neuropathy can be severe but is usually self-limited if the drug is discontinued, highlighting the importance of early recognition. Low-dose methotrexate in combination with leflunomide is an infrequently employed, but proven, strategy for treating refractory RA.

Beginning gabapentin as a treatment for peripheral neuropathy would be an appropriate adjunctive therapy to stopping leflunomide, but the definitive treatment is to stop the offending agent.

High-dose glucocorticoids would be appropriate in the setting of rheumatoid vasculitis. Although peripheral

neuropathy may be present in this rare complication of RA, rheumatoid vasculitis invariably occurs in the setting of poorly controlled disease. In addition, other manifestations of vasculitis would typically be present, including cutaneous findings (ulcers) and ocular disease (scleritis, episcleritis, uveitis). This patient has well-controlled RA and has no associated systemic or cutaneous findings of vasculitis, making the diagnosis extremely unlikely and the need for increasing the prednisone unnecessary.

Methotrexate inhibits folic acid metabolism and increases extracellular adenosine levels. It is the recommended initial disease-modifying antirheumatic drug for most patients with RA. Methotrexate is administered weekly along with daily folic acid supplementation, which limits toxicity without affecting efficacy. Potential toxicities include hepatitis and bone marrow suppression (leukopenia, anemia). Patients with liver disease should not receive methotrexate, and limiting alcohol intake is strongly advised. Methotrexate does not cause peripheral neuropathy and should not be discontinued.

KEY POINT

- An uncommon side effect of leflunomide is peripheral neuropathy, and definitive treatment is discontinuation of the medication.

Bibliography

Richards BL, Spies J, McGill N, Richards GW, Vaile J, Bleasel JF, et al. Effect of leflunomide on the peripheral nerves in rheumatoid arthritis. Intern Med J. 2007;37:101-7. [PMID: 17229252]

Item 87 Answer: C

Educational Objective: Treat tophaceous gout with appropriate urate-lowering therapy.

Increasing allopurinol to 500 mg/d is the most appropriate next step in management for this patient with symptomatic tophaceous gout. Although she has stage 3 chronic kidney disease (with an estimated glomerular filtration rate <60 mL/min/1.73 m^2), she is tolerating allopurinol, 400 mg/d, without issue and does not take a diuretic, so she is not at high risk for allopurinol hypersensitivity. Allopurinol can be titrated to a maximum of 800 mg/d in 100-mg increments.

It is important to note that two recently published guidelines differ regarding the role of pharmacologic urate-lowering therapy in patients with gout. The 2016 American College of Physicians guideline (http://annals.org/aim/article/2578528/management-acute-recurrent-gout-clinical-practice-guideline-from-american-college) notes a lack of evidence supporting a specific target level for urate lowering; this guideline stresses discussing the risks and benefits of urate-lowering therapy with patients and suggests a "treat to avoid symptoms" approach without specifically considering the serum urate levels. The 2016 European League Against Rheumatism (EULAR) recommendations support a "treat-to-target" approach (consistent with the 2012 American College of Rheumatology gout guidelines), reducing the serum urate level to less than 6.0 mg/dL (0.35 mmol/L) in patients without tophi and less than 5.0 mg/dL (0.30 mmol/L) in patients with tophi. Based on both the ACP and EULAR guidelines, this patient meets criteria for more aggressive therapy.

Adding probenecid might be reasonable in some cases but is contraindicated in this patient because of her estimated glomerular filtration rate of less than 60 mL/min/1.73 m^2, tophi, and recurrent nephrolithiasis.

Pegloticase is a costly drug that should be considered only when other options have been exhausted.

Increasing colchicine to twice daily for prophylaxis of acute attacks offers no clear benefit over once daily dosing. More importantly, this would not affect the serum urate level or cause resorption of the tophi.

KEY POINT

- For patients with inadequately treated tophaceous gout who tolerate allopurinol, the dose can be titrated to a maximum of 800 mg/d in 100-mg increments to alleviate symptoms.

Bibliography

Qaseem A, Harris RP, Forciea MA; Clinical Guidelines Committee of the American College of Physicians. Management of Acute and Recurrent Gout: A Clinical Practice Guideline From the American College of Physicians. Ann Intern Med. 2017;166:58-68. [PMID: 27802508] doi:10.7326/M16-0570

Item 88 Answer: C

Educational Objective: Identify pulmonary arterial hypertension as a leading cause of mortality in mixed connective tissue disease.

Pulmonary arterial hypertension (PAH) and interstitial lung disease are the two conditions most commonly associated with premature mortality in patients like this with mixed connective tissue disease (MCTD). MCTD is rare (1:1,000,000). Age at onset is between 30 and 50 years, with a 9:1 female predominance. Most patients have no known risk factors. MCTD is an overlap syndrome that includes features of systemic lupus erythematosus (SLE), systemic sclerosis, and/or polymyositis in the presence of anti–U1-ribonucleoprotein (RNP) antibodies. More than 50% of patients with MCTD have hand edema and synovitis at disease onset. About one third develop myositis, and nearly half develop decreased esophageal motility and fibrosing alveolitis. PAH occurs in 20%, with fatigue often the initial symptom. PAH (and interstitial lung disease) is associated with poor prognosis and is a major cause of mortality in patients with MCTD. The course of MCTD is variable; the likelihood of developing PAH, interstitial lung disease, and/or cardiovascular disease increases with disease duration. Regular follow-up and monitoring for these conditions is warranted. Patients with MCTD should undergo high-resolution CT of the chest, echocardiography, and pulmonary function testing.

Central nervous system (CNS) disease is common in MCTD, with trigeminal neuralgia occurring in up to 25% of patients. CNS vasculitis is extremely rare, and CNS disease is not typically a cause of mortality in patients with MCTD.

Pericarditis is likely the most common cardiac manifestation of MCTD and while contributing to excess morbidity, it does not result in premature death. As with other chronic inflammatory diseases, premature atherosclerosis is common in patients with MCTD and can contribute to both morbidity and early mortality.

Kidney disease is found in approximately 25% of patients with MCTD and most often presents as a membranous nephropathy that typically does not lead to premature death. Glomerulonephritis is rarely observed. Renovascular hypertension as seen in systemic sclerosis is a rare cause of mortality.

KEY POINT

- In patients with mixed connective tissue disease, pulmonary arterial hypertension and interstitial lung disease are associated with premature mortality; therefore, regular follow-up and monitoring for these conditions is warranted.

Bibliography

Hajas A, Szodoray P, Nakken B, Gaal J, Zöld E, Laczik R, et al. Clinical course, prognosis, and causes of death in mixed connective tissue disease. J Rheumatol. 2013;40:1134-42. [PMID: 23637328] doi:10.3899/jrheum.121272

Item 89 Answer: C

Educational Objective: Treat osteoarthritis with intra-articular glucocorticoids.

Intra-articular glucocorticoid injection is an appropriate treatment option for this patient with knee osteoarthritis (OA) not adequately controlled with acetaminophen or an exercise program. Given the localized nature of her symptoms, and her more specific desire for short-term relief while she travels, she could benefit from targeted treatment. Despite a lack of high quality of evidence, trials comparing intra-articular glucocorticoids and placebo generally show that the treatment is safe and may significantly improve pain and function for patients in the short term. Furthermore, U.S. and international OA guidelines support the use of intra-articular glucocorticoids for knee OA. A recent 2-year study has called the efficacy and long-term safety of intra-articular glucocorticoid injections into question, with possible negative effects on cartilage thickness, an outcome with unclear clinical meaning. Arthrocentesis and joint injections are safe procedures in patients receiving therapeutic doses of anticoagulation therapy, and are rarely associated with significant bleeding.

Alendronate is an osteoporosis medication that inhibits bone resorption via actions on osteoclasts or on osteoclast precursors. Risedronate, another bisphosphonate, has been studied in osteoarthritis, but results have not been favorable for OA symptom modification. Risedronate did reduce a marker of cartilage degradation; nevertheless, it is not a currently recommended OA treatment.

For patients with symptomatic knee OA, the American Academy of Orthopaedic Surgeons recommends against the use of arthroscopy with debridement. This recommendation is based on evidence from randomized trials and systematic reviews that fail to show benefit for knee pain with or without radiographic knee OA.

Pregabalin, which binds to the $\alpha2$-δ subunit of voltage-gated calcium channels within the central nervous system and inhibits excitatory neurotransmitter release, is not a recognized treatment for OA. It is currently FDA approved for fibromyalgia, neuropathic pain, postherpetic neuralgia, and partial-onset seizures. Because it can cause euphoria, pregabalin is categorized as a schedule V controlled substance.

Tramadol is a centrally acting synthetic opioid analgesic that also weakly inhibits the reuptake of norepinephrine and serotonin. Tramadol may rarely be warranted to control pain in patients with OA who have not responded to other agents or are poor candidates for other interventions to treat painful joints, such as surgery. Compared with placebo, tramadol results in a statistically significant but relatively small improvement of OA-related knee pain. Significant side effects sufficient to warrant drug discontinuation include nausea, vomiting, and constipation.

KEY POINT

- Intra-articular glucocorticoid injection is a treatment option for patients with localized osteoarthritis.

Bibliography

Jüni P, Hari R, Rutjes AW, Fischer R, Silletta MG, Reichenbach S, et al. Intra-articular corticosteroid for knee osteoarthritis. Cochrane Database Syst Rev. 2015:CD005328. [PMID: 26490760] doi:10.1002/14651858.CD005328.pub3

Item 90 Answer: C

Educational Objective: Treat refractory systemic lupus erythematosus with belimumab.

Belimumab is the most appropriate therapeutic option to consider in this patient with a history of systemic lupus erythematosus (SLE) who continues to have active disease manifestations primarily affecting the skin and joints while she is on appropriate standard immunosuppressive therapy, including glucocorticoids. She has not been able to tolerate other immunosuppressive agents commonly used to treat active disease manifestations. Therefore, an alternative approach or escalation of the therapy is appropriate for this patient. Belimumab is FDA approved as an addition to standard therapy in patients who have SLE with mild to moderately active disease. Belimumab is designed to inhibit B-lymphocyte stimulator (BLyS) protein. BLyS plays a key role in the selection, maturation, and survival of B cells, and it has a significant role in the pathogenesis of SLE. The addition of belimumab to standard therapy reduces disease activity levels and delays flares in patients with serologically active SLE or prior glucocorticoid use. Its use is also associated with improved quality of life in appropriately selected patients. Belimumab has been found to be most effective in patients with mucocutaneous and joint

manifestations; its role in other disease manifestations continues to be studied and evolve.

Abatacept is a T-cell costimulatory inhibitor that has been tried in SLE but not found to be effective.

Adalimumab is a tumor necrosis factor (TNF)-α inhibitor effective in the treatment of rheumatoid arthritis and spondyloarthritis. Blocking TNF in patients with SLE has not been effective and may potentially worsen the disease.

The interleukin (IL)-17 inhibitor secukinumab is an approved therapy for psoriatic arthritis and ankylosing spondylitis. The role of IL-17 and its blockade in SLE is under investigation but is currently not well elucidated in SLE. Secukinumab has not been studied in SLE and is not an appropriate therapy.

KEY POINT

- Belimumab is FDA approved as an addition to standard therapy in patients who have systemic lupus erythematosus with persistent mild to moderately active disease.

Bibliography

Garcia A, De Sanctis JB. A review of clinical trials of belimumab in the management of systemic lupus erythematosus. Curr Pharm Des. 2016;22:6306-6312. [PMID: 27587201] doi:10.2174/1381612822666160831103254

Item 91 Answer: C

Educational Objective: Diagnose diffuse idiopathic skeletal hyperostosis.

Diffuse idiopathic skeletal hyperostosis (DISH) is the most likely diagnosis. DISH is a noninflammatory condition involving ossification of spinal ligaments and entheses. DISH can be asymptomatic or present in various ways, including as pain and stiffness in the spine, with the thoracic spine being most often involved. Although features such as ligamentous ossification are shared with ankylosing spondylitis, the sacroiliac joints are not involved in DISH. The most characteristic radiographic change of DISH is confluent ossification of at least four contiguous vertebral levels, usually on the right side of the spine. The left-sided sparing is possibly related to mechanical pressure from the aorta, and its pulsations, as a barrier toward production of bony hyperostosis on the left side.

Ankylosing spondylitis is characterized by bilateral sacroiliac joint abnormalities on spinal radiographs. Other spinal sections may also be involved, but sacroiliac joint involvement is cardinal for diagnosis. Inflammatory back pain is the most common symptom and is usually comprised of four of five of the following features: onset of back discomfort before the age of 40 years; insidious onset; improvement with exercise; no improvement with rest; and pain at night (with improvement upon arising).

Calcium pyrophosphate deposition may affect the axial spine but more often affects the peripheral skeleton. It is often asymptomatic, is not known to have a predilection for a particular segment of the spine, and appears as punctate and linear radiodensities of calcification within the cartilage on radiographs. It does not result in ossification of spinal ligaments and entheses.

Psoriatic arthritis can affect the spine, with inflammatory back pain symptoms similar to those listed with ankylosing spondylitis. Differences between psoriatic arthritis and DISH include that sacroiliac joints may be asymmetrically involved in psoriatic arthritis but are not involved in DISH, and the spondylitis is random and not necessarily continuous in psoriatic arthritis, whereas a defining characteristic of DISH is involvement of four or more vertebral bodies. DISH syndesmophytes (ligamentous ossification) are located on the anterior and lateral margins of vertebrae, but they tend to be nonmarginal in psoriatic arthritis.

KEY POINT

- Diffuse idiopathic skeletal hyperostosis is a noninflammatory condition that involves ossification of spinal ligaments and entheses and usually presents as back pain and stiffness; characteristic radiographic changes include confluent ossification of at least four contiguous vertebral levels, usually on the right side of the spine.

Bibliography

Mader R, Verlaan JJ, Buskila D. Diffuse idiopathic skeletal hyperostosis: clinical features and pathogenic mechanisms. Nat Rev Rheumatol. 2013;9:741-50. [PMID: 24189840] doi:10.1038/nrrheum.2013.165

Item 92 Answer: C

H

Educational Objective: Diagnose colchicine and clarithromycin drug interaction.

Discontinuation of colchicine and clarithromycin is the most appropriate next step in management. The coadministration of colchicine and clarithromycin can result in potentially fatal colchicine toxicity that manifests as rhabdomyolysis, acute kidney injury, and pancytopenia. Colchicine is metabolized in the liver by the CYP3A4 cytochrome and should be avoided in patients taking CYP3A4 inhibitors such as clarithromycin and fluconazole. Coadministration with clarithromycin is particularly concerning, because there have been several case reports of fatal outcomes with the combination (even when taken for a short time). Once the patient recovers, however, colchicine may be reinitiated (as it is the combination of the two drugs that led to the current scenario).

High-dose glucocorticoid therapy would be indicated in the event of immune-mediated hemolytic anemia and leukopenia (Evans syndrome). Colchicine toxicity, however, is not immune mediated and would not respond to glucocorticoids.

Plasma exchange would be appropriate for thrombotic thrombocytopenic purpura (TTP). Although TTP can cause thrombocytopenia and acute kidney injury, the lack of schistocytes on blood smear argues against microangiopathic hemolytic anemia, and other features of TTP such as fever and mental status changes are also absent. Plasma exchange is not effective for colchicine toxicity.

H CONT.

There is no need to discontinue febuxostat; this drug can be continued in patients with chronic kidney disease and would not cause the clinical picture described.

KEY POINT

- Coadministration of colchicine and CYP3A4 inhibitors (such as clarithromycin and fluconazole) should be avoided because potentially fatal colchicine toxicity with kidney failure, rhabdomyolysis, and bone marrow suppression may occur.

Bibliography

Hung IF, Wu AK, Cheng VC, Tang BS, To KW, Yeung CK, et al. Fatal interaction between clarithromycin and colchicine in patients with renal insufficiency: a retrospective study. Clin Infect Dis. 2005;41:291-300. [PMID: 16007523]

Item 93 Answer: D

Educational Objective: Diagnose subacute cutaneous lupus erythematosus.

This patient has subacute cutaneous lupus erythematosus (SCLE) and likely has systemic lupus erythematosus (SLE). She has a new rash on the torso with annular and patchy papular areas. This rash is most likely SCLE, a photosensitive rash occurring especially on the arms, neck, upper trunk, and face. The rash can be annular with central clearing or papulosquamous with patchy erythematous plaques and papules. In some patients, the rash may have both of the characteristics, as seen in this patient. SCLE often has a fine scale that may leave postinflammatory hypo- or hyperpigmentation. SCLE is associated with anti-Ro/SSA antibodies, with a prevalence of 75%. About 50% of patients with SCLE also have SLE. These patients more typically have mild systemic symptoms, most commonly arthritis and myalgias; patients with lupus vasculitis, central nervous system lupus, and nephritis are found in less than 10% of patients with SCLE. Psoriasis can present with similar lesions but are usually photoresponsive (improve with sun exposure), unlike this patient.

Essentially 100% of patients with acute cutaneous lupus erythematosus (ACLE) have SLE. ACLE may present in multiple forms, with the most commonly recognized being a characteristic localized malar (butterfly) eruption. Less commonly it can appear as a generalized eruption, which typically appears as an erythematous maculopapular eruption of sun-exposed skin such as the extensor surfaces of the arms and hands.

Patients with dermatomyositis frequently have areas of poikiloderma with ill-defined patchy erythema and "salt-and-pepper" dyspigmentation accompanied by telangiectasias on the chest or upper back. There may be slightly violaceous erythema over the "V" of the neck, chest, and the upper back (the "Shawl sign") or on the lateral hips (the "holster sign").

Discoid lupus erythematosus (DLE) occurs in 20% of patients with SLE but more commonly occurs as an isolated, nonsystemic finding; patients with isolated DLE usually do not go on to develop SLE. DLE usually affects the scalp and face and presents as hypo- and/or hyperpigmented, possibly erythematous, patches or thin plaques that may be variably atrophic or hyperkeratotic.

KEY POINT

- Subacute cutaneous lupus erythematosus (SCLE) can present as annular with central clearing or papulosquamous with patchy erythematous plaques and papules, and both forms can be seen in the same patient; about 50% of patients with SCLE also have systemic lupus erythematosus.

Bibliography

Okon LG, Werth VP. Cutaneous lupus erythematosus: diagnosis and treatment. Best Pract Res Clin Rheumatol. 2013;27:391-404. [PMID: 24238695] doi:10.1016/j.berh.2013.07.008

Item 94 Answer: D

Educational Objective: Diagnose ankylosing spondylitis.

The most appropriate test to perform next is plain radiography of the sacroiliac joints. This patient has features of inflammatory back pain (onset before age 45 years, duration >3 months, insidious onset, morning stiffness >30 minutes, improvement with exercise, no improvement with rest, awaking from pain with improvement on arising, alternating buttock pain), as well as antecedent history of anterior uveitis. He should therefore be evaluated for ankylosing spondylitis. The American College of Radiology appropriateness criteria recommend radiography of the sacroiliac joints and spine as the initial evaluation of patients with inflammatory sacroiliac or back symptoms for evidence of sacroiliitis, including erosions, evidence of sclerosis, and widening, narrowing, or partial ankylosis of the sacroiliac joints. The presence of such findings would confirm the diagnosis of ankylosing spondylitis.

A bone scan lacks specificity for the changes of sacroiliitis and is not of value in the diagnosis of ankylosing spondylitis.

CT of the sacroiliac joints is not considered an appropriate initial diagnostic test for ankylosing spondylitis. It exposes the patient to unnecessary amounts of radiation.

MRI is also unnecessary in most cases of suspected ankylosing spondylitis because the diagnosis can often be confirmed with less costly radiography. Although MRI is more sensitive than radiography or CT in detecting sacroiliitis, it is less specific and can result in a high yield of false-positive test results. MRI may be useful to detect inflammation in patients with high clinical suspicion but normal or equivocal radiographs.

KEY POINT

- Plain radiography of the sacroiliac joints should be obtained in patients with suspected ankylosing spondylitis to evaluate for evidence of sacroiliitis, including erosions, sclerosis, and widening, narrowing, or partial ankylosis of the sacroiliac joints.

Bibliography

Taurog JD, Chhabra A, Colbert RA. Ankylosing spondylitis and axial spondyloarthritis. N Engl J Med. 2016;374:2563-74. [PMID: 27355535] doi:10.1056/NEJMra1406182

Item 95 Answer: C

Educational Objective: Prevent gout attacks during the initiation of urate-lowering therapy.

Discontinuing colchicine and beginning an NSAID such as meloxicam is the most appropriate next step to decrease the frequency of this patient's gout attacks. He has experienced several acute gout attacks since beginning allopurinol 2 months ago. It is common to experience "mobilization attacks" at the initiation of urate-lowering therapy, which occur when urate body stores shift from joints and soft tissues to the vasculature. Hence, all patients beginning urate-lowering therapy should also receive a prophylactic agent to prevent against mobilization flares for 6 to 12 months, without which the average patient will experience several acute attacks. Colchicine is the primary prophylactic agent employed (once or twice daily) for this role, but low-dose glucocorticoids and low-dose NSAIDs are also effective. Choice of therapy should be tailored to the individual's comorbid conditions. This patient is currently taking colchicine, which is most likely causing the diarrhea. In this case, discontinuation of colchicine and initiating a low-dose NSAID such as meloxicam is the most appropriate choice. All NSAIDs are considered equivalent for this purpose.

Adding prednisone would be a reasonable option for prophylaxis but is not ideal for this patient with insulin-dependent type 2 diabetes mellitus, because even low-dose glucocorticoids may result in hyperglycemia and increase insulin requirements.

Adding the uricosuric agent probenecid or increasing the allopurinol would not afford protection against mobilization flares because they are both urate-lowering agents, not prophylactic agents. Intensifying urate-lowering therapy would be a reasonable choice if the recurrent attacks are thought to represent a failure of urate-lowering therapy, rather than mobilization attacks, as is suspected with this patient.

Increasing colchicine would be a reasonable option, were it not for the diarrhea that began with the institution of colchicine 2 months ago. Diarrhea is one of the most common side effects of colchicine, and increasing the dose would worsen gastrointestinal toxicity.

KEY POINT

- All patients with gout beginning urate-lowering therapy should also receive a prophylactic agent such as colchicine, low-dose glucocorticoids, or low-dose NSAIDs to prevent mobilization flares; the choice of prophylactic drug is determined by patient comorbidities.

Bibliography

Latourte A, Bardin T, Richette P. Prophylaxis for acute gout flares after initiation of urate-lowering therapy. Rheumatology (Oxford). 2014;53:1920-6. [PMID: 24758886] doi:10.1093/rheumatology/keu157

Item 96 Answer: B

Educational Objective: Diagnose hip osteonecrosis related to systemic lupus erythematosus.

MRI of the hip is the most appropriate test to perform next in this patient with systemic lupus erythematosus (SLE) and a past exposure to high-dose glucocorticoids, who now presents with unexplained groin pain. She is at high risk for developing osteonecrosis affecting the hip/femur. Osteonecrosis is a serious complication of SLE that most commonly affects the hips but can also involve other large joints and should be suspected when there is otherwise unexplained pain and/or reduced range of motion. Chronic prednisone doses (>20 mg/d), severe/active SLE, and vasculitis are all associated with increased risk. Hip radiography can detect advanced disease, but MRI is the modality of choice for sensitive evaluation of early disease. Small lesions can improve and resolve spontaneously, but larger lesions usually lead to bony collapse and structural sequelae. MRI should be performed in this patient with normal pelvic and hip radiographs.

The American College of Radiology (ACR) approach to imaging for suspected osteonecrosis recommends CT only for patients who cannot undergo MRI. CT is somewhat more sensitive than plain radiography in the diagnosis of osteonecrosis but not nearly as sensitive as MRI.

Radionuclide bone scan will detect increased bone turnover at the junction, osteonecrosis, and reactive bone resulting in an image of increased tracer uptake surrounding a cold area (doughnut sign). However, radionuclide bone scan is significantly less sensitive and less specific than MRI in the detection of early osteonecrosis lesions and is not usually recommended as a first-line diagnostic test.

If MRI cannot be performed in patients with suspected early osteonecrosis, a reasonable alternative is bone scan with single photon emission CT (SPECT). This imaging modality is more sensitive than radiography, but the ACR Appropriateness Criteria for Osteonecrosis of the Hip designated SPECT as a second-line test to MRI for the detection of early lesions.

KEY POINT

- Osteonecrosis is a complication of systemic lupus erythematosus most commonly affecting the hips and should be suspected when there is otherwise unexplained pain and/or reduced range of motion; MRI is the modality of choice for evaluation of early disease.

Bibliography

Gontero RP, Bedoya ME, Benavente E, Roverano SG, Paira SO. Osteonecrosis in systemic lupus erythematosus. Reumatol Clin. 2015;11:151-5. [PMID: 25441491] doi:10.1016/j.reuma.2014.05.005

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13 (A) (B) (C) (D) (E)	58 (A) (B) (C) (D) (E)	103 (A) (B) (C) (D) (E)	148 (A) (B) (C) (D) (E)
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17 (A) (B) (C) (D) (E)	62 (A) (B) (C) (D) (E)	107 (A) (B) (C) (D) (E)	152 (A) (B) (C) (D) (E)
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19 (A) (B) (C) (D) (E)	64 (A) (B) (C) (D) (E)	109 (A) (B) (C) (D) (E)	154 (A) (B) (C) (D) (E)
20 (A) (B) (C) (D) (E)	65 (A) (B) (C) (D) (E)	110 (A) (B) (C) (D) (E)	155 (A) (B) (C) (D) (E)
21 (A) (B) (C) (D) (E)	66 (A) (B) (C) (D) (E)	111 (A) (B) (C) (D) (E)	156 (A) (B) (C) (D) (E)
22 (A) (B) (C) (D) (E)	67 (A) (B) (C) (D) (E)	112 (A) (B) (C) (D) (E)	157 (A) (B) (C) (D) (E)
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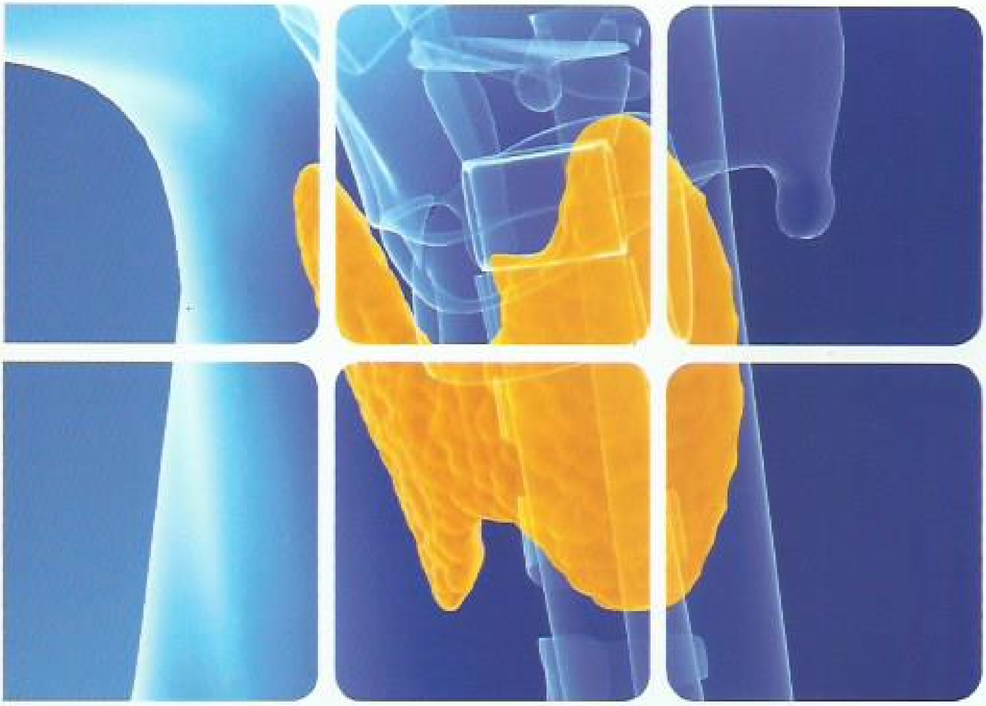

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On behalf of the many internists who have offered their time and expertise to create the content for MKSAP 18 and the editorial staff who work to bring this material to you in the best possible way, we are honored that you have chosen to use MKSAP 18 and appreciate any feedback about the program you may have. Please feel free to send any comments to mksap_editors@acponline.org.

Sincerely,

Patrick Alguire

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- Diagnose disease states that are less common and sometimes overlooked and confusing
- Improve management of comorbid conditions that can complicate patient care
- Determine when to refer patients for surgery or care by subspecialists
- Pass the ABIM Certification Examination
- Pass the ABIM Maintenance of Certification Examination

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- General internists and primary care physicians
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Endocrinology and Metabolism High Value Care Recommendations

The American College of Physicians, in collaboration with multiple other organizations, is engaged in a worldwide initiative to promote the practice of High Value Care (HVC). The goals of the HVC initiative are to improve health care outcomes by providing care of proven benefit and reducing costs by avoiding unnecessary and even harmful interventions. The initiative comprises several programs that integrate the important concept of health care value (balancing clinical benefit with costs and harms) for a given intervention into a broad range of educational materials to address the needs of trainees, practicing physicians, and patients.

HVC content has been integrated into MKSAP 18 in several important ways. MKSAP 18 includes HVC-identified key points in the text, HVC-focused multiple choice questions, and, for subscribers to MKSAP Digital, an HVC custom quiz. From the text and questions, we have generated the following list of HVC recommendations that meet the definition below of high value care and bring us closer to our goal of improving patient outcomes while conserving finite resources.

High Value Care Recommendation: A recommendation to choose diagnostic and management strategies for patients in specific clinical situations that balance clinical benefit with cost and harms with the goal of improving patient outcomes.

Below are the High Value Care Recommendations for the Endocrinology and Metabolism section of MKSAP 18.

- Tight inpatient glycemic control is not consistently associated with improved outcomes and may increase mortality.
- The sole use of "sliding-scale insulin" is not recommended since it leads to large glucose fluctuations.
- Treatment with an ACE inhibitor or angiotensin receptor blocker is not recommended for patients with diabetes who have a normal blood pressure, a urine albumin-creatinine ratio level less than 30 mg/g, and an estimated glomerular filtration rate (eGFR) greater than 60 mL/min/1.73 m^2.
- In the evaluation of fasting or postprandial hypoglycemia, specimens for C-peptide, insulin, proinsulin, β-hydroxybutyrate are obtained but are not sent for analysis unless a simultaneous glucose is less than 60 mg/dL (3.3 mmol/L).
- A history of normal menses rules out hypogonadotropic hypogonadism and additional testing is not required.
- Elevated plasma renin activity in patients taking an ACE inhibitor or angiotensin receptor blocker rules out hyperaldosteronism.
- Fine-needle aspiration biopsy is generally not needed for isolated subcentimeter thyroid nodules.
- Measurement of triiodothyronine in the setting of hypothyroidism is not needed.
- In the evaluation of Hashimoto thyroiditis, measurement of thyroid perioxidase (TPO) antibody titer is not necessary unless the diagnosis is unclear.
- Thyroid function should not be assessed in hospitalized patients unless there is a strong clinical suspicion of thyroid dysfunction.
- Before making the diagnosis of subclinical hypothyroidism, transient elevation of serum thyroid-stimulating hormone should be ruled out by repeating the measurement of thyroid-stimulating hormone in 2 to 3 months (see Item 65).
- Screening men with nonspecific symptoms of hypogonadism is not recommended.
- Testosterone therapy in men without biochemical evidence of deficiency is not beneficial and may be associated with significant harms.
- Routine screening for vitamin D deficiency is not recommended in healthy populations.
- For low-risk osteoporotic women, treatment with antiresorptive therapy for 5 years is sufficient (see Item 20).
- Screening for osteoporosis in premenopausal women is not indicated in the absence of risk factors (see Item 70).

Endocrinology and Metabolism

Disorders of Glucose Metabolism

Hyperglycemia results from abnormal carbohydrate metabolism secondary to insulin deficiency, peripheral resistance to insulin action, or a combination of both. Hyperglycemia that exceeds the normal glucose range but does not meet the diagnostic criteria for diabetes mellitus is defined as prediabetes, which increases the risk for the development of diabetes.

Diabetes Mellitus

Screening for Diabetes Mellitus

Screening for type 2 diabetes mellitus in the general adult population is indicated because: (1) type 2 diabetes is often preceded by a prolonged asymptomatic hyperglycemic period in which microvascular and macrovascular damage may occur; (2) lifestyle interventions and medications have demonstrated the ability to delay or prevent onset of type 2 diabetes in persons with prediabetes, and (3) early intensive glucose control and management of hyperlipidemia and hypertension may prevent or reduce the progression of microvascular and macrovascular cardiovascular disease (CVD).

The American Diabetes Association (ADA) and the U.S. Preventive Services Task Force (USPSTF) include age, BMI, race/ethnicity, and other risk factors as part of their criteria for screening recommendations for type 2 diabetes (**Table 1**). These risk factors are associated with a high risk of incident diabetes.

Screening for type 1 diabetes is not recommended. Antibody screening in a high-risk person with a relative with type 1 diabetes should occur within the context of a clinical trial (www.diabetestrialnet.org).

H Diagnostic Criteria for Diabetes Mellitus

Diabetes mellitus can be diagnosed by an abnormal result in one of three tests: hemoglobin A_{1c}, fasting plasma glucose (FPG), or 2-hour plasma glucose (2-hr PG) after a 75-gram carbohydrate challenge during an oral glucose tolerance test (OGTT) (**Table 2**). An abnormal result in asymptomatic persons should be confirmed with repeat testing. A single random plasma glucose value greater than or equal to 200 mg/dL (11.1 mmol/L) in the setting of symptomatic hyperglycemia is diagnostic of diabetes.

The results of testing for diabetes differ depending on which test is done, FPG, 2-hr PG, or hemoglobin A_{1c}. The 2-hr PG test has a higher sensitivity for the diagnosis of diabetes compared with FPG or hemoglobin A_{1c}. The advantages and disadvantages of the tests must be considered when determining the best screening option for a patient (**Table 3**). H

KEY POINTS

- Diabetes mellitus can be diagnosed by an abnormal result in one of the following screening tests: hemoglobin A_{1c}, fasting plasma glucose, or 2-hour plasma glucose after a 75-gram carbohydrate challenge during an oral glucose tolerance test.
- An abnormal result in asymptomatic persons should be confirmed with repeat testing.

Classification of Diabetes Mellitus

The underlying insulin abnormality, whether absolute or relative insulin deficiency, peripheral insulin resistance, or an overlap of both abnormalities, is important for classifying the type of diabetes mellitus and has implications for treatment options (**Table 4**).

Insulin Deficiency

Type 1 Diabetes Mellitus

Type 1 diabetes mellitus is characterized by a state of insulin deficiency secondary to the destruction of the insulin-producing beta cells in the pancreas. The destruction may be secondary to autoimmunity, idiopathic, or acquired.

Immune-Mediated Diabetes Mellitus

Immune-mediated type 1 diabetes mellitus (type 1A) is the underlying cause in 5% to 10% of persons newly diagnosed with diabetes. The mechanism of the beta cell destruction is multifactorial and likely due to environmental factors in persons with genetic susceptibilities. Specific human leukocyte antigen (HLA) alleles demonstrate a strong association with immune-mediated type 1 diabetes. At diagnosis, one or more autoantibodies directed at the following targets are typically present: glutamic acid decarboxylase (GAD65), tyrosine phosphatases IA-2 and IA-2β, islet cells, insulin, and zinc transporter (Zn T 8). Owing to highly automated available assays, GAD65 and IA-2 autoantibodies are recommended for initial screening. GAD65 autoantibodies have a high prevalence (70%) at the time of diagnosis and may remain detectable for years.

Immune-mediated type 1 diabetes has a variable presentation that ranges from moderate hyperglycemia to life-threatening diabetic ketoacidosis (DKA). At the time of diagnosis, approximately 90% of the functioning beta cells have been destroyed. Initiating insulin at the time of diagnosis may decrease toxicity associated with extreme hyperglycemia allowing the beta cell

TABLE 1. Screening Guidelines for Type 2 Diabetes Mellitus in Asymptomatic Adults

	ADA (2018)[a]	USPSTF (2015)
Screening criteria	Screen overweight adults (BMI ≥25 or ≥23 in Asian Americans) with at least one additional risk factor: First-degree relative with diabetes High-risk race/ethnicity (black, Hispanic/Latino, American Indian, Asian, Native Hawaiian/Pacific Islander) History of gestational diabetes mellitus History of cardiovascular disease Physical inactivity Hypertension (≥140/90 or on antihypertensive therapy) HDL cholesterol <35 mg/dL (0.90 mmol/L) and/or triglyceride >250 mg/dL (2.82 mmol/L) Polycystic ovary syndrome Hemoglobin A_{1c} ≥5.7% (39 mmol/mol), IGT, or IFG on previous testing Other conditions associated with insulin resistance (severe obesity, acanthosis nigricans)	Screen adults aged 40 to 70 years who are overweight or obese as part of risk assessment for cardiovascular disease. Other risk factors: High percentage of abdominal fat Hyperlipidemia Hypertension Physical inactivity Smoking
Additional screening criteria	All adults age 45 years or older	—
Additional screening considerations	Consider screening patients on medications known to increase the risk of diabetes, such as glucocorticoids, thiazide diuretics, HIV medications, and atypical antipsychotics.	Diabetes may occur in younger patients or at a lower BMI. Consider screening earlier if one of the following risk factors is present: Family history of diabetes History of gestational diabetes Polycystic ovary syndrome High-risk race/ethnicity (black, Hispanic/Latino, Asian American, American Indian/Alaskan Native, Native Hawaiian/Pacific Islander)
Screening intervals	Rescreen every 3 years if results are normal. Yearly testing recommended if prediabetes is diagnosed (hemoglobin A_{1c} between 5.7% and 6.4%, IGT, IFG).	Data supporting optimal screening intervals are limited. Rescreening every 3 years may be reasonable.

ADA = American Diabetes Association; CVD = cardiovascular disease; IFG = impaired fasting glucose; IGT = impaired glucose tolerance; USPSTF = U.S. Preventive Services Task Force.

[a]An optional ADA screening tool for diabetes risk can be found at www.diabetes.org/are-you-at-risk/diabetes-risk-test/. Accessed May 16, 2018.

Recommendations from American Diabetes Association. 2. Classification and diagnosis of diabetes: standards of medical care in diabetes-2018. Diabetes Care. 2018;41:S13-S27. [PMID: 29222373]

Recommendations from Siu AL; U.S Preventive Services Task Force. Screening for abnormal blood glucose and type 2 diabetes mellitus: U.S. Preventive Services Task Force Recommendation Statement. Ann Intern Med. 2015;163:861-8. [PMID: 26501513] doi:10.7326/M15-2345.

to regain some ability to produce insulin. Although this "honeymoon period" can last several weeks to years, insulin use should be continued to decrease stress on the remaining functioning beta cells and prolong their lifespan. Insulin deficiency requires life-long use of insulin therapy.

Patients with immune-mediated type 1 diabetes also have an increased risk for other autoimmune disorders, including celiac disease, thyroid disorders, vitiligo, and autoimmune primary adrenal gland failure.

Late autoimmune diabetes in adults (LADA) is characterized by autoantibody development leading to beta cell destruction and ultimately insulin deficiency. Individuals with LADA are typically not insulin-dependent initially and are frequently misclassified as having type 2 diabetes. There is a slow progression toward insulin dependence over months to years after diagnosis in the setting of positive autoantibodies.

KEY POINT

- Autoantibodies glutamic acid decarboxylase (GAD65) and tyrosine phosphatase IA-2 demonstrate a strong association with immune-mediated type 1 diabetes and should be measured at initial diagnosis to determine etiology.

Idiopathic Type 1 Diabetes Mellitus

Idiopathic type 1 diabetes (type 1B) is characterized by variable insulin deficiency due to beta cell destruction without the

TABLE 2. Diagnostic Criteria for Diabetes Mellitus[a]

Test	Normal Range	Increased Risk for Diabetes (Prediabetes)	Diabetes
Random plasma glucose	—	—	Hyperglycemic symptoms plus a random glucose ≥200 mg/dL (11.1 mmol/L)
Fasting plasma glucose[b]	<100 mg/dL (5.6 mmol/L)	100-125 mg/dL (5.6-6.9 mmol/L)	≥126 mg/dL (7.0 mmol/L)
2-Hour plasma glucose during an OGTT[c]	<140 mg/dL (7.8 mmol/L)	140-199 mg/dL (7.8-11.0 mmol/L)	≥200 mg/dL (11.1 mmol/L)
Hemoglobin A_{1c}[d,e]	<5.7% (39 mmol/mol)	5.7%-6.4% (39-46 mmol/mol)	>6.5% (48 mmol/mol)

OGTT = oral glucose tolerance test.

[a]In the absence of hyperglycemic symptoms, an abnormal fasting plasma glucose, OGTT, or hemoglobin A_{1c} should be confirmed by repeating the same test on a separate day. If two different tests demonstrate discordant results, the American Diabetes Association recommends repeating the test with the abnormal results.

[b]Fasting for at least 8 hours.

[c]An OGTT involves the consumption of a 75-g glucose load dissolved in water.

[d]The American Diabetes Association recommends a National Glycohemoglobin Standardization Program (NGSP) certified hemoglobin A_{1c} assay that is standardized to the Diabetes Control and Complication Trial (DCCT) assay.

[e]The Veterans Affairs/Department of Defense guidelines recommend confirmation of diabetes based upon an elevated hemoglobin A_{1c} value of 6.5% to 6.9% with an elevated fasting plasma glucose of ≥126 mg/dL (7.0 mmol/L) due to strong evidence supporting racial differences between glycemic control and hemoglobin A_{1c} values for diagnosis and treatment.

Data from American Diabetes Association. 2. Classification and diagnosis of diabetes: Standards of Medical Care in Diabetes—2018. Diabetes Care. 2018;41 (Suppl. 1):S13-S27. [PMID: 29222373]

Data from U.S. Department of Veterans Affairs/U.S. Department of Defense. VA/DoD Clinical Practice Guidelines for the management of diabetes mellitus in primary care. 2017. www.healthquality.va.gov/guidelines/cd/diabetes. Accessed May 16, 2018.

presence of autoantibodies. Individuals with idiopathic type 1 diabetes may develop episodic DKA. There is typically a strong family history of type 2 diabetes in persons with idiopathic diabetes, and it is more common in Asian and African American patients, particularly with sub-Saharan African ancestry.

Acquired Type 1 Diabetes Mellitus

Beta cell destruction may occur from diseases affecting the pancreas or from the effect of drugs or infections (see Table 4). This may result in impaired insulin production or secretion with the subsequent development of type 1 diabetes.

Insulin Resistance

The ineffective use of insulin by the peripheral cells to utilize glucose and fatty acids characterizes insulin resistance. Blood glucose levels remain in the normal range as long as the beta cells can increase insulin production. Hyperglycemia results from a relative insulin deficiency when the pancreas can no longer produce enough insulin. Obesity increases the risk for insulin resistance, which is also a component of the metabolic syndrome and predisposes to the development of type 2 diabetes.

Metabolic Syndrome

Metabolic syndrome comprises a constellation of risk factors for development of type 2 diabetes and CVD, which includes abdominal obesity, impaired glucose metabolism, hyperlipidemia, and hypertension. Multiple organizations define metabolic syndrome differently (**Table 5**). The Endocrine Society recommends screening patients with risk factors for metabolic syndrome every 3 years to evaluate fasting plasma glucose, fasting lipid panel, blood pressure, and waist circumference. Calculation of the 10-year cardiovascular risk, using either the Framingham Risk Score or the American College of Cardiology (ACC)/American Heart Association (AHA) risk calculator, is recommended for patients with metabolic syndrome.

Type 2 Diabetes Mellitus

Most cases of diabetes (90% to 95%) meet the criteria for type 2 diabetes. Hyperglycemia accompanied by insulin resistance and/or relative insulin deficiency defines type 2 diabetes. The extent of beta cell dysfunction determines the degree of hyperglycemia, which may worsen over time with progressive decrease in insulin production. The pathogenesis of type 2 diabetes is multifactorial with influence from both genetic and environmental factors. Type 2 diabetes is commonly present in first-degree relatives of both individuals at high risk for or diagnosed with type 2 diabetes. There is also an increased risk in several ethnicities including: Hispanic/Latino, African American, American Indian, Asian American. Additional risk factors for diabetes risk include increasing age and decreased physical activity.

Type 2 diabetes classically presents in adults, although there is an increased incidence among children and adolescents as the rate of overweight/obesity increases in these populations. Type 2 diabetes has a gradual onset with most

TABLE 3. Comparison of Screening Tests for Diabetes Mellitus

Test	Advantages	Disadvantages
Hemoglobin A_{1c}	Convenient: Does not require fasting and no restrictions on collection time Not altered by illness, stress, etc. Measures blood glucose concentration over the prior 8-12 weeks Minimal biological variability Blood sample remains stable Standardized assay Test accuracy is monitored Measurement correlates with microvascular and macrovascular outcomes	Lower sensitivity for diagnosis compared with FPG or 2-hr PG Erroneous increases or decreases in hemoglobin A_{1c} result secondary to factors affecting erythrocyte survival[a]: Iron deficiency anemia Blood loss/hemolysis Kidney disease Liver disease Pregnancy Hemoglobin variants in individuals with African, Southeast Asian, and Mediterranean heritage[b] Higher value in black compared with non-Hispanic white persons[c] Affected by some glucose-6-phosphate dehydrogenase variants[d] Unavailable in some areas of the world Expensive
FPG	Inexpensive Widely available Automated assay	Inconvenient: ≥ 8 hour fasting required and restriction on time of collection Affected by illness and stress Measures single point in time High biological variability within patient Blood sample unstable after collection Diurnal variation Diabetes complications not as closely linked to FPG compared with hemoglobin A_{1c} Sample source (capillary, venous, or arterial blood) alters the measurement Assay standardization incomplete
2-hr PG during an OGTT	Highly sensitive to detect risk of developing diabetes Detects early abnormalities in glucose metabolism	Similar disadvantages as FPG test Prolonged patient preparation Risk of hypoglycemia at 4-6 hours in normal persons Poor reproducibility Expensive

2-hr PG = 2-hour prandial glucose; FPG = fasting plasma glucose; OGTT = oral glucose tolerance test.

[a]Blood glucose tests should be used instead of hemoglobin A_{1c} to screen for diabetes in the setting of altered red blood cell turnover.

[b]Some methods used to measure hemoglobin A_{1c} can accurately measure hemoglobin A_{1c} in individuals with hemoglobin variants who are heterozygous for HbS, HbE, HbC, HbD, and increased HbF. For individuals who are homozygous for HbS, HbC, or HbSC, blood glucose should be used instead of hemoglobin A_{1c} for diagnostic purposes. Blacks who are heterozygous for HbS can have a hemoglobin A_{1c} 0.3% lower than individuals without the trait for any level of mean glycemia.

[c]Hemoglobin A_{1c} is higher in blacks compared with non-Hispanic whites in the setting of similar FPG and postprandial glucose values. Despite this, the risk of complications associated with A_{1c} remains similar in blacks and non Hispanic white persons.

[d]There is an association between a lower hemoglobin A_{1c} and hemizygous men and homozygous women with X-linked glucose-6-phosphate dehydrogenase G202A by 0.8% and 0.7%, respectively.

Data from American Diabetes Association. 2. Classification and diagnosis of diabetes: Standards of Medical Care in Diabetes—2018. Diabetes Care. 2018;41:S13-S27. [PMID: 29222373]

Data from American Diabetes Association. 6. Glycemic targets: Standards of Medical Care in Diabetes—2018. Diabetes Care. 2018;41:S55-S64. [PMID: 29222377]

Data from Sacks DB. A1C versus glucose testing: a comparison. Diabetes Care. 2011;34:518-23. [PMID: 21270207]

Data from NGSP. Harmonizing Hemoglobin A1c Testing web site. www.ngsp.org. Accessed June 2018.

Data from National Institute of Diabetes and Digestive and Kidney Diseases. Comparing tests for diabetes and prediabetes. Mar. 2014. NIH Publication No. 14-7850. www.diabetes.niddk.nih.gov. Accessed June 2018.

TABLE 4. Classification of Diabetes Mellitus

Insulin Deficiency[a]
Immune-mediated (type 1A)
Type 1 diabetes
LADA
Rare forms: "stiff man" syndrome, anti-insulin receptor antibodies
Idiopathic (type 1B) (seronegative)
Acquired
Diseases of the exocrine pancreas: pancreatitis, trauma/pancreatectomy, neoplasia, cystic fibrosis, hemochromatosis, fibrocalculous pancreatopathy
Drug-related: Vacor (rat poison), intravenous pentamidine
Infections: congenital rubella, enteroviruses
Insulin Resistance
Type 2 diabetes[b]
Ketosis-prone[c]
Other or Rare Types
Genetic defects in beta-cell function (including six distinct MODY syndromes)
Genetic defects in insulin action
Endocrinopathies:
Acromegaly, Cushing syndrome, glucagonoma, pheochromocytoma, hyperthyroidism[d]
Somatostatinoma, aldosteronoma[d]
Drug-related:
Glucocorticoids, thiazides, β-blockers, diazoxide, tacrolimus, cyclosporine, niacin, HIV protease inhibitors, atypical antipsychotics (clozapine, olanzapine)[e]
Genetic syndromes:
Down syndrome[f]
Wolfram syndrome (DIDMOAD)[g]
Klinefelter, Turner, and Prader-Willi syndromes; myotonic dystrophy[d]

DIDMOAD = diabetes insipidus, diabetes mellitus, optic atrophy, and deafness; LADA = late autoimmune diabetes in adults; MODY = maturity onset diabetes of the young.

[a]Beta-cell destruction usually leading to absolute insulin deficiency.

[b]Insulin resistance with progressive relative insulin deficiency.

[c]More common in nonwhite persons who present with diabetic ketoacidosis but become non-insulin-dependent over time.

[d]Impaired insulin action.

[e]Impaired insulin secretion, impaired insulin action, or altered hepatic glucose metabolism.

[f]Insulin deficiency, immune-mediated.

[g]Insulin deficiency.

Data from American Diabetes Association. 2. Classification and diagnosis of diabetes: Standards of Medical Care—2018. Diabetes Care. 2018;41:S13-S27. [PMID: 29222373]

affected persons remaining asymptomatic for several years. At the time of diagnosis, these patients may already have microvascular and/or macrovascular CVD. Although the beta cell does not produce sufficient insulin to overcome insulin resistance and maintain euglycemia, there is adequate insulin production to suppress lipolysis and prevent DKA in type 2 diabetes. DKA in type 2 diabetes may rarely occur in the setting of extreme stress or illness.

The development of type 2 diabetes in high-risk individuals can be delayed or prevented with modifications to lifestyle (diet, exercise), pharmacologic intervention, or metabolic surgery. The goal of these interventions is weight loss and the reduction of insulin resistance. In the Diabetes Prevention Program (DPP), lifestyle modifications reduced the incidence of type 2 diabetes in persons with prediabetes by 58%. Thus, the ADA recommends the DPP goals of 7% weight loss over 6 months and at least 150 min/week of moderate intensity exercise to reduce the risk of diabetes development. A diet rich in monounsaturated fat, whole grains, vegetables, whole fruits, and nuts is recommended.

Several pharmacologic interventions have demonstrated efficacy in diabetes risk reduction (**Table 6**). Safety data, cost, and long-term durability of each intervention must be considered for each individual patient. Metformin reduced the incidence of diabetes by 31% compared with placebo in the DPP. In addition metformin has long term safety data. The ADA and the American Association of Clinical Endocrinologists (AACE) recommend metformin initially for diabetes risk prevention in individuals with prediabetes, particularly in those with increasing hemoglobin A_{1c} values despite lifestyle modifications who are younger than 60 years of age, are obese, or have a history of gestational diabetes.

KEY POINTS

- According to the Diabetes Prevention Program, lifestyle modifications, including weight loss, healthy diet, and exercise, reduced the incidence of type 2 diabetes in persons with prediabetes by 58%.
- The American Diabetes Association (ADA) and the American Association of Clinical Endocrinologists (AACE) recommend metformin initially for diabetes risk prevention in individuals with prediabetes, particularly in those with increasing hemoglobin A_{1c} values despite lifestyle modifications who are younger than 60 years of age, are obese, or have a history of gestational diabetes.

Ketosis-Prone Diabetes Mellitus

H

The term "ketosis-prone diabetes" (KPD) incorporates several glycemic syndromes also known as ketosis-prone type 2 diabetes, "Flatbush diabetes," type 1B diabetes, or atypical diabetes. These syndromes present with episodic DKA resulting from insulin deficiency but have variable periods of insulin dependence and independence.

For individuals with KPD, insulin therapy for the treatment of DKA is required until DKA has resolved and the beta cells are no longer impaired by glucose toxicity, if possible, and can produce sufficient amounts of insulin to suppress

TABLE 5. Criteria for the Definition of Metabolic Syndrome

Qualifying Criteria	NCEP ATP III 2005 (Meets at Least 3 of 5 Criteria)	International Diabetes Federation (2006) (Required Central Obesity and at Least 2 of 4 Remaining Criteria)
Waist circumference	Men ≥40 in (102 cm) Women ≥35 in (88 cm)	Europids Men ≥37 in (94 cm) Women ≥31 in (80 cm) South Asians Men ≥35 in (90 cm)[a] Women ≥31 in (80 cm) Chinese Men ≥35 in (90 cm)[a] Women ≥31 in (80 cm) Japanese Men ≥35 in (90 cm)[a] Women ≥31 in (80 cm) South/Central Americans Men ≥35 in (90 cm)[a] Women ≥31 in (80 cm) Sub-Saharan Africans Men ≥37 in (94 cm) Women ≥31 in (80 cm) Eastern Mediterranean and Middle East Men ≥37 in (94 cm) Women ≥31 in (80 cm)
Fasting TG	≥150 mg/dL (1.7 mmol/L) or Drug therapy treating increased TG	≥150 mg/dL (1.7 mmol/L) or Drug therapy treating increased TG
HDL cholesterol	Men <40 mg/dL (1.0 mmol/L) Women <50 mg/dL (1.3 mmol/L) or Drug therapy targeting decreased HDL cholesterol	Men <40 mg/dL (1.0 mmol/L) Women <50 mg/dL (1.3 mmol/L) or Drug therapy targeting decreased HDL cholesterol
Blood pressure	Systolic ≥130 mmHg Diastolic ≥85 mmHg or Drug therapy for hypertension	Systolic ≥130 mmHg Diastolic ≥85 mmHg or Drug therapy for hypertension
Fasting glucose	Blood glucose ≥100 mg/dL or Drug therapy for increased glucose	Blood glucose ≥100 mg/dL or Drug therapy for increased glucose

HDL = high-density lipoprotein cholesterol; NCEP ACP III = National Cholesterol Education Program - Adult Treatment Panel III; TG = triglyceride.

[a]Waist circumference is 90 cm (35 inches) according to the International Diabetes Foundation and 88 cm (35 inches) according to the NCEP ATP III.

Data from Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, et al; International Diabetes Federation Task Force on Epidemiology and Prevention. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation. 2009;120:1640-5. [PMID: 19805654]

Data from International Diabetes Federation. The IDF consensus worldwide definition of the metabolic syndrome. 2006. www.idf.org/our-activities/advocacy-awareness/resources-and-tools/60:idfconsensus-worldwide-definitionof-the-metabolic-syndrome.html. Accessed June 2018.

H CONT

lipolysis. Given the variable clinical course exhibited with KPD, uncertainty prevails regarding the need for short-term and long-term insulin treatment regimens. Four classification systems have therefore been developed to provide predictive guidance on the length of insulin therapy. A longitudinal study demonstrated greater accuracy in predicting beta-cell reserve and insulin dependence 12 months after the initial episode of DKA with the Aβ system when compared to the other classification systems, with a sensitivity of 99% and specificity of 96%. With the Aβ system, autoantibody status (A) and

TABLE 6. Strategies to Prevent or Delay Onset of Type 2 Diabetes Mellitus

Intervention	Effectiveness
Diet and exercise[a]	Shown to delay onset of diabetes by up to 10-20 years
Smoking cessation	Modestly effective as long as it does not cause weight gain, but is always recommended
Bariatric surgery	Effective if used in morbidly obese persons (BMI >40)
Metformin[a]	Shown to delay onset of diabetes by up to 10 years
Lipase inhibitors (orlistat)	Shown to delay onset of diabetes up to 4 years
α-Glucosidase inhibitors (acarbose, voglibose)	Shown to delay onset of diabetes up to 3 years
Thiazolidinediones (troglitazone, rosiglitazone, pioglitazone)	Shown to delay onset of diabetes up to 3 years
Glucagon-like peptide 1 (GLP-1) receptor agonists (exenatide, liraglutide)	Significant weight loss and improvements in glycemic control in high-risk persons in short-term studies
Insulin and insulin secretagogues (sulfonylureas, meglitinides)	Ineffective
ACE inhibitors and angiotensin receptor blockers	Ineffective
Estrogen-progestin	Modest effect only

[a]Preferred.

Data from American Diabetes Association. 5. Prevention or delay of type 2 diabetes: Standards of Medical Care in Diabetes—2018. Diabetes Care. 2018;41:S51-S54. [PMID: 29222376]

Data from Garber AJ, Abrahamson MJ, Barzilay JI, Blonde L, Bloomgarden ZT, Bush MA, et al. Consensus statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the comprehensive type 2 diabetes management algorithm—2018 Executive Summary. Endocr Pract. 2018;24:91-120. [PMID: 29368965]

beta-cell function (β) are key determinants affecting whether an individual will require long-term insulin. Longitudinal data from KPD cohorts indicate individuals without beta-cell reserve regardless of the antibody status ($A^{+}\beta^{-}$ and $A^{-}\beta^{-}$) are more likely to have poor glycemic control and develop long-term insulin dependence after the development of DKA compared to individuals with preserved beta-cell function.

Gestational Diabetes Mellitus

An increase in insulin resistance during the second and third trimester of pregnancy is a normal physiologic phenomenon driven by placental hormones. With impaired beta-cell function, insulin production will be inadequate to overcome the insulin resistance with subsequent development of hyperglycemia.

Gestational diabetes is defined as hyperglycemia during the second or third trimester in women without a prepregnancy diagnosis of type 1 or type 2 diabetes. Risk factors include age over 25 years, overweight/obesity, family history of type 2 diabetes, and high-risk racial/ethnic groups (blacks, Hispanic/Latino Americans, South or East Asians, Pacific Islanders, and American Indians). Adverse maternal and neonatal outcomes related to gestational diabetes increase with worsening hyperglycemia. Complications include macrosomia, labor and delivery complications, preeclampsia, fetal defects, neonatal hypoglycemia, spontaneous abortion, and intrauterine fetal demise.

Given the increased prevalence of undiagnosed type 2 diabetes in the general population, the ADA recommends standard screening for any pregnant woman with diabetes risk factors at the initial prenatal visit. Women with hyperglycemia identified during the first trimester are classified as having type 2 diabetes instead of gestational diabetes. For all other pregnant women without a prior diabetes diagnosis, gestational diabetes screening should occur between gestation weeks 24 and 28. The screening method recommended varies among expert groups. The "one-step" OGTT involves blood glucose measurements at baseline (fasting) and 1 and 2 hours after a 75-g oral glucose load. One abnormal value above the cut-point is diagnostic of gestational diabetes. The "two-step" OGTT involves an initial blood glucose measurement 1 hour after a 50-g OGTT. If the blood glucose is abnormal, the second step is initiated. Glucose is measured at baseline (fasting) and 1, 2, and 3 hours after a 100-g oral glucose load. Two abnormal blood glucose values after the 100-g load are diagnostic for gestational diabetes.

Most women with gestational diabetes have glucose normalization after pregnancy, but they are at an increased risk for development of recurrent gestational diabetes and type 2 diabetes. The ADA recommends a 75-g OGTT 4 to 12 weeks postpartum to confirm resolution of hyperglycemia. If the initial postpartum screen is normal, life-long screening should continue every 1 to 3 years with a 75-g OGTT, hemoglobin A_{1c}, or fasting plasma glucose.

Uncommon Types of Diabetes Mellitus

Genetic defects impairing either insulin secretion or insulin action are rare forms of diabetes mellitus (see Table 4). Maturity-onset diabetes of the young (MODY) is characterized as an autosomal dominant monogenetic defect on different chromosomal loci resulting in six subtypes defined by the specific gene affected. Although insulin action remains normal in MODY, glucose sensing and insulin secretion are altered. Autoantibodies are absent. Individuals with MODY present with a clinical course that is frequently atypical of type 1 or type 2 diabetes. The onset of symptoms occurs before 25 years of age, and there is typically a strong family history of atypical diabetes in nonobese patients.

Excess hormone production associated with several endocrinopathies can also impair insulin secretion or insulin action inducing hyperglycemia (see Table 4).

Management of Diabetes Mellitus

Effective diabetes management is best achieved through a patient-centered approach with patients and their caregivers developing individualized goals and treatment plans

compatible with patient preferences, lifestyle requirements, comorbidities, and safety. Management should also incorporate patient education, self-monitoring of blood glucose, lifestyle modifications, and pharmacologic therapies.

KEY POINT

- Effective diabetes management requires a patient-centered approach that individualizes goals and treatment plans, taking into consideration unique characteristics of the patient and patient preferences.

Patient Education

Diabetes self-management education and support (DSMES) provides the knowledge and skills for patients to perform diabetes-related self-care and develop effective problem-solving strategies. The ADA recommends consideration of referral for DSMES at several critical periods in care: at time of diagnosis, annually to reassess needs during care transitions, and when self-management skills are impacted by health status changes. DSMES has been shown to improve outcomes, such as hemoglobin A_{1c} and quality of life, and also reduce costs, as patients are able to reduce utilization of acute care and inpatient facilities for diabetes management.

Self-Monitoring of Blood Glucose

Self-monitoring of blood glucose (SMBG) is recommended for patients on intensive insulin regimens (multiple-dose insulin regimens or insulin pump therapy). Specific regimens for SMBG monitoring are individualized and may include prior to meals, at bedtime, before and after exercise, and before operation of machinery. SMBG may be used to detect and correct hypoglycemia. SMBG may be informative when preprandial blood glucose values are at the target goal, but the hemoglobin A_{1c} is above goal. Measuring postprandial blood glucose levels may identify undetected hyperglycemia.

In motivated patients on nonintensive insulin regimens, SMBG can be considered; however, the optimal testing frequency has not been determined in these patients.

Hemoglobin A_{1c} generally correlates with average 3-month blood glucose level in patients without hemoglobinopathies or increased erythrocyte turnover; therefore, treatment efficacy can be measured by combining SMBG and hemoglobin A_{1c} data (**Table 7** and **Table 8**).

Another option is a continuous glucose monitoring system (CGMS), which can alert the user to retrospective and current trends of hypoglycemia and hyperglycemia. In addition, the FDA has approved a CGMS for real-time insulin dosing as well as monitoring. The goals in using a CGMS are to improve diabetes care by lowering hemoglobin A_{1c} and avoiding hypoglycemia, which is critical for those with hypoglycemic unawareness. The ADA endorses CGMS use in adults (≥18 years of age) with type 1 diabetes who are not meeting glycemic targets. The Endocrine Society endorses the use of CGMS in patients with type 1 diabetes with an elevated hemoglobin A_{1c} or an A_{1c} level at goal when worn daily, since data demonstrate improved glycemic control with longer duration of CGMS use. In the future, CGMS may be indicated for patients with type 2 diabetes on intensive insulin regimens as well.

KEY POINT

- Self-monitoring of blood glucose or a continuous glucose monitoring system is recommended for patients on intensive insulin regimens (multiple-dose insulin regimens or insulin pump therapy).

Recommended Vaccinations and Screening

Persons with diabetes should receive age-appropriate vaccinations as recommended by the Advisory Committee on Immunization Practices guidelines. Additionally, patients with diabetes should receive influenza vaccinations annually, the pneumococcal polysaccharide vaccine (PPVS23), and the series of hepatitis B vaccinations. The CDC's recommended immunization schedule can be reviewed at: https://www.cdc.gov/vaccines/schedules/hcp/imz/adult.html.

Nonpharmacologic Approaches to Diabetes Management

Lifestyle changes are essential for the long-term management of diabetes and prevention of cardiovascular complications. While they should be individualized, diet and physical activity are critical components for patients with type 1 and type 2 diabetes.

Medical nutrition therapy with a registered dietitian provides individualized diabetes-specific education to promote healthy diet choices to achieve glycemic goals and weight management and has also been associated with reductions in hemoglobin A_{1c} in patients with type 1 and type 2 diabetes. The ADA does not recommend a specific diet; however, in overweight and obese patients with type 2 diabetes, a goal of at least 5% weight loss is recommended and has been shown to improve glycemic control.

Physical activity recommendations are the same as those of the DPP program: moderate to vigorous intensity aerobic activity for 150 minutes/week, vigorous-intensity aerobic activity for 75 minutes/week, or a combination of both. This has been shown to reduce hemoglobin A_{1c}, decrease weight, improve a sense of wellbeing, and improve CAD risk factors. Resistance training is recommended two or more times per week. Older adults with diabetes should engage in flexibility and balance training two to three times per week, if possible. Prolonged sedentary behavior should be interrupted at 30-minute intervals with light activity or standing.

Weight loss medications or metabolic surgery are alternative options to consider if medical nutrition therapy and physical activity are unsuccessful (see MKSAP 18 General Internal Medicine). Metabolic surgery should be considered in obese persons with type 2 diabetes. Significant weight loss and improvements in glycemic control, including diabetes remission, can occur postoperatively.

Additional factors to consider and address in patients with diabetes mellitus include anxiety, depression, and

TABLE 7. American Diabetes Association Recommended Outpatient Glycemic Goals for Adults with Diabetes Mellitus

State of Health	Characteristics of Patients	Hemoglobin A_{1c}[a]	Preprandial Capillary Glucose	Postprandial Capillary Glucose (1-2 Hours After Meal)[c]	Bedtime Capillary Glucose
Healthy	Early in disease course Few comorbidities Preconception Patient preference Life expectancy >10 years	<7.0% <6.5% for select patients[b]	80-130 mg/dL (4.4-7.2 mmol/L)	<180 mg/dL[c] (10.0 mmol/L)	
Complex health issues	Significant comorbidities including advanced atherosclerosis or microvascular complications Longer duration of diabetes with difficulty achieving glycemic goals despite appropriate management Frequent hypoglycemia Hypoglycemia unawareness Life expectancy <10 years	<8.0%			
Older adults	Healthy Few comorbidities Extended life expectancy No impairment of cognition or function	<7.5%	90-130 mg/dL (5.0-7.2 mmol/L)		90-150 mg/dL (5.0-8.3 mmol/L)
	Complex/Intermediate Multiple comorbidities Hypoglycemia risk Fall risk Multiple instrumental ADL impairments Mild-to-moderate impairment in cognition	<8.0%	90-150 mg/dL (5.0-8.3 mmol/L)		100-180 mg/dL (5.6-10.0 mmol/L)
	Very complex/poor health Chronic comorbidities with end-stage disease Long-term care placement Moderate-to-severe impairment in cognition Multiple ADL dependencies Limited life expectancy	<8.5%	100-180 mg/dL (5.6-10.0 mmol/L)		110-200 mg/dL (6.1-11.1 mmol/L)
Pregnant women[d]	Preexisting type 1 diabetes, preexisting type 2 diabetes, or gestational diabetes	6.0-6.5% without severe hypoglycemia[e] (<6.0% may be optimal as pregnancy progresses)	Fasting ≤95 mg/dL (5.3 mmol/L)	1-hour postprandial ≤140 mg/dL (7.8 mmol/L) or 2-hour postprandial ≤120 mg/dL (6.7 mmol/L)	

ADL = activities of daily living.

[a]Recommended if goal can be met without severe recurrent hypoglycemia. If severe recurrent hypoglycemia is present, there is no recommended hemoglobin A_{1c} goal, as modification of the patient's diabetes regimen to resolve severe recurrent hypoglycemia should take precedence. When severe recurrent hypoglycemia has resolved, a hemoglobin A_{1c} goal can be chosen, and treatment decisions can again be made based on that individualized goal without frequent hypoglycemia. Hemoglobin A_{1c} should be measured at diagnosis followed by 3-month intervals as changes to lifestyle modifications and/or pharmacologic therapies occur. Hemoglobin A_{1c} measurements can be reduced to every 6 months once glycemic targets are achieved.

[b]This can be considered for patients with an early diagnosis of diabetes mellitus, no significant cardiovascular disease, long life expectancy, or managed with lifestyle modifications or metformin.

[c]When the hemoglobin A_{1c} is not at goal despite meeting preprandial glucose goals, the postprandial glucose values should be targeted. Elevated postprandial glucose values have a greater impact on A_{1c} values near 7%.

[d]Both preprandial and postprandial glucose monitoring are recommended in pregnant women.

[e]Preprandial and postprandial glucose measurements should be the primary evaluation of glycemic control, as hemoglobin A_{1c} values decrease with increased red blood cell turnover associated with pregnancy.

Recommendations from American Diabetes Association. 6. Glycemic targets: Standards of Medical Care in Diabetes—2018. Diabetes Care. 2018;41(Suppl. 1):S55-S64. [PMID: 29222377]

Recommendations from American Diabetes Association. 11. Older adults: Standards of Medical Care in Diabetes—2018. Diabetes Care. 2018;41(Suppl. 1):S119-S125. [PMID: 29222382]

Recommendations from American Diabetes Association. 13. Management of diabetes in pregnancy: Standards of Medical Care in Diabetes—2018. Diabetes Care. 2018;41:S137-S143. [PMID: 29222384]

TABLE 8. Comparison of Hemoglobin A_{1c} Value and Estimated Plasma Glucose Level

Hemoglobin A_{1c}	Estimated Average Plasma Glucose Level	Estimated Average Plasma Glucose Level
(%)	mg/dL (95% CI)	mmol/L (95% CI)
6	126 (100-152)	7.0 (5.5-8.5)
7	154 (123-185)	8.6 (6.8-10.3)
8	183 (147-217)	10.2 (8.1-12.1)
9	212 (170-249)	11.8 (9.4-13.9)
10	240 (193-282)	13.4 (10.7-15.7)
11	269 (217-314)	14.9 (12.0-17.5)
12	298 (240-347)	16.5 (13.3-19.3)

Data from American Diabetes Association. 6. Glycemic targets: Standards of Medical Care in Diabetes—2018. Diabetes Care. 2018;41:S55-S64. [PMID: 29222377]

diabetes-related distress. Screening for psychosocial issues and behavioral health conditions should occur at the time of diabetes diagnosis and periodically. These conditions can adversely affect glycemic control directly and through challenges with patient adherence to management plans.

H Pharmacologic Therapy

Pharmacologic therapy should be individualized taking into consideration a person's age, state of health, weight, the pathophysiology of his/her hyperglycemia, specific risks/benefits of a potential therapeutic agent, medication cost, and the person's lifestyle and personal treatment goals. The hemoglobin A_{1c} goals are generally not stringent in patients with significant comorbid conditions, macrovascular CVD, short life expectancy, long duration of diabetes, limited resources and social support, low health literacy/numeracy, nonadherence, and at high risk for complications from hypoglycemia. Most clinical practice guidelines, including the ADA, recommend target hemoglobin A_{1c} thresholds based on a patient's state of health (see Table 7). In contrast, the VA/DoD guidelines for the management of type 2 diabetes recommend a hemoglobin A_{1c} target range instead of a target threshold. The VA/DoD guidelines attempt to avoid intensification of pharmacologic therapy based solely upon marginal changes in hemoglobin A_{1c} caused by known patient characteristics and laboratory limitations that could potentially cause greater harm than benefit in individuals with major comorbidities, microvascular complications, or advancing age.

The American College of Physicians (ACP) recommends a hemoglobin A_{1c} level between 7% and 8% in most patients with type 2 diabetes, and clinicians should consider deintensifying pharmacologic therapy in patients who achieve hemoglobin A_{1c} levels less than 6.5%. The rationale for these targets is based on evidence that collectively shows treating to targets of less than 7% compared with targets around 8% did not reduce death or macrovascular events over about 5 to 10 years of treatment but did result in substantial harms. More stringent targets may be appropriate for patients who have a long life expectancy (>15 years) and are interested in more intensive glycemic control with pharmacologic therapy despite the risk for harms, including but not limited to hypoglycemia, patient burden, and pharmacologic costs. ACP also recommends avoiding targeting an hemoglobin A_{1c} level in patients with a life expectancy less than 10 years due to advanced age (80 years or older), residence in a nursing home, or chronic medical conditions because the harms outweigh the benefits in this population.

Several landmark studies provide guidance on glycemic goals and CVD risk reduction. Intensive glycemic control compared with standard control significantly reduces the incidence and progression of microvascular complications in patients with type 1 and type 2 diabetes, as demonstrated by the Diabetes Control and Complications Trial (DCCT) and the UK Prospective Diabetes Study (UKPDS). Long-term follow-up demonstrated continued reductions in microvascular complications despite convergence in glycemic control between the study arms. Action to Control Cardiovascular Risk in Diabetes (ACCORD), Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE), and the Veterans Affairs Diabetes Trial (VADT) further reinforced the association of reduced microvascular complications with tight glycemic control, but also highlighted that patients and providers must balance the risks/benefits of a labor-intensive regimen with the potential morbidity and mortality in specific populations.

Long-term follow-up evaluation of participants in the intensive insulin arms of the DCCT and UKPDS trials who were early in the course of diabetes demonstrated a significant reduction in CVD and mortality. In contrast, ACCORD, ADVANCE, and VADT evaluated tight glycemic control in older persons with more advanced type 2 diabetes and preexisting CVD or CVD risk factors. CVD was not significantly reduced in the ACCORD and ADVANCE trials. VADT demonstrated a significant reduction in cardiovascular events, but no change in cardiovascular or overall mortality.

Recently, the EMPA-REG Outcome trial, a randomized controlled trial (RCT), found that in patients with established CVD, empagliflozin, a sodium-glucose cotransporter 2 (SGLT2) inhibitor, reduced the composite outcome (cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke); it was primarily driven by a significant relative risk reduction in rates of cardiovascular death by 38%. There was also a significant reduction in all-cause mortality by 32% and hospitalization for heart failure by 35%. As a result of this trial, empagliflozin received FDA approval for reduction of cardiovascular death in adults with type 2 diabetes and CVD. Another SGLT2 inhibitor, canagliflozin, also demonstrated a reduction in cardiovascular events, but not cardiovascular death, in patients with type 2 diabetes at high risk for cardiovascular disease when compared to placebo in the CANVAS (Canagliflozin Cardiovascular Assessment Study) Program.

The Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) RCT included subjects at risk for CVD and found that liraglutide, a glucagon-like peptide 1 (GLP-1) analogue, significantly reduced the primary composite outcome (cardiovascular death, nonfatal MI, or nonfatal stroke) by 13% compared with placebo (relative risk reduction). Liraglutide also significantly reduced cardiovascular death (22%) and all-cause mortality (15%) relative to placebo. Based on the LEADER data, the FDA approved liraglutide for the reduction of major cardiovascular events and cardiovascular deaths in adults with type 2 diabetes and CVD.

KEY POINT

- Pharmacologic therapy should be individualized taking into consideration a person's age, state of health, weight, the pathophysiology of his/her hyperglycemia, specific risks/benefits of a potential therapeutic agent, medication cost, and the person's lifestyle and personal treatment goals.

Therapy for Type 1 Diabetes Mellitus

Due to destruction of the beta cells and subsequent insulin deficiency, life-long insulin therapy is required for persons with type 1 diabetes mellitus. Ideally, an intensive insulin regimen should be prescribed, which includes multiple daily doses of insulin (MDI) to mimic the physiologic action of the pancreas. The insulin regimen should include basal coverage to maintain glycemic control while fasting and between meals, prandial coverage, and supplemental insulin for correction of hyperglycemia. This can be accomplished with subcutaneous insulin injections, inhaled insulin preparations, or continuous subcutaneous insulin infusions (CSII) with an insulin pump.

Initial total daily insulin dosing ranges from 0.4 to 1.0 U/kg/day in patients with type 1 diabetes. Basal insulin typically encompasses approximately 50% of the total daily dose of insulin, with prandial insulin covering the remaining 50%. The available insulin formulations and their activity profiles are summarized in **Table 9**.

The timing and mode of prandial insulin delivery varies based on patient needs/preferences and dietary habits. MDI prandial dosing can be accomplished with fixed-dosing, carbohydrate counting, or modified carbohydrate counting. In general, 1 unit of insulin covers 10 to 20 grams of carbohydrates consumed. A modified carbohydrate counting method can be used when the grams of carbohydrates consumed can not be accurately counted. With this method, regular or analogue insulin doses can be adjusted by 50% based on the portion of food consumed. For example, the dose for the size of the meal would be as follows: small (50%), regular (100%), large (150%). MDI should also incorporate supplemental insulin to correct hyperglycemia. A common method to calculate the correction dose of insulin is to give an additional 1 unit of regular or analogue insulin at the time of the premeal measurement for every glucose value 50 mg/dL (2.8 mmol/L) above the target glucose value in insulin-sensitive individuals and 1 unit for every 25 mg/dL (1.4 mmol/L) in insulin-resistant individuals. The supplemental insulin can be given with the prandial insulin in one injection. For example, an additional 3 units of insulin would be given with the prandial insulin if the target glucose was 120 mg/dL (6.7 mmol/L) and the current glucose was 270 mg/dL (15.0 mmol/L) in someone with type 1 diabetes.

TABLE 9. Pharmacokinetic Properties of Insulin Products[a]

Insulin Type	Onset	Peak	Duration
Rapid-acting analogues			
Lispro, aspart, glulisine	5-15 min	45-90 min	2-4 h
Inhaled insulin	5-15 min	50 min	2-3 h
Concentrated rapid-acting analogue			
Lispro (200 U/mL)	5-15 min	45-90 min	2-4 h
Short-acting			
Human regular	0.5 h	2-5 h	4-8 h
Intermediate-acting			
NPH insulin	1-3 h	4-10 h	10-18 h
Concentrated human regular			
Human regular U-500 (500 U/mL)	0.5 h	2-5 h	13-24 h
Long-acting basal analogues			
Detemir	1-2 h	None[b]	12-24 h[c]
Glargine	2-3 h	None[b]	20-24+ h
Degludec	1-3 h	None	24-42 h
Concentrated basal analogue (ultra long-acting)			
Glargine (300 U/mL)	6 h	None	24-36 h
Degludec (200 U/mL)	1-3 h	None	24-42 h
Premixed insulins[d]			
70% NPH/30% regular	0.5-1 h	2-10 h	10-18 h
75% NPL/25% lispro	10-20 min	1-6 h	10-18 h
50% NPL/50% lispro	10-20 min	1-6 h	10-18 h
70% NPA/30% aspart	10-20 min	1-6 h	10-18 h
70% degludec/30% aspart	10-30 min	0.5-2 h	24+ h

NPA = neutral protamine aspart; NPH = neutral protamine Hagedorn; NPL = neutral protamine lispro.

[a]The time course of each insulin varies significantly between persons and within the same person on different days. Therefore, the time periods listed should be considered general guidelines only.

[b]Both detemir insulin and glargine insulin can produce a peak effect in some persons, especially at higher doses.

[c]The duration of action for detemir insulin varies depending on the dose given.

[d]Premixed insulins containing a larger proportion of rapid- or short-acting insulin tend to have larger peaks occurring at an earlier time than mixtures containing smaller proportions of rapid- and short-acting insulin.

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Premixed insulin formulations combine intermediate-acting or long-acting basal insulin and rapid-acting or short-acting insulin in fixed concentrations. These formulations are typically administered twice daily and should be considered for those who are unable or unwilling to perform more frequent daily insulin injections. Premixed formulations can increase glycemic excursions, including hypoglycemia, since this is a nonphysiologic regimen.

Inhaled insulin is a rapid-acting formulation for prandial dosing. The availability of inhaled insulin in cartridges with preset doses of insulin (4, 8, and 12 units) limits the flexibility of insulin dosing. Pulmonary function should be assessed at baseline and monitored because lung function may decline with use of inhaled insulin.

CSII provides continuous delivery of basal insulin and uses a bolus calculator programmed to achieve individual glycemic goals to calculate prandial and bolus correction doses. The Endocrine Society recommends CSII over MDI for all adults with type 1 diabetes who have not attained their hemoglobin A_{1c} goal and for those who have attained their A_{1c} goal but have large glycemic variability, severe hypoglycemia, or hypoglycemia unawareness. Additional considerations include a need for flexibility in insulin delivery, early morning hyperglycemia ("dawn phenomenon"), active lifestyle, or patient preference. There are CSII systems that will decrease or stop delivery of insulin if glucose levels fall below a threshold value that is set within the CSII system and will increase delivery if glucose levels are above a threshold value. Insulin delivery will be reinitiated or increased/decreased back to baseline when the threshold is no longer met.

Hypoglycemia and weight gain are risks associated with insulin use. The risk of hypoglycemia is lower with analogue insulin compared with regular insulin due to a shorter duration of action. Hypoglycemia caused by insulin stacking occurs when insulin dosing is too frequent and overlaps with the duration of action of a prior insulin injection. This can be avoided by allowing at least 3 to 4 hours between sequential injections of analogue insulin.

An adjunctive therapy approved for use with insulin in type 1 diabetes is pramlintide, an amylin analogue. Pramlintide can lead to improved glycemic control, decreased insulin doses, and weight loss through delayed gastric emptying, increased satiety, and decreased glucagon secretion. H

KEY POINTS

- Life-long insulin therapy is required for persons with type 1 diabetes mellitus.
- The Endocrine Society recommends continuous subcutaneous insulin infusions over multiple daily doses of insulin for all adults with type 1 diabetes who have not attained their hemoglobin A_{1c} goal and for those who have attained their A_{1c} goal but have large glycemic variability, severe hypoglycemia, or hypoglycemia unawareness.

Therapy for Type 2 Diabetes Mellitus

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As beta cell function declines, pharmacologic therapies must often be combined with lifestyle modifications to obtain glycemic control. Therapeutic options may include monotherapy or a combination of oral agents with injectable agents (**Table 10**).

The ADA recommends initiation of monotherapy if the A_{1c} is less than 8% at the time of diagnosis. Metformin is the recommended first-line oral agent for newly diagnosed type 2 diabetes due to known effectiveness and low hypoglycemia risk. Gastrointestinal side effects of metformin are common and may be reduced by slow titration of doses, administration with food, and/or use of an extended-release formulation. Lactic acidosis is a rare, potential risk associated with metformin use. Heart failure requiring pharmacologic treatment and hepatic dysfunction may increase the risk. An estimated glomerular filtration rate (eGFR) greater than 45 mL/min/1.73 m² is recommended for metformin initiation to avoid potential lactic acidosis with kidney dysfunction. Clinicians should assess benefits and risks of continuing therapy in patients whose eGFR falls below 45 mL/min/1.73 m² during therapy. Metformin is contraindicated at eGFR less than 30 mL/min/1.73 m².

If an iodinated contrast agent is administered with an eGFR between 30 and 60 mL/min/1.73 m², metformin should be held until kidney function is stable for 48 hours. Metformin should also be held in situations that may induce dehydration, such as vomiting or diarrhea. A reduction in vitamin B_{12} intestinal absorption occurs in up to 30% of patients on metformin whereas 5% to 10% develop vitamin B_{12} deficiency. Periodic monitoring may be warranted, particularly in the setting of anemia or peripheral neuropathy.

Glycemic control should be assessed every 3 months with adjustments to therapy until the glycemic target is achieved, and every 6 months if at goal. There are limited data on comparative effectiveness to guide the addition of additional agents when glycemic goals are not met with metformin and lifestyle modifications; thus, many guidelines are based on expert opinion. If the hemoglobin A_{1c} level is 9% or higher at the time of diagnosis or after 3 months of metformin therapy, the ADA recommends advancing to dual therapy defined as metformin combined with another therapeutic agent (see Table 9 and Table 10). For individuals with CVD, therapeutic agents that have been shown to reduce major adverse cardiovascular events (canagliflozin, empagliflozin, and liraglutide) and cardiovascular mortality (empagliflozin and liraglutide) should be considered for dual therapy. AACE/ACE recommends initiation of metformin if the hemoglobin A_{1c} level is less than 7.5% at diagnosis.

Dual therapy should be initiated if the hemoglobin A_{1c} level is 7.5% or higher at diagnosis or after 3 months of monotherapy. The ADA and AACE/ACE both recommend advancement to triple therapy if dual therapy fails to meet glycemic goals after 3 months. Triple therapy should be advanced to combination injectable therapy if glycemic goals are still

TABLE 10. Pharmacologic Agents Used to Lower Blood Glucose Levels in Type 2 Diabetes Mellitus[a,b]

Class	Mechanism of Action	Effect on Weight	Disadvantages	Long-Term Studies on Definitive Outcomes
Insulin	Decreases hepatic glucose production Increases peripheral glucose uptake Suppresses ketogenesis	Increase	Hypoglycemia, weight gain, training required, injectable forms, pulmonary toxicity with inhaled insulin	Decrease in microvascular events (UKPDS)[c,d]
Sulfonylureas (tolbutamide, chlorpropamide, glipizide, glyburide, gliclazide, glimepiride	Stimulates insulin secretion	Increase	Hypoglycemia (especially in drugs with long half-lives or in older populations); weight gain; lacks glucose-lowering durability	Decrease in microvascular events (UKPDS)[c]; possible increase in CVD events
Biguanides (metformin)	Decreases hepatic glucose production Increases insulin-mediated uptake of glucose in muscles	Neutral	Diarrhea and abdominal discomfort, vitamin B_{12} deficiency, lactic acidosis (rare). Contraindicated with progressive liver, kidney, or cardiac failure.	Decrease in CVD events (UKPDS)[d]
α-Glucosidase inhibitors (acarbose, miglitol)	Inhibits polysaccharide absorption	Neutral	Flatulence, abdominal discomfort	Possible decrease in CVD events in prediabetes (STOP-NIDDM)[e]
Thiazolidinediones (rosiglitazone, pioglitazone)	Increases peripheral uptake of glucose	Increase	Fluid retention, heart failure, edema, fractures, possible increased risk of bladder cancer with pioglitazone	Possible decrease in CVD events with pioglitazone (PROactive)[f]
Meglitinides (repaglinide, nateglinide)	Stimulates insulin release	Increase	Hypoglycemia, weight gain, frequent dosing	None
Amylin mimetic (pramlintide)	Slows gastric emptying Suppresses glucagon secretion Increases satiety	Decrease	Nausea, vomiting, exacerbates gastroparesis, increased hypoglycemia risk with concomitant use of insulin, training required, injectable, frequent dosing	None
GLP-1 receptor agonists (exenatide, exenatide extended release, liraglutide, albiglutide, lixisenatide, dulaglutide, semaglutide)	Glucose-dependent increase in insulin secretion Slows gastric emptying Glucose-dependent suppression of glucagon secretion Increases satiety	Decrease	Hypoglycemia when used in combination with sulfonylureas, nausea, vomiting, diarrhea, exacerbates gastroparesis, increased heart rate, possible pancreatitis, animal studies demonstrate C-cell hyperplasia and medullary thyroid tumors, training required, injectable	Decrease in CVD events and mortality in high-risk individuals with type 2 diabetes with liraglutide (LEADER)[g]
DPP-4 inhibitors (sitagliptin, saxagliptin, linagliptin, alogliptin)	Glucose-dependent increase in insulin secretion Glucose-dependent suppression of glucagon secretion	Neutral	Hypoglycemia when used in combination with sulfonylureas, increased risk of infections, possible increased risk of pancreatitis, dermatologic reactions, requires dose adjustments for decreasing kidney function except for linagliptin	Increased heart failure hospitalizations [saxagliptin (SAVOR-TIMI 53)][h]

(Continued on the next page)

TABLE 10. Pharmacologic Agents Used to Lower Blood Glucose Levels in Type 2 Diabetes Mellitus[a,b] *(Continued)*

Class	Mechanism of Action	Effect on Weight	Disadvantages	Long-Term Studies on Definitive Outcomes
SGLT2 inhibitors (canagliflozin, dapagliflozin, empagliflozin, ertugliflozin)	Increases kidney excretion of glucose	Decrease	Hypoglycemia with insulin secretagogues, dehydration/hypotension, acute kidney injury (canagliflozin, dapagliflozin), hypersensitivity reactions, increased candida infections and urinary tract infections, "euglycemic" DKA, possible increase in amputations (canagliflozin), hyperkalemia (canagliflozin), fractures (canagliflozin), bladder cancer (dapagliflozin)	Decrease in CVD events and mortality in high-risk individuals with type 2 diabetes with empagliflozin (EMPA-REG OUTCOME)[i] Decreases incident or worsening nephropathy in high CVD risk individuals with type 2 diabetes (EMPA-REG OUTCOME)[i] Decrease in CVD events in high-risk individuals with type 2 diabetes with canagliflozin (CANVAS Program)[j]
Bile acid sequestrants (colesevelam)	Incompletely understood: Possible decrease in hepatic glucose production Possible increase in incretin levels	Neutral	Constipation, dyspepsia, increased triglycerides, possible interference with absorption of other medications	None
Dopamine 2 agonists (bromocriptine quick release)	Increases insulin sensitivity Alters metabolism via hypothalamus	Neutral	Nausea, orthostasis, fatigue	Possible decrease in CVD events (Cycloset Safety Trial)[k]

CVD = cardiovascular disease; DKA = diabetic ketoacidosis; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; SGLT2 = sodium-glucose cotransporter-2.

[a]Data from American Diabetes Association. 8. Pharmacologic approaches to glycemic treatment: Standards of Medical Care in Diabetes—2018. Diabetes Care. 2018;41(Suppl. 1):S73-S85. [PMID: 29222379]

[b]Recommendations from Garber AJ, Abrahamson MJ, Barzilay JI, Blonde L, Bloomgarden ZT, Bush MA, et al; American Association of Clinical Endocrinologists (AACE). Consensus Statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the Comprehensive Type 2 Diabetes Management Algorithm—2018 Executive Summary. Endocr Pract. 2018;24:91-120. [PMID: 29368965]

[c]Data from Intensive blood-glucose control with sulfonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. Lancet. 1998;352:837-53. [PMID: 9742976]

[d]Data from Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group. Lancet. 1998;352:854-65. [PMID: 9742977]

[e]Data from Chiasson JL, Josse RG, Gomis R, Hanefeld M, Karasik A, Laakso M; STOP-NIDDM Trial Research Group. Acarbose treatment and the risk of cardiovascular disease and hypertension in patients with impaired glucose tolerance: the STOP-NIDDM trial. JAMA. 2003;290:486-94. [PMID: 12876091]

[f]Data from Dormandy JA, Charbonnel B, Eckland DJ, Erdmann E, Massi-Benedetti M, Moules IK, et al; PROactive Investigators. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. Lancet. 2005;366:1279-89. [PMID: 16214598]

[g]Data from Marso SP, Daniels GH, Brown-Frandsen K, Kristensen P, Mann JF, Nauck MA, et al; LEADER Steering Committee. Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2016;375:311-22. [PMID: 27295427]

[h]Data from Scirica BM, Bhatt DL, Braunwald E, Steg PG, Davidson J, Hirshberg B, et al; SAVOR-TIMI 53 Steering Committee and Investigators. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. N Engl J Med. 2013;369:1317-26. [PMID: 23992601]

[i]Data from Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, et al; EMPA-REG OUTCOME investigators. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med. 2015;373:2117-28. [PMID: 26378978]

[j]Data from Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N, et al; CANVAS Program Collaborative Group. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med. 2017;377:644-657. [PMID: 28605608]

[k]Data from Gaziano JM, Cincotta AH, O'Connor CM, Ezrokhi M, Rutty D, Ma ZJ, et al. Randomized clinical trial of quick-release bromocriptine among patients with type 2 diabetes on overall safety and cardiovascular outcomes. Diabetes Care. 2010;33:1503-8. [PMID: 20332352]

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unmet. This includes continued metformin and initiation of a GLP-1 receptor agonist or basal insulin if not already prescribed, initiation of basal insulin on background GLP-1 receptor agonist therapy, or initiation of a GLP-1 receptor agonist or prandial insulin on optimized background basal insulin.

Algorithms from the ADA and AACE/ACE provide guidance on initiation and dosing of basal and prandial insulin regimens (**Table 11**). The ADA recommends combination injectable therapy initially in the setting of symptomatic hyperglycemia (polydipsia, polyuria), hemoglobin A_{1c} 10% or higher, or a glucose level of 300 mg/dL (16.6 mmol/L) or higher.

AACE/ACE recommends initiating insulin therapy with other agents if the initial hemoglobin A_{1c} is more than 9% in a

TABLE 11. Comparison of Insulin Dosing Algorithms from the ADA and AACE/ACE

Insulin Initiation or Modification	ADA	AACE/ACE
Basal insulin	Starting dose: 10 U/d or 0.1-0.2 U/kg/d	Starting dose: If A_{1c} <8%: 0.1-0.2 U/kg/d If A_{1c} >8%: 0.2-0.3 U/kg/d
Basal insulin dose titration	For hyperglycemia: Increase dose 1-2 times/week until glycemic goal met Increase dose by: 10%-15% or 2-4 U For hypoglycemia: Decrease dose by: 10%-20% or 4 U	For hyperglycemia: Increase dose every 2-3 days until glycemic goal met Increase dose by: 2 U or 20% if FBG >180 mg/dL (10 mmol/L) 10% if FBG 140-180 mg/dL (7.8-9.9 mmol/L) 1 U if FBG is 110-139 mg/dL (6.1-7.7 mmol/L) For hypoglycemia: Decrease dose by: 10%-20% if FBG <70 mg/dL (3/9 mmol/L) 20%-40% if FBG <40 mg/dL (2.2 mmol/L)
Prandial insulin plus basal insulin (1 meal)	Initiate prandial insulin at largest meal Starting dose: 4 U, 10% of basal dose, or 0.1 U/kg To avoid hypoglycemia, consider decreasing basal dose by same amount if A_{1c} <8%.	Initiate prandial insulin at largest meal Starting dose: 5 U or 10% of basal dose
Basal-bolus insulin regimen (≥2 or more meals)	Prandial insulin starting dose: 4 U, 10% of basal dose, or 0.1 U/kg/meal To avoid hypoglycemia, consider decreasing basal dose by same amount if A_{1c} <8%.	Prandial insulin starting dose: 0.3-0.5 U/kg = TDD 50% of TDD = basal insulin 50% of TDD = prandial insulin Each meal-time dose = 1/3 prandial insulin dose
Prandial insulin dose titration	For hyperglycemia: Increase dose 1-2 days/week until glycemic goal met Increase dose by: 10%-15% or 1-2 U If hyperglycemia persists at other meals, add additional meal-time insulin doses (basal-bolus) For hypoglycemia: Decrease dose by: 10%-20% or 2-4 U	For hyperglycemia: Increase dose every 2-3 days until glycemic goal met Increase dose by: 10% or 1-2 U if BG >140 mg/dL (7.8 mmol/L) 2 hours after meal or at next meal. If hyperglycemia persists at other meals, add additional meal-time insulin doses (basal-bolus). For hypoglycemia: Decrease TDD dose (basal and/or prandial) by: 10%-20% if BG <70 mg/dL (3.9 mmol/L) 20%-40% if BG <40 mg/dL (2.2 mmol/L)
Premixed insulin 2× daily	Starting dose: Current basal dose given at breakfast and dinner distributed as 2/3 AM and 1/3 PM or 1/2 AM and 1/2 PM	
Premixed analog insulin 3× daily	Add additional insulin dose at lunch	
Premixed insulin dose titration	For hyperglycemia: Increase dose 1-2 days/week until glycemic goal met Increase dose by: 10%-15% or 1-2 U For hypoglycemia: Decrease dose by: 10%-20% or 2-4 U	

ADA = American Diabetes Association; AACE = American Association of Clinical Endocrinologists; ACE = American College of Endocrinology; BG = blood glucose; FBG = fasting blood glucose; TDD = total daily dose.

Data from American Diabetes Association. 8. Pharmacologic approaches to glycemic treatment: Standards of Medical Care in Diabetes—2018. Diabetes Care. 2018;40(Suppl. 1): S73-S85. [PMID: 2922379]

Data from Garber AJ, Abrahamson MJ, Barzilay JI, Blonde L, Bloomgarden ZT, Bush MA, et al; American Association of Clinical Endocrinologists (AACE). Consensus statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the comprehensive type 2 diabetes management algorithm—2018 Executive Summary. Endocr Pract. 2018;24:91-120. [PMID: 29368965]

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symptomatic individual. After optimizing the basal insulin dose, prandial insulin should be added prior to the largest meal if hyperglycemia persists. A basal-bolus insulin regimen, with prandial insulin prior to two or more meals, should be employed for continued hyperglycemia.

Ultralong-acting basal analogue insulins may be advantageous compared with long-acting basal analogue insulins due to a prolonged action profile (>24 hours), peakless insulin delivery, and decreased variability in action between and within individuals. The pharmacodynamic profile may decrease hypoglycemia in high-risk patients, improve glycemic fluctuations, and allow for flexibility in dosing beyond 24-hour time periods.

In patients with type 2 diabetes not at glycemic goal despite adherence to glucose monitoring and multiple treatment modalities, CSII may be considered. H

KEY POINTS

- Metformin is the recommended first-line oral agent for newly diagnosed type 2 diabetes due to known effectiveness and low hypoglycemia risk.
- Glycemic control should be assessed every 3 months with subsequent adjustments to therapeutic agents until the glycemic target is achieved, and every 6 months if at goal.

Therapy for Gestational Diabetes Mellitus

Pharmacologic therapy should be prescribed for patients with gestational diabetes to improve perinatal outcomes if lifestyle interventions do not achieve glycemic targets. Insulin is the recommended therapy. While metformin or sulfonylurea therapy may be considered, both therapies cross the placenta, and there is no long-term safety data for their use during pregnancy. Additionally, sulfonylurea therapy has been associated with higher rates of neonatal macrosomia and hypoglycemia.

Drug-Induced Hyperglycemia

Several drugs can induce hyperglycemia through multiple mechanisms: increased hepatic glucose production, impaired insulin action, or decreased insulin secretion (**Table 12**). Whereas hyperglycemia with temporary drug therapies may resolve after discontinuation, many of these drugs are used indefinitely for chronic medical conditions. Persons at risk for hyperglycemia and the development of diabetes due to medications should be monitored periodically.

H Inpatient Management of Hyperglycemia

Tight inpatient glycemic control (80-110 mg/dL [4.4-6.1 mmol/L]) is not consistently associated with improved outcomes and may increase mortality. As a result, current inpatient glycemic goals strive to avoid complications from severe hypoglycemia and hyperglycemia, such as electrolyte abnormalities and dehydration.

Modifications to diet are necessary with consistent values above 140 mg/dL (7.8 mmol/L). If hyperglycemia persists, therapy should be initiated. Clinical status changes may increase the risk of adverse events associated with noninsulin therapies. Insulin is therefore preferred for inpatient management of hyperglycemia 180 mg/dL (10.0 mmol/L) and higher and adjusted to maintain a glucose level between 140 and 180 mg/dL (7.8-10.0 mmol/L) for most patients. Glucose values less than 140 mg/dL (7.8 mmol/L) may be reasonable in select noncritically ill patients if hypoglycemia is avoided, according to the ADA and AACE. In contrast, the American College of Physicians (ACP) does not recommend glucose values less than 140 mg/dL (7.8 mmol/L) due to increased hypoglycemia risk. Several factors may lead to inpatient hypoglycemia: altered mental status, fasting (expected or unexpected), illness, insulin-meal timing mismatch, poor oral intake, and alterations in hyperglycemia-inducing therapies. H

KEY POINT

- Tight inpatient glycemic control (80-110 mg/dL [4.4-6.1 mmol/L]) is not consistently associated with improved outcomes and may increase mortality. HVC

H Hospitalized Patients with Diabetes Mellitus

In critically ill patients with type 1 and type 2 diabetes mellitus, intravenous insulin therapy is recommended. Intravenous insulin dose adjustments should be based on a validated algorithm that incorporates point-of-care (POC) monitoring every 1 to 2 hours.

For noncritically ill patients, subcutaneous insulin is appropriate. Persons with type 1 diabetes require continuous insulin therapy. Basal insulin must be provided to avoid development of DKA. Persons with type 2 diabetes with glucose values 180 mg/dL (10.0 mmol/L) or higher should also receive insulin therapy.

If the patient is eating, the ideal insulin regimen is a basal-bolus regimen with prandial coverage and correction boluses for premeal hyperglycemia. POC measurements and prandial insulin injections should occur prior to meal consumption. Postprandial insulin administration may be appropriate to allow for dose reduction with decreased oral intake for some persons or those with delayed gastric emptying. Overnight POC measurements are warranted if there are concerns for undetected hypoglycemia; otherwise glucose checks overnight should be avoided due to sleep disruption and increased risk of insulin stacking. The sole use of correction insulin ("sliding-scale insulin") is not recommended since it is a reactive, nonphysiologic approach that leads to large glucose fluctuations.

Continuation of outpatient CSII therapy may be appropriate for those patients with normal mental status who can

TABLE 12. Drug-Induced Hyperglycemia

Drug Category	Drug	Mechanism of Hyperglycemia
Glucocorticoid	All systemic glucocorticoids	Decreased insulin production Increased peripheral insulin resistance Increased hepatic glucose production
Immunosuppressants	Calcineurin inhibitors Sirolimus Tacrolimus Cyclosporine	Decreased insulin production and release
Antiretrovirals	Protease inhibitors	Increased peripheral insulin resistance
	NRTIs	Pancreatic damage through drug-induced pancreatitis (didanosine)
Cardiovascular medications	Niacin	Increased hepatic glucose production
	Statins	Impaired pancreatic beta-cell function Increased peripheral resistance
	β-blockers Atenolol Metoprolol Propranolol	Decreased insulin release Increased peripheral insulin resistance Carvedilol (α-blocking) has a neutral effect on glucose
	Thiazides Hydrochlorothiazide Chlorthalidone Chlorothiazide Indapamide	Decreased insulin secretion secondary to hypokalemia Increased insulin resistance
	Vasopressors Epinephrine Norepinephrine	Decreased insulin secretion Increased glycogenolysis Increased hepatic glucose production Stimulation of glucagon and cortisol
Hormonal medications	Oral contraceptives Combined estrogen-progestin Progestin only	Abnormal hepatic glucose metabolism Increased peripheral insulin resistance Decreased risk of hyperglycemia with low-dose pills containing ≤35 μg ethinyl estradiol
	Progestin Megestrol acetate	Increased peripheral insulin resistance
	Growth hormone	Increased peripheral insulin resistance
Atypical antipsychotics (second generation)	Clozapine Olanzapine Ziprasidone Quetiapine Risperidone Iloperidone Paliperidone	Unclear Possible increased peripheral insulin resistance
Antibiotics	Moxifloxacin Gatifloxacin	Altered insulin secretion

NRTI = nucleoside reverse transcriptase inhibitors.

Data from Fathallah N, Slim R, Larif S, Hmouda H, Ben Salem C. Drug-induced hyperglycaemia and diabetes. Drug Saf. 2015;38:1153-68. [PMID: 26370106]

Data from Thomas Z, Bandali F, McCowen K, Malhotra A. Drug-induced endocrine disorders in the intensive care unit. Crit Care Med. 2010;38:S219-30. [PMID: 20502175]

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manage the device under the supervision of health care providers proficient in this technology. If a hospitalized patient becomes unable to safely manage CSII therapy, it should be discontinued and replaced with either a subcutaneous insulin regimen or intravenous insulin.

Continuation of outpatient oral or noninsulin injectable agents is not recommended when patients are admitted due to potential hemodynamic and/or nutritional changes that may occur. Insulin therapy should be initiated for glycemic management. As a patient nears hospital discharge with stability in nutritional status and hemodynamics, reinitiation of these agents may be considered if organ function has returned to baseline. H

KEY POINTS

- Critically ill patients with type 1 and type 2 diabetes mellitus require intravenous insulin therapy with dosing based on a validated algorithm incorporating point-of-care monitoring every 1 to 2 hours.
- Noncritically ill persons with type 1 diabetes require basal insulin in addition to prandial insulin therapy; persons with type 2 diabetes with glucose values 180 mg/dL (10.0 mmol/L) or higher should also receive insulin therapy.
- HVC The sole use of correction insulin ("sliding scale insulin") is not recommended since it is a reactive, nonphysiologic approach that leads to large glucose fluctuations.

H

Hospitalized Patients Without Diabetes Mellitus

Stress associated with acute illness, enteral/parenteral nutrition, and hyperglycemia-inducing medications in the inpatient setting may induce glucose abnormalities in persons without diabetes.

Hyperglycemia management should follow the same guidelines as hospitalized patients with diabetes.

It is important to recognize that inpatient hyperglycemia may occur in the setting of previously unrecognized diabetes. An inpatient hemoglobin A_{1c} measurement of 6.5% or higher is indicative of glucose abnormalities prior to the hospitalization, and these patients require discharge planning for management of newly diagnosed diabetes.

Acute Complications of Diabetes Mellitus

Diabetic Ketoacidosis/Hyperglycemic Hyperosmolar Syndrome

Diabetic ketoacidosis (DKA) and hyperglycemic hyperosmolar syndrome (HHS) occur with extreme hyperglycemia and must be treated early and aggressively to avoid life-threatening consequences from dehydration and electrolyte abnormalities. Severe hyperglycemia is a consequence of insufficient insulin levels coupled with an increase in counterregulatory hormones. This impairs efficient glucose utilization and subsequently drives glycogenolysis and gluconeogenesis for fuel production.

DKA typically occurs in individuals with type 1 diabetes younger than 65 years of age. It is a relative or absolute insulin deficiency state resulting in unsuppressed lipolysis. Fatty acid oxidation occurs with subsequent ketone body production and development of metabolic acidosis. HHS typically occurs in individuals with type 2 diabetes who are older than 65 years of age. It is associated with a higher mortality rate compared with DKA. It is characterized as a partial insulin deficiency that is able to suppress lipolysis and prevent ketone body production, but unable to correct hyperglycemia or prevent the subsequent dehydration and electrolyte abnormalities. Younger patients with type 1 diabetes have a higher glomerular filtration rate, which allows a higher level of glucosuria compared with those with type 2 diabetes. As a result, HHS is associated with more extreme hyperglycemia compared to DKA (**Figure 1**).

Inciting factors for the development of DKA or HHS include infection, myocardial infarction, accidental or deliberate nonadherence to diabetes therapy, stress, trauma, and confounding medications (atypical antipsychotics, glucocorticoids, and SGLT2 inhibitors). DKA or HHS may be the initial presentation of a person with undiagnosed diabetes.

DKA and HHS may present with a multitude of symptoms and plasma glucose levels that can be normal to very high. Symptoms from DKA typically occur within 24 hours of onset, whereas symptoms from HHS may not appear for several days. DKA and HHS symptoms may include abdominal pain, nausea, polyuria, polydipsia, vomiting, weight loss, or shortness of breath. Extreme glucosuria causes an osmotic diuresis and severe volume depletion, which may be exacerbated by gastrointestinal losses of volume and electrolytes. The condition may progress to lethargy, obtundation, and death if the hyperglycemia, dehydration, and electrolyte abnormalities are not treated aggressively and early.

Initial evaluation includes the measurement of serum glucose levels, serum electrolytes, serum ketones, blood urea nitrogen and serum creatinine, plasma osmolality, complete blood count, arterial blood gases, urinalysis, and urine ketones. An electrocardiogram should also be reviewed. Cultures (blood, sputum, urine) and a chest radiograph may be obtained if an infection is suspected after a history is gathered and examination performed.

Multiple laboratory abnormalities are present with DKA and HHS. An increased anion gap metabolic acidosis is present in DKA secondary to production of acetoacetic acid and β-hydroxybutyrate. Although some patients with HHS may have an increased anion gap, typically with glucose levels above 400 to 600 mg/dL (22.2-33.3 mmol/L), they do not develop significant ketoacidosis as seen in DKA.

A moderate to severe reduction in serum bicarbonate levels is present in DKA, but levels may remain normal or mildly reduced (>20 mEq/L [20 mmol/L]) in HHS. Serum pH is typically

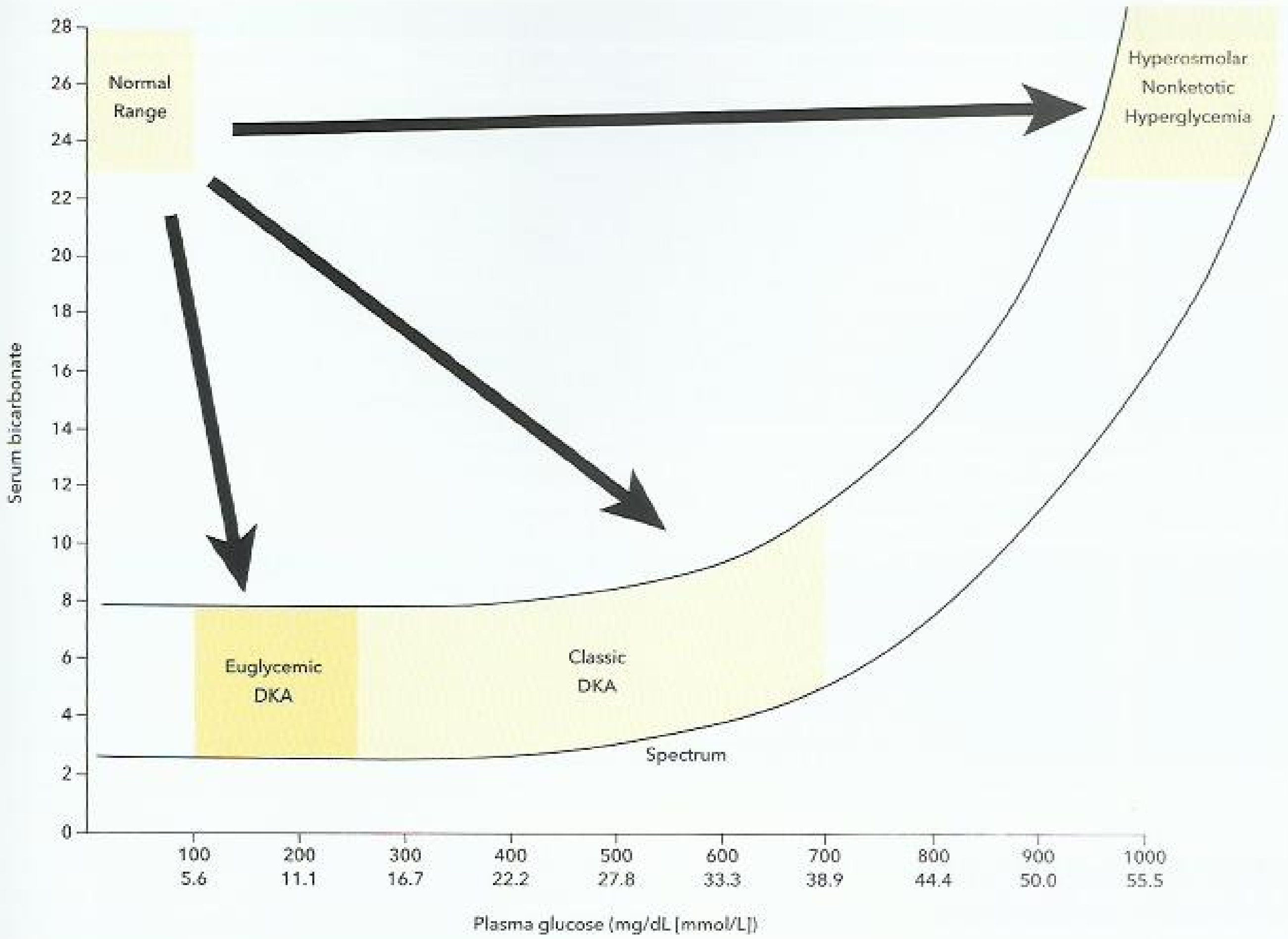

FIGURE 1. Spectrum of metabolic decompensation that occurs in diabetic ketoacidosis. DKA = diabetic ketoacidosis.

greater than 7.3 in HHS. Pseudohyponatremia may occur in DKA and HHS with extreme hyperglycemia and osmotic shifts of water from intracellular to extracellular compartments. A normal or elevated sodium level indicates severe dehydration. Increased osmolality, frequently greater than 320 mOsm/kg H_2O, is often present in HHS secondary to more severe hyperglycemia and water loss from osmotic diuresis compared with type 1 diabetes. Serum potassium levels may be elevated due to shifts from the intracellular to extracellular spaces due to ketoacidosis and the absence of sufficient insulin. Normal or low serum potassium levels indicate a depletion of body stores and require supplementation prior to insulin therapy to avoid cardiac arrhythmias. Stress may induce mild leukocytosis, but higher levels may indicate an infectious cause for DKA or HHS.

A multi-pronged approach is required to treat DKA and HHS (**Table 13**). Intravenous hydration is necessary for volume repletion. Electrolyte deficits, such as potassium, should be repleted. Hyperglycemia should be corrected preferably with intravenous insulin with hourly glucose measurements to guide dose adjustments. Frequent electrolyte measurements are necessary to guide repletion as hydration and insulin therapy continues. Most patients with DKA or HHS are managed in the ICU due to the high complexity of care required. Other conditions that contributed to the development of DKA or HHS, such as infection, should be treated.

KEY POINTS

- Diabetic ketoacidosis and hyperglycemic hyperosmolar syndrome occur with extreme hyperglycemia and must be treated early and aggressively to avoid life-threatening consequences from dehydration and electrolyte abnormalities.
- Inciting factors for the development of diabetic ketoacidosis and hyperglycemic hyperosmolar syndrome include infection, myocardial infarction, accidental or deliberate nonadherence to diabetes therapy, stress, trauma, and confounding medications (SGLT2 inhibitors, atypical antipsychotics, and glucocorticoids).
- Treatment of diabetic ketoacidosis and hyperglycemic hyperosmolar syndrome requires correction of hyperglycemia, intravenous hydration, electrolyte repletion, and treatment of suspected infections.

TABLE 13. Management of Hyperglycemic Crisis: Diabetic Ketoacidosis and Hyperglycemic Hyperosmolar Syndrome

Fluids	Insulin (Regular)	Potassium	Correction of Acidosis
Assess for volume status, then give 0.9% saline IV at 1 L/h initially in all patients, and continue if patient is severely hypovolemic. Switch to 0.45% normal saline at 250-500 mL/h if corrected serum sodium level becomes normal or high. When the plasma glucose level reaches 200 mg/dL (11.1 mmol/L) in patients with DKA or 300 mg/dL (16.7 mmol/L) in HHS in the setting of continued IV insulin, switch to 5% dextrose with 0.45% normal saline at 150-250 mL/h to maintain the blood glucose and avoid hypoglycemia.	Give regular insulin, 0.1 U/kg, as an IV bolus followed by 0.1 U/kg/h as an IV infusion. If the plasma glucose level does not decrease by 10% in the first hour, give an additional bolus of 0.14 U/kg and resume previous infusion rate. When the plasma glucose level reaches 200 mg/dL (11.1 mmol/L) in DKA and 300 mg/dL (16.7 mmol/L) in HHS, reduce to 0.02-0.05 U/kg/h, and maintain the plasma glucose level between 150-200 mg/dL (8.3-11.1 mmol/L) until anion gap acidosis is resolved in DKA. The plasma glucose should be maintained between 250-300 mg/dL in HHS until the patient is alert and the hyperosmolar state resolves.	Assess for adequate kidney function, with adequate urine output (approximately 50 mL/h). If serum potassium is <3.3 mEq/L (3.3 mmol/L), do not start insulin but instead give IV potassium chloride, 20-30 mEq/h, through a central line catheter until the serum potassium level is >3.3 mEq/L (3.3 mmol/L). Then add 20-30 mEq of potassium chloride to each liter of IV fluids to keep the serum potassium level in the 4.0-5.0 mEq/L (4.0-5.0 mmol/L) range. If the serum potassium level is >5.2 mEq/L (5.2 mmol/L), do not give potassium chloride, but instead start insulin and IV fluids, and check the serum potassium level every 2 hours.	If pH is <6.9, consider sodium bicarbonate, 100 mmol in 400 mL of water, and potassium chloride, 20 mEq, infused over 2 hours. If pH is 6.9 or greater, do not give sodium bicarbonate.

DKA = diabetic ketoacidosis; HHS = hyperglycemic hyperosmolar syndrome; IV = intravenous.

Recommendations from Kitabchi AE, Umpierrez GE, Miles JM, Fisher JN. Hyperglycemic crises in adult patients with diabetes. Diabetes Care. 2009;32:1335-43. [PMID: 19564476]

Chronic Complications of Diabetes Mellitus

H Cardiovascular Morbidity

A major cause of morbidity and mortality in persons with diabetes mellitus is cardiovascular disease (CVD). Diabetes is an independent risk factor for CVD. Other significant risk factors for CVD include hypertension, dyslipidemia, tobacco use, family history, and albuminuria. Simultaneous management of CVD risk factors is recommended to decrease morbidity and mortality. Screening interval guidelines for risk factors are listed in **Table 14**.

Hypertension contributes to the development of macrovascular and microvascular complications. The American Diabetes Association (ADA) defines hypertension as sustained blood pressures 140/90 mm Hg or higher. Citing concerns for increased treatment complications with a lower blood pressure target below 130/80 mm Hg, the ADA treatment goal for most persons is below 140/90 mm Hg. Those persons at high risk for CVD may aim for lower blood pressure targets if this can be achieved safely. In contrast, guidelines from the American Association of Clinical Endocrinologists/American College of Endocrinology (AACE/ACE) and the American College of Cardiology/American Heart Association (ACC/AHA) and nine other organizations advocate for a treatment target below 130/80 mm Hg for most patients with diabetes. ADA recommended treatment strategies include lifestyle modifications (for blood pressure >120/80 mm Hg) and pharmacologic therapies (for blood pressure >140/90 mm Hg). Initial recommended antihypertensive regimens include ACE inhibitors, angiotensin receptor blockers (ARBs), dihydropyridine calcium channel blockers, and thiazide diuretics. Multiple agents are frequently required to reach the blood pressure target. Underlying comorbidities should guide selection of therapeutic agents, such as the use of an ACE inhibitor or ARB in the presence of microalbuminuria.

Lipid management in diabetes frequently requires a combination of lifestyle modifications and pharmacologic agents. The ACC/AHA risk calculator can determine the 10-year atherosclerotic cardiovascular disease (ASCVD) risk to guide therapeutic management. Statin therapy is the recommended initial pharmacologic treatment for all qualifying persons with diabetes (see MKSAP 18 General Internal Medicine).

Antiplatelet therapy with aspirin (75-162 mg/day) is recommended by the ADA for secondary prevention in those persons with diabetes and ASCVD. Aspirin therapy for primary prevention of ASCVD in persons with type 1 and type 2 diabetes may not provide universal benefit, so aspirin therapy (75-162 mg/day) may be considered in persons 50 years of age and older with at least one additional ASCVD risk factor. The ADA does not recommend aspirin therapy for persons younger than 50 years of age at low risk for ASCVD. H

TABLE 14. Screening Recommendations for Chronic Complications of Diabetes Mellitus

Chronic Complication	Clinical Situation	When to Start Screening	Screening Frequency	Preferred Screening Test
Retinopathy	Type 1 diabetes	At 5 years after diagnosis	Annually[a]	Dilated and comprehensive eye examination[b]
	Type 2 diabetes	At diagnosis	Annually[a]	Dilated and comprehensive eye examination[b]
	In pregnant women with either type of diabetes	First trimester	Every trimester and then closely for 1 year postpartum	Dilated and comprehensive eye examination[b]
	In women with either type of diabetes planning to conceive	During preconception planning	Same as recommendations for pregnant women once conception occurs	Dilated and comprehensive eye examination[b]
Nephropathy	Type 1 diabetes	At 5 years after diagnosis	Annually[c]	Albumin-creatinine ratio on random spot urine, eGFR
	Type 2 diabetes	At diagnosis	Annually[c]	Albumin-creatinine ratio on random spot urine, eGFR
Neuropathy (distal symmetric polyneuropathy)[d]	Type 1 diabetes	At 5 years after diagnosis	Annually	Skin assessment, evaluate for foot deformities, lower extremity pulse assessment, neurologic assessment (10-g monofilament plus 128-Hz tuning fork, ankle reflexes, pinprick, or temperature)
	Type 2 diabetes	At diagnosis	Annually	Skin assessment, evaluate for foot deformities, lower extremity pulse assessment, neurologic assessment (10-g monofilament plus 128-Hz tuning fork, ankle reflexes, pinprick, or temperature)
Cardiovascular disease	Hypertension	At diagnosis	Every visit	Blood pressure measurement
	Dyslipidemia	At diagnosis and prior to initiating statin therapy	Annually[e]	Lipid profile

eGFR = estimated glomerular filtration rate.

[a]It is reasonable to screen every 1 to 2 years if no diabetic retinopathy is present and to screen more often than annually if diabetic retinopathy is advanced or progressing rapidly.

[b]Retinal photography is a possible alternative means of screening for diabetic retinopathy that may improve access to care and reduce costs. Retinal photography, when interpreted by eye care specialists, can detect most clinically significant diabetic retinopathy.

[c]The American Diabetes Association guidelines state that it is reasonable to assess progression of disease and response to therapeutic interventions with continued monitoring of urinary albumin-creatinine excretion.

[d]Although diabetes commonly causes peripheral neuropathy, other differential diagnoses to consider during the screening process include vitamin B_{12} deficiency, alcoholism, hypothyroidism, renal disease, malignancy and chemotherapies, vasculitis, and inherited neuropathies.

[e]Annual or periodic screening to monitor therapeutic response after initiation of statin therapy. May screen every 5 years if not on statin therapy.

Recommendations from American Diabetes Association. 9. Cardiovascular disease and risk management: Standards of Medical Care in Diabetes—2018. Diabetes Care. 2018;41(Suppl. 1):S86-S104. [PMID: 29222380]

Recommendations from American Diabetes Association. 10. Microvascular complications and foot care: Standards of Medical Care in Diabetes—2018. Diabetes Care. 2018; 41 (Suppl. 1):S105-S118. [PMID: 29222381]

Recommendations from Garber AJ, Abrahamson MJ, Barzilay JI, Blonde L, Bloomgarden ZT, Bush MA, et al; American Association of Clinical Endocrinologists (AACE). Consensus Statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the comprehensive type 2 diabetes management algorithm—2018 executive summary. Endocr Pract. 2018;24:91-120. [PMID: 29368965]

KEY POINTS

- The American Diabetes Association (ADA) recommends a blood pressure treatment goal below 140/90 mm Hg or lower for persons at high risk for CVD if this can be achieved safely; the American Association of Clinical Endocrinologists/American College of Endocrinology (AACE/ACE) and the American College of Cardiology/American Heart Association (ACC/AHA) and nine other organizations recommend a target below 130/80 mm Hg for most patients with diabetes.

(Continued)

KEY POINTS *(continued)*

- Lipid management in diabetes frequently requires a combination of lifestyle modifications and pharmacologic agents; statin therapy is the recommended initial pharmacologic treatment for all qualifying persons with diabetes.
- The American Diabetes Association (ADA) does not recommend aspirin therapy for persons younger than 50 years of age at low risk for atherosclerotic cardiovascular disease. **HVC**

Diabetic Retinopathy

Retinopathy is the leading cause of preventable blindness among persons with diabetes between 20 and 74 years of age in developed countries. Risk factors for retinopathy include duration of diabetes, degree of hyperglycemia, hypertension, albuminuria, and dyslipidemia.

Diabetic retinopathy changes are classified as nonproliferative (occurs within the retina) or proliferative (occurs in the vitreous or retinal inner surface). Nonproliferative retinopathy findings may include microaneurysms, dot and blot hemorrhages, hard exudates (lipid deposition), soft exudates or cotton-wool spots (ischemic superficial nerve fibers), venous bleeding, and intraretinal microvascular abnormalities. Neovascularization due to chronic ischemia characterizes proliferative retinopathy, which may cause intraocular hemorrhage, retinal detachment, and vision loss.

Macular edema may occur with nonproliferative and proliferative retinopathy.

Screening guidelines were developed for early detection of asymptomatic abnormalities to allow for treatment interventions to prevent vision loss (see Table 14).

Optimal control of blood pressure, glucose, and lipid parameters can prevent and delay the progression of retinopathy. Panretinal laser photocoagulation can treat high-risk proliferative diabetic retinopathy and severe nonproliferative retinopathy. In addition, intravitreal injections with anti-vascular endothelial growth factor (anti-VEGF) to reduce vision loss associated with proliferative retinopathy is not inferior to panretinal laser photocoagulation. Retinopathy may develop or accelerate during pregnancy or with rapid glycemic improvements, and may require laser photocoagulation to decrease the risk of vision loss. Macular edema is preferentially treated with anti-VEGF intravitreal injections to improve vision loss. Anti-VEGF injections require monthly injections for at least 12 months followed by intermittent injections to prevent recurrent macular edema.

KEY POINTS

- Patients with type 2 diabetes should have an eye examination at the time of diagnosis.
- Optimal control of glucose, blood pressure, and lipid parameters can prevent and delay the progression of retinopathy.
- Panretinal laser photocoagulation or intravitreal injections of anti-vascular endothelial growth factor can treat high-risk proliferative diabetic retinopathy and severe nonproliferative retinopathy.

H Diabetic Nephropathy

Diabetic nephropathy is the leading cause of end-stage kidney disease (ESKD). Diabetes is typically present for 5 to 10 years prior to the development of nephropathy. Individuals with a first-degree relative with ESKD due to diabetic nephropathy have increased risk of progressing to ESKD themselves.

Measurement of estimated glomerular filtration rate (eGFR) and screening for the presence of microalbuminuria is recommended for early detection of kidney disease (see Table 14). Urinary albumin excretion can be determined from a random urine collection as an albumin-creatinine ratio (UACR). An elevated UACR level (≥30 mg/g creatinine) should be confirmed by multiple measurements over 3 to 6 months due to possible temporary elevations from biological variability, illness, hyperglycemia, heart failure, hypertension, exercise, and menstruation. Annual measurements of eGFR and UACR may identify progression of nephropathy and guide therapeutic decisions. More frequent assessments may be necessary with worsening kidney function. An eGFR less than 30 mL/min/1.73 m^2 warrants a referral to a nephrologist.

Uncontrolled hyperglycemia and hypertension are risk factors for diabetic nephropathy; thus treatment to attain glucose and blood pressure goals is recommended. The ADA recommends an ACE inhibitor or an angiotensin receptor blocker (ARB) as first-line therapy to slow progression of nephropathy and prevent CVD in nonpregnant persons with diabetes, hypertension, a reduced eGFR (<60 mL/min/1.73 m^2), and an elevated UACR (≥300 mg/g creatinine). An ACE inhibitor or an ARB is also recommended for treatment of an elevated UACR between 30 and 299 mg/g creatinine in nonpregnant persons with hypertension. Treatment with an ACE inhibitor or ARB is not recommended for patients with diabetes who have a normal blood pressure, a UACR level less than 30 mg/g creatinine, and an eGFR level greater than 60 mL/min/1.73 m^2. H

KEY POINTS

- Measurement of estimated glomerular filtration rate and screening for the presence of microalbuminuria are recommended for early detection of kidney disease.
- The American Diabetes Association recommends an ACE inhibitor or an angiotensin receptor blocker as first-line therapy to slow progression of nephropathy and prevent cardiovascular disease in nonpregnant persons with diabetes, hypertension, a reduced estimated glomerular filtration rate (<60 mL/min/1.73 m^2), and an elevated urine albumin-creatinine ratio (≥300 mg/g creatinine).
- Treatment with an ACE inhibitor or angiotensin receptor blocker is not recommended for patients with diabetes who have a normal blood pressure, a urine albumin-to-creatinine ratio level less than 30 mg/g creatinine, and an estimated glomerular filtration rate level greater than 60 mL/min/1.73 m^2. HV

Diabetic Neuropathy

Diabetic neuropathy involves damage to nerves or nerve roots due to hyperglycemia. Symptoms are dependent on the affected nerve(s) and may be focal or diffuse in nature. Neuropathy may occur peripherally and/or affect the autonomic nervous system. Glycemic control may prevent peripheral neuropathy and cardiac autonomic neuropathy in individuals with type 1 diabetes and can delay progression of neuropathy in type 2 diabetes.

Diabetic peripheral neuropathy (distal symmetric polyneuropathy) typically has an ascending presentation with a "stocking and glove" distribution. It may involve damage to both small and large nerve fibers. Symptoms from small nerve fiber damage include pain, burning, and tingling. Small nerve fiber abnormalities can be detected on examination by assessment of pinprick and temperature sensations. Abnormalities in position sense, vibration, and light touch are indicative of large nerve fiber damage and convey an increased risk for foot ulcerations. Assessment of large nerve fiber damage can be achieved by assessing ankle reflexes and with a 128-Hz tuning fork and a 10-g monofilament. Since diabetic peripheral neuropathy may be asymptomatic, screening should occur for early detection to prevent limb loss (see Table 14).

Autonomic neuropathy may affect one or multiple organs with symptoms varying based on the affected organ. Symptoms may include hypoglycemia unawareness, gastroparesis, constipation, diarrhea, erectile dysfunction, and bladder dysfunction. Symptoms from cardiac autonomic dysfunction may include orthostatic hypotension, resting sinus tachycardia, and exercise intolerance. Cardiac autonomic neuropathy is an independent risk factor for sudden death.

The goal of treatment of diabetic neuropathy is symptom control. Two FDA-approved medications, pregabalin or duloxetine, are recommended as initial therapy. Other agents may provide symptom relief but are not FDA approved and include tricyclic antidepressants, venlafaxine, carbamazepine, capsaicin, and gabapentin. The primary treatment of orthostatic hypotension is nonpharmacologic and includes diet, use of compression stockings, and changing positions slowly. Medications that cause or worsen the orthostatic changes should be discontinued and other agents (fludrocortisone, midodrine, or droxidopa) added for refractory symptoms. Small and frequent low-fat, low-fiber meals may improve symptoms of gastroparesis. Metoclopramide is the only prokinetic agent approved by the FDA for the treatment of gastroparesis. Given the risk of side effects, including dystonia, careful assessment of risks and benefits should be undertaken before prescribing (see MKSAP 18 Gastroenterology and Hepatology).

Diabetic amyotrophy is a rare condition affecting the lumbosacral plexus that may occur secondary to infarction or immune vasculopathy. Presentation is acute and associated with severe asymmetric pain or proximal weakness in a leg with associated muscle wasting. Partial remission may occur over many months. Treatment is supportive.

Mononeuropathies and nerve compression syndromes (carpal tunnel syndrome, peroneal palsy) can occur in patients with diabetes. Mononeuropathies frequently resolve without intervention within a few months. Compression syndromes may respond to conservative management, or surgery may be necessary for symptom relief. H

KEY POINTS

- Diabetic peripheral neuropathy (distal symmetric polyneuropathy) presents with a "stocking and glove" distribution, involving damage to both small and large nerve fibers; symptoms include pain, burning, and tingling.
- Glycemic control can delay progression of neuropathy in type 2 diabetes.

Diabetic Foot Ulcers

Significant morbidity and mortality are associated with lower extremity ulcers and amputations (see MKSAP 18 Infectious Disease). Lower extremities should be inspected at every visit and a comprehensive foot examination, including 10-g monofilament testing, should be performed at least annually. Risk factors for ulcer include: hyperglycemia, peripheral artery disease, history of foot ulcer or amputation, foot deformity, peripheral neuropathy, impaired vision, tobacco use, and diabetic nephropathy. Vascular assessment should occur in persons with absent pedal pulses or symptoms concerning for claudication. Foot care specialists should be involved in the care of high-risk individuals. Patients should be educated on the importance of daily foot inspections and properly fitting footwear.

Hypoglycemia

Hypoglycemia is defined as a glucose value less than 70 mg/dL (3.9 mmol/L). Glucose values less than 54 mg/dL (3.0 mmol/L) are serious and clinically significant. Severe hypoglycemia is any glucose value at which a person requires external assistance to correct the glucose.

Hyperadrenergic symptoms (sweating, tremors, anxiety, tachycardia) are the normal physiologic response to the development of hypoglycemia. Counterregulatory hormones (glucagon, epinephrine, norepinephrine, cortisol, and growth hormone) are subsequently released by the body to correct hypoglycemia. Neuroglycopenic signs (altered mental status, dysarthria, confusion) are associated with severe hypoglycemia. Obtundation, seizures, and death may occur if severe hypoglycemia is not corrected rapidly.

Hypoglycemia in Patients with Diabetes Mellitus

Hypoglycemia can become a rate-limiting step in achieving glycemic goals for many persons. Severe recurrent hypoglycemia is

H CONT.

associated with acquired cognitive deficits and can lead to dementia. Therapies must be adjusted to eliminate hypoglycemia, and glycemic goals should be individualized to accommodate targets that can be safely achieved.

Several factors contribute to hypoglycemia including a mismatch of food consumption and insulin delivery, increased physical exertion, weight loss, worsening kidney impairment, abnormalities in gastrointestinal motility and absorption, and accidental/intentional overdose of insulin. Older adults are also at an increased risk for hypoglycemia.

Hypoglycemia can also occur with the use of oral antidiabetic agents due to incorrect dosages, drug-drug interactions, and intercurrent illnesses that alter the metabolism or excretion of drugs.

Hypoglycemia treatment in an alert person includes consumption of 15 to 20 grams of a fast-acting carbohydrate followed by a self-monitored blood glucose (SMBG) measurement 15 to 20 minutes later. If the glucose has not improved, repeat treatment with 15 grams of carbohydrates should occur. After glucose normalization (>70 mg/dL [3.9 mmol/L]), a meal or snack should be consumed to avoid recurrent hypoglycemia. Glucagon should be provided to those persons at risk for developing clinically significant hypoglycemia (<54 mg/dL [3.0 mmol/L]) and used intramuscularly by close contacts if the person is not able to safely consume carbohydrates to correct hypoglycemia.

Relative hypoglycemia characterizes symptoms of hypoglycemia in the setting of plasma glucose values greater than 70 mg/dL (3.9 mmol/L). This may occur with a large, rapid decrease in glucose or rapid normalization of glucose with treatment intensification in an individual with prolonged plasma glucose values above 200 mg/dL (11.1 mmol/L). Relative hypoglycemia can be prevented by avoiding large glycemic excursions and by slow correction of long-standing hyperglycemia to goal to allow a longer adjustment period. H

KEY POINTS

- Hypoglycemia is defined as a glucose value less than 70 mg/dL (3.9 mmol/L) and serious hypoglycemia as less than 54 mg/dL (3.0 mmol/L).
- Initial treatment of hypoglycemia requires oral consumption of carbohydrates or administration of glucagon with a goal of increasing the glucose to greater than 70 mg/dL (3.9 mmol/L).
- Relative hypoglycemia can be prevented by avoiding large glycemic excursions and by slow correction of long-standing hyperglycemia to goal to allow a longer adjustment period.

H Hypoglycemia in Patients Without Diabetes Mellitus

Hypoglycemia without concomitant diabetes is uncommon and warrants further assessment. A hypoglycemia evaluation should commence if the criteria for Whipple triad are met: neuroglycopenic symptoms, hypoglycemia at or below 55 mg/dL (3.1 mmol/L), and resolution of symptoms with glucose ingestion. Laboratory measurement of glucose must confirm true hypoglycemia, as point-of-contact (POC) glucose values are not reliable in this scenario. Hypoglycemia in persons without diabetes may be attributable to the following causes: drugs, alcohol, illness, organ dysfunction (kidney or liver), hormonal deficiencies (adrenal insufficiency), malnutrition, and pancreatogenous insulinoma or noninsulinoma (endogenous hyperinsulinemic hypoglycemia that is not caused by an insulinoma).

Although there may be overlap in presentation, hypoglycemia typically occurs in the fasting or in the postprandial state. Diagnostic blood and urine studies should be obtained during a hypoglycemic episode in which Whipple triad has been demonstrated. If a spontaneous episode is not witnessed, measures should be implemented to recreate circumstances that normally induce hypoglycemia (fasting or ingestion of a typical meal that causes an episode in that particular patient). Imaging studies for tumor localization should only occur after confirmation of endogenous hyperinsulinism from the diagnostic blood and urine studies. H

KEY POINT

- Imaging studies for tumor localization should only occur after confirmation of endogenous hyperinsulinism from the diagnostic blood and urine studies. HVC

H Fasting Hypoglycemia

A prolonged fast, up to 72 hours, should be initiated if the hypoglycemia typically occurs while fasting.

Five blood specimens are drawn simultaneously every 6 hours: glucose, C-peptide, insulin, proinsulin, β-hydroxybutyrate. Insulin antibodies and an oral hypoglycemic agent screen should also be measured at the beginning of the fast. Blood specimen collection should increase to every 1 to 2 hours when the glucose measurement is less than 60 mg/dL (3.3 mmol/L).

Testing is complete when one of the following parameters is met: plasma glucose 45 mg/dL (2.5 mmol/L) or below with neuroglycopenia, or plasma glucose less than 55 mg/dL (3.1 mmol/L) if Whipple triad was documented previously. POC glucose values and hyperadrenergic symptoms should not be used to determine the end of the fast. Blood specimens should be collected again at the end of the 72-hour time period if neither of the above criteria has been met.

The interpretation of the diagnostic testing results is found in **Table 15**. To decrease the cost of this procedure, the plasma glucose should be sent to the laboratory as soon as possible, and if it is less than 60 mg/dL (3.3 mmol/L), the other four blood samples should be sent. H

TABLE 15. Differential Diagnosis of Spontaneous Fasting Hypoglycemia[a] in a Person Without Diabetes Mellitus

Diagnosis	Serum Insulin	Plasma C-Peptide[b]	Plasma Proinsulin[b]	Serum β-hydroxybutyrate[c]	Serum Insulin Antibodies	Urine or Blood Metabolites of Sulfonylureas or Meglitinides
Insulinoma[d,e]	↑	↑	↑	↓	Negative	Negative
Surreptitious use of sulfonylureas or meglitinides	↑	↑	↑	↓	Negative	Positive
Surreptitious use of insulin	↑	↓	↓	↓	Negative	Negative
Insulin autoimmune hypoglycemia	↑	↑	↑	↓	Positive	Negative
IGF-II[f]	↓	↓	↓	↓	Negative	Negative

[a]Symptomatic hypoglycemia, fasting plasma glucose 55 mg/dL (3.1 mmol/L) or lower, and prompt symptomatic relief with correction of hypoglycemia (Whipple triad).

[b]C-peptide and proinsulin are indicative of endogenous insulin production.

[c]β-hydroxybutyrate will be suppressed in the presence of insulin, but elevated with hypoglycemia that is not mediated by insulin.

[d]Blood specimens should be collected at the end of testing and glucagon should be administered followed by serial glucose measurements over 30 minutes. Insulin suppresses glycogenolysis and preserves glycogen stores. In the setting of an insulinoma, glucose will increase in response to glucagon as the glycogen stores are utilized.

[e]Similar results can also be seen with non-insulinoma pancreatogenous hypoglycemia syndrome or post-gastric bypass hypoglycemia.

[f]Insulin-like growth factor (IGF)-II or its precursors may be produced by tumors and induce hypoglycemia by stimulating the insulin receptors with subsequent increases in glucose use.

Data from Cryer PE, Axelrod L, Grossman AB, Heller SR, Montori VM, Seaquist ER, et al; Endocrine Society. Evaluation and management of adult hypoglycemic disorders: an Endocrine Society Clinical Practice Guideline. Clin Endocrinol Metab. 2009;94:709-28. [PMID: 19088155]

KEY POINT

HVC

- For fasting hypoglycemia, five blood specimens are drawn simultaneously every 6 hours: glucose, C-peptide, insulin, proinsulin, β-hydroxybutyrate; to decrease the cost of this procedure, the plasma glucose should be sent to the laboratory as soon as possible, and if it is less than 60 mg/dL (3.3 mmol/L), the other four blood samples should be sent.

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Postprandial Hypoglycemia

Postprandial hypoglycemia typically occurs within 5 hours of the last meal. Altered gastrointestinal anatomy, as occurs after Roux-en-Y gastric bypass surgery, is frequently the cause of the postprandial hypoglycemia. Meals consisting of simple carbohydrates (pancakes, syrup, juice) are frequently the culprit. A mixed-meal test consisting of the types of food that normally induce the hypoglycemia should be performed to determine the cause. Baseline laboratory studies including glucose, C-peptide, insulin, and proinsulin should be obtained prior to meal consumption. These tests should be repeated every 30 minutes for 5 hours. If neuroglycopenia occurs, the tests should be repeated prior to administration of carbohydrates. To decrease the cost of this procedure, the plasma glucose should be sent to the laboratory as soon as possible, and if it is less than 60 mg/dL (3.3 mmol/L), the other three blood samples should be sent.

Screening should also occur for insulin antibodies and oral hypoglycemic agents if symptomatic hypoglycemia occurs. Interpretation of the results is similar to those obtained during fasting hypoglycemia (see Table 15).

Treatment generally consists of small frequent mixed meals with a balance of protein, fat, and carbohydrates. H

KEY POINT

- For postprandial hypoglycemia, baseline laboratory studies including glucose, C-peptide, insulin, and proinsulin should be obtained prior to meal consumption; to decrease the cost of this procedure, the plasma glucose should be sent to the laboratory as soon as possible, and if it is less than 60 mg/dL (3.3 mmol/L), the other three blood samples should be sent. HVC

Hypoglycemia Unawareness

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Hypoglycemia unawareness is characterized by insufficient release of counterregulatory hormones and an inadequate autonomic response to hypoglycemia. Prior episodes of hypoglycemia increase the risk of developing hypoglycemia unawareness. Treatment involves relaxation of glycemic targets and modifications of hypoglycemia-inducing diabetes therapies to avoid continued hypoglycemia. Avoidance of hypoglycemia for several weeks may reverse hypoglycemia unawareness in some persons and result in the return of adrenergic symptoms with glucose levels less than 70 mg/dL (3.9 mmol/L). A continuous glucose monitoring system may be beneficial in appropriate individuals to provide early detection of impending severe hypoglycemia for early intervention. H

Disorders of the Pituitary Gland

Hypothalamic and Pituitary Anatomy and Physiology

The pituitary gland is located in the sella turcica posterior to the sphenoid sinus. The optic chiasm is located superior to the pituitary gland, and the carotid arteries are lateral (**Figure 2**). The gland is composed of the anterior pituitary (adenohypophysis), which is glandular tissue, and the posterior pituitary gland (neurohypophysis), which arises from neural tissue. A rich portal vascular network connects the hypothalamus to the anterior pituitary, whereas the posterior pituitary gland consists of nerve endings projected from neurons in the supraoptic and paraventricular nuclei in the hypothalamus. Both the portal network and hypothalamic neurons travel from the hypothalamus to the pituitary through the pituitary stalk. The carotid arteries provide blood to the pituitary through the hypophysial arteries, and venous drainage occurs by means of the petrosal sinuses to the jugular vein.

Stimulatory and inhibitory hormones, secreted into the portal blood by the hypothalamus, regulate the anterior pituitary, and the posterior pituitary hormones are synthesized in the hypothalamic nuclei and travel through neurons to be released by the posterior pituitary gland.

The anterior pituitary secretes six pituitary hormones: luteinizing hormone (LH), follicle-stimulating hormone (FSH), adrenocorticotrophic hormone (ACTH), prolactin, thyroid-stimulating hormone (TSH), and growth hormone (GH). Gonadotropin-releasing hormone (GnRH) is released from the hypothalamus in pulses, which in turn control the release of LH and FSH. LH and FSH regulate male and female reproduction including stimulation of the gonads to produce testosterone and estrogen, as well as stimulation of ovarian follicles and spermatogenesis (see Reproductive Disorders). Corticotropin-releasing hormone (CRH), produced in the hypothalamus, stimulates the production of ACTH in the pituitary, which then stimulates cortisol production from the adrenal glands. Prolactin is synthesized in the lactotroph cells. Its synthesis and secretion is suppressed by hypothalamic dopamine, which traverses the pituitary stalk through the portal circulation. TSH is released in response to stimulation from thyrotropin-releasing hormone (TRH) produced in the hypothalamus. TSH binds to receptors on the thyroid, resulting in synthesis and secretion of thyroid hormone. GH release is regulated by two hypothalamic hormones, growth hormone-releasing hormone (GHRH), which stimulates GH release, and somatostatin, which inhibits GH release.

The posterior pituitary gland secretes oxytocin, necessary for parturition and lactation, and antidiuretic hormone (ADH), which maintains water balance.

Table 16 lists the pituitary hormones and the initial evaluation for suspected pituitary excess or deficiency of each hormone.

Pituitary Abnormalities

Incidentally Noted Pituitary Masses

When a pituitary lesion is discovered incidentally on imaging obtained for an unrelated reason, the lesion is termed a "pituitary incidentaloma." Small incidentally noted pituitary lesions are quite common. In patients undergoing MRI for nonpituitary reasons, microadenomas are found in 10% to 38%, whereas incidental macroadenomas are seen in 0.2%. Most pituitary incidentalomas are benign nonfunctional pituitary adenomas; however, a small percentage may be Rathke cleft cysts, craniopharyngiomas, or meningiomas. In patients with a history of malignancy, metastatic disease should be considered. Pituitary adenomas measuring 1 cm or larger are

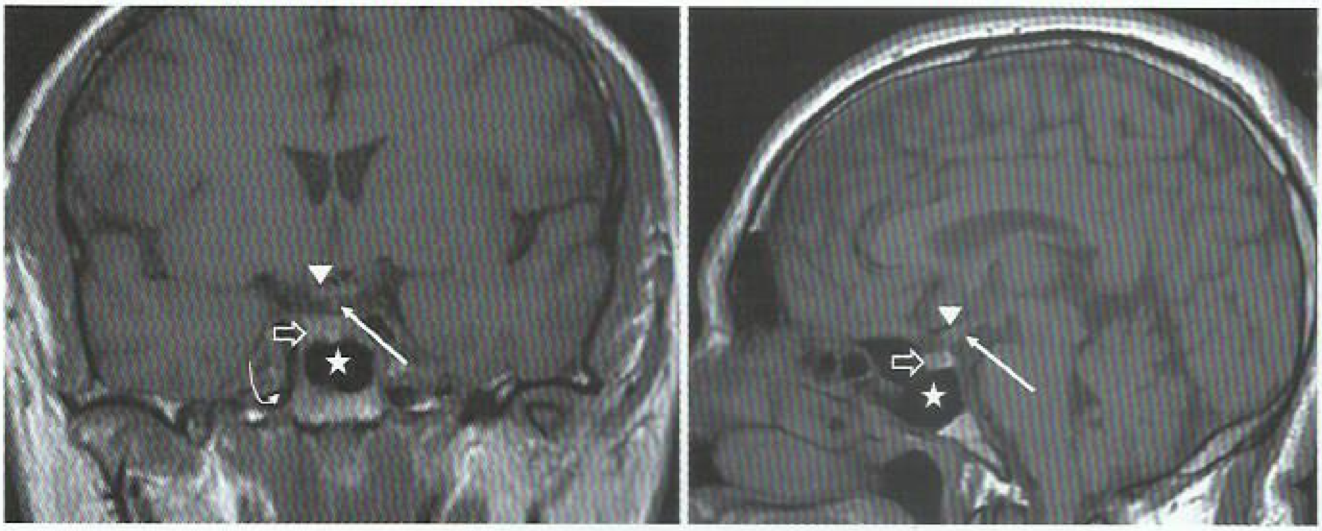

FIGURE 2. A coronal MRI (*left*) and sagittal MRI (*right*) showing the pituitary gland (*open arrow*), pituitary stalk (*thin arrow*), optic chiasm (*arrowhead*), sphenoid sinus (*star*), and carotid artery (*curved arrow*).

TABLE 16. Initial Testing for Pituitary Hormone Deficiency and Excess

		Pituitary Hormone Excess	
Pituitary Hormone	**Peripheral Hormone**	**Initial Test(s)**	
ACTH	Cortisol	24-Hour urine free cortisol (×2) OR nocturnal salivary cortisol (×2) OR overnight low-dose dexamethasone test	
ADH	ADH	Simultaneous serum sodium, serum osmolality, urine sodium, and urine osmolality	
GH	IGF-1	IGF-1	
TSH	Thyroxine, triiodothyronine	TSH, free (or total) thyroxine	
PRL	Prolactin	Serum prolactin	
		Pituitary Hormone Deficiency	
Pituitary Hormone	**Peripheral Hormone**	**Initial Test(s)**	**Confirmatory Test[a]**
ACTH	Cortisol	Simultaneous ACTH, cortisol	ACTH stimulation test
ADH	ADH	Simultaneous serum sodium, urine and serum osmolality	Water deprivation test
LH and FSH[b]	Testosterone or estradiol	Simultaneous LH, FSH, total testosterone (male), estradiol (female)	
TSH	Thyroxine, triiodothyronine	Simultaneous TSH, free (or total) thyroxine	
GH	IGF-1	IGF-1	GHRH-arginine test Insulin-tolerance test

ACTH = adrenocorticotropic hormone; ADH = antidiuretic hormone; FSH = follicle-stimulating hormone; GH = growth hormone; GHRH = growth hormone-releasing hormone; IGF-1 = insulin-like growth factor 1; LH = luteinizing hormone; PRL = prolactin; TSH = thyroid-stimulating hormone.

[a]See Table 18 for additional information on confirmatory testing for pituitary dysfunction.

[b]Routine testing for deficiency is not recommended without specific signs of deficiency, such as amenorrhea, gynecomastia, or impotence.

macroadenomas; those measuring less than 1 cm are microadenomas (see Evaluation of Pituitary Tumors).

KEY POINT

- Most incidentally noted pituitary masses are benign nonfunctional pituitary adenomas; however, a small percentage may be Rathke cleft cysts, craniopharyngiomas, or meningiomas.

Empty Sella

Empty sella is also typically an incidental finding on imaging done for a nonpituitary-related reason. It is a radiologic finding, rather than a medical condition. This term is used when the sella turcica is enlarged and not entirely filled with pituitary tissue. No gland may be visualized, or it is inordinately small. Primary empty sella is the result of herniation of subarachnoid space into the sella, compressing the normal pituitary gland. Primary empty sella is caused by incompetence of the sellar diaphragm, increased intracranial pressure, or volumetric changes in the pituitary gland (as can occur in pregnancy, particularly in multiparous women). Secondary empty sella can be related to infarction of a pituitary tumor or other causes including infection, autoimmune disease, trauma, or radiotherapy.

Patients with an empty sella usually have normal pituitary function because there is gland present, but it is lining the enlarged sella, like the rind of an orange. All patients with empty sella should have clinical assessment for signs and symptoms of pituitary deficiencies. Hyperprolactinemia, the most common pituitary abnormality in empty sella, can be treated with dopamine agonist therapy when needed. Asymptomatic patients should be screened with 8 AM cortisol level measurement, as well as TSH and free T_4 measurement. Additional testing should be targeted to the pituitary axes if there are signs or symptoms of deficiency.

Patients with no initial abnormalities are unlikely to develop hormonal or radiologic changes. Because of the theoretical risk of progression, however, it is recommended that asymptomatic patients with empty sella have repeat endocrine, radiologic, and ophthalmologic evaluation in 24 to 36 months. If no progression, further evaluation can be limited to those who require it clinically.

KEY POINT

- Empty sella is diagnosed when the sella turcica is enlarged and not entirely filled with pituitary tissue; all patients with empty sella should have clinical assessment for signs and symptoms of pituitary deficiencies.

Other Abnormalities

The pituitary gland can also be affected by other pathologic processes, such as autoimmune disease, infection, infiltrative diseases, metastatic disease, or infarction (**Table 17**).

Drug-Induced Abnormalities

There are a number of drugs that can affect pituitary gland function. Any hormone administered exogenously provides negative feedback to the normal cells in the pituitary gland. Exogenous estrogen or testosterone will suppress the gonadotropins, LH and FSH, whereas excess exogenous thyroid hormone will suppress TSH. Likewise, physiologic and supraphysiologic doses of glucocorticoids will suppress ACTH. Opiates have a number of effects. Most notably, chronic opioid use suppresses gonadotroph function, resulting in hypogonadotropic hypogonadism, and is increasingly recognized as a cause of ACTH deficiency.

A relatively new class of drugs, checkpoint-blocking antibodies, has been associated with pituitary abnormalities related to hypophysitis. These drugs, including nivolumab, ipilimumab, tremelimumab, and pembrolizumab, are used to treat metastatic melanoma, renal cell carcinoma, non-small cell lung cancer, and head and neck cancers. Hypophysitis occurs in 0.5% to 5% of patients and often presents with headache and fatigue. Endocrine evaluation usually reveals secondary adrenal insufficiency (ACTH deficiency) and secondary hypothyroidism (TSH deficiency), as well as low levels of LH, GH, and prolactin. Imaging demonstrates enhancement and/or enlargement of the pituitary gland with thickening of the pituitary stalk. Diabetes insipidus is uncommon. Treatment includes replacement of the hormone deficiencies along with high-dose glucocorticoids to treat the inflammatory process. Despite resolution of the inflammation, hormone deficiencies often persist.

Mass Effects of Pituitary Tumors

Mass effects of pituitary tumors most commonly include compression of the pituitary gland resulting in hormone deficiencies or compression of the optic chiasm most commonly resulting in bitemporal hemianopsia; other patterns of visual loss can also occur. Stalk compression can lead to hyperprolactinemia. Headaches can be a symptom of pituitary tumors but do not correlate well with tumor size. Headache alone is not an indication for surgery.

Pituitary deficiencies related to compression of the gland can vary from an isolated hormone deficiency, most often gonadotropin deficiency, to panhypopituitarism (deficiency of all anterior pituitary hormones).

Similarly, pituitary tumors can have variable effects on compression of surrounding structures. A rapidly growing

TABLE 17. Other Pituitary Abnormalities

Pathology	Cause	Mass Effect	Hormone Abnormalities	Clinical Context
Inflammation				
Lymphocytic hypophysitis	Autoimmune	Possible	Most common is ACTH deficiency	Pregnancy, postpartum
Malignancy				
Pituitary metastasis	Metastasis of malignant tumor to pituitary gland	Optic nerve dysfunction occurs in 24% Can also have cranial nerve palsies and headache	Diabetes insipidus most common Also can have anterior pituitary deficits	Patients with the following primary malignancies: breast (most common), lung, lymphoma, renal cell
Pituitary carcinoma (rare) 0.1% of all pituitary tumors	Malignant pituitary tumor	Often present initially as macroadenoma	Most often there is some pituitary hypersecretion rather than deficiency	Patients found to have pituitary adenoma with significant cavernous sinus invasion or suprasellar extension
Infiltrative				
Sarcoidosis	Pituitary infiltration	Possible	Combination of anterior and posterior pituitary abnormalities	Occurs in up to 10% of patients with sarcoidosis
Hemochromatosis	Iron deposition	No	Gonadotropin deficiency	*HFE* gene mutation
Langerhans cell histiocytosis	Deposition of Langerhans cells within the pituitary gland	No	Diabetes insipidus Less likely anterior pituitary deficiencies	Rarely occur in adults

ACTH = adrenocorticotropic hormone.

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pituitary tumor or rapid expansion due to pituitary apoplexy (sudden hemorrhage or infarction of a pituitary adenoma) causing compression of the optic chiasm may result in complete bitemporal hemianopsia or even blindness. Pituitary apoplexy may even result in cranial nerve (CN) palsies of CNs III, IV, and VI, whereas a slowly growing pituitary tumor that abuts the optic chiasm may cause minimal or no loss in peripheral vision. All patients with pituitary tumors that abut or compress the optic chiasm should have an evaluation by an ophthalmologist (preferentially a neuro-ophthalmologist). Any abnormality on visual examination is an indication for surgery, unless the tumor is a prolactinoma. H

Pituitary tumors can invade the cavernous sinus but rarely cause mass effect on brain tissue or narrowing of the carotid within the cavernous sinus.

KEY POINT

- Mass effects of pituitary tumors most commonly include compression of the pituitary gland resulting in hormone deficiencies or compression of the optic chiasm most commonly resulting in bitemporal hemianopsia; stalk compression can lead to hyperprolactinemia.

Evaluation of Pituitary Tumors

In patients with a pituitary tumor on CT imaging, a dedicated pituitary MRI with and without contrast with dynamic cuts through the sella should be obtained. A formal visual field examination is required for any tumor that abuts or compresses the optic chiasm.

Pituitary hypersecretion should be ruled out by measurement of prolactin and insulin-like growth factor 1 (IGF-1). Evaluation for Cushing disease is not necessary in patients without signs or symptoms of cortisol excess.

Pituitary tumors can also cause hypopituitarism. Screening for hypopituitarism is recommended in all pituitary tumors regardless of symptoms with measurement of FSH, LH, cortisol, TSH, free thyroxine (T_4), and additionally total testosterone in men. Hypogonadotropic hypogonadism can be assessed in premenopausal women through menstrual history. A history of oligomenorrhea or amenorrhea would raise concern for hypogonadotropic hypogonadism and require further hormone testing, whereas a history of normal menses would essentially rule out hypogonadotropic hypogonadism. Abnormal baseline testing may prompt further stimulatory testing to confirm hypopituitarism (**Table 18**), and referral to an endocrinologist is recommended.

If a patient does not require surgical intervention for mass effect or pituitary hypersecretion, repeat pituitary hormone assessment and imaging is performed in 6 months for macroadenomas and then yearly if no change.

Microadenomas should be reassessed with imaging in 1 year and then every 1 to 2 years thereafter. Repeat evaluation of pituitary function is not necessary in microadenomas if initial testing is normal and there has been no change clinically or in the pituitary MRI.

After 3 years of imaging follow up for a pituitary tumor (both microadenomas and macroadenomas), imaging can be performed less frequently, as long as clinical status of the patient remains stable.

KEY POINTS

- Pituitary hypersecretion should be ruled out by measurement of prolactin and insulin-like growth factor 1; evaluation for Cushing disease is not necessary in patients without signs or symptoms of cortisol excess. **HVC**
- A history of oligomenorrhea or amenorrhea would raise concern for hypogonadotropic hypogonadism and require further hormone testing, whereas a history of normal menses would essentially rule out hypogonadotropic hypogonadism. **HVC**

Treatment of Clinically Nonfunctioning Pituitary Tumors

Patients with a nonfunctioning pituitary tumor should be referred for neurosurgical evaluation if any of the following are present: visual deficits related to the tumor, a lesion abuts or compresses the chiasm or optic nerves on pituitary MRI, or pituitary apoplexy with visual disturbance. Surgery should also be considered for a tumor with clinically significant growth, such as growth toward the optic chiasm, and for patients with new loss of endocrine function. Women with a macroadenoma close to the optic chiasm who are planning pregnancy may benefit from surgical decompression of the pituitary tumor due to the risk of enlargement during pregnancy. Microadenomas rarely increase in size during pregnancy. The most common surgical approach for these tumors is transsphenoidal through the nares or mouth. Occasionally, craniotomy is needed for very large tumors. Most nonfunctioning macroadenomas will have immunocytochemistry consistent with a gonadotroph adenoma and are clinically "silent" (without hypersecretion of functional gonadotropins).

KEY POINTS

- Patients with a nonfunctioning pituitary tumor should be referred for neurosurgical evaluation if there are visual deficits related to the tumor, a lesion abuts or compresses the chiasm or optic nerves on pituitary MRI, or pituitary apoplexy with visual disturbance is present.
- Surgery should be considered for a tumor with clinically significant growth, such as growth potentially affecting vision, and for patients with new loss of endocrine function.

Pituitary Hormone Deficiency

Hypopituitarism is defined as one or more pituitary hormone deficiencies. It can occur as a result of compression of the normal pituitary cells by a tumor or as a complication of cranial surgery or radiation therapy. Somatotrophs and gonadotrophs

TABLE 18. Dynamic Testing for Pituitary Dysfunction

Indication	Test	Technique	Interpretation
ACTH (cortisol) deficiency	ACTH stimulation test	Measure baseline serum cortisol level. Administer 250 µg of synthetic ACTH IM or IV. Measure cortisol levels at 30 and 60 minutes.	Serum cortisol level >18 µg/dL (496.8 nmol/L) at any measurement indicates a normal response.
ADH deficiency (DI)	Water deprivation test, followed by desmopressin challenge, if indicated	Patient empties bladder, and baseline weight is measured. Measure urine volume and osmolality hourly. Measure serum sodium, osmolality, and weight every 2 h. *The test is stopped when one of the following occurs:* Urine osmolality/plasma osmolality is >2 Patient has lost >3% of body weight Urine osmolality is stable for 2-3 h while serum osmolality rises Plasma osmolality >295 mOsm/kg H_2O Serum sodium >145 mEq/L (145 mmol/L) *Desmopressin challenge:* If final urine osmolality <600 mOsm/kg, serum osmolality >295 mOsm/kg H_2O, or serum sodium >145 mEq/L (145 mmol/L): give desmopressin 2 µg subcutaneously. Measure urine osmolality and urine volume hourly for 4 hours after desmopressin.	*Water deprivation test interpretation:* Urine osmolality >750-800 mOsm/kg H_2O is a normal response to water deprivation, indicating ADH production and peripheral effect are intact. Serum osmolality >295 mOsm/kg H_2O and/or serum sodium >145 mEq/L (145 mmol/L) with inappropriately dilute urine (urine osmolality/plasma osmolality <2) is diagnostic of DI. *Desmopressin challenge interpretation:* Urine osmolality >800 mOsm/kg after desmopressin is consistent with complete central DI. No increase in urine osmolality (remains <300 mOsm/kg) is diagnostic of complete nephrogenic DI. Urine osmolality between 300 and 800 mOsm is consistent with partial DI
Growth hormone excess (acromegaly)	Glucose tolerance test	75-g oral glucose tolerance test. Measure glucose and GH at 0, 30, 60, 90, 120, and 150 minutes.	GH <0.2 ng/mL (0.2 µg/L) is a normal response. GH nadir ≥1.0 ng/mL (1.0 µg/L) (or ≥0.3 ng/mL [0.3 µg/L] on an ultrasensitive assay) is diagnostic of acromegaly.

ACTH = adrenocorticotropic hormone; ADH = antidiuretic hormone; DI = diabetes insipidus; GH = growth hormone.

appear to be the most sensitive to injury, so GH as well as LH and FSH are the most common pituitary deficiencies. ACTH and TSH deficiency are less common, but more serious.

Pituitary apoplexy and Sheehan syndrome (pituitary infarction associated with postpartum hemorrhage) can cause acute life-threatening hypopituitarism due to ACTH deficiency.

A full list of causes of hypopituitarism can be found in **Table 19**.

Panhypopituitarism

Panhypopituitarism occurs when a patient lacks adequate production of all anterior pituitary hormones, usually due to a large tumor or complications of pituitary surgery. These patients require daily replacement of thyroxine and cortisol. Replacement of sex steroids and GH is individualized, based on the clinical situation and evaluation of risks and benefits of treatment. Patients with panhypopituitarism should wear medical alert identification as a deficiency of glucocorticoids can be life threatening.

Adrenocorticotropic Hormone Deficiency (Secondary Cortisol Deficiency)

The most common cause of adrenocorticotropic hormone (ACTH) deficiency is iatrogenic following administration of exogenous glucocorticoids and suppression of ACTH production. Oral, injectable (intraarticular, intramuscular), and even occasionally topical glucocorticoids can suppress ACTH. Inhaled glucocorticoids attenuate the recovery of endogenous ACTH production but rarely cause suppression of ACTH production directly. Patients with iatrogenic adrenal insufficiency have intact renin-aldosterone systems; they are at lower risk for hypotension and adrenal crisis.

Glucocorticoids prescribed in supraphysiologic doses for 3 weeks or longer should be tapered off to allow recovery of the pituitary-adrenal axis. Once the glucocorticoid dose is

TABLE 19. Causes of Hypopituitarism

Neoplastic
Pituitary adenoma
Meningioma
Craniopharyngioma
Metastatic cancer
Lymphoma
Infiltrative Disease
Sarcoidosis
Hemochromatosis
Langerhan cell histiocytosis
Inflammation
Lymphocytic hypophysitis
Iatrogenic
Surgery
Radiation
Congenital Deficiencies
Vascular
Pituitary infarction
Pituitary apoplexy
Empty Sella
Hypothalamic Disease
Traumatic Brain Injury
Medications
Opiates
Checkpoint inhibitors (nivolumab, ipilimumab, tremelimumab, pembrolizumab)

close to physiologic (equivalent of 15-20 mg hydrocortisone), hydrocortisone should be substituted. The dose can then be reduced by 5 mg every 1 to 2 weeks as tolerated. AM-only dosing may facilitate recovery of the adrenal axis.

Once on physiologic AM-only hydrocortisone, the adrenal axis can then be tested for recovery. An 8 AM cortisol level higher than 10 µg/dL (276 nmol/L) after withholding glucocorticoids for 24 hours suggests recovery of the pituitary-adrenal axis. This should be confirmed with an ACTH stimulation test. Despite recovery of the pituitary-adrenal axis, patients may take longer to recover their ability to respond to stress and may require stress-dose or sick-day dosing of glucocorticoids in the setting of an illness for up to a year.

ACTH deficiency can also occur in the setting of damage to the pituitary gland. Symptoms of secondary cortisol deficiency can include fatigue, malaise, weight loss, nausea, vomiting, asymptomatic hypoglycemia, dizziness, and hyponatremia. Because only cortisol production is affected (mineralocorticoid production is intact), patients do not develop hyperkalemia and are less likely to have hypotension. Furthermore, patients with secondary adrenal insufficiency do not develop hyperpigmentation. Nonetheless, patients with secondary adrenal insufficiency do require physiologic glucocorticoid replacement and stress dosing during illness.

Morning cortisol levels less than 3 µg/dL (82.8 nmol/L) are diagnostic of cortisol deficiency; however, a morning cortisol level greater than 15 µg/dL (414 nmol/L) likely rules it out. Patients with cortisol levels between 3 and 15 µg/dL (82.8-414 nmol/L) should undergo an ACTH stimulation test (see Table 18). A peak cortisol level greater than or equal to 18 µg/dL (496.8 nmol/L) at 0, 30, or 60 minutes rules out cortisol deficiency. Once diagnosed, secondary adrenal insufficiency should be treated with hydrocortisone 15 to 20 mg in two divided doses, such as 10 to 15 mg in the morning and 5 mg in the afternoon. In the setting of an emergency such as pituitary apoplexy, an immediate intravenous dose of 100 mg hydrocortisone should be administered.

Glucocorticoid dosing must be adjusted in the setting of physiologic stress or acute illness. Administering two to three times the baseline dose of cortisol replacement for 2 to 3 days is usually sufficient for minor to moderate illness including minor or moderate surgery. In patients with major physiologic stress including major surgery or active labor, 100 mg hydrocortisone should be administered by intravenous injection followed by a continuous infusion of 200 mg every 24 hours or 50 mg intravenous injection every 6 hours (see Disorders of the Adrenal Glands).

KEY POINTS

- The most common cause of adrenocorticotropic hormone deficiency is iatrogenic following administration of exogenous glucocorticoids and suppression of adrenocorticotropic hormone production. **HVC**
- Glucocorticoids prescribed in greater than physiologic doses for 3 weeks or longer should be tapered off to allow recovery of the pituitary-adrenal axis.
- Glucocorticoid dosing must be adjusted in the setting of physiologic stress or acute illness.

Thyroid-Stimulating Hormone Deficiency

Deficiency of thyroid-stimulating hormone (TSH) results in the inability of the thyroid gland to produce thyroxine (T_4). The result is insufficient T_4 production with low or inappropriately normal TSH. The clinical symptoms of secondary hypothyroidism are the same as seen with primary hypothyroidism.

The treatment is daily administration of levothyroxine. TSH cannot be used to monitor therapy and should not be measured. Dosing based on TSH level can lead to underdosing. Free T_4 should be used to monitor dose adequacy and should be maintained in the mid to upper half of the normal range. While it takes 6 to 8 weeks for TSH to accurately reflect thyroid

hormone status in primary hypothyroidism, free T_4 levels can be checked 2 to 3 weeks after a dose change to assess for adequacy in secondary hypothyroidism.

KEY POINT

- Treatment of thyroid-stimulating hormone deficiency is daily administration of levothyroxine; only free thyroxine can be used to monitor dose adequacy, and free thyroxine should be maintained in the mid to upper half of the normal range.

Gonadotropin Deficiency

Gonadotropin deficiency can be a result of pituitary disease or a result of gonadotropin-releasing hormone (GnRH) deficiency as is seen in Kallmann syndrome and hypothalamic amenorrhea. Certain drugs, including opiates, can also suppress GnRH. Deficiency of gonadotropins, LH and FSH, results in deficiency of male and female sex hormones. The combination of low or inappropriately normal LH and FSH with low sex steroids is termed "central" or "hypogonadotropic" hypogonadism.

Treatment of hypogonadotropic hypogonadism can usually be achieved by replacing sex steroids in those with no contraindication and who do not desire fertility; testosterone treatment in men and combined estrogen-progesterone treatment in premenopausal women are used. While oral contraceptive pills may be more acceptable in young women for this purpose, other forms of estrogen and progesterone (such as estradiol patch with cycled oral progesterone) may be preferred in certain cases. In men and women who desire fertility, replacement of gonadotropins is necessary because exogenous testosterone and estrogen suppresses spermatogenesis in men and ovulation in women, respectively.

Growth Hormone Deficiency

Growth hormone (GH) is necessary for linear growth. Deficiency of GH in children causes short stature. Symptoms of growth hormone deficiency in adults are more subtle and include fatigue, loss of muscle mass, and increased ratio of fatty tissue to lean mass.

While isolated GH deficiency can occur in children, idiopathic isolated GH deficiency in adults is quite rare. Only patients with a history of hypothalamic or pituitary disease, surgery or radiation to these areas, head trauma, or other pituitary hormone deficiencies should be considered for evaluation of adult-onset isolated GH deficiency.

Owing to the pulsatile nature of GH, direct measurement is uninterpretable and GH deficiency should be assessed through measurement of insulin-like growth factor 1 (IGF-1). An IGF-1 level below the normal range for gender and age is highly suggestive of GH deficiency, whereas a normal IGF-1 level does not completely rule out growth hormone deficiency if pretest suspicion is high. Provocative tests such as an insulin tolerance test or GnRH-arginine test can be performed in consultation with an endocrinologist to establish the diagnosis of adult GH deficiency.

Benefits of treatment in those with GH deficiency include improvement in exercise capacity, body composition, and bone density. The decision to start growth hormone replacement should be individualized. It is contraindicated in the setting of malignancy or with an untreated pituitary tumor because of the potential for stimulation of tumor growth. Additionally, caution should be used in those with diabetes mellitus as it may worsen hyperglycemia. When therapy is indicated in adults, GH can be replaced with a low-dose daily injection titrated to a normal IGF-1 level and clinical assessment.

KEY POINT

- Idiopathic isolated growth hormone deficiency in adults is rare; only adults with a history of hypothalamic or pituitary disease, surgery or radiation to these areas, head trauma, or other pituitary hormone deficiencies should be evaluated. HVC

Central Diabetes Insipidus

Inability of the posterior pituitary gland to produce adequate antidiuretic hormone (ADH) results in central diabetes insipidus (DI). Absent antidiuretic hormone (ADH) (complete DI) and reduced ADH (partial DI) prevent the reabsorption of water in the kidneys resulting in polyuria and polydipsia. Although significant hypernatremia is rare in patients with an intact thirst mechanism and free access to water, it can be severe if patients cannot drink to thirst.

An inappropriately low urine osmolality in the setting of an elevated serum osmolality and hypernatremia in a patient with polyuria (>50 mL/kg/24 hours in the absence of glucosuria) is diagnostic of DI. A water deprivation test can be performed when the diagnosis is uncertain (see Table 18).

DI is treated with desmopressin (DDAVP) administered intranasally, orally, or subcutaneously. Bioavailability of oral DDAVP is much lower and doses are considerably higher than with intranasal and subcutaneous routes. Despite this, oral preparations may be preferred in certain circumstances as intranasal absorption of DDAVP may be altered by changes in nasal mucosa. Doses are usually administered once nightly to prevent nocturia and ensure uninterrupted sleep, or twice daily if symptoms interfere with daily function. Caution should be taken to avoid overreplacement as this can result in hyponatremia, water intoxication, and volume overload.

KEY POINTS

- An inappropriately low urine osmolality in the setting of an elevated serum osmolality and hypernatremia in a patient with polyuria (>50 mL/kg/24 hours in the absence of glucosuria) is diagnostic of diabetes insipidus.
- Diabetes insipidus is treated with desmopressin administered intranasally, orally, or subcutaneously; caution should be taken to avoid overreplacement as this can result in hyponatremia, water intoxication, and volume overload.

Pituitary Hormone Excess

Pituitary tumors are considered functional when they secrete pituitary hormones in excess. The most common functional pituitary tumors are prolactinomas. Although pituitary tumors that produce ACTH or GH are less common, they are important to recognize because of the clinical consequences. TSH-secreting adenomas are a very rare cause of hyperthyroidism. Pituitary tumors rarely cosecrete more than one excess hormone. Cosecretion most commonly occurs with GH and prolactin.

Hyperprolactinemia and Prolactinoma

The most common cause of hyperprolactinemia is physiologic, related to pregnancy and lactation. Physiologic stress, coitus, sleep, and nipple stimulation are other nonpathologic causes of mild hyperprolactinemia. A comprehensive list of causes of hyperprolactinemia is provided in **Table 20**. Symptoms of hyperprolactinemia include amenorrhea, and sometimes galactorrhea, in premenopausal women. Men often present later with symptoms of mass effect or hypogonadism, such as decreased libido or difficulty with erections; less commonly, they experience gynecomastia and breast tenderness.

TABLE 20. Causes of Hyperprolactinemia

Physiologic	Medication	Other
Coitus	Antipsychotics	Chest wall trauma
Exercise	Typical antipsychotics	Chronic kidney disease
Lactation	Chlorpromazine	Cirrhosis
Nipple stimulation	Fluphenazine	Cocaine
Pregnancy	Haloperidol	Empty sella syndrome
Sleep	Prochlorperazine	Herpes zoster
Stress	Atypical antipsychotics	Polycystic ovary syndrome
	Amisulpride	Prolactinoma
	Olanzapine (rarely)	Seizures
	Paliperidone	Severe hypothyroidism
	Risperidone	Stalk compression
	Ziprasidone (rarely)	
	SSRIs	
	Citalopram	
	Escitalopram	
	Fluoxetine	
	Paroxetine	
	Sertraline	
	Antihypertensives	
	Methyldopa	
	Verapamil	
	Other	
	Cimetidine	
	Domperidone	
	Estrogen	
	Metoclopramide	
	Opiates	

SSRI = selective serotonin reuptake inhibitor.

The most common cause of pathologic non-tumor-related hyperprolactinemia is medications. Of patients taking typical antipsychotics (see Table 20), 40% to 90% will have hyperprolactinemia caused by the dopamine antagonist effect of these medications. While medication-induced hyperprolactinemia most often results in prolactin levels of 25 to 100 ng/mL (25-100 µg/L), drugs such as metoclopramide, risperidone, and phenothiazines can lead to prolactin levels above 200 ng/mL (200 µg/L). Confirming that the hyperprolactinemia is related to medication can be challenging. If possible, the offending medication should be withheld for 3 days to determine whether prolactin levels return to normal.

Discontinuation of any psychotropic drug should be done only in consultation with the patient's psychiatrist. If the medication cannot be withheld and the prolactin elevation cannot be correlated to the timing of the drug initiation, a pituitary MRI should be performed to rule out prolactinoma. Antipsychotic medication-induced hyperprolactinemia is best treated in consultation with the patient's psychiatrist by switching to a drug that is less likely to cause hyperprolactinemia. While asymptomatic hyperprolactinemia related to medication does not require treatment, patients with hypogonadism should be treated with estrogen or testosterone to preserve bone mass. Treating medication-induced hyperprolactinemia with a dopamine agonist (cabergoline or bromocriptine) is controversial as it can exacerbate psychosis.

An MRI of the pituitary is indicated in all patients with unexplained hyperprolactinemia. Assessment and treatment decisions are then based on the prolactin level and MRI findings.

A prolactin level above 500 ng/mL (500 µg/L) is diagnostic of a macroprolactinoma. While levels greater than 250 ng/mL (250 µg/L) are suggestive of a macroprolactinoma, there are some medications that can raise prolactin to this level. Prolactin levels generally correlate with tumor size. Therefore when a macroadenoma is present with a prolactin level below 100 ng/mL (100 µg/L), pituitary stalk compression from a nonfunctioning tumor should be suspected for the cause of the hyperprolactinemia, rather than prolactinoma.

Patients with asymptomatic microadenomas do not require treatment. Women with hypogonadism related to a microadenoma can be treated with a combined oral contraceptive if they do not desire fertility or with a dopamine agonist if they do. Postmenopausal women with microadenomas do not require treatment.

In patients with macroadenomas, dopamine agonist therapy is recommended to lower prolactin, reduce tumor size, and restore gonadal function. Cabergoline is the preferred agent because of its superior efficacy in lowering prolactin and

tumor shrinkage compared with bromocriptine. In addition, cabergoline dosing is twice per week compared with 1 to 3 times daily for bromocriptine. Prolactin can be monitored 2 to 4 weeks after initiation of therapy and then every 3 to 4 months once stable. MRI should be repeated for a microadenoma in 1 year. If both the tumor and prolactin are stable at 1 year follow up, no further imaging is needed. A macroadenoma should be reimaged 3 months after medical therapy and then every 6 to 12 months until stability is confirmed. Reimaging should be performed if the prolactin level rises despite therapy.

Surgery is not first-line therapy because up to 50% of prolactinomas recur after resection. Surgery should only be considered for prolactinomas in symptomatic patients who cannot tolerate dopamine agonist therapy or whose tumors do not shrink or even grow while on dopamine agonist therapy.

KEY POINTS

HVC
- The most common cause of hyperprolactinemia is physiologic, related to pregnancy and lactation.

HVC
- The most common cause of pathologic non-tumor-related hyperprolactinemia is medications.

HVC
- Patients with asymptomatic microadenomas do not require treatment; for patients with macroadenomas, dopamine agonist therapy is recommended to lower prolactin, reduce tumor size, and restore gonadal function.

HVC
- Surgery is not first-line therapy because up to 50% of prolactinomas recur after resection.

Prolactinomas and Pregnancy

Due to lactotroph hyperplasia in pregnancy, there is concern for enlargement of prolactinomas in pregnancy. Because microadenomas are not likely to enlarge during pregnancy, dopamine agonist therapy should be discontinued when pregnancy is discovered. However, patients who have macroadenomas without prior surgical or radiation therapy have a significant risk of tumor growth. Surgical tumor debulking prior to pregnancy or dopamine agonist therapy throughout pregnancy may be required in these patients. Bromocriptine is the preferred agent in pregnancy.

Patients with macroadenomas should be monitored with visual field testing each trimester while those with microadenomas can be monitored clinically. Headaches or visual field changes should prompt a noncontrast pituitary MRI.

Acromegaly

Acromegaly is caused by excess secretion of GH from a pituitary tumor in 95% of patients. In fewer than 5% of patients with GH excess, a growth hormone-releasing hormone (GHRH)-secreting tumor or neuroendocrine tumor is the cause of acromegaly. When GH-secreting pituitary tumors are present in children prior to puberty, the result is increased longitudinal growth resulting in gigantism. While gigantism is easily recognized in children, features of excess growth hormone are more subtle in adults, often not recognized for many years. A list of clinical features of acromegaly can be found in **Table 21**.

An IGF-1 level should be obtained to screen for suspected acromegaly. In those with an elevated level, an oral glucose tolerance test should be performed to confirm the diagnosis (see Table 18). A level above 1 ng/mL (1 µg/L) confirms the diagnosis of acromegaly. Once GH excess is demonstrated, a pituitary MRI should be obtained.

Transsphenoidal resection (TSR) of the GH-secreting tumor is the mainstay of therapy. Those who do not achieve remission with surgery can be treated with medical therapy and/or stereotactic radiation. Somatostatin analogues are the medications of choice as they result in reduction of tumor size as well as reduction in GH levels. Pegvisomant, a GH receptor antagonist, can be used in combination with a somatostatin analogue when needed; cabergoline can sometimes be used as well. Stereotactic radiotherapy (gamma knife) is used in certain cases. Once remission is achieved, MRI and IGF-1 levels are followed annually.

Patients with acromegaly can have increased mortality due to heart disease, sleep apnea, and cancer, but risk returns to baseline when IGF-1 is kept in the normal range. Appropriate screening and treatment for comorbidities are as important as managing the IGF-1 level.

TABLE 21. Features of Acromegaly

Clinical Signs and Symptoms
Prognathism
Macroglossia
Wide-spaced teeth (typically the first sign of growth hormone excess)
Wide nose
Enlarged and swollen hands and feet
Increased sweating
Skin tags
Joint pain
Headache
Disease Associations
Sleep apnea
Hypertension
Insulin resistance
Hypertrophic cardiomyopathy
Colon polyps and colon cancer
Thyroid nodules and thyroid cancer
Valvular heart disease
Arthropathy
Carpal tunnel syndrome

KEY POINTS

- An insulin-like growth factor 1 level should be obtained to screen for suspected acromegaly; in those with an elevated level, an oral glucose tolerance test should be performed to confirm the diagnosis followed by a pituitary MRI.
- Transsphenoidal resection of the growth hormone-secreting tumor is the mainstay of therapy; however, somatostatin analogues reduce the tumor size as well as growth hormone levels in those who do not achieve remission with surgery.

Thyroid-Stimulating Hormone-Secreting Tumors

Thyroid-stimulating hormone (TSH)-secreting pituitary tumors are extremely rare. Signs and symptoms of a TSH-secreting adenoma are those seen in hyperthyroidism, although laboratory evaluation reveals elevated T_4 and T_3 levels with an inappropriately normal or elevated TSH level. Once other causes of the laboratory abnormalities have been excluded (thyroid assay interference, thyroid hormone resistance, or familial dysalbuminemic hyperthyroxinemia), a pituitary MRI should be performed. TSR of the TSH-producing tumor is the treatment of choice. Medical therapy with somatostatin analogues can be used to control hyperthyroidism prior to surgery and following surgery in those who do not achieve remission.

Excess Antidiuretic Hormone Secretion

The syndrome of inappropriate antidiuretic hormone secretion (SIADH) results in water retention with resultant hyponatremia, often severe. CNS disorders (trauma, stroke, brain metastases, infection) drugs, pulmonary disease, and pituitary surgery (3-7 days postoperatively) can result in excess release of ADH. SIADH is a diagnosis of exclusion. Treatment involves correcting the underlying pathology, fluid restriction, vasopressin receptor antagonists, and hypertonic saline in severe hyponatremia. If hypertonic saline is being considered, consultation with an endocrinologist or nephrologist is recommended (see MKSAP 18 Nephrology).

Excess Adrenocorticotropic Hormone from Pituitary Source (Cushing Disease)

Cushing syndrome is a term used to describe hypercortisolism regardless of the cause; Cushing disease (the most common cause of endogenous Cushing syndrome) is the term used to describe hypercortisolism as a result of excess ACTH secretion from a pituitary tumor. Symptoms and signs of Cushing syndrome are listed in **Table 22**.

The diagnosis of Cushing syndrome is made by first establishing evidence of hypercortisolism (see Disorders of Adrenal Glands). Measuring ACTH establishes whether it is ACTH-dependent or ACTH-independent.

Once diagnosis of ACTH-dependent Cushing syndrome is established, a pituitary MRI should be performed for confirmation. If no pituitary tumor is seen or if the tumor is less than 6 mm, a high-dose 8-mg dexamethasone suppression test (DST) is done to evaluate for the presence of an ectopic ACTH-producing tumor (lung, pancreas, thymus carcinoma most commonly), which is highly resistant to dexamethasone suppression. Inferior petrosal sinus sampling (IPSS) is often recommended prior to TSR to confirm a pituitary source of ACTH excess due to low sensitivity and specificity of the high-dose DST.

TABLE 22. Symptoms and Signs of Cushing Syndrome

Symptoms
Depression
Fatigue
Rapid weight gain
Decreased libido
Menstrual abnormalities
Signs
Striae (especially if reddish purple and >1 cm in width)[a]
Easy bruising[a]
Facial plethora[a]
Muscle weakness (proximal myopathy)
Abdominal obesity
Skin tears (secondary to thinning of the epidermis)
Acne
Hirsutism
Dorsocervical fat pad (buffalo hump)[a]
Supraclavicular fad pad[a]
Hypokalemia
Hypertension
Diabetes

[a]Features that best discriminate Cushing syndrome from the general population.

The treatment of choice is TSR of the pituitary adenoma. Remission is generally defined by a morning serum cortisol level less than 5 µg/dL (138 nmol/L) within 7 days of surgery. Patients require glucocorticoid replacement postoperatively until the normal corticotroph cells recover from prolonged cortisol suppression. Recovery can take up to a year, and occasionally there is no recovery and the patient will require life-long cortisol replacement therapy.

If remission is not achieved following surgery, radiation or medical therapy (**Table 23**) may be required. Rarely, bilateral adrenalectomy is needed in patients unresponsive to all other therapies; these patients will require life-long glucocorticoid and mineralocorticoid replacement for acquired primary adrenal insufficiency. In addition, there is the risk of pituitary tumor enlargement following adrenalectomy (Nelson syndrome) due to unfettered stimulation of ACTH production.

Patients with Cushing disease require imaging and biochemical follow-up (urine free cortisol or late-night salivary

TABLE 23. Medication Management for Treatment of Cushing Syndrome

Steroidogenesis Inhibitors (Inhibits Cortisol Synthesis)	Pituitary Directed (Inhibits ACTH Secretion)	Glucocorticoid Receptor Antagonist (Inhibits Cortisol Action)
Ketoconazole	Pasireotide	Mifepristone
Metyrapone	Cabergoline	
Mitotane		
Etomidate		

ACTH = adrenocorticotropic hormone.

cortisol measurement) every year for several years, and then on a less frequent basis. The first biochemical sign of recurrence is often elevated late-night salivary cortisol levels. Recurrences are managed by repeat TSR, radiation, and/or medical therapy.

KEY POINTS

- The diagnosis of Cushing syndrome is made by first establishing evidence of hypercortisolism; once adrenocorticotropic hormone-dependent Cushing disease is confirmed, a pituitary MRI should be performed.
- The treatment of choice for adrenocorticotropic hormone-dependent Cushing disease is transsphenoidal resection of the pituitary adenoma, followed by glucocorticoid replacement until the normal corticotroph cells recover from cortisol suppression.

Disorders of the Adrenal Glands

Adrenal Anatomy and Physiology

Although considered one organ, the adrenal glands have two functionally distinct regions: an outer cortex and an inner medulla. The cortex secretes hormones that are classified as mineralocorticoid (aldosterone), glucocorticoid (cortisol), and androgen (dehydroepiandrosterone [DHEA]). The medulla secretes catecholamines.

The adrenal cortex is composed of three zones: the zona glomerulosa (outer), zona fasciculate (middle), and zona reticularis (inner). Aldosterone production in the zona glomerulosa is regulated by the renin-angiotensin system and promotes sodium reabsorption and potassium excretion across the distal tubule of the kidney. The resultant expansion of extracellular volume increases blood pressure. Aldosterone also has direct inflammatory and fibrotic effects on other organs that are independent of its effects on blood pressure. Major stimuli to aldosterone secretion include hypotension, hypovolemia, and hyperkalemia.

Cortisol production in the zona fasciculata is regulated by release of adrenocorticotropic hormone (ACTH) from the pituitary gland. Cortisol exhibits a distinct diurnal rhythm characterized by peak levels on awakening that decrease to very low levels by bedtime. Superimposed on this diurnal rhythm are small oscillations of cortisol secretion while awake. Most cortisol circulates in the blood attached to cortisol-binding protein, with only a small fraction circulating as biologically active, free hormone. Cortisol is crucial to the body's adaptive response to physiologic stress, and levels increase in response to psychological stress, as well as physical illness. Cortisol actions are diverse and include immune, vascular, anti-inflammatory, and metabolic effects.

DHEA, produced in the zona reticularis, and its sulfate DHEAS, are weak adrenal androgens that mediate their effects through peripheral conversion to testosterone. In women the adrenal gland is a significant contributor to circulating androgen levels. In men the adrenal contribution to androgen effect is negligible.

The adrenal medulla secretes the catecholamines norepinephrine and epinephrine in response to hypotension, hypoglycemia, fear, anxiety, acute illness, and other causes of psychological and physical stress. Catecholamines interact with α- and β-adrenergic receptors to increase pulse and blood pressure, relax smooth muscle, dilate bronchioles, and increase metabolic rate. A small fraction of norepinephrine and epinephrine is excreted in the urine as free hormone; the rest is degraded in the liver to metanephrine and normetanephrine prior to urinary excretion.

Adrenal Hormone Excess

Cortisol Excess (Cushing Syndrome Due to Adrenal Mass)

Cortisol-secreting adrenal adenomas and, rarely, carcinomas account for 20% of endogenous causes of Cushing syndrome. Excess cortisol secretion from these tumors suppresses ACTH production from the pituitary gland, resulting in a form of Cushing syndrome classified as ACTH-independent. ACTH-dependent Cushing syndrome is more common and is most commonly caused by pituitary adenomas (see Disorders of the Pituitary Gland). While many of the symptoms and signs of Cushing syndrome are common in the general population, some, including supraclavicular fat pads, proximal muscle weakness, facial plethora, and wide violaceous striae (**Figure 3**), are considered more discriminatory (see Disorders of the Pituitary Gland). Diagnosis of Cushing syndrome is challenging because patients present along a spectrum ranging from mild disease with subtle findings to severe, life-threatening disease. In addition, hypercortisolemia from psychological stress and physical illness can also occur in the absence of Cushing syndrome. In severe stress states such as major depression, anxiety, psychosis, poorly controlled diabetes mellitus, and severe visceral obesity, a pseudo-Cushing state may occur in which

FIGURE 3. Wide violaceous striae are seen on the abdomen of a patient with Cushing syndrome. Striae larger than 1 cm in width are highly specific for hypercortisolism.

hypercortisolemia and nonspecific clinical features of Cushing syndrome coexist.

Evaluation for Cushing syndrome in patients without specific signs of Cushing syndrome is not recommended.

The evaluation of Cushing syndrome involves (1) initial testing followed by confirmatory testing for Cushing syndrome; (2) determining Cushing syndrome as ACTH-independent or -dependent; and (3) localizing the source of ACTH in ACTH-dependent disease or confirming the presence of adrenal mass (or masses) in ACTH-independent disease. It is imperative that biochemical Cushing syndrome be confirmed with certainty prior to looking for the source, as misdiagnosis may lead to unnecessary testing and treatment.

The diagnosis of Cushing syndrome necessitates a combination and repetition of tests (**Figure 4**). Measurement of morning or random serum cortisol is unreliable, due to overlap of serum cortisol levels among normal patients, those with Cushing syndrome, and those with mild hypercortisolism/pseudo-Cushing state in the absence of Cushing syndrome. In addition, total cortisol levels are unreliable when binding proteins are affected by oral estrogen, acute illness, and low protein states.

Initial tests for Cushing syndrome have similar diagnostic accuracy and include measurement of 24-hour urine free cortisol, serial late night salivary cortisols, and the 1-mg overnight dexamethasone suppression test. When suspicion for Cushing syndrome is low, a single test, if negative, makes Cushing syndrome unlikely. When there is a higher index of suspicion for Cushing syndrome, two different initial tests are recommended.

Urine free cortisol and late night salivary cortisol represent the serum free cortisol fraction and avoid pitfalls in interpretation related to changes in cortisol-binding proteins. Spurious elevation of urine free cortisol can result from hypercortisolemia not related to Cushing syndrome/pseudo-Cushing state or when significant polyuria (>5 L/d) is present. False-negative results can occur in advanced kidney disease or in patients with variable secretory rates of cortisol.

Late-night salivary cortisol is collected at home by the patient between 11 PM and midnight on at least two different nights. This test assesses for the normal diurnal rhythm of cortisol, which is lost in Cushing syndrome, and the cortisol level will not be low as expected. This test is not recommended in patients who do shift work or have an inconsistent sleep pattern. Recent cigarette smoking or contamination of the sample by topical glucocorticoids can falsely increase results.

The 1-mg (low-dose) dexamethasone suppression test depends on the principle that autonomous cortisol secretion is not subject to feedback suppression with exogenous glucocorticoids. Dexamethasone is taken at 11 PM and serum total cortisol is measured at 8 AM the following morning.

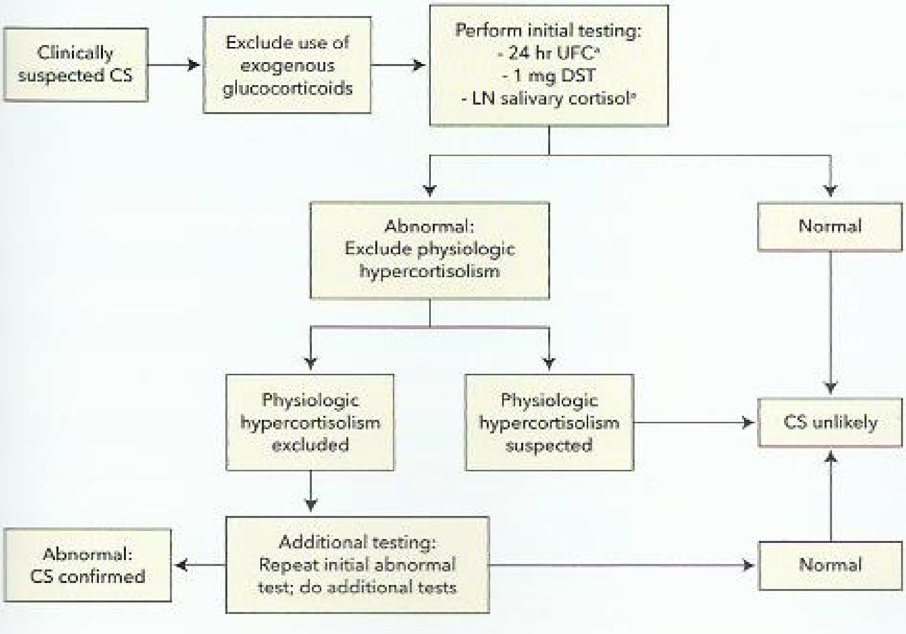


FIGURE 4. Algorithm to confirm or rule out the diagnosis of Cushing syndrome. CS = Cushing syndrome; DST = dexamethasone suppression test; LN salivary cortisol = late-night salivary cortisol; UFC = urine free cortisol.

*Must be performed at least twice.

A post-dexamethasone cortisol level of greater than 5 µg/dL (138 nmol/L) is considered a positive test. A lower cut-off cortisol value of greater than 1.8 µg/dL (49.7 nmol/L) has been advocated to improve test sensitivity, but this occurs at the expense of reduced specificity. False-positive results may occur with concomitant use of medications (carbamazepine, phenytoin, and pioglitazone) that induce hepatic CYP3A4 enzymes and accelerate dexamethasone metabolism. Simultaneous measurement of serum dexamethasone can confirm patient adherence or altered dexamethasone metabolism.

Many factors can raise cortisol levels in the absence of Cushing syndrome, so test interpretation should incorporate the pretest probability of Cushing syndrome. A urine free cortisol level greater than 3 times the upper normal range in the setting of clinical manifestations of Cushing syndrome is considered diagnostic of the disorder, whereas a positive test in the setting of low suspicion for Cushing syndrome does not support the diagnosis. If initial testing is positive, confirmation and further evaluation should involve consultation with an endocrinologist. Once the diagnosis of Cushing syndrome is established, the next step is measurement of ACTH; if suppressed (<5 pg/mL [1.1 pmol/L]) indicating an ACTH-independent cause of Cushing syndrome, a dedicated adrenal CT or MRI is indicated. If adrenal glands appear normal on imaging, the diagnosis of Cushing syndrome should be questioned.

Surgical resection is the definitive treatment for benign and malignant cortisol-secreting adrenal tumors.

Following adrenalectomy, patients require daily hydrocortisone therapy to allow recovery from prolonged ACTH suppression due to hypercortisolism. Recovery of adrenal fasciculate function may take up to 1 year or longer depending on the severity of Cushing syndrome (see Disorders of the Pituitary Gland).

KEY POINTS

- The evaluation of Cushing syndrome involves (1) initial testing followed by confirmatory testing for Cushing syndrome; (2) determining Cushing syndrome as adrenocorticotropic hormone (ACTH)-independent or -dependent; and (3) localizing the source of ACTH in ACTH-dependent disease or confirming the presence of adrenal mass (or masses) in ACTH-independent disease.
- Initial tests for Cushing syndrome have similar diagnostic accuracy and include measurement of 24-hour urine free cortisol, serial late-night salivary cortisols, and the 1-mg overnight dexamethasone suppression test.
- HVC Evaluation for Cushing syndrome in patients without specific signs of Cushing syndrome is not recommended.

Primary Aldosteronism

Primary aldosteronism (PA) is a common cause of secondary hypertension. Traditionally, hypokalemia was considered to be a biochemical prerequisite for the diagnosis of PA, but it is now recognized that more than 60% of patients have normal potassium levels. As hypertension is often the only sign of primary aldosteronism, the condition frequently goes undiagnosed. Identification of patients with primary aldosteronism is important because aldosterone has deleterious effects on the cardiovascular system and treatment prevents progression and can sometimes reverse changes. Higher cardiovascular morbidity and mortality have been noted in patients with primary aldosteronism compared to those with primary hypertension with similar blood pressure control. The potential health impact of untreated primary aldosteronism and the importance of recognizing primary aldosteronism is reflected in updated guidelines on case detection testing for primary aldosteronism (**Table 24**).

Primary aldosteronism is caused by hyperplasia of both adrenal glands (idiopathic hyperaldosteronism) in two-thirds of cases, and a unilateral aldosterone producing adenoma (APA) in one-third of cases. The diagnosis of primary aldosteronism involves performing stepwise case detection, as well as confirmatory and localization studies. The most reliable case-detection test is calculation of an plasma aldosterone-plasma renin ratio (ARR) by measuring plasma aldosterone concentration and plasma renin activity (or

TABLE 24. Case Detection Indications for Primary Aldosteronism and Pheochromocytoma

Primary Aldosteronism
Untreated hypertension with sustained BP >150/100 mm Hg
Hypertension (>140/90 mm Hg) on three-drug therapy
Hypertension and an incidentally discovered adrenal mass
Hypertension associated with spontaneous or diuretic-induced hypokalemia
Hypertension in the setting of a first-degree relative with PA
Hypertension in the setting of family history of hypertension onset age <40 years
Pheochromocytoma
Adrenergic-type spells (headache, sweating, and tachycardia) with or without hypertension
Incidentally discovered adrenal mass with or without hypertension
Hypertension (>140/90 mm Hg) on three-drug therapy
Hypertension with onset age <20 years
Idiopathic cardiomyopathy
Hypertensive episode induced by anesthesia, surgery, or angiography
Paraganglioma
Familial syndromes that predispose to pheochromocytoma: VHL, NF-1, and MEN 2
Family history of pheochromocytoma or paraganglioma

BP = blood pressure; MEN 2 = multiple endocrine neoplasia type 2; NF-1 = neurofibromatosis type 1; PA = primary aldosteronism; VHL = von Hippel-Lindau.

direct renin concentration) in a mid-morning seated sample. In patients taking an ACE inhibitor or an angiotensin receptor blocker, renin should be elevated, so in these patients, a simple initial test is plasma renin activity measurement. If the plasma renin activity is suppressed, the likelihood of primary aldosteronism is high and an ARR should be performed; if not, hyperaldosterone state is ruled out. Mineralocorticoid receptor antagonists (spironolactone and eplerenone) and high-dose amiloride can significantly interfere with interpretation of ARR and should be discontinued 6 weeks prior to evaluation.

Other antihypertensive agents can be continued, but because some may have minor effects on aldosterone and/or renin levels (**Table 25**), the results of the ARR should be interpreted with these effects in mind. Hydralazine, a selective α-adrenergic receptor blocker, and slow-release verapamil have minimal effects on aldosterone and renin secretion, and they can be substituted when feasible for other agents if the ARR is equivocal. An ARR greater than 20 with a plasma aldosterone concentration of at least 15 ng/dL (414 pmol/L) is considered a positive result, and patients should be referred to an endocrinologist, who may perform additional testing to confirm inappropriate aldosterone secretion in a salt-replete state.

The localization study of choice for primary aldosteronism is a dedicated adrenal CT. Findings may include normal adrenal glands or unilateral or bilateral adenoma(s)/hyperplasia. In one third of patients, the CT may not identify the cause of primary aldosteronism because some APAs are too small to see or there is an incidental adrenal mass unrelated to primary aldosteronism. Consequently, most patients with confirmed primary aldosteronism should undergo adrenal vein sampling to confirm the source of the hyperaldosteronism.

TABLE 25. The Effect of Commonly Prescribed Medications on Measurements of Plasma Renin Activity and Plasma Aldosterone Concentration

Effect on Test Results	Medication Class	PRA	PAC	PAC/PRA
False-Positive	α_2-Adrenoceptor agonist	↓↓	↓	↑
	β-Adrenoceptor blocker	↓↓	↓	↑
	Direct renin inhibitor	↓	↓	↑
	NSAID	↓↓	↓	↑
False-Negative	ACE inhibitor/ARB	↑↑	↓	↓
	Dihydropyridine CCB	↑	↓	↓
	Diuretic[a]	↑↑	↑	↓
	Mineralocorticoid receptor antagonist	↑↑	↑	↓
	SSRI		↑	↓

ARB = angiotensin receptor antagonist; CCB = calcium channel blocker; PAC = plasma aldosterone concentration; PRA = plasma renin activity; SSRI = selective serotonin reuptake inhibitor.

[a]Both potassium-sparing (amiloride) and potassium-wasting (hydrochlorothiazide) diuretics.

Medical therapy with an aldosterone receptor antagonist (spironolactone or eplerenone) is the treatment of choice for primary aldosteronism due to idiopathic hyperaldosteronism, or when patients with APA are not candidates for, or do not wish to undergo, surgery. Spironolactone is often preferred over eplerenone because it is less expensive and more potent. However, patients on spironolactone are more likely to develop dose-dependent side effects of gynecomastia and erectile dysfunction in men and menstrual irregularities in women. Hypokalemia almost always resolves with treatment, but blood pressure control may require additional agents. No studies clearly show superiority of adrenalectomy compared to medical therapy for APA, but surgery may be more cost-effective in the long term.

Laparoscopic adrenalectomy is effective for unilateral disease and reduces plasma aldosterone and its attendant increased risk of cardiovascular disease. Hypertension is improved in most patients and cured in about 40% of patients. Persistent hypertension following adrenalectomy may be due to vascular changes caused by chronic hypertension or coexistent primary hypertension. Patients are more likely to achieve resolution of hypertension if they were taking fewer than three antihypertensive agents preoperatively, and if they have one or fewer first-degree relatives with hypertension. Serum potassium should be monitored weekly for the first month postoperatively, and patients should be instructed to eat a high-salt diet due to risk of hyperkalemia from transient reduction in aldosterone production in the remaining adrenal gland due to chronic suppression of the renin-angiotensin system during the period of hyperaldosteronism. Short-term mineralocorticoid replacement is required in those patients who develop hyperkalemia.

KEY POINTS

- The most reliable case-detection test for primary aldosteronism is calculation of a plasma aldosterone-plasma renin ratio by measuring plasma aldosterone concentration and plasma renin activity (or direct renin concentration) in a mid-morning seated sample; if the plasma renin activity is suppressed, the likelihood of primary aldosteronism is high.
- In patients taking an ACE inhibitor or an angiotensin receptor blocker, renin should be elevated, so in these patients, a simple initial test is a plasma renin activity measurement; if the plasma renin activity is suppressed, the likelihood of primary aldosteronism is high and a plasma aldosterone-plasma renin ratio should be performed; if not, hyperaldosterone state is ruled out. HVC

(Continued)

KEY POINTS *(continued)*

- Laparoscopic adrenalectomy for unilateral disease results in reduction of plasma aldosterone; medical therapy with an aldosterone receptor antagonist (spironolactone or eplerenone) is the treatment of choice for primary aldosteronism due to idiopathic hyperaldosteronism, or when patients with aldosterone-producing adenoma are not candidates for, or do not wish to undergo, surgery.

Pheochromocytoma and Paraganglioma

Pheochromocytomas and paragangliomas are catecholamine-secreting tumors that arise from chromaffin cells of the adrenal medulla (80%) and extra-adrenal (mostly abdominal) sympathetic ganglia, respectively. Tumors can also arise from parasympathetic ganglia in the head and neck, but these rarely secrete catecholamines.

At least one-third of pheochromocytomas/paragangliomas are associated with a germline mutation. Pheochromocytomas may occur in familial syndromes including multiple endocrine neoplasia type 2, von Hippel-Lindau syndrome, and neurofibromatosis type 2 (**Table 26**). All patients with catecholamine-secreting tumors should, therefore, be offered genetic counseling.

Hypertension associated with pheochromocytoma/paraganglioma can show a sustained pattern, with or without paroxysms, or occur as paroxysms only. Some patients (10% to 15%) remain normotensive. The classic triad of palpitations, headache, and diaphoresis is seen in fewer than 50% of patients with pheochromocytoma. Multiple symptoms related to catecholamine excess can occur including abdominal pain, skin pallor, blurred vision, or polyuria. Rarely, patients can present with acute myocardial infarction, cardiomyopathy, or stroke.

Indications for testing for pheochromocytoma are shown in Table 24. Initial tests for pheochromocytoma include measurement of plasma-free metanephrine collected in a supine position or 24-hour urine fractionated metanephrine and catecholamine levels. Elevation in catecholamines can occur in patients under psychological or physical stress. Medications can affect results (**Table 27**) and should be discontinued at least 2 weeks prior to testing. Accurate diagnosis is further confounded by the fact that patients with or without hypertension may have adrenergic-type spells in the absence of a catecholamine-secreting tumor. Interpretation of the test results must consider the extent of metanephrine elevation rather than whether the result is normal or abnormal. Mild elevations may require repeat testing. Levels more than four times the upper limit of normal, in the absence of acute stress or illness, are consistent with a catecholamine-secreting tumor. The plasma-free metanephrine is highly sensitive (96% to 100%). The specificity is 85% to 89%. Urine fractionated metanephrine and catecholamines have higher specificity (98%) and high sensitivity (up to 97%). Neither test is superior, so clinicians can use an estimate of pretest probability to select the initial test. When there is a high index of suspicion, plasma-free metanephrine is chosen, and when suspicion is low, urine fractionated metanephrine and catecholamines may be a better option.

The search for a tumor should begin when a biochemical diagnosis of pheochromocytoma/paraganglioma is supported by laboratory results, to avoid misdiagnosing an incidental nonfunctioning adrenal mass as a pheochromocytoma. It is difficult to determine clinical relevance of significantly elevated metanephrine levels in hospitalized patients. The imaging modality of choice is an abdominal and pelvic contrast-enhanced CT as 85% of catecholamine secreting tumors are intra-adrenal (and 95% reside in the abdomen or pelvis). Typical imaging features of pheochromocytomas are shown in **Table 28**. The average size of a symptomatic pheochromocytoma at diagnosis is 4 cm. If the CT is negative, reconsidering the diagnosis is the first step; however, if suspicion of a catecholamine-secreting tumor is high, the

TABLE 26. Multiple Endocrine Neoplasm Syndromes

Type	Mutation	Most Common Feature	Associated Features
1	*MEN1* (inheritance of one mutated allele with somatic mutation in other allele leads to neoplasia)	Parathyroid adenoma (often multiple)	Pancreatic islet cell and enteric tumors (gastrinoma, insulinoma most common) Pituitary adenoma Other (carcinoid tumors, adrenocortical adenoma)
2A	*RET* (exon 11, codon 634[a])	Medullary thyroid carcinoma	Pheochromocytoma (often multifocal) Parathyroid hyperplasia
2B	*RET* (exon 16, codon 918[a])	Medullary thyroid carcinoma	Pheochromocytoma (often multifocal) Mucosal neuroma Gastrointestinal ganglioneuroma Marfanoid body habitus

[a]Most common mutation observed.

TABLE 27. Substances Associated with False-Positive Biochemical Testing for Pheochromocytoma

Drug Class	Medication/Substance
Analgesics	Acetaminophen
Antiemetics	Prochlorperazine
Antihypertensives	Phenoxybenzamine[a]
Psychiatric medications	Antipsychotics
	Buspirone
	Monoamine oxidase inhibitors
	Serotonin norepinephrine reuptake inhibitors (SNRIs)
	Tricyclic antidepressants[a]
Stimulants	Amphetamines
	Methylphenidate
	Cocaine
	Caffeine
Other agents	Levodopa
	Decongestants (pseudoephedrine)
	Reserpine
Withdrawal	Clonidine
	Ethanol
	Illicit drugs

[a]Most likely to cause false-positive results.

next step is iodine 123 (^{123}I)-metaiodobenzylguanidine scanning. This test may also be indicated in patients with very large pheochromocytomas (>10 cm) to detect metastatic disease or paragangliomas to detect multiple tumors. Fludeoxyglucose-position emission tomography is more sensitive for detection of metastatic disease, but its use is generally reserved for those patients with established malignant tumors.

The definitive treatment for pheochromocytoma/paraganglioma is surgical resection. Preoperative β-receptor blockade with phenoxybenzamine for 10 to 14 days before surgery is essential to prevent hypertensive crises during surgery. The dose is progressively increased to achieve a blood pressure of 130/80 mm Hg or less and pulse of 60 to 70/min seated, and systolic pressure of 90 mm Hg or higher with pulse of 70 to 80/min standing. Side effects include dizziness, nasal congestion, and fatigue. To facilitate dose escalation and mitigate the volume contraction effects of α-receptor blockade, patients are instructed to liberalize their salt and fluid intake. A β-blocker is added once α-blockade is achieved to manage reflex tachycardia, but it should never be started prior to adequate α blockade because unopposed α-adrenergic vasoconstriction can result in a hypertensive crisis.

For large pheochromocytomas with a high hormone secretion rate, other agents such as a calcium channel blocker and/or metyrosine are added to the treatment regimen. Calcium channel blockers can also be used in patients who develop significant hypotension on small doses of α-blocker. Selective α-1 receptor blockers such as doxazosin can be used as an alternative to phenoxybenzamine if availability or lack of insurance coverage of the latter is a problem. Postoperatively, patients can have significant hypotension, and most require fluid and vasopressor support at least briefly in the

TABLE 28. Typical Imaging Characteristics of Adrenal Masses

Adrenal Mass	Overall	CT	MRI Signal Intensity[a]
Adrenal adenoma	Diameter <4 cm	Density <10 HU	Isointense on T2-weighted images
	Homogeneous enhancement[b]	Contrast washout >50% (10 min)	
	Round, clear margins		
Adrenocortical carcinoma	Usually >4 cm	Density >10 HU	Hyperintense on T2-weighted images
	Heterogeneous enhancement[b]	Contrast washout <50% (10 min)	
	Irregular margins		
	Calcifications, necrosis		
Pheochromocytoma	Variable size	Density >10 HU	Hyperintense on T2-weighted images
	Heterogeneous enhancement[b], cystic areas	Contrast washout <50% (10 min)	
	Round, clear margins		
	Can be bilateral		
Metastases	Variable margins	Density >10 HU	Hyperintense on T2-weighted images
	Can be bilateral	Contrast washout <50% (10 min)	

HU = Hounsfield units (measure of radiodensity compared with water).

[a]Signal intensity as compared with liver.

[b]Enhancement following intravenous contrast administration.

H CONT. postoperative period. Patients with pheochromocytoma may have impaired fasting glucose or type 2 diabetes related to insulin resistance induced by catecholamine excess. This can improve or reverse following adrenalectomy. H

Approximately 83% of pheochromocytomas/paragangliomas are benign. Pathologic findings do not predict which tumors will become malignant and develop metastases. Since metastases can occur decades after the initial diagnosis, patients should undergo long-term annual biochemical screening, typically with plasma-free metanephrine.

KEY POINTS

- Initial tests for pheochromocytoma include measurement of plasma free metanephrine levels or 24-hour urine fractionated metanephrine and catecholamine levels; certain medications can affect results and need to be discontinued at least 2 weeks prior to testing.
- The search for a tumor should begin when a biochemical diagnosis of pheochromocytoma/paraganglioma is clear in laboratory results, to avoid misdiagnosing an incidental nonfunctioning adrenal mass as a pheochromocytoma.
- The definitive treatment for pheochromocytoma/paraganglioma is surgical resection; preoperative α-blockade with phenoxybenzamine is essential to prevent hypertensive crises during surgery.
- HVC Selective α-1 receptor blockers such as doxazosin can be used as an alternative to phenoxybenzamine if availability or lack of insurance coverage of the latter is a problem.

Androgen-Producing Adrenal Tumors

Androgen-producing adrenal tumors are rare and lead to menstrual irregularities and virilization in women including hirsutism, voice-deepening, increased muscle mass, increased libido, and clitoromegaly. Tumors secrete DHEA/DHEAS and androstenedione, which are subsequently converted to testosterone in the periphery. DHEAS-secreting tumors of the adrenal gland are readily visible on CT imaging, and adrenal vein sampling to localize the tumor is rarely required. Approximately 50% are benign, and the treatment of choice is resection.

Adrenal Hormone Deficiency

Primary Adrenal Insufficiency

Causes and Clinical Features

Primary adrenal insufficiency (AI) is a life-threatening disorder that often presents with insidious onset of symptoms making diagnosis a challenge (**Table 29**). It may also present as adrenal crisis, often precipitated by an acute illness or the initiation of thyroid hormone replacement in a patient with unrecognized chronic AI. Although skin hyperpigmentation from stimulation of melanocytes by high ACTH levels is considered a hallmark of primary adrenal insufficiency, it is not present in approximately 5% patients. The most common cause of primary adrenal insufficiency is autoimmune destruction of all layers of the adrenal cortex leading to progressive mineralocorticoid, glucocorticoid, and adrenal androgen deficiency. Most patients have positive 21-hydroxylase antibodies, and approximately 50% will develop another autoimmune

TABLE 29. Clinical and Laboratory Manifestations of Primary Adrenal Failure

Hormone Deficiency	Symptoms	Signs	Laboratory Findings
Cortisol	Fatigue Weakness Low-grade fever Weight loss Anorexia Nausea/vomiting Abdominal pain Arthralgia Myalgia	Hyperpigmentation[b] (palmar creases, extensor surfaces, buccal mucosa) Decrease in BP	↓Serum cortisol ↑Plasma ACTH ↓Serum sodium[c] ↓Plasma glucose[d]
Aldosterone	Salt craving Dizziness	Orthostasis Hypotension	↑PRA ↓Serum sodium ↑Serum potassium
DHEAS	Reduced libido[a]	Decreased axillary or pubic hair[a]	↓Serum DHEAS

ACTH = adrenocorticotropic hormone; BP = blood pressure; DHEAS = dehydroepiandrosterone sulfate; PRA = plasma renin activity.

[a]Women only.

[b]Occurs exclusively in primary adrenal failure.

[c]Cortisol inhibits the secretion of antidiuretic hormone (ADH), so hypocortisolemia will lead to increased secretion of ADH and hyponatremia.

[d]Rare in adults.

endocrine disorder in their lifetime (primary hypothyroidism, primary ovarian insufficiency, celiac disease, hypoparathyroidism, or type 1 diabetes mellitus).

Primary adrenal insufficiency can also be caused by infiltrative disorders such as infection (tuberculosis, fungal infections), sarcoidosis, and lymphoma, which result in bilateral adrenal gland enlargement. Metastatic disease involving the adrenals, most commonly from lung cancer, renal cell carcinoma, and melanoma rarely leads to adrenal insufficiency even if both adrenal glands are involved.

Bilateral adrenal hemorrhage can present as acute adrenal insufficiency and should be considered if unexpected hypotension develops. Risk factors for bilateral adrenal hemorrhage include protein C deficiency, anticoagulation, disseminated intravascular coagulopathy, and sepsis.

Diagnosis

An algorithm for the diagnosis of adrenal insufficiency is outlined in **Figure 5**. Initial evaluation includes the measurement of morning serum total cortisol and ACTH levels. Primary adrenal insufficiency is confirmed by the combination of low serum cortisol and elevated serum ACTH levels. Important considerations in the interpretation of the results are shown in Figure 5 and often require referral to an endocrinologist. Additional evaluation may include measurement of 21-hydroxylase antibodies; positive 21-hydroxylase antibodies are found in approximately 90% of autoimmune adrenalitis cases. If negative, CT scan of the adrenal glands should be obtained.

Treatment

Both glucocorticoid and mineralocorticoid therapy is required for treatment of primary AI. The preferred glucocorticoid is hydrocortisone taken 2 or 3 times daily. Adherence to multiple daily doses can be challenging so prednisone can be used as an alternative (**Table 30**). The principle of replacement is to administer a higher dose in the morning and to avoid replacement in the evening. Despite this attempt to mimic diurnal variation, patients with primary AI report a decrease in health-related quality of life. It is imperative to avoid overreplacement with glucocorticoid, to avoid iatrogenic Cushing syndrome with its risk of obesity, type 2 diabetes mellitus, hypertension, hyperlipidemia, bone loss, and cardiovascular disease. Some patients "feel better" at higher than physiologic replacement doses, but the risks outweigh the benefits of supraphysiologic doses. Mineralocorticoid replacement is achieved with daily fludrocortisone. DHEAS replacement is controversial in women due to lack of robust data for benefit and concerns regarding the safety and quality of U.S. preparations, which are supplements and not regulated as drugs.

H

Patients cannot mount an appropriate increase in cortisol with illness, and therefore, instruction in "sick day" rules is essential to prevent adrenal crisis (**Table 31**). For minor physiologic stress states such as respiratory infection, fever, or minor surgery under local anesthesia, patients should double or triple their baseline glucocorticoid dose for 2 to 3 days. Higher doses of glucocorticoid are required during moderate or major physiologic stress. Patients who present with adrenal

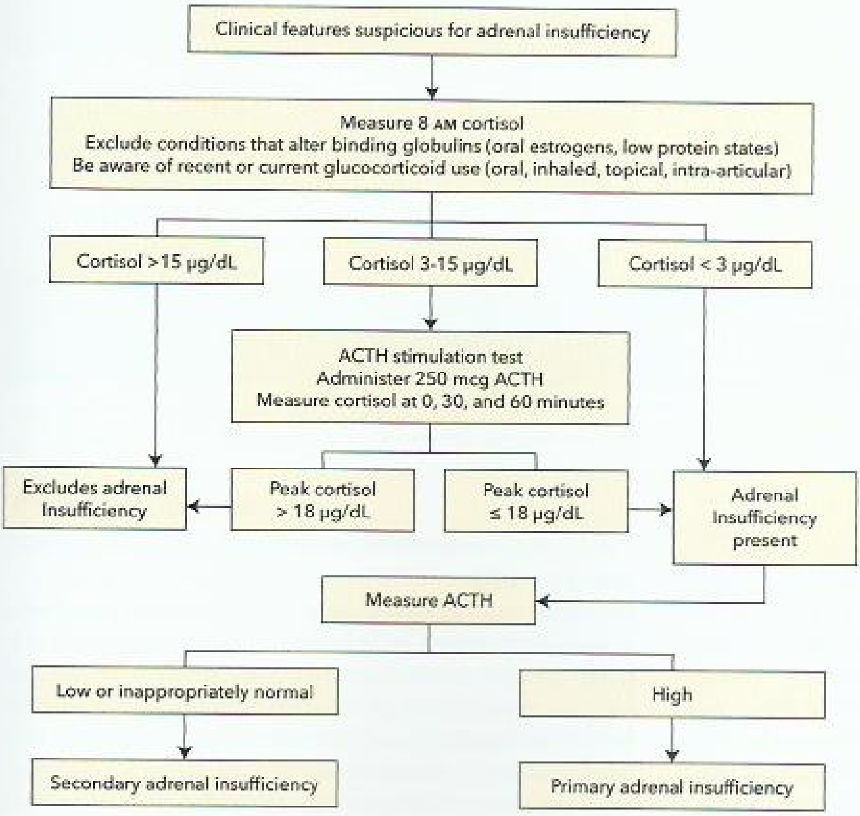


FIGURE 5. Algorithm for the diagnosis of adrenal insufficiency. ACTH = adrenocorticotropic hormone.

TABLE 30. Dose Equivalence and Relative Potencies of Common Synthetic Oral Glucocorticoids

Synthetic Glucocorticoid	Equivalent Dose (mg)	Biologic Half-Life (hours)	Relative Anti-Inflammatory Potency[a]	Relative Mineralocorticoid Potency[b]
Hydrocortisone	20	8-12	1	1/125
Prednisolone/ prednisone	5	18-36	4	1/150
Methylprednisolone	4	18-36	5	0
Dexamethasone	0.75	36-54	25-50	0

[a]Anti-inflammatory potency relative to hydrocortisone.

[b]Mineralocorticoid potency relative to fludrocortisone.

TABLE 31. Chronic Medical Treatment of Primary Adrenal Failure

Medication	Basal Dose	Considerations
Glucocorticoid[a]		*"Sick day rules"*:
Hydrocortisone	Usually 15-25 mg/d, divided into 2-3 doses over the day	Patient follows at home.
Prednisone	Prednisone 5 mg once daily *How to dose:* Titrate to clinical response with goal of no signs or symptoms of cortisol deficiency or excess (increase dose if symptoms of cortisol deficiency remain; decrease if CS signs and symptoms are present)	*For minor physiologic stress (upper respiratory infection, fever, minor surgery under local anesthesia):* 2-3 times basal dose for 2-3 days *Stress dosing:* Health care providers follow while patient is in the hospital. *For moderate physiologic stress (minor or moderate surgery with general anesthesia):* Hydrocortisone 25-75 mg/d orally or IV for 1-2 days *For major physiologic stress* (major surgery, trauma, critical illness, or childbirth): Hydrocortisone 100 mg IV followed by 50 mg every 6 h IV; rapid tapering and switch to oral regimen depending on clinical state
Mineralocorticoid		
Fludrocortisone	0.05-0.2 mg once daily in the morning *How to dose:* Titrate to: 1. Normal BP 2. Normal serum Na, K	Fludrocortisone is not required if hydrocortisone dose is >40 mg/d.
Adrenal androgen		
DHEA	25-50 mg once daily	Consider DHEA for women with impaired mood or sense of well-being when glucocorticoid replacement has been optimized.

BP = blood pressure; CS = Cushing syndrome; DHEA = dehydroepiandrosterone; IV = intravenous; Na = sodium; K = potassium.

[a]Shorter-acting glucocorticoids are preferred over longer-acting agents due to lower risk of glucocorticoid excess. Longer-acting preparations have the advantage of once-daily dosing.

H CONT. crisis should receive fluid resuscitation and an initial immediate dose of intravenous hydrocortisone (100 mg), followed by intravenous hydrocortisone (100 mg) every 8 hours for the next 24 hours, with subsequent dosing governed by clinical status. Patients with concomitant untreated adrenal insufficiency and hypothyroidism should always receive glucocorticoid replacement therapy first to prevent precipitation of adrenal crisis by thyroid hormone replacement. Patients should also be counselled to wear a medic alert identification at all times. No increase in mineralocorticoid dose is necessary with illness. H

The term "adrenal fatigue" is used by some alternative medicine providers to represent a constellation of symptoms purported to occur in patients who experience chronic emotional or physical stress that are claimed to be caused by simultaneous hyper- and hypocortisolism. There is no scientific evidence to support such a condition. Patients may undergo salivary cortisol testing, but

interpretation of the results is often unreliable. Some patients labeled with "adrenal fatigue" are given hydrocortisone therapy or animal-derived adrenal gland extract that may contain active glucocorticoid, leading to exogenous suppression of ACTH production and iatrogenic Cushing syndrome. Sudden discontinuation of these products can lead to acute adrenal insufficiency. Patients with "adrenal fatigue" should be carefully tapered off any glucocorticoid therapy and other potential causes for their symptoms explored.

KEY POINTS

- The most common cause of primary adrenal insufficiency is autoimmune destruction of all layers of the adrenal cortex leading to progressive mineralocorticoid, glucocorticoid, and adrenal androgen deficiency.
- Both glucocorticoid and mineralocorticoid therapy is required for treatment of primary adrenal insufficiency.
- Patients cannot mount an appropriate increase in cortisol with illness, and therefore, instruction in "sick day" rules regarding glucocorticoid dosing is essential to prevent adrenal crisis.

H

Adrenal Function During Critical Illness

During times of physiologic stress, the hypothalamic-pituitary-adrenal axis is stimulated to produce increased levels of cortisol. In some patients, the increase in cortisol secretion is thought to be suboptimal and termed "relative AI." There is debate, however, as to whether the entity of relative adrenal insufficiency is a true disease. Cortisol-binding globulin and albumin decrease in critical illness, lowering the measured total cortisol. There is no agreement on a set of diagnostic criteria for relative AI despite the ability to measure free cortisol, calculated free cortisol, and basal and ACTH-stimulated total cortisol level in critically ill patients. Studies to date do not show improved survival in patients with relative AI treated with high-dose glucocorticoid therapy. Reversal of shock, however, may be improved, and hence it is currently recommended that stress-dose hydrocortisone be administered to patients with shock that is resistant to standard fluid and vasopressor therapy. H

Adrenal Mass

Incidentally Noted Adrenal Masses

An adrenal incidentaloma is defined as an adrenal mass greater than 1 cm in diameter that is detected on imaging performed for purposes other than suspicion of adrenal disease. The prevalence of adrenal incidentaloma increases with age and is estimated to be approximately 10% in those 70 years of age or older. Most lesions are benign, nonfunctioning adenomas, and approximately 10% to 15% secrete excess hormones. Other causes include metastases (probability increases if known primary malignancy), myelolipoma, cysts, and adrenocortical carcinoma.

The finding of an incidental adrenal mass prompts two main questions: (1) Is it secreting excess hormone (aldosterone, cortisol, or catecholamines)? and (2) Is it benign or malignant? Patients with hypertension or with hypokalemia require testing for primary aldosteronism. Biochemical testing for pheochromocytoma, such as a 24-hour urine total metanephrine measurement, should be undertaken in all patients, even in the absence of typical symptoms or hypertension.

All patients should also be evaluated for subclinical Cushing syndrome, a condition characterized by ACTH-independent cortisol secretion that may result in metabolic (hyperglycemia and hypertension) and bone (osteoporosis) effects of hypercortisolism, but not the more specific clinical features of Cushing syndrome, such as supraclavicular fat pads, wide violaceous striae, facial plethora, and proximal muscle weakness. Initial testing for subclinical Cushing syndrome is achieved with a 1-mg overnight dexamethasone suppression test, with a cortisol level greater than 5 µg/dL (138 nmol/L) considered a positive test. Following a positive result, further tests are required to confirm cortisol autonomy and may include measurement of ACTH (suppressed), DHEAS (low), 24-hour urine free cortisol, and an 8-mg overnight dexamethasone suppression test; referral to an endocrinologist is recommended at this point. The decision whether to proceed to adrenalectomy should take into account the risks versus benefits of surgery. Studies to date have not been robust enough to show clear postoperative improvement in clinically important outcomes but suggest improved glucose, lipid, blood pressure, and bone density measurements.

Imaging findings can help differentiate between a benign and a malignant adrenal mass (see Table 28). Most adrenocortical carcinomas measure more than 4 cm at the time of discovery. Approximately 75% of benign adrenal masses, however, are also in this size range. Approximately 66% of benign adenomas are lipid-rich and exhibit low attenuation (<10 HU) on CT imaging. Benign adrenal adenomas also exhibit rapid washout (>50%) of contrast material compared to non-benign lesions. Adrenal biopsy has a limited role in evaluation of incidentalomas and is reserved for lesions suspicious for metastases or an infiltrative process such as lymphoma or infection. Pheochromocytomas should be ruled out prior to biopsy to avoid the possibility of a hypertensive crisis. Biopsy should not be performed when there is suspicion for primary adrenocortical carcinoma because, without review of the whole specimen, pathology cannot reliably distinguish this from a benign cortical adenoma, and tumor seeding is possible. If the former is suspected, the diagnosis should be established by adrenalectomy.

An algorithm for management of adrenal incidentaloma, including monitoring of lesions that do not require adrenalectomy, is shown in **Figure 6**.

KEY POINTS

- All patients with adrenal incidentaloma should be evaluated for pheochromocytoma; those with hypertension or hypokalemia should also be evaluated for primary aldosteronism, and all patients should be evaluated for subclinical Cushing syndrome.
- Imaging findings can help differentiate between a benign and malignant adrenal mass.

Adrenocortical Carcinoma

Adrenocortical carcinoma (ACC) is a rare, aggressive tumor that often secretes excess cortisol and/or androgens. Patients may present with rapid onset of Cushing syndrome, with or without virilization and/or symptoms from mass effect, such as increased abdominal girth and lower extremity edema. Fifty percent of ACCs secrete cortisol; 20% secrete multiple hormones, including cortisol and aldosterone precursors; and less than 10% secrete aldosterone. Some ACCs are discovered as an incidental adrenal mass that is either indeterminate or suspicious for ACC (see Table 28). Lesions are often large (>4 cm), and disease is at an advanced stage at the time of diagnosis. For localized disease, first-line therapy includes open resection. Debulking surgery, radiation therapy, and/or chemotherapy may also be options for palliation in advanced ACC.

Mitotane is an adrenolytic agent commonly used as adjuvant therapy that has been shown to be associated with longer recurrence-free survival. Mitotane causes primary AI, and daily glucocorticoid replacement therapy is required, often in supraphysiologic doses, due to mitotane-induced accelerated metabolism of glucocorticoids. Some patients also develop aldosterone deficiency manifested by hyponatremia, hyperkalemia, elevated renin levels, and postural hypotension, requiring fludrocortisone replacement. Five-year survival rates range from 62% to 82% for those with disease confined to the adrenal gland and 13% for tumors associated with distant metastases.

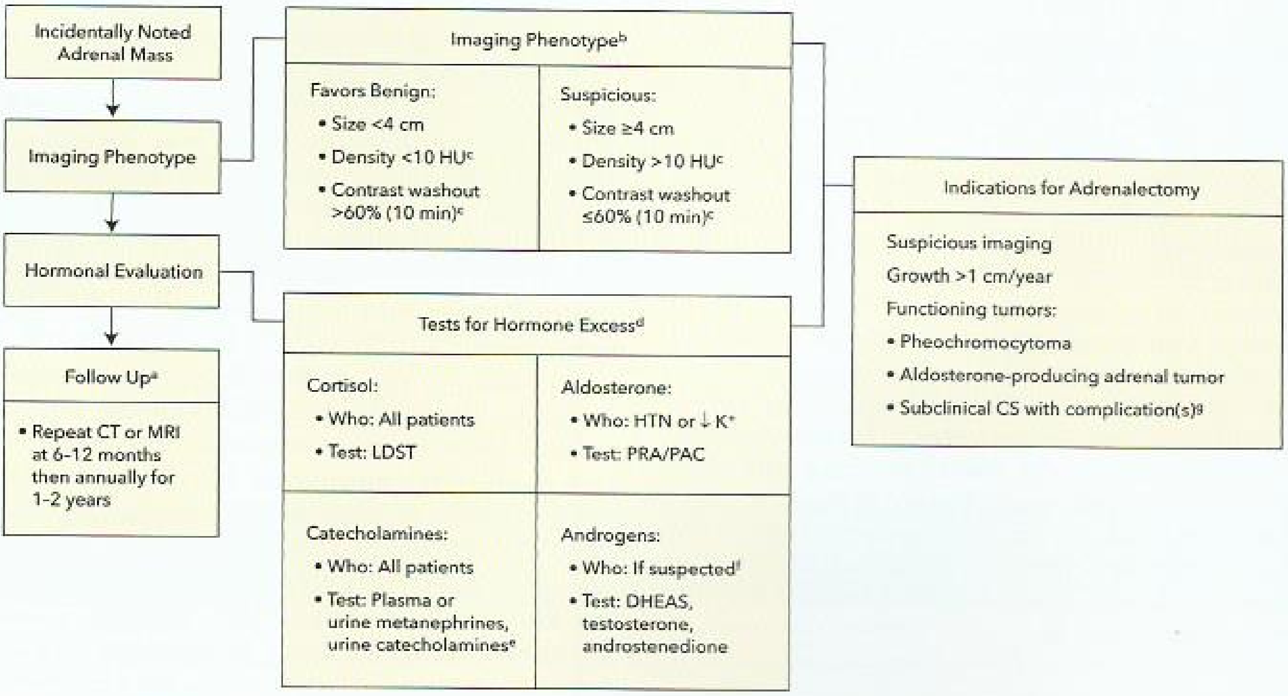


FIGURE 6. Algorithm for the initial diagnostic evaluation and follow up of an incidentally noted adrenal mass. CS = Cushing syndrome; DHEAS = dehydroepiandrosterone sulfate; HTN = hypertension; HU = Hounsfield units; K = potassium; LDST = low-dose (1-mg) dexamethasone suppression test; PAC = plasma aldosterone concentration; PRA = plasma renin activity.

[a]Repeat imaging is indicated for adrenal masses not meeting criteria for surgery at initial diagnosis.

[b]Refer to Table 28 for more CT and MRI findings. If imaging is suspicious in a patient with known malignancy, biopsy should be considered to confirm adrenal metastasis after screening for pheochromocytoma is completed.

[c]CT scan findings.

[d]Positive screening tests usually require further biochemical evaluation to confirm the diagnosis (see text).

[e]Measure plasma metanephrines if radiographic appearance is typical for a pheochromocytoma; otherwise measure 24-hour urine metanephrines and catecholamines.

[f]Hormonal evaluation for an androgen-producing adrenal tumor is indicated only if clinically suspected based on the presence of hirsutism, virilization, or menstrual irregularities in women.

[g]Adrenalectomy is considered for confirmed cases of subclinical CS associated with recent onset of diabetes, hypertension, obesity, or low bone mass.

KEY POINTS

- Adrenocortical carcinoma is a rare, aggressive tumor that often secretes excess cortisol and/or androgens and hormonal precursors causing hypertension and Cushing syndrome; patients may present with rapid onset of Cushing syndrome with or without virilization and/or symptoms from mass effect, such as increased abdominal girth and lower extremity edema.
- For localized disease, first-line therapy includes open resection; debulking surgery, radiation therapy, and/or chemotherapy may also be options for palliation in advanced adrenocortical carcinoma.
- Mitotane is an adrenolytic agent, commonly used as adjuvant therapy, that has been associated with longer recurrence-free survival.

Disorders of the Thyroid Gland

Thyroid Anatomy and Physiology

The thyroid gland is the largest dedicated endocrine organ. The usual anatomic location of the isthmus is just anterior to the second to fourth tracheal rings. The parathyroid glands are often located posterior to the superior and middle portions of each thyroid lobe. The recurrent laryngeal nerves, which innervate most of the intrinsic muscles of the larynx, course behind the thyroid gland. Thyroid pathology may cause compressive symptoms including shortness of breath, cough, dysphagia, and voice changes due to the close proximity of the thyroid to the trachea, esophagus, and recurrent laryngeal nerves.

The thyroid gland contains thyroid follicular cells and parafollicular cells (c-cells). Calcitonin is produced by the parafollicular cells and inhibits bone resorption; however, it plays a minor role in bone physiology. Follicular cells produce the thyroid hormones, thyroxine (T_4) and triiodothyronine (T_3). The synthesis and secretion of thyroid hormones is tightly regulated by the hypothalamic-pituitary-thyroid axis. Thyrotropin-releasing hormone (TRH) from the hypothalamus triggers the pulsatile release of thyroid-stimulating hormone (TSH) from thyrotrope cells in the anterior pituitary gland. TSH, through activation of the TSH receptor, stimulates thyroid cell growth, iodide metabolism, and thyroid hormone synthesis and secretion. T_4 and T_3 exert negative feedback on the hypothalamus and pituitary gland to moderate further hormone synthesis.

Iodine is an essential dietary micronutrient and a key structural component of T_4 and T_3.

The thyroid gland is the exclusive source of T_4, whereas approximately 80% of T_3 is the result of removing one iodine molecule from T_4, through deiodinase activity in peripheral tissues. This occurs primarily in the liver and kidney. Most of T_4 (99.96%) and T_3 (99.6%) are bound to proteins in serum. Approximately 70% of T_4 and T_3 are bound to thyroxine-binding globulin. Albumin, transthyretin, and lipoproteins carry a smaller proportion. Only the tiny amount of free T_4 and T_3 is biologically active. While T_4 largely serves as a prohormone, T_3 binds with high affinity to thyroid hormone nuclear receptors affecting gene transcription in target tissues and mediating its physiologic effects. It has positive inotropic and chronotropic effects in the heart and enhances myocardial adrenergic sensitivity. It also increases the rate of myocardial diastolic relaxation, augments intravascular volume, and lowers peripheral vascular resistance. It increases gastrointestinal motility, bone turnover, and regulates heat generation and energy expenditure.

Thyroid Examination

The thyroid gland is located in the neck midway between the sternal notch and thyroid cartilage. It attaches to the trachea posteriorly and elevates with swallowing. Examination involves both visualization and palpation while the patient swallows liquid. It can be palpated with the examiner behind the patient with circumferential hand positioning to allow focus on palpation or with the examiner facing the patient, which allows the examiner to see the thyroid during palpation. The anterior approach is preferred with necks of larger diameter.

Structural Disorders of the Thyroid Gland

Thyroid Nodules

Thyroid nodules are discrete structural lesions, distinct from the background gland parenchyma on ultrasound. They are most commonly detected as incidental findings on imaging studies performed for other reasons. The prevalence of nodules palpated on examination is 5% in women and 1% in men. They are detected on ultrasound in 40% of the U.S. population and are more common with increasing age. Thyroid nodules can result from multiple pathologic processes, ranging from benign cysts and inflammatory nodules, to malignancies including primary thyroid, lymphoma, or metastatic lesions. Non-thyroidal lesions, such as parathyroid adenomas, can also present as nodules. Primary thyroid neoplasms are clonal in origin and include follicular adenomas and thyroid cancer.

The initial evaluation of a thyroid nodule begins with measuring serum TSH (**Figure 7**). TSH suppression may indicate the presence of autonomously functioning or "hot" nodules, which account for 5% to 10% of palpable thyroid nodules. Autonomous nodules may cause hyperthyroidism and are associated with a very low risk of malignancy. They do not require fine-needle aspiration biopsy (FNAB). Patients with thyroid nodules and a suppressed TSH are evaluated with thyroid scintigraphy. A radioactive isotope, preferably iodine

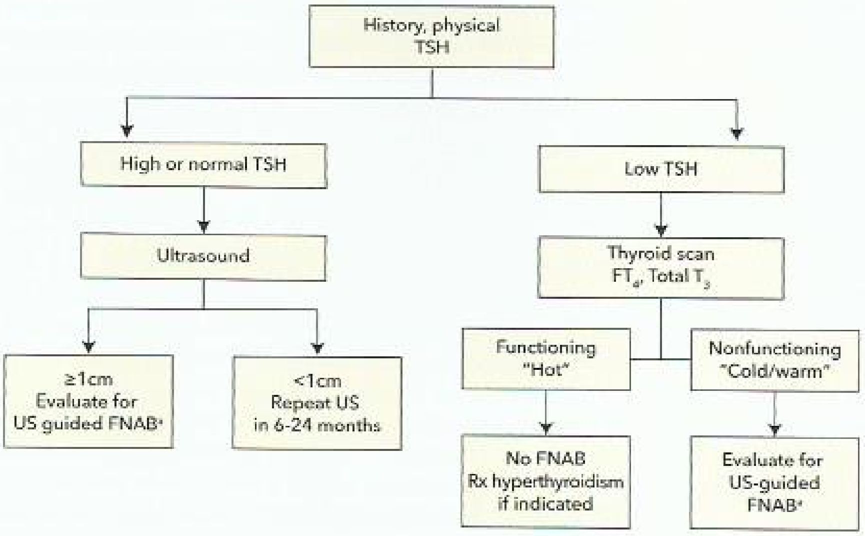


FIGURE 7. Initial evaluation of a thyroid nodule. There are size thresholds for FNAB based on US appearance. A less suspicious lesion may not need FNAB until it is larger than 2 cm, suspicious nodules if larger than 1 cm. FNAB = fine-needle aspiration biopsy; FT_3 = free triiodothyronine; FT_4 = free thyroxine; TSH = thyroid-stimulating hormone; US = ultrasound.

*Need for US guided FNAB depends on clinical risk factors for thyroid cancer, nodule size, and US appearance.

123 (^{123}I), is administered, the percentage taken up by the thyroid is calculated (radioactive iodine uptake [RAIU]), and an image is obtained (thyroid scan). Hot nodules concentrate radioactive iodine to a greater extent than normal thyroid tissue.

Thyroid/neck ultrasound is performed in patients with a normal or elevated TSH to confirm the presence of thyroid nodules. The management of nonfunctioning thyroid nodules is determined by the ultrasound results and presence of symptoms. The 2015 American Thyroid Association guidelines classify thyroid nodules into five sonographic patterns based on echogenicity, whether they are solid, cystic, or both, and features of malignancy (**Table 32**). Hyperechoic nodules are brighter, isoechoic nodules are equally bright, and hypoechoic nodules are darker than the background parenchyma. Ultrasound can determine the size of the nodule. FNAB is not recommended for subcentimeter nodules unless associated with symptoms, pathologic lymphadenopathy, or extrathyroidal extension.

Thyroid nodule FNAB should be performed under ultrasound guidance when possible because of improved accuracy compared with palpation biopsy. Thyroid cytopathology is usually interpreted and classified according to criteria developed at the National Cancer Institute Thyroid Fine Needle Aspiration State of the Science Conference (Bethesda Conference). The Bethesda classification system is summarized in **Table 33**. Thyroid FNAB cytology can be nondiagnostic in up to 5% to 10% of specimens. Approximately 60% to 70% of biopsied nodules have benign cytology, 20% are indeterminate, and 5% to 10% have evidence of malignancy.

The management of cytologically indeterminate thyroid nodules (Bethesda III-V) can be challenging, and referral to an endocrinologist is recommended. Clinical monitoring is indicated for all thyroid nodules and should include measurement of serum TSH, as structurally abnormal thyroid glands are at increased risk for thyroid dysfunction (see Disorders of Thyroid Function). American Thyroid Association sonographic pattern and clinical context guide the timing of initial ultrasound follow up for benign nodules and those not evaluated with FNAB. Repeat ultrasound should be performed in 6 to 12 months for all high suspicion nodules, 12 to 24 months for intermediate and low suspicion nodules, and 24 months or longer for very low suspicion nodules. Repeat FNAB is indicated for all high suspicion nodules, nodules with concerning new sonographic findings, and intermediate or low suspicion nodules that increase significantly in size, which is defined as a 20% increase in at least two dimensions or an increase in nodule volume of more than 50%. Repeat FNAB is not recommended for nodules that have had two negative biopsies.

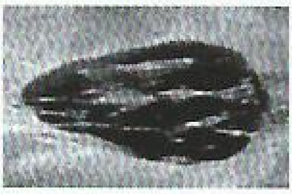
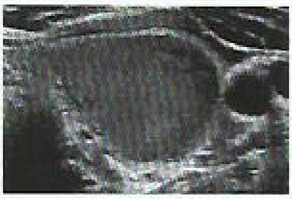
KEY POINTS

- The initial evaluation of a thyroid nodule begins with measuring serum thyroid-stimulating hormone.
- Patients with a suppressed thyroid-stimulating hormone level are evaluated with thyroid scintigraphy; those patients with normal or elevated thyroid-stimulating hormone are evaluated with ultrasonography.
- Patients with nodules 1 cm or larger should be evaluated with fine-needle aspiration biopsy.
- Fine-needle aspiration biopsy is not recommended for subcentimeter nodules unless associated with symptoms, pathologic lymphadenopathy, or extrathyroidal extension. HVC

Goiters

The term "goiter" denotes an enlarged thyroid gland. Goiters can be seen in the setting of normal thyroid function, hypothyroidism, or hyperthyroidism. The most common cause worldwide is endemic goiter due to severe iodine deficiency. Patients presenting with goiter should be questioned about iodine intake, rate of change in size, and risk factors for thyroid cancer (see Thyroid Cancer). Clinical history should focus on

TABLE 32. Summary of 2015 American Thyroid Association Guidelines: Sonographic Patterns and Recommendations for Fine-Needle Aspiration Biopsy

Sonographic Pattern	Representative Image	Description	Estimated Risk of Malignancy	Size Threshold for Fine-Needle Aspiration Biopsy
Benign		Pure cyst (anechoic with no internal blood flow)	<1%	Fine-needle aspiration biopsy not recommended
Very low suspicion		Some mixed cystic and solid nodules (spongiform nodules)[a]	<3%	2 cm[c]
Low suspicion		Isoechoic/hyperechoic solid nodules; some mixed cystic and solid nodules	5%-10%	1.5 cm
Intermediate suspicion		Hypoechoic solid nodules	10%-20%	1 cm
High suspicion		Hypoechoic solid nodules with one or more suspicious feature[b]	>70%-90%	1 cm

[a]Microcystic spaces occupying more than 50% of the nodule volume is highly correlated with benign cytology.

[b]Microcalcifications, shape taller than wide in the transverse plane, irregular margins, extrathyroidal extension or pathologic lymph nodes (image shows hypoechoic solid nodule with irregular margins).

[c]Clinical observation is an acceptable alternative.

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symptoms suggestive of thyroid hormone excess or deficiency and compression. Compressive symptoms include shortness of breath, cough, dysphagia, and voice changes and are evident in 10% to 20% of patients with goiter, most of whom also have clinically apparent thyromegaly. On examination tracheal deviation should be assessed and the size, symmetry, and consistency of the thyroid and presence of nodules should be noted. Possible venous obstruction should be assessed by having the patient raise the arms above the head. The findings of jugular venous distension, facial plethora, and flushing indicate possible thoracic outlet obstruction with reduced venous return (Pemberton sign) (**Figure 8**). Serum TSH level should be assessed in patients with goiter. If low, free T_4 and total T_3 should be measured and thyroid scintigraphy performed. If normal or elevated, thyroid/neck ultrasound is indicated in patients with risk factors for thyroid cancer, palpable thyroid nodules, gland asymmetry, large goiters, rapid growth pattern, or compressive symptoms. Patients with signs or symptoms of compression require additional testing as outlined below, and surgery may be needed for symptomatic

TABLE 33. Diagnoses Obtained by Fine-Needle Aspiration Biopsy of Thyroid Nodules and Risk for Malignancy

Fine-Needle Aspiration Biopsy Diagnosis	Risk for Malignancy[a]	Management
Benign	0%-3%	Repeat ultrasound in 6-24 months[b]
Atypia of uncertain significance/follicular lesion of uncertain significance	10%-30%	Repeat FNAB in 3 months[c]
Suspicious for follicular neoplasm	25%-40%	Lobectomy[b]
Suspicious for malignancy	50%-70%	Lobectomy or total thyroidectomy
Malignant	97%-99%	Lobectomy or total thyroidectomy
Nondiagnostic	5%-10%	Repeat FNAB If two nondiagnostic FNABs, surgery

FNAB = fine-needle aspiration biopsy.

[a]Risk for malignancy by cytology diagnosis includes noninvasive follicular thyroid neoplasm with papillary like nuclear features (NIFTP), a "pre-cancerous" lesion. If counted as benign, the risk of malignancy is reduced for all Bethesda categories except nondiagnostic and benign readings. Data from Cibas ES, Ali SZ. The 2017 Bethesda System for reporting thyroid cytopathology. Thyroid. 2017 Nov;27(11):1341-1346. doi: 10.1089/thy.2017.0500. PubMed PMID: 29091573.

[b]If American Thyroid Association "high suspicion" pattern, repeat ultrasound and FNAB in 6 to 12 months.

[c]Supplementary management strategies include molecular genetic testing of the nodule and selective use of thyroid scintigraphy (when serum thyroid stimulation hormone level is low-normal).

management. Treatment of hypothyroid and hyperthyroid conditions in the setting of goiter is discussed below.

KEY POINTS

- The most common worldwide cause of goiter is severe iodine deficiency.
- Patients with goiter should be questioned about iodine intake, rate of change in size, assessed for signs and symptoms of compression, and evaluated for clinical manifestations of thyroid hormone excess or deficiency.
- Serum thyroid-stimulating hormone should be assessed in patients with goiter; if low, free thyroxine (T_4) and total triiodothyronine (T_3) should be measured and thyroid scintigraphy performed; if T_4 and T_3 are normal or elevated, a thyroid/neck ultrasound is indicated in the presence of risk factors for thyroid cancer, palpable thyroid nodules, gland asymmetry, large goiters, rapid growth pattern, or compressive symptoms.

Multinodular Goiter

Multinodular goiter is the most common cause of goiter in older adults in the United States. Evaluation includes measurement of serum TSH and, when TSH is not suppressed, thyroid/

FIGURE 8. The Pemberton sign. Head and neck with arms down (*left*) and arms elevated (*right*).

neck ultrasound should be performed and discrete nodules evaluated as discussed previously (see Thyroid Nodules). The frequency of thyroid malignancy in patients with multinodular goiter is similar to those with solitary thyroid nodules. Signs and symptoms of compression or suspected substernal extension require additional testing. CT or MRI of the neck and chest (when substernal goiter is suspected) can define anatomic relationships and assess for tracheal narrowing. The administration of iodinated contrast should be avoided when possible to avoid precipitating iodine-induced hyperthyroidism (Jod-Basedow phenomenon). A flow-volume loop study is indicated in patients with symptoms of airway compression or when the tracheal lumen measures less than 1 cm in diameter on CT or MR (see MKSAP 18 Pulmonary and Critical Care Medicine). Endoscopy or a swallowing study can assess for extrinsic compression of the esophagus in patients with cervical dysphagia. Consultation with an otolaryngologist is indicated to confirm clinically suspected vocal cord paralysis. Surgery is indicated for significant compression or suspected malignancy.

Diffuse Goiter

The most common cause of diffuse goiter is autoimmune thyroid disease associated with thyroid dysfunction (Hashimoto thyroiditis and Graves disease). Infiltrative disorders, such as Riedel (IgG4-related) thyroiditis, are rare causes of diffuse goiter. Diffuse goiter may also occur in euthyroid patients in the absence of predisposing inflammatory or neoplastic processes. Genetic predisposition, iodine insufficiency, and cigarette smoking are contributing factors. Thyroid/neck ultrasound is indicated in euthyroid patients with diffuse goiter. It is recommended for patients with Graves disease or Hashimoto thyroiditis when there is thyroid gland asymmetry or nodules on examination. As discussed previously, additional testing is indicated if compressive signs or symptoms are present. Thyroid surgery is considered in the setting of significant compression.

Thyroid Cancer

Thyroid cancer is diagnosed in 13.9 per 100,000 people per year in the United States. The incidence of thyroid cancer has increased over the last four decades and now is the fifth most common cancer in women. Much of this change is attributable to a rise in the diagnosis of small noninvasive cancers, initially detected incidentally on imaging done for other reasons (carotid Doppler studies, neck/chest CT, PET scan). Mortality rates have remained stable with an overall 5-year survival rate of 98.1%. Papillary thyroid carcinoma and follicular thyroid carcinoma, collectively known as differentiated thyroid cancer, account for the most thyroid cancer diagnoses in the United States. Papillary thyroid carcinoma commonly spreads to cervical lymph nodes but is associated with a low risk of distant metastases; whereas lymph node metastases are rare in follicular thyroid carcinoma, metastases to lung, bone, and other sites can be seen. The types and frequency of thyroid cancer are shown in **Figure 9**.

Thyroid cancer is often identified incidentally; however, it may be detected on neck examination. Risk factors for thyroid cancer include a personal history of ionizing radiation exposure with a higher prevalence of papillary thyroid carcinoma in persons exposed to ionizing radiation (>10 rads), with the highest risk seen following childhood exposures, such as with nuclear accidents (Chernobyl), and a personal or family history of thyroid malignancy. Additional risk factors for thyroid cancer include extremes of age (younger than 30 or older than 60) and male gender. Findings suggestive of malignancy include rapid nodule growth, a hard fixed nodule, dysphagia, vocal cord paralysis (hoarseness), and cervical lymphadenopathy. The diagnosis is confirmed by fine-needle aspiration biopsy.

Surgery is the mainstay of thyroid cancer treatment. Either total thyroidectomy or hemithyroidectomy is acceptable for unilateral differentiated thyroid cancers measuring 1 to 4 cm, as long as locoregional spread is not suspected. Total thyroidectomy is otherwise indicated. Unique risks of

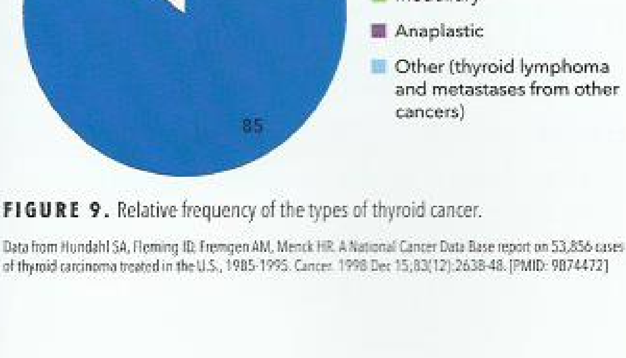

FIGURE 9. Relative frequency of the types of thyroid cancer.

Data from Hundahl SA, Fleming ID, Fremgen AM, Menck HR. A National Cancer Data Base report on 53,856 cases of thyroid carcinoma treated in the U.S., 1985-1995. Cancer. 1998 Dec 15;83(12):2638-48. [PMID: 9874472]

thyroid surgery include hypocalcemia as a result of removal or devascularization of the parathyroid glands and difficulty breathing or voice changes from recurrent laryngeal nerve injury. Referral to a high-volume thyroid surgeon (>90 cases per year) is preferred due to a lower risk of postoperative complications.

Postoperative radioactive iodine (^{131}I) should be considered for the dual purposes of thyroid remnant ablation and adjuvant therapy for patients with differentiated thyroid cancer and an intermediate to high risk of recurrence, such as with extrathyroidal extension, lymphovascular invasion, poorly differentiated/more aggressive histology, or metastatic disease. TSH stimulation, achieved either by withdrawal of thyroid hormone (levothyroxine) replacement or administration of recombinant human TSH (rhTSH), is required to promote ^{131}I uptake by thyroid follicular cells. Following ^{131}I therapy, patients undergo whole-body scanning to identify areas of ^{131}I uptake corresponding to metastatic disease. Uptake is expected in the postsurgical thyroid bed but not elsewhere. ^{131}I therapy is also used to treat thyroid cancer recurrences not amenable to surgical resection.

After initial cancer treatment, serum thyroglobulin (Tg), a sensitive marker for the detection of persistent or recurrent disease, and thyroglobulin antibody (TgAb) titers are monitored. When TgAb is present, Tg levels are uninterpretable because TgAb can falsely lower Tg measurement. In this case, the TgAb level serves as a surrogate marker. A falling TgAb titer over time correlates with a favorable prognosis, whereas a rising titer is suspicious for persistent or recurrent disease.

Neck ultrasound is regularly performed in routine thyroid cancer surveillance, usually 6 to 12 months after the initial cancer treatment. In patients at high risk of recurrent disease, diagnostic radioactive iodine (^{123}I or ^{131}I) whole-body scanning with TSH-stimulated Tg measurement can be performed. If residual or recurrent thyroid cancer is suspected, such as when serum Tg is persistently elevated or rising over time but not identified by neck ultrasound or radioactive iodine whole-body scanning, adjunctive imaging tests including CT, MRI, bone scan, or PET/CT can be useful in disease localization.

Treatment of intermediate to high-risk differentiated thyroid cancer includes TSH suppression with daily levothyroxine. Thyroid follicular cells are TSH responsive, as are most well-differentiated thyroid cancers. To reduce cancer recurrence, a sufficient dose of levothyroxine is administered to suppress the serum TSH below normal with the specific goal individualized. A serum TSH level less than or equal to 2 but at or above the lower limit of the reference range can be targeted in patients with low risk thyroid cancer. Monitoring and dose adjustment by internists is appropriate in conjunction with the endocrinologist. Metastatic thyroid cancer is managed with active surveillance, additional surgery, or ^{131}I therapy, followed by external beam radiation therapy and/or chemotherapy (tyrosine kinase inhibitors).

Anaplastic thyroid cancer is a rare but aggressive thyroid malignancy that can occur in patients with preexisting differentiated thyroid cancer or de novo. It carries a dismal prognosis with median survival of 5 months. Anaplastic thyroid cancer presents with a rapidly enlarging neck mass and may be unresectable at the time of diagnosis. Treatment is palliative in most cases with surgery, external beam radiation therapy, and chemotherapy.

Medullary thyroid cancer arises from parafollicular cells. Germline *RET* oncogene mutations occur with familial medullary thyroid cancer and multiple endocrine neoplasia (MEN) 2A and 2B. MEN should be ruled out with genetic testing prior to surgery, given its association with pheochromocytoma. Medullary thyroid cancer is treated with total thyroidectomy and central neck lymph node dissection. Levothyroxine is indicated to treat postoperative hypothyroidism in patients with medullary thyroid cancer with a goal serum TSH level within the reference range. Serum calcitonin, serum carcinoembryonic antigen levels, and neck ultrasound are part of routine cancer surveillance.

Low-risk papillary thyroid cancer, confined to the thyroid gland, that has been completely resected, has not metastasized, and does not demonstrate aggressive pathologic features (lymphovascular invasion or tall cell variant), requires no additional treatment. The risk of disease-related death is less than 1%, and the risk of structural disease recurrence is 1% to 2% for low-risk unifocal papillary microcarcinomas. Patients receiving either lobectomy or thyroidectomy have similarly excellent outcomes.

KEY POINTS

- Thyroid cancer is often detected incidentally but can be detected when a thyroid nodule or abnormal lymph node is noted on neck examination.
- Surgery is the mainstay of thyroid cancer treatment; either hemithyroidectomy or total thyroidectomy is acceptable for unilateral differentiated thyroid cancers measuring 1 to 4 cm, as long as locoregional spread is not suspected, while total thyroidectomy is preferred in all other cases.
- In addition to surgery, patients with differentiated thyroid cancer and an intermediate to high risk of recurrence are treated with radioactive iodine therapy (^{131}I) and thyroid-stimulating hormone suppression with levothyroxine.

Evaluation of Thyroid Function

Serum TSH is the most sensitive and recommended initial test of thyroid function. It is used to determine euthyroidism, hypothyroidism or hyperthyroidism. If TSH is suppressed, free T_4 and total T_3 should be assessed to detect overt or subclinical hyperthyroidism, and if TSH is elevated, free T_4 should be assessed to detect overt or subclinical hypothyroidism. Measuring serum TSH alone is sufficient except in certain circumstances, such as suspected central hypothyroidism, where free T_4 measurement is also indicated (see Disorders of the Pituitary Gland).

Total and free T_4 and total T_3 concentrations can be assessed with a variety of assays and can be accurately measured in most patients with overt thyroid dysfunction. Commercially available free T_3 assays are less reliable. Perturbations in thyroxine-binding globulin and other binding proteins can occur with physiologic changes (pregnancy), certain disease states (nephrotic syndrome), and as a result of medications (oral estrogen therapy). Levels of total T_4 and T_3 will vary based on increasing or decreasing binding proteins and do not reflect actual thyroid function. Measurement of free T_4, the unbound fraction of T_4 in serum, is most commonly determined using widely available immunometric assays. These tests are accurate in most clinical settings, including in patients with mild binding protein derangements; however, they can be inaccurate with more significant perturbations (familial dysalbuminemic hyperthyroxinemia). Measuring free T_4 by equilibrium dialysis is highly accurate, but expensive, not widely available, and rarely necessary.

Patients taking more than 5 to 10 mg/day of biotin should be counseled to discontinue ingestion for 2 days prior to the laboratory assessment of thyroid function. Biotin is a water-soluble vitamin that is commonly found in over-the-counter dietary supplements. High circulating levels of biotin have been shown to interfere with laboratory assays that utilize streptavidin-biotin as an immobilizing system. Biotin interference causes falsely high results with competitive immunoassays used to measure small molecules (free T_4, free T_3, total T_4, and total T_3) and causes falsely low results with sandwich assays used to measure large molecules (TSH).

Measurement of T_3 is recommended in three settings: (1) in the evaluation of thyrotoxicosis to identify isolated T_3 toxicosis, (2) to assess the severity of hyperthyroidism and response to therapy, and (3) potentially, to differentiate hyperthyroidism from destructive thyroiditis. In T_3 toxicosis, the T_3:T_4 ratio is often greater than 20 due to preferential secretion of T_3. Multiple drugs can affect thyroid function and replacement (**Table 34**).

Measurement of T_3 in the setting of hypothyroidism is not necessary or recommended; normal levels are maintained unless hypothyroidism is severe. TSH will become elevated in hypothyroidism first, followed by abnormalities in T_4 level.

There is no clinical indication to assess reverse T_3 levels, and thus it is not recommended.

KEY POINT

- Measurement of triiodothyronine in the setting of hypothyroidism is not necessary or recommended; normal levels are maintained unless hypothyroidism is severe. HV

TABLE 34. Medications that Affect Thyroid Function or Replacement

Mechanism of Action	Drugs	Comments
Decreased absorption or enterohepatic circulation of levothyroxine	Calcium Proton pump inhibitors Iron Cholestyramine Aluminum hydroxide Soybean oil Sucralfate Psyllium	Recommend that levothyroxine administration be separated from these medications by several hours
Increased metabolism of levothyroxine	Phenytoin Carbamazepine Rifampin Phenobarbital Sertraline	Higher levothyroxine doses may be required to maintain TSH in the normal range
Thyroiditis	Amiodarone Lithium Interferon alfa Interleukin-2	May cause hypo- or hyperthyroidism
	Tyrosine kinase inhibitors	Sunitinib
	Immune checkpoint inhibitors	Nivolumab, pembrolizumab
De novo development of antithyroid antibodies	Interferon alfa	May develop Hashimoto thyroiditis, Graves disease, or painless thyroiditis
Inhibition of TSH synthesis or release	Glucocorticoids Dopamine Dobutamine Octreotide	Leads to TSH suppression; TSH should be rechecked 6-8 weeks after these medications are stopped to assess for return to normal.
Increased thyroxine-binding globulin	Estrogen Tamoxifen Methadone	False elevation of total T_3 and T_4 levels; free T_3 and T_4 are a more accurate reflection of hormone levels
Decreased thyroxine-binding globulin	Androgen therapy Glucocorticoids Niacin	False lowering of total T_3 and T_4 levels; free T_3 and T_4 are a more accurate reflection of hormone levels

T_3 = triiodothyronine; T_4 = thyroxine; TSH = thyroid-stimulating hormone.

Disorders of Thyroid Function

Thyroid Hormone Excess (Hyperthyroidism and Thyrotoxicosis)

The term *thyrotoxicosis* describes the exposure of tissues to high levels of circulating thyroid hormones (T_4 and/or T_3) from any cause. Hyperthyroidism is thyrotoxicosis caused by excessive endogenous production of thyroid hormones. The overall prevalence of hyperthyroidism in the United States is 1.3%. In primary hyperthyroidism, the thyroid gland is the anatomic site of dysfunction. Increased secretion of TSH is a rare secondary cause of hyperthyroidism.

Clinical Features and Diagnosis

Table 35 lists signs and symptoms of thyroid hormone excess. In elderly patients hyperthyroidism may be apathetic instead of presenting with classic symptoms. Lid lag (eyelid retraction) can be seen in thyrotoxicosis of any cause and results from increased adrenergic tone. The diagnosis of hyperthyroidism is based on biochemical testing demonstrating a low-serum TSH level and elevated concentrations of free T_4 and/or total T_3. Thyroid scintigraphy with radioactive iodine uptake (RAIU) can verify the cause. RAIU is high (above 30%) or inappropriately normal in hyperthyroidism and low (less than 10%) in other causes of thyrotoxicosis.

TABLE 35. Clinical Manifestations of Thyrotoxicosis and Thyroid Hormone Deficiency[a]

Sign or Symptom	Thyrotoxicosis	Thyroid Hormone Deficiency
General	Fatigue, weight loss,[b] heat intolerance	Fatigue, weight gain, cold intolerance
Neuropsychiatric	Decreased concentration, anxiety, irritability, insomnia	Decreased concentration, depression, psychomotor retardation, hypersomnolence
	Hyperreflexia, tremor, lid lag	Delayed relaxation of DTRs
Cardiovascular	Palpitations, tachycardia, systolic hypertension, high output heart failure	Bradycardia, diastolic hypertension
Gastrointestinal	Hyperphagia, increased frequency of bowel movements, loose stools, diarrhea	Constipation
Genitourinary	Menstrual disturbance (oligomenorrhea, amenorrhea)	Menstrual disturbance (menorrhagia)
Musculoskeletal	Muscle weakness	Myalgia, arthralgia
Cutaneous	Hair loss, increased sweating, increased oil production/acne; periorbital edema	Hair loss, dry skin, brittle nails, periorbital edema, lateral truncation of the eyebrows, myxedematous skin changes

DTRs = deep tendon reflexes.

[a]Goiter may be present in thyrotoxicosis or thyroid hormone deficiency. See text for physical findings characteristic of Graves disease.

[b]Mild weight gain can occur with subclinical hyperthyroidism (thyroid-stimulating hormone suppression without T_4 or T_3 elevation) due to appetite stimulation.

Additional testing can be done when the clinical diagnosis is not clear; when RAIU is unavailable or unreliable (patients on amiodarone, lithium, or exposed to recent iodinated contrast material); or when scintigraphy is contraindicated (pregnancy and lactation). Tests include measurement of thyroid-stimulating immunoglobulin (TSI) or thyrotropin (TSH) receptor antibodies (TRAb) if Graves disease is suspected but the diagnosis remains clinically unclear, and thyroid ultrasound to assess for patterns of vascularity.

KEY POINTS

- The diagnosis of hyperthyroidism is based on biochemical testing demonstrating a low serum thyroid-stimulating hormone level and elevated concentrations of free thyroxine and/or total triiodothyronine.
- Thyroid scintigraphy with determination of radioactive iodine uptake can verify the cause of hyperthyroidism.

Causes

Causes of thyrotoxicosis are listed in **Table 36**. Graves disease, toxic multinodular goiter, and toxic adenoma are the most common causes of hyperthyroidism.

Graves Disease

Graves disease is a multisystem disease and can affect the thyroid, ocular muscles, and skin. It causes 80% of hyperthyroidism in iodine-sufficient areas. It is an autoimmune thyroid disorder predominantly affecting women with a peak incidence among patients aged 30 to 60 years. Graves disease is also more common in patients with other autoimmune disorders or a family history of thyroid autoimmunity. T lymphocytes become sensitized to thyroid antigens and

TABLE 36. Causes of Thyrotoxicosis

Disorder	Comments
Graves disease	Common; TRAb mediated activation of TSHR
Toxic multinodular goiter	Common; autonomously functioning thyroid tissue
Toxic adenoma	Common; autonomously functioning thyroid tissue
Thyroiditis (acute, subacute, painless)	Common; thyroid inflammation resulting in release of stored thyroid hormones
Medication induced	Common; amiodarone, lithium, interferon alfa, interleukin-2, tyrosine kinase inhibitors, immune checkpoint inhibitors
Thyrotoxicosis factitia	Common; administration of exogenous thyroid hormone; ingestion of contaminated pork or beef products
HCG-mediated (Pregnancy, trophoblastic disease, germ cell tumor)	Common in pregnancy, other forms rare; indiscriminant binding of HCG to TSHR due to common alpha subunit shared by TSH and HCG.
Struma ovarii	Rare; autonomously functioning thyroid tissue in an ovarian teratoma accounting for >50% of the tumor
Follicular thyroid cancer metastases	Rare; autonomously functioning follicular thyroid carcinoma metastases
Thyrotrope adenoma	Rare; TSH-secreting pituitary adenoma

HCG = human chorionic growth hormone; TSH = thyroid-stimulating hormone; TRAb = thyrotropin (TSH) receptor antibodies; TSHR = TSH receptor.

stimulate B lymphocytes to produce antibodies against the TSH receptor (TSI or TRAb). The thyroid is diffusely enlarged, may have a bruit, and has a firm, smooth texture on examination; cervical lymphadenopathy can occur. Systolic hypertension, tachycardia, hyperreflexia, and warm moist skin are often present.

Graves ophthalmopathy affects 25% of patients. Cigarette smoking is a risk factor. Clinical manifestations include periorbital edema, chemosis (conjunctival edema), proptosis (protrusion of the globe), diplopia (due to oculomotor paresis), and vision loss. Graves ophthalmopathy does not respond to the treatment of hyperthyroidism and often requires glucocorticoids or surgery.

Pretibial myxedema is a rare infiltrative dermopathy of Graves disease that affects 2% to 3% of patients; it is a nonpitting edema that is indurated, with a peau d'orange appearance, typically on the shins (see MKSAP 18 Dermatology).

KEY POINTS

- In Graves disease, the thyroid is diffusely enlarged, may have a bruit, and has a firm, smooth texture on examination; cervical lymphadenopathy can also occur.
- Graves ophthalmopathy does not respond to the treatment of hyperthyroidism and often requires glucocorticoids or surgery.

Toxic Adenoma and Multinodular Goiter

Toxic adenoma and multinodular goiter typically affect older adults as the prevalence of thyroid nodules increases with age. Thyroid nodules synthesize and secrete thyroid hormones independent of TSH stimulation. Exposure to iodinated contrast can precipitate conversion from nontoxic to toxic adenoma(s), such as with contrasted CT scanning and cardiac catheterization.

Destructive Thyroiditis

Thyrotoxicosis occurs in destructive thyroiditis as a result of unregulated release of preformed thyroid hormone from thyroid follicles damaged by inflammation. Causes are listed in **Table 37**. Thyroiditis typically has three phases: thyrotoxic, hypothyroid, and return to euthyroidism. The first two phases can last up to 3 months each. A person has increased risk of additional bouts of thyroiditis once the initial thyroiditis has resolved.

TABLE 37. Causes of Destructive Thyroiditis

Disorder	Comments
Painless (silent) thyroiditis	Seen with underlying autoimmune thyroid disease (Hashimoto thyroiditis)
Postpartum thyroiditis	Painless thyroiditis occurring postpartum; permanent hypothyroidism occurs in 20%
Medication-induced thyroiditis	Painless thyroiditis; amiodarone, lithium, interferon alfa, interleukin-2, tyrosine kinase inhibitors, immune checkpoint inhibitors
Subacute thyroiditis (de Quervain or subacute granulomatous)	Painful thyroiditis; follows a viral upper respiratory tract infection
Infectious (suppurative)	Painful thyroiditis; *Staphylococcus* or *Streptococcus* species infection usually seen in immunocompromised patients
Radiation-induced thyroiditis	Painful thyroiditis; occurs after radioactive iodine therapy or neck external beam radiation therapy

Management

Most thyrotoxic patients benefit from β blockers (atenolol, metoprolol, propranolol) to reduce adrenergic symptoms rapidly. Propranolol decreases the peripheral conversion of T_4 to T_3, but is non-cardioselective and requires twice or three times daily dosing. Atenolol and metoprolol are preferred owing to once-daily dosing that increases adherence and their cardioselective nature that decreases central nervous system side effects.

There are three treatment modalities for hyperthyroidism: thioamides (methimazole and propylthiouracil [PTU]), radioactive iodine (^{131}I) ablative therapy, and thyroidectomy. The choice of treatment is predicated on the cause of the hyperthyroidism and patient preference. Short-term use of methimazole to normalize thyroid function prior to ^{131}I therapy or thyroidectomy is recommended for patients 65 years of age or older or who have prevalent cardiovascular disease or multiple comorbidities. Referral to an endocrinologist is recommended.

Graves Disease

Antithyroid drugs (thionamides) are often used in the initial treatment of Graves hyperthyroidism because up to 50% will have spontaneous remission of hyperthyroidism within 24 months, especially if the goiter is small and only low doses of thioamide are required to achieve euthyroidism. Recurrent hyperthyroidism is likely if TRAb levels remain elevated at the time of drug discontinuation. If Graves hyperthyroidism recurs, definitive treatment is recommended.

Agranulocytosis and liver dysfunction are two rare but serious side effects of thioamides. Prior to treatment, baseline CBC with differential and liver profile should be assessed. Agranulocytosis should be suspected and the patient's neutrophil count assessed in the setting of fever or pharyngitis. Liver function should be assessed in any patient with symptoms or signs of hepatic dysfunction (jaundice, icterus). Methimazole is the antithyroid drug of choice, except in the first trimester of pregnancy, because PTU has been associated with fatal hepatonecrosis.

The goal of ^{131}I ablative therapy in Graves disease is to render the patient hypothyroid. Women receiving ^{131}I therapy must avoid pregnancy for 6 to 12 months after treatment. In patients with Graves ophthalmopathy, there is an acute escalation of thyroid autoantibody titers following radioiodine therapy that may exacerbate ocular symptoms. Pretreatment of

Graves ophthalmopathy or selection of alternative treatments depends on the severity of the eye disease.

Thyroidectomy in Graves hyperthyroidism is most appropriate when there is a large goiter with compressive symptoms, moderate to severe Graves ophthalmopathy, and/or with coexistent thyroid cancer or primary hyperparathyroidism.

Other Causes

First-line therapy for a toxic adenoma or toxic multinodular goiter is either ^{131}I therapy or thyroid surgery. Choice is determined by patient preference, presence of compressive symptoms, and access to a high-volume thyroid surgeon.

Destructive thyroiditis is managed expectantly with β-blockers to control adrenergic symptoms and NSAIDs, followed by high-dose glucocorticoid therapy, for pain control in painful thyroiditis.

KEY POINTS

- Most thyrotoxic patients benefit from β-blockers to reduce adrenergic symptoms.
- The three treatment modalities for hyperthyroidism are thionamides (methimazole and propylthiouracil), radioactive iodine (^{131}I) ablative therapy, and thyroidectomy; the choice of treatment is predicated on the cause of the hyperthyroidism and patient preference.
- Antithyroid drugs (thionamides) are associated with up to a 50% spontaneous remission rate within 24 months; agranulocytosis and liver dysfunction are two rare but serious side effects.

Subclinical Hyperthyroidism

Subclinical hyperthyroidism diagnosis is based on suppression of the serum TSH, with normal T_4 and T_3 levels. Subclinical hyperthyroidism affects 0.7% of the U.S. population. Approximately 0.5% to 7% progress to overt hyperthyroidism per year and 5% to 12% revert to normal thyroid function. The most common cause is toxic multinodular goiter.

Subclinical hyperthyroidism has been associated with an increased risk of atrial fibrillation and cardiovascular events. A recent large prospective cohort study demonstrated higher rates of hip fracture with subclinical hyperthyroidism (7% in subclinical hyperthyroidism vs. 4.5% in euthyroid patients); however, it is unknown whether treatment reduces fracture risk.

The TSH will normalize at 6 weeks in more than 25% of patients with subclinical hyperthyroidism. Therefore, observation and rechecking thyroid function prior to the initiation of treatment is reasonable unless the risk of complications is high, such as in patients with cardiac disease. Higher risk of cardiovascular and skeletal complications is seen with serum TSH level under 0.1 µU/mL (0.1 mU/L). Treatment of subclinical hyperthyroidism is recommended for patients with serum TSH levels below 0.1 µU/mL (0.1 mU/L) and with symptoms, cardiac risk factors, heart disease, or osteoporosis, as well as for postmenopausal women not taking estrogen therapy or bisphosphonates.

KEY POINTS

- Subclinical hyperthyroidism is diagnosed based on suppression of the serum thyroid-stimulating hormone, but normal thyroxine and triiodothyronine levels.
- Treatment of subclinical hyperthyroidism is recommended for patients with serum thyroid-stimulating levels below 0.1 µU/mL (0.1 mU/L) and symptoms, cardiac risk factors, heart disease, or osteoporosis, as well as for postmenopausal women not taking estrogen therapy or bisphosphonates.

Thyroid Hormone Deficiency

Thyroid hormone deficiency affects more than 10 million Americans. It is 10 times more common in women than men.

Clinical Features and Diagnosis

Signs and symptoms of thyroid hormone deficiency are listed in Table 35. Thyroid hormone deficiency is also associated with laboratory abnormalities including anemia, elevated LDL cholesterol, and hyponatremia.

The diagnosis of primary hypothyroidism is made by measuring serum TSH, and if elevated, measuring free T_4, which can be added on in most laboratories. Serum TSH is elevated in both overt and subclinical hypothyroidism, but free T_4 is normal when subclinical and low in overt hypothyroidism. Thyroid autoantibodies [thyroid perioxidase (TPO) antibodies] are present in most patients with Hashimoto thyroiditis; however, measurement of TPO antibody titer is not necessary unless the diagnosis is unclear. The diagnosis of hypothyroidism is discussed elsewhere (see Disorders of the Pituitary Gland).

KEY POINTS

- The diagnosis of hypothyroidism is made by measuring serum thyroid-stimulating hormone, and if elevated, then measuring free thyroxine.
- Serum thyroid-stimulating hormone is elevated in both overt and subclinical hypothyroidism, but free thyroxine is normal in subclinical hypothyroidism and low in overt hypothyroidism.
- Thyroid autoantibodies [thyroid perioxidase (TPO) antibodies] are present in most patients with Hashimoto thyroiditis; however, measurement of TPO antibody titer is not necessary unless the diagnosis is unclear.

Causes

Causes of hypothyroidism are listed in **Table 38**. The most common cause in the United States is autoimmune thyroid gland failure (due to Hashimoto thyroiditis), while iodine deficiency, which affects 2 billion people worldwide, is the most common cause globally. Iodide deficiency is uncommon in the

TABLE 38. Causes of Thyroid Hormone Deficiency

Disorder	Comments
Hashimoto thyroiditis	Autoimmune thyroid disorder associated with anti-TPO antibodies
Post-thyroidectomy	Treatment of Graves disease, goiter, thyroid nodules, or thyroid cancer
Post-radioactive iodine therapy	Treatment of Graves disease or toxic adenoma/multinodular goiter
External beam radiation to the neck	Treatment of Hodgkin lymphoma and head/neck malignancies
Thyroiditis (acute, subacute, suppurative)	Typically a transient hypothyroidism prior to recovery of euthyroid state
Central hypothyroidism	TSH deficiency from hypothalamic or pituitary disease; TSH should not be used to assess for replacement dose adequacy; T_4 level should be used for dosing
Congenital hypothyroidism	Universal neonatal screening in the United States where the incidence is 1 in 3500
Iodide deficiency	Common worldwide in developing countries with severe iodine deficiency
Drug-induced	Amiodarone, lithium, interferon-alpha, interleukin-2, iodine, thionamides (methimazole), ethionamide, tyrosine kinase inhibitors (sunitinib), immune checkpoint inhibitors (ipilimumab)

Anti-TPO = anti-thyroid peroxidase; TSH = thyroid-stimulating hormone; T_4 = thyroxine.

United States as a result of efforts to fortify food (iodized salt). Central hypothyroidism is also uncommon.

Primary Hypothyroidism

Hashimoto thyroiditis (chronic lymphocytic thyroiditis) is an autoimmune thyroid disorder characterized by diffuse infiltration of the thyroid gland by lymphocytes and plasma cells with subsequent follicular atrophy and scarring. It is more common in patients with other autoimmune disorders or a family history of thyroid autoimmunity. Diffuse goiter can be seen most commonly in younger patients. Most patients (90%) have TPO antibodies, and the risk of developing hypothyroidism is four times higher in euthyroid patients with TPO antibodies.

Hypothyroidism occurs in all patients after thyroidectomy and 20% of patients after thyroid lobectomy. Postablative hypothyroidism occurs after ^{131}I therapy in 90% of patients with Graves disease within 1 year of radioactive iodine therapy, and in 60% of patients with toxic multinodular goiter, although onset of hypothyroidism may be delayed for many years in the latter case. External beam radiation to the neck also can cause hypothyroidism, as with Hodgkin lymphoma and head/neck malignancies.

Drug-induced hypothyroidism is another cause of primary hypothyroidism (see Table 38).

KEY POINTS

- The most common cause of primary hypothyroidism is autoimmune thyroid gland failure due to Hashimoto thyroiditis, typically associated with thyroid perioxidase antibodies.
- In addition to Hashimoto thyroiditis, common causes of hypothyroidism include thyroid surgery and postablative hypothyroidism following ^{131}I therapy for treatment of Graves disease or toxic multinodular goiter.

Subclinical Hypothyroidism

Subclinical hypothyroidism is typically asymptomatic and diagnosed by a serum TSH level above the upper limit of the reference range and a normal free T_4 level. It affects 5% to 10% of the general population. Transient elevation of serum TSH should be ruled out by repeating the measurement in 6 to 8 weeks. The rate of progression from subclinical to overt hypothyroidism is 2% to 4% per year, while one-third of patients spontaneously revert to normal thyroid function. The normal range for TSH increases with age, and a TSH level of up to 10 µU/mL (10 mU/L) is within the normal range for persons 80 years of age and older.

Subclinical hypothyroidism with TSH above 10 µU/mL (10 mU/L) may be a risk factor for coronary artery disease and heart failure. There is no evidence that treating subclinical hypothyroidism improves quality of life, cognitive function, blood pressure, or weight, but in patients with elevated LDL cholesterol, normalization of the TSH will lower LDL cholesterol.

Management

Thyroid hormone replacement with levothyroxine is the treatment of choice for thyroid hormone deficiency. Goals of treatment are to normalize serum TSH (in primary hypothyroidism) or free T_4 (in central hypothyroidism) and to resolve signs and symptoms of hypothyroidism. Beginning a full replacement dose (1.6 µg/kg lean body weight) is appropriate for most patients with overt hypothyroidism, except in older adults and patients with cardiovascular disease for whom lower initial doses (25-50 µg/day) are recommended. Assessment of the adequacy of treatment should be done with a repeat serum TSH level at least 6 weeks after initiation or change in dose with a goal of a normal TSH.

T_3-containing compounds are not recommended in the treatment of hypothyroidism due to its short half-life, which results in spikes in T_3 levels. Studies have failed to show that T_3 alone or in combination with T_4 has clear benefit in treatment of hypothyroidism.

Subclinical hypothyroidism with a serum TSH value above 10 µU/mL (10 mU/L) should be treated. Initial treatment is 25 to 50 µg of levothyroxine per day. There is unclear benefit and potential for harm in treating mild subclinical hypothyroidism

(TSH > 5-10 µU/mL [5-10 mU/L]). Overtreatment is seen in more than one-third of patients over 65, which may increase risk for dysrhythmia and bone loss.

Oral levothyroxine is absorbed in the jejunum and ileum. Ideally it should be taken on an empty stomach (60 minutes before breakfast or coffee are consumed). If the patient is having difficulty adhering to morning administration, then it can be taken before bed. Missed doses can be taken the following day in younger patients struggling with daily adherence. The absorption of an orally administered dose is 70% to 80% under optimum fasting conditions. Gastrointestinal disorders (such as celiac disease) may impact absorption and result in higher than expected levothyroxine dose requirements. Medications can also interfere with the absorption or metabolism of levothyroxine (see Table 34).

KEY POINTS

- Levothyroxine is the treatment of choice for thyroid hormone deficiency; it should be taken on an empty stomach 60 minutes before eating breakfast or consuming coffee.
- HVC Triiodothyronine-containing compounds are not recommended in the treatment of hypothyroidism due to its short half-life, which results in spikes in triiodothyronine levels.
- HVC Overtreatment of subclinical hypothyroidism is common, especially in patients older than 65 years of age, and should be avoided.

Drug-Induced Thyroid Dysfunction

Many medications can affect thyroid function and are listed in Table 34.

Amiodarone is an antiarrhythmic medication with high iodine content (37%) and prolonged half-life of approximately 60 days. Thyroid dysfunction occurs in approximately 25% of amiodarone-treated patients and can present as hypothyroidism, hyperthyroidism, painless thyroiditis, or goiter. Hypothyroidism, seen in 20% of affected patients, is usually seen in the setting of Hashimoto thyroiditis. All patients can have a transient rise in TSH levels in the first few months of amiodarone therapy due to the Wolff-Chaikoff effect (temporary decrease in thyroid production due to iodine load), but most regain normal thyroid function.

Thyrotoxicosis affects 5% of patients treated with amiodarone. Type 1 (hyperthyroidism) amiodarone-induced thyrotoxicosis occurs in patients with Graves disease or thyroid nodules. It is a form of iodine-induced hyperthyroidism (Jod-Basedow phenomenon). It is treated with thioamides, typically methimazole. Type 2 (destructive thyroiditis) amiodarone-induced thyrotoxicosis is more common and occurs in patients without underlying thyroid disease. It is usually self-limiting but sometimes requires treatment with moderate- to high-dose glucocorticoids. The decision to discontinue amiodarone depends on the patient's cardiac condition and type of thyrotoxicosis (type 1 or 2).

KEY POINT

- Thyroid dysfunction occurs in approximately 25% of patients taking amiodarone and can present as hypothyroidism, hyperthyroidism, painless thyroiditis, or goiter.

Thyroid Function and Dysfunction in Pregnancy

Thyroid hormones are essential for normal fetal development. The size of the maternal thyroid gland can increase up to 40% during pregnancy. Production of T_4 and T_3 increases up to 50% to compensate for the increased thyroxine-binding globulin production associated with pregnancy-related increase in estrogen. Iodine requirements also increase up to 50%. Pregnant and lactating women should therefore be counseled to supplement their dietary iodine intake with a daily oral supplement containing 150 µg of iodine, which is included in some but not all over-the-counter and prescription prenatal vitamins. Universal screening of TSH in pregnant women is not recommended. However, those at increased risk of thyroid dysfunction should be screened, which includes those 30 years of age and older; with known hypothyroidism and/or a strong family history of thyroid dysfunction; prior head/neck irradiation; prior neck surgery; positive TPO, TSI, or TRAb status; or other autoimmune disorders.

Changes in thyroid function tests are depicted in **Figure 10**. Placental human chorionic gonadotropin (hCG) stimulates

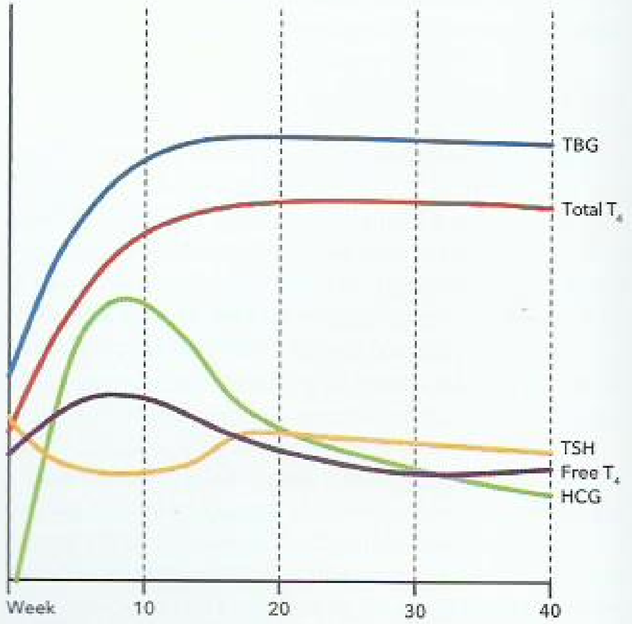

FIGURE 10. Changes in thyroid function tests in pregnancy. HCG = human chorionic gonadotropin; T_4 = thyroxine; TBG = thyroid-binding globulin; TSH = thyroid-stimulating hormone.

thyroid hormone secretion and TSH may be mildly suppressed as a result. In the late first trimester (weeks 7-12) the lower limit of the TSH reference range decreases by 0.4 µU/mL (0.4 mU/L) and upper limit by 0.5 µU/mL (0.5 mU/L). Serum TSH gradually returns to the nonpregnant reference range in the second and third trimester.

Measured total T_4 concentrations increase linearly during pregnancy. After week 16, the upper limit of the total T_4 reference range can be estimated by multiplying the nonpregnant upper limit by 1.5. Free T_4 measured by indirect analogue immunoassays are inaccurate in pregnancy unless method and trimester-specific reference ranges are applied.

Consultation with an endocrinologist is indicated for management of thyrotoxicosis during pregnancy. Gestational thyrotoxicosis from high human chorionic gonadotropin levels is the most common cause of transient TSH suppression. If serum total or free T_4 remains within the trimester-specific reference range, treatment is not needed. Women with moderate to severe hyperthyroidism in early pregnancy should be treated with PTU because potential teratogenic effects are less severe than with methimazole. After the first trimester, women can be transitioned to methimazole. Thyroid function should be followed closely and the serum total or free T_4 should be maintained at or just above the trimester-specific reference range to avoid fetal hypothyroidism.

Graves disease affects 0.2% of pregnant women and can be confirmed by classic physical findings or elevated TSI or TRAb. Women with Graves disease are considered high-risk pregnancies and should be followed by maternal fetal specialists throughout the pregnancy.

Hypothyroidism in pregnancy is associated with increases in miscarriage, premature birth, low birth weight, and decreased infant neurocognitive function. Levothyroxine is the treatment of choice.

For women with preexisting hypothyroidism, levothyroxine dosing can be empirically increased by 30% when pregnancy is confirmed. In treatment-naïve pregnant women with positive TPO antibodies, levothyroxine is started if TSH level is ≥2.5 µU/mL (2.5 mU/L). Treatment is indicated for TPO-negative pregnant women if TSH is above the pregnancy-specific reference range. TSH should be measured every 4 weeks for the first half of pregnancy and around 30 weeks in all hypothyroid women and in those at risk for hypothyroidism (antibody positive or history of hemithyroidectomy or ^{131}I therapy). A TSH level less than 2.5 µU/mL (2.5 mU/L) should be targeted in treated hypothyroid women both preconception and during pregnancy.

Thyroid nodules detected in pregnant women should be evaluated as in nonpregnant patients. The timing of FNAB, whether during or after pregnancy, is determined by the likelihood of cancer and patient preference. Consultation with an endocrinologist is indicated for management of thyroid cancer detected during pregnancy. Pregnant women with a history of thyroid cancer should be managed as when not pregnant.

KEY POINTS

- For women with preexisting hypothyroidism, levothyroxine dosing can be empirically increased by 30% when pregnancy is confirmed.
- In treatment-naïve pregnant women with positive thyroid peroxidase (TPO) antibodies, levothyroxine is started if thyroid-stimulating hormone level is 2.5 µU/mL (2.5 mU/L) or higher; and treatment is indicated for TPO-negative pregnant women if the thyroid-stimulating hormone level is above the pregnancy-specific reference range.

Nonthyroidal Illness Syndrome (Euthyroid Sick Syndrome)

H

Nonthyroidal illness syndrome (NTIS) commonly occurs in patients who are hospitalized and critically ill. Up to 75% of hospitalized patients have thyroid function test abnormalities. Nonthyroidal illness suppresses thyrotropin-releasing hormone, which typically results in suppressed but detectable TSH. An undetectable TSH is not consistent with NTIS. Infrequently, TSH can be mildly elevated in NTIS, but a TSH level of 20 µU/mL (20 mU/L) or greater is not consistent with NTIS. T_4 is typically normal, but due to decreased deiodinase activity in T_4 metabolism, T_3 decreases and reverse T_3 increases (biologically inactive). Thyroid-binding globulin decreases in illness, lowering the total T_4 and T_3 levels. NTIS can be interpreted as an adaptive response to systemic illness and macronutrient restriction.

Treatment of NTIS is not recommended due to lack of significant clinical benefit. In general, thyroid function should not be assessed in hospitalized patients unless there is a strong clinical suspicion of thyroid dysfunction. If NTIS is diagnosed, TSH should be rechecked approximately 6 weeks after the patient has recovered from their nonthyroidal illness to assess for return to normal. H

KEY POINTS

- Treatment of nonthyroidal illness syndrome is not recommended due to lack of significant clinical benefit. HVC
- Thyroid function should not be assessed in hospitalized patients unless there is a strong clinical suspicion of thyroid dysfunction. HVC

Thyroid Emergencies

Thyroid Storm

H

Thyroid storm is a rare disorder with high mortality (up to 30%) characterized by severe thyrotoxicosis (suppressed TSH, elevated free T_4 and/or total T_3) and systemic hemodynamic decompensation (shock). Serum thyroid hormone concentrations do not

differentiate thyroid storm from severe thyrotoxicosis. It is the presence of shock that makes the diagnosis of thyroid storm.

Presentation often follows discontinuation of antithyroid drug therapy, systemic illness, labor and delivery, surgery, or trauma. Patients with Graves disease are at higher risk. Clinical manifestations include high fever, tachycardia, altered mental status, and cardiac and hepatic dysfunction. A scoring system, such as the Burch and Wartofsky Point Scale (**Table 39**), can support the diagnosis, but thyroid storm is diagnosed clinically.

Management includes ICU-level care, treatment of any precipitant illness, thyrotoxicosis-directed therapy, and supportive measures. Thyrotoxicosis is treated with intravenous β-blockers (esmolol infusion), thioamide (typically PTU, transitioning to methimazole when more stable), intravenous high-dose glucocorticoids, and potassium iodide. Iodide should be administered more than 1 hour after antithyroid drugs to avoid providing substrate to the gland. Glucocorticoid therapy is a potent inhibitor of peripheral T_4 to T_3 conversion. Bile acid sequestrants can be used to decrease T_4 and T_3 levels, especially in patients unable to take thioamides. Plasmapheresis or emergent thyroidectomy is used in patients who respond poorly to medical therapy. Definitive treatment with thyroidectomy or ^{131}I therapy is indicated in patients who survive thyroid storm.

KEY POINTS

- Thyroid storm is a rare disorder with high mortality (up to 30%) characterized by severe thyrotoxicosis and systemic hemodynamic decompensation.
- Thyroid storm often occurs with discontinuation of antithyroid drug therapy, systemic illness, labor and delivery, surgery, or trauma.
- ICU-level care; treating any precipitating illness; and the use of intravenous β-blockers, thioamide, intravenous high-dose glucocorticoids, and potassium iodide are all used to manage thyroid storm.

Myxedema Coma

Myxedema coma is a life-threatening presentation of severe hypothyroidism with hemodynamic compromise that affects 0.22 people per million per year. Mortality is high (up to 40%), and ICU-level care is required. Risk factors for myxedema coma are female gender, advanced age, cold exposure, or a precipitant event in patients with undiagnosed hypothyroidism, such as myocardial infarction, sepsis, trauma, or stroke. Mental status changes ranging from lethargy to coma to psychosis, coupled with hypothermia (temperature below 34.4 °C (94.0 °F) are the most common clinical manifestations. Bradycardia, hypotension, or decreased respiration rate with resultant hypoxia and hypercapnia are also frequently present. Careful examination of the neck for thyroidectomy scar is critical. Free T_4 is low in myxedema coma. TSH is typically elevated, but without an overtly low free T_4, myxedema coma

TABLE 39. Burch and Wartofsky Point Scale to Support the Diagnosis of Thyroid Storm[a]

Criteria	Points
Thermoregulatory Dysfunction	
Temperature °F (°C)	
99-99.9 (37.2-37.7)	5
100-100.9 (37.8-38.2)	10
101-101.9 (38.3-38.8)	15
102-102.9 (38.9-39.3)	20
103-103.9 (39.4-39.9)	25
≥104 (40)	30
Cardiovascular	
Tachycardia (bpm)	
100-109	5
110-119	10
120-129	15
130-139	20
≥140	25
Atrial fibrillation	
Absent	0
Present	10
Congestive heart failure	
Absent	0
Mild	5
Moderate	10
Severe	20
Gastrointestinal-Hepatic Dysfunction	
Absent	0
Moderate (diarrhea, abdominal pain, nausea, vomiting)	10
Severe (jaundice)	20
Central Nervous System Disturbance	
Absent	0
Mild (agitation)	10
Moderate (delirium, psychosis, extreme lethargy)	20
Severe (seizure, coma)	30
Precipitant History	
Absent	0
Present	10
Scores Totaled	
<25	Thyroid storm is unlikely
25-45	Impending thyroid storm
>45	Thyroid storm is likely

[a]Thyroid storm is diagnosed clinically in the presence of hemodynamic compromise.

From Burch HB, Wartofsky L. Life-threatening thyrotoxicosis: thyroid storm. Endocrinol Metab Clin North Am. 1993 Jun;22(2):263-77. Review. PMID: 8325286.

H CONT is unlikely regardless of how high the TSH. Other metabolic derangements include hyponatremia and hypoglycemia. Cortisol should be drawn with initial laboratory studies to assess for concomitant cortisol deficiency.

Aggressive supportive measures include fluids, vasopressors if necessary, ventilator support, and passive warming rather than active warming to avoid vasodilation, which can worsen hypotension. Stress dose glucocorticoids (100 mg intravenous hydrocortisone every 8 hours) are administered empirically before thyroid hormone is initiated to treat possible concomitant adrenal insufficiency. If random cortisol level is above 18 mg/dL (496.8 nmol/L), hydrocortisone can be discontinued. Replacement of thyroid hormone requires consideration of the need to normalize the thyroid hormone level rapidly and the risk of a fatal cardiac event caused by thyroid hormone administration. Initial treatment is intravenous levothyroxine with loading dose of 200 to 400 µg, followed by a daily oral dose of 1.6 µg/kg. The dose should be reduced to 75% if administered intravenously. Lower levothyroxine doses are recommended with advanced age and/or cardiac disease. Goals of treatment are improved mental status, metabolic parameters, and cardiopulmonary function. When the patient is stable, transition to oral levothyroxine is the goal. H

KEY POINTS

- Myxedema coma is a life-threatening presentation of severe hypothyroidism with hemodynamic compromise; it most often occurs when a systemic illness is superimposed on previously undiagnosed hypothyroidism.
- In addition to aggressive supportive measures, stress-dose glucocorticoids (100 mg intravenous hydrocortisone every 8 hours) are administered empirically before thyroid hormone is initiated to treat possible concomitant adrenal insufficiency.

Reproductive Disorders

Physiology of Female Reproduction

Coordinated actions of the hypothalamus, pituitary gland, and ovaries (known as the hypothalamic-pituitary-ovarian axis) give rise to ovulatory cycles in women. The pulsatile release of gonadotropin-releasing hormone (GnRH) drives the anterior pituitary cells to secrete follicle-stimulating hormone (FSH) and luteinizing hormone (LH) (**Figure 11**). FSH regulates estradiol production and follicle growth in the follicular phase of the menstrual cycle. A sudden rise in LH levels causes release of an ovum midcycle, signaling the start of the luteal phase, which is a constant 14 days. Endometrial sloughing follows decreased estrogen or progesterone levels if a fertilized embryo does not implant. Menses occur every 25 to 35 days; menstrual cycles shorter than 25 days or longer than 35 days in women

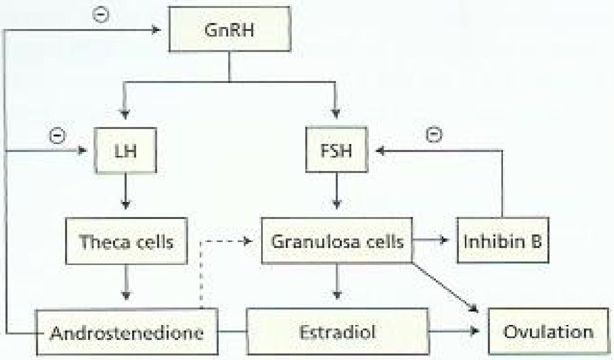

FIGURE 11. Female reproductive axis. Pulses of GnRH drive LH and FSH production. LH acts on theca cells to stimulate androgen (principally androstenedione) production. Androstenedione is metabolized to estradiol in granulosa cells. FSH acts on granulosa cells to enhance follicle maturation. Granulosa cells produce inhibin B as a feedback regulator of FSH production. FSH = follicle-stimulating hormone; GnRH = gonadotropin-releasing hormone; LH = luteinizing hormone; – (*circled*) = negative feedback.

younger than age 40 years are likely anovulatory, resulting in abnormal uterine bleeding or oligomenorrhea. Before puberty, ovaries are quiescent due to immaturity of the hypothalamus. After menopause, all reproductive function and most endocrine function of the ovaries ceases.

KEY POINT

- In women younger than age 40 years, menstrual cycles shorter than 25 days or longer than 35 days are likely anovulatory.

Amenorrhea

Amenorrhea, the absence of menses, can be intermittent or permanent. It may result from hypothalamic, pituitary, ovarian, uterine, or outflow tract disorders.

Clinical Features

Primary Amenorrhea

Primary amenorrhea is defined as absence of menses at age 15 years in the presence of normal growth and secondary sexual characteristics. Primary amenorrhea is most commonly caused by a genetic (50%) or anatomic (15%) abnormality. Most causes of secondary amenorrhea can also present as primary amenorrhea.

The most common cause of primary amenorrhea is gonadal dysgenesis, most commonly with Turner syndrome (45,XO). Turner syndrome is caused by loss of part or all of an X chromosome. It occurs in 1 in 2500 live female births. It is associated with short stature and primary ovarian insufficiency (POI); primary amenorrhea is seen in approximately 90% of patients with Turner syndrome.

Anatomic abnormalities that can cause primary amenorrhea include an intact hymen, transverse vaginal septum, and vaginal agenesis. Vaginal agenesis (also known as müllerian agenesis or Mayer-Rokitansky-Küster-Hauser syndrome) is the

second most common cause of primary amenorrhea, with an incidence of 1 in 5000 live female births. Women with vaginal agenesis have a normal female karyotype and ovarian function, and thus, normal external genitalia and secondary sexual characteristics.

Secondary Amenorrhea

Secondary amenorrhea is defined as absence of menses for more than 3 months in women who previously had regular menstrual cycles or for 6 months in women who have irregular menses. In women with oligomenorrhea, defined as fewer than nine menstrual cycles per year or cycle length longer than 35 days, the evaluation is the same as for secondary amenorrhea.

Functional hypothalamic amenorrhea (FHA) is caused by a disruption of the hypothalamic-pituitary-ovarian axis and is the most common cause of secondary amenorrhea after pregnancy. Disruption of the pulsatile release of hypothalamic GnRH may occur due to stress, weight loss, or exercise. In many cases, all three factors are present. FHA is a diagnosis of exclusion; history and physical examination, biochemical testing, and, imaging, when appropriate, should be undertaken to rule out other causes of secondary amenorrhea including intracranial tumor, infiltrative or destructive disorders such as lymphocytic hypophysitis, histiocytosis X, sarcoidosis, Sheehan syndrome, and acute or chronic systemic illness.

Premenopausal women with hyperprolactinemia present more often with oligomenorrhea or amenorrhea than galactorrhea. Hyperprolactinemia accounts for 10% to 20% of non-pregnancy-mediated amenorrhea. Menstrual dysfunction in hyperprolactinemia results from inhibition of GnRH.

Menstrual dysfunction is common in women with thyroid disorders; while heavy bleeding is typical with hypothyroidism, secondary amenorrhea can also occur.

Hyperandrogenic disorders are associated with amenorrhea, with polycystic ovary syndrome by far the most common hyperandrogenic cause.

Spontaneous primary ovarian insufficiency (POI) can be diagnosed in women younger than age 40 years with menstrual dysfunction in association with two serum FSH levels in the menopausal range. POI affects 1 in 100 women. In addition to disordered menses, affected women may develop symptoms related to estrogen deficiency, such as vasomotor symptoms, sleep disturbance, and dyspareunia related to vaginal dryness. Most cases are sporadic, but a first-degree relative with POI suggests a familial etiology, whereas a personal history of autoimmune disorders can suggest an autoimmune polyglandular syndrome. Women with POI have increased risk for development of autoimmune adrenal insufficiency.

Intrauterine adhesions are the only uterine cause of secondary amenorrhea. Amenorrhea results from the development of scar tissue within the uterine cavity preventing build up and shedding of endometrial cells. Adhesions develop following uterine instrumentation, most commonly associated with uterine curettage for pregnancy complications (Asherman syndrome).

KEY POINTS

- Primary amenorrhea is defined as absence of menses at age 15 years in the presence of normal growth and secondary sexual characteristics; it is most commonly caused by a genetic (50%) or anatomic (15%) abnormality.
- Secondary amenorrhea is defined as absence of menses for more than 3 months in women who previously had regular menstrual cycles or for 6 months in women who have irregular menses.

Evaluation of Amenorrhea

A thorough history and physical examination is the first step in evaluating amenorrhea. Important data include medication and illicit drug exposure, changes in weight, exercise history, psychosocial stressors, and family history related to menarche. Symptoms can include headaches or visual changes suggesting pituitary pathology, symptoms of thyroid excess or deficiency, galactorrhea suggesting hyperprolactinemia, or vasomotor symptoms associated with estrogen deficiency.

Physical examination should include a pelvic examination to evaluate the vagina, cervix, and uterus for abnormalities. Imaging may be necessary to confirm a normal uterus. Physical examination should also include evaluation for features of Turner syndrome, such as a low hairline, webbed neck, shield chest, and widely spaced nipples.

In patients with primary or secondary amenorrhea, measurement of height, weight, and BMI is important. A low BMI (<18.5) may suggest FHA due to an eating disorder, excessive exercise, or systemic illness. A high BMI (≥30) is frequently seen in women with polycystic ovary syndrome (PCOS). Additional physical examination findings suggestive of PCOS include acne and hirsutism. Hypercortisolism is associated with acne and hirsutism, as well as abnormal fat pad distribution, centripetal obesity, facial plethora, proximal muscle weakness, and wide (>1 cm) violaceous striae. Vitiligo or other signs of autoimmune disease increase the likelihood of autoimmune POI. Breast examination should include assessment for expressible galactorrhea. Vulvovaginal atrophy suggests estrogen deficiency.

After ruling out pregnancy, initial laboratory testing in both primary and secondary amenorrhea should include measurement of FSH, thyroid-stimulating hormone (TSH), free thyroxine, and prolactin levels. Next steps are guided by these laboratory results (**Figure 12**).

If the TSH level is abnormal, evaluation and management of thyroid dysfunction should occur (see Disorders of the Thyroid Gland).

If the prolactin level is elevated, repeat prolactin testing is needed to confirm the diagnosis. A careful review of medications is essential because many drugs can cause hyperprolactinemia. Kidney and liver function testing is also required (see Disorders of the Pituitary Gland).

If the FSH level is elevated, testing should be repeated in 1 month with simultaneous serum estradiol testing. If the FSH

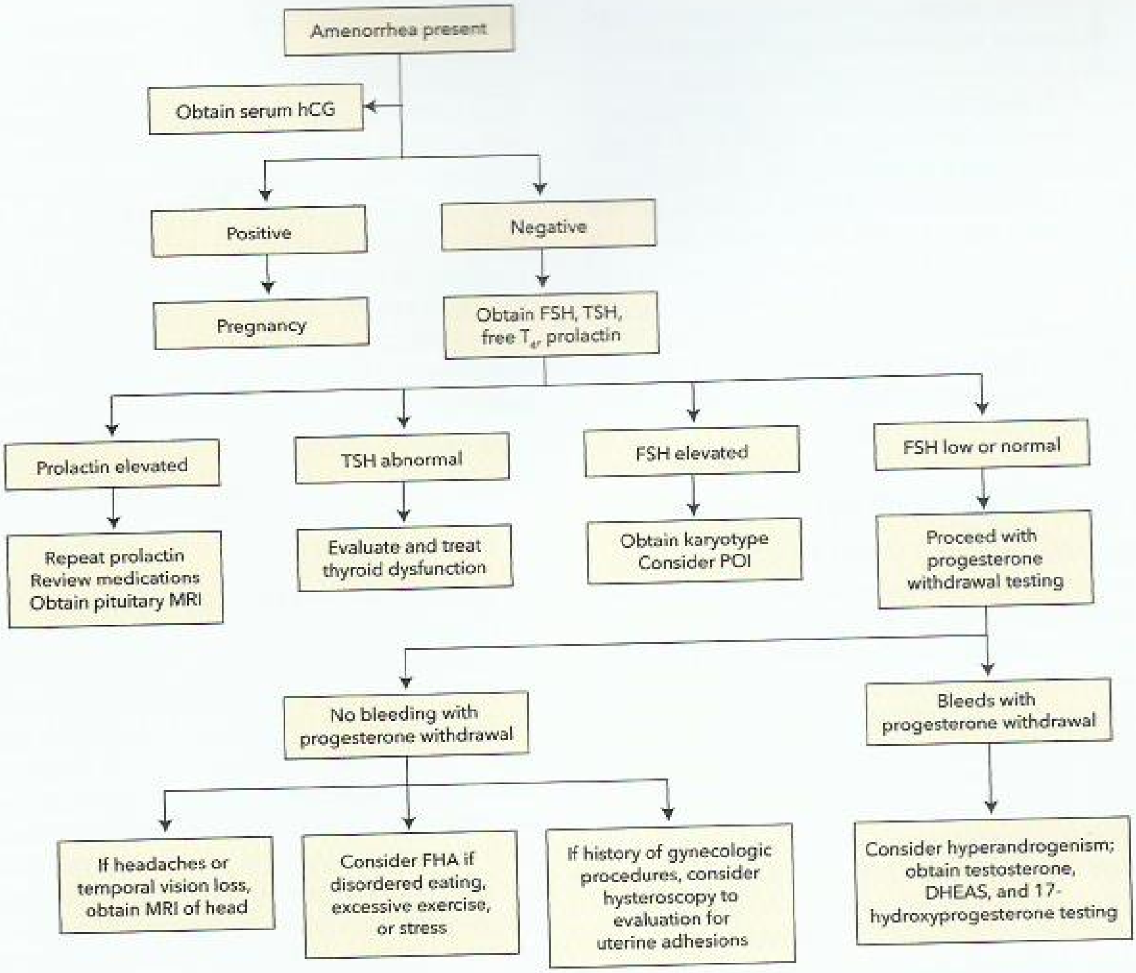

FIGURE 12. Algorithm for evaluating amenorrhea. FHA = functional hypothalamic amenorrhea; FSH = follicle-stimulating hormone; DHEAS = dehydroepiandrosterone sulfate; hCG = human chorionic gonadotropin; POI = primary ovarian insufficiency; T_4 = thyroxine; TSH = thyroid-stimulating hormone.

level is elevated on repeat testing and estradiol level is low, karyotype analysis is indicated to evaluate for Turner syndrome. POI and menopause also cause elevated FSH levels.

In women with normal or low FSH levels, the history and physical examination findings determine next steps. Further assessment of estrogen status can be determined by a progestin withdrawal test. If a normal estrogen state is confirmed (bleeding within a week of stopping progesterone), hyperandrogenism should be considered. Laboratory evaluation for hyperandrogenism includes measurement of total testosterone and sex hormone-binding globulin (SHBG) levels. PCOS is the most likely cause of menstrual dysfunction in women with hyperandrogenism; however, other hyperandrogenic disorders must be excluded before diagnosing PCOS. If no bleeding occurs, a low-estrogen state due to hypothalamic hypogonadism is most likely.

Imaging studies that can be utilized in the evaluation of amenorrhea include MRI of the sellar region (to evaluate for structural integrity of the pituitary), pelvic ultrasound (to assess for anatomic abnormalities of uterus, vagina, and ovaries), hysterosalpingogram and hysteroscopy (to assess for uterine outflow obstructions). Choice of imaging study, as well as necessity of imaging at all, is predicated on prior biochemical test results indicating the cause of the amenorrhea.

KEY POINT

- After ruling out pregnancy, initial laboratory testing in both primary and secondary amenorrhea should include measurement of follicle-stimulating hormone, thyroid-stimulating hormone, free thyroxine, and prolactin.

Treatment of Amenorrhea

Almost all women with Turner syndrome will need exogenous estrogen therapy with cyclic progestin to prevent endometrial hyperplasia. Estrogen-progestin therapy is continued until age 51 years, the average age of menopause.

Treatment for FHA includes less-restrictive eating patterns, weight gain, or a reduction in strenuous exercise to restore menses. Additionally, it is important to treat conditions associated with FHA, including low bone mass, eating disorders, anxiety, and other mood disorders.

Amenorrhea due to hyperprolactinemia with a lactotroph adenoma is managed with dopamine agonist therapy if fertility is desired, or with estrogen/progestin if not, to prevent bone loss. If hyperprolactinemia-induced amenorrhea is related to medications that cannot be stopped (such as antipsychotic agents), estrogen/progestin therapy is indicated.

Treatment of POI includes estrogen/progestin therapy until approximately age 51 years. Psychosocial support is important due to higher scores on depression, anxiety, and negative affect scales in patients with POI; subspecialty consultation to discuss fertility options is also indicated.

Treatment of vaginal agenesis includes nonsurgical vaginal dilation; surgical options can be considered if nonsurgical therapy fails.

Hyperandrogenism Syndromes

Hirsutism and Polycystic Ovary Syndrome

Elevated serum concentrations of androgens in women most commonly manifest with hirsutism and may also present with acne, androgenetic alopecia, and/or virilization. Hirsutism is the presence of excessive terminal hair in male-pattern growth distribution; it affects approximately 10% of women. Virilization (voice deepening, clitoromegaly, male pattern baldness, severe acne) occurs only in severe hyperandrogenism and raises concern for ovarian hyperthecosis or an androgen-producing ovarian or adrenal tumor. Onset of hirsutism in a woman older than age 30 years also raises concern for an androgen-producing tumor. Although androgen-secreting ovarian tumors are rare, they should be considered in patients with abrupt, rapidly progressive hirsutism or severe hyperandrogenism as well as in women with marked hyperandrogenemia (total testosterone >150 ng/dL [5.2 nmol/L]).

Women with chronic hirsutism and menstrual cycles every 25 to 35 days most likely have idiopathic hirsutism or PCOS. Fifteen to 40% of women with hyperandrogenism and menses every 21 to 35 days have ovulatory dysfunction. PCOS is the most common cause of hirsutism, accounting for 95% of cases.

PCOS is a disorder characterized by hyperandrogenism and ovulatory dysfunction. PCOS affects 6% to 10% of women and is the most common cause of anovulatory infertility in women. It is associated with rapid GnRH pulses, an excess of LH, and insufficient FSH secretion, resulting in excessive ovarian androgen production and ovulatory dysfunction. It is accompanied by insulin resistance. Elevated insulin levels in PCOS further enhance ovarian and adrenal androgen production, as well as increase bioavailability of androgens related to a reduction in SHBG. PCOS is associated with increased incidence of metabolic syndrome, prediabetes, type 2 diabetes mellitus, hypercholesterolemia, and obesity.

There are a variety of diagnostic criteria for PCOS (**Table 40**). It is important to remember that PCOS is a diagnosis of exclusion; other causes of oligo-/anovulation must be considered including thyroid dysfunction, nonclassical congenital adrenal hyperplasia, hyperprolactinemia, and androgen-secreting tumors.

KEY POINTS

- Polycystic ovary syndrome is a disorder characterized by hyperandrogenism and ovulatory dysfunction affecting 6% to 10% of women.
- Polycystic ovary syndrome is a diagnosis of exclusion; other causes of oligo-/anovulation must be considered including thyroid dysfunction, nonclassical congenital adrenal hyperplasia, hyperprolactinemia, and androgen-secreting tumors.

Evaluation of Hyperandrogenism

The history and physical examination should include details about the onset of hirsutism and other symptoms/signs of hyperandrogenism, menstrual history, family history of hyperandrogenism, signs of insulin resistance (obesity, acanthosis nigricans, skin tags), distribution of terminal hair growth, and hair loss. Exposure to exogenous testosterone (topical, oral, or injected) should be assessed as a possible cause of hyperandrogenism and virilization.

Women with hirsutism should have total testosterone with SHBG measured, as well as morning 17-hydroxyprogesterone to screen for congenital adrenal hyperplasia. Laboratory evaluation for oligomenorrhea or amenorrhea (human chorionic gonadotropin [hCG], prolactin, FSH, TSH, free thyroxine) is also indicated. Serum dehydroepiandrosterone sulfate (DHEAS) measurement should be obtained in cases of recent onset of rapidly progressive hirsutism and/or virilization.

Markedly high DHEAS and/or testosterone levels are not consistent with PCOS. Patients with total testosterone levels

TABLE 40. Diagnostic Criteria for Polycystic Ovary Syndrome

NIH Consensus Criteria 1990 (All Required)	Rotterdam Criteria 2003 (Two of Three Required)	Androgen Excess and Polycystic Ovary Syndrome Society Criteria (All Required)
Menstrual irregularity due to oligo-/anovulation	Oligo-/anovulation	Clinical and/or biochemical signs of hyperandrogenism
Clinical and/or biochemical signs of hyperandrogenism	Clinical and/or biochemical signs of hyperandrogenism	Ovarian dysfunction - oligo-/anovulation and/or polycystic ovaries on ultrasound
Exclusion of other disorders	Polycystic ovaries on ultrasound	Exclusion of other androgen excess or ovulatory disorders

greater than 200 ng/dL (6.9 nmol/L) or DHEAS values greater than 7.0 µg/mL (18.9 µmol/L) require imaging to assess for adrenal tumor (adrenal CT or MRI) or ovarian tumor (transvaginal ultrasound).

Management of Hyperandrogenism

Mechanical hair removal (threading, depilatories, electrolysis, laser) may be adequate for cosmesis in women with idiopathic hirsutism. First-line pharmacologic management of hirsutism is combined hormonal (estrogen-progestin) oral contraceptive agents; these agents suppress gonadotropin secretion and ovarian androgen production, as well as increase SHBG levels. Antiandrogen therapy (spironolactone) can be added for a better cosmetic response; concomitant contraception is mandatory with this therapy due to teratogenesis in male fetuses. Topical eflornithine is also approved for treatment of unwanted hair growth.

In PCOS, weight loss is a first-line intervention in patients with BMI of 25 or greater. Sustained weight loss of 5% to 10% improves androgen levels, menstrual function, and possibly fertility. Oral contraceptive agents are first-line pharmacologic therapy for hirsutism and menstrual dysfunction unless fertility is desired. An antiandrogen agent is added after 6 months if cosmesis is suboptimal with oral contraceptive agents. If fertility is desired, clomiphene citrate or letrozole can be used to correct oligo-/anovulation. Metformin reduces hyperinsulinemia and androgen levels but has minimal impact on hirsutism and ovulation.

Patients with PCOS should be screened for prediabetes/diabetes mellitus, hypercholesterolemia, obesity, hypertension, and obstructive sleep apnea due to increased risk for these conditions. Metformin is indicated when impaired glucose tolerance, prediabetes, or type 2 diabetes mellitus does not respond adequately to lifestyle modification.

KEY POINTS

- Oral contraceptive agents are first-line drug therapy for hirsutism and menstrual dysfunction; an antiandrogen agent may be added for better cosmetic response.
- Patients with polycystic ovary syndrome should be screened for prediabetes/diabetes mellitus, hypercholesterolemia, obesity, hypertension, and obstructive sleep apnea.

Female Infertility

Infertility evaluation is appropriate after 1 year of unprotected intercourse, on average twice weekly, in women younger than age 35 years and after 6 months in women age 35 years or older. Treatment of infertility is typically managed by a reproductive endocrinologist. Both partners should be evaluated concurrently; often, multiple factors are present (see Male Infertility).

History and physical examination findings may suggest the cause of infertility. Key factors include menstrual history (to determine ovulatory status) and assessment for thyroid dysfunction, galactorrhea, hirsutism, pelvic pain, dysmenorrhea, and dyspareunia. History of previous pregnancies, cancer therapy, substance use disorder, sexually transmitted infections, pelvic inflammatory disease, and gynecologic procedures should be explored. Frequency of coitus is important information. Physical examination should include BMI and assessment for signs of hyperandrogenism, estrogen deficiency, hyperprolactinemia, and thyroid dysfunction.

Assessment of ovulatory function is the first step in evaluation. Women with menses approximately every 28 days with molimina symptoms (breast tenderness, abdominal bloating, ovulatory pain) are likely ovulatory. In women without such cycles, assessment of ovulatory status is assessed with a midluteal phase serum progesterone level (obtained 1 week before the expected menses); a progesterone level greater than 3 ng/mL (9.5 nmol/L) is evidence of recent ovulation. If anovulatory cycles are suspected, the initial evaluation includes prolactin, TSH, and FSH measurements, with subsequent assessment for PCOS.

Hysterosalpingogram is used to assess for tubal occlusion and to evaluate the uterine cavity. Exploratory laparoscopy may be used if endometriosis or pelvic adhesions are suspected. If no abnormalities are found, fertility treatments will be offered under the direction of a reproductive endocrinologist, possibly including ovarian stimulation with clomiphene citrate or letrozole, intrauterine insemination, and in vitro fertilization, which may be offered to women age 40 years or older as first-line therapy.

KEY POINTS

- Infertility evaluation is appropriate after 1 year of unprotected intercourse in women younger than age 35 years and after 6 months in women age 35 years or older.
- Both partners should be evaluated concurrently; often, multiple factors are present. HVC
- Assessment of ovulatory function is the first step in evaluation for female infertility.

Physiology of Male Reproduction

The testes contain two anatomical units: the spermatogenic tubules composed of germ cells and Sertoli cells, and the interstitium containing Leydig cells. The three steroids of primary importance in male reproduction are testosterone, dihydrotestosterone, and estradiol. It is the pulsatile secretion of gonadotropin-releasing hormone (GnRH) by the hypothalamus that elicits pulsatile secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) by the gonadotroph cells of the anterior pituitary.

LH regulates testosterone synthesis in Leydig cells in a diurnal pattern; LH secretion is regulated by negative feedback of testosterone and estradiol. FSH regulates Sertoli cell spermatogenesis. Inhibin B is an important peptide inhibitor of pituitary FSH secretion (**Figure 13**). The hypothalamic-pituitary-testicular axis is sensitive to stressors, including acute and chronic illness, fasting, and strenuous exercise, all of which can lower testosterone levels.

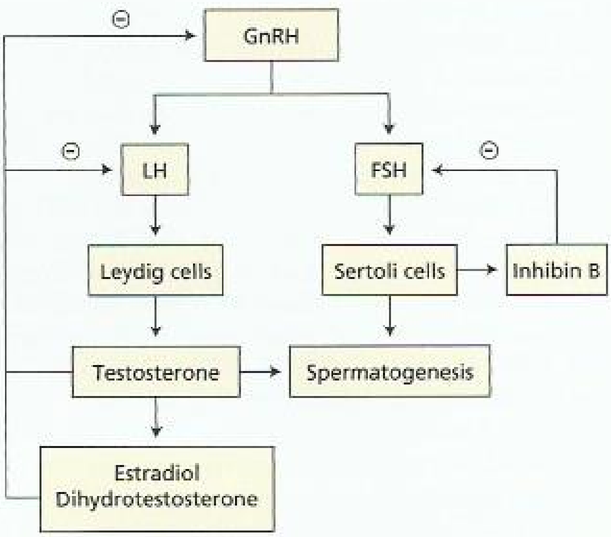

FIGURE 13. Male reproductive axis. Pulses of GnRH elicit pulses of LH and FSH. FSH acts on Sertoli cells, which assist sperm maturation and produce inhibin B, the major negative regulator of basal FSH production. The Leydig cells produce testosterone, which feeds back to inhibit GnRH and LH release. Some testosterone is irreversibly converted to dihydrotestosterone or estradiol, which are both more potent than testosterone in suppressing GnRH and LH. FSH = follicle-stimulating hormone; GnRH = gonadotropin-releasing hormone; LH = luteinizing hormone; – (*circled*) = negative feedback.

Hypogonadism

Causes

Male hypogonadism is a clinical syndrome that results from failure of the testes to produce physiologic levels of testosterone and a normal number of spermatozoa due to disruption of the hypothalamic-pituitary-testicular axis.

Primary hypogonadism is caused by testicular abnormalities. Common causes of acquired primary hypogonadism in adults include mumps orchitis, sequelae of radiation treatment, antineoplastic agents or toxins, testicular trauma or torsion, and acute and chronic systemic illnesses. Klinefelter syndrome (47,XXY) is the most common congenital cause of primary hypogonadism and is associated with tall stature, small testes, developmental delay, and socialization difficulties.

Secondary hypogonadism reflects a hypothalamic (GnRH) and/or pituitary (LH/FSH) deficiency. There are rare congenital causes, such as Kallmann syndrome, which are associated with anosmia. Common causes of acquired hypogonadotrophic hypogonadism are hyperprolactinemia, medications, critical illness, untreated sleep disorders, obesity, liver and kidney disease, alcoholism, marijuana use, and disordered eating. Tumors, trauma, thalassemias, and infiltrative diseases that cause disruption of gonadotropin production (such as sarcoidosis and hemochromatosis) are uncommon causes.

KEY POINT

- Primary hypogonadism is caused by testicular abnormalities; secondary hypogonadism reflects hypothalamic and/or pituitary dysfunction.

Clinical Features

Specific symptoms of hypogonadism in the adult male include decreased morning and spontaneous erections, decreased libido, mastodynia, gynecomastia, decreased need for shaving, and/or decreased axillary and genital hair. Hot flashes, decreased bone mass, and low-trauma fractures are associated with profound and/or longstanding testosterone deficiency. Nonspecific symptoms include decreased mood, energy, concentration, muscle strength and bulk, and stamina, as well as poor sleep and memory. Infertility is more likely to occur with primary than secondary hypogonadism.

Men who develop hypogonadism before puberty have small testes and phallus and lack secondary sexual characteristics. With onset after puberty, there may be some regression of secondary sexual characteristics. A decrease in testes and/or phallus size and development of gynecomastia in adults is more likely due to a primary cause.

Evaluation

Screening men with nonspecific symptoms of hypogonadism is not recommended. In men with specific signs and symptoms, measuring an 8 AM total testosterone level is indicated. If the testosterone level is low, a second 8 AM testosterone level is measured. The diagnosis is made with two low serum testosterone measurements. Measurement of free testosterone is appropriate in obese men because obesity lowers SHBG, leading to a falsely low measured total testosterone level. If testosterone is low, a serum LH measurement is indicated.

An elevated LH level reflects primary hypogonadism and further evaluation should be directed toward identifying the cause.

A low or normal LH level with simultaneous low testosterone reflects secondary hypogonadism. Medications including GnRH analogues (prostate therapy treatment), gonadal steroids (such as anabolic steroid use or megestrol for appetite stimulation), high-dose glucocorticoid treatment, and chronic opiate use can all suppress gonadotropins, resulting in secondary hypogonadism. Additional evaluation includes measurement of serum prolactin and screening for hemochromatosis. Assessment for other pituitary hormone deficiencies is indicated if signs or symptoms are present. Dedicated pituitary MRI should be performed if hyperprolactinemia is present, other pituitary hormone abnormalities are identified, testosterone level is less than 150 mg/dL (5.2 nmol/L), or if there are signs or symptoms of mass effect (**Figure 14**).

KEY POINTS

- Screening men with nonspecific symptoms of hypogonadism is not recommended.
- The diagnosis of male hypogonadism is made with two 8 AM low serum total testosterone measurements.

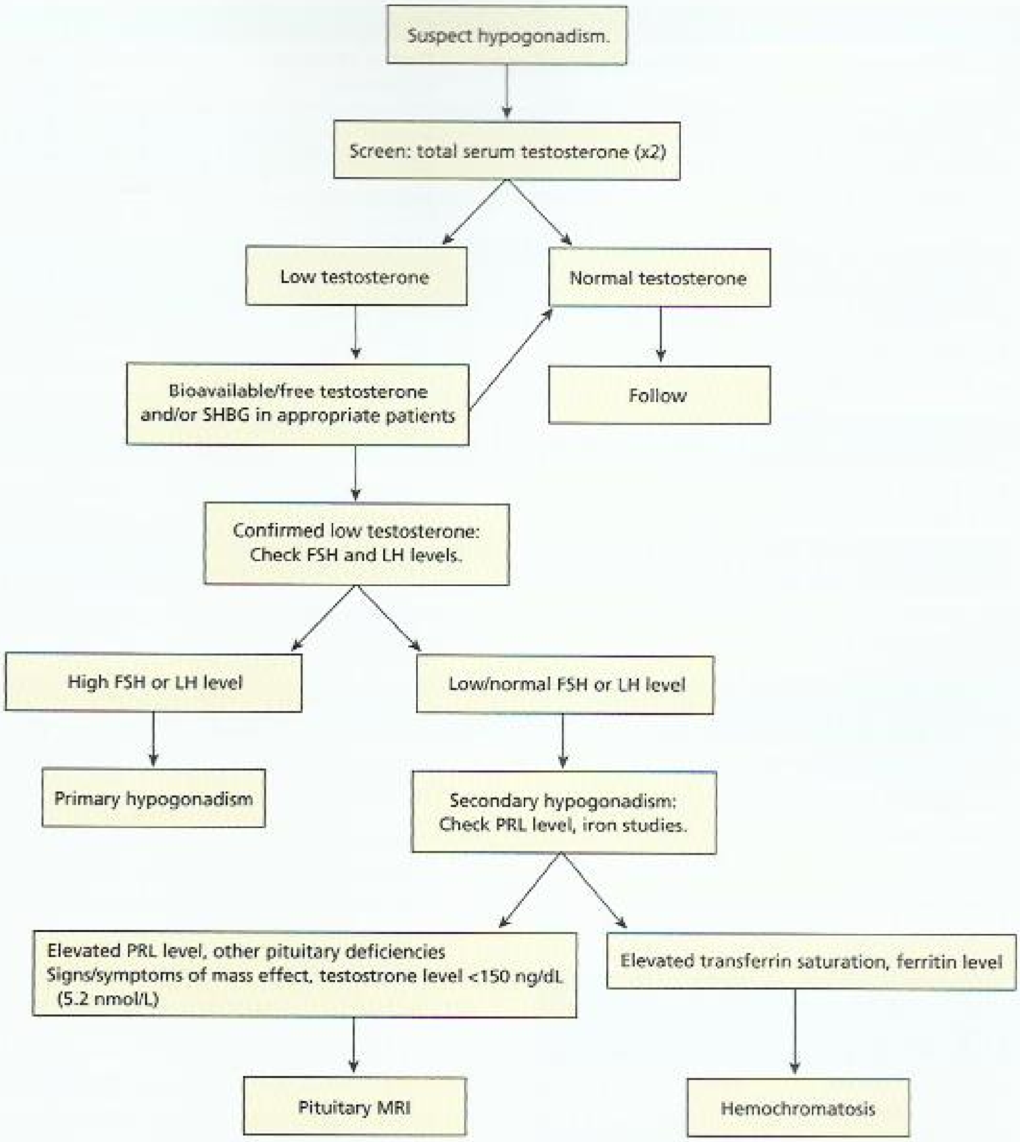

FIGURE 14. Algorithm for evaluating male hypogonadism. FSH = follicle-stimulating hormone; LH = luteinizing hormone; PRL = prolactin; SHBG = sex hormone-binding globulin; ×2 = two separate measurements.

Management

In men with biochemically proven hypogonadism, testosterone therapy can be initiated, after the etiology is determined. There are a variety of testosterone replacement preparations available (**Table 41**). The goal is to replace testosterone so that the measured total testosterone value is in the mid-normal range.

Clinical benefits of testosterone therapy include an increase in libido, lean muscle mass, fat free mass, bone density, and secondary sexual characteristics. Potential adverse effects include acne, impact on prostate tissue, obstructive sleep apnea, thrombophilia, and erythrocytosis (**Table 42**).

Testosterone therapy is only indicated for treatment of testosterone deficiency; it is not used for impaired spermatogenesis, and in fact further impairs spermatogenesis by suppressing pituitary FSH secretion. Patients should be counselled on the decreased fertility associated with exogenous testosterone therapy.

KEY POINTS

- After the etiology of hypogonadism is determined, testosterone therapy should be initiated with a goal of achieving a mid-normal range total testosterone measurement.
- Testosterone therapy is only indicated for treatment of testosterone deficiency; it is not used for impaired spermatogenesis. HVC

TABLE 41. Recommended Testosterone Replacement Therapy

Route of Administration	Preparation	Typical Dosing Pattern	Timing of Initial Monitoring	Advantages; *Disadvantages*
Intramuscular injection	Testosterone cypionate	100-200 mg every 2 weeks	Testosterone midway between injections	Low cost; *fluctuation in testosterone level*
Intramuscular injection	Testosterone enanthate	100-200 mg every 2 weeks	Testosterone midway between injections	Low cost; *fluctuation in testosterone level*
Transdermal patch	Testosterone transdermal 24-hour patch	2-6 mg/day	Morning testosterone ~14 days after starting therapy	Stable levels; *skin rash/ poor adherence to skin*
Transdermal gel	AndroGel 1%	50-100 mg daily	Morning testosterone ~14 days after starting therapy	Stable levels; *potential for skin transfer to others*
Transdermal gel	AndroGel 1.62%	20.25-81 mg daily	Morning testosterone 14-28 days after starting therapy	Stable levels; *potential for skin transfer to others*
Transdermal gel	Fortesta	10-70 mg daily	2 hours after application ~14 days after starting therapy	Stable levels; *potential for skin transfer to others*
Transdermal gel	Testim	50-100 mg daily	Morning testosterone ~14 days after starting therapy	Stable levels; *potential for skin transfer to others*
Transdermal gel	Vogelxo	50-100 mg daily	Morning testosterone ~14 days after starting therapy, prior to application	Stable levels; *potential for skin transfer to others*
Transdermal solution	Axiron	30-120 mg daily	2-8 hours after application ~14 days after starting therapy	Stable levels; *potential for skin transfer to others*
Subcutaneous implants	Testosterone implant pellets	150-450 mg every 3-6 months	Measure at the end of the dosing interval	Infrequent dosing/Incision required for insertion; *risk of recurrent symptomatic hypogonadism as the duration of action is widely variable*

TABLE 42. Endocrine Society Clinical Guidelines for Monitoring Adverse Effects of Testosterone Replacement Therapy

Parameter	Recommended Screening Schedule	Alerts
Hematocrit	Value obtained at baseline and then at 3 months and 6 months after therapy initiation, followed by yearly measurements.	Value >54%
PSA level	For patients >40 years of age with a baseline value >0.6 ng/mL (0.6 µg/L), DRE and PSA level (determined at 3 and 6 months after therapy initiation followed by regular screening).	Increase >1.4 ng/mL (1.4 µg/L) in 1 year or >0.4 ng/mL (0.4 µg/L) after 6 months of use; abnormal results on DRE; AUA prostate symptoms score/ IPSS >19

AUA = American Urological Association; DRE = digital rectal examination; IPSS = International Prostate Symptom Score; PSA = prostate-specific antigen.

Data from Bhasin S, Cunningham GR, Hayes FJ, Matsumoto AM, Snyder PJ, Swerdloff RS, et al; Task Force, Endocrine Society. Testosterone therapy in men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2010;95:2536-59. [PMID: 20525905]

Anabolic Steroid Abuse in Men

Abuse of anabolic steroids is a serious public health concern that goes beyond the professional athlete. The prevalence of anabolic steroids use in men approaches 7%. Steroids are often purchased on the internet and dosing patterns vary. Labile mood, acne, excessive muscle bulk, and small testes may indicate anabolic steroid abuse. Reproductive side effects of anabolic steroid abuse include gynecomastia (due to peripheral conversion of testosterone to estradiol), testicular atrophy, diminished spermatogenesis and fertility, and iatrogenic hypogonadotropic hypogonadism, which may be permanent. Laboratory evidence suggestive of anabolic steroid abuse includes elevated hematocrit, undetectable or low LH level, low SHBG level, and low total testosterone level with elevated testosterone precursor(s), such as androstenedione.

KEY POINTS

- Labile mood, acne, excessive muscle bulk, and small testes may indicate anabolic steroid abuse.
- Side effects of anabolic steroid abuse include gynecomastia, testicular atrophy, diminished spermatogenesis and fertility, and iatrogenic hypogonadotropic hypogonadism, which may be permanent.

Testosterone Changes in the Aging Man

With aging, total testosterone and free testosterone levels in men decline and SHBG increases, which results from testicular and hypothalamic-pituitary dysfunction. While serum testosterone levels decline 1% to 2% per year, most men do not become hypogonadal. Sperm production does not change significantly with age. The consequences of "andropause" are not fully elucidated, but adverse effects may include a negative impact on sexual function, muscle mass, erythropoiesis, and bone health.

The Endocrine Society supports treating older men with biochemically confirmed testosterone deficiency. The goal is replacement to a low-normal range of testosterone. Prior to initiation of treatment, some recommend shared decision making with the patient and discussion of the uncertainty of harms and benefits of testosterone therapy. This strategy is controversial.

Testosterone therapy in men without biochemical evidence of deficiency has not been shown to be beneficial, and studies have shown increased risk for cardiovascular disease and death, venous thromboembolism, and prostate cancer with use of testosterone therapy.

KEY POINTS

- Testosterone changes in men associated with aging do not result in symptomatic hypogonadism in most men.
- HVC Testosterone therapy in men without biochemical evidence of deficiency has not been shown to be beneficial, and studies have shown increased risk for cardiovascular disease and death, venous thromboembolism, and prostate cancer with use of testosterone therapy.

Male Infertility

In couples with infertility, assessment of male infertility should be undertaken concurrently with female assessment. A comprehensive history should focus on potential causes of infertility: developmental history, chronic illness, infection, surgery, drugs and environmental exposures, sexual history, and prior fertility. Physical examination should focus on evidence of androgen deficiency, with careful examination of the external genitals. If testicular examination is abnormal, consider referral to a urologist. Semen analysis is the initial laboratory assessment; collection should occur after 2 to 3 days of sexual abstinence, but no longer to avoid decreased sperm motility. If semen analysis is abnormal, it should be repeated at least 2 weeks later, and if results are abnormal, referral to a reproductive endocrinologist is recommended.

KEY POINT

- Semen analysis is the initial laboratory assessment for male infertility; if results are abnormal, testing should be repeated at least 2 weeks later, with referral to a reproductive endocrinologist if results are abnormal again.

Gynecomastia

Gynecomastia, a benign proliferation of breast glandular tissue due to an increased action of estrogen relative to androgens, occurs in one- to two-thirds of older men. A thorough history and careful review of medications is necessary. Antiandrogen agents, such as spironolactone, cimetidine, and protease inhibitors, have a clear association with gynecomastia. Other identified causes include substance use disorder, malnutrition, cirrhosis, hypogonadism, testicular germ cell tumors, hyperthyroidism, and chronic kidney disease.

On physical examination, gynecomastia presents as a rubbery, concentric, subareolar mass. It is typically bilateral and may be tender if early in its course of development. Unilateral, nontender, and/or fixed breast masses should prompt an evaluation for breast cancer with a mammogram. Pseudogynecomastia is characterized by increased subareolar fat without glandular enlargement.

In a male presenting with painful gynecomastia, measurement of human chorionic gonadotropin, LH, morning total testosterone, and estradiol levels should be obtained if no clear cause is identified on history and physical examination.

Treatment of a specific cause of gynecomastia during the active proliferative phase may result in regression. If gynecomastia is longstanding, regression (spontaneously or with medical therapy) is unlikely due to fibrotic changes. In this scenario, plastic surgery referral may be the best option for cosmetic improvement.

KEY POINT

- Treatment of a specific cause of gynecomastia during the active proliferative phase may result in regression; if gynecomastia is longstanding, regression is unlikely due to fibrotic changes.

Transgender Hormone Therapy Management

Transgender medicine involves the care of persons whose gender identity differs from their sexual assignment at birth. Gender incongruence is persistent incongruence between gender identity and external sexual anatomy at birth not arising from a confounding mental disorder; gender dysphoria is discomfort arising from incongruence between a person's gender identity and their external sexual anatomy at birth. A transgender man is someone with a male gender identity and a female birth-assigned sex; a transgender woman is someone with a female gender identity and a male birth-assigned sex.

Transgender people may avoid health care because of discriminatory or disrespectful interactions in prior health care encounters. Providing a safe environment is critical to ensure that transgender people establish and continue primary and gendering-affirming care. It is important for

providers to understand basic terminology used by the trans community, which varies regionally.

Psychological and medical care must be provided in an environment that avoids preconceptions, and proper environmental signage, terminology, and staff training is essential (see WPATH Standards of Care). Accurate collection of gender identity information is also important; many organizations use a "two-step" method to collect these data: (1) gender identity and (2) sex listed on the original birth certificate, thus avoiding invisibility of transgender status.

Prior to a physical examination, history taking is necessary to understand an individual's anatomic changes associated with gender-affirming hormone therapy (GAHT) and surgical intervention. Secondary sex characteristics present on a wide spectrum of development in transgender patients. Providers should offer appropriate health maintenance and cancer screening based on an individual's anatomy.

GAHT is the most common medical intervention sought by transgender people and does not require subspecialty care. Primary care providers, gynecologists, and endocrinologists may prescribe this therapy. Treatment includes medications for hirsutism (spironolactone), contraception (estradiol/progestin), abnormal uterine bleeding (estradiol/progestins), menopause (estradiol/progestin), testosterone deficiency (testosterone), and benign prostatic hyperplasia (5-α reductase inhibitors).

GAHT must be patient-centered and individualized to the patient's goals. A discussion of the risks/benefits associated with treatment and informed consent are essential before beginning treatment. Criteria to consider before initiating GAHT include persistent, well-documented gender dysphoria, capacity to make a fully informed decision, age of majority in a given country, and if present, control of significant medical or psychological conditions. GAHT limits fertility, thus reproductive options should be discussed with patients prior to initiation of GAHT. Endocrine Society Clinical Practice Guidelines for GAHT are available. With GAHT, most physical changes occur over the course of 2 years, but the exact timeline of change is highly variable.

Feminizing hormone therapy is typically estradiol in combination with an androgen blocker. Goals are breast development; fat redistribution; and reductions in muscle mass, body hair, erectile function, sperm count, and testicular size. Estrogen therapy increases risk of deep venous thrombosis (DVT) and, to a lesser extent based on cohort study results, ischemic stroke and myocardial infarction; contraindications to estrogen therapy include a history of DVT, estrogen-sensitive neoplasm, and end-stage liver disease. Tobacco cessation should be encouraged prior to initiation of estrogen therapy due to increased risk of DVT. Anti-androgen therapy, such as spironolactone, diminishes secondary male sex characteristics and minimizes the estrogen dose needed, thus reducing risks associated with high-dose exogenous estrogen therapy. Monitoring testosterone and estradiol levels for adequate response to therapy is necessary for the first year.

Masculinizing hormone therapy is achieved using topical or injected testosterone with a goal of cessation of menses, facial hair growth, voice deepening, fat redistribution, increased muscle mass and body hair, and clitoral growth. Contraindications to testosterone therapy include pregnancy, unstable coronary artery disease, and polycythemia. Monitoring testosterone and estradiol levels for adequate response to therapy should occur for the first year. Hemoglobin also should be monitored.

Gender confirmation surgery is often the last intervention in transgender persons. Many transgender persons do not pursue surgery, but it is essential for alleviation of gender dysphoria in others. For transgender women, surgical procedures may include augmentation mammoplasty, genital surgery (penectomy, orchiectomy, vaginoplasty, clitoroplasty, vulvoplasty), and non-genital, non-breast surgery (facial feminization, voice surgery, thyroid cartilage reduction). For transgender men, surgical procedures may include mastectomy, hysterectomy with oophorectomy, phalloplasty, vaginectomy, scrotoplasty, and implantation of penile and/or testicular prostheses.

Stringent criteria must be met prior to undergoing irreversible gender reassignment surgery.

KEY POINTS

- Gender-affirming hormone therapy is the most common medical intervention sought by transgender people and does not require subspecialty care; criteria for gender-affirming hormone therapy include persistent, well-documented gender dysphoria, capacity to make a fully informed decision, age of majority in a given country, and if present, control of significant medical or psychological conditions.
- Screening and preventive medicine in transgender patients should be based on the individual's anatomy.

Calcium and Bone Disorders

Calcium Homeostasis and Bone Physiology

Regulation of serum calcium level is complex and dependent on the actions of vitamin D and parathyroid hormone (PTH). The primary effect of vitamin D is to enhance the absorption of calcium within the intestinal tract, whereas the effects of PTH are primarily mediated through regulation of calcium retention and excretion in the kidney (**Figure 15**). Measured calcium levels depend on the amount bound to albumin, which can be affected by nutrition and acid-base status. Hypoalbuminemia of any cause, such as cirrhosis or

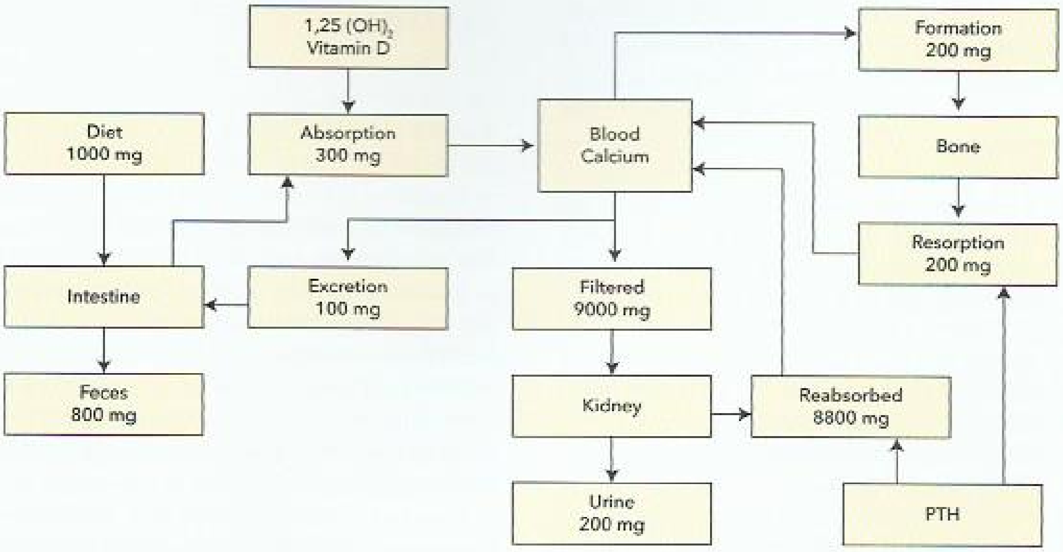

FIGURE 15. Neutral flux of calcium between bone and blood in adults is coordinated by parathyroid hormone (PTH). While most calcium filtered into urine is reabsorbed independent of PTH, PTH further increases retention of calcium from the urine. PTH indirectly augments calcium absorption in the gut by increasing production of 1,25 (OH)$_2$ vitamin D. Both effects of PTH are increasingly important at lower intakes of calcium and as blood levels of calcium decline. Amounts of calcium shown illustrate relative contribution of each organ to calcium homeostasis in a healthy adult.

malignancy-related cachexia, will cause low total calcium levels. When albumin concentration is low, measurement of ionized calcium or calculation of corrected total calcium is required to accurately assess calcium levels.

The level of vitamin D is determined by both production in the skin in response to sunlight and by ingestion, either from food or supplements. While vitamin D_2 (ergocalciferol) and vitamin D_3 (cholecalciferol) are available as supplements, the latter may be more efficacious due to greater potency, longer half-life, and being identical to that formed from ultraviolet light exposure. Activation of vitamins D_2 and D_3 requires hydroxylation initially by the liver and subsequently by the kidney, resulting in the active form of vitamin D, 1,25-dihydroxyvitamin D, calcitriol. 25-Hydroxyvitamin D is the storage form of vitamin D in the body, and measurement of 25-hydroxyvitamin D is the most appropriate test for assessing vitamin stores.

The initial response to a decline in serum calcium is an increase in PTH secretion, which decreases renal calcium excretion and increases calcium resorption from the bones to raise the serum calcium level. PTH also induces increased renal conversion of 25-hydroxyvitamin D to the active metabolite 1,25-dihydroxyvitamin D, which improves the efficiency of intestinal calcium absorption. Continued PTH-mediated mobilization of calcium from bone over months to years in response to chronic negative calcium balance can lead to metabolic bone disease. In contrast, the skeleton, gut, and vitamin D metabolism do not significantly contribute to the correction of hypercalcemia. Instead, an increased filtered load and suppression of PTH secretion leads to robust excretion of calcium by the kidneys provided that effective circulating volume is adequate.

In addition to its role in mineral metabolism, the adult skeleton provides a reservoir of calcium, structural support for mobility, muscle attachment, and protection of vital organs. Bone remodeling allows for continuous skeletal adaptation and repair. Osteocytes coordinate bone remodeling, which is initiated by osteoclastic resorption then followed by much slower osteoblastic bone formation and mineralization of a collagen/protein matrix. The entire skeleton is remodeled approximately every 10 years.

KEY POINTS

- The primary effect of vitamin D is to enhance the absorption of calcium within the intestinal tract, whereas the effects of parathyroid hormone are primarily mediated through regulation of calcium retention and excretion in the kidney.
- Measurement of 25-hydroxyvitamin D is the most appropriate test for vitamin D deficiency.

Hypercalcemia

Clinical Features of Hypercalcemia

Hypercalcemia is diagnosed when the calcium level exceeds normal levels, typically 10.5 mg/dL (2.6 mmol/L). Incidental finding of asymptomatic hypercalcemia on routine or screening blood tests is common.

Classic symptoms of hypercalcemia include polyuria, polydipsia, and nocturia. Additional symptoms may include anorexia, nausea, abdominal pain, constipation, and mental status changes. At higher levels, patients may become obtunded. Symptoms do not correlate linearly with serum calcium or PTH levels.

Severe hypercalcemia and hypercalciuria can lead to volume depletion and acute kidney injury, nephrolithiasis, or nephrocalcinosis. Skeletal manifestations reflect the underlying cause of hypercalcemia. Primary hyperparathyroidism may present as osteoporosis with fragility fractures and low bone density. Severe hyperparathyroidism from parathyroid carcinoma or secondary hyperparathyroidism due to kidney disease may be associated with bone pain and osteitis fibrosa cystica (a radiographic diagnosis). Hypercalcemia associated with lytic bone lesions is often the result of multiple myeloma or breast cancer.

KEY POINT

- Symptoms of hypercalcemia are variable but may include polyuria, polydipsia, nocturia, anorexia, nausea, abdominal pain, constipation, and mental status changes, and they may be associated with acute kidney injury, nephrolithiasis, nephrocalcinosis, and skeletal changes.

Causes and Diagnosis of Hypercalcemia

Clues to the underlying cause of hypercalcemia include the severity, acuity of illness, and patient factors including concurrent illnesses. Hypercalcemia is categorized as mild (<12 mg/dL [3 mmol/L]), moderate (12-14 mg/dL [3-3.5 mmol/L]), or (severe >14 mg/dL [3.5 mmol/L]). When hypercalcemia is incidentally noted, repeat measurement is indicated. If hypercalcemia is confirmed, simultaneous measurement of serum calcium and PTH is a critical first step in diagnosing the cause and categorizing PTH-mediated and non-PTH-mediated hypercalcemia. Ionized calcium measurement is not helpful when the serum albumin level is normal or when there are no acute acid-base disorders. A thorough history and physical examination, as well as careful review of all medications including supplements, should be done in all patients with hypercalcemia.

KEY POINT

- Initial diagnostic testing for hypercalcemia requires simultaneous measurement of serum calcium and parathyroid hormone (PTH), which allows classification as PTH-related and non-PTH-related disease.

Medications Causing Hypercalcemia

Thiazide diuretics may cause mild hypercalcemia, especially in the setting of previously unrecognized, mild primary hyperparathyroidism. Hypercalcemia associated with lithium therapy is due to altered PTH secretion and may occur years after initiation of therapy. If possible, stopping the medication and rechecking calcium levels is a reasonable first step in management. If the calcium returns to normal, this suggests the medication was responsible.

Parathyroid Hormone–Mediated Hypercalcemia

PTH secretion decreases abruptly in response to a rise in serum calcium concentration. Therefore, an elevated or inappropriately normal (usually in the upper half of the reference range) PTH level in a patient with hypercalcemia is diagnostic of PTH-mediated hypercalcemia (**Figure 16**). Patients with an elevated PTH level but normal levels of calcium and vitamin D (normocalcemic primary hyperparathyroidism) may be managed similarly to those with asymptomatic primary hyperparathyroidism.

Primary Hyperparathyroidism

Primary hyperparathyroidism is typically caused by a solitary parathyroid adenoma. Women are more often affected than men, with a peak incidence in the seventh decade of life. Hypercalcemia is usually mild (within 1 mg/dL [0.25 mmol/L] of the upper limits of normal) and may be intermittently normal. Hypercalciuria is present in up to 30% of patients. Since

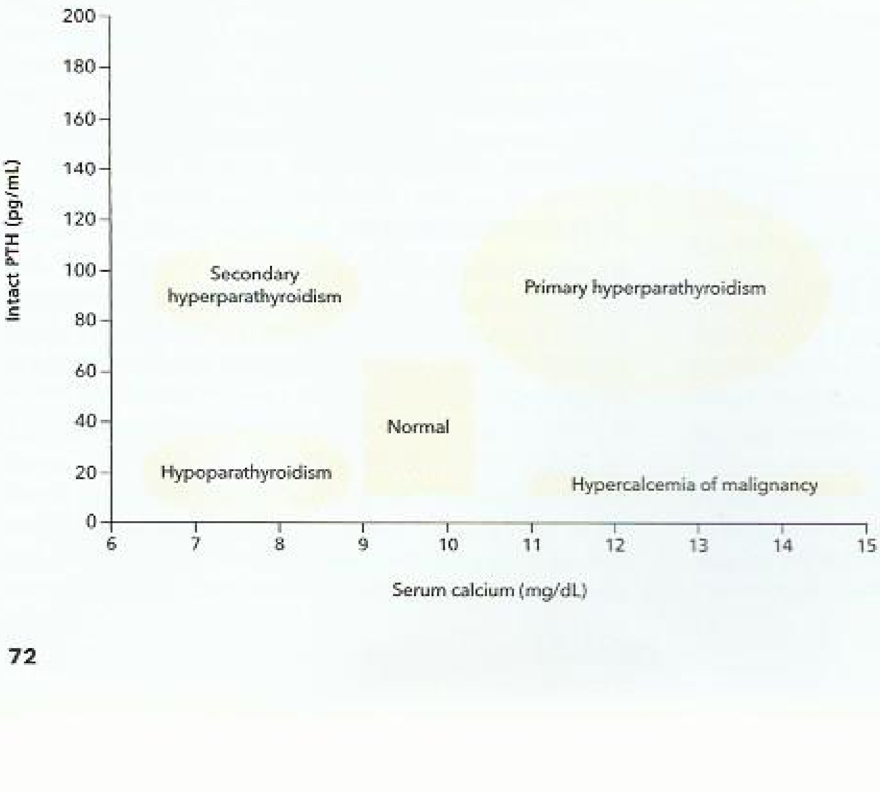

FIGURE 16. Relationship of calcium and parathyroid hormone (PTH) in normal conditions and in several diseases.

PTH enhances kidney phosphate excretion, low or low-normal serum phosphorus concentrations support the diagnosis. Assessment of bone mineral density (BMD) with dual-energy x-ray absorptiometry (DEXA) should include the nondominant forearm, which can be particularly affected in patients with hyperparathyroidism. Although parathyroid imaging with sestamibi or neck ultrasound may localize an adenoma, the presence of an adenoma does not influence the decision to proceed with surgery in the setting of primary hyperparathyroidism. Imaging may be beneficial to the surgeon for planning surgical intervention. In the absence of a history of calcium nephrolithiasis, kidney imaging may be indicated to exclude occult stones if this finding would change management.

Dietary calcium intake should be approximately 1000 mg/d to avoid further increases in urine calcium excretion and PTH secretion. Measurement of 25-hydroxyvitamin D and cautious correction of vitamin D deficiency is important. Repletion is recommended in patients whose levels are below 30 ng/dL (75 nmol/L) with careful attention to urine calcium excretion and serum calcium once vitamin D values are greater than 30 ng/dL (75 nmol/L).

Changes in specific endpoints during monitoring that lead to a recommendation for parathyroid surgery are outlined in **Table 43**. Surgery results in a 95% cure rate and less than 1% rate of complications with an experienced surgeon using minimally invasive techniques. Preoperative correction of vitamin D deficiency is important to avoid postoperative hypocalcemia, which is the result of relative hypoparathyroidism and reduced PTH-mediated production of 1,25-dihydroxyvitamin D culminating in a rapid flux of calcium into bone (hungry bone syndrome). Patients with mild primary hyperparathyroidism commonly require calcium supplementation for up to 1 week after parathyroidectomy until residual parathyroid tissue normalizes serum calcium concentrations. Reassessment of BMD 1 year after parathyroidectomy may show improvement in BMD, especially at the spine.

TABLE 43. Indications for Parathyroid Surgery During Monitoring

Assessment	Indication[a]
Serum calcium (>upper limit of normal)	>1 mg/dL (>0.25 mmol/L)
Skeletal	T-score <−2.5 at lumbar spine, total hip, femoral neck, or distal 1/3 radius; or a significant reduction in BMD[a]
	Vertebral fracture by x-ray, CT, MRI, or VFA
Renal	CrCl <60 mL/min
	Clinical development of a kidney stone or by imaging (x-ray, ultrasound, or CT)

CrCl = creatinine clearance; MRI = magnetic resonance imaging; VFA = vertebral fracture assessment.

[a]A significant change is defined by a reduction that is greater than the least significant change as defined by the International Society for Clinical Densitometry.

From Bilezikian JP, Brandi ML, Eastell R, Silverberg SJ, Udelsman R, Marcocci C, et al. Guidelines for the Management of Asymptomatic Primary Hyperparathyroidism: Summary Statement from the Fourth International Workshop. J Clin Endocrinol Metab. 2014;99:3561-9. [PMID: 25162665]

Approximately one in three patients with asymptomatic primary hyperparathyroidism who initially defer surgery will develop indications for surgery during 10 to 15 years of observation. In those not deemed eligible or who elect not to undergo surgery, evaluation should include annual measurement of serum calcium, creatinine, and glomerular filtration rate (GFR). If kidney stones are suspected, imaging and 24-hour urine collection for biochemical stone profile should be considered. BMD should be obtained every 2 years, and spine imaging should be considered if the patient has significant loss of height or back pain in the setting of a normal BMD.

KEY POINT

- Measurement of 25-hydroxyvitamin D and cautious correction of vitamin D deficiency is important in patients with primary hyperparathyroidism.

Parathyroid Carcinoma

Parathyroid carcinoma is very rare, but may present with symptoms of severe hypercalcemia, with serum levels greater than 14 mg/dL (3.5 mmol/L) and markedly high PTH concentrations. Imaging is not useful and fine-needle aspiration is not recommended due to concerns of tumor seeding. The primary treatment is surgical resection. Unfortunately, 50% of patients may have residual or recurrent disease. Severe hypercalcemia in parathyroid carcinoma that is not amenable to surgery can be treated chronically with cinacalcet. Medical management options are limited, and patients are most likely to die from complications of hypercalcemia.

Tertiary Hyperparathyroidism

In patients with end-stage kidney disease, multigland hyperplasia results from chronic stimulus of PTH (a sequela of long-standing secondary hyperparathyroidism) due to poorly controlled hypocalcemia and hyperphosphatemia. In some cases of secondary hyperparathyroidism, the serum calcium can normalize if the hyperplasia and associated PTH secretion is robust. Chronic stimulation of the parathyroid glands can lead to autonomous production of PTH by all four glands, resulting in hypercalcemia. Tertiary hyperparathyroidism is most commonly recognized after kidney transplantation. Although historically treated with subtotal multigland parathyroidectomy, the hypercalcemia can be resolved in most patients by treatment with paricalcitol or cinacalcet.

Genetic Causes of Hypercalcemia

Familial Hypocalciuric Hypercalcemia

Familial hypocalciuric hypercalcemia (FHH) is an autosomal dominant condition and the most common type of familial hypercalcemia. Patients are asymptomatic. The parathyroid glands and kidney detect serum calcium concentrations

through the calcium-sensing receptor (CaSR). In FHH, inactivating mutation of the CaSR gene causes the parathyroid gland to perceive serum calcium concentrations as low, resulting in increased PTH secretion and a higher serum calcium level. Simultaneously, the mutated CaSR in the kidney increases kidney reabsorption of calcium, leading to paradoxical hypocalciuria in the setting of hypercalcemia.

Although these patients appear to have primary hyperparathyroidism, FHH is a benign condition that is not treated with parathyroidectomy. Hypercalcemia will not resolve with surgery. Patients do not have sequelae of hypercalcemia, such as stones or osteoporosis. Signs suggestive of FHH include: mild hypercalcemia since childhood; low 24-hour urine calcium excretion, especially if calcium-creatinine clearance ratio is below 0.01; and/or family history of parathyroidectomy without resolution of hypercalcemia. If clinically ambiguous, the diagnosis can be confirmed by CaSR genetic testing.

KEY POINT

- The distinction between primary hyperparathyroidism and familial hypocalciuric hypercalcemia can be made by a 24-hour urine collection for calcium and creatinine, which will establish the amount of kidney calcium excretion and will allow evaluation of the calcium-creatinine clearance ratio.

Multiple Endocrine Neoplasia Syndrome

Primary hyperparathyroidism in adolescents and young adults may be the first sign of multiple endocrine neoplasia syndrome (MEN). Primary hyperparathyroidism is associated with MEN1 and MEN2A syndromes. If the family history reveals primary hyperparathyroidism, pituitary tumor, Zollinger-Ellison syndrome, early death from pancreatic neoplasm, pheochromocytoma, or medullary thyroid cancer, MEN is more likely and screening should be considered. In contrast to sporadic primary hyperparathyroidism, MEN syndromes have recurrence of hyperparathyroidism due to ongoing hyperplasia in the remaining parathyroid tissue after parathyroidectomy. MEN1 is associated with mutation of the tumor suppressor *MEN1* gene, and MEN2A is associated with mutation of the *RET* gene. This is best managed in conjunction with or by an endocrinologist.

Non-Parathyroid Hormone-Mediated Hypercalcemia

The differential diagnosis of hypercalcemia with suppressed PTH is broad. In patients with severe hypercalcemia, the history, symptoms, and findings may suggest the underlying cause. Treatment should commence without delay while awaiting results of laboratory testing. In PTH-independent hypercalcemic states, hypercalciuria can be severe and may precede hypercalcemia. PTH is usually undetectable but may be very low (<20 pg/mL [20 ng/L]) if hypercalcemia is mild.

H

Malignancy-Associated Hypercalcemia

The most common cause of non-parathyroid hormone-mediated hypercalcemia is malignancy, and it is typically severe (>14 mg/dL [3.5 mmol/L]). It is often the result of tumor-produced PTH-related protein (PTHrP) leading to extensive resorption of bone. Renal cell carcinoma, breast cancer, and squamous cell cancers are associated with PTHrP-related hypercalcemia. Rarely, locally mediated osteolysis from extensive skeletal metastases, typically in multiple myeloma and breast cancer, may cause efflux of calcium from bone resulting in significant hypercalcemia. For more information, see MKSAP 18 Hematology and Oncology. H

Vitamin D-Dependent Hypercalcemia

Vitamin D-dependent hypercalcemia is associated with normal to elevated serum phosphorus levels because vitamin D enhances intestinal absorption of phosphorus and suppressed PTH secretion reduces kidney phosphorus excretion.

Unregulated conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D may occur in granulomatous tissue associated with fungal infection, tuberculosis, sarcoidosis, and lymphoma, leading to increased intestinal absorption of calcium. These conditions are associated with an inappropriately normal or frankly elevated 1,25-dihydroxyvitamin D level and suppressed PTH. Decreased serum and urine calcium after intake of calcium and vitamin D is restricted or a rapid decrease in calcium after glucocorticoid therapy (which inhibits the hydroxylation of 25-hydroxyvitamin D) is consistent with these disorders.

Vitamin D intoxication from chronic high-dose ingestion of vitamin D (typically >50,000 units daily in patients without malabsorptive conditions) and increased storage in fat causes protracted hypercalciuria, nephrolithiasis, impaired kidney function, and elevated 25-hydroxyvitamin D levels.

Other Causes

Ingestion of large amounts of calcium typically from antacid use (for example, calcium carbonate), especially with coexistent chronic kidney disease, causes milk-alkali syndrome.

Glucocorticoid and mineralocorticoid replacement and volume repletion resolve the mild hypercalcemia sometimes associated with Addisonian crisis.

Severe thyrotoxicosis occasionally causes hypercalcemia or hypercalciuria by increasing bone resorption.

Acute prolonged immobilization, as seen in spinal cord injuries, can cause large efflux of calcium from the skeleton through uncoupled bone remodeling with decreased osteoblastic activity despite increased osteoclastic activity. Patients with primary hyperparathyroidism or skeletal metastases are predisposed to hypercalcemia due to immobilization as are young patients where increased bone remodeling is normal.

Management of Hypercalcemia

H

Management is dependent on the severity of the hypercalcemia. If mild (<12 mg/dL [3 mmol/L]), treatment of the underlying disorder (for example, parathyroidectomy in primary hyperparathyroidism) is sufficient. Hospitalization

H CONT may be needed in patients with acute kidney injury, mental status changes, or calcium levels above 12 mg/dL (3 mmol/L). Initial treatment of severe hypercalcemia is aggressive hydration to replete volume loss and increase kidney excretion of calcium. Loop diuretics are not recommended unless kidney failure or heart failure is present, in which case volume expansion should precede the administration of loop diuretics to avoid hypotension and further kidney injury. For the acutely symptomatic patient, subcutaneous calcitonin can be used; however, the drug effect wanes after 48 hours. Long-term management of hypercalcemia may require intravenous bisphosphonate therapy to prevent mobilization of calcium from the skeleton, but requires adequate kidney function. Glucocorticoids and restriction of calcium and vitamin D intake are uniquely beneficial in vitamin D–dependent hypercalcemia. Hemodialysis is reserved for the treatment of severe hypercalcemia in oliguric patients. H

KEY POINT

- Initial treatment of moderate to severe hypercalcemia is aggressive hydration to replete volume loss and increase kidney excretion of calcium; loop diuretics are not recommended unless kidney failure or heart failure is present, in which case volume expansion should precede the administration of loop diuretics to avoid hypotension and further kidney injury.

Hypocalcemia

Clinical Features of Hypocalcemia

Signs and symptoms of hypocalcemia reflect its severity and acuity. Hypocalcemic disorders in outpatients are typically detected on screening blood tests and are mild, with serum calcium 7.5 to 8.9 mg/dL (1.9-2.2 mmol/L). It may also be detected during evaluation for low-intensity traumatic fractures or low bone mass. Most patients will be asymptomatic or report symptoms of intermittent paresthesia of the hands and feet or perioral numbness. Hypocalcemia due to chronic hypoparathyroidism can also be associated with cataract formation, basal ganglia calcification, papilledema, and dental enamel hypoplasia.

H Patients with severe hypocalcemia may present with neuromuscular symptoms and signs. Carpopedal spasm with characteristic hand posture (flexion at metacarpophalangeal joints and extension at interphalangeal joints) may be spontaneous or triggered by transient distal limb ischemia during blood pressure assessment (Trousseau sign). Facial nerve hyperirritability and muscle spasm can be demonstrated by percussion of the facial nerve just anterior to the ear (Chvostek sign). Importantly, laryngospasm, seizure, myocardial dysfunction, and QT-interval prolongation leading to sudden cardiac death due to severe hypocalcemia (<7.5 mg/dL [1.9 mmol/L]) can occur without prodromal paresthesia or muscle cramping. H

KEY POINT

- Laryngospasm, seizure, myocardial dysfunction, and QT-interval prolongation leading to sudden cardiac death due to severe hypocalcemia (<7.5 mg/dL [1.9 mmol/L]) can occur without prodromal paresthesia or muscle cramping.

Causes and Diagnosis of Hypocalcemia

Hypocalcemia should be confirmed with a second measurement, which requires assessment of and correction for serum albumin concentrations. Ionized calcium measurement is indicated in the setting of fluctuating acid/base status. Simultaneous measurement of serum calcium, phosphorus, creatinine, and PTH is the next step. PTH should be elevated in the setting of hypocalcemia (see Figure 16).

Hypoparathyroidism

H Hypoparathyroidism is most commonly caused by inadvertent injury during anterior neck surgery (thyroidectomy, parathyroidectomy) or surgery to treat parathyroid gland hyperplasia, both of which present within a few hours of surgery. Depending on the extent of injury/resection, surgical hypoparathyroidism may last days to weeks. Permanent hypoparathyroidism may be partial or complete; the latter is associated with undetectable serum PTH levels and a higher prevalence of hyperphosphatemia. H

Inappropriately normal PTH levels with concurrent hypocalcemia represents the former. Other causes of hypocalcemia due to insufficient PTH secretion include infiltrative disorders (hemochromatosis or Wilson disease), radiation, autoimmunity, and congenital disorders (such as 22q11.2 deletion syndrome). Chronic hypocalcemia with inappropriately normal PTH occurring within a family may represent an activating mutation of the *CaSR* gene. Hypomagnesemia, seen in the settings of malnutrition, alcoholism, and with use of loop diuretics and chronic proton pump inhibitor therapy, causes functional, reversible parathyroid hypofunction and must be excluded before a low or inappropriately normal PTH level is attributed to hypoparathyroidism. PTH resistance (pseudohypoparathyroidism) is a rare genetic cause of hypocalcemia.

KEY POINT

- Hypomagnesemia causes functional, reversible parathyroid hypofunction and must be excluded before a low or inappropriately normal parathyroid hormone level is attributed to hypoparathyroidism.

Other Causes of Hypocalcemia

Malnutrition and/or malabsorption of either or both vitamin D and calcium may be suspected based on clinical history (bariatric surgery, celiac disease) and confirmed by low serum 25-hydroxyvitamin D level or low 24-hour urine calcium excretion (a proxy indicator of calcium intake and absorption). The most common cause of acquired hypocalcemia is chronic

kidney failure due to impaired production of 1,25-dihydroxy-vitamin D and hyperphosphatemia. Hypercalciuria is most often idiopathic, but can also be due to chronic loop diuretic use. Rhabdomyolysis and tumor lysis syndrome increase serum phosphorus and calcium phosphate binding in the vascular space, causing low ionized calcium.

Hungry bone syndrome (rapid flux of calcium into bone after parathyroidectomy for severe primary hyperparathyroidism) and widespread osteoblastic metastases (prostate cancer, breast cancer) can cause hypocalcemia, as can saponification of calcium (and magnesium) in necrotic fat in acute pancreatitis.

Potent antiresorptive drugs, such as intravenous bisphosphonates and denosumab, can cause severe and protracted hypocalcemia by impairing physiologic efflux of calcium from the skeleton in patients with vitamin D deficiency. Therefore, it is important to assess vitamin D levels and correct deficiency before beginning treatment with an antiresorptive drug.

Management of Hypocalcemia

H Because severe neuromuscular complications of hypocalcemia can occur in the absence of prodromal muscle tetany, severe hypocalcemia (<7.5 mg/dL [1.9 mmol/L]) requires urgent treatment with intravenous calcium. Slow administration through central intravenous access with electrocardiographic monitoring is preferred. Alternatively, teriparatide 20 µg twice per day rapidly eliminates hypocalcemic symptoms in acute postsurgical hypoparathyroidism (off-label indication). H

Vitamin D supplementation 1000 to 4000 IU/d and oral calcium carbonate or calcium citrate at doses of 1 to 3 g/d in divided doses may normalize or sufficiently treat mild or chronic hypocalcemia. Calcitriol is needed in the setting of hypoparathyroidism with undetectable PTH and kidney failure because 1,25-dihydroxyvitamin D activation requires both PTH and sufficient kidney function.

In chronic hypoparathyroidism, goals of therapy are to eliminate symptoms while avoiding complications of therapy. A reasonable goal for most patients is a serum calcium concentration at or just below the reference range without hypercalciuria. Monitoring of urine calcium excretion is mandatory because hypercalciuria often limits therapy. Correction of coexisting hypomagnesemia is also required. Thiazide diuretics are commonly used because they decrease urine calcium excretion.

Initial treatment of hyperphosphatemia is reduction of dietary phosphorus but occasionally requires the addition of oral phosphate binders if serum phosphorus exceeds the normal range. Recombinant human PTH is available for patients who do not meet treatment goals with calcium and calcitriol therapy alone.

KEY POINT

- A reasonable goal for most patients with hypoparathyroidism is a serum calcium concentration at or just below the reference range without hypercalciuria.

Metabolic Bone Disease

Low Bone Mass and Osteoporosis

Bone mass, mineral content, and macro- and microarchitecture determine bone strength. Bone mineral density (BMD) reflects bone mass and mineral content and, in older adults, predicts deterioration of microarchitecture. This relationship and epidemiologic data underpin the use of BMD determined by dual-energy x-ray absorptiometry (DEXA) to diagnose low bone mass and refine fracture risk assessment in older adults. Fragility fractures (those occurring with minimal trauma, equivalent or less than a fall from a standing height) after age 50 indicate low bone strength and define clinical osteoporosis regardless of BMD. Skull, feet, and hand fractures cannot, by definition, be fragility fractures.

Pathophysiology

Low bone mass in adults may represent poor bone formation, bone loss, or both. Factors that can affect peak bone mass formation include genetic conditions, lifestyle factors, and poor health, especially in the second decade of life. Net loss of bone mass can occur in adults when osteoclastic bone remodeling is faster than osteoblastic bone formation. The list of risk factors for low bone mass and osteoporosis is extensive and is included in **Table 44** and **Table 45**. Some patients, however, have osteoporosis caused by secondary causes. Testing for secondary causes is summarized in **Table 46**.

Screening for Osteoporosis

Current guidelines recommend screening average-risk postmenopausal women beginning at age 65. Guidelines vary in their recommendations for routine screening for osteoporosis in men. The American College of Rheumatology recommends BMD testing within 6 months of starting long-term glucocorticoid therapy in adults 40 years of age and older and in adults under 40 years of age with risk factors for osteoporosis or a history of fragility fractures.

Patients with risk factors for low bone mass or osteoporosis, fragility fractures of the femur, vertebra (**Figure 17**), pelvis, humerus or radius, height loss of 4 cm (1.6 in) or more, or kyphosis, should have BMD testing earlier than standard screening recommendations. BMD may also be indicated if the risk of fractures is elevated based on the results of risk assessment tools such as the Simple Calculated Osteoporosis Risk Estimate (SCORE), Osteoporosis Self-Assessment Tool (OST), the Osteoporosis Risk Assessment Instrument (ORAI), and Fracture Risk Assessment Tool (FRAX). **Table 47** lists recommendations for BMD testing and vertebral imaging.

Screening of younger women may be indicated if one or more risk factors for osteoporosis are present. In premenopausal women without risk factors, assessment of BMD for fracture risk is not advised or validated. However, if testing is done in an otherwise healthy person, results that are below age- and gender-matched averages (Z-score <0) generally do not require further evaluation or serial monitoring.

TABLE 44. Risk Factors for Low Bone Density and Osteoporosis

Lifestyle/Modifiable	Non-Modifiable	Medications/Supplements
Alcohol use	Race/Ethnicity	Anticonvulsants
Immobilization	Age	Antiretroviral therapy (tenofovir)
BMI <17	Gender	Aromatase inhibitors
Low calcium intake	First-degree relative with low BMD	Calcineurin inhibitors
Smoking	Genetic	Depo-medroxyprogesterone
Vitamin D deficiency	Cystic fibrosis	Glucocorticoids (≥5 mg/day prednisone or equivalent for ≥3 months)
Weight loss	Hypophosphatasia	Heparin
Recurrent falls	Ehlers-Danlos	GnRH agonists
	Osteogenesis imperfecta	Proton pump inhibitors
		Thiazolidinediones
		Lithium
		Androgen deprivation therapy

BMD = bone mineral density; GnRH = gonadotropin-releasing hormone.

TABLE 45. Conditions and Comorbidities Associated with Increased Risk for Low Bone Mass and Osteoporosis

Endocrine	Gastrointestinal	Hematologic	Rheumatologic	Neurologic	Other
Anorexia nervosa	Bariatric surgery	Amyloidosis	Ankylosing spondylitis	Multiple sclerosis	AIDS/HIV
Cushing syndrome	Celiac disease	Leukemia and lymphoma	Rheumatoid arthritis	Muscular dystrophy	Chronic obstructive lung disease
Diabetes mellitus	Inflammatory bowel disease	Monoclonal gammopathies	Systemic lupus	Spinal cord injury with paralysis	End-stage kidney disease
Hyperparathyroidism	Malabsorption	Multiple myeloma			Idiopathic hypercalciuria
Hypogonadism	Primary biliary	Amyloidosis			
Thyrotoxicosis					
Turner syndrome					

TABLE 46. Diagnostic Studies to Evaluate for Secondary Causes of Osteoporosis

Blood Testing
Complete blood count
Calcium, phosphorus, and magnesium
Kidney function tests
Liver function tests
Thyroid-stimulating hormone
25-hydroxyvitamin D
Total testosterone (younger men)
Tryptase
Urine Testing
24-h urinary calcium
Urinary free cortisol level

Extent of testing should be influenced by clinical suspicion and severity of osteoporosis.

KEY POINT

- Current guidelines recommend screening average risk postmenopausal women beginning at age 65; screening recommendations for men vary by organization.

Diagnosis

In postmenopausal women and men over 50 years of age, the diagnosis of osteopenia is determined by BMD testing (T-score between −1 and −2.5) alone, whereas osteoporosis can be diagnosed clinically based on the presence of fragility fractures, hip fracture, vertebral compression fracture, or by DEXA. Without secondary causes of low BMD or a fragility fracture, osteoporosis is diagnosed when the femur neck, total hip, nondominant radius, or composite (two or more consecutive diagnostic vertebrae) lumbar spine T-score is −2.5 or less, as defined by the World Health Organization. If hip or spine cannot be accurately measured by BMD, DEXA of the distal third of the radius can be used.

Diagnosis of osteoporosis in premenopausal women and men under 50 years can be made with diagnosis of a fragility fracture or low bone mass on DEXA defined by a Z-score less than −2, which indicates "low bone mass for age."

BMD assessment using quantitative calcaneal ultrasonography may be used to screen for osteoporosis, but abnormal results require confirmation by DEXA. Quantitative CT provides a DEXA equivalent T-score, is not hindered by degenerative changes in the lumbar spine, and is highly sensitive for detection of vertebral compression fractures, but its cost and

FIGURE 17. Asymptomatic vertebral compression fractures detected by spine radiograph in a patient with height loss and kyphosis. Depicted is vertebral endplate depression without loss of vertebral height in upper lumbar vertebrae (*empty arrows*) and severe wedging and height loss of multiple mid-thoracic vertebral bodies (*solid arrows*).

TABLE 47. Recommendations for Measurement of Bone Mineral Density and Vertebral Imaging

Bone Mineral Density Testing[a]
Women age 65 and older
For men, evidence is insufficient to assess the benefits/harms of screening for osteoporosis[b]
Postmenopausal women and men age 50 to 69, based on risk-factor profile
Those who have had a fracture, to determine degree of disease severity
Radiographic findings suggestive of osteoporosis or vertebral deformity
Glucocorticoid therapy for more than 3 months
Primary hyperparathyroidism
Vertebral Imaging[c]
Women ≥70 and men ≥80 if T-score at the spine, total hip, or femoral neck is ≤ −1.0
Women aged 65-69 and men aged 75-79 if T-score at the spine, total hip, or femoral neck is ≤1.5
In postmenopausal women age 50-64 and men aged 50-69 with the following risk factors:
Low-trauma fractures
Historic height loss of 1.5 in or more (4 cm)
Height loss of 0.8 inches or more (2 cm)
Recent or ongoing long-term glucocorticoid treatment

[a]BMD testing should be performed at DEXA facilities using accepted quality assurance measures.

[b]The National Osteoporosis Foundation recommends screening men 70 and older, and the Endocrine Society recommends screening men 70 and older and men aged 50-69 who have risk factors such as low body weight, prior fracture as an adult, or smoking.

[c]Vertebral imaging should be repeated when a new loss of height is noted or new back pain is reported.

radiation exposure are greater and is not recommended for osteoporosis screening.

KEY POINTS

- Osteoporosis can be diagnosed clinically based on fragility fractures, hip fracture, vertebral compression fracture, or a bone mineral density measurement of ≤−2.5.
- HVC Quantitative CT provides a dual-energy x-ray absorptiometry equivalent T-score, is not hindered by degenerative changes in the lumbar spine, and is highly sensitive for detection of vertebral compression fractures, but its cost and radiation exposure are greater and is not recommended for osteoporosis screening.

Evaluation of Secondary Causes of Low Bone Mass

Non-modifiable factors are the most common cause of low bone mass, but there are many other causes (see Table 44 and Table 45). Low bone mass may be the presentation for conditions such as idiopathic hypercalciuria or celiac disease. All patients should have a thorough history and physical examination and additional testing based on findings (see Table 46). Although BMD may not be required in all patients to make the diagnosis of osteoporosis, it may be helpful to determine if additional testing is needed and to guide treatment.

Osteomalacia

Osteomalacia is most commonly caused by severe and prolonged vitamin D deficiency, which results in inadequate concentrations of calcium and/or phosphate in the bone, which in turn prevents mineralization of newly formed bone matrix. Unlike osteoporosis, osteomalacia does not result in permanent loss of bone structure. A period of months to years of disordered mineralization is required before bone strength is compromised.

Symptoms of osteomalacia include diffuse bone pain, bone tenderness to palpation (tibial plateau and sternum), and proximal muscle weakness; however, early osteomalacia may present only with low bone mass on DEXA and can be indistinguishable from osteoporosis without further testing. Very low BMD (Z-score ≤−2), low or low-normal serum calcium and

phosphorus levels, very low 25-hydroxyvitamin D (<10 ng/mL [25 nmol/L]) level, and secondary hyperparathyroidism distinguishes osteomalacia from osteoporosis. Elevated serum alkaline phosphatase level is particularly suggestive of osteomalacia, although mild elevation can be seen with recent osteoporotic fracture. Radiographs may display an unusual distribution of fractures in severe osteomalacia (**Figure 18**). When bone pain is not explained by conventional radiographic findings in the setting of suspected osteomalacia, imaging with radionuclide bone scan or MRI may reveal fractures.

The goal of treatment is to optimize conditions for bone mineralization using supplementation to normalize serum 25-hydroxyvitamin D (>30 ng/mL [75 nmol/L]), calcium, and phosphorus concentrations. The skeletal response to treatment is reflected by gradual normalization of alkaline phosphatase level and symptom relief. Resolution of osteomalacia may take as long as 12 months; subsequent BMD testing will show significant increases and/or normalization of BMD.

Other Causes

Low bone mass and fragility fractures in young and middle-aged adults may result from genetic disorders (see Table 45). Patients with mild (type 1) osteogenesis imperfecta may present with a history of childhood fractures that decrease in frequency as adults. Hypermobility raises suspicion for Ehlers-Danlos and related syndromes. Hypophosphatasia should be suspected in middle-aged patients with fractures and serum alkaline phosphatase levels well below the reference range.

Nonpharmacologic Management

Exercise involving weight-bearing, resistance, and balance is important for bone health and may reduce fracture risk at any age, but especially in patients over 65 years. Although the measurable treatment effect may be small, calcium and vitamin D were universally supplemented in osteoporosis pharmacotherapy trials; the National Academy of Medicine recommends calcium intake of 1000 to 1200 mg/d, ideally from dietary sources. A calcium supplement may be used for patients whose diets are insufficient, but should not be recommended independent of dietary assessment and intervention. As many osteoporosis clinical trials, including those testing pharmacotherapy, sought to achieve 25-hydroxyvitamin D levels of at least 30 ng/mL (75 nmol/L), a vitamin D supplement of 1000 to 2000 IU/d may be appropriate in the context of osteoporosis care.

FIGURE 18. Pseudofractures appear as radiolucent areas perpendicular to the bone surface and are typically bilateral and/or symmetrical. The pubic rami (shown here), medial aspect of the proximal femur, proximal fibula, and metatarsals are common sites.

Pharmacologic Management

The goal of treatment is reduce risk of fractures in patients with osteoporosis or those at increased risk of fracture (primary prevention). The U.S. National Osteoporosis Foundation recommends pharmacologic treatment for patients with osteoporosis-related hip or spine fractures, those with a BMD T-score of −2.5 or less, and those with a BMD T-score between −1 and −2.5 with a 10-year risk of 3% or greater for hip fracture or risk of 20% or greater for major osteoporosis-related fracture as estimated by the Fracture Risk Assessment Tool (FRAX). Some studies suggest that different thresholds for initiation of treatment should be considered in other at-risk populations. The American College of Rheumatology recommends treatment for glucocorticoid-induced osteoporosis based on age, gender, and fracture risk.

Pharmacotherapy may also be used to prevent loss of BMD in postmenopausal women at risk of osteoporosis and to prevent or treat glucocorticoid-induced osteoporosis. Although estrogen therapy may be considered for management of vasomotor symptoms in postmenopausal women, it is no longer considered first-line therapy for prevention of osteoporosis. The FDA has recently approved a combination pill, bazedoxifene and conjugated estrogen, for prevention of postmenopausal osteoporosis. FDA-approved drugs for treatment of osteoporosis and options for prevention are listed in **Table 48**.

Bisphosphonates

Oral bisphosphonates, alendronate and risedronate, are antiresorptive agents and are generally first-line treatment in postmenopausal women and men over 50 years of age. They have been shown to reduce the risk for spine, hip, and nonvertebral fractures. Another bisphosphonate, ibandronate, has only shown efficacy in reducing vertebral fractures. In glucocorticoid-induced osteoporosis with moderate to high fracture risk, oral bisphosphonates are recommended as first-line therapy in adult men and women regardless of age. Intravenous zoledronic acid once a year is an option if patients experience upper gastrointestinal symptoms or have difficulty taking the medication as directed. An acute-phase response reaction including pyrexia and myalgia may occur after first administration in as many as one in three patients, but does not occur typically with subsequent administrations. Bisphosphonates

TABLE 48. FDA-Approved Medications for Treatment and Prevention of Osteoporosis and Skeletal Sites of Proven Fracture Prevention When Used to Treat Osteoporosis

	Prevention		Documented Fracture Prevention			
	PMO	**GIO**	**Recurrent**	**Hip**	**Vertebral**	**Non-Vertebral**
Bisphosphonates						
Alendronate	√			√	√	√
Risedronate	√	√		√	√	√
Ibandronate	√				√	
Zoledronic acid (IV)	√	√	√	√	√	√
Denosumab				√	√	√
Raloxifene	√				√	
Anabolic						
Abaloparatide					√	√
Teriparatide					√	√

GIO = glucocorticoid-induced osteoporosis; PMO = postmenopausal osteoporosis.

are contraindicated in patients with reduced kidney function (glomerular filtration rate [GFR] <35 mL/min/1.73 m^2) and should not be given until vitamin D deficiency and hypocalcemia are treated, if present.

Rare side effects of antiresorptive agents are osteonecrosis of the jaw and atypical femur fracture. Osteonecrosis of the jaw may occur at any point in therapy; whereas the risk for atypical femur fracture appears to increase with duration of therapy. For most patients, the benefits in reduction of osteoporosis fractures far outweigh the risk of these uncommon side effects. A drug holiday can be considered in women who are not at high fracture risk after 3 years (intravenous) to 5 years (oral) of bisphosphonate treatment. In postmenopausal women at high risk due to a T-score −3.5 or below, previous osteoporotic fracture, or who sustain a fracture while on therapy, continuation of treatment for up to 10 years (oral) or 6 years (intravenous) should be considered. While there are no data to guide the duration of the drug holiday, factors taken into consideration include the bisphosphonate used and whether BMD is maintained on DEXA.

KEY POINTS

- Bisphosphonates are generally the first-line treatment of osteoporosis; only alendronate and risedronate reduce the risk for spine, hip, and nonvertebral fractures.
- A drug holiday can be considered in postmenopausal women who are not at high fracture risk after 3 years (intravenous) to 5 years (oral) of bisphosphonate treatment.

Receptor Activator of Nuclear Factor KB (RANK) Ligand Inhibitors

Denosumab is a monoclonal antibody that inhibits osteoclast activation. When administered subcutaneously twice yearly, denosumab suppresses bone resorption, increases bone density, and reduces the incidence of osteoporotic fractures in men and women. The effects of denosumab are not sustained when treatment is stopped. Denosumab may be preferred in patients with stage 4 chronic kidney disease and in those intolerant of or incompletely responding to bisphosphonate therapy. Adverse effects include hypocalcemia, especially in older patients with vitamin D deficiency, and an increased rate of cellulitis and bronchitis. Medication-related osteonecrosis of the jaw and atypical femur fracture have been reported with denosumab use as well.

Anabolic Agents

Teriparatide, rhPTH (1-34), is approved for use in postmenopausal women and men or women with glucocorticoid-induced osteoporosis who are at high risk of osteoporotic fracture. It is also used to improve bone mass in men with primary or hypogonadism-related osteoporosis at high risk of fracture. Abaloparatide, rhPTHrP (1-34), is approved for the treatment of postmenopausal women with osteoporosis at high risk for fracture. Both agents stimulate bone formation and require daily subcutaneous injection. Treatment should be limited to 2 years. Improvement in BMD is most evident at the spine. To prevent the loss of newly formed bone, sequential therapy with an antiresorptive agent must begin within 1 month of completing the course of anabolic treatment.

Follow-up of Patients with Low Bone Mass

Routine serial DEXA measurements of BMD are not indicated for follow-up of low-risk patients who do not have osteoporosis. Subsequent BMD testing depends on baseline BMD. Repeating after 15 years may be reasonable if the hip T-score is normal (>−1), while retesting at 2 years may be considered if the hip T-score is −2 to −2.4.

The primary reason for repeating BMD testing in patients taking antiresorptive agents is to detect treatment failure. Declining BMD, indicated by a statistically significant percent drop in g/cm² of bone (not declining T-scores in subsequent DEXA scans) or a fracture while on treatment, raises concern for an unrecognized secondary cause, nonadherence, or insufficient response that necessitates reevaluation. The American College of Physicians recommends against monitoring of bone mineral density during treatment because data from several studies showed that women treated with antiresorptive treatment benefited from reduced fractures even if BMD did not increase. Instead follow-up management should include review of indication for treatment, monitoring of adherence to treatment, and reinforcement of lifestyle measures to prevent fractures, minimize bone loss, and avoid frailty. Drug holiday from antiresorptive therapy usually involves measurement of BMD to establish a baseline and repeated measurement in 2 to 3 years. Although this approach would ostensibly inform subsequent treatment decisions, it has not been validated.

Vitamin D Deficiency

The most appropriate test to assess adequacy of vitamin D is measurement of serum 25-hydroxyvitamin D, which reflects dietary and skin-derived vitamin D. At least 20 ng/mL (50 nmol/L) is recommended to prevent metabolic bone disease in otherwise healthy populations and generally can be met with an intake of 600 to 800 IU/d.

Routine screening for vitamin D deficiency is not recommended in healthy populations; however, testing for deficiency is appropriate in groups at high risk or in patients presenting with low bone mass, fractures, hypocalcemia, or hyperparathyroidism. In patients with bone, parathyroid, or calcium disorders, to raise blood levels consistently above 30 ng/dL (75 nmol/L) may require 1000 to 2000 U/d. Patients with malabsorption, chronic lack of sun exposure, BMI greater than 40, advanced liver disease, and medications interfering with vitamin D metabolism, such as phenytoin and phenobarbital, may require 2000 to 4000 U/d for repletion and maintenance of vitamin D stores as guided by 25 hydroxyvitamin D levels obtained 3 months after initiation of treatment.

Loading doses using 50,000 U/d of either vitamin D_2 (ergocalciferol) or vitamin D_3 (cholecalciferol) once weekly for 8 weeks is appropriate in severe deficiency especially in the setting of malabsorption. Candidates for loading doses include: undetectable 25-hydroxyvitamin D, hypocalcemia, and osteomalacia due to vitamin D deficiency. Maintenance therapy of 1000 to 4000 U/d is recommended to maintain sufficiency after a loading dose.

Widespread public interest and a proliferation of scientific publications regarding vitamin D stem from established autocrine and paracrine effects in most tissues as well as extensive observational data associating 25-hydroxyvitamin D levels with extraskeletal health outcomes. However, intervention trials have not convincingly demonstrated a benefit of vitamin D supplementation on most disease outcomes, suggesting that low 25-hydroxyvitamin D levels may be a marker rather than a cause of ill health.

KEY POINT

HVC

- Routine screening for vitamin D deficiency is not recommended in healthy populations; however, testing for deficiency is appropriate in groups at high risk or patients presenting with low bone mass, fractures, hypocalcemia, or hyperparathyroidism.

Paget Disease of Bone

Although Paget disease of bone may present with localized symptoms, it is most commonly diagnosed in asymptomatic older patients presenting with elevated alkaline phosphatase levels or incidental radiographic findings. Commonly affected bones include the skull, spine, sacrum, pelvis, femur, and tibia. The skeletal site and extent of involvement including rate of bone turnover determine clinical features. Involvement of weight-bearing bones of the lower extremity may result in bone pain, deformity, or fracture. Involvement of a bone approximating a joint can contribute to degenerative joint disease (**Figure 19**). Expansion of Pagetic bone of the upper spine or skull base may cause spinal cord or cranial nerve compression.

Diagnosis is based on radiographic findings of thickening of cortical bone, coarsened trabecular markings, and distortion and expansion of involved bone. Biopsy is rarely needed. Serum alkaline phosphatase, a marker of increased bone turnover, is generally elevated but may not be elevated in some patients with longstanding disease that has become metabolically inactive. Alkaline phosphatase may be elevated in other

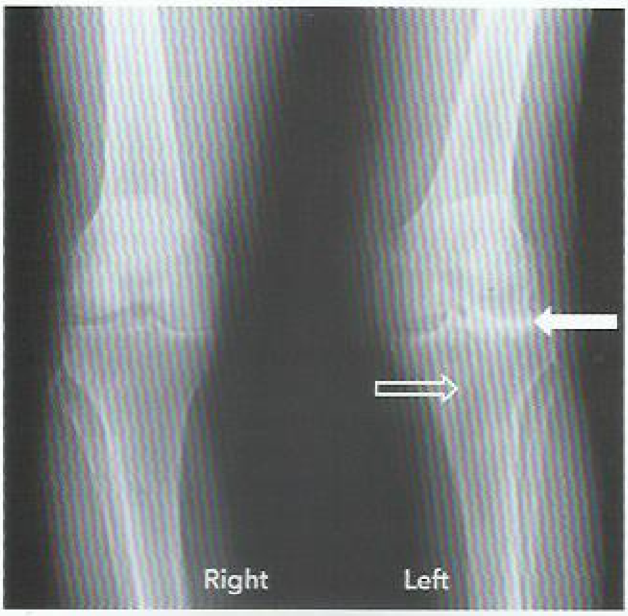

FIGURE 19. Coarsening of trabecular structures (*empty arrow*) without cortical deformity is diagnostic of Paget disease of bone in the proximal left tibia. Also shown is advanced degenerative arthritis in the adjacent left knee (*solid arrow*).

conditions, including vitamin D deficiency, other metabolic bone disease (such as osteomalacia), or recent fracture. Therefore, all patients with suspected Paget disease of bone require assessment of serum calcium, 25-hydroxyvitamin D, and a whole-body radionuclide bone scan. If the bone scan reveals other skeletal sites suspicious for Paget disease of bone, radiography of those sites is required for further evaluation.

Management of Paget disease is based on symptoms, location of involvement, and disease activity. Indications for treatment include: bone pain; risk for fracture and progressive deformity that could compromise bone, joint, or neurologic function; and elevated alkaline phosphatase concentrations. Bisphosphonates, particularly a one-time dose of 5 mg of intravenous zoledronic acid, often achieve the treatment goal of reducing pain and normalizing of alkaline phosphatase for up to 5 years. Oral bisphosphonates may also be used, but duration of treatment is variable.

Annual alkaline phosphatase levels should be monitored. Retreatment is indicated if previously normalized levels of alkaline phosphatase exceed normal levels. Imaging is required if there is a dramatic rise in alkaline phosphatase levels or acceleration in symptoms, which raises a concern for the rare sarcomatous transformation of Pagetic bone.

KEY POINTS

- Although Paget disease of bone may present with localized symptoms, it is most commonly diagnosed in asymptomatic older patients presenting with elevated alkaline phosphatase levels or incidental radiographic findings.
- Indications for treatment of Paget disease include bone pain; risk for fracture and progressive deformity that could compromise bone, joint, or neurologic function; and alkaline phosphatase concentrations.
- A one-time dose of intravenous zoledronic acid will often achieve the treatment goal of reducing pain and normalizing of alkaline phosphatase in patients with Paget disease of bone.

Bibliography

Disorders of Glucose Metabolism

American Diabetes Association. Standards of medical care in diabetes—2018. 2018; 41(Suppl 1): S1-S159.

Bergenstal RM, Klonoff DC, Garg SK, Bode BW, Meredith M, Slover RH, et al; ASPIRE In-Home Study Group. Threshold-based insulin-pump interruption for reduction of hypoglycemia. N Engl J Med. 2013;369:224-32. [PMID: 23789889] doi:10.1056/NEJMoa1303576

Cryer PE, Axelrod L, Grossman AB, et al. Evaluation and management of adult hypoglycemic disorders: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metabl. 2009; 94:709-28. [PMID: 19088155]

Duckworth W, Abraira C, Moritz T, Reda D, Emanuele N, Reaven PD, et al; VADT Investigators. Glucose control and vascular complications in veterans with type 2 diabetes. N Engl J Med. 2009;360:129-39. [PMID: 19092145] doi:10.1056/NEJMoa0808431

Garber AJ, Abrahamson MJ, Barzilay JI, et al. Consensus statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the comprehensive type 2 diabetes management algorithm-2018 executive summary. Endoc Pract. 2018; 24:91-120. [PMID: 29368965]

Hayward RA, Reaven PD, Wiitala WL, Bahn GD, Reda DJ, Ge L, et al; VADT investigators. Follow-up of glycemic control and cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2015;372:2197-206. [PMID: 26039600] doi:10.1056/NEJMoa1414266

Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med. 2008;359:1577-89. [PMID: 18784090] doi:10.1056/NEJMoa0806470

Ismail-Beigi F, Craven T, Banerji MA, Basile J, Calles J, Cohen RM, et al; ACCORD trial group. Effect of intensive treatment of hyperglycaemia on microvascular outcomes in type 2 diabetes: an analysis of the ACCORD randomised trial. Lancet. 2010;376:419-30. [PMID: 20594588] doi:10.1016/S0140-6736(10)60576-4

Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, et al; Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med. 2002;346:393-403. [PMID: 11832527]

Maldonado M, Hampe CS, Gaur LK, et al. Ketosis-prone diabetes: dissection of a heterogeneous syndrome using an immunogenetic and β-cell functional classification, prospective analysis, and clinical outcomes. J Clin Endocrinol Metab 2003;88:5090-98. [PMID: 14602731]

Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2016; 375:311-322. [PMID:27295427]

Nathan DM, Cleary PA, Backlund JY, Genuth SM, Lachin JM, Orchard TJ, et al; Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. N Engl J Med. 2005;353:2643-53. [PMID: 16371630]

Nathan DM, Zinman B, Cleary PA, Backlund JY, Genuth S, Miller R, et al; Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Research Group. Modern-day clinical course of type 1 diabetes mellitus after 30 years' duration: the diabetes control and complications trial/epidemiology of diabetes interventions and complications and Pittsburgh epidemiology of diabetes complications experience (1983-2005). Arch Intern Med. 2009;169:1307-16. [PMID: 19636033] doi:10.1001/archinternmed.2009.193

Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med. 2017;377:644-57. [PMID: 28605608]

Patel A, MacMahon S, Chalmers J, Neal B, Billot L, Woodward M, et al; ADVANCE Collaborative Group. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med. 2008;358:2560-72. [PMID: 18539916] doi:10.1056/NEJMoa0802987

Peters AL, Ahmann AJ, Battelino T, Evert A, Hirsch IB, Murad MH, et al. Diabetes technology-continuous subcutaneous insulin infusion therapy and continuous glucose monitoring in adults: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2016;101:3922-3937. [PMID: 27588440]

Qaseem A, Wilt TJ, Kansagara D, Horwitch C, Barry MJ, Forciea MA; Clinical Guidelines Committee of the American College of Physicians. Hemoglobin A1c targets for glycemic control with pharmacologic therapy for nonpregnant adults with type 2 diabetes mellitus: a guidance statement update from the American College of Physicians. Ann Intern Med. 2018 Mar 6. doi: 10.7326/M17-0939. [Epub ahead of print] PubMed PMID: 29507945.

Siu AL; U.S. Preventive Services Task Force. Screening for abnormal blood glucose and type 2 diabetes mellitus: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2015;163:861-868. [PMID: 26501513]

U.S. Department of Veterans Affairs/U.S. Department of Defense. VA/DoD Clinical Practice Guidelines for the management of diabetes mellitus in primary care. 2017. www.healthquality.va.gov/guidelines/cd/diabetes. Accessed May 16, 2018.

Whelton PK, Carey RM, Aronow WS, Casey DE Jr, Collins KJ, Dennison Himmelfarb C, et al; 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guidelines for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2017; doi: 10.1016/j.jacc.2017.11.006.

Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med. 2015; 373: 2117-2128. [PMID: 26378978]

Disorders of the Pituitary Gland

Corsello SM, Barnabei A, Marchetti P, De Vecchis L, Salvatori R, Torino F. Endocrine side effects induced by immune checkpoint inhibitors. J Clin Endocrinol Metab. 2013;98:1361-75. [PMID: 23471977] doi:10.1210/jc.2012-4075

Fleseriu M, Hashim IA, Karavitaki N, Melmed S, Murad MH, Salvatori R, et al. Hormonal replacement in hypopituitarism in adults: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2016;101:3888–3921. [PMID: 27736313]

Freda PU, Beckers AM, Katznelson L, Molitch ME, Montori VM, Post KD, et al; Endocrine Society. Pituitary incidentaloma: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2011;96:894–904. [PMID: 21474686] doi:10.1210/jc.2010-1048

Guielman M, Basavilbaso, NG, Vitale M et al. Primary empty sella (PES). Pituitary. 2013;16:270–274. [PMID: 22875743]

Katznelson L, Laws ER Jr, Melmed S, Molitch ME, Murad MH, Utz A, et al; Endocrine Society. Acromegaly: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2014;99:3933–51. [PMID: 25356808] doi:10.1210/jc.2014-2700

Melmed S, Casanueva FF, Hoffman AR, Kleinberg DL, Montori VM, Schlechte JA, et al; Endocrine Society. Diagnosis and treatment of hyperprolactinemia: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2011;96:273–88. [PMID: 21296991] doi:10.1210/jc.2010-1692

Molitch ME, Clemmons DR, Malozowski S, Merriam GR, Vance ML; Endocrine Society. Evaluation and treatment of adult growth hormone deficiency: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2011;96:1587–609. [PMID: 21602453] doi:10.1210/jc.2011-0179

Nieman LK, Biller BM, Findling JW, Murad MH, Newell-Price J, Savage MO, et al; Endocrine Society. Treatment of Cushing's syndrome: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2015;100:2807–31. [PMID: 26222757] doi:10.1210/jc.2015-1818

Nieman LK, Biller BM, Findling JW, Newell-Price J, Savage MO, Stewart PM, et al. The diagnosis of Cushing's syndrome: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2008;93:1526–40. [PMID: 18334580] doi:10.1210/jc.2008-0125

Disorders of the Adrenal Glands

Bornstein SR, Allolio B, Arlt W, Barthel A, Don-Wauchope A, Hammer GD, et al. Diagnosis and treatment of primary adrenal insufficiency: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2016;101:364–89. [PMID: 26760044] doi:10.1210/jc.2015-1710

Fassnacht M, Arlt W, Bancos I, Dralle H, Newell-Price J, Sahdev A, et al. Management of adrenal incidentalomas: European Society of Endocrinology Clinical Practice Guideline in collaboration with the European Network for the Study of Adrenal Tumors. Eur J Endocrinol. 2016;175:G1–G34. [PMID: 27390021] doi:10.1530/EJE-16-0467

Funder JW, Carey RM, Mantero F, Murad MH, Reincke M, Shibata H, et al. The management of primary aldosteronism: case detection, diagnosis, and treatment: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2016;101:1889–916. [PMID: 26934393] doi:10.1210/jc.2015-4061

Lacroix A, Feelders RA, Stratakis CA, Nieman LK. Cushing's syndrome. Lancet. 2015 Aug 29;386(9996):913–27. doi: 10.1016/S0140-6736(14)61375-1. Epub 2015 May 21. Review. PubMed PMID: 26004339.

Lenders JW, Duh QY, Eisenhofer G, Gimenez-Roqueplo AP, Grebe SK, Murad MH, et al; Endocrine Society. Pheochromocytoma and paraganglioma: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2014;99:1915–42. [PMID: 24893135] doi:10.1210/jc.2014-1498

Libé R. Adrenocortical carcinoma (ACC): diagnosis, prognosis, and treatment. Front Cell Dev Biol. 2015;3:45. [PMID: 26191527] doi:10.3389/fcell.2015.00045

Nieman LK, Biller BM, Findling JW, Newell-Price J, Savage MO, Stewart PM, et al. The diagnosis of Cushing's syndrome: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2008;93:1526–40. [PMID: 18334580] doi:10.1210/jc.2008-0125

Rossi GP, Cesari M, Cuspidi C, Maiolino G, Cicala MV, Bisogni V, et al. Long-term control of arterial hypertension and regression of left ventricular hypertrophy with treatment of primary aldosteronism. Hypertension. 2013;62:62–9. [PMID: 23648698] doi:10.1161/HYPERTENSIONAHA.113.01316

Disorders of the Thyroid Gland

Alexander EK, Pearce EN, Brent GA, Brown RS, Chen H, Dosiou C, et al. 2017 Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and the postpartum. Thyroid. 2017;27:315–389. [PMID: 28056690] doi:10.1089/thy.2016.0457

Burch HB, Cooper DS. Management of Graves disease: a review. JAMA. 2015;314:2544–54. [PMID: 26670972] doi:10.1001/jama.2015.16535

Cohen-Lehman J, Dahl P, Danzi S, Klein I. Effects of amiodarone therapy on thyroid function. Nat Rev Endocrinol. 2010;6:34–41. [PMID: 19935743] doi:10.1038/nrendo.2009.225

Cooper DS, Biondi B. Subclinical thyroid disease. Lancet. 2012;379:1142–54. [PMID: 22273398] doi:10.1016/S0140-6736(11)60276-6

De Leo S, Lee SY, Braverman LE. Hyperthyroidism. Lancet. 2016;388:906–18. [PMID: 27038492] doi:10.1016/S0140-6736(16)00278-6

Demers LM, Spencer CA. Laboratory medicine practice guidelines: laboratory support for the diagnosis and monitoring of thyroid disease. Clin Endocrinol (Oxf). 2003;58:138–40. [PMID: 12580927].

Fliers E, Bianco AC, Langouche L, Boelen A. Thyroid function in critically ill patients. Lancet Diabetes Endocrinol. 2015;3:816–25. [PMID: 26071885] doi:10.1016/S2213-8587(15)00225-9

Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, et al. 2015 American Thyroid Association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: the American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid. 2016;26:1–133. [PMID: 26462967] doi:10.1089/thy.2015.0020

Hennessey JV. The emergence of levothyroxine as a treatment for hypothyroidism. Endocrine. 2017;55:6–18. [PMID: 27981511] doi:10.1007/s12020-016-1199-8

Kundra P, Burman KD. The effect of medications on thyroid function tests. Med Clin North Am. 2012;96:283–95. [PMID: 22443976] doi:10.1016/j.mcna.2012.02.001

Ross DS, Burch HB, Cooper DS, Greenlee MC, Laurberg P, Maia AL, et al. 2016 American Thyroid Association guidelines for diagnosis and management of hyperthyroidism and other causes of thyrotoxicosis. Thyroid. 2016;26:1343–1421. [PMID: 27521067]

Reproductive Disorders

Bhasin S, Brito JP, Cunningham GR, Hayes FJ, Hodis HN, Matsumoto AM, Snyder PJ, Swerdloff RS, Wu FC, Yialamas MA. Testosterone therapy in men with hypogonadism: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2018 May 1;103(5):1715–1744. [PMID: 29562364] doi: 10.1210/jc.2018-00229.

Bhasin S, Cunningham GR, Hayes FJ, Matsumoto AM, Snyder PJ, Swerdloff RS, et al; Task Force, Endocrine Society. Testosterone therapy in men with androgen deficiency syndromes: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2010;95:2536–59. [PMID: 20525905] doi:10.1210/jc.2009-2354

Bondy CA; Turner Syndrome Study Group. Care of girls and women with Turner syndrome: a guideline of the Turner Syndrome Study Group. J Clin Endocrinol Metab. 2007;92:10–25. [PMID: 17047017]

Brennan MJ. The effect of opioid therapy on endocrine function. Am J Med. 2013;126:S12–8. [PMID: 23414717] doi:10.1016/j.amjmed.2012.12.001

Fourman LT, Fazeli PK. Neuroendocrine causes of amenorrhea—an update. J Clin Endocrinol Metab. 2015;100:812–24. [PMID: 25581597] doi:10.1210/jc.2014-3344

Gordon CM. Clinical practice. Functional hypothalamic amenorrhea. N Engl J Med. 2010;363:365–71. [PMID: 20660404] doi:10.1056/NEJMcp0912024

Legro RS, Arslanian SA, Ehrmann DA, Hoeger KM, Murad MH, Pasquali R, et al; Endocrine Society. Diagnosis and treatment of polycystic ovary syndrome: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2013;98:4565–92. [PMID: 24151290] doi:10.1210/jc.2013-2350

Lindsay TJ, Vitrikas KR. Evaluation and treatment of infertility. Am Fam Physician. 2015;91:308–14. [PMID: 25822387]

Pope HG Jr, Wood RI, Rogol A, Nyberg F, Bowers L, Bhasin S. Adverse health consequences of performance-enhancing drugs: an Endocrine Society scientific statement. Endocr Rev. 2014;35:341–75. [PMID: 24423981] doi:10.1210/er.2013-1058

Transgender Hormone Therapy Management

American Psychological Association. Guidelines for psychological practice with transgender and gender nonconforming people. Am Psychol. 2015 Dec;70(9):832–64. doi: 10.1037/a0039906. PubMed PMID: 26653312. www.apa.org/practice/guidelines/transgender.pdf. Accessed May 15, 2018.

Center for Excellence for Transgender Health website. www.transhealth.ucsf.edu/trans?page=guidelines-home. Accessed May 15, 2018.

Coleman E, Bockting W, Botzer M, et al. Standards of care for the health of transsexual, transgender, and gender-nonconforming people, version 7. Int J Transgend. 2012;13:165.

Getahun D, Nash R, Flanders WD, Baird TC, Becerra-Culqui TA, Cromwell L, et al. Cross-sex hormones and acute cardiovascular events in transgender persons: a cohort study. Ann Intern Med. 2018 Jul 10. doi: 10.7326/M17-2785. [Epub ahead of print] PubMed PMID: 29987313.

Hembree WC, Cohen-Kettenis P, Delemarre-van de Waal HA, Gooren LJ, Meyer WJ 3rd, Spack NP, et al; Endocrine Society. Endocrine treatment of transsexual persons: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2009;94:3132–54. [PMID: 19509099] doi:10.1210/jc.2009-0345

Wylie K, Knudson G, Khan SI, Bonierbale M, Watanyusakul S, Baral S. Serving transgender people: clinical care considerations and service delivery models in transgender health. Lancet. 2016;388:401-11. [PMID: 27323926] doi:10.1016/S0140-6736(16)00682-6

Calcium and Bone Disorders

Adler RA, El-Hajj Fuleihan G, Bauer DC, Camacho PM, Clarke BL, Clines GA, et al. Managing osteoporosis in patients on long-term bisphosphonate treatment: report of a task force of the American Society for Bone and Mineral Research. J Bone Miner Res. 2016;31:1910. [PMID: 27759931] doi:10.1002/jbmr.2918

Bilezikian JP, Brandi ML, Eastell R, Silverberg SJ, Udelsman R, Marcocci C, et al. Guidelines for the management of asymptomatic primary hyperparathyroidism: summary statement from the Fourth International Workshop. J Clin Endocrinol Metab. 2014;99:3561-9. [PMID: 25162665] doi:10.1210/jc.2014-1413

Black DM, Rosen CJ. Postmenopausal osteoporosis [Letter]. N Engl J Med. 2016;374:2096-7. [PMID: 27223157] doi:10.1056/NEJMc1602599

Brandi ML, Bilezikian JP, Shoback D, Bouillon R, Clarke BL, Thakker RV, et al. Management of hypoparathyroidism: summary statement and guidelines. J Clin Endocrinol Metab. 2016;101:2273-83. [PMID: 26943719] doi:10.1210/jc.2015-3907

Buckley L, Guyatt G, Fink HA, Cannon M, Grossman J, Hansen KE, et al. 2017 American College of Rheumatology Guideline for the Prevention and Treatment of Glucocorticoid-Induced Osteoporosis. Arthritis & Rheumatology. 2017;69(8):1521-37.[PMID: 28585373] doi:10.1002/art.40137

Camacho PM, Petak SM, Binkley N, Clarke BL, Harris ST, Hurley DL, et al. American Association of Clinical Endocrinologist and American College of Endocrinology Clinical Practice Guidelines for the Diagnosis and Treatment of Postmenopausal Osteoporosis - 2016. Endocrine Practice. 2016;22(9):1111-8. [PMID 27643923] doi: 10.4158/EP161435.ESGL

Cosman F, de Beur SJ, LeBoff MS, Lewiecki EM, Tanner B, Randall S, et al; National Osteoporosis Foundation. Clinician's guide to prevention and treatment of osteoporosis. Osteoporos Int. 2014;25:2359-81. [PMID: 25182228] doi:10.1007/s00198-014-2794-2

Manson JE, Brannon PM, Rosen CJ, Taylor CL. Vitamin D deficiency - is there really a pandemic? N Engl J Med. 2016;375:1817-1820. [PMID: 27959647]

Singer FR, Bone HG 3rd, Hosking DJ, Lyles KW, Murad MH, Reid IR, et al; Endocrine Society. Paget's disease of bone: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2014;99:4408-22. [PMID: 25406796] doi:10.1210/jc.2014-2910

Endocrinology and Metabolism Self-Assessment Test

This self-assessment test contains one-best-answer multiple-choice questions. Please read these directions carefully before answering the questions. Answers, critiques, and bibliographies immediately follow these multiple-choice questions. The American College of Physicians (ACP) is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

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CME credits and MOC points are available from the publication date of December 31, 2018, until December 31, 2021. You may submit your answer sheet or enter your answers online at any time during this period.

Directions

*Each of the numbered items is followed by lettered answers. Select the **ONE** lettered answer that is **BEST** in each case.*

Item 1

A 32-year-old woman is seen for follow-up evaluation of thyroid nodules. At her visit 2 weeks ago, a 3-cm right thyroid nodule and 2-cm right lateral neck mass were palpated on examination. The patient is asymptomatic. At age 12 she was treated with combination chemotherapy plus involved-field radiation for Hodgkin lymphoma. There is no family history of thyroid disease.

Laboratory studies show a serum thyroid-stimulating hormone level of 3.0 µU/mL (3.0 mU/L). Results of other laboratory studies are normal.

Thyroid ultrasound demonstrates a 3.1 × 2.8 × 1.6-cm hypoechoic solid right thyroid nodule with irregular margins. Right cervical lymphadenopathy was confirmed on ultrasonography.

Which of the following is the most likely diagnosis?

(A) Benign follicular thyroid nodule
(B) Follicular thyroid cancer
(C) Medullary thyroid cancer
(D) Papillary thyroid cancer

H Item 2

A 45-year-old woman is evaluated for management of type 2 diabetes mellitus diagnosed 3 months ago. She was asymptomatic at diagnosis with an initial hemoglobin A_{1c} value of 9.7%. Her initial interventions included lifestyle modifications with weight loss and metformin. She is motivated to continue to lose weight. Medical history is significant for hypertension, hyperlipidemia, and frequent vulvovaginal candidiasis. She has no family history of thyroid or pancreatic malignancy. Medications are metformin, lisinopril, and atorvastatin.

On physical examination, vital signs are normal. BMI is 30. The remainder of the examination is unremarkable.

Results of laboratory studies show a hemoglobin A_{1c} level of 9.1%. Chemistry panel and creatinine levels are normal.

Which of the following is the most appropriate management for this patient's diabetes?

(A) Initiate empagliflozin
(B) Initiate glipizide
(C) Initiate insulin glargine
(D) Initiate liraglutide

Item 3

A 33-year-old man is evaluated for fatigue, headache, loss of appetite, and nausea for 6 months' duration. He has lost 9.1 kg (20 lb). Medical history is unremarkable, and he takes no medications.

On physical examination, temperature is normal, blood pressure is 118/70 mm Hg sitting and 98/68 mm Hg standing, pulse rate is 88/min sitting and 106/min standing, and respiration rate is 18/min. BMI is 19. The remainder of the physical examination is normal.

Laboratory studies:

Potassium	5.6 mEq/L (5.6 mmol/L)
Sodium	136 mEq/L (136 mmol/L)
Adrenocorticotropic hormone (ACTH)	450 pg/mL (99 pmol/L)
Cortisol, 8 AM	2.6 µg/dL (71.8 nmol/L)

Which of the following is the most appropriate next test?

(A) Cosyntropin stimulation test
(B) 21-Hydroxylase antibody measurement
(C) Pituitary MRI
(D) Serum aldosterone measurement

Item 4

A 23-year-old woman is seen in follow-up for evaluation of amenorrhea of 4 months' duration. Her only other medical problem is schizophrenia treated with risperidone.

On physical examination, vital signs and physical examination are normal.

Laboratory studies:

Prolactin	220 ng/mL (220 µg/L)
Thyroid-stimulating hormone	2.2 µU/mL (2.2 mU/L)
Thyroxine (T_4), free	1.2 ng/dL (15.5 pmol/L)
Urine human chorionic gonadotropin	Negative

Which of the following is the most appropriate next step?

(A) Obtain a pituitary MRI
(B) Start cabergoline
(C) Start an oral contraceptive
(D) Stop risperidone

Item 5

A 22-year-old woman is evaluated for loss of appetite and fatigue and 4.5-kg (10-lb) weight loss over the past 6 months. Medical history is otherwise unremarkable, and she takes no medications.

On physical examination, blood pressure is 100/70 mm Hg and pulse rate is 94/min. Other vital signs are normal. BMI is 22. The patient looks tanned, even in areas not exposed to the sun, and has buccal and palmar hyperpigmentation.

Laboratory studies:

Potassium	5.3 mEq/L (5.3 mmol/L)
Sodium	134 mEq/L (134 mmol/L)
Adrenocorticotropic hormone (ACTH)	650 pg/mL (143 pmol/L)
Cortisol	2.8 µg/dL (77.3 nmol/L)

Which of the following is the most appropriate treatment?

(A) Dexamethasone twice daily
(B) Hydrocortisone twice daily
(C) Hydrocortisone twice daily and fludrocortisone once daily
(D) Prednisone twice daily
(E) Prednisone twice daily and fludrocortisone once daily

Item 6

A 72-year old man is evaluated during a follow-up office visit. Medical history is significant for prostate cancer managed with active surveillance since the age of 69 years. His only symptom is new-onset upper back pain. He takes no medication.

On physical examination, vital signs are normal. The upper spine is tender to palpation.

Laboratory studies show a serum calcium level of 9.9 mg/dL (2.5 mmol/L), serum creatinine level of 1.2 mg/dL (106.1 µmol/L), and prostate-specific antigen less than 4 ng/mL (4 µg/L).

Whole body radionuclide bone scan shows focal increased uptake at T7. There are no other abnormalities. Spine radiograph shows coarsening of trabeculae and expansion of body of T7 without cortical disruption consistent with Paget disease of bone.

Which of the following is the most appropriate management?

(A) Alkaline phosphatase measurement
(B) Bone mineral density testing
(C) Thoracic spine CT scan
(D) Zoledronic acid therapy

Item 7

A 25 year-old woman is evaluated for anterior neck pain, fatigue, exercise intolerance, excessive sweating, and tremors that began 6 weeks ago. Other than an upper respiratory infection 2 months ago, she has been healthy. Medical history is otherwise unremarkable, and she takes no medications.

On physical examination, pulse rate is 105/min. Other vital signs are normal. The patient's thyroid gland is tender to palpation and is without discrete nodules. No thyroid bruit is auscultated. Bilateral lid lag is noted, but there is no proptosis, conjunctival injection, or chemosis. There is a fine tremor of her outstretched hands. Deep tendon reflexes are brisk.

Laboratory studies show a serum thyroid-stimulating hormone (TSH) level less than 0.01 µU/mL (0.01 mU/L), a serum free thyroxine (T_4) level of 2.8 ng/dL (36.1 pmol/L), and a serum total triiodothyronine (T_3) level of 190 ng/dL (2.9 nmol/L). Urine pregnancy test is negative.

Which of the following is the most likely diagnosis?

(A) Graves disease
(B) Molar pregnancy
(C) Subacute thyroiditis
(D) Toxic multinodular goiter

Item 8

A 24 year-old woman is evaluated for management of type 1 diabetes mellitus. She was first diagnosed at 13 years of age. Having recently completed nursing school, the patient is motivated to gain control of diabetes to prevent complications, particularly diabetic neuropathy. Her only medication is insulin lispro, delivered through continuous subcutaneous insulin infusion pump therapy.

On physical examination, blood pressure is 142/92 mm Hg; the remainder of the vital signs is normal. BMI is 26. A comprehensive foot examination is normal.

Laboratory studies show hemoglobin A_{1c} level of 8.7% and an LDL cholesterol level of 110 mg/dL (2.8 mmol/L).

Which of the following is the most appropriate measure to reduce the risk of diabetic neuropathy?

(A) Improve blood pressure control
(B) Improve glycemic control
(C) Improve lipid control
(D) Initiate pregabalin
(E) Weight loss

Item 9

H

A 77 year old woman is evaluated in the emergency department for new onset generalized weakness and myalgia 2 days after receiving zoledronic acid for a recent diagnosis of osteoporosis. Medical history is significant for rheumatoid arthritis. She is mainly sedentary and uses a walker for ambulation. She lives alone and prepares her own meals. Her medications are zoledronic acid, methotrexate, prednisone, folic acid, and tramadol.

On physical examination, vital signs are normal; however, she develops hand spasm during the blood pressure measurement. BMI is 18. The patient is frail appearing. There is ulnar deviation at the metacarpophalangeal joints of both hands, but no signs of active synovitis.

Laboratory studies show a calcium level of 7.5 mg/dL (1.9 mmol/L).

Which of the following is the most likely diagnosis?

(A) Hungry bone syndrome
(B) Hyperphosphatemia
(C) Hypoparathyroidism
(D) Hypovitaminosis D

Item 10

A 65 year old woman is evaluated for a 6-month history of increased facial and body hair and loss of scalp hair. Her voice has become deeper. Medical history is otherwise unremarkable, and she takes no medications. She has been menopausal since age 52 years.

On physical examination, blood pressure is 140/95 mm Hg and pulse rate is 82/min. Other vital signs are normal. BMI is 28. There are coarse dark hairs on the upper lip, chin, chest, and abdomen. She also has a deep voice, frontal hair loss, and clitoromegaly.

Laboratory studies show a total testosterone level of 89 ng/dL (3.1 nmol/L) and a dehydroepiandrosterone sulfate (DHEAS) level of 890 µg/dL (24.0 µmol/L) (normal <50-450 µg/dL [1.35-12.2 µmol/L]).

Which of the following is the most appropriate diagnostic test to perform next?

(A) Abdominal CT
(B) Adrenal vein sampling
(C) Pelvic MRI
(D) Pelvic ultrasound

H

Item 11

A 70-year-old man was admitted to the hospital 3 days ago with an ST-elevation myocardial infarction complicated by pulmonary edema and atrial fibrillation. He underwent emergency cardiac catheterization and left anterior descending (LAD) artery stent placement. Today the patient is feeling much better with complete resolution of his initial presenting symptoms.

Medications are aspirin, atorvastatin, clopidogrel, lisinopril, metoprolol, and low-molecular-weight heparin.

On physical examination, pulse rate is 92/min. Other vital signs are normal.

Cardiac examination reveals new findings of an irregularly irregular rhythm and an S_4. His physical examination is otherwise normal.

Laboratory studies obtained at the time of cardiac catheterization:

Thyroid-stimulating hormone (TSH)	0.2 µU/mL (0.2 mU/L)
Thyroxine (T_4), total	6.5 µg/dL (83.8 nmol/L)
Thyroxine (T_4), free	1.0 ng/dL (12.9 pmol/L)
Triiodothyronine (T_3), total	60 ng/dL (0.9 nmol/L)

Which of the following is the most likely diagnosis?

(A) Central hypothyroidism
(B) Heparin-induced thyroid function test abnormality
(C) Nonthyroidal illness syndrome
(D) Subclinical hyperthyroidism

H

Item 12

A 27-year-old woman was diagnosed with a 2-cm left cortisol-producing adrenal adenoma. She is admitted to the hospital for an adrenalectomy. Medical history is otherwise unremarkable, and she takes no medications.

On physical examination, blood pressure is 152/88 mm Hg; the remainder of the vital signs is normal. Centripetal obesity, facial plethora, fat deposition in the supraclavicular areas, and wide violaceous striae are present.

Which of the following is the most appropriate management following adrenalectomy?

(A) Epinephrine
(B) Fludrocortisone
(C) Hydrocortisone
(D) Phenoxybenzamine

Item 13

A 47-year-old man is evaluated during a follow-up visit to manage fatigue and decreased libido. Medical history is significant for hypertension and dyslipidemia. Medications are hydrochlorothiazide and atorvastatin.

On physical examination, vital signs are normal. He has normal hair distribution, no gynecomastia, and normal testicular examination.

Laboratory studies obtained at 3 PM revealed a total testosterone level of 275 ng/dL (9.5 nmol/L) and a luteinizing hormone level of 5 mU/mL (5 U/L).

Which of the following is the most appropriate management?

(A) Initiate testosterone replacement therapy
(B) Measure serum iron and total iron binding capacity
(C) Measure testosterone at 8 AM
(D) Obtain pituitary MRI

Item 14

A 58-year-old woman is evaluated during a follow-up visit 6 months after thyroidectomy for differentiated papillary thyroid cancer. She developed symptomatic hypocalcemia following surgery but is currently asymptomatic. Medications are calcium citrate, calcitriol, and levothyroxine.

Vital signs and physical examination are normal.

Laboratory studies:

Calcium	9.5 mg/dL (2.4 mmol/L)
Creatinine	1.0 mg/dL (88.4 µmol/L)
Phosphorus	4.5 mg/dL (1.5 mmol/L)
Magnesium	2.3 mg/dL (0.95 mmol/L)
Parathyroid hormone	<10 pg/mL (10 ng/L)

Which additional measurement is appropriate now?

(A) Bone mineral density
(B) 1,25-Dihydroxyvitamin D
(C) 24-Hour urine calcium
(D) 25-Hydroxyvitamin D
(E) Ionized calcium

Item 15

A 52-year-old woman is evaluated for a 1-year history of a 6.8-kg (15-lb) weight gain, easy bruising, hypertension, and worsening diabetes control. Medical history is also significant for a history of depression and anxiety. Medications are metformin and lisinopril.

On physical examination, blood pressure is 155/97 mm Hg and pulse rate is 82/min. Other vital signs are normal. BMI is 33. The patient has central obesity, supraclavicular and dorsocervical fat pads, and facial hirsutism. There are a few bruises on her arms and no abdominal striae.

Laboratory studies show a 24-hour urine free cortisol level of 205 µg/24 h, (564.9 nmol/24 h), midnight salivary cortisol of 298 ng/mL (821.2 nmol/L)(normal <100 ng/mL [275.6 nmol/L]), and adrenocorticotropic hormone (ACTH) less than 5 pg/mL (1.1 pmol/L).

Which of the following is the most likely cause of this patient's hypercortisolism?

(A) Adrenal tumor
(B) Bronchial carcinoid
(C) Pituitary tumor
(D) Psychiatric illness

Item 16

A 27-year-old man is evaluated for decreased libido. He is a professional body builder and reports longstanding use of

anabolic steroids to improve physical appearance and muscular performance. His medical history is otherwise unremarkable, and he currently takes no medications other than anabolic steroids.

On physical examination, vital signs are normal. He has a muscular build, acne, bilateral symmetric gynecomastia, and small testes.

Laboratory studies:

Hematocrit	52%
Follicle-stimulating hormone	2 mU/mL (2 U/L)
Luteinizing hormone	3 mU/mL (3 U/L)
Testosterone, total (8 AM)	170 ng/dL (5.9 nmol/L)

Liver enzyme testing is normal.

Which of the following is the most appropriate management?

(A) Anastrozole
(B) Cessation of anabolic steroid use
(C) Clomiphene citrate
(D) Human chorionic gonadotropin
(E) Testosterone replacement

Item 17

A 25-year-old woman comes to the office to establish care. She is 5 weeks pregnant. She has hypothyroidism due to Hashimoto thyroiditis that was diagnosed 4 years ago. She is asymptomatic. Her only medications are levothyroxine and folic acid.

On physical examination, vital signs are normal. The patient's thyroid gland is nontender and diffusely enlarged without nodules. Pregnancy test is positive.

Serum thyroid-stimulating hormone level measured 4 months ago was 2.2 µU/mL (2.2 mU/L).

Which of the following is the most appropriate management of this patient's hypothyroidism?

(A) Check serum thyroid-stimulating hormone in 2 months
(B) Decrease levothyroxine dose by 30%
(C) Increase levothyroxine dose by 30%
(D) Stop levothyroxine and start liothyronine

Item 18

A 34-year-old transgender woman is evaluated during a routine examination. She desires gender-affirming hormone therapy. Her gender incongruence diagnosis has been made and confirmed by qualified medical providers. She smokes one pack of cigarettes per day, with a 15-pack-year history. Medical history is otherwise unremarkable. She takes no medications.

On physical examination, vital signs are normal. She has male hair distribution. Normal male genitalia are present. There are no evident inguinal hernias.

In addition to advising smoking cessation, which of the following is the most appropriate next step in management?

(A) Initiation of an androgen blocker
(B) Initiation of estradiol therapy
(C) Refer for gender confirmation surgery consultation
(D) Refer for discussion on fertility preservation options
(E) Return for treatment 1 year after living in desired gender role

Item 19

A 54-year-old woman is evaluated for flushing of the face of 1 year's duration. These episodes occur two or three times per week and last about 30 minutes. She went through menopause at age 50 and is on estrogen and progesterone hormone therapy. She also experiences episodes of anxiety, diaphoresis, and tachycardia. Medical history is significant for increasingly frequent migraine headaches, difficult to control hypertension, and gastroesophageal reflux disease. Medications are amitriptyline, chlorthalidone, metoprolol, conjugated estrogens, progesterone, and omeprazole.

On physical examination, blood pressure is 156/92 mm Hg; the remainder of the vital signs is normal. BMI is 32. The remainder of the examination is unremarkable.

Which of the following medications should be discontinued prior to screening for secondary causes of hypertension?

(A) Amitriptyline
(B) Chlorthalidone
(C) Metoprolol
(D) Omeprazole
(E) Progesterone

Item 20

A 74-year-old woman is seen in follow-up for osteoporosis diagnosed 5 years ago. She has been taking alendronate (70 mg weekly) without adverse effect for 5 years. Medical history is otherwise unremarkable. Alendronate is her only medication.

On physical examination, vital signs are normal. She has no kyphosis or height loss, and the remainder of her examination is also normal.

Her recent bone mineral density by dual-energy x-ray absorptiometry (DEXA) scan showed a lumbar spine T-score of −2.2 and femoral neck T-score of −2.4.

Which of the following is the most appropriate management?

(A) C-terminal peptide of type 1 collagen (CTx) measurement
(B) Continue alendronate for 5 additional years
(C) Decrease alendronate dose
(D) Discontinue alendronate

Item 21

A 67-year-old woman is evaluated for management of her type 2 diabetes mellitus. Medical history is significant for type 2 diabetes diagnosed 15 years ago, hypertension, hyperlipidemia, and obesity. She also has diabetic complications including nephropathy, retinopathy, and neuropathy. She does not have hypoglycemia. Medications are enalapril, atorvastatin, insulin glargine, insulin aspart, and metformin.

On physical examination, vital signs are normal. BMI is 31. Ophthalmoscopic examination reveals nonproliferative diabetic retinopathy. A foot examination reveals an insensate foot with intact skin. Vibratory sense is absent in the toes and ankle. The remainder of the physical examination is unremarkable.

Laboratory studies show a hemoglobin A_{1c} level of 7.7% and serum creatinine level of 1.4 mg/dL (123.8 µmol/L). She has had a gradual decline in her estimated glomerular filtration rate (eGFR) from 50 to 39 mL/min/1.73 m² over the last 5 years.

Which of the following is the most appropriate management?

(A) Continue current regimen
(B) Discontinue metformin dose
(C) Increase insulin glargine dose
(D) Increase glipizide dose

Item 22

A 19-year-old woman is evaluated for irregular menstrual cycles since menarche at 12 years of age, increasing amount of coarse facial hair, and acne. Symptoms have worsened since she stopped playing high school sports and subsequently gained weight. She is most concerned about the hair growth and acne. Medical history is otherwise unremarkable, and she takes no medications.

On physical examination, vital signs are normal. BMI is 31. She has coarse terminal hair on the upper lip and chin, acne on the face and back, and non-discolored striae on the abdomen. There is no galactorrhea and no other evidence of virilization such as deepening of the voice, clitoromegaly, or male pattern balding.

Laboratory studies show a total testosterone level of 73 ng/dL (2.5 nmol/L), dehydroepiandrosterone sulfate level of 1.8 µg/mL (4.9 µmol/L), and hemoglobin A_{1c} of 5.4%. Other laboratory results are normal. Serum pregnancy test is negative.

In addition to exercise and weight loss, which of the following is the most appropriate next step in management?

(A) Combined oral contraceptive therapy
(B) Metformin
(C) Pelvic ultrasound
(D) Spironolactone

Item 23

A 43-year-old man is evaluated for a change in his usual migraine headache. The headaches are now more frequent and respond poorly to his previously effective migraine headache medications. His medical history is otherwise unremarkable. Medications include ibuprofen and sumatriptan.

On physical examination, vital signs are normal. Physical examination including funduscopic examination is normal.

MRI reveals a 1-cm pituitary adenoma with suprasellar extension with no compression or abutment of the optic chiasm or optic nerves.

Laboratory studies show a cortisol level of 17 µg/dL (469.2 nmol/L), thyroid-stimulating hormone level of 2.6 µU/mL (2.6 mU/L), and thyroxine (T_4) level of 1.2 ng/dL (15.5 pmol/L).

Which of the following is the most appropriate diagnostic test to perform next?

(A) Measurement of prolactin and insulin-like growth factor 1 (IGF-1)
(B) Measurement of urine free cortisol
(C) Visual field examination
(D) No further evaluation is needed

Item 24

H

A 42-year-old woman is evaluated prior to surgery following a diagnosis of pheochromocytoma. Her symptoms are palpitations, hypertension, and sweating for 8 months' duration. Medications are lisinopril and hydralazine.

On physical examination, blood pressure is 155/98 mm Hg. Other vital signs and the remainder of the examination are normal.

Which of the following is the most appropriate next step in management?

(A) Increase hydralazine
(B) Increase lisinopril
(C) Start chlorthalidone
(D) Start metoprolol
(E) Start phenoxybenzamine

Item 25

A 60-year-old man is evaluated during a routine office visit. He was diagnosed with type 2 diabetes mellitus 6 years ago. Medical history is significant for coronary artery disease, hypertension, hyperlipidemia, and biliary pancreatitis. Medications are lisinopril, metoprolol, metformin, aspirin, and atorvastatin.

On physical examination, other than a blood pressure of 152/91 mm Hg, the vital signs are normal. BMI is 27. The remainder of the examination is normal.

Laboratory studies show a hemoglobin A_{1c} level of 8.2%.

Which of the following is the most appropriate treatment for this patient?

(A) Empagliflozin
(B) Glipizide
(C) Liraglutide
(D) Sitagliptin

Item 26

A 24-year-old woman is evaluated for a 6-month history of amenorrhea. Previously, menstrual cycles were regular. She also notes vaginal dryness. She reports no acne, stretch marks, breast discharge, or changes in weight. Medical history is otherwise unremarkable, and she takes no medications.

On physical examination vital signs are normal. BMI is 26. Vulvovaginal atrophy is noted on pelvic examination. The remainder of the examination is unremarkable.

Laboratory studies show undetectable beta-human chorionic gonadotropin. Prolactin and thyroid-stimulating hormone levels are within normal limits.

Which of the following is the most appropriate next diagnostic test?

(A) Dehydroepiandrosterone sulfate (DHEAS) measurement
(B) Follicle-stimulating hormone measurement
(C) Pelvic MRI
(D) Testosterone measurement
(E) Transvaginal ultrasound

H Item 27

A 66-year-old woman was admitted to the hospital 24 hours ago with community-acquired pneumonia. Since admission, she has been confused and her oral intake has been poor. Appropriate antibiotics, intravenous fluids, and oxygen have been initiated. She has no other known medical problems.

On physical examination, temperature is 39 °C (102.2 °F), blood pressure is 142/88 mm Hg, pulse rate is 98/min, and respiration rate is 20/min. Oxygen saturation is 98% on oxygen, 2 L/min by nasal cannula. Crackles are evident in the right posterior thorax.

Laboratory studies show glucose values of 185 to 215 mg/dL (10.3-11.9 mmol/L) and a hemoglobin A_{1c} level is 5.5%.

A chest radiograph demonstrates a right lower lobe infiltrate.

Which of the following is the most appropriate management of this patient's hyperglycemia?

(A) Empagliflozin and sliding-scale insulin
(B) Metformin and sliding-scale insulin
(C) Scheduled basal insulin and correction insulin
(D) Sliding-scale insulin only

Item 28

A 45-year-old man is evaluated for anorexia, dizziness, and weakness. He was discharged from the hospital 5 days ago after transsphenoidal pituitary surgery for a pituitary macroadenoma abutting the optic chiasm. His postoperative course was uneventful, and his postoperative hormone evaluation was normal; he did not require any hormone replacement. He denies any polyuria or increase in thirst. He takes no medications.

On physical examination, vital signs and physical examination are normal.

Which of the following is the most appropriate diagnostic test to perform next?

(A) Antidiuretic hormone testing
(B) MRI of the pituitary
(C) Serum sodium measurement
(D) Thyroid-stimulating hormone measurement

Item 29

A 34-year-old woman is evaluated for new onset headaches of 4 months' duration. Her menstrual periods have been irregular for the last year. She has been trying to conceive for the last 6 months. Her last menstrual period was 7 weeks ago. She is otherwise healthy and takes no medications.

On physical examination, vital signs are normal. Visual field examination is normal. Examination of the optic discs and cranial nerve examination are normal. The remainder of the physical examination is noncontributory.

MRI obtained to evaluate her headaches reveals a partially empty sella with no evidence of pituitary tumor or other masses.

Laboratory studies:	
Cortisol (8:00 AM)	15 µg/dL (414 nmol/L)
Estradiol	20 pg/mL (73.4 pmol/L)
Follicle-stimulating hormone	5 mU/mL (5 U/L)
Human chorionic gonadotropin, serum	Negative
Luteinizing hormone	4 mU/mL (4 U/L)
Prolactin	62 ng/mL (62 µg/L)
Thyroid-stimulating hormone	2.4 µU/mL (2.4 mU/L)
Thyroxine (T_4), free	1.3 ng/dL (16.8 pmol/L)
Serum human chorionic gonadotropin	Negative

Which of the following is the most appropriate management?

(A) Dopamine agonist therapy
(B) Neurosurgery consultation
(C) Oral contraceptive pill
(D) No treatment necessary

Item 30

A 21-year-old woman is seen in the office following parathyroidectomy for hyperparathyroidism. The pathology of three resected enlarged parathyroid glands showed hyperplasia. Her medical history is significant for oligomenorrhea. Family history is notable for hypercalcemia and kidney stones in her father, who died at age 49 from pancreatic cancer, and a pituitary tumor in her sister at age 16.

Her vital signs are normal. Skin findings include dermatofibroma. Her physical examination is normal with the exception of the surgical scar on her neck.

Which of the following is the most likely diagnosis?

(A) Familial hypocalciuric hypercalcemia
(B) Multiple endocrine neoplasia type 1 (MEN1)
(C) Parathyroid carcinoma
(D) Secondary hyperparathyroidism
(E) Tertiary hyperparathyroidism

Item 31

A 57-year-old woman is evaluated for cough, exertional dyspnea, and fatigue for 12 months' duration. Medical history is otherwise unremarkable, and she takes no medications.

On physical examination, temperature is 38.1 °C (100.6 °F), blood pressure is 132/78 mm Hg, pulse rate is 84/min, respiratory rate is 18/min; oxygen saturation is 95% breathing ambient air. The cardiac examination is normal. There are no wheezes or crackles on pulmonary examination. The remainder of the examination is unremarkable.

Laboratory studies:

Calcium	11.1 mg/dL (2.8 mmol/L)
Creatinine	1.2 mg/dL (106.1 µmol/L)
Phosphorus	4.7 mg/dL (1.5 mmol/L)
Parathyroid hormone	<10 pg/mL (10 ng/L)

Chest radiograph is shown.

A tuberculin skin test is normal.

Which of the following is the most appropriate laboratory test to perform next?

(A) Alkaline phosphatase level
(B) Cortisol level
(C) 1,25-Dihydroxyvitamin D level
(D) Parathyroid hormone-related protein level

Item 32

A 28-year-old woman is evaluated for preconception counseling. She desires to achieve pregnancy in the next 6 months. Medical history is significant for type 1 diabetes mellitus diagnosed at 12 years of age. She has no known microvascular or macrovascular complications of diabetes. She is up to date on screening for microvascular complications with her last eye examination performed 11 months prior and a normal creatinine level, urine albumin-creatinine ratio, lipid panel, and foot examination 9 months prior. Thyroid-stimulating hormone level was 0.5 µU/mL (0.5 mU/L) 3 months ago. She is currently using a condom for contraception. Medical history also includes autoimmune thyroid disease. Medications are insulin lispro delivered through continuous subcutaneous insulin infusion and levothyroxine.

On physical examination, vital signs are normal. Nondilated retinal examination, thyroid examination, and monofilament testing are all normal.

Laboratory studies reveal that hemoglobin A_{1c} level is currently 6.7%, improved from 9% 3 months ago.

Which of the following is the most appropriate preconception management to perform next?

(A) Dilated eye examination
(B) Fasting lipid profile
(C) Nephrology referral
(D) Thyroid-stimulating hormone measurement
(E) Urine albumin-creatinine ratio

Item 33

A 38-year-old woman presents for first assessment of bone health 4 months into prednisone therapy. Medical history is significant for treatment of antiphospholipid syndrome with recurrent diffuse alveolar hemorrhage and secondary diabetes mellitus. She is not sexually active. She has had no fractures. Medications are prednisone, cyclophosphamide, neutral protamine Hagedorn (NPH) insulin, calcium citrate/vitamin D_3, sulfamethoxazole-trimethoprim, and omeprazole. She is expected to continue prednisone therapy, 7.5 mg or more, for at least the next 6 months.

On physical examination, vital signs are normal. BMI is 37. The remainder of the examination is normal.

Bone mineral density by dual-energy x-ray absorptiometry shows a lumbar spine Z-score of −2.1 and total hip Z-score of −3.1. Radiograph of the spine shows no vertebral compression.

Which of the following is the most appropriate treatment?

(A) Alendronate
(B) Teriparatide
(C) Zoledronic acid
(D) No additional therapy

Item 34

A 29-year-old woman is seen in follow-up for evaluation of abnormal thyroid laboratory results. She is currently 26 weeks pregnant. She was originally evaluated 1 week ago for concerns about lack of weight gain during pregnancy, palpitations, anxiety, and insomnia. There is no family history of thyroid or autoimmune disease. Medical history is unremarkable, and her only medication is a prenatal vitamin.

On physical examination, other than a pulse rate of 98/min, vital signs are normal. The patient is a thin, gravid woman with a mild tremor of the outstretched hands, lid lag, and small goiter. There is no exophthalmus.

Laboratory studies obtained last week show a thyroid-stimulating hormone level of 6.5 µU/mL (6.5 mU/mL) and a free thyroxine (T_4) level of 2.6 ng/dL (33.5 pmol/L).

Which of the following is the most likely diagnosis?

(A) Gestational thyrotoxicosis
(B) Graves disease
(C) Hypothyroidism
(D) Thyroid-stimulating hormone-secreting adenoma

Item 35

A 31-year-old woman is evaluated for amenorrhea. She stopped taking her oral contraceptive pill (OCP) 6 months ago with the goal of becoming pregnant. She has not had a menstrual cycle since stopping her OCP. Her cycles were regular prior to starting an OCP 6 years ago and while on the OCP. She notes a small amount of breast discharge with nipple stimulation; this has been a noted issue for approximately 3 months. Medical history is otherwise unremarkable. Her only medication is a folic acid supplement.

On physical examination, vital signs are normal. There is an elicitable milky discharge from the nipples bilaterally. Thyroid and skin examinations are normal. Visual field testing is normal.

Laboratory studies show a prolactin level of 75 ng/mL (75 µg/L). Serum pregnancy test is negative, and thyroid-stimulating hormone level, kidney function tests, and liver chemistry tests are normal.

MRI of the brain with and without contrast with fine cuts through pituitary reveals a 7-mm pituitary microadenoma.

Which of the following is the most appropriate management?

(A) Clomiphene citrate therapy
(B) Dopamine agonist therapy
(C) Pituitary surgery
(D) Resume oral contraceptive pill

Item 36

A 19-year-old man is evaluated during a follow-up evaluation of his type 1 diabetes mellitus. He was diagnosed 4 months ago with symptoms of hyperglycemia. His hemoglobin A_{1c} level at diagnosis was 11.1%, and antibodies to glutamic acid decarboxylase (GAD65) were positive. He was begun on prandial and basal insulin. He now reports progressive improvement in his glycemic control over the last 8 weeks without changes to his diet, activity level, or insulin doses. Data from his glucometer demonstrates an average fasting, preprandial, and bedtime blood glucose level of 80 mg/dL (4.4 mmol/L). He has several postprandial blood glucose values of approximately 60 mg/dL (3.3 mmol/L) associated with hypoglycemic symptoms. His current hemoglobin A_{1c} level is 5.0%. Medications are insulin glargine (8 U) and insulin aspart (2 U before meals).

His physical examination is notable for an increase in BMI from 18 at the time of his diabetes diagnosis, to now at 20. Vital signs and the remainder of the physical examination are normal.

Which of the following is the most appropriate management of this patient's diabetes?

(A) Continue insulin glargine dose, decrease insulin aspart dose
(B) Decrease insulin glargine dose, discontinue insulin aspart
(C) Discontinue insulin glargine, discontinue insulin aspart
(D) Discontinue insulin glargine, discontinue insulin aspart, add sliding-scale insulin regimen

Item 37

A 63-year-old woman was diagnosed with osteoporosis 6 years ago. Initial treatment with an oral bisphosphonate resulted in upper gastrointestinal symptoms, so subcutaneous denosumab twice yearly was prescribed. The patient has now completed 5 years of denosumab therapy. Medical history is otherwise unremarkable. Denosumab was last administered 6 months ago.

Vital signs and the remainder of the physical examination are normal.

Which of the following is the most appropriate management?

(A) Continue denosumab
(B) Dual-energy x-ray absorptiometry (DEXA) scan
(C) Osteoporosis drug holiday
(D) Switch to zoledronic acid

Item 38

H

A 55-year-old man with type 1 diabetes mellitus was admitted to the hospital for management of a non-ST-elevation myocardial infarction. He is clinically stable and eating well. He will begin fasting at midnight in preparation for a cardiac catheterization tomorrow. His current fasting blood glucose values range from 70 to 80 mg/dL (3.9-4.4 mmol/L), and his premeal blood glucose values range from 140 to 160 mg/dL (7.8-8.9 mmol/L) on his home doses of basal insulin glargine and prandial insulin aspart. His last hemoglobin A_{1c} value was 7.2%.

In addition to holding prandial insulin, which of the following is the most appropriate management for this patient's diabetes?

(A) Continue basal insulin dose
(B) Continue basal insulin dose and add correction insulin regimen
(C) Decrease basal insulin dose and add correction insulin regimen
(D) Hold basal insulin and add sliding-scale insulin regimen

Item 39

A 38-year-old woman is seen in follow up to discuss the findings of an abdominal and pelvic CT scan done to evaluate renal colic, which has since resolved. The abdominal CT scan showed two small nonobstructing renal calculi in the right kidney and a 1.6-cm left adrenal mass with a density of 21 Hounsfield units (indeterminate for adrenal adenoma). Other than nephrolithiasis, the remainder of the medical history is unremarkable, and she takes no medications.

On physical examination, vital signs and the remainder of the examination are unremarkable.

Laboratory studies show normal serum electrolytes.

Which of the following is the most appropriate test to perform next?

(A) 24-Hour urine free cortisol measurement
(B) 24-Hour urine total metanephrine measurement
(C) Plasma aldosterone-plasma renin ratio (ARR) measurement
(D) Serum dehydroepiandrosterone sulfate (DHEAS) measurement

H

Item 40

A 57-year-old woman is evaluated during hospitalization following surgical fixation of a right femur neck pathologic fracture. Pathology of the femur shows a neoplasm containing numerous giant cells consistent with brown tumor.

On physical examination, vital signs are normal. There is a palpable mass on the lower left side of the right neck. There is an incision with surgical staples on the right hip. The remainder of the examination is unremarkable.

Laboratory studies:

Alkaline phosphatase	260 U/L
Calcium	13.2 mg/dL (3.3 mmol/L)
Creatinine	1.6 mg/dL (141.4 µmol/L)
Phosphorus	1.9 mg/dL (0.6 mmol/L)
Parathyroid hormone	1142 pg/mL (1142 ng/L)

Neck ultrasound shows a solid hypervascular mass (6 × 2.9 × 3 cm) posterior to the left lobe of the thyroid, with compression and displacement of the trachea. A parathyroidectomy is planned.

Which of the following is the most appropriate test to perform next?

(A) 1,25-Dihydroxyvitamin D level
(B) 24-Hour urine calcium level
(C) 25-Hydroxyvitamin D level
(D) Ionized calcium level

Item 41

A 51-year-old woman underwent CT scan of the abdomen following a motor vehicle accident. This revealed a 2.5-cm right adrenal mass with a density of 6 Hounsfield units (compatible with adrenal adenoma). Medical history is significant for hypertension diagnosed 2 years ago. She is perimenopausal and has been experiencing sweating and hot flushes. Medications are hydrochlorothiazide and doxazosin.

On physical examination, blood pressure is 142/90 mm Hg, pulse rate is 90/min. Other vital signs are normal. BMI is 33. There are no supraclavicular fats pads or abdominal striae.

Laboratory studies show a cortisol level following a 1-mg overnight dexamethasone suppression test of 8 µg/dL (220.8 nmol/L), plasma aldosterone-plasma renin ratio (ARR) of 13, and plasma fractionated free metanephrines 32 pg/mL (0.17 nmol/L).

Which of the following is the most likely diagnosis?

(A) Non-hormone-secreting adrenal adenoma
(B) Pheochromocytoma
(C) Primary aldosteronism
(D) Subclinical Cushing syndrome

Item 42

A 48-year-old woman is evaluated for a 1-year history of 11.3-kg (25-lb) weight gain, fatigue, easy bruising, and difficulty remembering things. She works the night shift at a hotel reception desk. Medical history is significant for hypertension, type 2 diabetes mellitus, and menopausal hot flushes. Medications are lisinopril, estradiol, aspirin, and metformin.

On physical examination, blood pressure is 142/88 mm Hg. Other vital signs are normal. BMI is 34. The patient has central obesity and a dorsocervical fat pad is present. There are no abdominal striae, no proximal muscle weakness, and no supraclavicular fat pads.

Which of the following is the most appropriate next step in evaluation of this patient?

(A) 1-mg overnight dexamethasone suppression test
(B) 24-Hour urine free cortisol measurement
(C) Late night salivary cortisol measurement
(D) Morning serum total cortisol measurement

Item 43

A 52-year-old man is evaluated for gradual onset breast tenderness and enlargement over the past 6 months. Medical history is significant for hypertension and symptomatic heart failure with reduced ejection fraction diagnosed 1 year ago. His medications are metoprolol, lisinopril, and spironolactone. He has noticed no change in his sexual function over the past year and reports the presence of morning erections.

On physical examination, vital signs are normal. BMI is 31. There is notable bilateral breast tenderness with rubbery concentric masses noted bilaterally at the areolae. There is no thyroid enlargement, hepatomegaly, or testicular abnormalities including atrophy or mass.

Which of the following is the most likely diagnosis?

(A) Breast cancer
(B) Germ cell tumor
(C) Hypogonadal-associated gynecomastia
(D) Pseudogynecomastia
(E) Spironolactone-induced gynecomastia

Item 44

A 24-year-old man is seen for follow-up management of hypothyroidism. He was diagnosed with hypothyroidism due to Hashimoto thyroiditis 8 years ago. Until 6 months ago, he had been euthyroid on the same dose of levothyroxine. More recently he has required escalating doses of levothyroxine to maintain euthyroidism. He reports that he is still taking levothyroxine as he always has—first thing in the morning on an empty stomach at least 1 hour before eating breakfast. At present, the patient admits to hypothyroid symptoms and intermittent crampy abdominal pain. He has an unintentional weight loss of 2.3 kg (5 lb) over the last 2 months and a new, very pruritic rash on his knees and elbows. His only medication is levothyroxine.

On physical examination, vital signs are normal. The patient's thyroid gland is normal to palpation without nodules. He has papules and excoriated blisters on his elbows, knees, and buttocks.

Laboratory studies show a serum thyroid-stimulating hormone level of 14 µU/mL (14 mU/L) and a free thyroxine (T_4) level of 0.9 ng/dL (11.6 pmol/L).

Which of the following is the most likely diagnosis?

(A) Celiac disease
(B) Medication noncompliance
(C) Primary adrenal insufficiency
(D) Thyroid hormone resistance

Item 45

A 37-year-old woman is unable to achieve pregnancy despite 7 months of unprotected intercourse. Her menstrual cycles are normal, occurring every 28 days with associated breast tenderness and bloating. There have been no prior pregnancies or attempts to achieve pregnancy by either the patient or her male partner. There is no history of previous sexually transmitted infections. She is otherwise healthy.

Medical history is significant for appendicitis at age 26 for which she had an uncomplicated appendectomy. Her only medication is a prenatal vitamin.

On physical examination, vital signs are normal. She has a well-healed abdominal scar. Thyroid, skin, and pelvic examinations are all unremarkable. There is no elicitable breast discharge, no signs of hyperandrogenism, and no visual field cuts.

Which of the following is the most appropriate management?

(A) Obtain midluteal phase serum progesterone level
(B) Obtain semen analysis
(C) Recommend an additional 5 months of unprotected intercourse
(D) Refer for laparoscopy

Item 46

A 55-year-old man is referred for evaluation of fatigue, weight gain, decreased libido, and difficulty maintaining an erection. Sexual functioning was normal until 6 months ago, and he has fathered two children. Medical history is significant for polysubstance abuse that is being managed with daily methadone. His medical history is otherwise unremarkable, and his only medication is methadone.

On physical examination, vital signs are normal. Neurological, genitalia, and the remainder of the physical examination are normal.

Laboratory studies:

Follicle-stimulating hormone	5 mU/mL (5 U/L)
Luteinizing hormone	4 mU/ml (4 U/L)
Prolactin	12 ng/mL (12 µg/L)
Testosterone	185 ng/dL (6.4 nmol/L)
Thyroid-stimulating hormone	2.4 µU/mL (2.4 mU/L)
Thyroxine (T_4), free	1.3 ng/dL (16.8 pmol/L)

Which of the following is the most likely cause of this patient's hypogonadism?

(A) Age-related decline in gonadal function
(B) Chronic opioid therapy
(C) Pituitary tumor
(D) Primary gonadal failure

Item 47

An 18-year-old woman is evaluated for absence of menarche. She has undergone some breast development (Tanner stage II). Medical history is unremarkable, and she takes no medications.

On physical examination, her height is 150 cm (59 in) and weight is 47 kg (103.6 lb). BMI is 21. Vital signs and the remainder of the physical examination, including pelvic examination, are normal.

Laboratory studies show a follicle-stimulating hormone level of 74 mU/mL (74 U/L). Serum beta human chorionic gonadotropin level is undetectable. Thyroid-stimulating hormone and prolactin levels are normal.

On pelvic ultrasound, a uterus is present, but ovaries are difficult to visualize.

Which of the following is the most likely diagnosis?

(A) Functional hypothalamic amenorrhea
(B) Primary ovarian insufficiency
(C) Turner syndrome
(D) Vaginal agenesis

Item 48

A 47-year-old man is evaluated for intermittent episodes of anxiety, diaphoresis, and palpitations. These episodes occur approximately 4 hours after a meal. His first episode occurred while at work. A fingerstick blood glucose reading performed by the employee health nurse was 48 mg/dL (2.7 mmol/L). His symptoms resolved with juice. He has had three similar episodes over the last month. He has increased his consumption of snacks between meals in an attempt to avoid repeat episodes. He denies use of over-the-counter supplements or illicit drug use. He does not consume alcohol. He is asymptomatic today. Medical history is significant for Roux-en-Y gastric bypass surgery 3 years ago. He takes no glucose-lowering medications.

On physical examination, vital signs are normal. BMI is 31. The remainder of his examination is normal.

His fingerstick blood glucose level is 85 mg/dL (4.7 mmol/L). Laboratory studies show a hemoglobin A_{1c} level of 5%. All other laboratory results are normal.

Which of the following is the most appropriate diagnostic test to perform next?

(A) 72 Hour fast
(B) Mixed-meal testing
(C) Oral glucose tolerance test
(D) Pancreatic imaging

Item 49

A 65-year-old woman is admitted to the hospital for fatigue and weakness over the last 1 to 2 weeks. Medical history is significant for hypertension, type 2 diabetes mellitus, and rheumatoid arthritis. For the past 3 months, the patient's rheumatoid arthritis has been treated with methotrexate and prednisone. Because of inadequate control, etanercept was added 2 weeks ago. At that time, the patient decided to discontinue prednisone due to increased bruising of her skin.

H CONT.

Current medications are methotrexate, etanercept, amlodipine, folic acid, metformin, and aspirin.

On physical examination, blood pressure is 110/68 mm Hg sitting and 90/64 mm Hg standing, and pulse rate is 102/min sitting and 110/min standing. Symmetrical synovial bogginess is noted in the metacarpophalangeal joints and wrists bilaterally.

Laboratory studies show an 8 AM cortisol level of 2 µg/dL (55.2 nmol/L).

Which of the following is the most appropriate management?

(A) Initiation of hydrocortisone
(B) Initiation of hydrocortisone and fludrocortisone
(C) Performance of an adrenocorticotropic hormone (ACTH) stimulation test
(D) Performance of an ACTH stimulation test after administration of dexamethasone

Item 50

A 45-year-old woman comes to the office to review her thyroid function test results. Thyroid function testing was ordered in response to a recent diagnosis of hypercholesterolemia. The patient is otherwise well, and she takes no medications.

On physical examination, vital signs are normal. Her physical examination is normal with the exception of slowed relaxation phase of deep tendon reflexes.

Laboratory studies show a serum thyroid-stimulating hormone (TSH) level of 24 µU/mL (24 mU/L) and a free thyroxine (T_4) level of 0.65 ng/dL (8.4 pmol/L).

Which of the following is the most appropriate treatment?

(A) Desiccated thyroid extract
(B) Low-dose (25-µg) levothyroxine
(C) Weight-based replacement dose of levothyroxine
(D) No treatment

Item 51

A 24-year-old woman is evaluated for 6 months of amenorrhea, weight gain, and depressed mood. Medical history is otherwise unremarkable, and she takes no medications.

On physical examination, blood pressure is 134/86 mm Hg and pulse rate is 82/min. BMI is 31. Other vital signs are normal. The patient has facial plethora. Skin examination reveals multiple ecchymoses. There are wide pigmented striae on the abdomen as well as a dorsocervical fat pad.

Laboratory studies:

Cortisol, free, urine	
Initial measurement	120 µg/24 h (330.7 nmol/24 h)
Repeat measurement	240 µg/24 h (661.3 nmol/24 h)
Cortisol after 1 mg dexamethasone test	6.0 µg/dL (165.6 nmol/L)

Which of the following is the most appropriate diagnostic test to perform next?

(A) Adrenocorticotropic hormone (ACTH) level
(B) 8-mg Dexamethasone suppression test
(C) Inferior petrosal sinus sampling for ACTH
(D) Pituitary MRI

Item 52

A 56-year-old man is evaluated for palpitations and difficulty sleeping over the past month. His past medical history is significant for hypothyroidism following subtotal thyroidectomy 6 months ago for management of compressive symptoms from a multinodular goiter. Two months ago, he was diagnosed with hypogonadism and was prescribed intramuscular testosterone. He takes his levothyroxine on an empty stomach with a cup of coffee every morning. His medications are levothyroxine, testosterone enanthate, calcium carbonate, and omeprazole for gastroesophageal reflux disease.

On physical examination, his vital signs are normal. He has a well-healed anterior neck scar. There is a fine tremor of his outstretched hands. The remainder of the examination is normal.

Laboratory studies:

	2 Months Ago	Today
Serum thyroid stimulating hormone	1.5 µU/mL (1.5 mU/L)	0.08 µU/mL (0.08 mU/L)
Thyroxine (T_4), free	1.1 ng/dL (14.2 pmol/L)	1.4 ng/dL (18.1 pmol/L)

Which of the following is the most likely explanation for the thyroid function test results?

(A) Calcium carbonate
(B) Levothyroxine with coffee
(C) Omeprazole
(D) Testosterone

Item 53

A 74-year-old woman is evaluated for back pain after a fall occurring 2 weeks ago. Medical history is significant for deep venous thrombosis 3 years ago following a 12-hour airplane flight. Medications are acetaminophen as needed for back pain and calcium carbonate with vitamin D.

On physical examination, vital signs are normal. She has minimal pain to percussion over T8. Her examination is otherwise normal.

Laboratory studies:

Alkaline phosphatase	82 U/L
Calcium, serum	9.9 mg/dL (2.5 mmol/L)
Creatinine, serum	1.1 mg/dL (97.2 µmol/L)
25-Hydroxyvitamin D	40 ng/mL (99.8 nmol/L)

Lateral spine radiograph shows 30% compression of T8, not present on prior radiographs. Bone mineral density by DEXA shows a lumbar spine T-score of −3.0 and femur neck T-score of −2.8.

Which of the following is the most appropriate treatment?

(A) Alendronate
(B) Calcitonin
(C) Denosumab
(D) Raloxifene
(E) Teriparatide

Item 54

A 78-year-old man with type 2 diabetes mellitus is evaluated during a routine follow-up examination. He reports hypoglycemia occurring approximately twice per week before dinner. It is worse if he plays golf in the afternoon. He has had three episodes in the last 3 months in which he required assistance from his wife. Medical history is significant for dyslipidemia, hypertension, and obesity. Medications are aspirin, atorvastatin, glyburide, lisinopril, and metformin.

On physical examination, vital signs are normal. BMI is 32. The remainder of the examination is normal.

Laboratory studies show a hemoglobin A_{1c} level of 6.5% and an estimated glomerular filtration rate (eGFR) of 50 mL/min/1.73 m^2.

Which of the following is the most appropriate management of hypoglycemia?

(A) Increase carbohydrate intake with the noon meal
(B) Prescribe glucagon
(C) Stop glyburide therapy
(D) Stop metformin therapy

Item 55

A 58-year-old man is evaluated for resistant hypertension. He was first diagnosed with hypertension 10 years ago, and his blood pressure has been increasingly difficult to control. Testing for secondary causes of hypertension will be undertaken. Medical history is otherwise unremarkable. Medications are lisinopril, spironolactone, hydrochlorothiazide, and metoprolol.

On physical examination, blood pressure is 149/93 mm Hg. Other vital signs are normal. BMI is 29. The remainder of the physical examination is unremarkable.

Which of the following should be discontinued prior to screening for secondary causes of hypertension?

(A) Hydrochlorothiazide
(B) Lisinopril
(C) Metoprolol
(D) Spironolactone

Item 56

A 75-year old man is evaluated for ongoing management of his type 2 diabetes mellitus. He was diagnosed with diabetes 11 years ago. In addition to diabetes, medical history is significant for hypertension, hyperlipidemia, and chronic kidney disease stage G3b. He had a myocardial infarction 6 months ago with subsequent placement of two drug-eluting stents. His hemoglobin A_{1c} level has decreased from 8.7% to 7.8% with adherence to lifestyle modifications and his basal and prandial insulin regimen. Medications are rosuvastatin, lisinopril, metoprolol, chlorthalidone, low-dose aspirin, and clopidogrel.

On physical examination, vital signs are normal. BMI is 29. Other than an S4, the cardiac examination and the remainder of the physical examination are normal.

According to the American Diabetes Association, which of the following is the most appropriate hemoglobin A_{1c} goal for this patient?

(A) Less than 7%
(B) 7% to less than 7.5%
(C) 7.5% to less than 8%
(D) 8% to less than 9%

Item 57

A 67-year-old man is evaluated for headache, fatigue, and weakness for the past several weeks. Medical history is significant for metastatic melanoma that is being treated with ipilimumab, which is his only medication.

On physical examination, vital signs are normal. There is a well-healed excisional scar on his posterior right shoulder. The remainder of the physical examination is normal.

MRI shows enlarged pituitary with homogeneous enhancement. There is no compression of the optic chiasm.

Laboratory studies:

Cortisol (8 AM)	3 µg/dL (82.8 nmol/L)
Prolactin	12 ng/mL (12 µg/L)
Thyroid-stimulating hormone	0.2 µU/mL (0.2 mU/L)
Thyroxine (T_4), free	0.6 ng/dL (7.7 pmol/L)

Which of the following is the most likely cause of this patient's findings?

(A) Ipilimumab-induced hypophysitis
(B) Lymphocytic hypophysitis
(C) Pituitary adenoma
(D) Primary hypothyroidism

Item 58

A 45-year-old man underwent abdominal CT imaging for evaluation of bloating and constipation. The CT scan shows a 5-cm right adrenal mass with a density of 42 Hounsfield units and absolute contrast washout of 38% at 10 minutes. Testing for pheochromocytoma and subclinical Cushing syndrome was negative. Medical history is otherwise unremarkable, and he takes no medications.

On physical examination, vital signs and the remainder of the physical examination are normal.

Which of the following is the most appropriate next step in management?

(A) Adrenal biopsy
(B) Adrenalectomy
(C) Mitotane therapy
(D) Repeat CT at 6 months

Item 59

H

A 55-year-old woman returns to the emergency department for persistent weakness, shakiness, and intermittent hand spasms. Three days ago, she was diagnosed with hypocalcemia, and vitamin D and calcium were initiated at that time.

H CONT.

Medical history is significant for metastatic ovarian cancer, currently treated with cisplatin and etoposide chemotherapy. Additional medications are calcium carbonate and vitamin D_3.

On physical examination, vital signs are normal. Tetany of the hand is noted during blood pressure assessment. Chvostek sign is positive.

Laboratory studies:

Albumin	3.5 g/dL (35 g/L)
Calcium	7.6 mg/dL (1.9 mmol/L)
Creatinine	1.0 mg/dL (88.4 µmol/L)
Parathyroid hormone	19 pg/mL (19 ng/L)
Potassium	4.2 mEq/L (4.2 mmol/L)

The laboratory results are similar to those obtained 3 days ago.

Electrocardiography shows a prolonged QTc interval.

Which of the following measurements is most appropriate to perform next?

(A) Bicarbonate
(B) Ionized calcium
(C) Magnesium
(D) Phosphorus

Item 60

A 60-year-old man is evaluated for management of type 2 diabetes mellitus. Three months ago he was diagnosed with type 2 diabetes mellitus and chronic kidney disease. At that time, he received diabetes education and began lifestyle modifications. Medical history is significant for chronic kidney disease, hypertension, and hyperlipidemia. His medications are lisinopril and atorvastatin.

On physical examination, his blood pressure is 146/88 mm Hg. BMI is 28.5. The remainder of his vital signs and physical examination are normal.

Laboratory studies show a hemoglobin A_{1c} level of 8.3%, serum creatinine level of 1.5 mg/dL (132.6 µmol/L), and estimated glomerular filtration rate of 48 mL/min/1.73 m^2.

Which of the following is the most appropriate treatment of this patient's diabetes?

(A) Empagliflozin
(B) Glipizide
(C) Metformin
(D) Saxagliptin

Item 61

A 55-year-old woman is seen during a follow-up evaluation for hyperthyroidism that was diagnosed 1 week ago. Thyroid examination revealed a palpable right thyroid nodule.

Thyroid-stimulating hormone (TSH) was less than 0.01 µU/mL (0.01 mU/L), free thyroxine (T_4) and total triiodothyronine (T_3) were 2.1 ng/dL (27.1 pmol/L) and 210 ng/dL (3.2 nmol/L), respectively. Atenolol was prescribed, and thyroid scintigraphy with determination of radioactive iodine uptake was ordered.

On physical examination, vital signs are normal. The neck and corresponding thyroid technetium-99 scan is shown.

Uptake at 24 hours is 30% (normal 14% to 30%).

Which of the following is the most appropriate management?

(A) Fine-needle aspiration biopsy of the thyroid nodule
(B) Increase atenolol dosage
(C) Methimazole
(D) Radioactive iodine (^{131}I) therapy

Item 62

A 55-year-old man is evaluated during a follow-up visit after he was diagnosed with type 2 diabetes mellitus based on two hemoglobin A_{1c} measurements of 7.8%. His medical history is significant for dyslipidemia and hypertension. Medications are aspirin, atorvastatin, and lisinopril.

On physical examination, vital signs are normal. BMI is 33. The general physical examination, including nondilated eye examination, is normal.

The patient will initiate therapeutic lifestyle modifications, and metformin will be started.

In addition to spot urine albumin-creatinine ratio testing, which of the following screening tests should be done now?

(A) Comprehensive foot examination and dilated eye examination
(B) Fasting plasma glucose and 2-hour 75-g oral glucose tolerance test
(C) Serum B_{12} and folate concentrations
(D) 24-Hour urine protein and creatinine measurement

Item 63

A 45-year-man is seen in routine follow-up for his type 2 diabetes mellitus. He was diagnosed 5 years ago, and he does not have any diabetes-related complications. His current treatment includes insulin detemir, prandial insulin lispro, and metformin. His hemoglobin A_{1c} level has decreased to 7.4%. His fasting and preprandial blood glucose measurements range from 110 to 130 mg/dL (6.1-7.2 mmol/L). He has had no hypoglycemia. Medical history is significant for obesity. He wishes to reduce his hemoglobin A_{1c} level to below 7%, but he is reluctant to add another injectable medication to his regimen. Medications are insulin detemir, insulin lispro, and metformin.

On physical examination, vital signs are normal. BMI is 33. The remainder of the physical examination is unremarkable.

Which of the following is the most appropriate management of this patient's diabetes?

(A) Add liraglutide
(B) Continue current regimen
(C) Increase insulin detemir dose
(D) Measure postprandial blood glucose level

Item 64

A 65-year-old woman is evaluated for hypercalcemia that was incidentally discovered on routine blood testing for a new life insurance policy. She has no symptoms. Medical history is unremarkable. Her only medication is calcium carbonate taken as needed for occasional heartburn.

On physical examination, vital signs are normal. Height is unchanged from prior measurements. The remainder of her examination is normal.

Laboratory studies:

Estimate glomerular filtration rate	Greater than 60 mL/min/1.73 m^2
Calcium	10.6 mg/dL (2.6 mmol/L)
Phosphorus	3.1 mg/dL (1.0 mmol/L)
Parathyroid hormone	72 pg/mL (72 ng/L)
25-Hydroxyvitamin D	35 ng/mL (87.4 nmol/L)
24-Hour urine calcium	240 mg/24 h (6 mmol/24 h)

Kidney-urinary-bladder radiograph is negative for kidney stones. Dual-energy x-ray absorptiometry (DEXA) bone mineral density scan shows femur neck T-score of −1.4, lumbar spine T-score of −1.4, and one-third radius T-score of −1.7.

Which of the following is the most appropriate management?

(A) Parathyroid sestamibi scan
(B) Reevaluate in 6 months
(C) Start alendronate
(D) Start cinacalcet

Item 65

A 45-year-old man is seen for follow-up evaluation for depression and to review the results of laboratory testing. He was seen 1 month ago for a 6-month history of depressed mood, difficulty sleeping, decreased appetite, 2.3-kg (5-lb) weight loss, and fatigue. Major depressive disorder was diagnosed, and escitalopram was prescribed. Today the patient reports a significant improvement in his mood, appetite, and the quality of his sleep since starting treatment.

On physical examination, vital signs and physical examination are normal. Screening laboratory studies from 1 month ago show a thyroid-stimulating hormone (TSH) level of 7 µU/mL (7 mU/L) and a free thyroxine (T_4) level of 1.0 ng/dL (12.9 pmol/L).

Which of the following is the most appropriate management?

(A) Measure thyroid peroxidase antibodies
(B) Measure thyrotropin receptor antibodies
(C) Measure serum triiodothyronine (T_3) level
(D) Prescribe levothyroxine
(E) Repeat serum TSH testing in 2 months

Item 66

A 52-year-old man is evaluated for difficult-to-control hypertension. Biochemical evaluation confirms a diagnosis of primary aldosteronism. Medications are amlodipine, losartan, and metoprolol.

On physical examination, blood pressure is 149/98 mm Hg and pulse rate is 75/min. The remainder of the vital signs and physical examination are unremarkable.

CT scan shows a 0.8-cm right adrenal mass with a density of 13 Hounsfield units.

Which of the following is the most appropriate management?

(A) Adrenal vein sampling
(B) Increase metoprolol
(C) Increase losartan
(D) Right adrenalectomy

Item 67

A 65-year-old woman comes to the office to establish care. Her medical history is notable for hypothyroidism due to Hashimoto thyroiditis treated with levothyroxine. She does not have any symptoms at this time. There is no history of head or neck radiation exposure.

On physical examination, vital signs are normal. The patient's thyroid gland is enlarged. The right lobe is larger than the left, and a mobile 2-cm nodule is palpable in the lower pole. There is no palpable cervical adenopathy.

Laboratory studies show a serum thyroid-stimulating hormone level of 2.0 µU/mL (2.0 mU/L).

Which of the following is the most appropriate diagnostic test to perform next?

(A) CT scan of the neck
(B) Fine-needle aspiration biopsy of the thyroid nodule
(C) Thyroid uptake and ^{131}I scan
(D) Ultrasound of the neck

Item 68

A 59-year-old woman is evaluated for fatigue and weight gain over the past 2 months. Her medical history is significant for a pituitary tumor, treated with surgery followed by radiation therapy, at age 54. She has recently self-initiated calcium and vitamin D and a multivitamin. Her only other medication is levothyroxine.

On physical examination, vital signs are normal. BMI is 31. The remainder of the physical examination is normal.

Which of the following is the most appropriate next step in management?

(A) Increase the levothyroxine dose
(B) Measure free thyroxine (T_4) level
(C) Measure thyroid-stimulating hormone level
(D) MRI of the brain

Item 69

A 53-year-old man returns for a follow-up visit for management of his type 2 diabetes mellitus. He was diagnosed with diabetes 10 years ago. In addition to diabetes, his medical history is significant for hypertension. Medications are enalapril and insulin glargine at bedtime and aspart insulin at meals.

On physical examination, blood pressure is 142/84 mm Hg. BMI is 27. The remainder of the vital signs and physical examination are unremarkable.

His fasting blood glucose level ranges from 150 to 180 mg/dL (8.3-10.0 mmol/L). His remaining premeal and bedtime blood glucose levels range from 110 to 130 mg/dL (6.1-7.2 mmol/L). He has intermittent episodes of hypoglycemia with recorded values ranging from 30 to 65 mg/dL (1.7-3.6 mmol/L). These occur once per week without a clear cause or pattern. For many episodes of hypoglycemia he experiences no symptoms, but he is able to detect hypoglycemia at blood glucose values less than 40 mg/dL (2.2 mmol/L). His most recent hemoglobin A_{1c} level is 8.2%. He desires a hemoglobin A_{1c} level less than 7%.

Which of the following is the most appropriate treatment of this patient's diabetes?

(A) Decrease all insulin doses
(B) Increase glargine insulin dose
(C) Initiate empagliflozin
(D) Initiate metformin

Item 70

A 42-year-old woman is evaluated in the office for osteoporosis because she was told her heel ultrasound screening test was abnormal at a health fair. She has no history of fractures. Family history is significant for osteoporosis in her mother, diagnosed at age 68 years; she has no history of fracture. Her only medication is a combination estradiol-levonorgestrel oral contraceptive pill.

On physical examination, vital signs are normal. BMI is 19. The remainder of her physical examination is normal.

Report of the quantitative heel ultrasound shows a Z-score of −0.5.

Which of the following is the most appropriate management?

(A) Lifestyle counseling for osteoporosis prevention
(B) Dual-energy x-ray absorptiometry (DEXA) scan
(C) Evaluation of secondary causes of bone loss
(D) Serial quantitative heel ultrasound testing

Item 71

A 27-year-old woman is seen in a follow-up visit for hyperthyroidism. Three months ago she was diagnosed with Graves disease, and methimazole was initiated. Today the patient reports an overall improvement in hyperthyroid symptoms, but over the past week she has developed a fever, sore throat, and painful swallowing. She reports no cough. Medications are methimazole and propranolol.

On physical examination, temperature is 38.7 °C (101.6 °F), blood pressure is 112/78 mm Hg, pulse rate is 98/min, and respiration rate is 18/min. The patient's posterior oropharynx is erythematous without exudates. Her examination is otherwise normal.

Which of the following is the most appropriate management?

(A) Begin empiric oral penicillin V
(B) Obtain a rapid antigen detection test for Group A streptococcus
(C) Obtain a throat culture
(D) Stop methimazole and obtain complete blood count with differential

Item 72

H

A 66-year-old man recently diagnosed with type 2 diabetes mellitus is evaluated in the emergency department for nausea, vomiting, and fatigue. He was diagnosed with type 2 diabetes 18 months ago. In the past month metformin was discontinued due to severe diarrhea, and glipizide and empagliflozin were initiated. In addition to type 2 diabetes, medical history is significant for coronary artery disease, hypertension, and dyslipidemia. Medications are aspirin, lisinopril, metoprolol, atorvastatin, glipizide, and empagliflozin.

On physical examination, temperature is normal, blood pressure is 90/60 mm Hg, pulse rate is 120/min, and respiration rate is 22/min. Dry mucous membranes are noted. There is diffuse abdominal tenderness to palpation without guarding. Other than tachycardia, the remainder of the examination is normal.

Laboratory studies:

Sodium	133 mEq/L (133 mmol/L)
Bicarbonate	10 mEq/L (10 mmol/L)
Glucose	150 mg/dL (8.3 mmol/L)
Anion gap	17 mEq/L (17 mmol/L)
β-hydroxybutyrate	Elevated

Which of the following is most likely responsible for the patient's findings?

(A) Atorvastatin
(B) Discontinuation of metformin
(C) Empagliflozin
(D) Glipizide
(E) Lisinopril

Item 73

A 32-year-old man is evaluated for decreased libido and fatigue. His symptoms have increased over the last 6 months.

His medical history is otherwise unremarkable, and he takes no medications.

On physical examination, vital signs are normal. BMI is 26. He has gynecomastia. Visual field acuity testing and testicular examination are normal. Smell is intact.

Laboratory studies:

Follicle-stimulating hormone	4 mU/mL (4 U/L)
Luteinizing hormone	5 mU/mL (5 U/L)
Prolactin	100 ng/mL (100 µg/L)
Testosterone	110 ng/dL (3.8 nmol/L)

Which of the following is the most appropriate diagnostic test to perform next?

(A) Karyotype analysis
(B) Pituitary MRI
(C) Screening for anabolic steroid abuse
(D) Serum ferritin measurement
(E) Sex hormone-binding globulin measurement

H Item 74

A 74-year-old woman is evaluated in the emergency department for decreased responsiveness. She has become progressively confused and lethargic. She lives alone and stopped taking her medications at some time unknown. She was brought to the emergency department by a family member.

The patient had a near-total thyroidectomy for multinodular goiter 3 years ago.

On physical examination, temperature is 36.1 °C (97.0 °F), blood pressure is 80/45 mm Hg, pulse rate is 46/min, respiration rate is 10/min, and oxygen saturation is 92% breathing ambient air. BMI is 28. The patient is arousable with painful stimuli. She has a well-healed anterior neck scar. The patient's skin is cool and dry. She has periorbital edema and bipedal edema. Other than bradycardia, the cardiac examination is normal. The relaxation phase of her deep tendon reflexes is delayed.

Laboratory results show a sodium level of 129 mEq/L (129 mmol/L). Intravenous fluids are initiated.

Which of the following is the essential initial step in the management of this patient?

(A) Administer intravenous hydrocortisone
(B) Administer intravenous levothyroxine and liothyronine
(C) Administer norepinephrine
(D) Administer oral levothyroxine

Item 75

A 35-year old woman is seen in follow-up evaluation for her type 2 diabetes mellitus. She was diagnosed 3 years ago. She checks her fasting and 2-hour postprandial blood glucose values several times per week. Her fasting blood glucose levels range from 100 to 110 mg/dL (5.5-6.1 mmol/L) and her 2-hour postprandial values are 120 to 165 mg/dL (6.7-9.1 mmol/L). Her review of symptoms is positive for chronic heavy menses. Medications are metformin and liraglutide.

On physical examination, blood pressure is 123/74 mm Hg and pulse rate is 76/min. BMI is 31.2. The examination is otherwise unremarkable.

Laboratory studies:

Hematocrit	33%
Iron studies	
Ferritin	11 ng/mL (11 µg/L)
Iron	40 µg/dL (7.2 µmol/L)
Iron-binding capacity, total	600 µg/dL (107.4 µmol/L)
Hemoglobin A_{1c}	7.3%

Which of the following is the most appropriate management of the elevated hemoglobin A_{1c} level?

(A) Basal insulin
(B) Empagliflozin
(C) Ferrous sulfate
(D) Hemoglobin electrophoresis

Item 76

A 69-year-old woman is seen in the office following a left thyroid lobectomy and isthmusectomy 1 week ago for management of compressive symptoms related to a large left thyroid nodule. The preoperative thyroid/neck ultrasound showed the nodule without suspicious features and no abnormal cervical lymph nodes. The pathology report describes a 4.5-cm left adenomatous nodule in a background of multinodular hyperplasia. There is a single focus of papillary thyroid carcinoma measuring 0.5 cm in the greatest dimension. No lymphovascular or extrathyroidal invasion is noted. Surgical margins are negative.

The patient is currently feeling well and reports complete resolution of her prior symptoms. Her medical history is otherwise unremarkable, and she takes no medications.

On physical examination, vital signs are normal. There is a well-healed anterior neck scar. Laboratory studies show a serum thyroid-stimulating hormone (TSH) level of 1.8 µU/mL (1.8 mU/L).

Which of the following is the most appropriate treatment?

(A) Levothyroxine to suppress serum TSH
(B) Radioactive iodine (^{131}I) therapy
(C) Resection of the remaining thyroid lobe
(D) No additional treatment

Item 77 H

A 37-year-old man is evaluated in the hospital for polyuria 1 day after transsphenoidal pituitary surgery for a craniopharyngioma. The patient reports increased thirst overnight. Urine output is currently 300 mL/hour for the last 12 hours. He takes no medications.

On physical examination, vital signs are normal. He has dry mucous membranes.

Laboratory studies show a sodium level of 146 mEq/L (146 mmol/L).

Which of the following is the most appropriate diagnostic test to perform next?

(A) Desmopressin challenge
(B) Urine and serum osmolality
(C) Urine electrolytes
(D) Water deprivation test

H

Item 78

A 22-year-old woman is evaluated for tachycardia, fever, agitation, and confusion 3 days following laparoscopic cholecystectomy for acute cholecystitis.

Medical history is significant for type 1 diabetes mellitus well controlled on basal-bolus insulin and Graves disease previously treated with methimazole. Methimazole was discontinued 6 months ago when she was considered to be in remission. Medications are insulin glargine and insulin aspart.

On physical examination, temperature is 39.0 °C (102.2 °F), blood pressure is 95/50 mm Hg, pulse rate is 132/min and irregular, and respiration rate is 24/min. The patient is confused and appears flushed and diaphoretic. Lid lag is noted. The thyroid gland is diffusely enlarged with an audible bruit. Her deep tendon reflexes are brisk. There is a fine tremor of her hands. Her examination is otherwise normal.

Which of the following is the most likely diagnosis?

(A) Adrenal crisis
(B) Malignant hyperthermia
(C) Myxedema coma
(D) Thyroid storm

Item 79

A 54-year-old man is evaluated at a follow-up visit after being diagnosed with type 2 diabetes mellitus 3 months ago. His initial hemoglobin A_{1c} level was 8.5%. He opted for lifestyle modifications initially. He has lost 4.5 kg (10 lb) in the interim after making significant changes to his diet and increasing his activity level. His average blood glucose level currently is 180 mg/dL (10 mmol/L). Medical history is otherwise unremarkable.

On physical examination, blood pressure is 130/74 mm Hg and pulse is 70/min. BMI is 27. The examination is otherwise unremarkable.

His repeat hemoglobin A_{1c} level today is 7.9%, but he would like it lower. Results of other laboratory studies are within normal ranges.

Which of the following is the most appropriate management?

(A) Continue current management
(B) Initiate empagliflozin
(C) Initiate liraglutide
(D) Initiate metformin

H

Item 80

A 22-year-old man was admitted to the intensive care unit 24 hours ago with nausea, vomiting, and lethargy of 2 days' duration. Medical history is unremarkable, and he takes no medications. His admission laboratory values were consistent with diabetic ketoacidosis, and he was initiated on intravenous fluids and intravenous insulin therapy. After 24 hours, he is currently receiving 0.45% normal saline at 250 mL/h with 20 mEq (20 mmol) of potassium chloride per liter and an insulin drip at 5 U/h. His nausea continues, but his vomiting has ceased. He is unable to eat.

On physical examination, vital signs are normal. He is alert and oriented, and the remainder of his physical examination is unremarkable.

Laboratory studies:

Electrolytes	
Sodium	141 mEq/L (141 mmol/L)
Potassium	4.0 mEq/L (4.0 mmol/L)
Chloride	104 mEq/L (104 mmol/L)
Bicarbonate	20 mEq/L (20 mmol/L)
Glucose	180 mg/dL (10 mmol/L)
pH	7.32

Which of the following is the most appropriate management?

(A) Continue current insulin drip rate
(B) Decrease insulin drip rate and add intravenous dextrose
(C) Discontinue intravenous potassium
(D) Transition insulin drip to subcutaneous insulin regimen

Item 81

A 68-year-old man is evaluated in the office for increasing shortness of breath, palpitations, difficulty sleeping, fatigue, generalized weakness, and 4.5-kg (10-lb) weight loss over the past month. His medical history is significant for heart failure and atrial fibrillation. For the past 2 years his medications have been metoprolol, lisinopril, amiodarone, and dabigatran.

On physical examination, the patient is afebrile, blood pressure is 140/80 mm Hg, pulse is 102/min, and respiration rate is 24/min. Deep tendon reflexes are brisk and symmetric. A fine tremor of his outstretched hands, bilateral lid lag, and an irregularly irregular heart rhythm are noted. Examination of the thyroid gland and remainder of the physical examination are normal.

Laboratory studies show a serum thyroid-stimulating hormone (TSH) level less than 0.01 µU/mL (0.01 mU/L), a free thyroxine (T_4) level of 3.1 ng/dL (40 pmol/L), and a serum total triiodothyronine (T_3) level of 190 ng/dL (2.9 nmol/L). TSH receptor antibodies are undetectable. Other laboratory studies are normal.

On thyroid ultrasound, the thyroid lobes and isthmus are normal in size. No thyroid nodules are seen. The background thyroid parenchyma demonstrates no demonstrable vascularity on color flow Doppler. Chest radiograph is normal.

In addition to increasing the metoprolol dose, which of the following is the most appropriate initial management?

(A) Discontinue amiodarone
(B) Begin methimazole
(C) Begin prednisone
(D) Thyroid scintigraphy with radioactive iodine uptake

Item 82

A 36-year-old woman is evaluated for new-onset hirsutism noted on the face, chest, and abdomen. Hirsute hair growth has rapidly progressed over the last 6 months. Additionally, she notes frontal hair loss. Menstrual cycles have become irregular over the same time course. Medical history is otherwise unremarkable, and she takes no medications.

On physical examination, her blood pressure is 142/88 mm Hg; the remainder of the vital signs is normal. BMI is 26. On skin examination, acne is noted. Dark terminal hair appears on the face, chest, and abdomen. The patient has diffuse hair thinning on top of the head. The remainder of the physical examination is noncontributory.

Laboratory studies:

Estradiol	68 pg/mL (249.6 pmol/L)
Follicle-stimulating hormone	12 mU/mL (12 U/L)
Human chorionic gonadotropin, serum	Negative
Prolactin	Normal
Testosterone, total	220 ng/dL (7.6 nmol/L)
Thyroid-stimulating hormone	Normal

Which of the following is the most appropriate management?

(A) Adrenal vein sampling for cortisol and androgens

(B) 24-Hour urine free cortisol

(C) Oral contraceptive therapy

(D) Pelvic ultrasound

Item 83

A 62-year-old woman is evaluated for management of her type 2 diabetes mellitus. She was diagnosed 2 years ago, and treatment was advanced to include lifestyle modifications, metformin, liraglutide, and empagliflozin, but it was not successful in reaching her hemoglobin A_{1c} goal. Her current regimen includes metformin and basal and prandial insulins. Her fasting and preprandial blood glucose values range from 150 to 200 mg/dL (8.3-11.1 mmol/L) with intermittent episodes of hypoglycemia. She has had a weight gain of 2.3 kg (5 lb) over the last 3 months. Medical history is also significant for hypertension, hyperlipidemia, and osteoarthritis. Medications are detemir insulin, lispro insulin, metformin, lisinopril, and atorvastatin.

On physical examination, blood pressure is 142/90 mm Hg and pulse rate is 63/min. BMI is 36. The remainder of the physical examination is unremarkable. Laboratory studies show a hemoglobin A_{1c} level of 8.8%.

Which of the following is the most appropriate management of this patient's diabetes?

(A) Add sitagliptin

(B) Add pioglitazone

(C) Increase insulin

(D) Metabolic surgery referral

Item 84

A 57-year-old woman is evaluated for progressive right upper leg pain for the past 2 years. The pain is worse with weight bearing. She is postmenopausal and otherwise in good health. She has no family history of fractures. She takes no medications.

On physical examination, vital signs are normal. BMI is 36. She has difficulty bearing weight and limps when walking. She has discomfort on palpation over the anterior tibia. The remainder of the physical examination is normal.

Laboratory studies:

Alkaline phosphatase	150 U/L
Calcium	8.2 mg/dL (2.0 mmol/L)
Creatinine	0.8 mg/dL (70.7 µmol/L)
Phosphorus	2.4 mg/dL (0.8 mmol/L)
Parathyroid hormone	176 pg/mL (176 ng/L)
25-Hydroxyvitamin D	<6 ng/mL (15.0 nmol/L)

Which of the following is the most likely diagnosis?

(A) Osteitis fibrosa cystica

(B) Osteogenesis imperfecta

(C) Osteomalacia

(D) Postmenopausal osteoporosis

Answers and Critiques

Item 1 Answer: D

Educational Objective: Diagnose radiation-induced papillary thyroid cancer.

The most likely diagnosis is papillary thyroid cancer. Radiation exposure of the thyroid during childhood is the strongest environmental risk factor for thyroid cancer. Patients under the age of 15, especially those younger than 5 years, have the highest risk of subsequently developing papillary thyroid cancer following a significant radiation exposure (>10 rads).

A benign follicular nodule is not the most likely diagnosis due to the history of radiation exposure in childhood, ultrasound findings (hypoechoic solid nodule with irregular margins), and cervical lymphadenopathy. Fine needle aspiration biopsy (FNAB) of both the thyroid nodule and abnormal lymph nodes should be pursued to confirm the suspected diagnosis and inform surgical management. In addition to thyroidectomy, patients with thyroid cancer that has metastasized to cervical lymph nodes require dissection of the affected compartment (central neck dissection for central lymph node metastases, and central and lateral neck dissection for lateral metastases). Abnormal findings on sonography vary considerably in their specificity for predicting malignant lymph node involvement (range 43% to 100%). For this reason, FNAB of the thyroid nodule and any abnormal lymph nodes are usually performed simultaneously. The false-negative rate for lymph node FNAB is 6% to 8% overall, but increases to 20% for samples with inadequate cellularity. Inadequate cellularity is common for metastatic lymph nodes that have undergone cystic degeneration, which is common in papillary thyroid cancer. Measuring thyroglobulin in the aspirate can significantly improve diagnostic sensitivity of lymph node FNAB.

While radiation exposure is a risk factor for follicular thyroid cancer, this is a less likely diagnosis than papillary thyroid cancer. Follicular thyroid cancer is less common than papillary thyroid cancer, it tends to occur in older persons, and it rarely metastasizes to lymph nodes.

Medullary thyroid cancer is an unlikely diagnosis because it is the least common of the thyroid malignancies, representing about 1% to 2% of all thyroid cancers. Approximately 25% of medullary thyroid cancers are hereditary; all patients with medullary thyroid cancer should be screened with *RET* proto-oncogene sequencing. Medullary thyroid cancer may be associated with several syndromes, including multiple endocrine neoplasia type 2A (MEN2A) (which may include pheochromocytoma and hyperparathyroidism), MEN2B (marfanoid habitus and mucosal ganglioneuromas), or familial medullary thyroid cancer (medullary thyroid cancer alone).

KEY POINT

- Radiation exposure of the thyroid during childhood is the strongest environmental risk factor for thyroid cancer, most commonly papillary cancer.

Bibliography

Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, et al. 2015 American Thyroid Association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid. 2016;26:1-133. [PMID: 26462967] doi:10.1089/thy.2015.0020

Item 2 Answer: D

Educational Objective: Treat type 2 diabetes mellitus in an obese patient.

According to the American Diabetes Association (ADA), this patient's goal hemoglobin A_{1c} level is less than 7% given that she is healthy and early in the disease course. The American College of Physicians (ACP) recommends a target hemoglobin A_{1c} level between 7% and 8% for most patients with type 2 diabetes. The ACP notes that more stringent targets may be appropriate for patients who have a long life expectancy (>15 years) and are interested in more intensive glycemic control despite the risk for harms, including but not limited to hypoglycemia, patient burden, and pharmacologic costs. Her hemoglobin A_{1c} level remains above goal despite 3 months of lifestyle modifications and metformin. The ADA recommends advancing to dual therapy if the hemoglobin A_{1c} remains at 9% or above after 3 months of metformin therapy. Sequential therapeutic agents added to metformin should be selected based on the degree of hyperglycemia, comorbidities, weight, side effect profiles, cost, and patient preferences. Liraglutide, a glucagon-like peptide-1 (GLP-1) receptor agonist, is an appropriate adjunctive agent with metformin in this patient as it will improve glycemic control and contribute to desired weight loss. There are potential concerns for development of pancreatitis and medullary thyroid carcinoma with GLP-1 receptor agonists. The patient does not have a personal or family history of these abnormalities to preclude use of liraglutide.

Empagliflozin, a sodium-glucose transporter-2 (SGLT2) inhibitor, may be added to metformin when the hemoglobin A_{1c} remains above goal. SGLT2 inhibitor use improves glycemic control and induces weight loss, but it also increases the risk of genital mycotic infections. Empagliflozin should not be used in this patient because it may exacerbate her frequent vulvovaginal candidiasis infections.

Glipizide, a sulfonylurea, may also be added to metformin when the hemoglobin A_{1c} remains above goal. Glipizide will improve glycemic control, but it is associated with

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weight gain that is not in concordance with the patient's desire for continued weight loss.

Basal insulin coverage can be provided with one to two daily injections of insulin detemir, glargine, or neutral protamine Hagedorn (NPH) insulin. Basal insulin may be added to metformin when the hemoglobin A_{1c} level remains above goal. Basal insulin will improve glycemic control, but it is associated with weight gain that is not in concordance with the patient's desire for continued weight loss.

KEY POINT

- Liraglutide is an add-on therapy to metformin to achieve improvement in hemoglobin A_{1c} level and weight loss.

Bibliography

American Diabetes Association. 8. Pharmacologic approaches to glycemic treatment: Standards of Medical Care in Diabetes-2018. Diabetes Care. 2018;41(Suppl 1):S73-S85. doi: 10.2337/dc18-S008. [PMID: 29222379]

Item 3 Answer: B

Educational Objective: Diagnose the cause of primary adrenal insufficiency.

The most appropriate next test is measurement of 21-hydroxylase antibodies. This patient has primary adrenal insufficiency as confirmed by the combination of low serum cortisol and elevated serum adrenocorticotropic hormone (ACTH). The most common cause of primary adrenal insufficiency in the United States is autoimmune adrenalitis, and positive 21-hydroxylase antibodies are found in approximately 90% of those cases.

Patients with autoimmune adrenalitis are at risk for the development of other autoimmune disorders including primary hypothyroidism, primary ovarian insufficiency, type 1 diabetes mellitus, celiac disease, and autoimmune gastritis. If 21-hydroxylase antibody measurement is negative, abdominal CT imaging should be performed. In autoimmune disease, the adrenal glands often appear atrophic, although normal-sized adrenal glands do not rule out this diagnosis. Other causes of primary adrenal insufficiency typically cause enlargement of the adrenal glands. These include infiltrative disorders such as lymphoma, sarcoidosis, histoplasmosis, or tuberculosis (the latter can be associated with normal-sized adrenal glands). Bilateral adrenal enlargement is also seen in primary adrenal insufficiency caused by bilateral adrenal hemorrhage. Metastatic disease to the adrenal glands rarely causes adrenal insufficiency.

Cosyntropin stimulation testing is used to diagnose the presence of adrenal insufficiency, but it will not help determine the underlying cause. In this patient, the diagnosis of primary adrenal insufficiency is confirmed by the presence of a serum cortisol level of less than 3 µg/dL (82.8 nmol/L) in combination with an elevated serum ACTH level. Hence, cosyntropin stimulation testing will not add further to the diagnosis or management.

MRI of the pituitary gland is not indicated in this patient with primary adrenal insufficiency, but it is the imaging modality of choice for investigation of secondary adrenal insufficiency. The latter is characterized by low serum cortisol in the setting of low or inappropriately normal serum ACTH levels.

Measurement of serum aldosterone would not help determine the underlying cause of this patient's primary adrenal insufficiency. Low or inappropriately normal serum aldosterone levels (associated with elevated plasma renin activity) are present in most patients with primary adrenal insufficiency due to destruction of the layers of the adrenal cortex by the underlying disease process. Aldosterone deficiency results in hyperkalemia, as noted in this patient, and hyponatremia may also be present.

KEY POINT

- The most common cause of primary adrenal insufficiency in the United States is autoimmune adrenalitis, and positive 21-hydroxylase antibodies are found in approximately 90% of those cases.

Bibliography

Bancos I, Hahner S, Tomlinson J, Arlt W. Diagnosis and management of adrenal insufficiency. Lancet Diabetes Endocrinol. 2015;3:216-26. [PMID: 25098712] doi:10.1016/S2213-8587(14)70142-1

Item 4 Answer: A

Educational Objective: Diagnose the cause of hyperprolactinemia.

The most appropriate next step in managing this patient is to obtain a pituitary MRI. The most common cause of hyperprolactinemia is physiologic; prolactin is released during pregnancy and postpartum to cause lactation. Another common cause of hyperprolactinemia is primary hypothyroidism. Hypothyroidism can cause diffuse hypertrophy of the pituitary gland that may resemble enlargement due to a pituitary adenoma on imaging. Nonfunctioning pituitary adenomas can also cause hyperprolactinemia by compressing the pituitary stalk and decreasing dopamine inhibition of prolactin secretion. Medications are a common cause of hyperprolactinemia. Antipsychotic agents cause hyperprolactinemia due to their antidopaminergic effect that interrupts the inhibition of prolactin by dopamine. Agents such as risperidone may raise the prolactin level above 200 ng/mL (200 µg/L). Evaluation for pituitary hypersecretion when a patient is taking a medication known to raise the prolactin level is difficult. When the prolactin level is only mildly elevated (<50 ng/mL [50 µg/L]), it may be reasonable to assume that hyperprolactinemia is a medication side effect. When significantly elevated (>100 ng/mL [100 µg/L]), either the medication needs to be withheld to further assess or a pituitary MRI obtained to evaluate for prolactinoma. Caution is warranted when discontinuation of an antipsychotic agent is being considered, and consultation with a psychiatrist is recommended prior to discontinuation. If the medication cannot be discontinued, a pituitary MRI is required to exclude the diagnosis of pituitary tumor.

Prolactinomas are treated with dopamine agonists. The two FDA approved dopamine agonists are bromocriptine and cabergoline. Dopamine agonists typically decrease the size and hormone production of prolactinomas rapidly. Decreasing serum prolactin usually correlates with decreasing size of the tumor. Dopamine agonist therapy is not warranted without first diagnosing a prolactinoma with an MRI. Furthermore, addition of dopamine agonist therapy could worsen this patient's psychiatric disease.

Starting an oral contraceptive pill is inappropriate at this time since this patient needs a pituitary MRI to rule out a pituitary tumor prior to making a treatment decision. Once a pituitary tumor is ruled out, she can be started on an oral contraceptive pill to treat her estrogen deficiency caused by the hyperprolactinemia.

While stopping risperidone, or any psychiatric medication, may lead to decreased prolactin, this requires consultation and coordination of care with the patient's psychiatrist.

KEY POINT

- Antipsychotic agents cause hyperprolactinemia due to their antidopaminergic effect, which interrupts the inhibition of prolactin by dopamine; risperidone may raise the prolactin level above 200 ng/mL (200 µg/L).

Bibliography

Peuskens J, Pani L, Detraux J, De Hert M. The effects of novel and newly approved antipsychotics on serum prolactin levels: a comprehensive review. CNS Drugs. 2014;28:421-53. doi: 10.1007/s40263-014-0157-3. [PMID: 24677189]

Item 5 Answer: C

Educational Objective: Treat primary adrenal insufficiency.

This most appropriate treatment for this patient is hydrocortisone twice daily and fludrocortisone once daily. She has primary adrenal insufficiency, which affects all layers of the adrenal cortex, and therefore she requires both glucocorticoid and mineralocorticoid (aldosterone) therapy. Primary adrenal insufficiency is confirmed in this patient by the combination of low serum cortisol level and elevated serum adrenocorticotropic hormone (ACTH) level. Manifestations of aldosterone deficiency are hyponatremia and hyperkalemia. Some patients with primary adrenal insufficiency have normal serum electrolytes and therefore require measurement of plasma renin activity (high) and serum aldosterone (low or inappropriately normal) to confirm mineralocorticoid deficiency. The preferred glucocorticoid for treatment of adrenal insufficiency is hydrocortisone which, because of its shorter duration of action, can be prescribed two or three times daily to better mimic the circadian rhythm of endogenous cortisol secretion. The total daily recommended dose of hydrocortisone ranges from 15 to 25 mg. A higher dose of hydrocortisone (~15 mg) is given in the morning with the remaining dose (~5 mg) given in the afternoon (or in a thrice daily regimen, the second dose of hydrocortisone is given at noon with the third, smaller dose taken later in the afternoon). For patients who have difficulty adhering to a twice-daily medication regimen, prednisone once daily in the morning may be substituted.

Dexamethasone has a long duration of action with the potential to cause comorbidities from excess glucocorticoid exposure and therefore should not be used long-term to treat adrenal insufficiency.

There are no adequate trial data to direct optimal dose and timing of glucocorticoid replacement. Measurement of serum cortisol and/or ACTH is not helpful. Glucocorticoid dosing is guided by patient symptoms. Administration of doses of glucocorticoid in excess of physiologic replacement can be associated with decreased bone mineral density and features of Cushing syndrome, with increased risk of metabolic syndrome, type 2 diabetes mellitus, hypertension, hyperlipidemia, obesity, and cardiovascular disease. Adequate mineralocorticoid replacement is indicated by normal blood pressure without orthostasis, absence of edema, and normal serum electrolytes.

Only glucocorticoid therapy is required in the treatment of secondary adrenal insufficiency. Fludrocortisone replacement is not required as aldosterone secretion is not under the control of ACTH. Hence, patients with secondary adrenal insufficiency do not develop hyperkalemia. Hyponatremia may be present in secondary adrenal insufficiency due to inappropriate antidiuretic hormone secretion and action, with resultant inability to excrete free water.

KEY POINT

- Patients with primary adrenal failure require both glucocorticoid and mineralocorticoid replacement therapy.

Bibliography

Bancos I, Hahner S, Tomlinson J, Arlt W. Diagnosis and management of adrenal insufficiency. Lancet Diabetes Endocrinol. 2015;3:216-26. [PMID: 25098712] doi:10.1016/S2213-8587(14)70142-1

Item 6 Answer: A

Educational Objective: Evaluate Paget disease of bone.

The laboratory results and findings on radiographs are most consistent with Paget disease of bone. Measurement of serum total alkaline phosphatase is the next step after radiographic diagnosis and delineation of which bones are affected. It reflects the metabolic activity of Paget disease of bone at diagnosis and is used in follow-up evaluation whether treatment is given or not. Occasionally, total alkaline phosphatase may be normal in newly diagnosed patients with radiographic and radionuclide bone scan evidence of Paget disease. This quiescent or "burnt-out" stage of the disease does not require treatment.

Many patients with Paget disease are older and may have risk factors for osteoporosis. These two conditions, however, are unrelated, have different treatment endpoints, and different bisphosphonate dosing. If bone mineral density were to be ordered, it would be for reasons independent of the evaluation and treatment of Paget disease.

CT imaging of bones provides greater resolution and is superior to conventional radiographs in detecting and characterizing some metabolic bone disorders. With the exception of clarifying the extent of basilar skull involvement and risk for cranial nerve impingement, clinically relevant Paget disease is readily detected and diagnosed by conventional radiographs and radionuclide bone scans.

Bisphosphonates, particularly intravenous zoledronic acid, are highly effective, often requiring a single dose to normalize alkaline phosphatase for several years in patients with Paget disease. Given the risk for spinal cord compression or compression fracture, involvement of T7 with Paget disease would be an indication for treatment unless the disease were metabolically inactive. Therefore, zoledronic acid would not be given prior to assessment of serum total alkaline phosphatase.

KEY POINT

- Serum alkaline phosphatase, a marker of increased bone turnover, should be measured after radiographic diagnosis of Paget disease of bone.

Bibliography

Singer FR, Bone HG 3rd, Hosking DJ, Lyles KW, Murad MH, Reid IR, et al; Endocrine Society. Paget's disease of bone: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2014;99:4408-22. [PMID: 25406796] doi:10.1210/jc.2014-2910

Item 7 Answer: C

Educational Objective: Diagnose subacute thyroiditis.

The most likely diagnosis is subacute thyroiditis. Subacute thyroiditis is an uncommon cause of thyrotoxicosis that presents following a viral upper respiratory tract infection and is distinguished by a tender or painful thyroid. This is a form of destructive thyroiditis resulting from the leakage of stored thyroid hormone from damaged thyroid follicles. The diagnosis can be confirmed by determining radioactive iodine uptake, which would be low (<10%). Management is aimed at controlling symptoms. This includes treatment with β blockers and pain control with NSAIDs or, less commonly, glucocorticoids. In most cases, thyrotoxicosis typically lasts 2 to 6 weeks. It is followed by a hypothyroid phase after stored thyroid hormone is depleted, typically lasting 6 to 12 weeks. The patient may become clinically hypothyroid and require temporary levothyroxine therapy. Most patients with thyroiditis eventually recover to a euthyroid state.

Graves disease is the most common cause of thyrotoxicosis in the United States and most frequently affects young women. This patient does not have pathognomic features of Graves disease (thyroid bruit, eye disease, or dermopathy), making this an unlikely diagnosis.

Molar pregnancy is a rare cause of hyperthyroidism resulting from the binding of human chorionic gonadotropin (HCG) to the thyroid-stimulating hormone (TSH) receptor in the setting of very high HCG levels. The negative pregnancy test excludes this diagnosis.

Nodular thyroid disease (toxic adenoma and multinodular goiter) is the next most common cause of thyrotoxicosis after Graves disease and is more commonly seen in older adults. This patient lacks palpable thyroid nodules on examination, which is usually seen with hyperthyroidism from nodular thyroid disease. In addition, neither Graves disease nor nodular thyroid disease cause thyroid pain.

KEY POINT

- Subacute thyroiditis is an uncommon cause of thyrotoxicosis that presents following a viral upper respiratory tract infection and is distinguished by a tender or painful thyroid, suppressed thyroid-stimulating hormone, and elevated serum free thyroxine.

Bibliography

De Leo S, Lee SY, Braverman LE. Hyperthyroidism. Lancet. 2016;388:906-18. [PMID: 27038492] doi:10.1016/S0140-6736(16)00278-6

Item 8 Answer: B

Educational Objective: Reduce the risk of diabetic neuropathy in a patient with type 1 diabetes mellitus.

According to high-quality evidence, enhanced glucose control significantly prevents the development of clinical neuropathy and reduces nerve conduction and vibration threshold abnormalities in type 1 diabetes mellitus. Glycemic control can delay progression of neuropathy in type 2 diabetes. Other than glucose control, no other preventive strategies are available for diabetic neuropathy. Hemoglobin A_{1c} goals in patients with diabetes should be individually tailored taking into account the demonstrated benefits with regard to prevention and delay in microvascular complications with the risk of hypoglycemia. A reasonable goal of therapy might be a hemoglobin A_{1c} value less than or equal to 7% for most patients, with higher targets for older adult patients and those with comorbidities or a limited life expectancy and more stringent control for those patients with type 1 diabetes and during pregnancy.

The American Diabetes Association advocates for a target systolic blood pressure between 125 and 130 mm Hg in select patients (young, long life expectancy, increased risk of stroke), if this can be accomplished safely. While this patient will benefit from improved blood pressure control by reducing the risk of cardiovascular disease, it will have no impact on her risk for the development of diabetic neuropathy.

While lifestyle intervention to improve the lipid profile should be undertaken in all patients with diabetes, for patients without cardiovascular disease and under age 40 years, statin therapy should be considered only in those with multiple cardiovascular disease risk factors; the American College of Cardiology/American Heart Association risk calculator can determine the 10-year atherosclerotic cardiovascular disease risk to guide therapeutic management. Improved lipid control, while indicated and beneficial for the prevention of cardiovascular disease, does not assist in the prevention of diabetic neuropathy.

Although pregabalin is indicated to treat painful diabetic neuropathy, it does not prevent diabetic neuropathy.

Although weight loss should be discussed as part of a therapeutic lifestyle plan, there is no data to suggest weight loss prevents the development of diabetic neuropathy.

KEY POINT

- Enhanced glucose control significantly prevents the development of clinical neuropathy and reduces nerve conduction and vibration threshold abnormalities in type 1 diabetes mellitus.

Bibliography

Callaghan BC, Little AA, Feldman EL, Hughes RA. Enhanced glucose control for preventing and treating diabetic neuropathy. Cochrane Database Syst Rev. 2012:CD007543. [PMID: 22696371] doi:10.1002/14651858.CD007543.pub2

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Item 9 Answer: D

Educational Objective: Identify vitamin D deficiency as a cause of hypocalcemia after antiresorptive therapy for osteoporosis.

The most likely diagnosis is vitamin D deficiency. Special populations will have lower levels of vitamin D owing to medical conditions or medication side effects. Obesity has been correlated with lower vitamin D levels possibly related to fat sequestration. Phenobarbital and phenytoin may increase the metabolism of vitamin D to inactive forms. Glucocorticoids can decrease vitamin D metabolism to active forms. Agents that decrease absorption such as orlistat can decrease vitamin D absorption. Malabsorption disorders, including celiac disease and bariatric surgery, can also result in vitamin D deficiency. This patient has multiple risk factors for vitamin D deficiency including age, possible malnutrition, glucocorticoid use, and being home bound. In the face of ongoing vitamin D deficiency, normocalcemia is maintained through increased bone resorption through increased osteoclastic activity. Antiresorptive drugs, especially the first dose of intravenous bisphosphonates and denosumab, rapidly suppress osteoclastic bone resorption and can precipitate hypocalcemia in these patients. Vitamin D sufficiency should be assessed prior to initiating antiresorptive drugs, especially those administered parenterally.

High baseline bone turnover and abrupt alteration in calcium flux between blood and bone are also features of hungry bone syndrome. However, this syndrome specifically occurs after parathyroidectomy for primary hyperparathyroidism. It is caused by rapid influx of calcium from the blood into the skeleton. In the absence of parathyroidectomy, hungry bone syndrome cannot explain this patient's findings.

Acute hyperphosphatemia from tumor lysis syndrome or phosphorus-containing bowel preparations may cause acute hypocalcemia. Chronic hyperphosphatemia associated with chronic kidney disease can also result in hypocalcemia. However, these conditions are not present and, in the case of chronic kidney disease, cannot account for the patient's rapid clinical deterioration.

In contrast to surgery, hypoparathyroidism due to autoimmunity, radiation, or infiltrative processes develops slowly and serum calcium declines gradually over months to years, which is not consistent with the precipitous drop seen in this patient over 2 days.

KEY POINT

- Potent antiresorptive drugs can cause severe hypocalcemia by impairing efflux of calcium from the skeleton in patients with vitamin D deficiency; it is important to assess vitamin D levels and correct deficiency before beginning treatment with an antiresorptive drug.

Bibliography

Kaur U, Chakrabarti SS, Gambhir IS. Zoledronic acid-induced hypocalcaemia and hypophosphatemia in osteoporosis: a cause of concern. Curr Drug Saf. 2016;11:267-9. [PMID: 27113952]

Item 10 Answer: A

Educational Objective: Diagnose an androgen-producing adrenal tumor.

The most appropriate test to perform next is a CT scan of the abdomen. This postmenopausal woman has new-onset hyperandrogenism associated with significant elevation of serum dehydroepiandrosterone sulfate (DHEAS). The clinical picture of rapid-onset hirsutism and signs of virilization indicate an androgen-secreting tumor. Signs of virilization are deepening of the voice, clitoromegaly, hirsutism, and temporal hair loss. Under normal conditions, androgen production in women occurs in both the adrenal glands and ovaries, as well as by peripheral conversion. The major source of DHEAS is the adrenal gland, and an abdominal CT is recommended when serum DHEAS value is above 700 µg/dL (18.9 µmol/L).

DHEAS-secreting tumors of the adrenal gland are readily visible on CT imaging and adrenal vein sampling to localize the tumor is rarely required.

Pelvic MRI may be more sensitive at detecting small ovarian tumors and is often considered as second-line imaging when pelvic ultrasound is negative. If both pelvic ultrasound and MRI imaging are negative in the setting of suspicion for a testosterone-secreting ovarian tumor, ovarian vein sampling may be required to reveal the location of the tumor. Ovarian vein sampling is reserved for premenopausal women. Postmenopausal women can forego this invasive procedure and proceed directly to bilateral oophorectomy. Significant testosterone secretion can also be due to a non-tumorous condition called ovarian hyperthecosis. Hyperandrogenic symptoms are typically (but not always) of slower onset compared with that seen with androgen-secreting tumors.

A pelvic ultrasound is recommended as the first imaging study if testosterone is above 150 ng/dL (5.2 nmol/L). This

patient's testosterone level was only mildly elevated, but the DHEAS was quite elevated making a testosterone-producing ovarian tumor less likely than an adrenal tumor.

KEY POINT

- Signs of androgen excess such as progressive hirsutism and virilization over a short period of time in female patients suggest the diagnosis of an androgen-producing adrenal or ovarian tumor.

Bibliography

Markopoulos MC, Kassi E, Alexandraki KI, Mastorakos G, Kaltsas G. Hyperandrogenism after menopause. Eur J Endocrinol. 2015;172:R79-91. [PMID: 25225480] doi:10.1530/EJE-14-0468

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Item 11 Answer: C

Educational Objective: **Diagnose nonthyroidal illness syndrome.**

The most likely diagnosis is nonthyroidal illness syndrome (euthyroid sick syndrome), which is most often seen in critically ill hospitalized patients and is characterized by a reduced serum triiodothyronine (T_3) level, low or low-normal serum thyroxine (T_4) level, and normal or low (but detectable) serum thyroid-stimulating hormone (TSH) level. These findings result from changes in the peripheral uptake of thyroid hormones, reduced levels of thyroid hormone-binding proteins, and alterations in the expression and activity of deiodinases. Very low serum T_4 levels are associated with poor overall outcome. Treatment with levothyroxine or liothyronine is not indicated due to lack of evidence of benefit.

Central hypothyroidism is not the most likely diagnosis. The patient described here has no signs or symptoms suggestive of hypothyroidism. Characteristic biochemical findings in central hypothyroidism include low or inappropriately normal serum TSH in the setting of low total and free T_4 levels and reduced or low-normal serum T_3. In contrast to nonthyroidal illness, in which the T_3 to T_4 ratio is low, a high serum T_3 to T_4 ratio is seen in central hypothyroidism because conversion of T_4 to T_3 in peripheral tissues is maintained.

Heparin-induced thyroid function test abnormality is also incorrect. A single intravenous heparin injection may increase serum free T_4 up to 5 times the baseline value within minutes. This spurious laboratory finding is related to heparin-induced stimulation of lipoprotein lipase and generation of free fatty acids, which displace T_4 from binding proteins. Heparin has no effect on serum TSH, total T_4, or total T_3 values.

Subclinical hyperthyroidism is also not the most likely diagnosis. This patient has atrial fibrillation, but no other clinical findings suggestive of thyroid hormone excess. Although the low serum TSH level is consistent with this diagnosis, the total and free T_4 levels are near the lower limit of the normal range and total T_3 is reduced.

KEY POINT

- Nonthyroidal illness syndrome (euthyroid sick syndrome) is characterized by reduced serum T_3, low or low-normal serum T_4, and normal or low (but detectable) serum TSH levels.

Bibliography

Fliers E, Bianco AC, Langouche L, Boelen A. Thyroid function in critically ill patients. Lancet Diabetes Endocrinol. 2015;3:816-25. [PMID: 26071885] doi:10.1016/S2213-8587(15)00225-9

Item 12 Answer: C

H

Educational Objective: **Manage Cushing syndrome with glucocorticoid therapy following adrenalectomy.**

The most appropriate management of this patient following adrenalectomy for treatment of Cushing syndrome is hydrocortisone therapy. Patients who have undergone adrenalectomy for Cushing syndrome are at risk of secondary adrenal insufficiency due to hypercortisolism-induced suppression of the hypothalamic (corticotropin-releasing hormone [CRH]) and pituitary (adrenocorticotropic [ACTH] hormone) axis. Subsequent recovery of the hypothalamic-pituitary axis following removal of the source of excess cortisol secretion can take time, and hence endogenous cortisol production is impaired. In addition, cortisol-producing cells from the contralateral adrenal gland may have undergone atrophy due to lack of ACTH stimulation. Patients often require higher than physiologic doses of glucocorticoid therapy to prevent "glucocorticoid withdrawal syndrome," an ill-defined complex of symptoms of fatigue, loss of appetite, nausea, and/or myalgia. There is no agreed upon glucocorticoid regimen following adrenalectomy and treatment of Cushing syndrome. The process of tapering and eventual discontinuation of glucocorticoid therapy is guided by patient symptoms and can be a lengthy process, taking up to 1 year or longer for the remaining adrenal gland to produce adequate cortisol.

ACTH-dependent causes of Cushing syndrome also lead to suppression of endogenous CRH and ACTH production, and hence patients with these disorders also require glucocorticoid therapy following successful treatment of Cushing syndrome.

Epinephrine is also not under ACTH control, and therefore epinephrine replacement is not required after adrenalectomy. In addition, epinephrine replacement is not required following bilateral adrenalectomy, as lack of epinephrine is not known to be associated with clinical disease.

Likewise, fludrocortisone therapy is not required following adrenalectomy as mineralocorticoid secretion is not under ACTH control. Therefore, aldosterone secretion from the contralateral adrenal gland is not impacted by Cushing syndrome. Fludrocortisone therapy is required following bilateral adrenalectomy.

Phenoxybenzamine is used as a preoperative α-receptor blockade for 10 to 14 days before surgery for pheochromocytomas and paragangliomas to prevent hypertensive crises

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during surgery and is not indicated following adrenalectomy for Cushing syndrome.

KEY POINT

- Following adrenalectomy for Cushing syndrome, patients require daily glucocorticoid replacement therapy to allow recovery from prolonged suppression due to hypercortisolism; recovery of adrenal function may take up to 1 year or longer depending on the severity of Cushing syndrome.

Bibliography

Hochberg Z, Pacak K, Chrousos GP. Endocrine withdrawal syndromes. Endocr Rev. 2003;24:523-38. [PMID: 12920153]

Item 13 Answer: C

Educational Objective: Diagnose male hypogonadism.

The most appropriate management is to repeat testosterone measurement at 8 AM. The clinical diagnosis of hypogonadism is made on the basis of signs and symptoms consistent with androgen deficiency with the finding of low morning testosterone concentrations on at least two occasions. Timing of initial laboratory assessment is important due to the diurnal variation of testosterone. Additionally, assessment of hypogonadism should not be undertaken during acute illness. The next step in management of this patient would be to obtain a morning testosterone concentration; if low, testing should be confirmed with a repeat morning measurement. After the initial diagnosis, determination of primary or secondary hypogonadism is established by measurement of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels. Elevated gonadotropin levels are seen in primary hypogonadism with LH and FSH levels low or inappropriately normal in secondary hypogonadism.

Based on Endocrine Society guidelines, men with hypogonadism should be treated with exogenous testosterone when they have consistent signs and symptoms of hypogonadism and low serum testosterone levels. Patients requiring testosterone replacement therapy should have testosterone levels monitored at 3 and 6 months after initiation and annually thereafter; the goal total testosterone level should be in the mid-normal range. Monitoring of the prostate-specific antigen and hematocrit level should follow Endocrine Society guidelines. Before initiating testosterone therapy in this patient, the diagnosis of hypogonadism needs to be confirmed with two appropriately timed testosterone measurements.

The most sensitive and cost-effective initial diagnostic study in patients with suspected hemochromatosis is measurement of the fasting serum transferrin saturation (calculated as [serum iron/total iron binding capacity] ×100). Serum ferritin level measurement is indicated in patients with elevated transferrin saturation. Evaluation for hemochromatosis is only appropriate after the diagnosis of hypogonadism is established. The first diagnostic step for this patient is the collection of two properly collected serum testosterone levels to establish the diagnosis of hypogonadism.

If subsequent evaluation of the patient confirms the presence of hypogonadotrophic hypogonadism (low testosterone and low LH and FSH levels), MRI of the pituitary to detect a pituitary adenoma or other mass would be appropriate. A pituitary MRI would be premature at this point.

KEY POINT

- In men with specific signs and symptoms of hypogonadism, measuring an 8 AM total testosterone level is indicated; if the testosterone level is low, a second 8 AM confirmatory testosterone level is measured.

Bibliography

Basaria S. Male hypogonadism. Lancet. 2014;383:1250-63. [PMID: 24119423] doi:10.1016/S0140-6736(13)61126-5

Item 14 Answer: C

Educational Objective: Prevent complications of management of chronic hypoparathyroidism.

The most appropriate test to perform now is measurement of 24-hour urine calcium. In chronic hypoparathyroidism, goals of therapy are to eliminate symptoms while avoiding complications of therapy; monitoring of urine calcium excretion is mandatory because hypercalciuria often limits therapy. Without parathyroid hormone (PTH), urinary calcium excretion is higher than normal for any given serum calcium level. Complications of prolonged hypercalciuria include nephrolithiasis and impaired glomerular filtration rate. Serum calcium, magnesium, creatinine, and urine calcium levels should be assessed on a regular basis. The goal calcium levels should be low-normal without hypercalciuria. The magnesium level should ideally be greater than 2 mg/dL (0.83 mmol/L), and creatinine levels should remain in the normal range. If the urine calcium level is greater than 300 mg/24 h (hypercalciuria), calcium and/or vitamin D replacement needs to be decreased. Calcium is usually decreased first if the 25-hydroxyvitamin D level is within the normal sufficiency range (≥30 ng/mL [75 nmol/L]). Thiazide diuretics reduce urine calcium excretion and thus may permit sufficient calcium and vitamin D therapy to achieve goal calcium levels.

Hypoparathyroidism slows bone metabolism and is relatively protective against the development of postmenopausal osteoporosis. Further, osteoporosis medications would rarely be indicated in these patients. Therefore, bone mineral density testing is not indicated.

The dose of calcitriol administered is titrated by the serum calcium and/or phosphorus level rather than the serum 1,25-dihydroxyvitamin D level.

If serum PTH is not detectable 6 months after the onset of surgical hypoparathyroidism, it can be considered chronic. Without PTH, vitamin D activation, specifically the conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D (calcitriol) in the kidney, is severely impaired. Although vitamin D nutritional status as assessed by 25-hydroxyvitamin D

may be relevant for other health conditions, its measurement in not useful in the setting of chronic hypoparathyroidism unless residual PTH production remains.

Ionized calcium, rather than total calcium, is the relevant calcium fraction in the blood. However, in an otherwise healthy person in whom serum albumin concentrations are presumed to be normal, measurement of ionized calcium does not contribute to the management of hypoparathyroidism.

KEY POINT

- In chronic hypoparathyroidism, the goals of therapy are to eliminate symptoms while avoiding complications of therapy; monitoring urine calcium excretion is mandatory because hypercalciuria often limits therapy.

Bibliography

Brandi ML, Bilezikian JP, Shoback D, Bouillon R, Clarke BL, Thakker RV, Khan AA, Potts JT Jr. Management of hypoparathyroidism: summary statement and guidelines. J Clin Endocrinol Metab. 2016;101:2273-83. doi:10.1210/jc.2015-3907. [PMID: 26943719]

Item 15 Answer: A

Educational Objective: Diagnose adrenocorticotropic hormone (ACTH)-independent Cushing syndrome.

The most likely cause of this patient's hypercortisolism is adrenocorticotropic hormone (ACTH)-independent Cushing syndrome caused by an adrenal tumor. The diagnosis of Cushing syndrome is confirmed by the combination of clinical features (central obesity, dorsocervical and supraclavicular fat pads, new onset hypertension, and worsening diabetes control), in the setting of two positive diagnostic tests for Cushing syndrome: elevated 24-hour urine free cortisol level and elevated midnight salivary cortisol level. A 24-hour urine free cortisol that is three times the upper limit of the normal range (as in this patient) is considered to be confirmatory for Cushing syndrome if compatible clinical features are also present. Once Cushing syndrome is confirmed, the next step in the diagnosis is to categorize Cushing syndrome into ACTH-dependent and ACTH-independent types, which in turn governs subsequent localization tests. A low serum ACTH level, as in this patient, indicates ACTH-independent Cushing syndrome. Excluding glucocorticoid administration, the most common cause of ACTH-independent Cushing syndrome is a cortisol-secreting adrenal tumor. ACTH is suppressed in this situation due to elevated cortisol levels causing negative feedback at the level of the hypothalamus and pituitary gland, which inhibits ACTH production.

Cushing syndrome in the presence of a detectable or elevated serum ACTH indicates ACTH-dependent disease. Causes of ACTH-dependent Cushing syndrome include ACTH secretion from a pituitary tumor (most commonly) or from an ectopic source such as a bronchial carcinoid tumor.

Hypercortisolism in the absence of Cushing syndrome can occur with psychiatric illness. The mechanism of hypercortisolism associated with psychiatric illness is activation of the hypothalamic-pituitary axis; in this situation ACTH production is not suppressed. In addition, patients do not manifest clinical features of Cushing syndrome. This patient's suppressed serum ACTH rules out psychiatric illness as the primary cause of her hypercortisolism.

KEY POINT

- Excluding glucocorticoid administration, the most common cause of adrenocorticotropic hormone (ACTH)-independent Cushing syndrome is an adrenal tumor.

Bibliography

Loriaux DL. Diagnosis and differential diagnosis of Cushing's syndrome. N Engl J Med. 2017;376:1451-1459. doi: 10.1056/NEJMra1505550. [PMID: 28402781]

Item 16 Answer: B

Educational Objective: Manage anabolic steroid-induced hypogonadism.

Cessation of anabolic steroid use is the appropriate management plan at this time. This patient presents with symptoms and signs suggestive of anabolic steroid-induced hypogonadism including decreased libido, acne, gynecomastia, small testes, and suppressed gonadotropins with resultant hypogonadism. Extratesticular effects may also be noted, including low HDL cholesterol level, hepatotoxicity, erythrocytosis, and increased risk of obstructive sleep apnea. Mood disorders are common in anabolic steroid users. He will remain hypogonadal for an undetermined amount of time after stopping exogenous androgens before recovery of his hypothalamic-pituitary-gonadal axis.

Anastrozole is an aromatase inhibitor. It blocks the conversion of androgens to estrogens leading to increased serum testosterone levels. Clomiphene is a selective estrogen receptor modulator that stimulates pituitary gonadotropins and consequently testosterone production. Human chorionic gonadotropin (HCG) binds to the luteinizing hormone (LH) receptor resulting in stimulation of testosterone secretion by Leydig cells. While all of these agents may be requested by patients to mitigate the effects of anabolic steroid-induced hypogonadism, there is no strong evidence supporting their effectiveness and safety for management of anabolic steroid-induced hypogonadism.

Testosterone therapy has been associated with increased hemoglobin and hematocrit levels, worsened obstructive sleep apnea, and decreased HDL cholesterol levels. Since this patient's hemoglobin level is already significantly elevated, testosterone replacement therapy might be potentially harmful. Also, testosterone replacement therapy would not resolve his acne, gynecomastia, or small testes. Furthermore, initiation of testosterone replacement therapy would delay resolution of the expected hypogonadism seen following the discontinuation of anabolic steroids.

KEY POINT

- Cessation of anabolic steroid use is the most appropriate management of steroid-induced hypogonadism.

Bibliography

Karavolos S, Reynolds M, Panagiotopoulou N, McEleny K, Scally M, Quinton R. Male central hypogonadism secondary to exogenous androgens: a review of the drugs and protocols highlighted by the online community of users for prevention and/or mitigation of adverse effects. Clin Endocrinol (Oxf). 2015;82:624-32. [PMID: 25333666] doi:10.1111/cen.12641

Item 17 Answer: C

Educational Objective: Treat hypothyroidism in pregnancy.

For women with hypothyroidism adequately treated with levothyroxine before pregnancy, dosing can be empirically increased by 30% when pregnancy is confirmed. Levothyroxine is the treatment of choice for the management of hypothyroidism during pregnancy. Patients can be counseled to start taking an additional two tablets of their prepregnancy levothyroxine dose per week, which is roughly equivalent to a 30% increase. In euthyroid women without thyroid disease, the total body thyroxine (T_4) pool increases by 40% to 50% during pregnancy. This is mediated by the stimulatory effects of thyroid-stimulating hormone (TSH) and placental human chorionic gonadotropin. Pregnant women with hypothyroidism are unable to augment thyroidal production of T_4 and triiodothyronine (T_3). The levothyroxine dose of hypothyroid women must therefore be adjusted to maintain a euthyroid state. Because T_4 requirements may begin to increase as early as 4 to 6 weeks of pregnancy, women with hypothyroidism should increase their levothyroxine dose or serum TSH should be measured as soon as pregnancy is confirmed. TSH should be measured every 4 weeks for the first half of pregnancy and around 30 weeks of gestation in all women with hypothyroidism. A TSH value in the lower half of the reference range should be targeted (equivalent to a TSH level below 2.5 µU/mL [2.5 mU/L]) both in preconception planning and during pregnancy.

Continuing the patient on her current dose of levothyroxine and checking serum TSH in 2 months or decreasing the patient's levothyroxine dose are both inappropriate management and could precipitate maternal or fetal hypothyroidism. The use of liothyronine or T_3-containing preparations including desiccated thyroid is contraindicated in pregnancy because the fetal central nervous system is relatively impermeable to T_3. Thyroid hormone is essential for normal fetal development and is especially critical for the fetal brain.

KEY POINT

- For women with hypothyroidism adequately treated with levothyroxine before pregnancy, dosing can be empirically increased by 30% when pregnancy is confirmed.

Bibliography

Alexander EK, Pearce EN, Brent GA, Brown RS, Chen H, Dosiou C, et al. 2017 Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease During Pregnancy and the Postpartum. Thyroid. 2017;27:315-389. [PMID: 28056690] doi:10.1089/thy.2016.0457

Item 18 Answer: D

Educational Objective: Understand risks associated with gender-affirming therapy.

Transgender medicine is the care of persons whose gender identity differs from the sex that was assigned at birth. Gender incongruence is persistent incongruence between gender identity and external sexual anatomy at birth absent of a confounding mental disorder. A transgender man is someone with a male gender identity and a female birth assigned sex; a transgender woman (as in this patient) is someone with a female gender identity and a male birth assigned sex.

The most appropriate next step in management is to refer the patient for discussion on fertility preservation options. Gender-affirming hormone therapy is the primary medical intervention sought by transgender people. Criteria for hormone therapy include persistent, well-documented gender dysphoria; capacity to make a fully informed decision; age of majority in a given country; and if present, control of significant medical or psychological conditions. Gender-affirmation hormone therapy limits fertility, thus reproductive options should be discussed with patients prior to initiation of hormone therapy.

While feminizing hormone therapy is typically estradiol with an androgen blocker, it would not be appropriate to initiate therapy without first considering its impact on fertility. Additionally, due to the risk of thromboembolic disease with estrogen therapy, smoking cessation must first be undertaken. Gender confirmation surgery is often the last step in the treatment process for gender dysphoria. It is recommended that individuals undergoing irreversible gender-affirming surgery, which affects fertility, engage in at least 1 year of satisfactory social role change as well as consistent and compliant hormone treatment, unless hormone therapy is not desired or medically contraindicated.

KEY POINT

- Because gender-affirming hormone therapy limits fertility, reproductive options should be discussed with patients prior to initiation.

Bibliography

Hembree WC, Cohen-Kettenis PT, Gooren L, et al. Endocrine treatment of gender-dysphoric/gender-incongruent persons: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2017; 102:3869. [PMID: 28945902]

Item 19 Answer: A

Educational Objective: Recognize medications that can cause falsely elevated plasma free metanephrine levels.

Amitriptyline can cause falsely elevated normetanephrine levels and should be discontinued prior to screening for pheochromocytoma. Most pheochromocytomas secrete norepinephrine, resulting in episodic or sustained hypertension. Orthostatic hypotension can also be seen and likely reflects low plasma volume. In addition to the classic triad of diaphoresis, headache, and tachycardia, common symptoms include

palpitations, tremor, pallor, and anxiety. Screening for pheochromocytoma is appropriate in this patient, following discontinuation of amitriptyline. Amitriptyline acts by inhibiting norepinephrine uptake into nerve terminals, with subsequent elevation of its metabolite, normetanephrine. False-positive elevation of plasma free normetanephrine levels can occur with other tricyclic medications such as nortriptyline or combination serotonin/norepinephrine uptake inhibitors such as venlafaxine or duloxetine. False-positive elevation of plasma normetanephrine and metanephrine levels can also occur with other medications including levodopa (a substrate for catecholamine synthesis); psychoactive medications such as buspirone, prochlorperazine, amphetamines; and over-the-counter decongestant medications that contain adrenergic receptor agonists. Plasma free metanephrines can also be elevated during acute or stressful medical situations including psychiatric illness. Therefore, unless there is significant suspicion for pheochromocytoma, testing should be delayed until the acute illness has passed. Medications that can interfere with catecholamine metabolism should be discontinued (with tapering if indicated) at least 2 weeks prior to testing for pheochromocytoma.

Omeprazole, chlorthalidone, metoprolol, and progesterone do not impact catecholamine metabolism and, therefore, can be continued during screening for pheochromocytoma.

KEY POINT

- Many medications cause falsely high levels of catecholamines or metanephrines including certain antidepressants that inhibit norepinephrine uptake; therefore discontinuation of these agents at least 2 weeks prior to testing for pheochromocytoma is recommended.

Bibliography

van Berkel A, Lenders JW, Timmers HJ. Diagnosis of endocrine disease: biochemical diagnosis of phaeochromocytoma and paraganglioma. Eur J Endocrinol. 2014;170:R109-19. [PMID: 24347425] doi:10.1530/EJE-13-0882

Item 20 Answer: D

Educational Objective: Manage a patient who has completed 5 years of oral bisphosphonate therapy.

The most appropriate management of this patient is to discontinue alendronate. The Fracture Intervention Trial Long-term Extension (FLEX) trial showed that continuing alendronate treatment for 10 years compared with stopping after 5 years resulted in a small decrease in the incidence of clinical vertebral fractures but not nonvertebral fractures. Subject characteristics most predictive of incident fracture after alendronate discontinuation were age older than 76 years, current femur neck T-score below −2.5, and prior osteoporotic fracture. Importantly, women with femur neck T-score below −3.5 or who fractured during the initial 5 years of alendronate therapy were not included in the FLEX trial. The authors concluded that patients at high risk of fracture may benefit from continuing alendronate therapy for up to 10 years. There is inconsistency among expert groups regarding the need to monitor bone mineral density during osteoporosis therapy and at 5 years to inform decision making about discontinuation of therapy. Contrary to other groups, the American College of Physicians recommends against monitoring because data from several studies showed that women treated with antiresorptive treatment benefit from reduced fractures even if BMD did not increase.

The antiresorptive effect of alendronate can be assessed by bone turnover markers including serum C-terminal peptide of type 1 collagen (CTx). However, neither CTx levels on alendronate nor change with discontinuation predict which patients will fracture if alendronate is discontinued. Furthermore, serum CTx levels in patients taking alendronate vary widely and cannot be reliably interpreted without pretreatment values.

The FLEX trial included postmenopausal women who had taken 5 years of alendronate 5 mg daily (equivalent to 35 mg weekly) or 10 mg daily (equivalent to 70 mg weekly). There was no difference in outcomes based on alendronate dose. Therefore, the management decision to be made after 5 years of alendronate therapy is to continue or discontinue rather than to modify the dose.

KEY POINT

- For low-risk osteoporotic women, treatment with antiresorptive therapy for 5 years is sufficient.

Bibliography

Qaseem A, Forciea MA, McLean RM, Denberg TD; Clinical Guidelines Committee of the American College of Physicians. Treatment of low bone density or osteoporosis to prevent fractures in men and women: a Clinical Practice Guideline Update from the American College of Physicians. Ann Intern Med. 2017;166:818-839. doi: 10.7326/M15-1361. Epub 2017 May 9. [PMID: 28492856]

Item 21 Answer: A

Educational Objective: Manage type 2 diabetes mellitus in a patient with decreasing kidney function.

The most appropriate management of this patient's diabetes mellitus is to continue the current regimen. This is an older patient with multiple comorbidities. She is at her goal hemoglobin A_{1c} level of less than 8% per the American Diabetes Association guidelines with her current regimen. In contrast, the American College of Physicians recommends that clinicians should avoid targeting an hemoglobin A_{1c} level in patients with a life expectancy less than 10 years due to advanced age (80 years or older), residence in a nursing home, or chronic conditions (such as end-stage kidney disease) because the harms outweigh the benefits in this population.

The FDA previously considered serum creatinine levels of 1.4 mg/dL (123.8 µmol/L) or higher in women and 1.5 mg/dL (132.6 µmol/L) or higher in men a contraindication to metformin use due to concerns for development of lactic acidosis. After further review of safety data from multiple studies, the criteria for continued safe use of metformin

have been revised by the FDA. The use of serum creatinine for determining safe use of metformin was replaced by estimated glomerular filtration rate (eGFR) to better estimate kidney function. Patients who have a decrease in eGFR to 30 to 45 mL/min/1.73 m² while treated with metformin may continue use after consideration of risks and benefits. If metformin is continued, frequent monitoring of kidney function (every 3 months) is recommended. Metformin should be discontinued if the eGFR falls below 30 mL/min/1.73 m².

Because she is at her goal hemoglobin A_{1c} level of less than 8%, intensifying her therapy with either insulin glargine or glipizide is unnecessary. In addition, increasing the insulin glargine or glipizide dose in the setting of worsening kidney function could increase the risk for hypoglycemia. Additional weight gain may also occur with an increased insulin glargine or glipizide dose.

KEY POINT

- Metformin may be continued in patients with an estimated glomerular filtration rate to 30 to 45 mL/min/1.73 m² after consideration of risks and benefits; if metformin is continued, frequent monitoring of kidney function (every 3 months) is recommended.

Bibliography

American Diabetes Association. 8. Pharmacologic approaches to glycemic treatment: Standards of Medical Care in Diabetes-2018. Diabetes Care. 2018;41(Suppl 1):S73-S85. doi: 10.2337/dc18-S008. [PMID: 29222379]

Item 22 Answer: A

Educational Objective: Treat polycystic ovary syndrome.

This patient has ovulatory dysfunction with clinical and biochemical evidence of hyperandrogenism. While this is suggestive of polycystic ovary syndrome, this is a diagnosis of exclusion. The prolonged clinical course and absence of the more concerning findings of virilization also support the diagnosis of polycystic ovary syndrome. Given that this patient is most concerned about hirsutism and acne, oral contraceptive therapy is the first-line therapeutic agent. Oral contraceptive therapy suppresses gonadotropin secretion and resultant ovarian androgen production. Additionally, the estrogen component increases sex hormone-binding globulin resulting in less androgen bioavailability. Oral contraceptives that contain 30 to 35 µg of ethinyl estradiol appear to be more effective in managing hirsutism than formulations containing less ethinyl estradiol. Furthermore, oral contraceptive therapy reduces new terminal hair growth, improves acne, and regulates menses to prevent endometrial hyperplasia.

Metformin minimally effects hirsutism and is not recommended for this indication. In patients with polycystic ovary syndrome, metformin could be considered for off-label treatment of prediabetes or treatment of type 2 diabetes, in addition to lifestyle modification.

Pelvic ultrasound and adrenal CT should be performed to exclude an ovarian or adrenal neoplasm if the serum total testosterone level is greater than 150 ng/dL (5.2 nmol/L), and adrenal CT is necessary to exclude an adrenal cortisol-secreting and/or androgen-secreting neoplasm if the plasma dehydroepiandrosterone sulfate (DHEAS) level is greater than 7.0 µg/mL (18.9 µmol/L). Pelvic ultrasound and adrenal CT are not indicated in this patient as her testosterone and DHEAS levels are not elevated to the degree that ovarian tumor is a consideration.

While spironolactone can reduce the growth of terminal hair, it is used as an add-on treatment to oral contraceptive therapy. This antiandrogen medication may disrupt organogenesis in a male fetus; thus, concomitant reliable contraception is mandated when initiating this treatment.

KEY POINT

- Oral contraceptive agents are first-line pharmacologic therapy for hirsutism, acne, and menstrual dysfunction unless fertility is desired in a patient with polycystic ovary syndrome.

Bibliography

McCartney CR, Marshall JC. Clinical practice: polycystic ovary syndrome. N Engl J Med. 2016;375:54-64. [PMID: 27406348] doi:10.1056/NEJMcp1514916

Item 23 Answer: A

Educational Objective: Evaluate a pituitary tumor for hypersecretion.

Measurement of prolactin and insulin-like growth factor 1 (IGF-1) is recommended for the evaluation of possible hypersecretion of an incidentally discovered pituitary tumor. When a pituitary tumor is incidentally noted, investigation must determine (1) whether it is causing a mass effect, (2) whether it is secreting excess hormones, and (3) whether it has a propensity to grow and cause problems in the future. After a thorough history and physical examination, biochemical testing can be undertaken in a targeted fashion based on the patient's clinical signs and symptoms. Although not generally useful in the differential diagnosis of a pituitary mass, all patients should be evaluated for hormone hyposecretion in order to identify and replace hormone deficiencies. Initial tests to evaluate for hormone deficiency should include measurement of 8 AM cortisol, thyroid-stimulating hormone (TSH), free (or total) thyroxine (T_4), follicle stimulating hormone (FSH), testosterone in men and menstrual history in women (normal menstrual cycles eliminates the need to measure hormone levels). Prolactin and IGF-1 are measured to rule out pituitary hormone hypersecretion. Screening for growth hormone excess in pituitary incidentalomas may allow early detection of a growth hormone secreting tumor therefore increasing the chance of a surgical cure. If the tumor is not causing mass effect and there is no evidence of hormone excess, a pituitary MRI should be repeated in 6 months for a macroadenoma (≥1 cm) and 12 months for a microadenoma (<1 cm) to assess for growth. If no growth occurs, MRIs should be repeated every 1 to 2 years for the next 3 years and then intermittently thereafter.

Measurement of urine free cortisol is not necessary in every patient with a pituitary tumor. This should be measured only when Cushing disease is suspected based on clinical history and physical examination findings. This patient has no physical features suspicious for Cushing disease nor does he have diseases associated with Cushing disease such as diabetes or hypertension.

Visual field examination is absolutely necessary in all patients with a macroadenoma that abuts or compresses the optic chiasm, but it is not necessary in patients with no evidence of involvement of the optic chiasm on MRI. This patient's tumor does not abut or compress the optic chiasm or optic nerves.

No further evaluation is inappropriate as pituitary hypersecretion should be evaluated in all pituitary tumors.

KEY POINT

- In patients with pituitary tumors, pituitary hypersecretion should be ruled out by biochemical testing.

Bibliography

Freda PU, Beckers AM, Katznelson L, Molitch ME, Montori VM, Post KD, et al; Endocrine Society. Pituitary incidentaloma: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2011;96:894-904. [PMID: 21474686] doi:10.1210/jc.2010-1048.

H

Item 24 Answer: E

Educational Objective: Manage a patient with pheochromocytoma prior to surgery.

The most appropriate preoperative management in this patient with a pheochromocytoma is an α-adrenergic blocking agent. An α-receptor blockade is required prior to adrenalectomy to prevent potential hypertensive crisis caused by catecholamine release during anesthesia induction and/or manipulation of the tumor. Phenoxybenzamine is started approximately 10 to 14 days prior to surgery, and the dose progressively increased to achieve a desired blood pressure of 130/80 mm Hg or lower when seated, and systolic pressure of 90 mm Hg or higher when standing. Because phenoxybenzamine causes vasodilation, an expected consequence of therapy is postural hypotension. To counteract this and allow appropriate dose escalation of phenoxybenzamine, patients are advised to drink plenty of fluids, eat high salt-containing foods, and to make liberal use of the salt shaker at meal times. If blood pressure is not adequately controlled with an α-receptor blockade (or prohibitive side effects occur with required higher doses), a calcium channel blocker such as amlodipine can be added. A short-acting, selective α-blocker such as prazosin, doxazosin, or terazosin, can be considered alternatives to phenoxybenzamine, based on decreased cost and limited data suggesting similar patient outcomes.

Hydralazine or lisinopril do not provide the needed α-receptor blockade, and therefore increasing the dose of these medications would not be helpful before surgery.

Diuretics, such as chlorthalidone, should be avoided in patients with pheochromocytoma. These patients may have diminished intravascular volume secondary to intense vasoconstriction and further diuretic-induced volume depletion may lead to severe hypotension. Finally, diuretic treatment will not prevent hypertensive crisis during adrenalectomy.

Metoprolol or other β-blockers should never be started prior to adequate α-receptor blockade in patients with pheochromocytoma, as unopposed α-receptor stimulation can precipitate a hypertensive crisis. Once adequate α-receptor blockade has been achieved, however, a β-blocker is typically added to the medication regimen 2 to 3 days prior to surgery to counteract vasodilation-induced tachycardia.

In the case of very large tumors and/or significant metanephrine elevation, the catecholamine synthesis inhibitor metyrosine may also be added to the medication regimen. Metyrosine is not given routinely in the preoperative management of pheochromocytoma due to significant side effects associated with body-wide catecholamine deficiency.

KEY POINT

- An α-receptor blockade with phenoxybenzamine or another α-blocker is required prior to adrenalectomy for pheochromocytoma to prevent potential hypertensive crisis during anesthesia induction and/or manipulation of the tumor.

Bibliography

Lenders JW, Duh QY, Eisenhofer G, et al; Endocrine Society. Pheochromocytoma and paraganglioma: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2014 Jun;99(6):1915-42. doi: 10.1210/jc.2014-1498. PubMed PMID: 24893135.

Item 25 Answer: A

Educational Objective: Treat type 2 diabetes mellitus in a patient with cardiovascular disease.

The patient has uncontrolled diabetes in the setting of coronary artery disease, and empagliflozin is the most appropriate treatment. Empagliflozin increases excretion of glucose by the kidneys through inhibition of the sodium-glucose transporter-2 (SGLT2) receptors. Empagliflozin received approval from the FDA for patients with type 2 diabetes and established cardiovascular disease based upon the results of the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME). This study demonstrated a reduction in the primary composite outcome (cardiovascular-related death, nonfatal myocardial infarction, nonfatal stroke) and all-cause mortality when empagliflozin was added to standard care versus placebo. Empagliflozin has the additional potential benefit of inducing weight loss and blood pressure lowering in this overweight patient with uncontrolled hypertension.

Although the sulfonylurea, glipizide, could improve the patient's glycemic control, it has the potential side effect of weight gain; the combination of metformin plus an SGLT2 inhibitor is superior to metformin plus a sulfonylurea (mean between-group difference, 4.7 kg [CI, 4.4 to 5.0 kg]). The combination of metformin and an SGLT2 inhibitor reduces systolic

blood pressure more than that of metformin and a sulfonylurea (between-group difference, 5.1 mm Hg [CI, 4.2 to 6.0 mm Hg]).

In patients with type 2 diabetes and cardiovascular risk factors, a significant reduction in the primary composite outcome (cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke) and rates of cardiovascular death and all-cause mortality has also been associated with liraglutide. There have been postmarketing reports of fatal and nonfatal acute pancreatitis associated with liraglutide. While it is not known if liraglutide increases risk for development of pancreatitis in patients with a history of pancreatitis, many experts avoid its use in this patient population.

The dipeptidyl peptidase-4 (DPP-4) inhibitor, sitagliptin, could improve the patient's glycemic control; however, the combination of metformin and an SGLT2 inhibitor reduces systolic blood pressure more than metformin and a DPP-4 inhibitor (pooled between-group difference, 4.1 mm Hg [CI, 3.6 to 4.6 mm Hg]) and SGLT2 inhibitors reduced weight more than DPP-4 inhibitors (between group difference, 2.5 to 2.7 kg). There have been postmarketing reports of fatal and nonfatal acute pancreatitis associated with sitagliptin. While no causal relationship has been established, FDA labeling guidelines recommend that sitagliptin be used with caution in patients with a history of pancreatitis and some experts recommend against its use entirely in this population.

KEY POINT

- Empagliflozin has been shown to reduce cardiovascular-related events and all-cause mortality in patients with type 2 diabetes mellitus and cardiovascular disease.

Bibliography

Barry MJ, Humphrey LL, Qaseem A. Oral pharmacologic treatment of type 2 diabetes mellitus. Ann Intern Med. 2017;167:75-76. doi:10.7326/L17-0234. [PMID: 28672387]

Item 26 Answer: B

Educational Objective: Evaluate secondary amenorrhea.

This patient presents with secondary amenorrhea, defined as absence of menses for more than 3 months in women who previously had regular menstrual cycles. After ruling out pregnancy, the initial laboratory evaluation in secondary amenorrhea includes measurement of follicle-stimulating hormone (FSH), thyroid-stimulating hormone (TSH), and prolactin levels. Given negative pregnancy testing and normal TSH and prolactin levels in this patient, FSH testing is the remaining initial laboratory data point that has yet to be explored. If the FSH level is elevated, testing should be repeated in 1 month and accompanied by serum estradiol testing. If the FSH level is elevated on repeat testing and estradiol level is low, karyotype analysis is indicated to evaluate for Turner syndrome. Primary ovarian insufficiency is also associated with an elevated FSH and low estradiol levels. In women with normal or low FSH levels, the evaluation is typically directed by history and physical examination findings. For example, a high BMI (≥30) and acne are frequently seen in women with polycystic ovary syndrome. In addition, a progestin withdrawal test can be performed to further assess the estrogen status of the patient. If a normal estrogen state is confirmed (bleeding within a week of stopping progesterone), hyperandrogenism should be considered.

Testosterone and dehydroepiandrosterone sulfate (DHEAS) are measured in patients with suspected hyperandrogenism as the cause of amenorrhea based on history, physical examination, and following initial laboratory evaluation (serum human chorionic gonadotropin, FSH, TSH, and prolactin).

Primary amenorrhea is the absence of menses by age 16 years accompanied by normal sexual hair pattern and normal breast development. Approximately 15% of patients presenting with primary amenorrhea may have an anatomic abnormality of the uterus, cervix, or vagina such as müllerian agenesis, transverse vaginal septum, or imperforate hymen. Digital vaginal examination, transvaginal ultrasound, or pelvic MRI may help to identify outflow tract anomalies. Because this patient has secondary amenorrhea, evaluation for anatomic abnormalities with transvaginal ultrasound or pelvic MRI is not indicated.

KEY POINT

- After ruling out pregnancy, the initial laboratory evaluation in secondary amenorrhea includes measurement of follicle-stimulating hormone, thyroid-stimulating hormone, and prolactin levels.

Bibliography

Klein DA, Poth MA. Amenorrhea: an approach to diagnosis and management. Am Fam Physician. 2013;87:781-8. [PMID: 23939500]

Item 27 Answer: C

H

Educational Objective: Manage hyperglycemia in the hospital.

The most appropriate management of this patient's hyperglycemia is to initiate scheduled basal insulin and correction insulin. Inpatient hyperglycemia, defined as consistently elevated plasma glucose values above 140 mg/dL (7.8 mmol/L), is associated with poor outcomes. Attempts to decrease morbidity and mortality with tight glycemic control (80-110 mg/dL [4.4-6.1 mmol/L]) have not consistently demonstrated improvements in adverse outcomes and, in some settings, have shown increased rates of severe hypoglycemic events and mortality. As a result, revised inpatient glycemic targets are less stringent than outpatient glucose targets to avoid both hypoglycemia and severe hyperglycemia that can lead to volume depletion and electrolyte abnormalities. Dietary modifications should be made once glucose levels exceed 140 mg/dL (7.8 mmol/L). At persistent glucose levels of 180 mg/dL (10.0 mmol/L) and higher, the American Diabetes Association recommends initiation of scheduled insulin with a blood glucose target of 140 to 180 mg/dL (7.8-10.0 mmol/L) for most critically ill and noncritically ill patients to decrease

H CONT.

the risk of adverse outcomes. Scheduled basal insulin or basal insulin plus correction insulin is appropriate for patients who are fasting or who have poor oral intake, such as this patient, with frequent bedside point-of-care monitoring every 4 to 6 hours for insulin adjustments. Scheduled basal and prandial insulin plus correction insulin are appropriate for patients who are eating.

The safety of oral antihyperglycemic agents, including empagliflozin, in the hospital setting has not been fully studied or established. In addition, sodium-glucose transporter-2 (SGLT2) inhibitors have been associated with diabetic ketoacidosis and should be avoided in situations that may produce ketone bodies, such as severe illness or prolonged fasting. Scheduled insulin therapy is the recommended treatment regimen for hyperglycemia in the hospital setting.

The safety of oral antihyperglycemic agents, including metformin, in the hospital setting has not been fully studied or established. Scheduled insulin therapy is the recommended treatment regimen for hyperglycemia in the hospital setting.

The sole use of correction insulin for the management of hyperglycemia is not recommended. It is a reactive approach to hyperglycemia that can lead to large fluctuations in glucose levels coupled with the near universal lag time between measurement of glucose and injection of insulin that occurs in most hospitals.

KEY POINT

- To manage in-patient hyperglycemia, scheduled basal insulin or basal insulin plus correction insulin is appropriate for patients who are fasting or who have poor oral intake.

Bibliography

American Diabetes Association. 14. Diabetes care in the hospital: Standards of Medical Care in Diabetes-2018. Diabetes Care. 2018;41(Suppl 1): S144-S151.doi: 10.2337/dc18-S014. [PMID: 29222385]

Item 28 Answer: C

Educational Objective: Diagnose syndrome of inappropriate antidiuretic hormone secretion (SIADH) following transsphenoidal pituitary surgery.

Serum sodium level should be measured in this patient. Sodium and water imbalance are common after pituitary surgery. Patients may exhibit findings of diabetes insipidus (DI) (polyuria, elevated or high normal serum sodium, and dilute urine) followed by syndrome of inappropriate antidiuretic hormone secretion (SIADH) followed again by DI. Central DI may be transient, lasting only a few weeks, or permanent. There is great variability in the presentation of these disorders; some patients manifest all phases, whereas others may manifest only DI or SIADH. During the postoperative hospital recovery, patients are assessed for hormone deficiency that may have occurred as the result of surgery and are then monitored by measuring fluid intake and output, serum sodium, and urine osmolality. Following discharge, most experts measure serum sodium 1 week postoperatively to screen for SIADH. This patient denies any polyuria or polydipsia so it is unlikely that he has DI, but he is at risk for SIADH given the time frame of presentation. SIADH can occur 3 to 7 days after pituitary surgery. It is important to diagnose SIADH as treatment with fluid restriction will prevent further reduction in sodium levels.

Hyponatremia, defined as a serum sodium concentration less than 136 mEq/L (136 mmol/L), most often results from an increase in circulating antidiuretic hormone (ADH) in response to a true or sensed reduction in effective arterial blood volume with resulting fluid retention. Hyponatremia may also be caused by elevated ADH levels associated with SIADH. The first step in diagnosis of suspected SIADH is measurement of the serum sodium. The initial evaluation of patients with confirmed hyponatremia is measurement of plasma and urine osmolality and urine sodium as well as a careful assessment of the volume status. Measurement of antidiuretic hormone is not part of the diagnostic algorithm as ADH measurement is not quickly available, and results are difficult to interpret.

Pituitary MRI is unnecessary since the patient has no focal findings (cranial nerve deficit or fever) to suggest intracranial pathology or infection.

Measuring thyroid-stimulating hormone is incorrect as the result could be misleading in this patient following pituitary surgery. Measuring the free thyroxine (T_4) level would be more appropriate. In addition, given the long half-life of free T_4, testing is more appropriate 4 weeks after pituitary surgery to assess for secondary hypothyroidism. Symptoms occurring 5 days after pituitary surgery are not likely due to thyroid deficiency.

KEY POINT

- Syndrome of inappropriate antidiuretic hormone secretion (SIADH) is a common complication of pituitary surgery that may occur 3 to 7 days following surgery; treatment with fluid restriction will prevent further reduction in sodium levels.

Bibliography

Kiran Z, Sheikh A, Momin SN, Majeed I, Awan S, Rashid O, et al. Sodium and water imbalance after sellar, suprasellar, and parasellar surgery. Endocr Pract. 2017;23:309-317. [PMID: 27967227] doi:10.4158/EP161616.OR

Item 29 Answer: A

Educational Objective: Manage hypogonadotropic hypogonadism due to hyperprolactinemia.

The patient has hypogonadism due to hyperprolactinemia, and the most appropriate management is dopamine agonist therapy. Empty sella is diagnosed when the normal pituitary gland is not visualized or is excessively small on MRI. The pituitary sella is said to be "empty" because normal tissue is not seen. The finding may be primarily due to increased cerebrospinal fluid entering and enlarging the sella, or it may be

secondary to a tumor, previous pituitary surgery, radiation, or infarction. When empty sella is found incidentally on imaging, an evaluation should be completed to determine if there is a known cause for secondary empty sella and if the patient has signs or symptoms of pituitary hormone deficiency. A patient without signs or symptoms should be screened for cortisol deficiency and hypothyroidism. The most common pituitary abnormality in empty sella is hyperprolactinemia. Hyperprolactinemia should be treated with dopamine agonist therapy in a woman with irregular menstrual periods who is trying to conceive. This normalizes the prolactin level and allows recovery of the gonadal axis.

Neurosurgical consultation is not necessary in the absence of signs/symptoms of increased intracranial pressure or visual deficit. Although this patient's original MRI was done for headache, she has no current signs of increased intracranial pressure or visual deficit on examination.

An oral contraceptive pill could be used for treatment if she were not trying to conceive. This is appropriate treatment for hypogonadism related to hyperprolactinemia in empty sella or in women with hyperprolactinemia secondary to a pituitary microadenoma to reduce her risk of developing osteoporosis.

Providing no treatment at this time is inappropriate given the patient's menstrual irregularity. In her case, she requires dopamine agonist therapy to treat her hypogonadism as she is trying to conceive; however, even if she were not trying to conceive, she would require treatment with either dopamine agonist therapy or an oral contraceptive pill to treat her hypogonadism and reduce her risk of developing osteoporosis.

KEY POINT

- Dopamine agonist therapy should be used to treat hyperprolactinemia in women with irregular periods who are trying to conceive.

Bibliography

Guitelman M, Garcia Basavilbaso N, Vitale M, Chervin A, Katz D, Miragaya K, et al. Primary empty sella (PES): a review of 175 cases. Pituitary. 2013;16:270-4. [PMID: 22875743] doi:10.1007/s11102-012-0416-6

Item 30 Answer: B

Educational Objective: Diagnose multiple endocrine neoplasia type 1 (MEN1).

Multigland hyperplasia causing primary hyperparathyroidism should lead to further investigation for an underlying disorder, especially in younger persons and those with a family history of primary hyperparathyroidism. Although there are several familial hyperparathyroidism syndromes, multiple endocrine neoplasia type 1 (MEN1) is the most common. In addition to genetic testing, MEN1 can be discriminated from other disorders by personal or family history of recurrent primary hyperparathyroidism and neoplasia in other endocrine tissues, most prominently neuroendocrine tumors arising from the pancreas and tumors of the pituitary gland.

In contrast, familial hypocalciuric hypercalcemia (FHH) presents as mild, stable hypercalcemia with normal parathyroid hormone (PTH) level and relatively low urine calcium excretion. PTH may be elevated in a small percentage of patients with coexistence of vitamin D deficiency. Kidney health is unaffected. A family history of persistent hypercalcemia despite parathyroidectomy is suggestive. Genetic testing may help to discriminate FHH from primary hyperparathyroidism prior to surgical exploration.

Parathyroid carcinoma is rare. Rapidly worsening or severe hypercalcemia accompanied by very high PTH levels, increased alkaline phosphatase, and locally invasive tumor arising from a single parathyroid gland are diagnostic.

Secondary hyperparathyroidism is a response to hypocalcemia often related to vitamin D deficiency or chronic kidney disease-related hyperphosphatemia. Left untreated, a chronic stimulus to PTH secretion may lead to parathyroid gland hyperplasia. Tertiary hyperparathyroidism is the result of long-standing secondary hyperparathyroidism in which the hyperplastic parathyroid glands exhibit autonomous function even after correction of underlying disease (for example, following kidney transplantation). Although the biochemical profile is similar to primary hyperparathyroidism, a history of preexisting and long-standing hypocalcemia or hyperphosphatemia is evident.

KEY POINT

- Primary hyperparathyroidism may be the first sign of multiple endocrine neoplasia syndrome 1 (MEN1) in persons with a family history of recurrent primary hyperparathyroidism and neuroendocrine tumors arising from the pancreas and tumors of the pituitary gland.

Bibliography

Thakker RV, Newey PJ, Walls GV, Bilezikian J, Dralle H, Ebeling PR, et al; Endocrine Society. Clinical Practice Guidelines for Multiple Endocrine Neoplasia Type 1 (MEN1). J Clin Endocrinol Metab. 2012;97:2990-3011. [PMID: 22723327] doi:10.1210/jc.2012-1230

Item 31 Answer: C

Educational Objective: Diagnose vitamin D-dependent hypercalcemia.

The most likely diagnosis is vitamin D-dependent hypercalcemia, and 1,25-dihydroxyvitamin D level should be measured. Vitamin D-dependent hypercalcemia is most commonly due to disorders associated with granulomatous inflammation. The patient's chest radiograph shows extensive infiltrates that are most prominent in the upper lung zones and are associated with hilar enlargement, highly suggestive of pulmonary sarcoidosis. Sarcoidosis is a multisystem granulomatous disease of unclear cause with a predilection for the lung; pulmonary involvement occurs in more than 90% of patients. Macrophages within granulomas convert 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D without regulation by parathyroid hormone in contrast to renal conversion of vitamin D. An elevated 1,25-dihydroxyvitamin D level and suppressed

parathyroid hormone is diagnostic of vitamin D-dependent hypercalcemia. As vitamin D enhances absorption of both calcium and phosphorus, concurrent elevation of serum calcium and phosphorus is also suggestive of vitamin D dependent hypercalcemia.

There are two mechanisms of hypercalcemia of malignancy: local osteolytic and humoral. When lytic bone metastases are present, hypercalcemia is the result of increased mobilization of calcium from the bone. In these cases, the serum alkaline phosphatase level is typically elevated. Humoral hypercalcemia is less common and occurs when the tumor itself produces parathyroid-related protein (PTHrP) that binds to and activates the parathyroid receptor, raising serum calcium levels. Squamous cell carcinomas, breast cancers, and renal cell carcinomas are the tumors most commonly associated with hypercalcemia of malignancy. These diagnoses cannot explain the patient's prolonged clinical course, pulmonary infiltrates, and hilar lymphadenopathy.

When hypercalcemia is due to adrenal insufficiency, it is in the setting of adrenal crisis which is characterized by hypotension, fever, nausea, vomiting, abdominal pain, tachycardia, and even death. The patient's clinical course is not compatible with acute adrenal insufficiency.

KEY POINT

- An elevated 1,25-dihydroxyvitamin D level and suppressed parathyroid hormone is diagnostic of vitamin D-dependent hypercalcemia.

Bibliography

Donovan PJ, Sundac L, Pretorius CJ, d'Emden MC, McLeod DS. Calcitriol-mediated hypercalcemia: causes and course in 101 patients. J Clin Endocrinol Metab. 2013;98:4023-9. [PMID: 23979953] doi:10.1210/jc.2013-2016

Item 32 Answer: A

Educational Objective: Screen for diabetic retinopathy in a woman of childbearing age.

The most appropriate preconception management for this patient is a dilated eye examination. Women with type 1 or type 2 diabetes mellitus who are planning pregnancy should be counseled on the risk of development or progression of diabetic retinopathy. Additionally, rapid improvement in glycemic control in the setting of retinopathy is associated with temporary worsening of retinopathy. Given tight glycemic targets in pregnancy, this is often a time of intensified glycemic control for women placing them at greater risk for this complication. Dilated eye examinations should occur before pregnancy or in first trimester if not done prior to pregnancy. Patients should be monitored every trimester and then closely for 1 year postpartum as indicated by the degree of retinopathy.

This patient is up to date on lipid screening and additional screening as part of preconception management is not necessary.

Thyroid-stimulating hormone (TSH) levels should be monitored closely in pregnancy due to increased level of thyroid-binding globulin in pregnancy resulting in increased levothyroxine needs. This patient has had a TSH measurement with normal results 3 months ago. The dose of levothyroxine may need to be increased on average by 30% to 50% during pregnancy, and patients should have their TSH level checked as soon as a pregnancy test is positive.

A referral to a physician experienced in the care of kidney disease should be undertaken in patients with advanced kidney disease, which is not present in this patient as her most recent serum creatinine and urine albumin-creatinine ratio were normal.

KEY POINT

- Women with type 1 or type 2 diabetes mellitus who are planning pregnancy should be counseled on the risk of development or progression of diabetic retinopathy; rapid improvements in glycemic levels during pregnancy can temporarily worsen preexisting retinopathy.

Bibliography

American Diabetes Association. 10. Microvascular complications and foot care: Standards of Medical Care in Diabetes 2018. Diabetes Care. 2018;41(Suppl 1):S105-S118. doi: 10.2337/dc18-S010. [PMID: 29222381]

Item 33 Answer: A

Educational Objective: Treat glucocorticoid-induced osteoporosis.

The most appropriate treatment is alendronate. The American College of Rheumatology recommends that in all adults and children, an initial clinical fracture risk assessment for glucocorticoid-induced osteoporosis should be performed as soon as possible, but at least within 6 months of the initiation of long-term glucocorticoid treatment. Patients are categorized according to fracture risk. High fracture risk in patients younger than 40 years is defined as by a previous osteoporotic fracture. Moderate fracture risk is defined as hip or spine bone mineral density Z score less than −3 or rapid bone loss (>10% at the hip or spine over 1 year) and continuing glucocorticoid treatment at >7.5 mg/day for >6 months. Low risk is defined as no osteoporotic risk factors other than glucocorticoid use. Other criteria are used for defining low, moderate, and high fracture risk in patients age 40 years and older. Oral bisphosphonates are recommended as first-line therapy for patients with moderate to high fracture risk, such as this woman, regardless of age. This includes women of childbearing potential provided they are not planning a pregnancy during the period of bisphosphonate treatment.

Optimized calcium and vitamin D intake, lifestyle modifications, and reassessment of fracture risk including bone mineral density testing every 2 to 3 years is recommended over osteoporosis medications for patients younger than 40 at low risk of fracture. However, this patient is not low risk, and treatment with an oral bisphosphonate is indicated.

Teriparatide is indicated for the treatment of men and women with osteoporosis associated with sustained systemic glucocorticoid therapy at high risk for fracture. Although it increases bone mineral density at the spine and hip more than oral bisphosphonate therapy, it is less desirable due to expense and the requirement of daily injections.

Zoledronic acid is indicated for the treatment and prevention of glucocorticoid-induced osteoporosis in patients who cannot tolerate oral bisphosphonates. Due to uncertain impact on pregnancy outcomes, it is considered a third-line agent in younger women.

KEY POINT

- Oral bisphosphonates are recommended as first-line therapy in adult men and women on chronic glucocorticoid therapy with moderate to high fracture risk regardless of age.

Bibliography

Buckley L, Guyatt G, Fink HA, Cannon M, Grossman J, Hansen KE, Humphrey MB, Lane NE, Magrey M, Miller M, Morrison L, Rao M, Byun Robinson A, Saha S, Wolver S, Bannuru RR, Vaysbrot E, Osani M, Turgunbaev M, Miller AS, McAlindon T. 2017 American College of Rheumatology Guideline for the Prevention and Treatment of Glucocorticoid-Induced Osteoporosis. Arthritis Care Res (Hoboken). 2017;69:1095-1110. doi: 10.1002/acr.23279. Epub 2017 Jun 6. [PMID: 28585410]

Item 34 Answer: D

Educational Objective: Diagnose thyroid-stimulating hormone–secreting adenoma.

This patient most likely has a thyroid-stimulating hormone (TSH)-secreting adenoma. The initial evaluation based on clinical signs and/or symptoms of thyrotoxicosis should be measurement of serum TSH alone, followed by measurement of thyroxine (T_4) and triiodothyronine (T_3) levels if TSH is suppressed because the typical pattern of hyperthyroidism is TSH suppression with an elevated T_4 and/or T_3. However, this patient has signs and symptoms of hyperthyroidism with elevated TSH and free T_4 levels, which is concerning for a TSH-secreting adenoma. These tumors are extremely rare and are managed differently from other causes of thyrotoxicosis. Before this diagnosis is made, other causes of the laboratory abnormalities must be excluded (thyroid hormone resistance and familial dysalbuminemic hyperthyroxinemia). If there is no other explanation for elevated TSH and T_4 levels, a pituitary MRI should be performed. The patient's symptoms of hyperthyroidism and lack of family history of thyroid disease make a TSH-secreting adenoma more likely.

Serum TSH and human chorionic gonadotropin have a common α-subunit, allowing cross-reactivity at the TSH receptor. Gestational thyrotoxicosis typically occurs in the first trimester secondary to human chorionic gonadotropin (HCG) stimulation of the TSH receptor. Laboratory results would look similar to hyperthyroidism with suppressed TSH and elevated free T_4.

The clinical manifestations of hypothyroidism include fatigue, cold intolerance, constipation, heavy menses, weight gain, impaired concentration, dry skin, edema, depression, mood changes, muscle cramps, myalgia, and reduced fertility. Hypothyroidism is unlikely as her symptoms are not compatible and her TSH levels would be elevated with a normal or low free T_4 level.

The symptoms of thyrotoxicosis include heat intolerance, palpitations, dyspnea, tremulousness, menstrual irregularities, hyperdefecation, weight loss, increased appetite, proximal muscle weakness, fatigue, insomnia, and mood disturbances. The most common causes of hyperthyroidism are Graves disease and toxic adenoma(s). While the patient has thyrotoxicosis-related symptoms, hyperthyroidism due to Graves disease results in a suppressed TSH level with an elevated free T_4 level, which is not found in this case.

KEY POINT

- Signs and symptoms of a thyroid-stimulating hormone-secreting adenoma are those seen in hyperthyroidism, although laboratory evaluation reveals an elevated free thyroxine (T_4) level with an inappropriately normal or elevated thyroid-stimulating hormone level.

Bibliography

Amlashi FG, Tritos NA. Thyrotropin-secreting pituitary adenomas: epidemiology, diagnosis, and management. Endocrine. 2016;52:427-40. [PMID: 26792794] doi:10.1007/s12020-016-0863-3

Item 35 Answer: B

Educational Objective: Manage secondary amenorrhea due to a prolactinoma.

This patient has a prolactinoma resulting in amenorrhea and infertility due to the inhibitory effect of the elevated prolactin level on gonadotropin secretion. Prolactinomas are treated with dopamine agonists. The two FDA-approved dopamine agonists are bromocriptine and cabergoline. Cabergoline is much better tolerated and more effective at normalizing prolactin and tumor shrinkage, so it is typically the initial therapy chosen but is more expensive than bromocriptine. Dopamine agonists typically decrease the size and hormone production of prolactinomas rapidly. Response to therapy can be monitored by checking serum prolactin levels 1 month after initiating therapy and then every 3 to 4 months. Decreasing serum prolactin usually correlates with decreasing the size of the tumor. Normalization of prolactin concentrations with dopamine agonist therapy to allow spontaneous ovulation is the goal of management in women with microadenomas (<1 cm in size) considering pregnancy. Dopamine agonist therapy is effective at lowering prolactin levels, decreasing tumor size, and restoring gonadal function.

For women who do not ovulate with dopamine agonist therapy, clomiphene citrate therapy is sometimes added.

Unlike other pituitary tumors, medication rather than surgery is first-line therapy for prolactinomas. Even patients with severe mass effect such as vision loss are treated with medical therapy initially. Rarely, very large tumors or more

invasive prolactinomas do not shrink with medical therapy and, also rarely, continue to grow. In these patients, surgery should be considered, followed by radiotherapy if growth recurs or continues. After being debulked, the prolactinoma may respond better to medical therapy.

Resuming an oral contraceptive pill will not correct the underlying disorder and would not assist this patient in becoming pregnant.

KEY POINT

- Symptomatic prolactinomas are treated with dopamine agonists.

Bibliography

Melmed S, Casanueva FF, Hoffman AR, Kleinberg DL, Montori VM, Schlechte JA, et al; Endocrine Society. Diagnosis and treatment of hyperprolactinemia: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2011;96:273-88. [PMID: 21296991] doi:10.1210/jc.2010-1692

Item 36 Answer: B

Educational Objective: Manage the "honeymoon phase" of type 1 diabetes mellitus.

The most appropriate management of this patient's diabetes is to decrease the insulin glargine dose and discontinue insulin aspart. The drastic reduction in endogenous insulin production secondary to pancreatic beta cell destruction in type 1 diabetes creates a glucose toxicity that induces a functional impairment of the remaining beta cells. As exogenous insulin therapy improves glycemic control, the remaining beta cells experience less metabolic stress, resulting in an improvement in the ability to produce insulin. This "honeymoon phase" may occur shortly after the diagnosis of diabetes and may last months to years. It is characterized by drastic improvements in glycemic control and reductions in insulin requirements, as seen in this patient. To prevent rapid return of glucose toxicity and to preserve the remaining beta cells as long as possible, insulin therapy should be continued during the "honeymoon phase" if possible without causing hypoglycemia. It is appropriate to decrease this patient's basal glargine insulin dose to improve his fasting hypoglycemia while also maintaining continuous insulin therapy. Given the symptomatic postprandial hypoglycemia he is experiencing on low doses of prandial insulin, it is appropriate to discontinue it at this time with close monitoring for postprandial hyperglycemia at the end of the "honeymoon phase."

Sole use of a sliding-scale insulin regimen is not recommended for glycemic control as it is reactionary in nature to elevated glucose values only. Using this strategy, it would be possible that the patient may not receive daily insulin during the "honeymoon phase," which would accelerate the risk of developing glucose toxicity again.

KEY POINT

- Continuing insulin, even at low doses, is recommended during the "honeymoon phase" of type 1 diabetes mellitus to reduce metabolic stress on functioning beta cells and preserve any residual function for as long as possible.

Bibliography

DeWitt DE, Hirsch IB. Outpatient insulin therapy in type 1 and type 2 diabetes mellitus: scientific review. JAMA. 2003;289:2254-64. [PMID: 12734137]

Item 37 Answer: A

Educational Objective: Manage postmenopausal osteoporosis in patients taking denosumab.

The most appropriate management for this patient is to continue denosumab. Denosumab, a monoclonal antibody against the receptor activator of nuclear factor κB ligand (RANKL), reduces bone resorption by inhibiting the development of osteoclasts. It circulates in the blood for up to 9 months after subcutaneous injection, but once cleared from the circulation, bone resorption transiently but dramatically increases, resulting in an abrupt decline in bone mineral density and, in some cases, vertebral fractures. Once initiated, there is no defined endpoint for cessation of denosumab therapy.

Although bone mineral density increases in response to denosumab therapy, it does not impact management with respect to dose and duration of treatment. Therefore, a DEXA scan is not necessary.

In the pharmacologic management of osteoporosis, drug holidays are considered during the course of bisphosphonate therapy. Due to their binding to bone tissue, bisphosphonates have durable effects on bone remodeling and fracture risk after discontinuation. After 5 years of treatment, patients at low risk for fracture can be considered for a bisphosphonate drug holiday. One study showed no cumulative difference in the risk for nonvertebral fractures in women continuing alendronate therapy for 5 versus 10 years. Post hoc analysis of this study showed that women with femoral neck T scores of −2.5 or worse and baseline prevalent vertebral fracture had reduced fracture risk by continuing alendronate therapy for 10 years versus stopping after 5 years compared with placebo.

Zoledronic acid is an intravenous bisphosphonate indicated for the treatment of osteoporosis especially in patients intolerant to oral bisphosphonates. Patients switched from zoledronic acid to denosumab experience further gains in bone mineral density suggesting additive benefit from this sequence of therapy. However, in patients receiving long-term denosumab, switching to zoledronic acid attenuated but did prevent loss of bone mineral density suggesting that denosumab therapy should be continued once initiated.

KEY POINT

- When administered subcutaneously twice yearly, denosumab suppresses bone resorption, increases bone density, and reduces the incidence of osteoporotic fractures in men and women; the effects of denosumab are not sustained when treatment is stopped.

Bibliography

Anastasilakis AD, Polyzos SA, Makras P, Aubry-Rozier B, Kaouri S, Lamy O. Clinical features of 24 patients with rebound-associated vertebral fractures after denosumab discontinuation: systematic review and additional cases. J Bone Miner Res. 2017;32:1291-1296. [PMID: 28240371] doi:10.1002/jbmr.3110

Item 38 Answer: C

Educational Objective: Manage type 1 diabetes mellitus in a hospitalized patient.

The most appropriate management of this patient's type 1 diabetes mellitus is to decrease basal insulin dose by 10% to 20% and add correction insulin regimen. This patient's fasting blood glucose values were already low on his home basal insulin doses, thus it is most appropriate to continue his basal insulin but at a reduced dose to avoid diabetic ketoacidosis and hypoglycemia. Correction insulin with basal insulin will treat hyperglycemia while he is fasting. Patients with type 1 diabetes must have continuous insulin therapy, particularly basal insulin, to avoid the development of DKA. Because of the requirement of continuous insulin, prolonged fasting in a patient with type 1 diabetes can be complicated by hypoglycemia. Proactive adjustments to insulin doses are required to avoid extreme fluctuations in glycemic control while in the fasting state.

This patient's fasting blood glucose value of 70 mg/dL (3.9 mmol/L) on the current basal insulin dose meets the American Diabetes Association's threshold value for downward titration of insulin doses to avoid hypoglycemia. The basal insulin dose should be decreased in addition to holding the prandial insulin in the fasting state. A sliding-scale insulin regimen should also be added to the basal insulin to help manage hyperglycemia that may occur while fasting.

Efficient glucose utilization is impaired when continuous insulin therapy, such as basal insulin, is held in type 1 diabetes. This may cause the development of diabetic ketoacidosis as a result of increased glycogenolysis and gluconeogenesis for fuel production. A sliding-scale insulin regimen alone is not physiologic and may cause large fluctuations in the blood glucose levels owing to the inherent reactive nature of its dosing, coupled with the near universal lag time between measurement of glucose and injection of insulin that occurs in most hospitals.

KEY POINT

- In fasting hospitalized patients with type 1 diabetes mellitus, the basal insulin dose should be decreased, the prandial insulin held to avoid hypoglycemia, and a correction insulin regimen should be added to help manage hyperglycemia.

Bibliography

Chiang JL, Kirkman MS, Laffel LM, Peters AL; Type 1 diabetes sourcebook authors. Type 1 diabetes through the life span: a position statement of the American Diabetes Association. Diabetes Care. 2014;37:2034-54. [PMID: 24935775] doi:10.2337/dc14-1140

Item 39 Answer: B

Educational Objective: Screen for adrenal hyperfunction in an incidentally noted adrenal mass.

The most appropriate next test to perform is a 24-hour urine total metanephrine measurement to screen for pheochromocytoma. Even though this patient does not have hypertension, she should be screened for pheochromocytoma, as these tumors may exist in the absence of typical symptoms or hypertension. Approximately 50% of pheochromocytomas are now first discovered as an incidental adrenal mass. An alternative screening test for pheochromocytoma is measuring the fractionated free plasma metanephrine level. This test has a false-positive rate of approximately 11%, and, therefore, may be considered more useful when suspicion for pheochromocytoma is high. This patient should also be screened for subclinical Cushing syndrome with a 1-mg overnight dexamethasone suppression test. The prevalence of incidentally noted adrenal masses increases with age and is estimated to be about 10% in the elderly. Most lesions are benign, nonfunctioning adenomas, and approximately 10% to 15% secrete excess hormones.

The 24-hour urine free cortisol test is not sensitive enough to diagnose subclinical autonomous cortisol secretion from an adrenal mass. The 24-hour urine free cortisol levels are usually within the normal range in subclinical Cushing syndrome.

The patient does not require screening for primary aldosteronism with a plasma aldosterone-plasma renin ratio (ARR) as she does not have hypertension. Only patients with an incidental adrenal mass and hypertension require screening for primary aldosteronism. Hypokalemia, traditionally thought to be a key feature of primary aldosteronism, is no longer a prerequisite for diagnosis because many patients with this disorder have normal potassium levels.

In women, rapid onset of hirsutism, menstrual irregularities, and virilization should raise suspicion for tumoral hyperandrogenism. Measurement of dehydroepiandrosterone sulfate (DHEAS) is not indicated in this patient, as she did not show signs of hyperandrogenism (hirsutism, deep voice, male pattern balding, clitoromegaly). Serum DHEAS may be measured if signs of significant hyperandrogenism are present in the setting of an adrenal mass that has radiologic features suspicious for malignancy (size >4 cm, heterogeneous enhancement with contrast administration, irregular margins, presence of calcifications or necrosis).

KEY POINT

- Biochemical testing for pheochromocytoma should be undertaken in all patients with an adrenal mass, even in the absence of typical symptoms or hypertension.

Bibliography

Fassnacht M, Arlt W, Bancos I, Dralle H, Newell-Price J, Sahdev A, et al. Management of adrenal incidentalomas: European Society of Endocrinology Clinical Practice Guideline in collaboration with the European Network for the Study of Adrenal Tumors. Eur J Endocrinol. 2016;175:G1-G34. [PMID: 27390021] doi:10.1530/EJE-16-0467

Item 40 Answer: C

Educational Objective: Manage a patient with severe primary hyperparathyroidism who is to undergo parathyroidectomy.

The most appropriate test to perform next for this patient is measurement of her 25-hydroxyvitamin D level. Vitamin D

H CONT.

deficiency is common in patients with primary hyperparathyroidism (HPT) due to increased conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D. Supplementation of vitamin D in patients with HPT has been shown to reduce parathyroid hormone levels, decrease bone turnover, and improve bone mineral density. Identifying and treating vitamin D deficiency perioperatively helps manage transient hypocalcemia, which routinely occurs after parathyroidectomy and especially in severe HPT where high bone turnover (as evidence by an elevated alkaline phosphatase) portends hungry bone syndrome.

Due to increased conversion, 1,25-dihydroxyvitamin D levels are frankly elevated in most instances of hyperparathyroidism and even in patients who are vitamin D deficient. It is not a useful test to identify and manage vitamin D deficiency in any circumstance and could be falsely reassuring in patients with HPT.

Given kidney excretion of calcium is the dominant mechanism by which hypercalcemia is corrected, urine calcium excretion can be assumed to be high in severe hypercalcemia with the exception of patients with severe acute kidney injury. Although guidelines suggest routine assessment of 24-hour urine calcium in the evaluation of HPT to exclude familial hypocalciuric hypercalcemia, the need for such screening primarily occurs when parathyroid hormone and calcium levels are mildly elevated. Additionally, a clinical diagnosis has already been established for this patient making 24-hour urine calcium measurement unnecessary.

Ionized calcium is the best test to assess the state of calcium homeostasis and is recommended by some experts when managing HPT. However, it is primarily of use when evaluating and managing hypocalcemia, especially when assumptions cannot be made regarding serum protein concentrations and blood pH.

KEY POINT

- In patients with primary hyperparathyroidism who are undergoing parathyroidectomy surgery, identifying and correcting vitamin D deficiency is important to avoid postoperative hypocalcemia, which occurs due to rapid flux of serum calcium into bone (hungry bone syndrome).

Bibliography

Kaderli RM, Riss P, Dunkler D, Pietschmann P, Selberherr A, Scheuba C, Niederle B. The impact of vitamin D status on hungry bone syndrome after surgery for primary hyperparathyroidism. Eur J Endocrinol. 2017 Sep 6. pii: EJE-17-0416. doi: 10.1530/EJE-17-0416. [Epub ahead of print] [PMID: 28877925]

Item 41 Answer: D

Educational Objective: Diagnose subclinical Cushing syndrome in a patient with an incidentally noted adrenal mass.

The most likely diagnosis in this patient with an incidentally discovered adrenal mass is subclinical Cushing syndrome. All patients with an incidental adrenal mass should be screened for subclinical Cushing syndrome (SCS), a condition characterized by adrenocorticotropic hormone (ACTH)-independent cortisol secretion that may result in metabolic (hyperglycemia and hypertension) and bone (osteoporosis) effects of hypercortisolism, but not the more specific features of Cushing syndrome (centripetal obesity, facial plethora, abnormal fat deposition in the supraclavicular or dorsocervical areas, and wide violaceous striae). The preferred diagnostic test for SCS is a 1-mg overnight dexamethasone suppression test, with a morning cortisol level greater than 5 µg/dL (138 nmol/L) considered positive. Following a positive result for SCS, measurement of ACTH, dehydroepiandrosterone sulfate (DHEAS), urine free cortisol, and an 8-mg overnight dexamethasone suppression test are often required to confirm autonomous cortisol secretion. If SCS is confirmed, the risks and benefits of surgery need to be considered. Surgery for SCS has been associated with improvements in bone density and glucose, lipid, and blood pressure control.

This patient's serum cortisol level did not suppress to less than 5 µg/dL (138 nmol/L) following dexamethasone administration. Under normal conditions, exposure to dexamethasone results in suppression of ACTH secretion and hence suppression of adrenal cortisol secretion. In the setting of autonomous cortisol secretion from an adrenal mass, cortisol suppression following dexamethasone administration would not occur, as tumor production of cortisol is not under normal physiologic feedback control.

The patient's plasma free metanephrine levels were within the normal range. This test has excellent sensitivity, and a normal result rules out pheochromocytoma.

Primary aldosteronism is also unlikely based on a calculated plasma aldosterone-plasma renin ratio (ARR) of less than 20. Her blood pressure medications, hydrochlorothiazide and doxazosin, have minimal or mild effects on the ARR, and therefore the result can be reliably interpreted.

KEY POINT

- Initial testing for subclinical Cushing syndrome is a 1-mg overnight dexamethasone suppression test; a cortisol level greater than 5 µg/dL (138 nmol/L) is considered a positive test.

Bibliography

Fassnacht M, Wiebke A, Bancos, Dralle H, Newell-Price J, Sahdev A, Tabarin A, Terzolo M, Tsagarakis S, Dekkers OM. Management of adrenal incidentalomas: European Society of Endocrinology Clinical Practice Guideline in collaboration with the European Network for the Study of Adrenal Tumors. Eur J Endocrinol. 2016;175(2):G1-G34. PMID: 27390021.

Item 42 Answer: B

Educational Objective: Screen for Cushing syndrome in a patient with an alternate sleep schedule.

This patient should be screened for Cushing syndrome, and the best screening test in this patient is measurement of 24-hour urine free cortisol to quantify total daily cortisol secretion. Biochemical testing is used to establish the diagnosis of Cushing syndrome. It is critical that the

biochemical diagnosis is firmly established prior to any imaging studies due to the relatively high prevalence of clinically insignificant pituitary and adrenal masses. Initial tests include the 1-mg overnight dexamethasone suppression test, 24-hour urine free cortisol, and late-night salivary cortisol. While the 1-mg overnight dexamethasone test and the late-night salivary cortisol test may be more convenient, they are likely to be less accurate in this patient because of her shift work and estrogen use. Measurement of 24-hour urine free cortisol is not impacted by estrogen therapy or sleeping patterns. A threefold or greater increase over normal values is diagnostic of Cushing syndrome if compatible clinical features are present (centripetal obesity, facial plethora, abnormal fat deposition in the supraclavicular or dorsocervical areas, and wide violaceous striae); if this increase is present, test results should be repeated to confirm the abnormal result.

The 1-mg overnight dexamethasone suppression test is also not reliable in this patient because it relies on serum cortisol measurement.

The late night salivary cortisol test is not a reliable screening test in this patient because she works a night shift and therefore her diurnal cortisol secretion will be reversed.

Measurement of morning serum cortisol is unreliable as a screening test for Cushing syndrome because normal secretion of cortisol is pulsatile and the normal range is broad. Hence, there is considerable overlap between serum cortisol levels seen in normal people, those with Cushing syndrome, and those with hypercortisolism due to psychological or medical stressors.

In addition, serum cortisol measurement is unreliable in this patient as she is on oral estrogen, which leads to an increase in cortisol binding proteins and subsequent elevation of serum total cortisol levels without impacting free cortisol levels.

KEY POINT

- The 24-hour urine free cortisol test for Cushing syndrome is not impacted by either estrogen therapy or sleeping patterns.

Bibliography

Loriaux DL. Diagnosis and differential diagnosis of Cushing's syndrome. N Engl J Med. 2017;376:1451-1459. doi: 10.1056/NEJMra1505550. [PMID:28402781]

Item 43 Answer: E

Educational Objective: Diagnose medication-induced male gynecomastia.

This patient most likely has spironolactone-induced gynecomastia. Gynecomastia occurs due to an imbalance between free estrogen and free androgen actions in breast tissue. Spironolactone is a known cause of gynecomastia. Spironolactone can increase the aromatization of testosterone to estradiol, decrease the testosterone production by the testes, and displace testosterone from sex hormone-binding globulin, thereby increasing its metabolic clearance rate. Additionally, spironolactone also acts as an antiandrogen by binding to androgen receptors and displacing binding of testosterone and dihydrotestosterone to their receptors. Other recognized drug-related causes of gynecomastia include marijuana, alcohol, 5α-reductase inhibitors, H_2 receptor antagonists, digoxin, ketoconazole, calcium channel blockers, ACE inhibitors, antiretroviral agents, tricyclic antidepressants, and selective serotonin reuptake inhibitors.

Breast cancers are typically unilateral and nontender with a discrete fixed mass displaced from the nipple-areolar complex, whereas gynecomastia presents as a rubbery, concentric, subareolar mass. Gynecomastia is typically bilateral and often associated with breast tenderness.

Germ cell tumors account for 95% of testicular neoplasms with 6% of patients presenting with gynecomastia at time of diagnosis. The temporal association of gynecomastia with the initiation of a medication known to cause gynecomastia and a normal testicular examination makes germ cell tumor a much less likely diagnosis.

Hypogonadism, primary more so than secondary, is associated with gynecomastia due to an increase in estradiol relative to testosterone secretion. With primary hypogonadism, a rise in luteinizing hormone results in increased aromatization of testosterone to estradiol; this elevated luteinizing hormone is absent in secondary hypogonadism thus making gynecomastia a less prominent sign. This patient has unchanged sexual functioning, morning erections, and no evidence of testicular atrophy making hypogonadism an unlikely diagnosis.

Pseudogynecomastia is often seen in obese men. It occurs due to an increase in breast fat without any proliferation of glandular tissue. Gynecomastia and pseudogynecomastia are differentiated by examination. Pseudogynecomastia is characterized by the presence of subareolar adipose tissue, without glandular proliferation. True gynecomastia typically distorts the normally flat contour of the male nipple, causing it to protrude owing to the mass of glandular tissue beneath it. In pseudogynecomastia, the nipple is typically still flat but soft, and nondescript subcutaneous fat tissue is present in the breast area.

KEY POINT

- Gynecomastia can be an adverse effect of medications; spironolactone causes an imbalance between free estrogen and free androgen resulting in glandular breast tissue enlargement.

Bibliography

Dickson G. Gynecomastia. Am Fam Physician. 2012;85:716-22. [PMID: 22534349]

Item 44 Answer: A

Educational Objective: Diagnose celiac disease as a cause of thyroxine malabsorption.

The most likely diagnosis is celiac disease. The patient had been taking the same dose of levothyroxine for many years,

but recently has required increasing doses to maintain euthyroidism. Despite his levothyroxine dose being increased, his serum thyroid-stimulating hormone (TSH) level remains elevated, his free thyroxine (T_4) is at the lower limit of the normal reference range, and he continues to have symptoms of thyroid hormone deficiency. Rising levothyroxine requirements in the absence of obvious medication noncompliance or inappropriate administration should alert the treating physician about possible malabsorption. Since levothyroxine is principally absorbed in the jejunum and ileum, any disease process affecting the small bowel can affect the fraction of an orally administered dose that is absorbed. The patient reports diarrhea, abdominal pain, and weight loss, and a rash that is characteristic of dermatitis herpetiformis, a finding that is unique to celiac disease. Patients with celiac disease frequently experience malabsorption of medications, vitamins, and other nutrients.

Medication noncompliance is a less likely explanation for this patient's escalating levothyroxine requirements given his prior history of being easily maintained on a stable dose of levothyroxine and self-reported adherence to his prescribed regimen. Medication noncompliance would not explain his associated symptoms of abdominal cramping, skin rash, and unintentional weight loss.

Autoimmune primary adrenal insufficiency occurs more commonly in patients with other autoimmune disorders, and this patient does report gastrointestinal symptoms and weight loss; however, he does not demonstrate hyperpigmentation or hypotension. Moreover, adrenal insufficiency would not provide an explanation for his rising levothyroxine dose requirements or skin rash.

Thyroid hormone resistance is also unlikely. The patient would not be expected to have had normal thyroid function test results previously, and his free T_4 would be elevated.

KEY POINT

- Malabsorptive disorders may decrease levothyroxine absorption resulting in higher than expected levothyroxine dose requirements.

Bibliography

Centanni M, Benvenga S, Sachmechi I. Diagnosis and management of treatment-refractory hypothyroidism: an expert consensus report. J Endocrinol Invest. 2017 Jul 10. doi: 10.1007/s40618-017-0706-y. [Epub ahead of print] [PMID: 28695483]

Item 45 Answer: B

Educational Objective: Manage infertility.

When evaluating infertility, both female and male factors should be considered concurrently. Thus, semen analysis is part of the initial diagnostic evaluation. Collection should occur after 2 to 3 days of sexual abstinence, but no longer to avoid decreased sperm motility. If semen analysis is abnormal, it should be repeated at least 2 weeks later, and if results are abnormal, referral to a reproductive endocrinologist is recommended.

Given that this patient has regular menses every 28 days with molimina symptoms (breast pain and bloating), her cycles appear to be ovulatory. Thus, laboratory assessment of ovulatory function is not needed at this time. In patients who do not have normal menstrual cycles with ovulation, laboratory assessment should be performed. A midluteal phase serum progesterone level, obtained approximately 1 week before the expected menses, is an effective way to assess ovulatory status. A progesterone level above 3 ng/mL (9.5 nmol/L) is evidence of recent ovulation. Measurement of serum thyroid stimulating hormone and prolactin levels is appropriate to exclude thyroid disease and hyperprolactinemia as causes of oligo-ovulation.

In women over the age of 35 years, an infertility evaluation is initiated after 6 months of unprotected intercourse; in women under the age of 35, an infertility evaluation is initiated after 1 year of regular unprotected intercourse. Recommending an additional 5 months of unprotected intercourse is unnecessary for this 37-year-old woman.

Laparoscopy for evaluation of pelvic adhesions or mild endometriosis may be warranted in patients with dysmenorrhea, history of sexually transmitted infections, or previous pelvic surgery. While assessment of tubal patency may be indicated in this patient given her prior history of appendicitis and abdominal surgery (putting her at risk for adhesions), laparoscopy is not indicated at this immediate time prior to moving forward with an initial noninvasive diagnostic evaluation.

KEY POINT

- When evaluating infertility, both female and male factors should be considered concurrently; semen analysis is part of the initial diagnostic evaluation.

Bibliography

Marshburn PB. Counseling and diagnostic evaluation for the infertile couple. Obstet Gynecol Clin North Am. 2015;42:1-14. [PMID: 25681836] doi:10.1016/j.ogc.2014.10.001

Item 46 Answer: B

Educational Objective: Recognize the effect of opioids on pituitary function.

This patient's opioid use is most likely responsible for his sexual dysfunction. Secondary hypogonadism is typically a result of insufficient gonadotropin-releasing hormone production by the hypothalamus or deficient luteinizing hormone (LH)/follicle-stimulating hormone (FSH) secretion by the anterior pituitary. This patient has symptoms of hypogonadism and a low testosterone level. Low or inappropriately normal FSH and LH levels in the presence of simultaneous low testosterone levels are diagnostic of secondary hypogonadism (hypogonadotropic hypogonadism). Untreated sleep apnea, exogenous testosterone administration, and obesity are common causes of secondary hypogonadism. Other acquired causes include hyperprolactinemia, chronic opioid use, glucocorticoid use, or infiltrative disease (lymphoma or

hemochromatosis). Chronic opioid therapy is a well-established cause of hypogonadotropic hypogonadism. The mechanism of opioid-induced hypogonadism is thought to be central hypogonadism, with downregulation of gonadotropin-releasing hormone and subsequently LH and FSH. This, in turn, results in decreased testosterone production.

This patient's decline in gonadal function is not a result of his age. Although testosterone levels may decline with age, this patient's testosterone level of 185 ng/dL (6.4 nmol/L) is well below the normal range and below what would be expected for age-related decline in testosterone.

Although a pituitary tumor isn't completely ruled out without an MRI, the most likely cause of this patient's hypogonadism is the chronic opioid therapy. Testosterone levels greater than 150 ng/dL (5.2 nmol/L) are less likely to be related to a pituitary tumor. Patients with hypogonadotropic hypogonadism and testosterone levels less than 150 ng/dL (5.2 nmol/L) should have an MRI to evaluate for a pituitary tumor. The normal TSH and prolactin levels also argue against a pituitary or hypothalamic tumor.

In primary gonadal failure, there would be elevated FSH and LH levels with a low testosterone level. A low testosterone level with inappropriately normal or low FSH and LH levels is consistent with hypogonadotropic hypogonadism.

KEY POINT

- Chronic opioid use suppresses gonadotroph function, resulting in hypogonadotropic hypogonadism, which is increasingly recognized as a cause of secondary hypogonadism.

Bibliography

O'Rourke TK Jr, Wosnitzer MS. Opioid-induced androgen deficiency (opiad): diagnosis, management, and literature review. Curr Urol Rep. 2016;17:76. [PMID: 27586511] doi:10.1007/s11934-016-0634-y.

Item 47 Answer: C

Educational Objective: Diagnose Turner syndrome.

The most common cause of primary amenorrhea is gonadal dysgenesis caused by chromosomal abnormalities, most commonly those associated with Turner syndrome (TS). TS is caused by loss of part or all of an X chromosome (45,XO) occurring in 1 in 2500 live female births. In some studies, more than 20% of patients are diagnosed after 12 years of age; primary amenorrhea may be the presenting sign. The most consistent physical finding is short stature, as seen in this patient. Other findings may include neck webbing, hearing loss, aortic coarctation, and bicuspid aortic valve. Primary amenorrhea is seen in approximately 90% of women with TS. TS should be considered in women with primary or secondary amenorrhea, particularly those of short stature. Diagnosis is made by karyotype analysis.

Functional hypothalamic amenorrhea is caused by a functional disruption of the hypothalamic-pituitary-ovarian axis in which no anatomic or organic disease is identified. Disruption of the pulsatile release of hypothalamic gonadotropin-releasing hormone may occur due to stress, weight loss, or exercise; follicle-stimulating hormone (FSH) levels are not elevated in functional hypothalamic amenorrhea.

Primary ovarian insufficiency is considered when a woman younger than 40 years of age develops secondary amenorrhea with two serum FSH levels in the menopausal range (>35 mU/mL [35 U/L]). This condition impacts 1 in 100 women by the age of 40 years. If during the evaluation of secondary amenorrhea, an elevated FSH is found, it should be repeated in 1 month, along with a serum estradiol measurement. In young women, karyotype analysis is also indicated to rule out Turner syndrome.

Vaginal agenesis is the second most common cause of primary amenorrhea with an incidence of 1 in 5000. Vaginal agenesis is characterized by congenital absence of the vagina with variable uterine development. These women have a normal female karyotype and ovarian function, thus develop normal secondary sexual characteristics. Presentation is typically after age 15 years due to primary amenorrhea. Examination reveals normal external genitalia with a dimple or small pouch replacing the vagina. On laboratory testing, gonadotropins are unremarkable. This patient's normal pelvic examination eliminates this vaginal agenesis as a cause of primary amenorrhea.

KEY POINT

- The most common cause of primary amenorrhea is gonadal dysgenesis, most commonly associated with Turner syndrome (45,XO).

Bibliography

Pinsker JE. Clinical review: Turner syndrome: updating the paradigm of clinical care. J Clin Endocrinol Metab. 2012;97:E994-1003. [PMID: 22472565] doi:10.1210/jc.2012-1245

Item 48 Answer: B

Educational Objective: Evaluate postprandial hypoglycemia in a patient without diabetes.

The most appropriate diagnostic test to perform next is mixed-meal testing. Hypoglycemia in persons without diabetes is extremely rare and requires additional investigation. Causes of hypoglycemia in adults without diabetes include drug or alcohol use, critical illness, hormonal deficiency, non-islet cell tumor, endogenous hyperinsulinism, accidental or intentional hypoglycemia, and prior Roux-en-Y gastric bypass surgery. Postprandial hypoglycemia can develop 2 to 3 years after Roux-en-Y gastric bypass surgery. The patient either denies or does not have clinical evidence for the presence of many of these causes. The timing of the hypoglycemia can guide the appropriate next diagnostic test.

This patient is experiencing postprandial symptoms consistent with an increase in sympathetic activity within 5 hours of a meal. He meets two out of three criteria for a hypoglycemic disorder as defined by the Whipple triad: symptoms that can be attributed to hypoglycemia and resolution of symptoms with food consumption. He does not

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have documented hypoglycemia at the time of symptoms from a reliable laboratory method to meet the third criteria of the Whipple triad. Point-of-care fingerstick measurements lack precision to confirm hypoglycemia. An attempt should be made to recreate the scenario that is likely to cause the symptoms. Since his symptoms occur in the postprandial state, a mixed-meal test should be performed. The mixed-meal consists of food types that have induced the onset of symptoms in the past. The patient should have the following hypoglycemic laboratory tests measured at baseline and every 30 minutes for 5 hours after consuming the mixed-meal: plasma glucose, insulin, C-peptide, β-hydroxybutyrate (low in the presence of insulin), and proinsulin. He should also repeat these tests at the time of symptomatic hypoglycemia (<60 mg/dL [3.3 mmol/L]) before administering carbohydrates. If symptomatic hypoglycemia is documented during the mixed-meal testing, the patient should also be screened for insulin secretagogues (sulfonylureas and meglitinides) and insulin antibodies.

A 72-hour fast involves prolonged fasting while measuring the hypoglycemic laboratory test (plasma glucose, insulin, C-peptide, β-hydroxybutyrate, and proinsulin) every 6 hours, followed by every 1 to 2 hours once the glucose is less than 60 mg/dL (3.3 mmol/L) or the patient becomes symptomatic. Given that the patient is experiencing postprandial symptoms, the 72-hour fast would likely not induce hypoglycemia.

An oral glucose tolerance test (OGTT) consists of liquid caloric consumption that is usually not similar to the type of food that induces symptomatic postprandial hypoglycemia. The OGTT can produce unreliable results, particularly in those patients with altered gastric anatomy or gastric motility.

Pancreatic imaging should only occur after biochemical confirmation of endogenous hyperinsulinism.

KEY POINT

- A mixed-meal test consisting of the types of food that normally induce the hypoglycemia should be performed to determine the cause of postprandial hypoglycemia.

Bibliography

Cryer PE, Axelrod L, Grossman AB, Heller SR, Montori VM, Seaquist ER, et al; Endocrine Society. Evaluation and management of adult hypoglycemic disorders: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2009;94:709-28. [PMID: 19088155] doi:10.1210/jc.2008-1410

H

Item 49 Answer: A

Educational Objective: Treat secondary adrenal insufficiency.

This patient has secondary adrenal insufficiency, and hydrocortisone is the most appropriate treatment. Oral, injectable (including joint injections), and occasionally even topical glucocorticoids are able to suppress adrenocorticotropic hormone (ACTH) secretion. Glucocorticoids prescribed at doses above physiologic replacement for longer than 3 weeks should be tapered when discontinued allowing recovery of the pituitary-adrenal axis; if therapy has lasted less than 3 weeks, no taper is required for pituitary-adrenal axis recovery. The diagnosis of adrenal insufficiency is based on demonstrating inappropriately low serum cortisol levels. Because most assays measure total cortisol, abnormalities in cortisol-binding protein or albumin can trigger spurious results. An early morning (8 AM) serum cortisol of less than 3 µg/dL (82.8 nmol/L) is consistent with cortisol deficiency, whereas values greater than 15 to 18 µg/dL (414.0-496.8 nmol/L) exclude the diagnosis when binding protein abnormalities and synthetic glucocorticoid exposure are excluded.

Fludrocortisone in addition to hydrocortisone is unwarranted as fludrocortisone is needed only in primary adrenal insufficiency. There is no mineralocorticoid deficiency in secondary adrenal insufficiency.

An ACTH stimulation test is not necessary in this patient since the cortisol level less than 3 µg/dL (82.8 nmol/L) is diagnostic of adrenal insufficiency. If an ACTH stimulation test were necessary, dexamethasone can be given prior to the ACTH stimulation test since dexamethasone is not measureable in the cortisol assay. That is unnecessary given this patient's cortisol level.

KEY POINT

- Oral, injectable (including joint injections), and even topical glucocorticoids are able to suppress adrenocorticotropic hormone (ACTH) secretion and result in secondary adrenal insufficiency.

Bibliography

Pazderska A, Pearce SH. Adrenal insufficiency - recognition and management. Clin Med (Lond). 2017;17:258-262. doi: 0.7861/clinmedicine.17-3-258. [PMID: 28572228]

Item 50 Answer: C

Educational Objective: Treat hypothyroidism with weight-based dosing of levothyroxine.

This patient has hypothyroidism, and the most appropriate treatment is to prescribe a weight-based replacement dose of levothyroxine (1.6 µg/kg lean body weight). For patients with high body mass index values, an estimate of lean mass should be determined. Levothyroxine is the treatment of choice for thyroid hormone deficiency. Goals of therapy are to resolve signs and symptoms of hypothyroidism, normalize serum thyroid-stimulating hormone (TSH), and avoid overtreatment.

Although some patients express a preference for treatment with desiccated thyroid hormone (thyroid extract), there are potential safety concerns and lack of data on long-term outcomes. The physiologic ratio of thyroxine (T_4) to triiodothyronine (T_3) secreted by the human thyroid is approximately 15:1, whereas desiccated thyroid hormone, as originally derived from animal thyroid glands, contains supraphysiologic T_3 (T_4 to T_3 ratio 4:1). Patients taking desiccated thyroid hormone frequently experience low serum T_4

and supraphysiologic T_3 levels despite having a serum TSH within the reference range.

Although a full replacement dose of levothyroxine can be administered to most patients with overt hypothyroidism, older adults (age 65 years and older) and patients with cardiovascular disease should be prescribed a lower initial dose (25-50 µg/day) due to the effects of thyroid hormone on myocardial oxygen demand. The dose should be titrated based on TSH levels measured 6 to 8 weeks after any dose change. The patient described here is an otherwise healthy woman in her fifth decade of life. Prescribing a low initial dose of levothyroxine would unnecessarily delay correction of hypothyroidism.

Not prescribing treatment is also inappropriate. Although the patient does not currently report symptoms of thyroid hormone deficiency, she has overt hypothyroidism with physical findings consistent with this diagnosis (slowed reflexes) and evidence of metabolic complications (hypercholesterolemia). Hypothyroidism causes hypercholesterolemia through reduced cholesterol metabolism and contributes to the development cardiovascular disease. Treatment of patients with overt hypothyroidism and all nonpregnant adults with subclinical hypothyroidism and a serum TSH level above 10 µU/mL (10 mU/L) is indicated to ameliorate the risk of these complications.

KEY POINT

- Levothyroxine is the treatment of choice for thyroid hormone deficiency; for most younger adults without cardiac disease, a weight-based replacement dose of levothyroxine (1.6 µg/kg lean body weight) is recommended.

Bibliography

Hennessey JV. The emergence of levothyroxine as a treatment for hypothyroidism. Endocrine. 2017;55:6-18. [PMID: 27981511] doi:10.1007/s12020-016-1199-8

Item 51 Answer: A

Educational Objective: Diagnose the cause of Cushing syndrome.

The most appropriate diagnostic test for this patient is measurement of the adrenocorticotropic hormone (ACTH) level. Cushing disease is the term used to indicate excess cortisol production due to an ACTH-secreting pituitary adenoma. Cushing syndrome refers to hypercortisolism from any cause, exogenous or endogenous, ACTH-dependent or not. The most common cause of endogenous Cushing syndrome is Cushing disease. The initial step in evaluation for Cushing disease is to seek biochemical evidence of hypercortisolism. At least two first-line tests should be diagnostically abnormal before the diagnosis is confirmed. Initial tests include the overnight low-dose dexamethasone suppression test, 24-hour urine free cortisol, and late-night salivary cortisol. The 24-hour urine free cortisol and late night salivary cortisol tests should be performed at least twice to ensure reproducibility of results.

The abnormal dexamethasone suppression test and elevated urine free cortisol levels establish the diagnosis of Cushing syndrome in this patient. An ACTH measurement should be obtained once the diagnosis of Cushing syndrome is established to determine if it is ACTH dependent or ACTH independent.

Once ACTH-dependent Cushing syndrome is confirmed biochemically, a pituitary MRI should be obtained. If no pituitary tumor or a tumor less than 6 mm is visualized on MRI, an 8-mg dexamethasone suppression test is used to differentiate Cushing disease from an ectopic source of ACTH. Dexamethasone is administered at 11 PM, and cortisol is tested at 8 AM. A pituitary source of ACTH will respond to negative feedback from high doses of dexamethasone, suppressing plasma cortisol at 8 AM by more than 50%, whereas an ectopic source of ACTH will not have suppressible cortisol. However, this test has low sensitivity (88%) and specificity (57%) for Cushing disease, so inferior petrosal sinus sampling (IPSS) is often recommended before exploratory pituitary surgery. In IPSS, ACTH levels in the petrosal sinus are compared with those in the periphery after the administration of corticotropin-releasing hormone (CRH). A central to peripheral gradient greater than 2.0 before CRH or greater than 3.0 after CRH is diagnostic of Cushing disease.

An 8-mg dexamethasone suppression test, inferior petrosal sinus sampling, and pituitary MRI should follow, if necessary, ACTH testing. Their inclusion in the diagnostic algorithm at this point is premature and possibly unnecessary.

KEY POINT

- An adrenocorticotropic hormone (ACTH) measurement should be obtained once the diagnosis of Cushing syndrome is established to determine if it is ACTH dependent or ACTH independent.

Bibliography

Loriaux DL. Diagnosis and differential diagnosis of Cushing's syndrome. N Engl J Med. 2017;376:1451-1459. doi: 10.1056/NEJMra1505550. [PMID:28402781]

Item 52 Answer: D

Educational Objective: Diagnose testosterone-induced change in thyroxine-binding globulin.

The most likely explanation for the observed change in this patient's thyroid function test results is the initiation of testosterone. The administration of androgens and anabolic steroids leads to a reduction in thyroxine-binding globulin, which consequently increases the proportion of metabolically active free thyroxine that is available. Consequently, a reduction in levothyroxine dosing may be needed to prevent iatrogenic thyrotoxicosis. Conversely, higher levothyroxine doses are often required after the initiation of estrogen or selective estrogen receptor modulating therapies (tamoxifen and raloxifene) due to an increase in serum thyroxine-binding globulin concentrations.

Administering levothyroxine with coffee or calcium carbonate and treatment with omeprazole all decrease the absorption of thyroxine, resulting in reduced levels of free thyroxine (T_4) and elevated levels of thyroid-stimulating hormone. Calcium carbonate reduces the maximum absorption of levothyroxine by 25%. Because calcium and ferrous sulfate can bind levothyroxine, the ingestion of either medication, even as a component of a multivitamin, should be separated from levothyroxine by 4 hours. Administering levothyroxine with coffee, whether caffeinated or not, has been shown to reduce the absorption of levothyroxine. Ideally, levothyroxine should be taken 60 minutes before food or coffee is consumed. Oral levothyroxine is absorbed in the jejunum and ileum. The absorption of an orally administered dose is 70% to 80% under optimum fasting conditions, and an acidic gastric pH is important. Chronic therapy with omeprazole and other proton pump inhibitors impairs levothyroxine absorption by increasing gastric pH.

KEY POINT

- In patients receiving thyroxine replacement therapy, initiation of estrogen or raloxifene increases thyroxine-binding globulin levels whereas testosterone reduces thyroxine-binding globulin levels; in either situation a change in thyroxine dosage may be required.

Bibliography

Tahboub R, Arafah BM. Sex steroids and the thyroid. Best Pract Res Clin Endocrinol Metab. 2009 Dec;23(6):769-80. doi: 10.1016/j.beem.2009.06.005. [PMID: 19942152]

Item 53 Answer: A

Educational Objective: Treat postmenopausal osteoporosis.

The most appropriate treatment for this patient is alendronate. The American College of Physicians (ACP) recommends that clinicians offer pharmacologic treatment with alendronate, risedronate, zoledronic acid, or denosumab to reduce the risk for hip and vertebral fractures in women who have known osteoporosis. Individual patient factors and cost help decide which agent is initially used. Bisphosphonates are the most commonly prescribed first-line therapy as they have been shown to reduce the risk of fractures in large, randomized, placebo-controlled trials, and are generally well tolerated with low risk for serious adverse effects.

Although calcitonin increases spine bone mineral density in clinical trials, its anti-fracture efficacy is inconsistent at the spine. The availability of intravenous bisphosphonates and denosumab negates the argument for calcitonin in patients who cannot tolerate oral osteoporosis medications.

Denosumab is effective for prevention of vertebral fracture in postmenopausal women, yet it is expensive and, once started, should be continued indefinitely. Even if followed by intravenous bisphosphonate therapy, discontinuation results in loss of bone mineral density and has been associated with an increased risk of vertebral fracture. Denosumab may be used safely in the setting of compromised kidney function (KDIGO stage G3b and G4). It may also be preferred in patients with poor adherence or tolerance of oral bisphosphonates.

Raloxifene is approved in postmenopausal women for the prevention and treatment of osteoporosis and the prevention of invasive breast cancer in those at high risk. However, raloxifene is contraindicated in those at increased risk of venous thromboembolism. ACP recommends against raloxifene for the treatment of osteoporosis in women.

Teriparatide and abaloparatide are anabolic therapies that reduce the risk of vertebral fracture in postmenopausal osteoporosis. Each increases bone mass and strength of the spine more than antiresorptive drugs and may be preferred if spine bone mineral density is severely low (T-score ≤ −3.5), in patients who fail bisphosphonate therapy, and in glucocorticoid-induced osteoporosis. Neither drug should be prescribed for patients who are at increased risk for osteosarcoma including those with a history of radiation therapy.

KEY POINT

- Alendronate, risedronate, zoledronic acid, and denosumab have been shown to reduce the risk for spine, hip, and nonvertebral fractures, and are generally well tolerated with low risk for serious adverse effects.

Bibliography

Qaseem A, Forciea MA, McLean RM, Denberg TD; Clinical Guidelines Committee of the American College of Physicians. Treatment of low bone density or osteoporosis to prevent fractures in men and women: A Clinical Practice Guideline Update From the American College of Physicians. Ann Intern Med. 2017;166:818-839. [PMID: 28492856] doi:10.7326/M15-1361

Item 54 Answer: C

Educational Objective: Manage medication-related hypoglycemia.

The most appropriate management of hypoglycemia for this patient is to stop glyburide therapy. Hypoglycemia can become a rate-limiting step in achieving glycemic goals for many persons. Clinicians should consider de-intensifying pharmacologic therapy in patients with type 2 diabetes who achieve hemoglobin A_{1c} levels less than 6.5%; furthermore, benefits of targeting a specific hemoglobin A_{1c} target level in patients with a life expectancy less than 10 years due to advanced age should be considered carefully because the harms outweigh the benefits in this population. Therapies must be adjusted to eliminate hypoglycemia, and glycemic goals should be individualized to accommodate targets that can be safely achieved. Several factors contribute to hypoglycemia including a mismatch of food consumption and insulin delivery, increased physical exertion, weight loss, worsening kidney impairment, abnormalities in gastrointestinal motility and absorption, and accidental/intentional overdose of insulin or other hypoglycemic agents such as sulfonylureas. Older adults are also at an increased risk for hypoglycemia. Sulfonylureas stimulate insulin secretion regardless of glycemic

status. Thus, they pose risk for hypoglycemia, especially in drugs with long half-lives, such as glyburide, or in older persons. In light of this patient's age, kidney impairment, and frequency of hypoglycemia, glyburide should be stopped.

Immediate carbohydrate intake is the appropriate management of hypoglycemia in the alert individual; consumption of 15 grams of a fast-acting carbohydrate followed by a self-monitored blood glucose measurement 15 minutes later with repeat treatment if glucose is not improved. In this obese male, increased carbohydrate intake is not the appropriate way to manage this situation on a long-term basis as it can lead to further weight gain and increased insulin resistance.

If this patient was to remain on therapy that can induce hypoglycemia, glucagon should be prescribed. Glucagon should be provided to patients at risk for developing hypoglycemia and used intramuscularly by close contacts if the individual is not able to safely consume carbohydrates to correct hypoglycemia.

Metformin is the recommended first-line oral agent for type 2 diabetes due to known effectiveness and decreased hypoglycemia risk. Although this patient has a degree of kidney impairment, it is not such that metformin needs to be discontinued. After consideration of the risk and benefits, cautious continuation of metformin in kidney impairment may occur with an estimated glomerular filtration rate (eGFR) between 30 and 45 mL/min/1.73 m^2. Metformin should be discontinued if the eGFR falls below 30 mL/min/1.73 m^2.

KEY POINT

- Sulfonylureas stimulate insulin secretion, and they pose risk for hypoglycemia, especially drugs with long half-lives, such as glyburide, or in older persons.

Bibliography

Qaseem A, Wilt TJ, Kansagara D, Horwitch C, Barry MJ, Forciea MA, et al. Hemoglobin A_{1c} targets for glycemic control with pharmacologic therapy for nonpregnant adults with type 2 diabetes mellitus: a guidance statement update from tthe American College of Physicians. Ann Intern Med. [Epub ahead of print 6 March 2018]:. doi: 10.7326/M17-0939

Item 55 Answer: D

Educational Objective: Recognize medications that interfere with screening for primary aldosteronism.

Spironolactone can significantly interfere with interpretation of the plasma aldosterone-plasma renin ratio (ARR) and therefore should be discontinued approximately 6 weeks prior to screening for primary aldosteronism. Treatment-resistant hypertension is defined as blood pressure that remains above goal despite concurrent use of three antihypertensive agents of different classes, one of which is a diuretic. Possible situations in which screening for secondary causes of hypertension include: severe or resistant hypertension; young age of onset (in childhood or adolescence), especially in the absence of family history; abrupt worsening of blood pressure in a previously well-controlled patient; or clinical features of an underlying disorder associated with hypertension (for example, cushingoid features). Hyperaldosteronism, usually from an aldosterone-producing adenoma or bilateral idiopathic hyperaldosteronism, may be present in up to 10% of patients with hypertension. Testing for primary aldosteronism should be considered in all patients with difficult to control hypertension. It should also be performed in patients with hypertension and an incidentally noted adrenal mass or spontaneous or diuretic-induced hypokalemia. Spironolactone and eplerenone cause elevation of renin levels and hence can result in a false-negative ARR. On stopping a mineralocorticoid antagonist, the patient may develop hypokalemia if the underlying diagnosis is primary aldosteronism. Potassium should be replaced accordingly prior to screening for primary aldosteronism, as hypokalemia results in lowering of aldosterone levels and hence impacts the ARR.

In general, most antihypertensive agents can be continued during screening for primary aldosteronism except for spironolactone, eplerenone, and high-dose amiloride therapy. Specifically, verapamil, doxazosin, and hydralazine have minimal impact on the ARR and, therefore, can be continued during screening for primary aldosteronism.

Other antihypertensive agents that have minor effects on the ARR can also be continued during screening for primary aldosteronism as long as the results of the ARR are interpreted with these effects in mind. The hallmark of primary aldosteronism is a suppressed renin level. Any medication that increases renin can result in a false-negative result. On the other hand, a suppressed renin in the presence of a medication that usually would raise renin (an ACE inhibitor) raises the suspicion for primary aldosteronism.

KEY POINT

- Spironolactone and eplerenone can significantly interfere with interpretation of the plasma aldosterone-plasma renin ratio (ARR) and therefore should be discontinued approximately 6 weeks prior to screening for primary aldosteronism.

Bibliography

Funder JW, Carey RM, Mantero F, Murad MH, Reincke M, Shibata H, et al. The management of primary aldosteronism: case detection, diagnosis, and treatment: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2016;101:1889-916. [PMID: 26934393] doi:10.1210/jc.2015-4061

Item 56 Answer: C

Educational Objective: Manage type 2 diabetes mellitus by individualizing glycemic targets.

This patient is an older adult with a complex/intermediate medical history. The American Diabetes Association (ADA) defines complex/intermediate medical history as the presence of at least three coexisting chronic illnesses serious enough to require medications or lifestyle management and may include arthritis, cancer, heart failure, depression, emphysema, falls, hypertension, incontinence, stage 3 or worse chronic kidney disease, myocardial infarction, and stroke. These patients are

expected to have "intermediate life-expectancy," high treatment burden, hypoglycemia vulnerability, and fall risk. The ADA's recommended hemoglobin A_{1c} goal for a patient with similar characteristics and health status is 7.5% to 8%, if this can be achieved without significant hypoglycemia. Tighter glycemic control in this scenario would likely require an escalation in treatment burden with a subsequent increase in risks that may outweigh any potential long-term benefits. Additionally, the patient's reduced kidney function increases his hypoglycemia risk with more intense glycemic goals. The American College of Physicians (ACP) recommends that clinicians avoid targeting an hemoglobin A_{1c} level in patients with a life expectancy less than 10 years due to advanced age (80 years or older), residence in a nursing home, or chronic conditions (such as dementia, cancer, end stage kidney disease, severe chronic obstructive pulmonary disease, or heart failure) because the harms outweigh the benefits in this population.

Intensive glycemic control early in the disease course in patients with type 2 diabetes may decrease the incidence of long-term cardiovascular events, as suggested from the 10-year follow-up from the UK Prospective Diabetes Study (UKPDS). Similar reductions in cardiovascular disease did not occur when tight glycemic control was applied to older adults with long-standing type 2 diabetes with prior cardiovascular events or cardiovascular risk factors in three landmark studies: Action to Control Cardiovascular Risk on Diabetes (ACCORD), Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE), and Veterans Affairs Diabetes Trial (VADT). In addition, subjects in the intensive treatment arms had increased rates of hypoglycemia in all three studies and a higher rate of death in the ACCORD trial.

In an older healthy adult with little comorbidity, intact cognitive and functional status, the ADA recommends a hemoglobin A_{1c} goal of less than 7.5% given the expected longer life expectancy for that person. This patient does not meet these criteria. In contrast, the ACP recommends hemoglobin A_{1c} level between 7% and 8% in most patients with type 2 diabetes based on lack of mortality benefit for death or macrovascular events over 5 to 10 years and risk in substantial harms.

In patients with complex or poor health, a hemoglobin A_{1c} level less than 8.5% is recommended by the ADA, if it can be achieved without significant hypoglycemia. The ADA defines very complex or poor health requiring residence in a long-term care facility or end-stage chronic illnesses (stage 3-4 heart failure, oxygen-dependent lung disease, chronic kidney disease requiring dialysis, or uncontrolled metastatic cancer), moderate to severe cognitive impairment, or two or more activity of daily living dependencies.

Hemoglobin A_{1c} targets greater than 8.5% are generally not recommended due to an increased risk for hyperglycemia-related complications, such as dehydration from glycosuria, infections, and hyperglycemic hyperosmolar syndrome.

KEY POINT

- A hemoglobin A_{1c} goal of 7.5% to 8% is recommended for older adults with complex medical history and significant comorbidities.

Bibliography

American Diabetes Association. 11. Older adults: Standards of Medical Care in Diabetes-2018. Diabetes Care. 2018;41(Suppl 1):S119-S125. doi:10.2337/dc18-S011. [PMID: 29222382]

Item 57 Answer: A

Educational Objective: Diagnose ipilimumab-induced hypophysitis.

In this patient, the most likely cause of pituitary enlargement and evidence of hypopituitarism is drug-induced hypophysitis. Ipilimumab is a checkpoint inhibitor that has been repeatedly associated with the development of hypophysitis in up to 17% of treated patients. Most patients present with the combination of headache, pituitary enlargement, and hypopituitarism occurring during the early phase of therapy, typically within 10 weeks. While the pituitary enlargement often resolves spontaneously, the panhypopituitarism appears to be permanent.

Lymphocytic hypophysitis is an autoimmune disease most commonly occurring in women during pregnancy and postpartum. It leads to pituitary enlargement, possible mass effect, and often deficiency of adrenocorticotropic hormone (ACTH). While the imaging and laboratory characteristics described could be consistent with lymphocytic hypophysitis, the patient's exposure to a drug known to cause hypophysitis and other aspects of the clinical history are not consistent with this diagnosis.

A pituitary adenoma is less likely given the homogeneous enhancement on MRI. Pituitary adenomas are usually evident on MRI after contrast administration. They appear as a relatively nonenhancing lesion within a homogeneously enhancing pituitary gland. This patient's MRI is not consistent with a pituitary adenoma.

Untreated primary hypothyroidism can cause pituitary enlargement due to thyrotroph hyperplasia and can mimic a pituitary adenoma. This patient's low thyroid-stimulating hormone and free thyroxine levels do not support a diagnosis of primary hypothyroidism.

KEY POINT

- Checkpoint inhibitors such as nivolumab, ipilimumab, and pembrolizumab have been associated with the development of hypophysitis with most patients presenting with the combination of headache, pituitary enlargement, and hypopituitarism.

Bibliography

Byun DJ, Wolchok JD, Rosenberg LM, Girotra M. Cancer immunotherapy - immune checkpoint blockade and associated endocrinopathies. Nat Rev Endocrinol. 2017;13:195-207. [PMID: 28106152] doi:10.1038/nrendo.2016.205

Item 58 Answer: B

Educational Objective: Treat a large, indeterminate adrenal mass.

The most appropriate next step in management is adrenalectomy. The patient presented with an incidental adrenal mass with radiologic features that are indeterminate for adenoma and may indicate an adrenal malignancy (size >4 cm, density ≥10 Hounsfield units, and absolute contrast washout <50% at 10 minutes). Benign adrenal adenomas tend to be small (<4 cm), often have an intracytoplasmic fat content and appear less dense on noncontrast CT scan (<10 Hounsfield units), and exhibit rapid contrast washout during delayed contrast imaging (>50% at 10 minutes). These radiologic features are not diagnostic of malignancy, as one-third of benign adrenal masses are lipid poor (≥10 Hounsfield units) and many are larger than 4 cm. However, because adrenal carcinoma is an aggressive tumor and data indicate that prognosis may be more favorable when the disease is diagnosed and treated at an earlier stage, adrenalectomy is usually recommended.

Adrenal biopsy is not routinely indicated in the diagnostic evaluation of an incidentally discovered adrenal mass, even if the suspected diagnosis is primary adrenal malignancy, because adrenocortical carcinoma can be missed due to sampling error. Adrenal biopsy may be indicated when adrenal metastasis or an infiltrative disorder such as infection or lymphoma is suspected. Screening for pheochromocytoma should be performed prior to adrenal biopsy to avoid potential hypertensive crisis during the procedure.

Mitotane, an adrenolytic drug, may be used as adjuvant therapy following primary resection. Adrenalectomy is the first-line treatment of choice for patients with suspected adrenocortical carcinoma.

Repeat abdominal CT imaging at 6 months is suggested for adrenal masses that are small (<4 cm) and have benign radiologic features. The optimal time to repeat CT imaging in the radiologically benign appearing, or even indeterminate appearing, incidentally noted adrenal mass, is controversial. Repeat CT imaging is not indicated in this patient with high risk features for adrenal carcinoma.

KEY POINT

- Adrenalectomy is recommended for incidental adrenal masses with radiologic features that suggest increased risk of an adrenal malignancy (size >4 cm, density ≥10 Hounsfield units, and absolute contrast washout <50% at 10 minutes).

Bibliography

Fassnacht M, Arlt W, Bancos I, Dralle H, Newell-Price J, Sahdev A, et al. Management of adrenal incidentalomas: European Society of Endocrinology Clinical Practice Guideline in collaboration with the European Network for the Study of Adrenal Tumors. Eur J Endocrinol. 2016;175:G1-G34. [PMID: 27390021] doi:10.1530/EJE-16-0467

Item 59 Answer: C

H

Educational Objective: Diagnose hypomagnesemia as the cause of hypocalcemia.

The most appropriate test to perform next is measurement of magnesium. Hypocalcemia is likely the result of hypoparathyroidism, which is most commonly caused by surgical injury. Autoimmune, infiltrative (hemochromatosis, Wilson disease, granulomas), and radiation-related injury can also cause acquired hypoparathyroidism. Other, less common causes of hypocalcemia include poor calcium intake, activating mutations in the calcium-sensing receptor (*CASR*) gene, parathyroid hormone (PTH) resistance, increased phosphate binding in vascular space (rhabdomyolysis or tumor lysis syndrome), increased citrate chelation with large-volume blood transfusions, sepsis, vitamin D deficiency, and hypomagnesemia. Low levels of magnesium (due to medications, alcohol abuse, or malnutrition) activate G proteins that stimulate calcium-sensing receptors and decrease PTH secretion. Functional hypoparathyroidism due to hypomagnesemia must be excluded before other diagnoses are pursued. Hypomagnesemia to the extent required to cause hypoparathyroidism is most commonly due to medications impairing renal handling of magnesium including platinum-based chemotherapeutic agents. Prompt resolution of hypocalcemia following correction of hypomagnesemia confirms the diagnosis.

Measurement of serum bicarbonate would allow assessment of acid-base derangements. Acute respiratory alkalosis causes transient symptomatic hypocalcemia due to a rapid increase in the fraction of intravascular calcium bound to albumin. However, changes in blood pH due to metabolic alkalosis are relatively small and gradual, allowing prevention of hypocalcemia by an increase in parathyroid hormone. This patient has a more compelling reason for persistent hypocalcemia, and measurement of serum bicarbonate is not necessary.

Approximately 40% to 45% of the calcium in serum is bound to protein, principally albumin, although the physiologically active form of calcium is in an ionized (or free) state. In most patients with relatively normal serum albumin levels, the total calcium usually accurately reflects the ionized calcium fraction. In this case, the patient's albumin level is normal and the patient's symptoms correspond to the measured calcium level, therefore measurement of ionized calcium is not needed.

Given phosphorus homeostasis and calcium homeostasis are closely linked, changes in serum phosphorus concentration should be routinely explored when evaluating hypocalcemia. Even so, hyperparathyroidism rather than hypoparathyroidism would be present if the primary cause of hypocalcemia was due to hyperphosphatemia.

KEY POINT

- Hypomagnesemia causes functional, reversible parathyroid hypofunction and must be excluded before a low or inappropriately normal parathyroid level is attributed to hypoparathyroidism.

Bibliography

Brandi ML, Bilezikian JP, Shoback D, Bouillon R, Clarke BL, Thakker RV, Khan AA, Potts JT Jr. Management of hypoparathyroidism: summary statement and guidelines. J Clin Endocrinol Metab. 2016;101:2273-83. doi:10.1210/jc.2015-3907. [PMID: 26943719]

Item 60 Answer: C

Educational Objective: Treat type 2 diabetes mellitus in a patient with chronic kidney disease.

The most appropriate treatment of this patient's diabetes mellitus is to initiate metformin. This patient's hemoglobin A_{1c} is above goal despite lifestyle modifications, and his treatment plan should be intensified. The first-line therapy recommended by the American Diabetes Association in conjunction with lifestyle modifications for treatment of type 2 diabetes is metformin. Previously, metformin use was contraindicated at serum creatinine levels of 1.4 mg/dL (123.8 µmol/L) or higher in women and 1.5 mg/dL (132.6 µmol/L) or higher in men. However, in a recent update the FDA concluded that metformin is considered to be safe in those with an estimated glomerular filtration rate (eGFR) greater than 45 mL/min/1.73 m² and is contraindicated in those with an eGFR less than 30 mL/min/1.73 m². The FDA recommends not initiating metformin for patients with eGFR greater than 30 mL/min/1.73 m² to less than 45 mL/min/1.73 m², or alternately, initiating metformin at a reduced dose (50%) with frequent monitoring of kidney function (every 3 months). The patient qualifies metformin therapy and frequent monitoring with his current kidney function.

Empagliflozin, a sodium-glucose transporter 2 (SGLT2) inhibitor, is a second-line agent after metformin initiation. In addition, SGLT2 inhibitors may cause hypotension due to intravascular volume depletion, especially in patients with kidney impairment, and acute kidney injury has been reported with its use. The FDA advises that risk factors for acute kidney injury (hypovolemia, chronic kidney disease, heart failure, and use of diuretics, ACE inhibitors, angiotensin receptor blockers, or NSAIDs) be considered before initiating this class of drugs.

The sulfonylurea, glipizide, is a second-line agent after metformin initiation. Glipizide could be considered as part of dual therapy if the glycemic goal is not reached with metformin. While sulfonylureas are the least expensive oral agent to add to metformin, they are associated with an increased risk for hypoglycemia as well as weight gain as compared with other potential combination therapies.

Saxagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor, is a second-line agent after metformin initiation. Saxagliptin could be considered as part of dual therapy if the glycemic goal is not reached with metformin. However, the FDA has warned that the DPP-4 inhibitors saxagliptin and alogliptin may increase the risk for heart failure, especially in patients who already have heart or kidney disease.

KEY POINT

- Metformin is considered to be safe in those with an estimate glomerular filtration rate (eGFR) greater than 45 mL/minute/1.73 m² and is contraindicated in those with an eGFR less than 30 mL/min/1.73 m².

Bibliography

Barry MJ, Humphrey LL, Qaseem A. Oral pharmacologic treatment of type 2 diabetes mellitus. Ann Intern Med. 2017;167:75-76. doi:10.7326/L17-0234. [PMID: 28672387]

Item 61 Answer: D

Educational Objective: Treat toxic adenoma with radioactive iodine.

The most appropriate management is radioactive iodine (^{131}I) therapy. The patient's examination findings and thyroid scintigraphy results are consistent with a diagnosis of toxic adenoma. Toxic adenoma and multinodular goiter are the second most common cause of hyperthyroidism overall and are most frequently seen in older adults. These autonomously functioning nodules synthesize and secrete thyroid hormones independent of thyroid-stimulating hormone (TSH) stimulation as a result of activating mutations of the TSH receptor or $G_{s\alpha}$. They are usually large and can be easily palpated on examination. First-line treatment options include radioactive iodine therapy or surgery. Radioactive iodine is the most commonly used first-line treatment. The radioisotope ^{131}I emits both gamma and beta radiation. Gamma radiation can be detected by the camera to determine radioactive iodine uptake and create an image of the thyroid gland during thyroid scintigraphy, whereas beta radiation yields the therapeutic effect by triggering thyroid follicular cell death. If a patient has a particularly large goiter with compressive symptoms or if there is concern for malignancy, surgery is recommended as first-line therapy.

Autonomous nodules are associated with a very low risk of malignancy (<1%), and fine-needle aspiration biopsy is not indicated. If biopsy is performed, it frequently yields indeterminate cytology results, such as suspicion for follicular neoplasm, and generates inappropriate concern and unnecessary recommendations for follow-up examinations and biopsies.

Increasing the atenolol dosage and prescribing methimazole are also not the best management options. While β-blockers ameliorate adrenergic symptoms, they do not address the underlying cause. This patient has a normal heart rate and blood pressure on her current dose of atenolol, so increasing this further is not indicated.

Antithyroid drugs (methimazole) are not first line for managing hyperthyroidism because spontaneous remission does not occur and treatment would have to be continued indefinitely.

KEY POINT

- First-line therapy for toxic adenoma is radioactive iodine (^{131}I) therapy or surgery.

Bibliography

Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, Pacini F, Randolph GW, Sawka AM, Schlumberger M, Schuff KG, Sherman SI, Sosa JA, Steward DL, Tuttle RM, Wartofsky L. 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid. 2016;26:1-133. doi:10.1089/thy.2015.0020. [PMID: 26462967]

Item 62 Answer: A

Educational Objective: Screen for neuropathy and retinopathy in type 2 diabetes mellitus.

This patient requires a comprehensive foot examination and dilated eye examination. Patients with diabetes mellitus require monitoring for complications. A thorough foot examination should be done annually in patients with type 2 diabetes. Although this patient had an unremarkable visual foot inspection, he has not yet had a comprehensive foot examination, which is indicated at the time of diagnosis of type 2 diabetes and then annually thereafter. A comprehensive foot examination includes inspection of the skin, assessment of foot deformities, neurologic assessment (10-g monofilament testing with at least one other nerve assessment—pinprick, temperature, vibration, or ankle reflexes), and vascular assessment including pulses in the legs and feet. In patients with type 1 diabetes mellitus, a dilated comprehensive eye examination 5 years after diagnosis is appropriate; however, in patients with type 2 diabetes, a dilated comprehensive eye examination is indicated at time of diagnosis.

Prediabetes and diabetes can be diagnosed based on the elevated results from one of the following screening tests repeated on two separate occasions: fasting plasma glucose, 2-hour postprandial glucose during an oral glucose tolerance test, or hemoglobin A_{1c}. This patient has two abnormal hemoglobin A_{1c} measurements and additional testing with a fasting plasma glucose test and oral glucose tolerance test for the purposes of diagnosis is not warranted.

Although long-term use of metformin may be associated with vitamin B_{12} deficiency and periodic measurement of vitamin B_{12} levels should be considered in metformin treatment patients, B_{12} and folate measurements are not recommended at time of initiation of metformin therapy.

Annual screening for albuminuria in patients with type 2 diabetes should be undertaken starting at the time of diagnosis; this is done on a random spot urine sample as planned in this patient, not a 24-hour urine collection for protein and creatinine.

KEY POINT

- Screening for dyslipidemia, hypertension, a dilated eye examination, spot urine albumin-creatinine ratio, and a comprehensive foot examination should be performed at the time of diagnosis of type 2 diabetes.

Bibliography

American Diabetes Association. 10. Microvascular complications and foot care: Standards of Medical Care in Diabetes-2018. Diabetes Care. 2018;41(Suppl 1):S105-S118. doi: 10.2337/dc18-S010. [PMID: 29222381]

Item 63 Answer: D

Educational Objective: Diagnose hyperglycemia in a patient meeting preprandial glycemic targets.

Measuring postprandial blood glucose level is the most appropriate management of this patient's diabetes. This patient is healthy with few comorbidities. His preprandial blood glucose target is 80 to 130 mg/dL (4.4-7.2 mmol/L). Despite meeting his preprandial glycemic targets, his hemoglobin A_{1c} level remains above his goal of less than 7%. Postprandial hyperglycemia has a greater effect on hemoglobin A_{1c} when it is near 7%. Measuring postprandial blood glucose levels in this patient may identify undetected hyperglycemia that could be treated with an increase in his prandial insulin lispro dose.

Liraglutide is an injectable glucagon-like peptide-1 (GLP-1) receptor agonist with several mechanisms of action: slows gastric emptying, glucose-dependent increase in insulin secretion, and glucose-dependent suppression of glucagon secretion. Although liraglutide has the potential to aid with weight loss in this obese patient and improve his hemoglobin A_{1c} to goal, adding another injectable agent to the regimen of a patient who is reluctant to do this does not take into consideration patient preferences. In addition, liraglutide has not been approved by the FDA for combination use with prandial insulin.

Continuing his current regimen will not allow him to achieve his target hemoglobin A_{1c} goal. The American Diabetes Association recommends a hemoglobin A_{1c} goal of less than 6.5% to 7% for healthy persons with type 2 diabetes mellitus with few comorbidities to decrease the incidence of diabetes-related complications in the future. The American College of Physicians (ACP) recommends a target hemoglobin A_{1c} level between 7% and 8% for most patients with type 2 diabetes. ACP notes that more stringent targets may be appropriate for patients who have a long life expectancy (>15 years) and are interested in more intensive glycemic control despite the risk for harms.

The patient has reached the recommended preprandial glycemic goal of 80 to 130 mg/dL (4.4-7.2 mmol/L). Increasing his insulin detemir dose may increase his risk of developing hypoglycemia and would not adequately treat postprandial hyperglycemia that may be contributing to the elevated hemoglobin A_{1c}.

KEY POINT

- Measuring postprandial blood glucose levels may identify undetected hyperglycemia when preprandial blood glucose values are at target goal, but the hemoglobin A_{1c} is above goal.

Bibliography

American Diabetes Association. 6. Glycemic targets: Standards of Medical Care in Diabetes 2018. Diabetes Care. 2018;41(Suppl 1):S55-S64. doi:10.2337/dc18-S006. [PMID: 29222377]

Item 64 Answer: B

Educational Objective: **Manage a patient with asymptomatic primary hyperparathyroidism.**

The most appropriate management for this patient is to reassess the patient in 6 to 12 months. Guideline-recommended indications for parathyroidectomy include increase in serum calcium level ≥1 mg/dL (0.25 mmol/L) above upper limit of normal; creatinine clearance <60 mL/min, 24-hour urine calcium >400 mg/day (>10 mmol/day), or increased stone risk by biochemical stone risk analysis; presence of nephrolithiasis or nephrocalcinosis by radiograph, ultrasound, or CT; T-score (on DEXA scan) of less than or equal to −2.5 at any site or evidence of vertebral fracture; and age younger than 50 years. Parathyroidectomy is also indicated in patients in whom medical surveillance is neither desired nor possible, and those with complications of hyperparathyroidism including significant bone, kidney, gastrointestinal, or neuromuscular symptoms. Patients without indications for parathyroidectomy require periodic reassessment that includes serum calcium and creatinine every 6 to 12 months and bone mineral density of the lumbar spine, hip, and distal radius every 2 years.

Although imaging tests such as parathyroid sestamibi scan may be performed as part of evaluation of primary hyperparathyroidism, it is most appropriate once surgery is indicated. The results of imaging do not influence the management of nonsurgical patients.

Primary hyperparathyroidism is associated with increased bone turnover and decreased bone strength. Although alendronate suppresses bone resorption and improves bone mineral density at the lumbar spine in patients with primary hyperparathyroidism, it has not been shown to reduce fracture risk or to reduce serum calcium levels. Patients at high risk of fracture (T-score ≤−2.5 and/or prevalent fragility fracture) at presentation or during monitoring should undergo parathyroidectomy.

Cinacalcet is indicated to treat symptomatic, severe hypercalcemia in adults with primary hyperparathyroidism for whom parathyroidectomy cannot be performed. Although it may be used chronically, cinacalcet is more commonly used until surgery is feasible.

KEY POINT

- Patients with primary hyperparathyroidism who do not undergo surgery require monitoring of serum calcium and creatinine every 6 to 12 months and bone mineral density of the lumbar spine, hip, and distal radius every 2 years.

Bibliography

Bilezikian JP, Brandi ML, Eastell R, Silverberg SJ, Udelsman R, Marcocci C, et al. Guidelines for the management of asymptomatic primary hyperparathyroidism: summary statement from the Fourth International Workshop. J Clin Endocrinol Metab. 2014;99:3561-9. [PMID: 25162665] doi:10.1210/jc.2014-1413

Item 65 Answer: E

Educational Objective: **Manage subclinical hypothyroidism.**

This patient has subclinical hypothyroidism, and the most appropriate management is to repeat serum thyroid-stimulating hormone (TSH) testing in 2 months. Free thyroxine (T_4) and thyroid peroxide antibodies could also be measured at that time. Subclinical hypothyroidism is an early form of primary hypothyroidism affecting up to 10% of the population and is characterized by a serum TSH level above the upper limit of the reference range and normal free T_4 level. Before making this diagnosis; however, transient elevation of serum TSH levels should be ruled out by repeating the measurement of TSH in 2 to 3 months.

Thyroid peroxidase (TPO) antibodies are frequently seen in the setting of Hashimoto thyroiditis, the most common cause of hypothyroidism in the United States. TPO antibody positivity would support a diagnosis of primary hypothyroidism, predict risk of progression to overt hypothyroidism, and may impact treatment decisions accordingly. However, the most appropriate next step in the management of this patient is to confirm the diagnosis of subclinical hypothyroidism by documenting persistent serum TSH elevation.

Thyrotropin receptor antibodies would be more consistent with Graves disease and testing for these antibodies would not be appropriate in this setting.

Measurement of serum triiodothyronine (T_3) in patients with known or suspected primary hypothyroidism is generally not indicated. Elevation of serum TSH is the earliest biochemical change observed in the setting of primary hypothyroidism. Reductions in serum T_3 are not usually seen until after free T_4 levels are low. Measuring serum T_3 has little to no impact on diagnosis or management decisions.

More severe subclinical hypothyroidism, serum TSH greater than 10 µU/mL (10 mU/L), may increase the risk of coronary artery disease and heart failure, whereas serum TSH levels below 7 to 10 µU/mL (7-10 mU/L) are not associated with increased morbidity or mortality. Treatment with levothyroxine would be considered if the patient's serum TSH is similar or higher on reassessment, but this is not the most appropriate next step in management.

KEY POINT

- Subclinical hypothyroidism is characterized by a serum thyroid-stimulating hormone (TSH) level above the upper limit of the reference range and normal free thyroxine (T_4) level; before making this diagnosis, however, transient elevation of serum TSH should be ruled out by repeating the measurement of TSH in 2 to 3 months.

Bibliography

Peeters RP. Subclinical hypothyroidism. N Engl J Med. 2017 Jun 29; 376(26):2556-2565. doi: 10.1056/NEJMcp1611144. [PMID: 28657873]

Item 66 Answer: A

Educational Objective: Diagnose the cause of primary aldosteronism.

The next step in this patient's management is adrenal vein sampling. Once the diagnosis of primary aldosteronism has been confirmed biochemically, radiographic localization with abdominal CT is indicated. CT is recommended over MRI in most cases due to similar efficacy and lower cost. Adrenal hyperplasia and adenomas secreting excess aldosterone, however, may not always be visualized. Adrenal vein sampling is, therefore, needed in most patients to determine the source of aldosterone secretion when imaging is unrevealing and to confirm lateralization when imaging demonstrates an adrenal adenoma, such as in this case. Adrenal vein sampling is especially important in older patients because of a higher frequency of nonfunctioning adrenal incidentalomas. Patients with an aldosterone-secreting adenoma are usually offered adrenalectomy, whereas those with primary aldosteronism due to bilateral adrenal hyperplasia are treated medically. Omission of adrenal vein sampling can lead to misdiagnosis in approximately 25% of cases, and subsequent unnecessary adrenalectomy, or medical therapy when adrenalectomy could be offered. Right adrenalectomy should not be performed in this patient without further confirmation of the source of primary aldosteronism.

Aldosterone likely exerts direct toxic effects on cardiac cells as evidenced by a higher prevalence of left ventricular hypertrophy and decreased left ventricular function when compared with matched control patients with similar levels of hypertension. These deleterious effects are likely mediated by mineralocorticoid receptors in the heart, coronary arteries, aorta, and other blood vessels. Increasing this patient's losartan or metoprolol dose may lead to better control of his hypertension, but neither of these medications blocks the aldosterone receptor. Therefore, the patient would still be subject to the deleterious effects of excess stimulation of aldosterone receptors, which may lead to cardiac disease.

KEY POINT

- Most patients with biochemically confirmed primary aldosteronism should undergo adrenal vein sampling to confirm the source of the hyperaldosteronism.

Bibliography

Rossi GP, Auchus RJ, Brown M, Lenders JW, Naruse M, Plouin PF, et al. An expert consensus statement on use of adrenal vein sampling for the subtyping of primary aldosteronism. Hypertension. 2014;63:151-60. [PMID: 24218436] doi:10.1161/HYPERTENSIONAHA.113.02097

Item 67 Answer: D

Educational Objective: Evaluate a thyroid nodule with neck ultrasonography.

The most appropriate diagnostic test to perform next is ultrasound of the neck. Ultrasound can confirm the presence of thyroid nodules palpated on examination and those detected on other imaging studies. Ultrasound must be performed prior to fine needle aspiration biopsy (FNAB) to confirm the presence of a nodule, determine that biopsy is indicated, ensure that there are no additional nonpalpable nodules that warrant FNAB, and assess the cervical lymph nodes. In patients with solitary palpable nodules, 15% will have no corresponding nodule on ultrasound, and a similar proportion will have an additional nodule measuring 1 cm or larger.

Performing a CT scan of the neck is a more costly test, exposes the patient to unnecessary radiation, and is inferior to ultrasound at assessing the thyroid gland.

FNAB should not be performed prior to thyroid/neck ultrasound. Whether or not FNAB is indicated depends on the size and sonographic appearance of the nodule, clinical risk factors for malignancy, and presence of pathologic lymph nodes. Nodules that are predominantly cystic or posteriorly located within the thyroid gland are prone to sampling error.

Measurement of serum thyroid-stimulating hormone (TSH) is also part of the initial evaluation of a thyroid nodule. The purpose of measuring TSH is to evaluate for the presence of autonomously functioning or "hot" nodules, which account for 5% to 10% of palpable thyroid nodules. Autonomous nodules may cause hyperthyroidism and are associated with a very low risk of malignancy. Autonomous nodules can be confirmed by performing a thyroid uptake and scan. They concentrate radioactive iodine to a greater extent than normal thyroid tissue, which shows absent or diminished uptake. The TSH in this patient is normal, which does not support a diagnosis of an autonomously functioning thyroid nodule; therefore performing a thyroid uptake and ^{131}I scan is not indicated.

KEY POINT

- Ultrasound can confirm the presence of thyroid nodules palpated on examination and based on findings can help to determine if fine-needle aspiration is needed to assess for malignancy.

Bibliography

Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, et al. 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid. 2016;26:1-133. [PMID: 26462967] doi:10.1089/thy.2015.0020

Item 68 Answer: B

Educational Objective: Manage secondary hypothyroidism.

The most appropriate next step in management is measurement of the free thyroxine (T_4) level. Thyroid-stimulating hormone (TSH) deficiency leads to secondary or central hypothyroidism. Secondary hypothyroidism symptoms are clinically identical to primary hypothyroidism symptoms. Secondary hypothyroidism is diagnosed by demonstrating a simultaneously inappropriately normal or low TSH and low T_4 (free or

total). Patients are treated with levothyroxine replacement in the same manner as primary hypothyroidism; however, the serum TSH cannot be used to monitor and assess for adequacy of thyroid hormone replacement dosing. Instead, the levothyroxine dose is adjusted based on free T_4 levels with the goal of obtaining a value within the normal reference range. The patient's recent symptoms of fatigue and weight gain may be due to hypothyroidism resulting from impaired absorption of levothyroxine after recently starting a calcium supplement. A low T_4 level will confirm the diagnosis. In general the therapeutic goal is to keep the free T_4 in the upper half of the normal range. To improve gastrointestinal absorption, levothyroxine should be taken on an empty stomach, 1 hour before or 3 hours after ingestion of food. Medications that would interfere with absorption, such as calcium- or iron-containing supplements should be separated by 4 hours.

Increasing the levothyroxine would not be appropriate without first documenting the presence of hypothyroidism by measuring the T_4 level. In addition, the preferred initial therapy may simply be to discontinue the calcium, if not warranted, or to separate ingestion of calcium and levothyroxine by at least 2 to 3 hours.

The patient has no symptoms suggestive of a pituitary mass effect or other indication to recommend pituitary imaging.

KEY POINT

- Serum thyroid-stimulating hormone level cannot be used to monitor and assess for adequacy of thyroid hormone replacement dosing in secondary hypothyroidism; the levothyroxine dose is adjusted based on free thyroxine (T_4) levels with the goal of obtaining a value within the upper half of the normal reference range.

Bibliography

Beck-Peccoz P, Rodari G, Giavoli C, Lania A. Central hypothyroidism - a neglected thyroid disorder. Nat Rev Endocrinol. 2017;13:588-598. doi:10.1038/nrendo.2017.47. Epub 2017 May 26. [PMID: 28549061]

Item 69 Answer: A

Educational Objective: Treat hypoglycemic unawareness.

The most appropriate treatment of this patient's diabetes is to decrease all insulin doses. He is having hypoglycemia at least once per week with some of these events qualifying as clinically significant per the American Diabetes Association with glucose values less than 54 mg/dL (3.0 mmol/L). He is developing hypoglycemia unawareness as evidenced by his inability to detect decreases in his blood glucose until it is less than 40 mg/dL (2.2 mmol/L). This is secondary to an ineffective response of the autonomic system to hypoglycemia, in addition to an inadequate release of counterregulatory hormones to correct hypoglycemia. Blood glucose targets should be relaxed, and insulin dosing should be decreased in the setting of hypoglycemia unawareness. Avoidance of hypoglycemia for several weeks may restore the ability to detect hypoglycemia in some patients. Since the hypoglycemia is intermittent and without a pattern for this patient, all insulin doses should be decreased to avoid hypoglycemia.

The patient has fasting hyperglycemia and a hemoglobin A_{1c} level above goal. Increasing the dose of his glargine insulin could lower his glucose values, but it may potentially exacerbate his hypoglycemia.

Empagliflozin could improve this patient's hyperglycemia while also improving his blood pressure control and inducing weight loss; however, it may also exacerbate the hypoglycemia when used in conjunction with insulin.

Metformin could improve hyperglycemia for this patient, particularly fasting hyperglycemia secondary to hepatic gluconeogenesis. Given the clinically significant hypoglycemia experienced by this patient, that should be addressed first by relaxing his glycemic goals.

KEY POINT

- Treatment for hypoglycemic unawareness is to reduce the insulin dose and avoid hypoglycemia in order to provide the body an opportunity to restore the ability to detect hypoglycemia.

Bibliography

American Diabetes Association. 6. Glycemic targets: Standards of Medical Care in Diabetes-2018. Diabetes Care. 2018;41(Suppl 1):S55-S64. doi:10.2337/dc18-S006. [PMID: 29222377]

Item 70 Answer: A

Educational Objective: Avoid inappropriate screening for osteoporosis.

The most appropriate management for this patient is lifestyle counseling for osteoporosis prevention. Lifestyle measures include adequate calcium and vitamin D, exercise, smoking cessation, counseling on fall prevention, and avoidance of heavy alcohol use.

Most guidelines recommend screening for osteoporosis with dual-energy x-ray absorptiometry (DEXA) scan in women 65 years of age and older. Screening of younger women may be indicated if one or more risk factors for osteoporosis are present. In premenopausal women without risk factors, assessment of bone mineral density (BMD) for fracture risk is not advised or validated. However, if testing is done in an otherwise healthy person, such as this patient, results that are below age- and gender-matched averages (Z-score <0) generally do not require further evaluation or serial monitoring. The discovery of below average BMD could lead to a discussion regarding osteoporosis prevention with lifestyle modification and assessment of BMD after menopause, but prior to age 65, when screening might otherwise occur.

Testing for secondary causes of bone loss is unnecessary when BMD is normal for age. Below average BMD in adults may in fact represent below average peak bone mass rather than loss of bone.

Although BMD measured by quantitative heel ultrasound is predictive of osteoporotic fracture in older women and men, BMD measurement by DEXA scan remains the gold standard for diagnosis of osteoporosis and fracture risk assessment. Therefore, abnormal ultrasound results in these populations should be confirmed by DEXA scan. Even so, a DEXA scan should not be performed in this patient given that screening is not indicated and the heel ultrasound result is within the normal range.

KEY POINT

- Screening for osteoporosis in premenopausal women is not indicated in the absence of risk factors.

Bibliography

Cosman F, de Beur SJ, LeBoff MS, Lewiecki EM, Tanner B, Randall S, et al; National Osteoporosis Foundation. Clinician's guide to prevention and treatment of osteoporosis. Osteoporos Int. 2014;25:2359-81. [PMID: 25182228] doi:10.1007/s00198-014-2794-2

Item 71 Answer: D

Educational Objective: Diagnose methimazole-induced agranulocytosis.

The most appropriate management is to stop methimazole and order a complete blood count with differential. The patient has been receiving methimazole for treatment of Graves hyperthyroidism over the past 3 months. She has both a sore throat and a fever, which can be seen in patients with methimazole-induced agranulocytosis. Agranulocytosis affects between one in 300 and one in 500 patients taking antithyroid drug therapy. Agranulocytosis from methimazole usually occurs within the first several months of initiating therapy but generally is not seen with doses below 20 mg per day. Suspected agranulocytosis should be managed with cessation of the offending drug and assessment of the patient's neutrophil count. An absolute neutrophil count below 500/µL (0.5×10^9/L) confirms the diagnosis. Management of agranulocytosis may include hospitalization, broad-spectrum antibiotics, and hematopoietic growth factor therapy. Patients should be counseled regarding agranulocytosis as a potential side effect at the initiation of therapy and instructed to contact the prescribing physician immediately with occurrence of any suggestive symptoms.

Diagnosis and treatment of patients with Group A streptococcus (GAS) pharyngitis has traditionally been aided by the four-point Centor criteria: (1) fever, (2) absence of cough, (3) tonsillar exudates, and (4) tender anterior cervical lymphadenopathy. The Centor criteria have a low positive predictive value for GAS infection; according to the Infectious Disease Society of America, these criteria may be used to determine which patients have a low likelihood of GAS pharyngitis and require no further testing. No additional testing or treatment is needed for patients who meet fewer than three criteria. Patients who meet three or more criteria should have a confirmatory test (either a rapid antigen detection test for GAS or throat culture). Penicillin or amoxicillin is first-line treatment for GAS pharyngitis. However, the clinical situation of most immediate concern is the possibility of methimazole-induced agranulocytosis, a potentially fatal condition. The most appropriate management is to stop the drug and measure the neutrophil count.

KEY POINT

- Antithyroid drug-related agranulocytosis affects between one in 300 and one in 500 patients taking therapy and may present with fever and sore throat; initial management includes stopping the drug and assessment of the neutrophil count.

Bibliography

Vicente N, Cardoso L, Barros L, Carrilho F. Antithyroid drug-induced agranulocytosis: state of the art on diagnosis and management. Drugs R D. 2017;17:91-96. doi: 10.1007/s40268-017-0172-1. [PMID: 28105610]

Item 72 Answer: C

Educational Objective: Diagnose diabetic ketoacidosis associated with a sodium-glucose cotransporter 2 (SGLT2) inhibitor.

Sodium-glucose cotransporter 2 (SGLT2) inhibitors (canagliflozin, dapagliflozin, and empagliflozin) improve glycemia by increasing excretion of glucose by the kidney. SGLT2 is expressed in the proximal tubule and mediates reabsorption of approximately 90% of the filtered glucose load. SGLT2 inhibitors promote excretion of glucose by the kidneys and thereby modestly lower elevated blood glucose levels in patients with type 2 diabetes. Euglycemic diabetic ketoacidosis has been reported in patients with type 2 diabetes taking SGLT2 inhibitors. Because of this, the FDA issued a Drug Safety Communication that warns of an increased risk of diabetic ketoacidosis with uncharacteristically mild to moderate glucose elevations (euglycemic diabetic ketoacidosis) associated with the use of all the approved SGLT2 inhibitors. SGLT2 inhibitors should be discontinued in patients who develop acidosis on these agents.

Statins may cause myopathy and liver aminotransferase elevations and are associated with an increased risk of diabetes and, possibly, cognitive dysfunction. The incidence of these adverse effects ranges from 1% to 10%, but permanent disability related to statin intolerance is rare. Statin therapy is not associated with ketoacidosis.

According to labeling guidelines, initiation of metformin therapy is not recommended if the estimated glomerular filtration rate (eGFR) is between 30 and 45 mL/min/1.73 m² and is contraindicated if the eGFR is less than 30 mL/min/1.73 m² due to the risk of lactic acidosis. Metformin should be used cautiously in patients with heart failure or hepatic impairment. The discontinuation of metformin is not associated with the development of lactic acidosis or ketoacidosis.

Glipizide is a sulfonylurea. Sulfonylurea agents work by stimulating insulin secretion. Sulfonylurea agents are associated with weight gain, and they can cause hypoglycemia.

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Answers and Critiques

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They are not, however, associated with the development of ketoacidosis in patients with type 2 diabetes.

A common adverse effect of ACE inhibitors is a dry, nonproductive cough. Other common adverse effects include hyperkalemia and, occasionally, worsening kidney function. ACE inhibitors can cause life threatening angioedema but not ketoacidosis.

KEY POINT

- An increased risk of diabetic ketoacidosis with mild to moderate glucose elevations has been associated with the use of all the approved sodium-glucose transporter-2 (SGLT2) inhibitors (canagliflozin, dapagliflozin, and empagliflozin).

Bibliography

FDA Drug Safety Communication. FDA warns that SGLT2 inhibitors for diabetes may result in a serious condition of too much acid in the blood. May 15, 2015 https://www.fda.gov/downloads/drugs/drugsafety/ucm446954.pdf. Accessed March 1, 2018.

Item 73 Answer: B

Educational Objective: Evaluate secondary hypogonadism.

The most appropriate test for this patient is a pituitary MRI. With a low testosterone level and low serum luteinizing hormone (LH) and follicle stimulating hormone (FSH) concentrations, this patient has secondary hypogonadism. Hyperprolactinemia is the most likely cause of his hypogonadism; hyperprolactinemia leads to secondary hypogonadism through suppression of gonadotropin releasing hormone synthesis and secretion. This patient is on no medications that might cause hyperprolactinemia. In the absence of a culprit drug, the most likely cause of his hyperprolactinemia is a lactotroph adenoma; therefore a pituitary MRI is indicated.

A karyotype analysis is not indicated in the evaluation of secondary hypogonadism; however, it should be considered in men and women who have primary hypogonadism.

Anabolic steroid use will result in low or normal gonadotropin levels, a low testosterone level, and clinical evidence of hyperandrogenism such as excessive muscle bulk, acne, gynecomastia, and decreased testicular volume. Anabolic steroid abuse, however, would not cause hyperprolactinemia as seen in this patient.

Most patients with hereditary hemochromatosis are diagnosed in the presymptomatic phase when iron test results are abnormal. In patients with symptoms, clinical presentation varies and often includes nonspecific findings such as chronic fatigue, weakness, nonspecific abdominal pain, arthralgia, and elevated liver enzymes. Endocrine organs are commonly affected, and diabetes mellitus, hypothyroidism, and gonadal failure may occur. Laboratory evaluation of hemochromatosis-related gonadal failure most commonly demonstrates a hypogonadotropic state (low LH and FSH levels). While this patient is hypogonadotrophic, he has an elevated prolactin level, and a pituitary MRI is the best next diagnostic test.

Obesity results in decreased concentrations of sex hormone-binding globulin (SHBG); if SHBG is low, free testosterone should be measured in patients with low total testosterone concentrations. This patient is not obese and has evidence of secondary hypogonadism (low testosterone level and low serum LH and FSH concentrations), making determination of SHBG concentration unnecessary.

KEY POINT

- Secondary hypogonadism is characterized by low testosterone level and low or inappropriately normal serum luteinizing hormone and follicle-stimulating hormone concentrations; MRI of the pituitary is typically performed to evaluate secondary hypogonadism in the absence of obvious reversible causes such as drugs.

Bibliography

Basaria S. Male hypogonadism. Lancet. 2014;383:1250-63. [PMID: 24119423] doi:10.1016/S0140-6736(13)61126-5.

Item 74 Answer: A

H

Educational Objective: Treat myxedema coma.

The most appropriate next step in the management of this patient is to administer intravenous hydrocortisone. This patient has myxedema coma, which has a very high mortality rate if there is a delay in treatment. Myxedema coma is more common in elderly women; it may occur in those with a history of hypothyroidism or no antecedent illness. Myocardial infarction, infection, stroke, trauma, and gastrointestinal bleeding are common precipitating events. Mental status changes and hypothermia are the most common clinical manifestations. Ventilatory drive is decreased, resulting in hypoxemia and hypercapnia. Additional signs include bradycardia, hypoglycemia, hyponatremia, and/or hypotension. This patient's condition was likely precipitated by recent nonadherence with her prescribed medications. The serum cortisol level should be checked as soon as possible to evaluate for concomitant adrenal insufficiency prior to initiation of thyroid hormone replacement. While awaiting the results of the serum cortisol measurement, it is advisable to empirically initiate high-dose hydrocortisone. This therapy may be discontinued if the serum cortisol level is found to be normal or high. In patients with adrenal insufficiency, administering thyroid hormone prior to glucocorticoids could precipitate an adrenal crisis by augmenting cortisol metabolism.

Following the administration of glucocorticoids, intravenous thyroid hormone replacement should be initiated. Treatment with levothyroxine is universally recommended. Although controversial, some experts suggest administering liothyronine concomitantly. Once clinically improved, the patient can be transitioned to oral levothyroxine.

Hypotension can generally be resolved over a matter of hours with the administration of fluids and treatment of the hypothyroidism. Persistent hypotension can be treated

H CONT.

with a vasopressor drug. The initiation of norepinephrine is premature in this patient.

KEY POINT

- In patients with myxedema coma, intravenous hydrocortisone should be administered before thyroid hormones to treat possible adrenal insufficiency.

Bibliography

Ono Y, Ono S, Yasunaga H, Matsui H, Fushimi K, Tanaka Y. Clinical characteristics and outcomes of myxedema coma: analysis of a national inpatient database in Japan. J Epidemiol. 2017 Mar;27(3):117-122. Epub 2017 Jan 5. PMID: 28142035.

Item 75 Answer: C

Educational Objective: Recognize limitations of hemoglobin A_{1c} measurements.

The most appropriate management for this patient is to initiate ferrous sulfate. This patient has iron-deficiency anemia, a hypoproliferative anemia, which has been shown to erroneously increase the hemoglobin A_{1c} level due to an increase in the proportion of older erythrocytes. Hemoglobin A_{1c} testing measures hemoglobin glycation as a consequence of glucose exposure over the preceding 8 to 12 weeks. Given the patient's age and relatively few comorbidities, her goal hemoglobin A_{1c} level should be less than 6.5% to 7%. Her hemoglobin A_{1c} level is above this goal, but her fingerstick blood glucose data are within her fasting goal of 80 to 130 mg/dL (4.4-7.2 mmol/L) and within her 2-hour postprandial goal of less than 180 mg/dL (10 mmol/L) per the American Diabetes Association (ADA) guidelines. Initiating iron supplementation to correct her iron deficiency anemia will increase erythrocyte turnover and shift the proportion toward younger cells, thus allowing a more accurate measurement of glycemic exposure by the hemoglobin A_{1c} to guide therapeutic decisions.

The patient's fasting blood glucose values are within her goal range of 80 to 130 mg/dL (4.4-7.2 mmol/L) per the ADA guidelines. Initiating basal insulin based solely on the elevated hemoglobin A_{1c} value with her current fasting blood sugars will increase her risk of hypoglycemia. Similarly, the risk of hypoglycemia is increased by initiating empagliflozen. Increasing the accuracy of the hemoglobin A_{1c} measurement by correcting her iron deficiency anemia should be addressed before considering other drug therapy.

Hemoglobin A_{1c} measurements may be unreliable not only in the setting of anemia, but also in the presence of certain hemoglobinopathies or kidney or liver disease. For example, hemoglobin A_{1c} values may be falsely elevated in patients with hemoglobin F or low with hemoglobin S. However, this patient has an explanation for the discordant hemoglobin A_{1c} and blood glucose results, and the iron deficiency anemia should be the focus of management. Additionally, newer methods of measuring A_{1c} are not altered by the presence of the most common hemoglobinopathies. Therefore, a hemoglobin electrophoresis is not indicated at this time.

KEY POINT

- Iron-deficiency anemia can erroneously increase the hemoglobin A_{1c} level due to an increase in the proportion of older erythrocytes.

Bibliography

Sacks DB. A1C versus glucose testing: a comparison. Diabetes Care. 2011;34:518-23. [PMID: 21270207] doi:10.2337/dc10-1546

Item 76 Answer: D

Educational Objective: Treat low-risk papillary thyroid cancer.

No additional treatment is needed. The incidence of thyroid cancer has increased over the last four decades with much of this change attributable to a rise in the diagnosis of small noninvasive papillary thyroid carcinomas. The incidence of papillary microcarcinoma (<1 cm) is 5% to 15% in the United States based on autopsy series. Low-risk papillary thyroid cancer is that which is confined to the thyroid gland, completely resected at surgery, does not demonstrate aggressive pathologic features (lymphovascular invasion or tall cell variant), and has not metastasized. The risk of disease-related death is less than 1%, and the risk of structural disease recurrence is 1% to 2% for low-risk unifocal papillary microcarcinomas. Patients receiving either lobectomy or thyroidectomy have similarly excellent outcomes. Therefore, resection of the remaining thyroid lobe would not be required for this patient.

Suppression of thyroid-stimulating hormone (TSH) with levothyroxine therapy may also be used to improve morbidity and reduce mortality, particularly in patients with persistent disease or distant metastases. The necessary degree of TSH suppression varies according to the risk of cancer progression and comorbidities of the patient. Patients with persistent disease typically require lowering of their TSH level to less than 0.1 µU/mL (0.1 mU/L), whereas patients who are disease-free with a low risk of recurrence should maintain a TSH level of 0.3 to 2.0 µU/mL (0.3-2.0 mU/L). This is typically accomplished without the use of thyroxine suppressive therapy.

Patients with distant metastases have improved survival with successful radioiodine therapy, whereas administration of radioactive iodine may decrease the likelihood of recurrent disease in those patients with nodal metastases. Radioactive iodine (^{131}I) therapy offers this patient no appreciable benefit since her prognosis is already excellent and such therapy would result in substantial unnecessary costs and radiation exposure.

KEY POINT

- Lobectomy is the treatment of choice for low-risk papillary thyroid cancer that is confined to the thyroid gland, completely resected at surgery, does not demonstrate aggressive pathologic features (lymphovascular invasion or tall cell variant), and has not metastasized.

Bibliography

Vaccarella S, Franceschi S, Bray F, Wild CP, Plummer M, Dal Maso L. Worldwide thyroid-cancer epidemic? The increasing impact of overdiagnosis. N Engl J Med. 2016 Aug 18;375(7):614-7. doi: 10.1056/NEJMp1604412. [PMID: 27532827]

H

Item 77 Answer: B

Educational Objective: Diagnose diabetes insipidus.

The most appropriate diagnostic test for this patient is urine and serum osmolality measurement. Central diabetes insipidus (DI) results from inadequate production of antidiuretic hormone (ADH) by the posterior pituitary gland. In the presence of ADH, aquaporin water channels are inserted in the collecting tubules and allow water to be reabsorbed. In the absence of ADH, excessive water is excreted by the kidneys. Excretion of more than 3 liters of urine per day is considered polyuric. Frank hypernatremia is unusual because patients develop extreme thirst and polydipsia, and with free access to water, can maintain serum sodium in the high normal range. When patients do not drink enough to replace the water lost in the urine, due to poor or absent thirst drive or lack of free access to water, they develop hypernatremia. A low urine osmolality in the setting of a high serum osmolality and high serum sodium in a patient with polyuria is diagnostic of DI. Patients with craniopharyngiomas are at higher risk of developing central DI.

Desmopressin challenge is not appropriate at this time. Prior to initiating desmopressin, one must confirm the diagnosis of DI by measuring urine and serum osmolality. Once confirmed, desmopressin can be administered and urine osmolality remeasured to assure that administration of desmopressin resulted in an increase in urine osmolality. After desmopressin is given, urine concentrates to more than 800 mOsm/kg in central DI, less than 300 mOsm/kg in nephrogenic DI, and between 300 and 800 mOsm/kg in partial DI.

Measurement of urine electrolytes is not helpful in the diagnosis of DI.

A water deprivation test should not be performed in this patient. He already has hypernatremia so further water deprivation could result in serious hypernatremia. In the setting of hypernatremia, a urine and serum osmolality are the best tests to confirm the diagnosis of DI. A water deprivation test can be pursued when the diagnosis is unclear. Urine osmolality above 800 mOsm/kg H_2O is a normal response to water deprivation, indicating ADH production and peripheral effect are intact. A serum osmolality above 295 mOsm/kg with inappropriately hypotonic urine (urine osmolality-serum osmolality ratio <2) during fluid deprivation confirms DI.

KEY POINT

- A low urine osmolality in the setting of a high serum osmolality and high serum sodium in a patient with polyuria is diagnostic of diabetes insipidus.

Bibliography

Prete A, Corsello SM, Salvatori R. Current best practice in the management of patients after pituitary surgery. Ther Adv Endocrinol Metab. 2017;8:33-48. [PMID: 28377801] doi:10.1177/2042018816687240

Item 78 Answer: D

H

Educational Objective: Diagnose thyroid storm.

The most likely diagnosis is thyroid storm. Thyroid storm is characterized by severe thyrotoxicosis associated with systemic decompensation. Presentation often follows a precipitating event, such as non-thyroid surgery as in this patient's case. Clinical manifestations include high fever, altered mental status and seizures, tachycardia, atrial fibrillation and heart failure, and hepatic dysfunction. A diagnostic system, such as the Burch and Wartofsky Point Scale, can support the diagnosis with scores greater than or equal to 45 being highly suggestive. The patient's thyroid function tests should be assessed to confirm recurrent hyperthyroidism and aggressive treatment should be initiated in the ICU. Management includes treatment of any precipitant illness, supportive care, and thyrotoxicosis-directed therapy including β-adrenergic blockers (esmolol infusion), antithyroid drug therapy, intravenous glucocorticoids, and potassium iodide. Plasmapheresis and emergent thyroidectomy are utilized in patients who cannot be sufficiently managed with medical therapy alone.

Adrenal crisis is not the most likely diagnosis. Although autoimmune primary adrenal failure occurs more commonly in patients with other autoimmune disorders, patients with adrenal crisis usually present with hypotension, hyponatremia, and hyperkalemia, in addition to gastrointestinal manifestations. This diagnosis cannot explain the patient's hyperthermia, lid lag, thyromegaly, brisk reflexes, or tremor.

Malignant hyperthermia is an uncommon cause of severe hyperthermia that occurs in genetically susceptible individuals upon exposure to a volatile anesthetic such as halothane or isoflurane. Symptoms begin intraoperatively or in postoperative recovery, not 3 days following surgery. Features include mixed respiratory and metabolic acidosis, muscle rigidity, hyperkalemia, and rhabdomyolysis. This diagnosis does not explain the patient's thyrotoxicosis-related findings. Finally, the patient lacks muscle rigidity, a pathognomonic finding in malignant hyperthermia.

Myxedema coma is also unlikely. Although patients with myxedema coma may experience cardiac dysfunction and mental status changes, this patient is presenting with signs and symptoms of thyroid hormone excess, not deficiency. She has a history of Graves disease in remission after treatment with antithyroid drug therapy. She has not received radioactive iodine or thyroidectomy and thus the development of hypothyroidism at this point would be unusual.

KEY POINT

- Thyroid storm is a severe manifestation of thyrotoxicosis with life-threatening secondary systemic decompensation; it occurs most commonly with underlying Graves disease coupled with a precipitating factor such as surgery.

Bibliography

De Leo S, Lee SY, Braverman LE. Hyperthyroidism. Lancet. 2016;388:906-18. [PMID: 27038492] doi:10.1016/S0140-6736(16)00278-6

Item 79 Answer: D

Educational Objective: Manage early type 2 diabetes mellitus with metformin monotherapy.

The American Diabetes Association (ADA) recommends a hemoglobin A_{1c} goal of less than 6.5% to 7% in patients who are early in the disease course and with few comorbidities. This patient meets these criteria and should aim for tighter glycemic control than he is currently achieving with 3 months of lifestyle modifications alone. Pharmacologic therapy should now be added to his lifestyle modifications. The American College of Physicians recommends a hemoglobin A_{1c} level between 7% and 8% in most patients with type 2 diabetes. More stringent targets may be appropriate for patients who have a long life expectancy (>15 years) and are interested in more intensive glycemic control with pharmacologic therapy despite the risk for harms, including but not limited to hypoglycemia, patient burden, and pharmacologic costs. The ADA and the American College of Physicians (ACP) recommend metformin as first-line therapy for all patients with type 2 diabetes without contraindications. This recommendation is based on data from multiple studies demonstrating the effectiveness and safety of metformin. In addition, metformin is inexpensive.

The patient has had a reduction in his weight and hemoglobin A_{1c} with lifestyle modifications alone over a 3-month period. Despite this, he remains above his hemoglobin A_{1c} goal of less than 6.5% to 7%. Therefore, continuing his current management protocol would not be appropriate. Achieving glucose goals early in the disease course can reduce the risk of developing microvascular and possibly macrovascular complications in the future. He will require the addition of pharmacologic agents at this time to reach his glycemic target.

Empagliflozin has the ability to improve glycemic control while also reducing blood pressure and weight. Empagliflozin is considered second-line therapy after metformin by ADA and ACP.

Liraglutide also has the ability to improve glycemic control while also reducing weight. There are studies also demonstrating a reduction in blood pressure with liraglutide use. Liraglutide is considered second-line therapy after metformin by the ADA and ACP.

If the patient does not achieve his hemoglobin A_{1c} target after 3 months of lifestyle modifications and metformin, dual therapy with metformin and liraglutide or metformin and empagliflozin could be considered.

KEY POINT

- Metformin is first-line therapy for all patients with type 2 diabetes without contraindications.

Bibliography

Barry MJ, Humphrey LL, Qaseem A. Oral pharmacologic treatment of type 2 diabetes mellitus. Ann Intern Med. 2017;167:75-76.doi:10.7326/L17-0234. [PMID: 28672387]

Item 80 Answer: B

H

Educational Objective: Manage diabetic ketoacidosis.

The most appropriate management for this patient is to decrease the insulin drip rate and add intravenous (IV) dextrose. This patient continues to have anion gap acidosis and should remain on IV insulin therapy to suppress ketogenesis until this resolves. His current blood glucose level below 200 to 250 mg/dL (11.1-13.9 mmol/L) increases his risk for hypoglycemia with continued IV insulin therapy. This risk can be mitigated by transitioning his IV fluids to 5% dextrose with 0.45% normal saline at 150 to 250 mL/h to maintain his glucose between 150 and 200 mg/dL (8.3-11.1 mmol/L) until his diabetic ketoacidosis resolves. Reducing the insulin drip rate to maintain his blood glucose between 150 and 200 mg/dL (8.3-11.1 mmol/L) will also decrease the risk of hypoglycemia while still suppressing ketogenesis.

If he continues at the current insulin drip rate or if he does not have the addition of IV dextrose, he has an increased risk of developing hypoglycemia now that his blood glucose is less than 200 mg/dL (11.1 mmol/L).

Insulin deficiency and urinary potassium losses induce shifts in potassium from the intracellular to extracellular compartments. This can result in low or normal serum potassium levels in the setting of depleted potassium stores. Potassium shifts back from the extracellular to intracellular compartments with resultant hypokalemia as insulin administration corrects the hyperglycemia, anion gap acidosis, and hyperosmolality associated with diabetic ketoacidosis. To avoid cardiac complications, serum potassium must be greater than 3.3 mEq/L (3.3. mmol/L) before initiating IV insulin. Once potassium is 3.3 mEq/L (3.3 mmol/L) or higher and IV insulin has been initiated, 20 to 30 mEq (20-30 mmol/L) of potassium chloride will usually need to be added to each liter of IV fluid to maintain a serum potassium level of 4.0 to 5.0 mEq/L (4.0-5.0 mmol/L). He is at risk of developing hypokalemia if his potassium supplementation is discontinued at this time.

Although subcutaneous insulin would provide insulin to suppress ketogenesis, the IV insulin drip provides greater flexibility in dose adjustments than subcutaneous insulin. Once the patient's anion gap acidosis has resolved, transitioning from the insulin drip to a subcutaneous insulin regimen should occur.

KEY POINT

- In patients with diabetic ketoacidosis, intravenous insulin therapy should be continued until complete resolution of the anion gap acidosis; as acidosis improves, it may be necessary to reduce the insulin infusion rate and add intravenous dextrose to prevent hypoglycemia.

Bibliography

Fayfman M, Pasquel FJ, Umpierrez GE. Management of hyperglycemic crises: diabetic ketoacidosis and hyperglycemic hyperosmolar state. Med Clin North Am. 2017;101:587-606. doi: 10.1016/j.mcna.2016.12.011. [PMID:28372715]

Item 81 Answer: C

Educational Objective: Treat type-2 amiodarone-induced thyrotoxicosis.

The most appropriate initial management for this patient is to prescribe prednisone. Amiodarone is an antiarrhythmic medication with high iodine content and prolonged half-life of approximately 40 days. Thyrotoxicosis affects 5% of patients taking amiodarone and can occur at any time during or up to 9 months after treatment. Type 1 (hyperthyroidism) amiodarone-induced thyrotoxicosis occurs in patients with underlying multinodular goiter or latent Graves disease and is associated with increased vascularity on color flow Doppler ultrasonography. Type 2 (destructive thyroiditis) usually affects those without thyroid disease and is not associated with increased vascularity on color flow Doppler. Mixed forms can also be seen and making the correct diagnosis can be difficult. The patient's clinical presentation is most consistent with type 2 amiodarone-induced thyrotoxicosis given the absence of structural thyroid disease (no nodules or goiter), absent thyroid-stimulating hormone (TSH) receptor antibody, and absent parenchymal flow seen on Doppler ultrasound. Moderate- to high-dose prednisone is an effective treatment that can be gradually tapered over 1 to 3 months.

Discontinuation of amiodarone would not yield any immediate clinical benefit due to its prolonged half-life elimination. The decision to discontinue amiodarone depends on the patient's cardiac status, availability of effective alternatives, and type of thyrotoxicosis, with treatment cessation being more important in type 1 than type 2.

Methimazole is most effective in treating type 1 (hyperthyroidism) amiodarone-induced thyrotoxicosis, which occurs in patients with Graves disease or thyroid nodules. Since this patient's presentation is most consistent with type 2 amiodarone-induced thyrotoxicosis (destructive thyroiditis), prednisone is the preferred treatment.

Performing thyroid scintigraphy with radioactive iodine uptake is not indicated. Amiodarone has a very high iodine content, which results in high serum iodine levels. This iodine competes with the radioactive isotope used for the test (^{123}I or ^{131}I) resulting in very low radioactive iodine uptake (<1%) in most patients. This test does not discriminate well between type 1 and 2 amiodarone-induced thyrotoxicosis and is not clinically useful.

KEY POINT

- Type 2 amiodarone-induced thyrotoxicosis (destructive thyroiditis) can be treated with moderate- to high-dose prednisone that can be gradually tapered over 1 to 3 months.

Bibliography

Danzi S, Klein I. Amiodarone-induced thyroid dysfunction. J Intensive Care Med. 2015;30:179-85. doi: 10.1177/0885066613503278. Epub 2013 Sep 24. [PMID: 24067547]

Item 82 Answer: D

Educational Objective: Diagnose the cause of rapid-onset hirsutism.

A pelvic ultrasound is the most appropriate management for this patient. Although androgen-secreting ovarian tumors are rare, they should be considered in patients with abrupt, rapidly progressive, or severe hyperandrogenism as well as in women with marked hyperandrogenemia (total testosterone >150 ng/dL [5.2 nmol/L]). Given this patient's rapid onset of hirsutism coupled with significantly elevated total testosterone level, a pelvic ultrasound is the best next step in evaluation to assess for a possible ovarian tumor.

Adrenal vein sampling is a procedure used to confirm whether autonomous adrenal hormone production is unilateral or bilateral. It is most commonly performed in the evaluation of primary aldosteronism. Adrenal vein sampling is needed in most patients to determine the source of aldosterone secretion when imaging is unrevealing and to confirm lateralization when imaging demonstrates an adrenal adenoma. For this patient, adrenal CT is more appropriate to exclude an adrenal cortisol-secreting and/or androgen-secreting neoplasm and may be appropriate if the pelvic ultrasound is unrevealing. There is no indication for this procedure at this time in this patient.

Cushing syndrome (CS) results from elevated levels of cortisol. Clinical findings that are highly specific for CS include centripetal obesity, facial plethora, abnormal fat deposition in the supraclavicular or dorsocervical ("buffalo hump") areas, and wide (>1 cm) violaceous striae. Evaluation for CS is most appropriate in patients who have specific signs and symptoms of CS, rather than in patients who are diffusely obese, have nonpathologic striae, and are having trouble losing weight because endogenous CS is such a rare condition with a costly evaluation algorithm. At least two first-line tests should be abnormal before the diagnosis is confirmed. Initial tests include the overnight low-dose dexamethasone suppression test, 24-hour urine free cortisol, and late-night salivary cortisol. Since the patient has none of the specific findings of CS, a 24-hour urine cortisol test is not indicated.

In addition to weight loss, combined hormonal oral contraceptives are first-line agents for treatment of polycystic ovary syndrome. Polycystic ovary syndrome is a diagnosis of exclusion; given this patient's rapid onset of hirsutism coupled with degree of her total testosterone elevation, an androgen-secreting tumor must be considered.

KEY POINT

- An androgen-secreting ovarian tumor should be considered in patients with abrupt, rapidly progressive, or severe hyperandrogenism as well as in women with marked hyperandrogenemia (total testosterone >150 ng/dL [5.2 nmol/L]).

Bibliography

Mihailidis J, Dermesropian R, Taxel P, Luthra P, Grant-Kels JM. Endocrine evaluation of hirsutism. Int J Womens Dermatol. 2017;3(1 Suppl):S6-S10. doi: 10.1016/j.ijwd.2017.02.007. eCollection 2017 Mar. [PMID:28492032]

Item 83 Answer: D

Educational Objective: Treat type 2 diabetes mellitus with metabolic surgery in an obese patient.

This patient should be referred for metabolic surgery. The gastrointestinal tract plays an important role in glucose homeostasis and serves as an important physiologic target for improving glycemic control. Short- and mid-term data from randomized controlled trials of metabolic surgery demonstrated greater improvements in glycemic control and cardiovascular risk factors compared with optimized medical therapy and lifestyle modifications. Retrospective cohort studies and prospective observational studies suggest a reduction in cardiovascular deaths and lower incidence of cardiovascular events in patients undergoing metabolic surgery. Metabolic surgery should be recommended to patients with type 2 diabetes who have class III obesity (BMI ≥ 40) independent of glycemic control and diabetes treatment regimen and to patients with type 2 diabetes with class II obesity (BMI 35.0-39.9) who fail to meet their glycemic goals despite optimizing medical therapies and lifestyle modifications. In addition, patients with class I obesity (BMI 30.0-34.9) who do not meet their glycemic goals despite optimizing medical therapy should be considered for metabolic surgery. The patient has class II obesity with an inability to meet her hemoglobin A_{1c} goal of less than 7% on her current medical regimen. Further modifications to her current regimen may either exacerbate hypoglycemia and accelerate weight gain or not reach her glycemic goal.

Although sitagliptin, a dipeptidyl peptidase (DPP)-4-inhibitor, is a weight neutral oral agent that could potentially improve her hemoglobin A_{1c} level by 0.95% to 1.1%, it would not achieve her target hemoglobin A_{1c} of less than 7%.

Pioglitazone, a thiazolidinedione (TZD), improves insulin sensitivity and hemoglobin A_{1c} by 0.9% to 1.1%. The addition of pioglitazone in this patient would likely not achieve her target hemoglobin A_{1c} goal and could potentially induce additional weight gain, a known side effect of this drug class.

Increasing the patient's insulin doses may improve her hemoglobin A_{1c} to goal, but it will exacerbate her hypoglycemia and promote additional weight gain.

KEY POINT

- Metabolic surgery demonstrates greater improvements in glycemic control and cardiovascular risk factors compared with optimized medical therapy and lifestyle modifications.

Bibliography

Rubino F, Nathan DM, Eckel RH, Schauer PR, Alberti KG, Zimmet PZ, et al; Delegates of the 2nd Diabetes Surgery Summit. Metabolic surgery in the treatment algorithm for type 2 diabetes: a joint statement by International Diabetes Organizations. Diabetes Care. 2016;39:861-77. [PMID: 27222544] doi:10.2337/dc16-0236

Item 84 Answer: C

Educational Objective: Diagnose osteomalacia.

The most likely diagnosis in this patient is osteomalacia causing bone pain or fracture of the pelvis or proximal right lower extremity. An insidious, protracted course involving enigmatic pain is typical of osteomalacia, which may be dismissed by patients or symptomatically treated by health care providers. Chronically low levels of vitamin D can lead to rickets in children and osteomalacia in adults. Vitamin D deficiency is caused by factors such as intestinal malabsorption due to gastrointestinal disorders or restricted access to sunlight. In promoting absorption from the gut, vitamin D enables proper bone mineralization by maintenance of calcium and phosphorus levels. Vitamin D also modulates the actions of osteoblasts and osteoclasts to ensure proper bone growth and remodeling. The more common forms of osteomalacia related to malabsorption or dietary factors are characterized by low 25-hydroxyvitamin D (calcidiol), low calcium and phosphate, and elevated parathyroid hormone (PTH) (secondary hyperparathyroidism) and alkaline phosphatase levels. Depending on the duration and severity of vitamin D deficiency, the serum concentration of 1,25-dihydroxyvitamin D may be normal, low, or high and is not helpful in the diagnosis of most forms of osteomalacia.

Osteitis fibrosa cystica is due to abnormally high bone turnover that can occur after prolonged exposure of bone to sustained high levels of PTH in hyperparathyroidism. It is associated with very high bone turnover, expansion of osteoid surfaces, and exuberant bone resorption resulting in an increased risk of fracture. Patients can be asymptomatic, or they may have bone pain. Classic skeletal changes on radiograph may include subperiosteal resorption of bone, most prominently at the phalanges of the hands. Osteitis fibrosa cystica is most commonly seen in patients with chronic kidney failure and is rarely associated with severe primary hyperparathyroidism.

Osteogenesis imperfecta (OI) comprises four genetic syndromes characterized by autosomal dominant or recessive mutations in *COL* genes, leading to abnormalities in the structure of type I collagen. OI is associated with bone fractures, short stature, body deformity, hearing loss, and dental deformity. A classic feature of OI is blue sclerae (reflecting visibility of the underlying choroid), but it is not sensitive or specific to OI. The biochemical profile is usually normal in OI.

Postmenopausal osteoporosis is a diagnosis of exclusion, made only after having evaluated and eliminated other causes of low bone mineral density such as osteomalacia. Patients with osteoporosis have a normal biochemical profile.

KEY POINT

- Osteomalacia related to malabsorption or dietary factors is characterized by low 25-hydroxyvitamin D, calcium, and phosphate levels and elevated parathyroid hormone and alkaline phosphatase levels.

Bibliography

Uday S, Högler W. Nutritional rickets and osteomalacia in the twenty-first century: revised concepts, public health, and prevention strategies. Curr Osteoporos Rep. 2017 Aug;15(4):293-302. doi: 10.1007/s11914-017-0383-y. Erratum in: Curr Osteoporos Rep. 2017 Aug 14; [PMID: 28612338]

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- Diagnose disease states that are less common and sometimes overlooked and confusing
- Improve management of comorbid conditions that can complicate patient care
- Determine when to refer patients for surgery or care by subspecialists
- Pass the ABIM Certification Examination
- Pass the ABIM Maintenance of Certification Examination

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- General internists and primary care physicians
- Subspecialists who need to remain up to date in internal medicine
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Key Points in the text that relate to High Value Care concepts (that is, concepts that discuss balancing clinical benefit with costs and harms) are designated by the HVC icon [**HVC**].

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Errata

Errata for MKSAP 18 will be available through the MKSAP Resource Site at mksap.acponline.org as new information becomes known to the editors.

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General Internal Medicine High Value Care Recommendations

The American College of Physicians, in collaboration with multiple other organizations, is engaged in a worldwide initiative to promote the practice of High Value Care (HVC). The goals of the HVC initiative are to improve health care outcomes by providing care of proven benefit and reducing costs by avoiding unnecessary and even harmful interventions. The initiative comprises several programs that integrate the important concept of health care value (balancing clinical benefit with costs and harms) for a given intervention into a broad range of educational materials to address the needs of trainees, practicing physicians, and patients.

HVC content has been integrated into MKSAP 18 in several important ways. MKSAP 18 includes HVC-identified key points in the text, HVC-focused multiple choice questions, and, for subscribers to MKSAP Digital, an HVC custom quiz. From the text and questions, we have generated the following list of HVC recommendations that meet the definition below of high value care and bring us closer to our goal of improving patient outcomes while conserving finite resources.

High Value Care Recommendation: A recommendation to choose diagnostic and management strategies for patients in specific clinical situations that balance clinical benefit with cost and harms with the goal of improving patient outcomes.

Below are the High Value Care Recommendations for the General Internal Medicine section of MKSAP 18.

- High breast density alone does not necessitate adjunctive breast imaging other than routine screening mammography (see Item 154).
- Direct-to-consumer genomic testing contributes very little to overall disease risk.
- The U.S. Preventive Services Task Force does not recommend multivitamins or herbal supplements for the prevention of cardiovascular disease or cancer.
- Enteral or parenteral artificial nutritional support at the end of life does not improve survival, is invasive, and can cause side effects.
- No evidence supports the use of long-term opioid therapy in patients with chronic noncancer pain; long-term opioid use is associated with poorer overall functional status, worse quality of life, and worse pain.
- In patients with medically unexplained symptoms, clinicians should limit diagnostic tests to those deemed medically necessary.
- In patients with acute cough, chest radiography is not indicated in the absence of abnormal vital signs or abnormal lung examination findings.
- Treatment of acute cough is primarily symptomatic; antibiotics are not recommended without a clear bacterial cause.
- Routine imaging is not recommended for benign paroxysmal positional vertigo.
- In patients with central vertigo, MRI is more sensitive than CT in detecting ischemic stroke, whereas CT provides an expedited, cost-effective assessment for hemorrhagic stroke.
- The American College of Physicians recommends against routinely performing brain imaging in cases of syncope that do not involve objective focal neurologic findings.
- Diagnostic testing, such as polysomnography, is usually unnecessary in the evaluation of insomnia.
- Pharmacologic therapies for insomnia are associated with adverse effects and should only be initiated in patients with insomnia refractory to nonpharmacologic interventions.
- Most patients with nonspecific low back pain do not require imaging or other diagnostic testing.
- Most patients with neck pain do not require imaging studies.
- Most patients with rotator cuff disease do not require imaging studies.
- In patients with asymptomatic popliteal (Baker) cysts, no treatment is necessary.
- In patients in whom statin therapy is being considered, an alanine aminotransferase level should be obtained at baseline to evaluate for liver dysfunction; further hepatic monitoring is unnecessary if the baseline level is normal (see Item 148).
- There is little evidence that over-the-counter weight loss supplements are effective.
- Treatment is not indicated in patients with low testosterone levels only; it should be reserved for patients with a low testosterone level associated with symptoms.
- Routine laboratory testing for the diagnosis of menopause is not recommended.
- Medications have not been shown to be of benefit in the management of tinnitus.
- Acute rhinosinusitis is usually caused by viruses, allergies, or irritants, and avoidance of unnecessary antibiotics represents high value care.
- Patients with pharyngitis who present with fewer than three of the four Centor criteria do not need to be tested or treated for group A *Streptococcus* infection.

- In tobacco cessation, combining behavioral counseling with pharmacotherapy is more effective than either modality alone, and combining more than one type of nicotine replacement therapy (short- and long-acting) is more effective than monotherapy.
- Cognitive impairment is best measured with assessment examinations, such as the Mini-Cog and the Mini–Mental State Examination, rather than laboratory testing or imaging (see Item 48).
- No pharmacologic therapies are recommended for the treatment of stress urinary incontinence or functional incontinence.
- Hydrocolloid or foam dressings are superior to standard gauze dressings in the treatment of pressure injuries (see Item 118).
- Preoperative laboratory testing should be performed based on the patient's medical conditions, physical examination findings, and preoperative symptoms; routine laboratory panels expose patients to unnecessary testing and are not recommended.
- Patients with low cardiovascular risk (<1% risk for a perioperative major adverse cardiac event) may proceed to surgery without preoperative cardiac stress testing.
- Preoperative cardiac stress testing should generally be reserved for patients at elevated risk for a major adverse cardiac event with a functional capacity less than 4 metabolic equivalents, but only if the results of the test will change perioperative management (see Item 34).
- Routine electrocardiography is not indicated in asymptomatic patients undergoing low-risk surgical procedures.
- In patients with coronary artery disease, routine coronary angiography or revascularization should not be performed exclusively to reduce perioperative cardiovascular events.
- Preoperative chest radiography is indicated only in patients with signs or symptoms of pulmonary disease and in patients with underlying cardiac or pulmonary disease and new or unstable symptoms.
- Spirometry should not be routinely performed preoperatively except in patients undergoing lung resection.
- Asymptomatic carotid bruit is not predictive of perioperative stroke and requires no preoperative evaluation.
- Pregnant patients should undergo the same preoperative medical evaluation as nonpregnant patients; additional diagnostic testing is unnecessary.

General Internal Medicine

High Value Care in Internal Medicine

Although the United States spends more on health care than all other developed nations, it has higher rates of medical care-related mortality and shorter life expectancy. Compared with other high-income countries, patients in the United States pay more for prescription drugs, undergo more diagnostic tests, and pay the highest hospital and physician prices for procedures. In response to this unsustainable spending, health policy organizations and other expert groups advocate implementing a high value approach to patient care.

H High value care is individualized care that delivers proven benefits while minimizing risks and unnecessary costs. It requires a careful evaluation to determine whether the benefits of a diagnostic test or intervention justify the harms and costs. Importantly, when determining value, clinicians should consider the benefits of a test or intervention before the cost. Focusing primarily on cost increases the tendency to avoid an expensive test or intervention regardless of outcome or to continue a low-cost intervention that provides no benefit. Notably, some costly or risky tests and interventions, such as screening colonoscopy, are high value because their benefits may be substantial. Similarly, some inexpensive and low-risk tests and interventions, such as routine daily laboratory testing in hospitalized patients, represent low value care. Examples of high value and low value care are provided in **Table 1**. H

Shared decision making is essential to high value care, particularly because perceived patient demand is one driver of inappropriate testing and interventions. Including patients in the decision-making process provides opportunities to educate patients on balancing benefits with potential harms and costs and to incorporate their values and preferences into the care process.

H Resources to help clinicians determine the value of common tests and interventions are available from the American College of Physicians (https://www.acponline.org/clinical-information/high-value-care), Alliance for Academic Internal Medicine, and Society of Hospital Medicine. In addition, the Choosing Wisely campaign, an initiative of the American Board of Internal Medicine Foundation with medical specialty societies, has published specialty-specific lists of commonly used tests or procedures whose necessity should be questioned and discussed by clinicians and patients (www.choosingwisely.org). *Consumer Reports* works with many of the Choosing Wisely partners to develop patient-friendly materials from the lists of recommendations and to disseminate them to consumers through a network of Choosing Wisely consumer partners. H

TABLE 1. Examples of High Value and Low Value Care Interventions

Intervention	Cost	Benefit
High Value Care		
High-sensitivity D-dimer testing to exclude venous thromboembolism in patients with low likelihood of disease	Low	High negative predictive value
Influenza vaccination	Low	High benefit for reducing disease burden and complications
Low Value Care		
Antibiotic therapy in patients with upper respiratory tract infection	Low	No benefit for reducing duration or severity of illness
Carotid ultrasonography in patients with syncope	Intermediate	Low diagnostic value
Imaging studies in patients with low back pain in the absence of "red flag" findings (fever, involuntary weight loss, incontinence)	Intermediate	Low diagnostic value

KEY POINT

- High value care is individualized care that delivers proven benefits while minimizing risks and unnecessary costs. HVC

Interpretation of the Medical Literature

Introduction

The science of medicine is constantly evolving, and peer-reviewed literature is the primary means of disseminating new medical knowledge. The application of this information to patient-centered medical decision making requires an understanding of different study designs and how to interpret statistical tests for significance. Although research in the basic sciences (including pharmacology and physiology) provides the

basis for many clinical advances, this chapter will review interpretation of the literature that may be immediately applicable to the clinical setting.

Study Designs

Study designs can be divided into two broad categories: experimental studies and observational studies. The selection of a study design is guided by the suitability of the design to address the clinical question and the population being studied.

The validity, or trustworthiness, of a study's results may be limited by bias and/or confounders (see Validity of a Study).

Experimental Study Designs

Experimental studies systematically expose some or all of the individuals in the study to a potential causative or protective factor (the exposure, often a treatment) (**Table 2**). Exposed and unexposed participants are compared with respect to developing the outcome of interest. As an example, an experimental study might compare patients with diabetes mellitus treated with a statin to those treated with a placebo to determine whether patients receiving active treatment are more or less likely than untreated patients to experience cardiovascular events.

The process for allocating the exposure or treatment to the study participants affects the study strength and the validity of the findings. The strongest experimental design is the randomized controlled trial. By randomly allocating the treatment, confounders (both known and unknown) are randomly distributed in the treatment and control groups. The least rigorous experimental design is the quasi-experimental design, in which participants are not randomly assigned. One example of a quasi-experimental design is a pre-post trial, in which

TABLE 2. Experimental Study Designs

Study Design	Description	Best Uses	Common Limitations to Use/Validity	Common Measure of Association
Quasi-experimental study	All participants receive treatment of interest Example: phase I drug trial	Establishing treatment effect, defining risks of adverse events	Difficult to clearly establish that treatment caused outcome Risk for confounding, especially for factors not known	Before-and-after comparison of outcome of interest
Non-randomized controlled trial	Treatment is allocated in a prespecified manner but not using randomization; comparison is made between different treatment groups or between treatment and control groups Example: study of surgical and nonsurgical treatment options in which enrolled participants are assigned to the treatment type they prefer to receive	When patients/participants may not be amenable to being randomly assigned to a treatment or when randomization is not ethically permitted	Risk for confounding, especially for factors not known Risk for selection bias if patients are allowed choice in treatment allocated	Difference between treatment groups in outcome of interest Measure reported varies depending on outcome of interest and statistical technique
Cluster randomized trial	Participants are randomly assigned as a unit instead of individually Example: study of effect of diabetic education on average hemoglobin A_{1c} value, in which participants are community primary care practices	Treatments for which randomization of individual patients is not feasible or ethical When effect at a level larger than an individual level (i.e., institution or health system) is being studied	Complicated statistical analysis May be difficult to ensure groups being compared are similar (risk for confounding)	Difference between treatment groups in outcome of interest Measure reported varies depending on outcome of interest and statistical technique
Randomized controlled trial	Participants are randomly assigned to one of the treatment options (including control/placebo group)	Considered to be highest level of evidence for treatment studies Confounding is minimized if study is large enough	Generalizability is limited to the population included in the trial Expensive and resource intensive to conduct	Difference between treatment groups in outcome of interest Measure reported varies depending on outcome of interest and statistical technique

all participants receive the studied treatment and results are obtained by comparing measurements taken before and after the outcome; thus, participants serve as their own internal controls. Because there is no external control group, the ability of the quasi-experimental design to determine cause and effect is limited.

Observational Study Designs

In observational studies, no treatment is imposed on the persons being studied. Instead, researchers observe naturally occurring events in individuals who have or have not been exposed to a risk factor or treatment. The relationships between risk factors and disease may be explored, but the ability to assess for causality is limited.

Common observational study designs include ecologic, cross-sectional, case control, and cohort studies. Case reports or case series, which describe an individual case or a series of related cases, are not true studies but have the potential to identify new or unique relationships to be further studied.

Ecologic studies evaluate the prevalence or extent of an exposure across distinct populations. They are hypothesis generating and are used to identify compelling trends for an exposure of interest across different groups, which can be investigated subsequently in more focused studies. Ecologic studies cannot be used to determine causation. Incorrect assignment of causation based on ecologic study results is termed the ecologic fallacy.

Cross-sectional studies evaluate the relationship between exposures and health outcomes in a population of interest. These studies are characterized by the measurement of factors and outcomes at a single point in time. Because cross-sectional studies lack comparison groups and the temporal sequence is often unknown, these studies are best used to determine disease prevalence and generate hypotheses; they can also assess the relatedness between two exposures of interest. Surveys conducted by health services groups may serve as the basis for these studies. Examples include the National Health and Nutrition Examination Survey and the Behavioral Risk Factor Surveillance Survey, both conducted by the Centers for Disease Control and Prevention.

Case control studies compare past exposures in patients with and without disease. The events being studied have already occurred; therefore, there is potential for recall bias, which arises when patients with the disease of interest are more likely to recall past exposures compared with controls. However, for the study of rare diseases, case control studies may be the best way to collect enough data to determine meaningful relationships.

Cohort studies divide participants into groups based on the presence or absence of a critical exposure and evaluate for differences between the groups in the development of a disease or outcome. Cohort studies may enroll participants before the outcome develops and follow patients forward in time (prospective cohorts), or they may enroll participants after an event has occurred (retrospective cohorts). Cohort studies are ideal for studying diseases or outcomes that develop over time, evaluating the effect of rare potential causative factors, and performing time-to-event (survival) analyses; however, these studies are subject to losses to follow-up. Similar to case-control studies, retrospective cohorts may also be subject to recall bias.

Systematic Reviews and Meta-Analysis

Narrative review articles, a common source of information for clinicians, present an expert assessment of the known evidence on a certain topic. Although narrative reviews are valuable learning resources, the body of evidence they contain varies and is influenced by the experiences of the authors. In contrast, systematic reviews involve a systematic search of the literature using predefined criteria to collect all published and unpublished studies that address the topic. This systematic approach minimizes selection bias and increases the strength of the information presented. Systematic reviews that combine the results of the studies included in a statistical analysis are termed meta-analyses.

The value of meta-analysis often resides in the ability to pool data and increase sample size and statistical power, as the ability to detect a difference between two groups depends on the number of persons being studied. A larger sample size has a greater power to discriminate smaller differences between groups; however, larger studies carry a higher cost and are logistically more complicated to administer. Meta-analysis of high-quality randomized controlled trials is considered to be one of the highest levels of clinical evidence. Factors that limit the ability to combine study results meaningfully include differences in the study populations, research measures, and statistical techniques.

KEY POINTS

- Experimental studies systematically expose some or all of the individuals in the study to a potential causative or protective factor; the strongest experimental design is the randomized controlled trial. **HVC**
- Cross-sectional studies lack comparison groups, and the temporal sequence is often unknown; therefore, these studies are best used in determining disease prevalence and generating hypotheses. **HVC**
- Case-control studies compare past exposures in patients with and without disease; these studies are advantageous for the study of rare diseases. **HVC**
- Cohort studies are ideal for studying diseases or outcomes that develop over time, evaluating the effect of rare potential causative factors, and performing time-to-event (survival) analyses. **HVC**

Validity of a Study

Validity refers to the fidelity of the study results to what is correct or true. Validity can be further characterized as internal or

external. Internal validity refers to how well study error is minimized and to what degree the results are true. External validity is the extent to which the study results can be applied to settings other than the study setting; it represents the generalizability of the study results. Threats to the validity of a study include systematic error and random error.

Systematic error is the influence of confounders and bias on the results of a study. Confounders, factors other than the variables being studied that are associated with the studied population and may affect the end point being assessed, are a common threat to validity. An observational study, for example, may show that patients receiving statin therapy have an increased risk for cardiovascular events compared with those not taking statin therapy. However, the presence of a powerful confounder, specifically that patients receiving statin therapy are at high risk for cardiovascular events, influences the outcome of the study. The impact of confounding can be reduced by design strategies, such as matching, and evaluation techniques, including stratification of the analysis and regression techniques (or regression adjustment).

Bias refers to the presence of factors that skew the study results in a specific direction. Bias can be introduced at any point in a study design, including patient recruitment and outcome measurement. Careful study design can decrease the likelihood of bias; however, once bias has been introduced into the study, it cannot be eliminated or minimized.

Random error is error that is introduced by random variability or purely by chance. The role of chance is expressed by the *P* value or confidence interval and is determined by statistical analysis. The likelihood of random error can be decreased by increasing study size and using precise measurement strategies.

Statistical Analysis

Statistical significance is reported using *P* values or confidence intervals, which express the probability that chance alone accounts for the result. A *P* value less than or equal to 0.05 (≤5% probability that chance alone accounts for the result) is often considered as indicating a statistically significant finding. However, this determination is arbitrary, and some researchers may opt for a different level (typically more stringent).

Confidence intervals express the range of values within which the true result falls; the 95% confidence interval means that there is 95% confidence that the true value is within the confidence interval range. Narrower ranges imply greater confidence, or certainty, that the reported value is closer to the true value.

Sensitivity, Specificity, and Predictive Values

Sensitivity and specificity reflect the accuracy of a diagnostic or screening test (**Table 3**). Sensitivity is the ability of the test to detect those who truly have a disease or condition, or the probability that the test result will be positive in a patient with the disease. Specificity is the ability of the test to correctly identify those without the disease, or the probability that the test result will be negative in a patient without the disease. Therefore, sensitive tests are those with minimal rates of false-negative results, and specific tests are those with minimal rates of false-positive results.

Positive and negative predictive values reflect the validity of a positive or negative test result for predicting the presence or absence of disease in a specific population. The positive predictive value is the proportion of those with a positive test result who truly have the disease. The negative predictive value is the proportion of those with a negative test result who are truly free of the disease. Predictive values are determined not only by sensitivity and specificity but also by the prevalence of the disease in the population.

Likelihood Ratios

Likelihood ratios (LRs) are used to translate the impact of sensitivity and specificity of a specific clinical finding on the probability of a disease or outcome in a given patient; they provide a measure of the strength of association between the clinical finding and the specific disease. Each clinical finding, inclusive of symptoms, physical findings, and laboratory and imaging results, has a positive and negative LR for a specific disease. The positive LR is used when the test result is positive, and the negative LR is used when the test result is negative.

LRs are used in conjunction with the pretest probability of disease (the probability of disease in the patient before the test result is considered). The interaction of the pretest probability and LR results in a posttest probability of disease. The posttest probability may then serve as the rationale for treating a patient for the disease in question (if the positive test resulted in a high posttest probability) or ruling out a diagnosis (if the negative test resulted in a very low posttest probability). Mathematically, the pretest probability (a percentage) is converted to pretest odds (a ratio), the odds are multiplied by the appropriate LR, and the posttest odds are converted to a posttest probability.

For ease of clinical use, several general LR rules apply. Positive LR values of 2, 5, and 10 correspond to an increase in disease probability by 15%, 30%, and 45%, respectively; negative LR values of 0.5, 0.2, and 0.1 correspond to a decrease in disease probability by 15%, 30%, and 45%, respectively. Larger positive LRs and smaller negative LRs are more apt to affect clinical decisions.

Clinical calculators that provide a quick means for calculating LRs and their effect on probability of disease, such as one from the Centre for Evidence-Based Medicine (https://www.cebm.net/2014/06/catmaker-ebm-calculators/), are widely available. Alternatively, nomograms may be used to extrapolate the posttest probability of disease from the pretest probability of disease based on the LR (**Figure 1**).

Absolute and Relative Risk Reduction

Absolute risk reduction and relative risk reduction are measures commonly used to report the efficacy of an intervention

TABLE 3. Common Terms Used in Interpretation of the Medical Literature for Diagnostic Tests

Term	Definition	Calculation	Notes
Prevalence (Prev)	Proportion of patients with the disease in the population	Prev = (TP + FN) / (TP + FP + FN + TN)	
Sensitivity (Sn)	Proportion of patients with the disease who have a positive test result	Sn = TP / (TP + FN)	
Specificity (Sp)	Proportion of patients without the disease who have a negative test result	Sp = TN / (FP + TN)	
Positive predictive value (PPV)	Proportion of patients with a positive test result who have the disease	PPV = TP / (TP + FP)	Increases with *increasing* prevalence
Negative predictive value (NPV)	Proportion of patients with a negative test result who do not have the disease	NPV = TN / (TN + FN)	Increases with *decreasing* prevalence
Positive likelihood ratio (LR+)	The ratio of the probability of a positive test result among patients with the disease to the probability of a positive result among patients without the disease	LR+ = Sn / (1 − Sp)	
Negative likelihood ratio (LR−)	The ratio of the probability of a negative test result among patients with the disease to the probability of a negative result in patients without the disease	LR− = (1 − Sn) / Sp	
Pretest odds	The odds that a patient has the disease before the test is performed	Pretest odds = pretest probability / (1 − pretest probability)	
Posttest odds	The odds that a patient has the disease after a test is performed	Posttest odds = pretest odds × LR	LR+ is used if result of test is positive; LR− is used if result of test is negative A nomogram is available to calculate posttest probability using pretest probability and LR without having to convert pretest probability to odds (see Figure 1)
Pretest probability	Proportion of patients with the disease before a test is performed	Pretest probability can be estimated from population prevalence, clinical risk calculators, or clinical experience if no evidence-based tools exist	
Posttest probability	Proportion of patients with the disease after a test is performed	Posttest probability = posttest odds / (1 + posttest odds)	

FN = false negative; FP = false positive; TN = true negative; TP = true positive.

(Table 4). Absolute risk reduction is the difference in the response to treatment between experimental and control groups. Absolute risk reduction is particularly relevant when the measure reported is the rate of development of a clinically meaningful end point, such as the incidence of cardiovascular events or death in studies of lipid-lowering therapy. Because these differences may seem small, investigators will often also report the relative risk or risk ratio (the ratio of the risk for the event in the experimental group to the risk for the event in the control group) as well as relative risk reduction, or (1 − risk ratio) × 100%.

The difference in the magnitude of these measures can be illustrated with a study of lipid-lowering therapy in which the rate of acute coronary syndromes in 5 years is 3.6% in the treated group and 4.8% in the control group. The absolute risk reduction is 1.2%. The risk ratio, however, is 75%, and the relative risk reduction is 25%. Therefore, although the absolute difference in rates between the two groups is small (1.2%), the

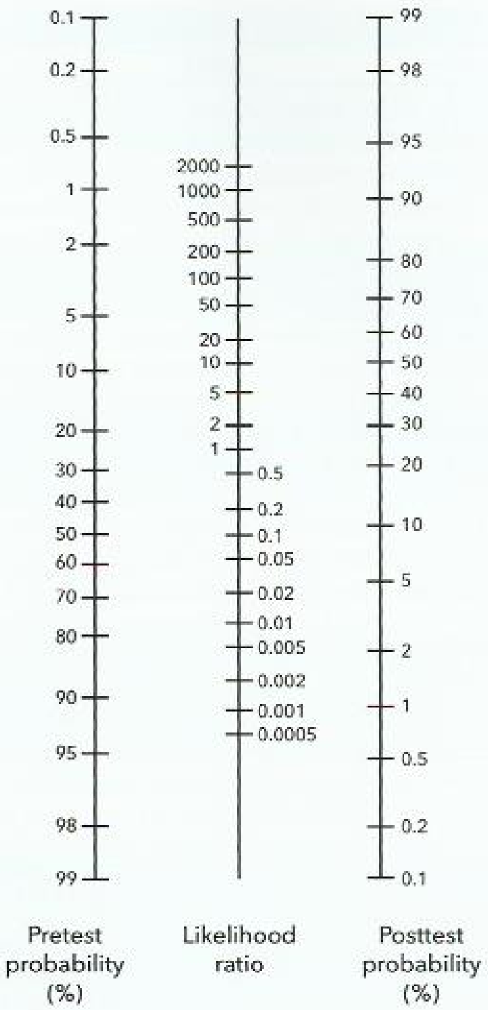

FIGURE 1. Nomogram for interpreting diagnostic test results. In this nomogram, a straight line drawn from a patient's pretest probability of disease (which is estimated from experience, local data, or published literature) through the likelihood ratio for the test result will indicate the posttest probability of disease.

Reproduced with permission from Fagan TJ. Letter: nomogram for Bayes theorem. N Engl J Med. 1975 Jul 31;293(5):257. [PMID: 1143310] Copyright 1975, Massachusetts Medical Society.

effect of a treatment may appear substantial when relative risk reduction (25%) is reported.

Numbers Needed to Treat and Harm

The clinical impact of an intervention can be further assessed by using the number needed to treat (NNT) and the number needed to harm (NNH). The NNT is the inverse of the absolute risk reduction. It represents the number of patients who must receive a treatment to cause one additional patient to benefit, and it provides a quantifiable measure of the treatment effect that is easily understood by physicians and patients. The acceptability of the NNT depends on the risks associated with the condition, the cost and side effects of the treatment, and other treatments available.

The NNH can be similarly calculated for studies measuring adverse outcomes, but it also needs to be considered in the context of the benefits of the treatment and the severity of the harm incurred.

KEY POINTS

- Sensitivity is the ability of the test to detect those who truly have a disease or condition, whereas specificity is the ability of the test to correctly identify those without the disease.
- Likelihood ratios are used to translate the impact of sensitivity and specificity of a specific clinical finding on the probability of a disease or outcome in a given patient.
- Absolute risk reduction is the difference in the response to treatment between experimental and control groups.
- The number needed to treat is the inverse of the absolute risk reduction and represents the number of patients who must receive a treatment to cause one patient to benefit.

Levels of Evidence

Levels of evidence describe the strength and quality of study results and can aid in clinical decision making. Systematic reviews, with or without meta-analysis, provide the highest level of evidence, followed by large, multicenter randomized, blinded, placebo-controlled trials. Large, meticulously controlled studies generally provide a higher level of evidence than smaller studies. Experimental studies provide a higher level of evidence than observational studies, and reports of expert opinion provide the lowest acceptable level of evidence. The U.S. Preventive Services Task Force and other organizations have developed grading systems to rank the relative rigor of clinical studies (**Table 5**). The grading system used by the U.S. Preventive Services Task Force for levels of benefit is provided in Routine Care of the Healthy Patient.

Routine Care of the Healthy Patient

History and Physical Examination

Periodic Health Examination

The periodic health examination has played a central role in patient care for the past century, becoming an expectation for physicians and patients alike. Although evidence suggests periodic health examinations may improve surrogate outcomes, such as reduction in cardiovascular risk factors and increased receipt of preventive services, there is no evidence that they reduce mortality or other patient-important outcomes. A 2012 Cochrane systematic review confirmed that general health checks result in more diagnoses and medication prescriptions but do not reduce morbidity, hospitalizations, or mortality. The Danish Inter99 trial showed that screening for

TABLE 4. Common Terms Used in Interpretation of the Medical Literature for Therapeutics

Term	Definition	Calculation	Notes
Absolute risk (AR)	The probability of an event occurring in a group during a specified time period	AR = patients with event in group / total patients in group	Also known as event rate; can be for benefits or harms. Often, an experimental event rate (EER) is compared with a control event rate (CER)
Relative risk (RR)	The ratio of the probability of developing a disease with a risk factor present to the probability of developing the disease without the risk factor present	RR = EER / CER	Used in cohort studies and randomized controlled trials
Absolute risk reduction (ARR)	The difference in rates of events between experimental group (EER) and control group (CER)	ARR = | EER − CER |	
Relative risk reduction (RRR)	The ratio of absolute risk reduction to the event rate among controls	RRR = | EER − CER | / CER	
Number needed to treat (NNT)	Number of patients needed to receive a treatment for one additional patient to benefit	NNT = 1 / ARR	A good estimate of the effect size
Number needed to harm (NNH)	Number of patients needed to receive a treatment for one additional patient to be harmed	NNH = 1 / ARI	ARI is the absolute risk increase and equals | EER − CER | when the event is an unfavorable outcome (e.g., drug side effect)

TABLE 5. U.S. Preventive Services Task Force Hierarchy of Research Design

Level	Description
I	Properly powered and conducted RCT; well-conducted systematic review or meta-analysis of homogeneous RCTs
II-1	Well-designed controlled trial without randomization
II-2	Well-designed cohort or case-control analytic study
II-3	Multiple time series with or without the intervention; results from uncontrolled studies that yield results of large magnitude
III	Opinions of respected authorities, based on clinical experience; descriptive studies or case reports; reports of expert committees

RCT = randomized controlled trial.

Reproduced from U.S. Preventive Services Task Force. Procedure Manual. https://www.uspreventiveservicestaskforce.org/Page/Name/procedure-manual. November 2017. Accessed June 27, 2018.

ischemic heart disease and repeated counseling over 5 years for those at high risk had no effect on risks for ischemic heart disease, stroke, or mortality after 10-year follow-up. Periodic health examinations also have a substantial financial impact, costing $5.2 billion annually without including costs of additional testing, visits, or missed work, according to a 2007 estimate. Overdiagnosis and overtreatment are other potential drawbacks to periodic health checks. Therefore, the Society of General Internal Medicine, through the Choosing Wisely campaign, specifically recommends against performing general health checks that include a comprehensive examination and laboratory testing for asymptomatic adults.

Despite this evidence, the periodic health examination may offer value that is difficult to measure in clinical trials. It provides dedicated time for screening and counseling and strengthens physician-patient relationships, which may improve adherence to physician recommendations. Notably, Medicare covers an initial preventive physical examination once in a lifetime within the first 12 months of a patient's enrollment in Medicare and an annual wellness visit thereafter. These visits are described as a focused physical and health review rather than a comprehensive head-to-toe physical examination.

Routine History and Physical Examination

Obtaining a basic history is essential in establishing a clinician-patient relationship and understanding the patient's health history, concerns, and expectations (**Table 6**). Patients may be sensitive about sharing certain information, such as substance use and sexual practices, and open and nonjudgmental communication can encourage sharing. Clinicians should preface these inquiries by informing the patient that these questions are asked of everyone, the information is necessary to provide the best care, and responses are confidential.

A focused physical examination should always be performed to address the patient's concerns and relevant historical findings. Irrespective of gender presentation, physicians should provide care for the present anatomy in a

TABLE 6. Components of the History

Past medical conditions and surgeries
Hospitalizations
Major childhood illnesses
Allergies and corresponding reactions
Social history
Alcohol use
Tobacco use
Illicit drug use
Spirituality
Work and home situation
Social support
Safety
• Home safety: intimate partner violence and abuse, working smoke alarms, water heater set to ≤49 °C (120 °F), weapons safety
• Safety outside of the home: seatbelt use while driving, helmet use while motorcycling or bicycling, no electronic device use while driving
Diet
Physical activity
Family history
Medication history
Prescription and over-the-counter medications
Past and current hormone use for transgender patients
Vitamins and supplements
Herbal preparations and nontraditional therapies
Sexual history[a]
Partners
• How many sex partners have you had in the past 2 months? 12 months?
• Have you had sex with men, women, or both?
Practices
• What kind of sexual contact have you had? Vaginal (penis in vagina), anal (penis in rectum/anus), or oral sex (mouth on penis/vagina)?
Protection/pregnancy
• Have you ever had a sexually transmitted infection?
• What do you do to protect yourself from sexually transmitted infections?
• Are you or your partner trying to get pregnant?
• What are you doing to prevent pregnancy?
Review of systems

[a]When taking a sexual history, do not assume heterosexuality, and use gender-neutral language when referring to partners ("partner" or "spouse" rather than "wife," "husband," "girlfriend," or "boyfriend").

sensitive, respectful, and affirming manner. In contrast to the focused physical examination, the value of the routine physical examination in asymptomatic patients has been debated. Regularly obtaining height and weight (to calculate BMI) as well as blood pressure is universally recommended. Additionally, pulse palpation in individuals older than 65 years has been found effective for detection of atrial fibrillation. The U.S. Preventive Services Task Force (USPSTF) recommends against routine abdominal, testicular, and bimanual pelvic examinations for cancer screening. The USPSTF has also concluded that there is insufficient evidence to recommend routine cardiac and lung auscultation, thyroid palpation, skin examination, visual acuity assessment, and hearing assessment, although these evaluations may be appropriate as part of a comprehensive physical examination in persons at increased risk. Relatively no harms arise from these examinations save for the opportunity cost of providing another service that may be more valuable. Routine laboratory tests, such as screening complete blood count and urinalysis, are not recommended.

Preparticipation physical examination is required for adolescents before participation in organized sports. In conjunction with the American Academy of Family Physicians and several professional sports medicine organizations, the American Academy of Pediatrics (AAP) created the Preparticipation Physical Evaluation, now in its fourth edition. Additionally, free templates for history, physical examination, and clearance forms are available on the website of the AAP (https://www.aap.org/en-us/about-the-aap/Committees-Councils-Sections/Council-on-sports-medicine-and-fitness/Pages/PPE.aspx). Mandatory components include evaluating for exertional symptoms, family history of premature or sudden cardiac death, and presence of a heart murmur.

Digital stethoscopes, point-of-care ultrasonography, smart phone applications, and other technological advances are gradually becoming more commonplace in the physical examination. However, it is unclear whether these tools improve diagnosis or contribute to overdiagnosis.

KEY POINT

- The periodic health examination may improve surrogate outcomes, such as reduction in cardiovascular risk factors and increased receipt of preventive services; however, the periodic health examination has not been shown to reduce mortality or other patient-important outcomes. HVC

Screening

Principles of Screening

Levels of prevention have traditionally been categorized as primary, secondary, and tertiary. Primary prevention is preventing disease or injury before it occurs (for example, through immunization). Secondary prevention is early detection and treatment of disease in asymptomatic patients to slow or stop disease progression. Most screening tests, such as those for colorectal and breast cancers, are secondary prevention measures. Tertiary prevention involves reducing morbidity and

mortality due to established disease, such as cardiac rehabilitation after myocardial infarction.

Screening is appropriate for common conditions for which (1) early intervention can decrease morbidity and mortality and (2) safe, acceptable, widely available, and reasonably priced screening tests exist. Screening tests must also have adequate sensitivity and specificity to minimize false-positive and false-negative results.

The effectiveness of screening tests in reducing morbidity and mortality is evaluated through clinical trials; however, studies of screening tests are problematic and subject to three types of bias. Lead-time bias occurs when early detection artificially leads to an increase in measured survival. The time between early detection and clinical diagnosis is mistakenly counted as survival time; however, only the measured time with diagnosed disease, not survival time, has increased (**Figure 2**). Using disease-specific mortality rates rather than survival time as the primary outcome in studies of screening tests can help minimize lead-time bias. Length-time bias occurs when screening detects more cases of disease with a prolonged asymptomatic phase than cases of disease with a short asymptomatic phase. Slowly progressive disease is more likely than aggressive disease to be detected with screening, leading to an overestimation of survival benefit in those with screen-detected disease. Overdiagnosis, or finding and treating illness that otherwise would not have become clinically apparent or caused harm in the patient's lifetime, is an extreme example of length-time bias. Overdiagnosis is an increasingly recognized harm of breast and prostate cancer screening and may also occur with incidental detection of thyroid and kidney cancers on imaging studies. Selection bias, also referred to as volunteer, referral, or compliance bias, occurs when patients who undergo screening tests are healthier and more interested in their health than nonadherent patients or the general population. Intention-to-treat analyses, in which patients are analyzed according to their original group assignment in randomized clinical trials regardless of intervention received, reduce selection bias.

Screening Recommendations for Adults

The USPSTF and many specialty societies routinely aggregate and review available evidence to inform clinical practice guidelines for screening, counseling, and use of preventive medications. The American College of Physicians (ACP) has developed several different types of clinical recommendations, including clinical practice guidelines, clinical guidance statements, best practice advice, and recommendations regarding high value care, all of which are available at https://www.acponline.org/clinical-information/guidelines. Although there is much agreement among screening recommendations, guidelines often disagree when (1) sufficient evidence is lacking and expert opinion plays a larger role or (2) potential benefits and harms both exist and the balance depends on a person's risk, preferences, and values.

An additional resource to help clinicians identify appropriate screening tests and preventive services is the electronic Preventive Services Selector (ePSS) created by the Agency for Healthcare Research and Quality (available at epss.ahrq.gov in web-based or mobile application-based formats). With this tool, users can select USPSTF-recommended practices based

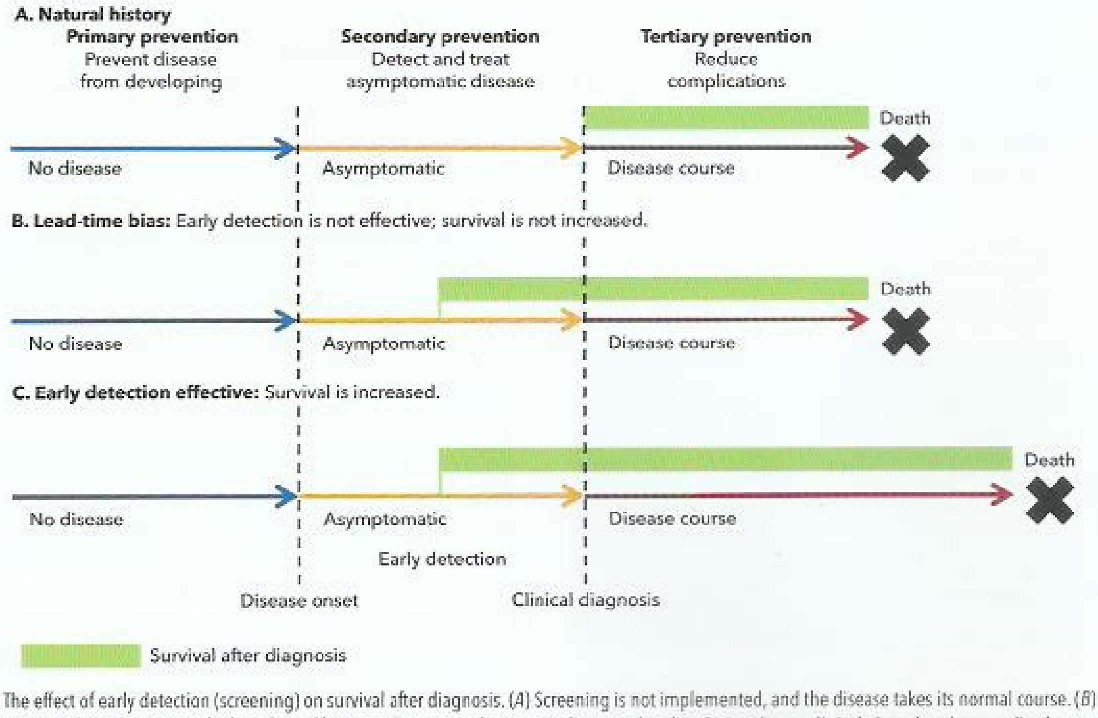

FIGURE 2. The effect of early detection (screening) on survival after diagnosis. (*A*) Screening is not implemented, and the disease takes its normal course. (*B*) Lead-time bias occurs when survival time appears to be lengthened because the screened patient is diagnosed earlier during the preclinical phase but does not live longer in actuality. (*C*) Screening effectively detects disease during the asymptomatic phase, and survival time is lengthened.

on patient age, sex, and other characteristics (such as tobacco use or pregnancy).

Screening recommendations frequently change as supportive evidence emerges. It is important to be aware of changes in recommendations as they occur, to reflect on the rationale and implications of the changes, to contemplate how to best help patients understand new recommendations, and to incorporate these changes appropriately into practice.

Specific Screening Tests

The following section describes screening recommendations from the USPSTF and other organizations. The grading system of the USPSTF (A, B, C, D, and I) is explained in **Table 7**.

TABLE 7. U.S. Preventive Services Task Force Grading and Suggestions for Practice

Grade	Definition	Suggestions for Practice
A	The USPSTF recommends the service. There is high certainty that the net benefit is substantial.	Offer or provide this service.
B	The USPSTF recommends the service. There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial.	Offer or provide this service.
C	The USPSTF recommends selectively offering or providing this service to individual patients based on professional judgment and patient preferences. There is at least moderate certainty that the net benefit is small.	Offer or provide this service for selected patients depending on individual circumstances.
D	The USPSTF recommends against the service. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits.	Discourage the use of this service.
I statement	The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of the service. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.	Read the Clinical Considerations section of USPSTF Recommendation Statement. If the service is offered, patients should understand the uncertainty about the balance of benefits and harms.

USPSTF = U.S. Preventive Services Task Force.

Reproduced from U.S. Preventive Services Task Force. Procedure Manual. https://www.uspreventiveservicestaskforce.org/Page/Name/procedure-manual. November 2017. Accessed June 27, 2018.

Screening for Chronic Diseases

Abdominal Aortic Aneurysm

The USPSTF recommends one-time abdominal ultrasonography to screen for abdominal aortic aneurysm (AAA) in all men aged 65 to 75 years who have ever smoked (grade B). Ever-smokers are commonly defined as persons who have smoked more than 100 cigarettes in their lifetime. The number needed to screen (NNS) to prevent one death from AAA in this population is 667. The number needed to treat (NNT) with surgery to prevent one death is 1.5, owing to the high mortality rate associated with AAA rupture. In men aged 65 to 75 years who have never smoked, selective screening is recommended (grade C), especially in those with a first-degree relative with a history of treated or ruptured AAA. The USPSTF makes no recommendation regarding screening for AAA in women who have smoked and specifically recommends against routine screening in women who have never smoked (grade D).

Cardiovascular and Cerebrovascular Disease

Cardiovascular risk assessment is performed in asymptomatic adults to evaluate a patient's risk for future cardiac events; it does not identify pre-existing disease and is therefore considered separate from screening (see MKSAP 18 Cardiovascular Medicine).

The USPSTF does not recommend screening for coronary artery disease with either resting or exercise electrocardiography (ECG) in asymptomatic patients at low risk, defined by the USPSTF as a 10-year cardiovascular event risk of less than 10% using the Pooled Cohort Equations (grade D). In patients at intermediate or high risk for such events, there was inadequate evidence to assess the relative benefits and harms of screening. Similarly, the ACP recommends against screening low-risk and asymptomatic adults with resting ECG or stress testing. No specialty organization recommends screening these populations with resting or exercise ECG, coronary calcium scoring, or coronary angiography.

The USPSTF also does not recommend screening for carotid artery stenosis in the general adult population (grade D).

Depression

The USPSTF suggests that all adults, including pregnant and postpartum women, be screened for depression, with adequate systems in place for assessment, treatment, and follow-up (grade B). Most adults can be screened with the brief PHQ-2, which consists of two questions: "During the past 2 weeks, how often have you been bothered by feeling down, depressed, or hopeless?" and "During the past 2 weeks, have you often been bothered by having little interest or pleasure in doing things?" Answers are graded on a scale of 0 to 6, with a score of 3 indicating a positive screen. The PHQ-2 has a sensitivity of 83% and specificity of 90% for detecting depression; longer screening instruments, such as the PHQ-9, do not have a clear advantage over the PHQ-2. Patients with a positive screening result should complete the PHQ-9, which can be used for diagnosis and monitoring of depression.

Other screening instruments may be more accurate in specific patient populations, such as the Geriatric Depression Scale in older adults and the Edinburgh Postnatal Depression Scale in postpartum and pregnant women.

Diabetes Mellitus

The USPSTF recommends screening for diabetes mellitus in adults aged 40 to 70 years who are overweight or obese (grade B). Screening can be accomplished by measuring levels of fasting plasma glucose or hemoglobin A_{1c}. Those with a positive screening result should undergo intensive behavioral counseling to promote a healthful diet and physical activity. Earlier screening should be considered in persons at increased risk, including individuals who belong to certain racial or ethnic groups (blacks, American Indians, Asian Americans, Hispanics or Latinos, Native Hawaiians, Pacific Islanders), and those with a family history of diabetes or a personal history of gestational diabetes or polycystic ovary syndrome.

In contrast to the USPSTF, the American Diabetes Association (ADA) recommends that screening be performed in obese or overweight patients of any age with one or more risk factors for diabetes (**Table 8**). The ADA also recommends screening all adults beginning at age 45 years, regardless of risk factors, and repeating screening at 3-year intervals. Patients with prediabetes (hemoglobin A_{1c} ≥5.7%, impaired glucose tolerance, or impaired fasting glucose) should be screened annually.

Dyslipidemia

The USPSTF recommends lipid screening for adults aged 40 to 75 years for the purposes of calculating 10-year risk for atherosclerotic cardiovascular disease (ASCVD) and guiding initiation of statin therapy for primary prevention (see Dyslipidemia chapter on p. 79). Measuring lipid levels every 5 years is reasonable. If lipid levels are close to those that require therapy, testing may be performed at shorter intervals, whereas longer intervals can be considered for persons without cardiovascular risk factors who have repeatedly normal levels. For adults aged 21 to 39 years, the USPSTF recommends that clinicians use their clinical judgment regarding screening for and treating dyslipidemia due to a lack of supportive data.

The American Heart Association recommends assessing traditional cardiovascular risk factors, including total and HDL cholesterol levels, starting at age 20 years. Risk factor assessment should be performed every 4 to 6 years if the patient is at low 10-year risk (<7.5%). Patients with a family history of premature coronary artery disease or patients with a family history of or evidence on examination of familial hypercholesterolemia should also be screened at a younger age.

TABLE 8. Risk Factors for Diabetes Mellitus
First-degree relative with diabetes
High-risk race/ethnicity (e.g., African American, Latino, Native American, Asian American, Pacific Islander)
History of cardiovascular disease
Hypertension (≥140/90 mm Hg or on therapy for hypertension)
HDL cholesterol level <35 mg/dL (0.90 mmol/L) and/or a triglyceride level >250 mg/dL (2.82 mmol/L)
Women with polycystic ovary syndrome
Physical inactivity
Other clinical conditions associated with insulin resistance (e.g., severe obesity, acanthosis nigricans)
History of gestational diabetes

Information from American Diabetes Association. 2. Classification and diagnosis of diabetes: Standards of Medical Care in Diabetes—2018. Diabetes Care. 2018;41:S13-S27. [PMID: 29222373] doi:10.2337/dc18-S002

Hypertension

The USPSTF supports screening all adults for hypertension (grade A). Screening should occur annually in adults aged 40 years and older and in younger adults at increased risk (including patients with high-normal blood pressure [130 to 139/85 to 89 mm Hg], patients who are overweight or obese, and black patients). Screening should otherwise occur every 3 to 5 years. Before treatment is initiated, the diagnosis should be confirmed with blood pressure measurements outside of the clinical setting, such as ambulatory or home blood pressure monitoring.

The American Heart Association/American College of Cardiology recommend evaluating patients with a normal blood pressure (<120/<80 mm Hg) annually and patients with elevated blood pressure (120-129/<80 mm Hg) whose 10-year estimated ASCVD risk is less than 10% every 3 to 6 months.

Obesity

The USPSTF suggests that all adults should be screened for obesity by calculating BMI (grade B), without specifically delineating how frequently screening should be repeated. The American College of Cardiology, American Heart Association, and The Obesity Society recommend annual screening with BMI and waist circumference measurements. Adults with a BMI of 30 or higher should be offered or referred for intensive behavioral interventions, according to the USPSTF.

Obstructive Sleep Apnea

According to the USPSTF, there is insufficient evidence to assess the balance of benefits and harms of screening for obstructive sleep apnea in asymptomatic adults with the currently available tools. Because obstructive sleep apnea is widely underrecognized, clinicians should have a low threshold for investigating for sleep apnea in patients with symptoms consistent with the disease (see MKSAP 18 Pulmonary and Critical Care Medicine).

Osteoporosis

The USPSTF recommends screening for osteoporosis in women aged 65 years and older and in postmenopausal

women younger than 65 years at increased risk for osteoporosis, as determined by a formal clinical risk assessment tool. One commonly used clinical risk assessment tool is the Fracture Risk Assessment (FRAX), available at www.shef.ac.uk/FRAX. Women who have a 10-year FRAX risk for major osteoporotic fracture equal to or higher than that of a 65-year-old white woman without additional risk factors (10-year risk of 8.4%) should undergo screening for osteoporosis. Screening can be accomplished with bone mineral density measurement, most commonly with dual-energy x-ray absorptiometry (DEXA) of the hip and lumbar spine.

The USPSTF concludes that there is insufficient evidence to recommend routine screening for osteoporosis in men (I statement); however, the National Osteoporosis Foundation recommends osteoporosis screening in men aged 70 years or older. Screening may be considered in men at high risk for osteoporosis on the basis of risk factors, such as low body weight, recent weight loss, physical inactivity, use of oral glucocorticoids, previous fragility fracture, alcohol use, and androgen deprivation through pharmacologic agents or orchiectomy.

Risk assessment and screening for osteoporosis are further discussed in MKSAP 18 Endocrinology and Metabolism.

Thyroid Disease

The USPSTF concludes that there is insufficient evidence to recommend for or against screening for thyroid disease (I statement). The American Thyroid Association and the American Association of Clinical Endocrinologists, however, recommend measuring thyroid-stimulating hormone in individuals at risk for hypothyroidism (for example, personal history of autoimmune disease, neck radiation, or thyroid surgery); they additionally recommend considering screening in adults aged 60 years and older.

Screening for Infectious Diseases

Screening for infectious diseases is primarily recommended for individuals at increased risk (**Table 9** and **Table 10**), although there are several diseases for which average-risk patients should be screened.

According to the USPSTF, screening for chlamydia and gonorrhea should be performed in all sexually active women aged 24 years or younger because of increased prevalence in this population.

One-time hepatitis C screening is recommended for adults born between 1945 and 1965 and those who received

TABLE 9. U.S. Preventive Services Task Force Recommendations on Screening for Infectious Diseases

Infectious Disease	Screening Recommendation	Screening Test	Populations at Risk
Chlamydia and gonorrhea	Screen all sexually active women aged ≤24 y and women aged >24 y who are at increased risk for infection	Nucleic acid amplification test	Persons with a history of STIs, persons with new or multiple sexual partners, those who use condoms inconsistently, persons who exchange sex for money or drugs
HIV	Perform one-time screening for all adults aged 15-65 y; repeat screening for adults at high risk	Combination HIV antibody immunoassay/p24 antigen test	Men who have sex with men, active injection drug users, persons who engage in risky behaviors (unprotected vaginal or anal intercourse; sexual partners who are HIV infected, bisexual, or injection drug users; exchanging sex for drugs or money), persons with other STIs, persons who live and receive care in a high-prevalence setting (HIV seroprevalence of ≥1%)
HBV	Screen all adults at high risk	Hepatitis B surface antigen test; obtain antibodies (anti-HBs, anti-HBc) to differentiate between immunity and infection	Persons born in countries with ≥2% prevalence of HBV infection, persons receiving dialysis or cytotoxic or immunosuppressive treatments, persons with HIV infection, injection drug users, men who have sex with men, household contacts or sexual partners of persons with HBV infection
HCV	Screen all adults at high risk and perform one-time screening in adults born between 1945 and 1965	Anti-HCV antibody test, followed by PCR viral load test if result is positive	Injection/intranasal drug users, persons who received a blood transfusion before 1992, persons receiving long-term hemodialysis, prisoners, and persons who received unregulated tattoos
Syphilis	Screen all adults at increased risk	VDRL or RPR test	Persons with HIV infection, prisoners, men who have sex with men, persons who exchange sex for money or drugs
Latent TB	Screen populations at increased risk	Tuberculin skin test or interferon-γ release assay	Persons born in or former residents of countries with high TB prevalence, close contacts of persons with known or suspected TB, persons who live or work in high-risk settings

Anti-HBc = hepatitis B core antibody; Anti-HBs = hepatitis B surface antibody; HBV = hepatitis B virus; HCV = hepatitis C virus; PCR = polymerase chain reaction; RPR = rapid plasma reagin; STIs = sexually transmitted infections; TB = tuberculosis; VDRL = Venereal Disease Research Laboratory.

TABLE 10. Screening for Infectious Diseases in High-Risk Populations

Specific Populations	Recommended Screening
Pregnant women	Chlamydia and gonorrhea, hepatitis B, HIV, syphilis
Persons engaging in high-risk sexual behavior	Hepatitis B and C, HIV, syphilis
Men who have sex with men	Chlamydia and gonorrhea[a], hepatitis B, HIV, syphilis
Injection drug users	Hepatitis B and C, HIV
Prisoners	Hepatitis C, syphilis, tuberculosis
Persons receiving hemodialysis	Hepatitis B and C, tuberculosis
Persons born in or living in certain countries[b]	Hepatitis B and tuberculosis depending on prevalence of disease
Health care workers	Tuberculosis (annually); pre-employment verification of immunity to hepatitis B virus, measles, mumps, rubella, and varicella

[a]The Centers for Disease Control and Prevention recommends screening for chlamydia and gonorrhea in men who have sex with men; however, the U.S. Preventive Services Task Force has found insufficient evidence to recommend screening for these diseases in men.

[b]Countries with ≥2% hepatitis B virus prevalence, including most of sub-Saharan Africa, central and southeast Asia, and parts of South America. See https://wwwnc.cdc.gov/travel/yellowbook/2018/infectious-diseases-related-to-travel/hepatitis-b for further details.

a blood transfusion before 1992. Screening is accomplished by testing for antibodies to the disease, followed by polymerase chain reaction viral load testing if results of initial testing are positive (see MKSAP 18 Gastroenterology and Hepatology).

The USPSTF recommends that all persons aged 15 to 65 years receive one-time HIV screening regardless of risk, and the Centers for Disease Control and Prevention (CDC) recommends routine HIV screening for all persons aged 13 to 64 years. The USPSTF suggests screening persons at very high risk for HIV (men who have sex with men and active injection drug users) at least annually. The CDC recommends at least annual screening for men who have sex with men. Combination HIV antibody immunoassay/p24 antigen testing is recommended for screening. Diagnosis of HIV is discussed in MKSAP 18 Infectious Disease.

Screening for Substance Use Disorders

The USPSTF recommends that clinicians ask all adults about tobacco use, advise them to stop using tobacco, and provide behavioral intervention and pharmacotherapy for tobacco cessation (grade A) (see Mental and Behavioral Health).

The USPSTF supports asking all adults about alcohol misuse and providing persons engaged in risky or hazardous drinking with brief behavioral counseling interventions to reduce alcohol misuse (grade B). Screening instruments to identify harmful drinking include the Alcohol Use Disorders Identification Test (AUDIT), the AUDIT-Consumption (AUDIT-C), and single-item screening. The AUDIT (https://pubs.niaaa.nih.gov/publications/Audit.pdf) is a validated 10-item screening test that takes approximately 2 to 3 minutes to administer; the AUDIT-C is a briefer (three-item) version of the AUDIT. With single-item screening, the clinician asks, "How many times in the past year have you had five [four for women] or more drinks in 1 day?" A positive test result, defined as any answer other than zero, has a sensitivity and specificity of approximately 80% for unhealthy alcohol use.

The USPSTF concluded that there is insufficient evidence to assess the balance of benefits and harms of routine screening for illicit drug use. Screening tools include the Drug Abuse Screening Test (DAST-10) (https://www.integration.samhsa.gov/clinical-practice/DAST_-_10.pdf) and the CAGE questionnaire expanded to include drugs (CAGE-AID) (https://www.integration.samhsa.gov/images/res/CAGEAID.pdf). Prescription opioids are the most commonly abused opioids and are the leading cause of opioid overdoses in the United States. Clinicians must be aware of the potential for opioid abuse. The opioid risk tool can be useful to assess risk for abuse of opioid medications; however, this tool needs further validation in clinical practice.

Screening for Abuse

The USPSTF recommends screening for intimate partner violence in all women of child bearing age (grade B). Available screening tools include the Hurt, Insult, Threaten, Scream (HITS); Ongoing Abuse Screen/Ongoing Violence Assessment Tool (OAS/OVAT); Slapped, Threatened, and Throw (STaT); Humiliation, Afraid, Rape, Kick (HARK); Modified Childhood Trauma Questionnaire-Short Form (CTQ-SF); and Woman Abuse Screen Tool (WAST).

Screening for abuse in elderly and vulnerable adults may be considered, although there is currently insufficient evidence to recommend universal screening (I statement) (see Geriatric Medicine).

Screening for Cancer

This section discusses cancer screening in asymptomatic, average-risk persons. Screening for cancer in patients at high risk is covered in the respective specialty books of MKSAP 18.

Breast Cancer

The balance of benefits and harms of screening mammography has shifted with the advent of increasingly effective breast cancer treatments, which reduce the benefits of early detection, as well as emerging information about overdiagnosis. In women aged 50 to 74 years, there is a clear benefit to screening mammography, and all breast cancer guidelines recommend screening mammography in this age group. Biennial screening mammography imparts most of the benefits of annual screening mammography with fewer harms, although the recommended screening frequency differs between guidelines. In women younger than 50 years or aged 75 years and older, the balance of benefits and harms is less clear, and screening recommendations vary widely (**Table 11**).

TABLE 11. Recommendations for Breast Cancer Screening in Women at Average Risk

Expert Group	Recommendation
American Cancer Society (2015)	Age 40-44 y: Provide women with the opportunity to begin annual screening mammography Age 45-54 y: Perform annual screening mammography Age ≥55 y: Perform biennial screening mammography with the opportunity to continue annual screening Do not perform CBE for breast cancer screening
American College of Obstetricians and Gynecologists (2017)	Age 25-39 y: May offer CBE every 1-3 y Age 40-49 y: Offer screening mammography and engage women in a shared decision-making process. May offer annual CBE Age 50-75 y: Perform annual or biennial screening mammography based on a shared decision-making process Age >75 y: Engage women in a shared decision-making process about discontinuing screening
American College of Physicians (2015)	Age <40 y: Do not perform screening Age 40-49 y: Discuss the benefits and harms of screening mammography and order biennial mammography screening if an informed woman requests it Age 50-74 y: Encourage biennial mammography screening Age >75 y: Do not perform screening
American College of Radiology (2017)	Age 40 y: Begin annual screening mammography
National Comprehensive Cancer Network (2016)	Age 25-39 y: Perform CBE every 1-3 y Age 40 y: Begin annual screening mammography and perform annual CBE
U.S. Preventive Services Task Force (2016)	Age 40-49 y: Decision to begin screening should be individualized (grade C) Age 50-74 y: Perform biennial screening mammography (grade B) Age ≥75 y: Insufficient evidence to assess the balance of benefits and harms of screening mammography (grade I)

CBE = clinical breast examination.

When recommendations differ, shared decision making with consideration of the patient's level of risk, values, and preferences guides the screening decision. The benefit of screening is largest in those aged 60 to 69 years but is substantially lower for younger and older women (**Table 12**). Potential harms of screening include false-positive results and overdiagnosis. For patients starting mammography at age 40 or 50 years, the 10-year cumulative false-positive rates are 42% with biennial screening and 61% with annual screening. Such results may cause unnecessary biopsies and substantial patient anxiety. Overdiagnosis accounts for roughly 30% of all breast cancers diagnosed.

TABLE 12. Breast Cancer Deaths Averted per 10,000 Women Screened Over 10 Years

Variable	Patient Age			
	40-49 Years	50-59 Years	60-69 Years	70-74 Years
Breast cancer deaths averted (95% CI)	3 (0-9)	8 (2-17)	21 (11-32)	13 (0-32)
NNS	3333	1250	476	769

NNS = number needed to screen for 10 years to avoid one breast cancer death.

Data from Nelson HD, Fu R, Cantor A, Pappas M, Daeges M, Humphrey L. Effectiveness of breast cancer screening: systematic review and meta-analysis to update the 2009 U.S. Preventive Services Task Force recommendation. Ann Intern Med. 2016;164:244-55. [PMID: 26756588] doi:10.7326/M15-0969

Approximately 50% of women have dense breasts on mammography. Increased breast density is associated with an increased breast cancer risk but decreased sensitivity of mammography (more so with film than digital mammography). As a result, legislation in many states requires that breast density be included on mammogram reports (**Table 13**). In women in whom increased breast density is the sole breast cancer risk factor, there is no evidence that adding MRI or ultrasonography to mammography affects breast cancer mortality, and most guidelines conclude that there is insufficient evidence to recommend adjunctive screening when dense breasts are present. The American College of Radiology, however, notes that ultrasonography may be considered in this circumstance. Women with dense breasts should undergo further risk stratification; for those at high risk, additional screening may be considered (see MKSAP 18 Hematology and Oncology).

Prostate Cancer

Screening for prostate cancer in asymptomatic, average-risk men has been controversial, and recommendations among professional organizations continue to evolve (**Table 14**). For men aged 55 to 69 years, the USPSTF recommends that the decision to undergo periodic prostate-specific antigen (PSA)-based screening should be an individual one and should include discussion of the potential benefits and harms of screening with their clinician. The USPSTF recommends that clinicians should not screen men who do not express a preference for screening and recommends against PSA-based screening for prostate cancer in men aged 70 years and older.

Benefits of screening for men aged 55 to 69 years include prevention of one prostate cancer–related death for every 1000 men screened for 10 years (NNS, 1000). Risks include overdiagnosis, overtreatment, and false-positive results that trigger unnecessary biopsies and patient anxiety. Estimated rates of overdiagnosis and overtreatment vary widely.

If the decision is made to proceed with screening, the American Urological Association (AUA) recommends

TABLE 13. Breast Imaging Reporting and Data System (BI-RADS) Breast Composition Categories

a.	The breasts are almost entirely fatty
b.	There are scattered areas of fibroglandular density
c.	The breasts are heterogeneously dense, which may obscure small masses
d.	The breasts are extremely dense, which lowers the sensitivity of mammography

Reproduced with permission of the American College of Radiology (ACR) from D'Orsi CJ, Sickles EA, Mendelson EB, et al. ACR BI-RADS® Atlas, Breast Imaging Reporting and Data System. Reston, VA, American College of Radiology; 2013. No other representation of this material is authorized without expressed, written permission from the ACR. Refer to the ACR website at https://www.acr.org/Clinical-Resources/Reporting-and-Data-Systems/Bi-Rads for the most current and complete version of the BI-RADS® Atlas.

TABLE 14. Recommendations for Prostate Cancer Screening

Expert Group	Recommendation
American Cancer Society (2010)	Age 40-44 y: Engage men at higher risk (≥2 first-degree relatives with prostate cancer before age 65 y) in shared decision making
	Age 45-49 y: Engage men at high risk (African American race or first-degree relative with prostate cancer before age 65 y) in shared decision making
	Age ≥50 y with life expectancy >10 y: Engage in shared decision making
American College of Physicians (2013)	Age 50-69 y: Inform men about the limited potential benefits and substantial harms of screening for prostate cancer; test only men who request screening after informed discussion
	Age <50 y, >69 y, or with a life expectancy <10 y: Recommend against screening
American Urological Association (2013, reviewed and confirmed 2015)	Men at higher risk (African American race or with positive family history): Individualize screening decisions
	Age <40 y: Recommend against screening
	Age 40-54 y: Do not recommend routine screening
	Age 55-69 y: Engage men considering PSA-based screening in shared decision making; proceed based on patient values and preferences. If proceeding with screening, consider PSA testing every 2 years or longer
	Age ≥70 y or with life expectancy <10-15 y: Do not recommend routine screening
U.S. Preventive Services Task Force (2018)	Age 55-69: Discuss potential benefits and harms of PSA-based screening for prostate cancer and individualize decision making by incorporating the patient's values and preferences
	Age ≥70 y: Recommend against PSA-based screening

PSA = prostate-specific antigen.

choosing less frequent screening intervals (≥2 years), which may reduce overdiagnosis and the number of false-positive results while preserving most of the screening benefit. The AUA also recommends that the interval for rescreening may be based on the baseline PSA level. Screening is not recommended for men with less than a 10- to 15-year life expectancy.

Methods to better use PSA testing, including one-time PSA measurement at prespecified ages, adjusted threshold testing, or PSA velocity and doubling time, are being investigated. However, there is currently insufficient evidence to support these methods.

Colorectal Cancer

The USPSTF recommends screening for colorectal cancer in asymptomatic adults aged 50 to 75 years (grade A). In contrast, the American Cancer Society makes a qualified recommendation to initiate screening for colorectal cancer at age 45 years. According to the USPSTF, screening decisions in patients aged 76 to 85 years should be individualized according to life expectancy and ability to tolerate treatment of colorectal cancer if diagnosed. Screening history should also be considered because patients who have not undergone screening are the most likely to benefit (grade C). The USPSTF suggests that screening may be discontinued in patients older than 85 years; most other guidelines recommend stopping screening if life expectancy is less than 10 years.

There is little head-to-head comparative evidence that any one recommended screening modality provides a greater benefit than the others. In addition, despite unequivocal evidence that colon cancer screening reduces mortality, an estimated one in three U.S. adults who are eligible for colon cancer screening has not been screened. Therefore, the USPSTF supports using the test that is most likely to result in completion of screening. Understanding a patient's values and preferences and selecting a test to which the patient is most likely to adhere may improve screening rates. Clinicians should be familiar with the characteristics of each screening strategy to facilitate effective discussion with patients (**Table 15**).

The U.S. Multi-Society Task Force on Colorectal Cancer (MSTF), an initiative of U.S. gastroenterology societies, has ranked colorectal cancer screening tests in tiers based on the available evidence, cost-effectiveness, test availability, and several other factors. The MSTF recommends colonoscopy every 10 years or annual fecal immunochemical testing (FIT) as first-tier tests; CT colonography every 5 years, FIT-fecal DNA testing every 3 years, or flexible sigmoidoscopy every 5 to 10 years as second-tier tests; and capsule colonography every 5 years as a third-tier test. The serum circulating methylated *SEPT9* DNA test is an FDA-approved screening strategy that holds promise because blood tests may result in increased adherence. However, this test's sensitivity for detecting colorectal cancer is only 48%, and the MSTF does not recommend its use.

TABLE 15. Characteristics of Colorectal Cancer Screening Strategies

Screening Strategy	Frequency	Reduction in Mortality Rate	Notes
Stool-based Tests (Cancer Detection)			
gFOBT	Every year	32%	High-sensitivity gFOBT has superior test performance characteristics than older tests Requires dietary restrictions; does not require bowel preparation, anesthesia, or transportation to and from the screening examination
FIT	Every year	Unknown	Improved accuracy compared with gFOBT Does not require bowel preparation, anesthesia, or transportation to and from the screening examination
FIT-DNA	Every 1 to 3 y	Unknown	Higher sensitivity but lower specificity than FIT, resulting in more false-positive results
Direct Visualization Tests (Cancer Prevention)			
Colonoscopy	Every 10 y	68%	Requires full bowel preparation Usually requires sedation and a patient escort ACG/MSTF recommend split-dose preparation[a]
CT colonography	Every 5 y	Unknown	Requires bowel preparation Imaging only (cannot remove polyps or biopsy) Extracolonic findings are common
Flexible sigmoidoscopy	Every 5 y	27%	Limited bowel preparation compared with colonoscopy
Flexible sigmoidoscopy with FIT	Flexible sigmoidoscopy every 10 y with FIT every year	38%	

ACG = American College of Gastroenterology; FIT = fecal immunochemical test; gFOBT = guaiac fecal occult blood test; MSTF = U.S. Multisociety Task Force on Colorectal Cancer.

[a]Split-dose preparation has been shown to increase detection rates for sessile polyps and possibly adenomas. It involves taking half of the preparation the evening before and half of the preparation on the day of colonoscopy, starting 4 to 5 hours before the procedure start and finishing 3 hours before the procedure start.

Adapted from U.S. Preventive Services Task Force. Final recommendation statement: colorectal cancer: screening. June 2017. https://www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementFinal/colorectal-cancer-screening2. Accessed June 28, 2018. The Agency for Healthcare Research and Quality and the U.S. Department of Health and Human Services do not endorse derivative or excerpted materials and cannot be held liable for this content.

Cervical Cancer

Cervical cancer incidence and mortality have steadily decreased over the last half-century, largely because of the implementation of widespread screening. The USPSTF, in a 2018 recommendation statement, recommends screening women aged 21 to 65 years every 3 years with cytology (Pap test). In women aged 30 to 65 years who want to lengthen the screening interval, high-risk human papillomavirus (HPV) testing (preferred) or cytology combined with high-risk HPV testing can be performed every 5 years. The USPSTF recommends against screening women younger than 21 years regardless of sexual history because screening has not been shown to reduce cervical cancer incidence or mortality compared with starting screening at age 21 years.

Screening can be discontinued at age 65 years in non-high-risk women with adequate prior screening, commonly defined as three consecutive negative cytology results or two consecutive negative cytology plus HPV test results within the last 10 years, with the most recent test occurring within 5 years. In women older than 65 years with life expectancy of at least 10 years and risk factors for cervical cancer (history of abnormal Pap smears, history of a high-grade precancerous lesion, in utero exposure to diethylstilbestrol, immunocompromise, previous HPV infection), continued screening should be considered.

Women who have never been screened have the highest incidence of and mortality from cervical cancer. The mortality reduction from screening in women who have not been previously screened may be as high as 74%. Women older than 65 years who have never been screened or in whom adequacy of prior screening cannot be confirmed should undergo screening with cytology every 3 years, high-risk HPV testing every 5 years, or combined high-risk HPV testing and cytology every 5 years.

Screening should not be performed in women who have had a hysterectomy with removal of the cervix unless a

high-grade precancerous lesion (cervical intraepithelial neoplasia 2 or 3) was present, in which case screening should be continued for at least 20 years after hysterectomy.

Additional Cancer Screening Tests

The USPSTF, Society of Gynecologic Oncology, and the American College of Obstetricians and Gynecologists all recommend against screening for ovarian cancer with serum CA-125 testing or ultrasonography in women at average risk. Women with a family history indicating a hereditary cancer syndrome should be referred to a genetic counselor for consideration of genetic testing (see MKSAP 18 Hematology and Oncology).

According to the USPSTF, evidence is insufficient to determine the balance of benefits and harms of screening for skin cancer with a visual skin examination. However, the USPSTF recommends that persons younger than 24 years who have fair skin receive counseling to minimize exposure to ultraviolet radiation to reduce risk for skin cancer (grade B) and recommends offering selective counseling to adults older than 24 years with fair skin types (grade C).

The USPSTF recommends against screening for pancreatic cancer in asymptomatic adults. Because up to 15% of pancreatic ductal adenocarcinomas are attributable to genetic factors, patients with a family history suggestive of a genetic syndrome associated with pancreatic cancer (*BRCA1/2* mutations, Peutz-Jeghers syndrome, Lynch syndrome) should be referred for genetic counseling and possible genetic testing.

There is insufficient evidence to recommend routine anal cancer screening in average-risk populations, but such screening may be considered in high-risk populations. The Infectious Diseases Society of America suggests screening patients with genital warts, men who have sex with men, and women who have a history of abnormal cervical cytology or participate in receptive anal intercourse.

Lung cancer screening with annual low-dose CT is recommended for persons aged 55 years to 74-80 years (guidelines vary) with a 30-pack-year smoking history, including former smokers who have quit in the last 15 years (see MKSAP 18 Pulmonary and Critical Care Medicine).

The USPSTF recommends against screening for testicular cancer and thyroid cancer in asymptomatic adults. Routine screening for bladder cancer is not recommended by any expert group, including the USPSTF.

KEY POINTS

- The U.S. Preventive Services Task Force supports routine screening for depression, hypertension, obesity, tobacco use, and alcohol misuse in asymptomatic, average-risk adults.
- Lipid screening is indicated in adults aged 40 to 75 years for the purposes of calculating 10-year risk for atherosclerotic cardiovascular disease and guiding initiation of statin therapy for primary prevention.

(Continued)

KEY POINTS ***(continued)***

- Adults aged 40 to 70 years who are overweight or obese should be screened for diabetes mellitus, according to the U.S. Preventive Services Task Force.
- The U.S. Preventive Services Task Force recommends that all persons aged 15 to 65 years receive one-time HIV screening regardless of risk.
- All women aged 50 to 74 years should undergo screening mammography; the recommended screening interval varies by expert group.
- Evidence has not demonstrated that any one recommended screening test for colorectal cancer provides a greater benefit than the others; therefore, the U.S. Preventive Services Task Force supports using the test that is most likely to result in screening completion.

Genetics and Genetic Testing

Taking a Family History

Obtaining a family history is an inexpensive and important risk assessment tool that allows clinicians to identify persons at increased risk for certain conditions. Up to 40% of genetic risk factors that would have otherwise been missed can be detected with a family history. Features that suggest the presence of a genetically inherited condition include earlier age of onset than expected for a common disease; two or more relatives with the same disorder, especially if the disorder is uncommon or known to be caused by a single gene mutation; and the presence of a disease in the less-often-afflicted sex, such as breast cancer in a man.

Agreement on the essential components of a family history is lacking; however, obtaining a complete three-generation family history is a reasonable approach. Although time consuming, documenting the history in the form of a family pedigree provides a helpful pictorial representation of the relationship between family members and the presence of medical conditions (**Figure 3**). Several easy-to-use family history tools are also available. The My Family Health Portrait tool (https://familyhistory.hhs.gov) can be self-administered and updated over time by patients.

Genetic Tests and Testing Strategies

Understanding different types of genetic tests and testing strategies is helpful in ensuring that genetic testing is used effectively (**Table 16**). Prenatal genetic testing is performed during pregnancy to identify conditions in utero, such as Down syndrome. In adults, genetic testing is most commonly performed in persons with a family history suggestive of a genetically inherited condition. Presymptomatic or predictive genetic testing is performed to detect the presence of a genetic mutation before the onset of symptoms. The presence of some genetic mutations, such as the *HD* gene for Huntington disease, will invariably lead to disease development. With other

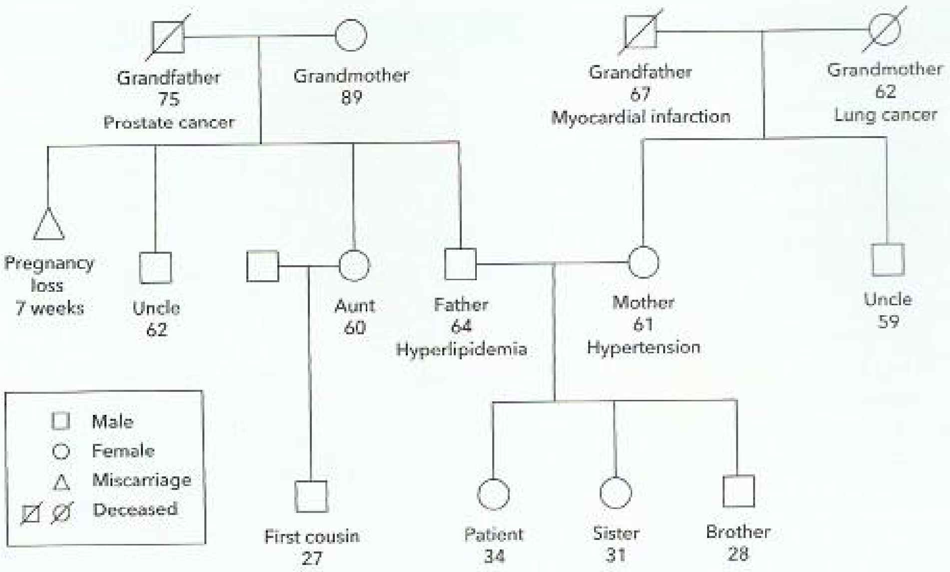

FIGURE 3. Example of a family history.

TABLE 16. Commonly Used Genetic Tests

Type of Testing	Description
Cytogenetic testing or karyotyping (Giemsa staining, in situ hybridization, microarray analysis)	Permits analysis of chromosomal structure Giemsa staining produces banding pattern, allowing for gross structural analysis In situ hybridization and microarray analysis allow for detection of more subtle abnormalities
Direct DNA testing (polymerase chain reaction analysis, Southern blot analysis)	Permits detection of specific genetic mutations
Indirect DNA testing (linkage analysis)	Useful when the genetic location for a condition is known but the genetic mutation is unknown
Biochemical testing	Involves measurement of metabolite levels to assess enzymatic activity
Whole exome sequencing	Useful when there is a clear family history of a genetic disorder based on pedigree but the affected gene is unknown

genetic mutations, such as those involving the breast cancer susceptibility genes *BRCA1* and *BRCA2*, the risk for the disease is significantly increased, but not everyone with the mutation will develop disease. Diagnostic testing refers to genetic testing performed in those with a suspected genetic condition based on clinical features.

All patients for whom genetic testing is being considered should undergo genetic counseling. The basic components of genetic counseling are education on the condition being tested, including the natural history, possible treatments, and preventive measures; the risks and benefits of genetic testing; alternatives to testing, including the option to forgo testing; and the implications for the patient and family members. Patients should be informed that the Genetic Information Nondiscrimination Act of 2008 protects against discrimination from obtaining employment and health insurance; however, this protection does not extend to discrimination involving other types of insurance, such as disability and life insurance. Clinicians can use a searchable database provided by the American College of Medical Genetics and Genomics (www.acmg.net/GIS) to locate a genetic counselor in their area.

Pharmacogenetics

Pharmacogenetics is the study of how genetic differences lead to varying drug responses. Genetic testing for several common enzymes that affect drug metabolism, such as CYP2C19 and CYP2D6, are increasingly available. The CYP2C19 enzyme is involved in metabolizing the antiplatelet agent clopidogrel to its active form. Patients who have one or two copies of the reduced-function *CYP2C19* gene have an attenuated antiplatelet effect when taking clopidogrel, which may be associated with an increased risk for cardiovascular events. The CYP2D6 enzyme is responsible for converting codeine to its active metabolite, morphine. The presence of *CYP2D6* polymorphisms leads to variation in enzyme activity between individuals. Patients with high CYP2D6 activity may be subject to serious side effects of codeine, including respiratory depression and death, whereas patients with low CYP2D6 activity are unlikely to achieve adequate analgesia with codeine. The role of pharmacogenetic testing is unclear, and routine testing is not widespread at present.

Direct-to-Consumer Genetic Testing

Direct-to-consumer (DTC) genomic testing is a commercial service that allows patients to obtain genetic information for a low cost. The FDA has approved DTC genetic testing for 10 disorders, including Parkinson disease and hemochromatosis,

and physicians may be asked to provide guidance to persons who have undergone testing. DTC genomic testing typically estimates the risk for many common medical conditions by genotyping polymorphic nucleotides. Single-nucleotide polymorphisms (SNPs) that are disproportionately found in affected individuals are identified, and odds ratios for each SNP are determined. The SNPs are usually common but have low penetrance (that is, most people with an SNP do not develop disease). Individually, SNPs contribute very little to overall disease risk; most SNPs have an odds ratio of less than 1.5. As an example, if a condition has a general population prevalence of 8%, possessing an associated SNP with an odds ratio of 1.3 would increase one's risk for the condition to approximately 10%. Advocates of these services argue that they promote patient autonomy because patients can directly access information on genetic predispositions without physician referral. Critics counter that DTC testing is not usually accompanied by pre- or posttest genetic counseling, potentially leading to patient harms.

KEY POINTS

- Obtaining a three-generation family history is an inexpensive and important risk assessment tool that allows clinicians to identify persons at increased risk for certain conditions.
- Presymptomatic or predictive genetic testing is performed to detect the presence of a genetic mutation before the onset of symptoms, such as identification of the breast cancer susceptibility genes *BRCA1/2*; all patients for whom genetic testing is being considered should undergo genetic counseling.
- Direct-to-consumer genomic testing estimates the risk for many common medical conditions by genotyping polymorphic nucleotides; however, the identified single-nucleotide polymorphisms contribute very little to overall disease risk.

Immunization

Immunization is a safe and cost-effective preventive health measure that is often underused in adult patients. In the United States, annual immunization recommendations are issued by the Advisory Committee on Immunization Practices (ACIP). ACIP recommendations can be accessed at https://www.cdc.gov/vaccines/acip.

It is important to adhere to recommended vaccine schedules as closely as possible. Administering doses at longer-than-recommended intervals does not appear to reduce immunologic response; however, doses should not be given at shorter-than-recommended intervals in order to allow for a complete immunologic response. If a vaccination series is interrupted, the series can be resumed at the point of interruption. Whenever possible, multiple vaccines should be given simultaneously to improve vaccination rates.

Vaccines can be safely administered to patients with mild acute febrile illness, during illness convalescence, and to patients who have previously developed low- or moderate-grade fever or local reactions with vaccination. Vaccines should be avoided if there is a history of anaphylaxis to the vaccine or the vaccine components. Contraindications to live vaccines are listed in **Table 17**.

Vaccinations Recommended for All Adults

Influenza

Influenza revaccination is necessary each year, owing to ongoing genetic changes in the influenza virus (antigenic drift). Annual vaccination is recommended for all individuals aged 6 months and older. The influenza vaccine should be administered as soon as it becomes available, preferably by October. The ACIP makes no preferential recommendation for one formulation over another, although use of the quadrivalent live attenuated influenza vaccine (LAIV4) was not recommended for the 2016 to 2018 influenza seasons as a result of poor efficacy against the H1N1 strain. A reformulated LAIV has received approval and a weak recommendation by the ACIP for the 2018 to 2019 influenza season. A high-dose, trivalent, inactivated formulation (IIV3-HD) is available for patients aged 65 years and older and is 24% more effective in preventing laboratory-confirmed influenza compared with its standard-dose counterpart.

Persons with a history of egg allergy of any severity can receive any influenza vaccine formulation; however, in persons who have had an egg-related reaction that caused symptoms other than hives, such as angioedema or respiratory distress, the vaccine should be administered by a provider trained in recognizing and managing severe allergic reactions.

Tetanus, Diphtheria, and Pertussis

Primary vaccination against tetanus, diphtheria, and acellular pertussis consists of a five-dose vaccine series administered during childhood. Persons aged 11 to 18 years who have completed the primary series should receive a single dose of the tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap) vaccine. Adults aged 19 years and older should receive a tetanus and diphtheria toxoids (Td) booster every

TABLE 17. Contraindications to Administration of Live Vaccines
Pregnancy or probable pregnancy within 4 weeks
HIV with CD4 count ≤200/µL or CD4% ≤15% of total lymphocytes
Immunosuppressant therapy, including high-dose glucocorticoids (≥20 mg/d of prednisone or equivalent for ≥2 wk)
Leukemia, lymphoma, or other bone marrow and lymphatic system malignancies
Cellular immunodeficiency
Solid organ transplant recipient
Recent hematopoietic stem cell transplantation

10 years. In adults who did not receive Tdap during adolescence, one of the 10-year Td booster doses should be replaced with a dose of the Tdap vaccine.

Unvaccinated adults should receive a three-dose series consisting of Td doses and at least one Tdap dose. Adults who have received fewer than three doses of the primary series should complete the series with the Td or Tdap (if not previously administered) vaccine.

Pregnant women should receive one dose of the Tdap vaccine between 27 weeks' and 36 weeks' gestation with every pregnancy, regardless of when the Td or Tdap vaccine was last administered.

Vaccinations Recommended for Some Adults

Varicella and Herpes Zoster

All immunocompetent adults without evidence of varicella immunity should receive two varicella vaccine doses. Evidence of varicella immunity includes laboratory-confirmed disease or immunity, diagnosis or verification of varicella or zoster by a provider, or documentation of age-appropriate varicella vaccination. U.S. birth before 1980 is also considered to be evidence of immunity, except in pregnant women and immunocompromised persons (who are at risk for severe disease) and health care workers (who are at risk for repeated varicella exposure and spreading the disease to those at high risk for severe disease). These patient groups must meet the other criteria for varicella immunity.

All adults aged 50 years and older, including those with a previous episode of zoster, should receive the recombinant (inactivated) herpes zoster vaccine to reduce the incidence of zoster and postherpetic neuralgia. The recombinant vaccine has demonstrated 97% efficacy in persons aged 50 to 69 years and 91% efficacy in those aged 70 years and older. It is recommended in preference to the live attenuated zoster vaccine, and adults who have been previously vaccinated with the live attenuated zoster vaccine should be revaccinated with the recombinant zoster vaccine after at least 8 weeks. The recombinant vaccine is administered intramuscularly in two doses, with an interval of 2 to 6 months between doses. The safety of the vaccine in pregnant women and patients with significant immunosuppression has not been determined. Healthy adults aged 60 years or older may receive either the recombinant vaccine (preferred) or the live attenuated vaccine. The live attenuated vaccine is administered subcutaneously in one dose.

Pneumococcal Disease

Pneumococcal vaccination is recommended in all adults aged 65 years and older and adults aged 19 to 64 years with certain high-risk conditions (**Table 18**). Two pneumococcal vaccines are available: the 13-valent conjugate vaccine (PCV13) and the 23-valent polysaccharide vaccine (PPSV23). In a randomized controlled trial involving more than 80,000 persons aged 65 years and older, the efficacy of PCV13 was 75% against vaccine-type invasive disease and 46% against vaccine-type pneumonia. PPSV23 is 60% to 70% effective in preventing vaccine-type invasive disease, although its effect on noninvasive disease is unclear.

All adults aged 65 years and older who have not previously been vaccinated should receive PCV13, followed by a dose of PPSV23 1 year later. In immunocompetent adults aged 65 years and older who have already received a dose of PPSV23, PCV13 should be administered no sooner than 1 year later. In adults aged 19 to 64 years with high-risk conditions who require vaccination with both PCV13 and PPSV23 but who have not yet received either vaccine, a single dose of PCV13 should be given first, followed by a single dose of PPSV23 given at least 8 weeks later. Adults aged 19 to 64 years with high-risk conditions who require vaccination with both PCV13 and PPSV23 and who have already received PPSV23 should be administered a single dose of PCV13 no sooner than 1 year after receiving the most recent PPSV23. A second dose of PPSV23 should also be administered 5 years after the first PPSV23 dose in adults aged 19 to 64 years with certain immunocompromising conditions (see Table 18).

Human Papillomavirus

HPV vaccination prevents persistent HPV infection, which can lead to cervical, anogenital, and nasopharyngeal cancers. Bivalent, quadrivalent, and nine-valent HPV vaccines are approved for use in females; quadrivalent and nine-valent vaccines are approved for use in males. Females should be administered the vaccine series at age 11 or 12 years or between the ages of 13 and 26 years if not given previously. In males, the series should be administered at age 11 or 12 years, between the ages of 13 and 21 years if not previously administered, or through age 26 years for immunocompromised men (including those with HIV infection) and men who have sex with men. If administered before the age of 15 years, a two-dose series is recommended, whereas a three-dose series is recommended in older individuals. Vaccination is not recommended during pregnancy, although no harmful effects have been noted when inadvertently given to pregnant women.

Measles, Mumps, and Rubella

All U.S. adults born before 1957 are considered to be immune to measles and mumps. Adults born in 1957 or later without documented evidence of receiving one or more doses of the measles, mumps, and rubella (MMR) vaccine or laboratory-confirmed immunity against all three diseases should receive at least one MMR dose. A second MMR dose should be administered to postsecondary students, health care workers, and international travelers. For persons who have been previously vaccinated with two doses of a mumps virus-containing vaccine but are at increased risk because of an outbreak, the ACIP recommends administering a third dose of mumps virus–containing vaccine to improve protection.

In women of childbearing age, it is necessary to determine rubella immunity. Nonpregnant women who lack immunity should be vaccinated. Pregnant women who lack

TABLE 18. Pneumococcal Vaccination Recommendations for Adults Aged 19 Years and Older With Underlying Medical Conditions

		PCV13	PPSV23	
Risk Group	**Underlying Medical Condition**	**Recommended**	**Recommended**	**Revaccination at 5 Years After First Dose**
Immunocompetent persons	Chronic heart disease[a]		X	
	Chronic lung disease[b]		X	
	Diabetes mellitus		X	
	CSF leaks	X	X	
	Cochlear implants	X	X	
	Alcoholism		X	
	Chronic liver disease		X	
	Cigarette smoking		X	
Persons with functional or anatomic asplenia	Sickle cell disease/other hemoglobinopathies	X	X	X
	Congenital or acquired asplenia	X	X	X
Immunocompromised persons	Congenital or acquired immunodeficiencies[c]	X	X	X
	HIV infection	X	X	X
	Chronic kidney failure	X	X	X
	Nephrotic syndrome	X	X	X
	Leukemia	X	X	X
	Lymphoma	X	X	X
	Hodgkin lymphoma	X	X	X
	Generalized malignancy	X	X	X
	Iatrogenic immunosuppression[d]	X	X	X
	Solid-organ transplant	X	X	X
	Multiple myeloma	X	X	X

CSF = cerebrospinal fluid; PCV13 = 13-valent pneumococcal conjugate vaccine; PPSV23 = 23-valent pneumococcal polysaccharide vaccine.

[a]Including heart failure and cardiomyopathies.

[b]Including COPD, emphysema, and asthma.

[c]Including B- (humoral) or T-lymphocyte deficiency, complement deficiencies (particularly C1, C2, C3, and C4 deficiencies), and phagocytic disorders (excluding chronic granulomatous disease).

[d]Diseases requiring treatment with immunosuppressive drugs, including long-term systemic glucocorticoids and radiation therapy.

Adapted from Centers for Disease Control and Prevention (CDC). Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine for adults with immunocompromising conditions: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Morb Mortal Wkly Rep. 2012 Oct 12;61(40):816-9. [PMID: 23051612]

immunity should be vaccinated at the time of delivery before leaving the hospital or at the time of pregnancy termination.

The MMR vaccine is a live virus vaccine and should not be administered to immunocompromised individuals.

Meningococcal Disease

Meningococcal vaccines used in the adult population include the quadrivalent meningococcal conjugate vaccine (MenACWY), which protects against serogroups A, C, W135, and Y, and the MenB vaccine, which protects against serogroup B disease. The quadrivalent conjugate vaccine is used in most patients, whereas the MenB vaccine is reserved for specific high-risk situations.

Indications for meningococcal vaccination in adults are summarized in **Table 19**.

Hepatitis A

Vaccination against hepatitis A is recommended for all persons who desire vaccination and for persons who are at increased risk for infection or complications of infection. Persons at increased risk include those who work in or travel to endemic areas, men who have sex with men, individuals with chronic liver disease, illicit drug users, persons with clotting disorders, persons who conduct hepatitis A–related research, and household or close contacts of children adopted from endemic areas.

TABLE 19. Indications for Meningococcal Vaccination in Adults

Vaccine	Indicated Populations
Quadrivalent meningococcal conjugate vaccine (MenACWY)	
Single dose[a]	First-year college students living in a dormitory
	Travelers to endemic areas
	Microbiologists exposed to *Neisseria meningitidis*
	Military recruits
	Adults at increased risk because of serogroup A, C, W, or Y meningococcal outbreak
Two-dose primary series[b]	Adults with anatomic or functional asplenia
	Adults with persistent complement component deficiencies (C5-C9, factor H, factor D, properdin, or patients taking eculizumab)
	Adults with HIV infection
Serogroup B meningococcal vaccine (MenB)[c,d]	Adults with persistent complement component deficiencies (C5-C9, factor H, factor D, properdin, or patients taking eculizumab)
	Adults with functional or anatomic asplenia
	Microbiologists exposed to *Neisseria meningitidis*
	Adults at increased risk because of serogroup B meningococcal outbreak
	May be administered to patients aged 16-23 years for short-term protection, preferably between age 16 and 18 years

[a]A single dose should be administered unless the patient has been vaccinated with MenACWY within the past 5 years. If exposure is ongoing, revaccination is indicated every 5 years.

[b]Doses should be administered 8-12 weeks apart, followed by a booster dose every 5 years.

[c]MenB vaccine is approved for use in persons aged >10 years.

[d]Persons who are considered to be at increased risk for infection should be given three separate doses at 0, 1-2, and 6 months. If the second dose is administered at >6 months, a third dose is not necessary.

Hepatitis B

Hepatitis B vaccination is recommended for any nonimmune adult who desires vaccination or who is considered to be at high risk for infection (**Table 20**). The typical hepatitis B vaccination series is a three-dose series, with doses administered at 0, 1, and 6 months. In adults aged 40 years and younger, 30% to 55% of patients will mount a protective antibody response after being administered one dose, 75% after the second dose, and more than 90% after the third dose. Older adults and patients undergoing hemodialysis have lower protective antibody response rates. A newer vaccine with a novel adjuvant, which was released in 2017 and endorsed by the ACIP in 2018, requires only two doses over a 1-month period and appears to be more immunogenic than previous vaccines.

Checking serum antibodies is not typically recommended after routine vaccination but is indicated in persons in whom subsequent clinical management is dependent upon knowledge of serologic response (chronic hemodialysis patients, persons with HIV, health care and public safety workers, and needle-sharing partners of persons with positive hepatitis B surface antigen).

TABLE 20. Populations With an Indication for Hepatitis B Vaccination

Any nonimmune adult desiring vaccination
Sexually active persons who are not in a monogamous relationship (any person with more than one sexual partner within the past 6 months)
Sexual partners of persons who are HBsAg positive
Persons seeking evaluation or treatment for sexually transmitted infection
Men who have sex with men
Household contacts of persons who are HBsAg positive
Residents and staff members of institutions for persons who are developmentally disabled
Current or recent injection drug users
Health care and public safety workers with anticipated risk for exposure
Persons with end-stage kidney disease, including those receiving hemodialysis and peritoneal dialysis
International travelers to regions with intermediate or high levels of endemic hepatitis B infection
Persons with chronic liver disease
Persons with HIV infection

HBsAg = hepatitis B surface antigen.

Vaccinations Recommended for Specific Populations

Health care workers (HCWs) are at increased risk for acquiring and transmitting hepatitis B, influenza, measles, mumps,

rubella, pertussis, and varicella viruses. All HCWs, regardless of patient contact, should receive the influenza vaccine annually. HCWs without immunity should be vaccinated against hepatitis B; measles, mumps, and rubella; and varicella. Additionally, all HCWs who have not previously received the Tdap vaccine should receive one dose, irrespective of when they last received the Td vaccine.

Patients with anatomic or functional asplenia are at increased risk for infection from encapsulated organisms, such as *Haemophilus influenzae* type B, meningococcus, and pneumococcus, and should be appropriately vaccinated.

Vaccination recommendations for international travelers vary depending on the destination. Trip-specific recommendations from the CDC can be accessed at https://wwwnc.cdc.gov/travel. For more information on vaccination in travelers, see MKSAP 18 Infectious Disease, Travel Medicine.

KEY POINTS

- Annual influenza vaccination is recommended for all individuals aged 6 months and older.
- Pregnant women should receive one dose of the tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap) vaccine during each pregnancy between 27 weeks' and 36 weeks' gestation.
- HVC All adults aged 50 years and older should receive the recombinant (inactivated) herpes zoster vaccine, regardless of previous immunization or clinical infection, to reduce the incidence of zoster and postherpetic neuralgia.
- Pneumococcal vaccination is recommended in all adults aged 65 years and older and adults aged 19 to 64 years with certain high-risk conditions.
- Patients with anatomic or functional asplenia should be vaccinated against *Haemophilus influenzae* type B, meningococcal, and pneumococcal diseases.

Aspirin as Primary Prevention

Aspirin therapy for primary prevention is a continually debated and constantly evolving topic. The decision to initiate low-dose aspirin for primary prevention of ASCVD and colorectal cancer is predominantly based on weighing the benefits of prevention with the harms of increased bleeding. Factors that increase bleeding risk include concurrent anticoagulant or NSAID use, history of gastrointestinal ulcer, upper gastrointestinal pain, uncontrolled hypertension, male sex, and increasing age. Other factors, such as patient preferences on taking aspirin, may also shift the balance.

Aspirin has been found to reduce nonfatal myocardial infarction (relative risk [RR], 0.78; 95% CI, 0.71-0.87) but not nonfatal stroke, cardiovascular mortality, or all-cause mortality. The benefits of ASCVD prevention are apparent within the first 5 years of therapy and continue for as long as aspirin is taken. The evidence for cancer prevention is stronger, with a 34% to 40% reduction in colorectal cancer mortality with at least 5 to 10 years of aspirin therapy. The benefit is not apparent until 10 to 20 years after initiation of aspirin; no mortality benefit was observed in the first 10 years of follow-up. Therefore, adults older than 60 years are less likely to experience these benefits.

The USPSTF recommends low-dose aspirin for the primary prevention of ASCVD and colorectal cancer in adults aged 50 to 59 years with a 10-year ASCVD risk of 10% or higher who do not have an increased risk for bleeding, have a life expectancy of at least 10 years, and are willing to take low-dose aspirin daily for at least 10 years (grade B). ASCVD risk can be calculated by using the American College of Cardiology/American Heart Association risk calculator based on the Pooled Cohort Equations, available at http://tools.acc.org/ASCVD-Risk-Estimator/. In those aged 60 to 69 years with a 10-year ASCVD risk of 10% or higher, the benefits of aspirin use for primary prevention are smaller but still outweigh the risk for bleeding; the decision to initiate low-dose aspirin in this population should be individualized (grade C). Owing to limited evidence, the USPSTF does not make a recommendation on aspirin use for primary prevention in persons younger than 50 years and older than 70 years (I statement).

In contrast to the USPSTF, the American Diabetes Association and American Heart Association suggest low-dose aspirin for primary prevention in adults with diabetes with a 10-year ASCVD risk greater than 10% who are not at increased risk for bleeding. Low-dose aspirin therapy may be considered in patients with diabetes and intermediate risk for ASCVD (10-year risk, 5%-10%). Notably, the European Society of Cardiology does not recommend any antiplatelet therapy for individuals without ASCVD because of the increased risk for bleeding and lack of convincing data on cardiovascular mortality benefit.

For patients in whom the balance of benefits and harms is unclear, the Aspirin Guide, a clinical decision-making support tool available online (www.aspiringuide.com) and as a mobile application, may offer guidance. The Aspirin Guide uses internal algorithms to calculate the patient's ASCVD risk and bleeding risk as well as the NNT with aspirin to prevent one ASCVD event and the number needed to harm (NNH) to cause one excess bleeding event due to aspirin. The tool has not yet been validated in clinical trials and does not include NNT for cancer prevention. In general, the Aspirin Guide advises initiating low-dose aspirin if the NNT is less than the NNH; however, clinical judgment is warranted.

KEY POINT

- The U.S. Preventive Services Task Force recommends aspirin for primary prevention of atherosclerotic cardiovascular disease (ASCVD) and colorectal cancer in adults aged 50 to 59 years with a 10-year ASCVD risk of 10% or greater who do not have an increased risk for bleeding, have a life expectancy of at least 10 years, and are willing to take low-dose aspirin daily for at least 10 years.

Healthy Lifestyle Counseling

Healthy lifestyle counseling is directed at the leading preventable causes of death. More than one third of preventable deaths are attributable to tobacco use and obesity and the resulting increased risks for cancer and cardiovascular disease. Other preventable causes of death include alcohol use, infectious diseases, toxins, accidents, deaths from firearms, and drug use.

Tobacco cessation is a high priority health intervention from a health and cost-effectiveness standpoint. Smokers should be offered pharmacologic therapy and behavioral interventions (see Mental and Behavioral Health).

All overweight and obese patients should undergo counseling on the benefits of a healthy weight, regular exercise, and a healthy diet (see Behavioral Counseling).

Injury prevention, including seat belt use, use of safety helmets for motorcycles and bicycles, and home safety measures (such as weapons safety), should be emphasized. Patients should be counseled to use smoke alarms in the home and to set water heaters to lower than 49 °C (120 °F). The "5 Ls" may be used for firearm safety counseling; they involve asking the following questions regarding a firearm in the home:

- Is it Locked?
- Is it Loaded?
- Are there Little children present?
- Anyone feeling Low in the house?
- Is the operator Learned about firearm safety?

Sleep and stress reduction are also components of a healthy lifestyle. The American Heart Association and the American Academy of Sleep Medicine recommend that adults obtain at least 7 hours of sleep per night for optimal health. Stress reduction, development of strong social ties, and community involvement are also associated with better health outcomes.

Even small changes at the population level, such as improving social determinants of health, can create large preventive benefits. Healthy People 2020 is a CDC initiative with the goal of creating social and physical environments that promote good health. Using strategies from behavioral economics, such as making healthy choices the default option or nudging (gently steering people in a certain direction), may help improve health outcomes. Pricing and taxation strategies and food stamp programs can help promote the purchase of fruits and vegetables and inhibit the purchase of unhealthy processed foods. Making neighborhoods and cities safer and improving bicycle lanes, walking paths, and stairs may encourage physical activity and reduce inequalities in health.

Climate change could cause numerous deleterious effects on human health, including higher rates of respiratory and heat-related illness, increased prevalence of vector-borne (malaria, chikungunya, dengue fever) and waterborne (cholera) diseases, food and water insecurity, and malnutrition. The ACP advises that physicians become educated about climate change, its effect on human health, and how to respond to future challenges.

Behavioral Counseling

For adults who are overweight or obese and have additional risk factors for cardiovascular disease (hypertension, dyslipidemia, impaired fasting glucose/diabetes), the USPSTF recommends offering or referral to intensive behavioral counseling interventions to promote a healthful diet and physical activity (grade B). Because the benefit of behavioral counseling is small in adults who do not meet these criteria, the USPSTF recommends an individualized approach to offering or referring these patients to behavioral counseling to promote a healthy lifestyle (grade C). Strategies such as motivational interviewing and setting specific and attainable goals can help facilitate lifestyle changes. Using a multidisciplinary team of health care professionals (dieticians, nurses, and psychologists) can be helpful when available.

Behavioral counseling does not need to be complex or time consuming. An analysis of more than 5000 patients who participated in the National Health and Nutritional Examination Survey found that patients who were informed that they were overweight by their physicians were more likely to report significant weight loss, although it has been shown that overweight and obesity are commonly unmentioned and undiagnosed. Advising patients to maintain a healthy weight and adopt healthy practices, including eliminating sugar-containing beverages, implementing a reduced calorie diet, avoiding processed foods, and practicing mindful eating can be beneficial. Providers may also help patients by modeling healthy behaviors; evidence shows that doctors who improve their health habits may be better able to counsel their patients regarding preventive and healthful behaviors.

Diet and Physical Activity

Adults who adhere to a healthful diet and engage in regular physical activity have lower cardiovascular mortality and may have improved cognitive function and decreased disability. Dietary guidelines from the U.S. Department of Health and Human Services recommend following a healthy eating pattern that consists of vegetables, whole fruits, whole grains, low-fat dairy, protein (poultry, fish, legumes), and oils (including nuts), while limiting consumption of added sugars, saturated and *trans* fats, and sodium. Adults of legal drinking age should be advised to limit consumption of alcohol to no more than one drink per day for women and two drinks per day for men.

Adults should perform at least 150 minutes of moderate-intensity physical activity per week or 75 minutes of vigorous-intensity physical activity per week. For increased benefit, 300 minutes of moderate-intensity activity or 150 minutes of vigorous-intensity activity is recommended. Muscle-strengthening activities (resistance training and weight lifting) are also beneficial, and adults should perform moderate- or high-intensity muscle-strengthening activities that involve all

major muscle groups 2 or more days per week. It is important to note that any physical activity is better than no activity. Physical activity need not be formal exercise; incorporating natural movement into the day offers some health benefits.

KEY POINTS

- For adults who are overweight or obese and have additional risk factors for cardiovascular disease, the U.S. Preventive Services Task Force recommends offering or referral to intensive behavioral counseling interventions to promote healthful diet and physical activity.
- Dietary guidelines from the U.S. Department of Health and Human Services recommend following a healthy eating pattern that consists of vegetables, whole fruits, whole grains, low-fat dairy, protein, and oils, while limiting consumption of added sugars, saturated and *trans* fats, and sodium.

Supplements and Herbal Therapies

Dietary supplements, including vitamins, minerals, botanicals, herbals, metabolites, and amino acids, are categorized as foods by the FDA and are therefore not subject to the same regulations as over-the-counter and prescription drugs. Manufacturers are not required to demonstrate efficacy or safety unless the supplement includes ingredients that were introduced after 1994. Manufacturers are also not allowed to make specific medical claims; however, the product's purported effect on body structure or function may be described.

Patients take dietary supplements for various reasons, such as to prevent illness, enhance health, and correct perceived deficiencies. In the United States, approximately 50% of adults report using vitamins or dietary supplements, with total consumer spending of more than $20 billion each year.

Despite their prevalent use, the USPSTF does not recommend multivitamins or herbal supplements for the prevention of cardiovascular disease or cancer. The USPSTF also concludes that there is insufficient evidence for use of vitamin D and calcium to prevent fractures. Evidence has shown that supplementation with vitamin D and calcium together increases the incidence of kidney stones. Multivitamins should not be used in the absence of a specific indication and are not effective in compensating for a poor diet. Smokers should avoid β-carotene altogether, as evidence has linked β-carotene with increased risk for lung cancer.

There are several populations for which vitamin or supplement use is strongly recommended. Women of childbearing age are advised to take 0.4 to 0.8 mg (400 to 800 µg) of folic acid daily to prevent fetal neural tube defects. Vegans and older adults may consider vitamin B_{12} supplementation to address dietary deficiency.

In addition to questionable efficacy, supplement use is associated with risk for both direct and indirect harms. Direct harms include side effects, interactions with other drugs, and harms related to inclusion of unadvertised additives, compounds, or toxins. Many supplements, such as St. John's wort, affect the cytochrome P450 system, which may affect warfarin and antidepressant metabolism. *Ginkgo biloba*, ginseng, garlic, vitamin E, and fish oil may interact with anticoagulant or antiplatelet medications, potentially causing increased risk for bleeding or inadequate anticoagulation. Harms may also occur indirectly when herbal supplement use replaces or delays standard treatments.

Despite these risks, many patients strongly believe in supplement use, and the role of the physician is to inform these patients of harmful supplements and suggest safer alternatives (**Table 21**). The National Institute of Health's MedlinePlus directory of herbs and supplements (https://medlineplus.gov/druginfo/herb_All.html) and Nutrition.gov (https://www.nutrition.gov/dietary-supplements) are useful resources.

KEY POINTS

- Manufacturers of dietary supplements are not required to demonstrate efficacy or safety unless the supplement includes ingredients that were introduced after 1994.
- The U.S. Preventive Services Task Force does not recommend multivitamins or herbal supplements for the prevention of cardiovascular disease or cancer. **HVC**

Patient Safety and Quality Improvement

Introduction

Patient safety is defined by the World Health Organization as the prevention of errors and adverse events related to medical care. Although it is a necessary component of high-quality health care, integrating safety into medical practice is a complex process that requires involvement and action at both the clinician and systems levels. Importantly, health care systems must be built on a culture of safety and structured to prevent errors, empower individuals to promote safety, and recognize and respond to errors that occur.

Quality in health care refers to the extent to which the clinician or organization meets or exceeds the needs and expectations of patients. Quality improvement involves the systematic and continuous implementation of changes that measurably improve patient care. Because quality improvement is based on the understanding that it is easier to improve that which can be measured, quality improvement usually entails ongoing monitoring and assessment.

Patient Safety and Quality Issues at the Clinician Level **H**

Common patient safety and quality issues that occur at the clinician level include diagnostic errors, medication errors, and errors occurring during transitions of care.

TABLE 21. Common Herbal Supplements

Name	Common Uses	Effectiveness	Adverse Effects	Important Drug Interactions
Black cohosh	Treatment of menopausal hot flashes	Likely effective, low-quality evidence	Possible estrogenic effect on breast Avoid in women with estrogen receptor-positive breast cancer Reports of hepatotoxicity	
Cranberry	Prevention of urinary tract infections	Likely ineffective, low-quality evidence	Increased glucose intake with juice, GI upset	
Echinacea	Prevention of common colds Treatment of common colds	Small effect Not effective	GI upset, nausea, allergic reactions	
Evening primrose oil	Treatment of breast pain Treatment of eczema Treatment of diabetic neuropathy	Mixed data on effectiveness Not effective Possibly effective	GI upset, headache May increase risk for pregnancy complications	May increase bleeding if used with warfarin
Garlic	Treatment of high cholesterol Treatment of hypertension	Not effective Possibly effective, weak evidence	Increased bleeding risk, breath and body odor, heartburn	May decrease effectiveness of isoniazid and saquinavir May increase bleeding if used with warfarin, likely due to antiplatelet effect
Ginger	Treatment of nausea Treatment of inflammation	Likely effective for pregnancy-related and chemotherapy-related nausea Possibly effective	Increased bleeding	May increase risk for bleeding when used with anticoagulants
Ginkgo biloba	Treatment and prevention of cognitive decline Treatment of claudication	Not effective Not effective	Headache, GI upset, allergic skin reactions, increased risk for bleeding	May increase risk for bleeding when used with anticoagulants and NSAIDs; potentiates MAOIs
Kava	Treatment of anxiety	Likely effective	Hepatotoxicity Use with caution in patients with liver disease or at risk for liver disease	
Milk thistle	Reduction in liver inflammation	Not effective	Nausea, indigestion, diarrhea	May interact with medications metabolized by CYP2C9
Red yeast rice (contains monacolin K, identical active ingredient to lovastatin)	Treatment of hyperlipidemia	Likely effective; risks likely outweigh benefits	Myalgia, liver function abnormalities Some may contain citrinin (a harmful contaminant), which can cause kidney failure	May interact with medications metabolized by CYP3A4 enzymes
Saw palmetto	Treatment of benign prostatic hyperplasia	Likely not effective	Headache, nausea, dizziness Contraindicated in pregnancy and lactation	
Soy (isoflavones)	Treatment of menopausal symptoms	Likely effective, low-quality evidence	GI upset, allergic reaction Avoid high doses in patients with breast cancer	

(Continued on the next page)

TABLE 21. Common Herbal Supplements (Continued)

Name	Common Uses	Effectiveness	Adverse Effects	Important Drug Interactions
St. John's wort	Treatment of depression	Mixed data on effectiveness	GI upset, fatigue, headache, dizziness	Inducer of CYP3A4 and CYP2C9 enzymes Many interactions Do not use with antidepressants
Valerian	Treatment of anxiety Treatment of sleep disorders, insomnia	Not effective Inconclusive	Tremor, headache, sedation, hepatotoxicity	

CYP2C9 = cytochrome P-450 2C9; CYP3A4 = cytochrome P-450 3A4; GI = gastrointestinal; MAOIs = monoamine oxidase inhibitors.

Diagnostic Errors

A diagnostic error occurs when a patient is not provided with a timely and correct diagnosis or the diagnosis is not communicated to the patient. More specifically, a diagnostic error is present when there was a missed opportunity to make the correct diagnosis in a timely manner. The rate of diagnostic error is approximately 10%, and most patients will be subject to a diagnostic error at some point in their lifetime. Diagnostic errors are also the leading cause of malpractice claims against internists.

Diagnostic errors are usually multifactorial in etiology, with flawed cognitive processes on the part of the clinician and issues at the systems level contributing to most errors. Examples of cognitive errors include premature closure, diagnostic momentum, confirmation bias, and faulty knowledge or knowledge application. Premature closure involves accepting a diagnosis and discontinuing the diagnostic process before the data necessary to establish the diagnosis have been obtained. Diagnostic momentum is a similar phenomenon in which a diagnosis is suggested early in the diagnostic process, and the diagnostic evaluation continues to move toward this diagnosis even if the data do not support it. Confirmation bias, the predisposition to seek evidence to confirm a suspected diagnosis without looking for evidence that disproves it, is a common feature of premature closure and diagnostic momentum. Faulty application of knowledge occurs when the clinician does not possess the underlying knowledge necessary to make the diagnosis or does not apply the knowledge properly.

Systems factors common to diagnostic error include poor communication, lack of test availability, and productivity pressures. Poor communication of crucial laboratory and imaging results (for example, the incidental finding of a pulmonary nodule) may result in delayed diagnosis and patient harm. Similarly, lack of test availability (such as advanced imaging in resource-poor environments) may result in delayed diagnoses. Productivity pressures and their effect on clinician time with patients may also contribute to diagnostic errors. **Table 22** provides techniques for avoiding some common diagnostic errors.

Medication Errors

Medication errors can occur from the time of prescription to the time of administration and may or may not result in patient harm. Medication errors are often caused by prescribing faults (inappropriate prescribing, underprescribing, or overprescribing) or prescription errors (errors in drug dose, route of administration, frequency of use, or duration of therapy; duplicative orders; prescription of drugs that interact; or prescription to the incorrect patient). In contrast, an adverse drug event is harm experienced by a patient as a result of exposure to a medication. Adverse drug events, which account for 100,000 hospitalizations in the United States each year, may be secondary to an accepted risk of a medication or may be the result of a medication error.

There are several known risk factors for medication errors. Polypharmacy, advanced patient age, and impaired kidney or liver function are patient-specific factors that increase the risk for medication errors. Clinician-specific risk factors include illegible handwriting and use of nonstandard abbreviations. Errors are also more likely to occur with the use of specific drugs, including those with look-alike or sound-alike names.

Measures to reduce medication errors include computerized physician order entry (CPOE) systems, medication reconciliation, improved labeling for medications with similar names, and barcode-assisted medication administration. The Institute for Healthcare Improvement (www.ihi.org) and the Institute for Safe Medication Practices (www.ismp.org/tools) have issued tools and resources to reduce harms related to medications. In addition, the Agency for Healthcare Research and Quality (AHRQ) has developed several strategies to prevent adverse drug events (**Table 23**).

Transitions of Care

Patient transitions between inpatient and outpatient settings, institutions, or hospital units present unique challenges to patient safety. A medication error occurs in almost 50% of patients at the time of hospital admission and is the most common form of postdischarge adverse event. The risk for diagnostic error at the time of hospital discharge is similarly high, as almost 40% of patients have test results pending or require

TABLE 22. Twelve Tips for Avoiding Diagnostic Errors

Technique	Comments
1. Understand heuristics[a]	Availability heuristic: Diagnosing based on what is most easily available in the physician's memory (e.g., because of a patient recently seen) rather than what is most probable Anchoring heuristic: Settling on a diagnosis early in the diagnostic process despite data that refute the diagnosis or support another diagnosis (premature closure) Representativeness heuristic: Application of pattern recognition (a patient's presentation fits a "typical" case; therefore, it must be that case)
2. Use "diagnostic timeouts"	Taking time to periodically review a case based on data but without assuming that the diagnosis is that which was previously reached
3. Practice "worst-case scenario medicine"	Consider the most life-threatening diagnoses first: • Lessens chance of missing these diagnoses • Does not mandate testing for them
4. Use systematic approach to common problems	For example, anatomic approach to abdominal pain beginning from exterior to interior
5. Ask why	For example, when a patient presents with diabetic ketoacidosis or a COPD exacerbation, ask what prompted this acute exacerbation of a chronic condition
6. Use the clinical examination	Decreases reliance on a single test and decreases chance of premature closure
7. Use Bayes theorem	Use pre- and posttest probabilities • Helps avert premature closure based on a single test result
8. Acknowledge the effect of the patient	How does the patient make the physician feel? • Physicians may avoid making unfavorable diagnoses in patients with whom they identify • Physicians may discount important data in patients with whom they have difficult encounters
9. Look for clinical findings that do not fit the diagnosis	Encourages a comprehensive approach and incorporates healthy skepticism
10. Consider "zebras"	Resist temptation to lock onto common diagnoses at risk of missing the uncommon
11. Slow down and reflect	Difficult to do in most health care systems, which stress the economy of "getting it right the first time"
12. Admit mistakes	Awareness of one's own fallibility may lead to fewer diagnostic errors later

[a]Heuristics are shortcuts in reasoning used in discovery, learning, or problem solving.

Information from Trowbridge RL. Twelve tips for teaching avoidance of diagnostic errors. Med Teach. 2008;30:496-500. [PMID: 18576188] doi:10.1080/01421590801965137

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completion of a diagnostic evaluation as an outpatient. Furthermore, almost one fifth of discharged Medicare patients are rehospitalized within 30 days of discharge; at least 25% of these readmissions are potentially preventable.

Medication reconciliation, predischarge patient education, and timely scheduling of posthospitalization appointments can improve safety during care transitions. Medication reconciliation entails creating an accurate, comprehensive list of the patient's prescription and nonprescription medications (including the dosage, frequency, and route of administration) and comparing the list to medication orders (at admission, transfer, or discharge) to resolve inconsistencies. Completion of medication reconciliation has been shown to decrease adverse drug events, and although the effect on hospital readmissions is less clear, medication reconciliation should occur at all care transitions to prevent medication errors. The Institute for Healthcare Improvement has published a guide to implementing medication reconciliation and measuring improvement, available at www.ihi.org/Topics/ADEsMedicationReconciliation.

Detailed communication between the hospital discharge and receiving teams is also recommended to promote patient safety. A discharge summary that includes the evaluations performed, medication reconciliation, pending test results, required follow-up tests, and follow-up appointments is an important tool in the communication between the hospital and the follow-up physician. A meta-analysis, however, revealed that crucial information on pending test results and required follow-up testing is omitted from up to two thirds of discharge summaries, and only one third of summaries are received by the accepting outpatient clinician by the time of the initial posthospitalization visit. H

KEY POINTS

- Diagnostic error is a common cause of patient harm and is usually the result of a combination of cognitive and systems errors.
- Measures to reduce medication errors include computerized physician order entry systems, medication reconciliation, improved labeling for medications with similar names, and barcode-assisted medication administration. HVC

(Continued)

TABLE 23. Strategies to Prevent Adverse Drug Events

Stage	Safety Strategy
Prescribing	Avoid unnecessary medications by adhering to conservative prescribing principles
	Use computerized provider order entry, especially when paired with clinical decision support systems
	Perform medication reconciliation at times of transitions in care
Transcribing	Use computerized provider order entry to eliminate handwriting errors
Dispensing	Have clinical pharmacists oversee the medication dispensing process
	Use "tall man" lettering and other strategies to minimize confusion between look-alike, sound-alike medications (for example, **DOP**amine and **DOBUT**amine)
Administration	Adhere to the "five rights" of medication safety (administering the right medication, in the right dose, at the right time, by the right route, to the right patient)
	Use barcode medication administration to ensure medications are given to the correct patient
	Minimize interruptions to allow nurses to administer medications safely
	Use smart infusion pumps for intravenous infusions
	Use patient education and revised medication labels to improve patient comprehension of administration instructions

Adapted from Agency for Healthcare Research and Quality. Patient safety primer: medication errors. https://psnet.ahrq.gov/primers/primer/23/medication-errors. Updated June 2017. Accessed June 27, 2018.

KEY POINTS ***(continued)***

HVC • A discharge summary that includes the evaluations performed, medication reconciliation, pending test results, required follow-up tests, and follow-up appointments is an important tool in the communication between the hospital and the follow-up physician.

Patient Safety and Quality Issues at the Systems Level

Diagnostic errors, medication errors, and communication errors (especially errors associated with care transitions) are among the many patient safety issues that require systems-level interventions to effect improvement. Similarly, improvement of many quality measures (such as readmission rates, health care–associated infections, and appropriate treatment) largely depends on systems-level changes. Individual clinicians play an important role in systems-level quality and safety programs by identifying areas in need of improvement and participating in improvement activities.

Quality Improvement Models

Successful quality improvement programs include the following components: (1) a health care delivery system with resources (people, information, technology), processes (what is done and how it is done), and outcomes (change in health behavior, patient satisfaction); (2) the objective of meeting the needs and expectations of the patient; (3) a team-based interprofessional approach; and (4) outcome assessment using both qualitative and quantitative data. Several different quality improvement models are used in the health care setting; these models focus on identifying, measuring, and correcting areas that need improvement.

Model for Improvement

The Model for Improvement focuses on achieving specific and measurable results in a specified population. This model relies on identifying a goal to be accomplished with a change, determining how the results of a change will be measured, and deciding on the changes that will bring about an improvement. These changes are tested and implemented by using a Plan-Do-Study-Act (PDSA) cycle. PDSA cycles are rapid tests of improvement, and additional PDSA cycles are completed until the desired results are achieved. A medical center, for example, may set the specific goal of decreasing central line–associated bloodstream infections and use a PDSA cycle to rapidly implement and assess the impact of changes, such as using a central line bundle.

Lean

The Lean model aims to maximize value and minimize waste by closely examining a system's processes and eliminating non-value-added activities within the system. Value stream mapping can be used to graphically display the steps of a process and the time required for each step, thereby highlighting process inefficiencies or areas of waste and allowing for their improvement. Lean also uses a 5S strategy (Sort, Shine, Straighten, Systemize, and Sustain) to create an organized workplace. Lean, for example, may be used to improve the time used to obtain, submit, analyze, and report the results of a laboratory test.

Six Sigma

Six Sigma is a quality improvement model that improves processes by identifying and removing causes of error and minimizing variability in patient care. The term Six Sigma is derived from statistical quality control measures in manufacturing processes and refers to a process that delivers nearly perfect production quality. The Six Sigma model achieves quality improvement by implementing several methods, including the stepwise DMAIC (Define, Measure, Analyze, Improve, and Control) process. The Define step of DMAIC involves developing the objectives of the project. In the Measure step, baseline data on the number and types of defects within the system are measured. The Analyze stage uses the data collected to

determine the magnitude of the effects. The Improve step involves implementation of tools to improve the process. Finally, in the Control phase, future processes are controlled to sustain the gains. Six Sigma may be applied to complex, multistep health care processes, such as the ordering and administration of high risk medications like chemotherapy, to decrease medication errors.

Operational Excellence

As its name suggests, Operational Excellence is a management system that focuses on the consistent and reliable operation of an institutional strategy. It also involves building and sustaining a culture in which each person is empowered and engaged, often by using aspects of Lean, Six Sigma, and other improvement methods. Operational Excellence can be used to improve quality by focusing key performance indicators on quality and safety metrics, such as timely completion of medication reconciliation.

KEY POINTS

HVC
- Successful quality improvement programs include a health care delivery system, the objective of meeting the needs and expectations of the patient, a team-based approach, and outcome assessment using both qualitative and quantitative data.

HVC
- The Model for Improvement, Lean, Six Sigma, and Operational Excellence are examples of quality improvement models that can be used in the health care setting.

H Measurement of Quality Improvement

Multiple organizations and payers now assess quality of care as a condition of accreditation or participation. For example, quality of care and patient safety are important elements in the Joint Commission accreditation process. The Joint Commission assesses a wide variety of quality metrics, such as timely provision of reperfusion therapy in acute myocardial infarction, the incidence of potentially preventable venous thromboembolic disease cases, and rates of immunization.

Medicare also has a significant impact on measurement of health care quality. The Medicare Access and CHIP Reauthorization Act of 2015 (MACRA) includes a new payment structure, the Merit-based Incentive Payment System (MIPS). MIPS consolidates previous quality-based programs and includes elements of the Physicians Quality Reporting System and Meaningful Use programs. More specifically, MIPS includes payment incentives and penalties related to quality and safety, value-based care, improvement activities, and meaningful use of the electronic health record (EHR). Clinicians will be required to report clinical quality metrics, participate in improvement activities (such as the patient-centered medical home), and continue to implement the EHR. Medicare will adjust reimbursement, with bonuses and penalties based on overall performance, as determined by these measures. For American College of Physicians (ACP) resources on MACRA, see https://www.acponline.org/practice-resources/business-resources/payment/medicare/macra. H

Patient Safety and Quality Improvement Initiatives

Patient-Centered Medical Home

The patient-centered medical home is a model of providing health care in which the patient's care is coordinated by a primary provider in a team-based practice. The functions of the patient-centered medical home include providing comprehensive care (including preventive, acute, and chronic care), supporting and partnering with patients to make care patient centered, coordinating care across settings with a specific focus on care transitions, delivering accessible services with extended clinician availability, and engaging in quality and safety improvement programs. Further information about the patient-centered medical home is available from AHRQ (www.pcmh.ahrq.gov/page/defining-pcmh).

The concept of the patient-centered medical home has been expanded in the patient-centered medical neighborhood, which includes other clinicians and institutions involved in an individual patient's care (such as specialists and hospitals).

High Value Care

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The ACP High Value Care initiative aims to improve health, avoid harms, and eliminate wasteful practices. This initiative addresses high value care broadly, offering learning resources for clinicians and medical educators, curricula, clinical guidelines, best practice advice, case studies, and patient resources on a wide variety of related topics (https://www.acponline.org/clinical-information/high-value-care). Some learning opportunities offer free Continuing Medical Education credits and Maintenance of Certification points. Components of the High Value Care initiative that are evident in MKSAP 18 include the identification of High Value Care key points in the text and a list of high value care recommendations assembled for each MKSAP section.

Choosing Wisely

The Choosing Wisely initiative was developed by the American Board of Internal Medicine Foundation in collaboration with *Consumer Reports* to encourage discussions between clinicians and patients on selecting tests, treatments, and procedures that are evidence based and truly necessary, thereby avoiding unnecessary evaluations and treatments. More than 80 specialist organizations have participated to create lists of overused tests and treatments in their specialties (www.choosingwisely.org/clinician-lists), and *Consumer Reports* has generated patient education materials based on these lists to engage and empower patients to participate in care discussions.

National Patient Safety Goals

The Joint Commission establishes annual National Patient Safety Goals to address important issues in health care safety (https://www.jointcommission.org/standards_information/npsgs.aspx). The National Patient Safety Goals are recommended by a panel of patient safety experts and apply to a variety of patient care settings. The Joint Commission focuses on goals that will have the highest impact on both quality and safety and provides specific metrics for each goal to facilitate implementation. The 2018 National Patient Safety Goals for the hospital setting emphasize improving the accuracy of patient identification, improving staff communication, using medications safely, reducing harms associated with alarm systems, preventing infection, identifying patient safety risks, and preventing surgical mistakes.

Health Information Technology and Patient Safety

Health information technology (HIT) is the use of an electronic environment to share patient health information. The EHR, CPOE, and clinical decision support (CDS) are some common examples of HIT.

The EHR is a compilation of all health data for a specific patient, including medical notes and test results, in a digital format. The EHR enables the timely sharing of patient information by multiple users, including those spread across several geographic sites, resulting in improved communication and care efficiency.

CPOE is a system by which clinicians electronically enter medication, radiology, and laboratory orders, thereby eliminating errors related to illegible handwriting, improving efficiency by reducing delays between order entry and receipt, and ensuring that directions for use are shared exactly as ordered.

CDS refers to the use of information technology to facilitate clinical decision making. When integrated into a CPOE system, for example, CDS can highlight potential contraindications to diagnostic tests, specify dose recommendations, identify potential drug interactions, and suggest modifications to drug dosage in patients with kidney or liver dysfunction. When integrated into EHR systems, CDS can promote protocols to improve care and provide ready access to clinical guidelines.

Limitations of HIT include the expense associated with system implementation and maintenance as well as concerns related to protection of patient privacy. Although useful for preventing many types of errors, HIT does not provide a failsafe against errors and may facilitate errors itself, such as those resulting from charting templates and use of the copy-and-paste function in composing notes.

For more information on how to incorporate HIT in practice, useful resources are available from ACP (https://www.acponline.org/practice-resources/business-resources/health-information-technology) and AHRQ (https://www.ahrq.gov/professionals/prevention-chronic-care/improve/health-it). H

Health Literacy

As defined by AHRQ, health literacy is the degree to which individuals have the capacity to obtain, process, and understand the information required to make informed health decisions. Low health literacy is more common among older adults, minority populations, persons with lower socioeconomic status, and medically underserved groups. Low health literacy may hinder patients' ability to describe their health concerns, complete health forms accurately, understand medical information, and manage their health conditions. Furthermore, evidence shows that low health literacy is associated with poorer health outcomes as well as decreased utilization of care.

Clinicians need to be aware of the health literacy of their patients and identify those who may need assistance. Tools to assess health literacy in specific populations are available at the Health Literacy Tool Shed (http://healthliteracy.bu.edu). Steps the clinician can take to improve patient understanding include using simple sentences, repeating information, providing an opportunity for the patient to ask questions, and supplying the patient with educational materials written in plain language. ACP offers a collection of patient education materials developed to help patients and their families understand health conditions and facilitate communication between patients and the health care team at https://www.acponline.org/practice-resources/patient-education-resources-and-tools.

Professionalism and Ethics

Professionalism

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Professionalism is the foundation of medicine's relationship with society and governs the conduct of the physician community. Professionalism in medicine is specifically characterized by the placement of the patient's interests above the physician's self-interests (the fiduciary relationship); acquisition, maintenance, and expansion of specialized medical knowledge; adherence to ethical principles; and self-regulation of members and responsibilities. The Charter on Medical Professionalism from the American Board of Internal Medicine Foundation, the American College of Physicians-American Society of Internal Medicine Foundation, and the European Federation of Internal Medicine sets forth three fundamental principles along with 10 professional commitments that form the ideals and values to be pursued by all physicians (**Table 24**).

Primacy of Patient Welfare

The principle of primacy of patient welfare is rooted in the importance of placing the patient's interests at the heart of the clinical enterprise. The patient's welfare must supersede all economic, personal, societal, and administrative forces. Under this principle, the physician has a duty to act for the benefit of the patient (beneficence) and to minimize patient harm

TABLE 24. Principles and Commitments of Professionalism	
Principle or Commitment	**Comment**
Fundamental Principle	
Primacy of patient welfare	Altruism is a central trust factor in the physician-patient relationship. Market forces, societal pressures, and administrative exigencies must not compromise this principle.
Patient autonomy	Patients' decisions about their care must be paramount, as long as those decisions are in keeping with ethical practice and do not lead to demands for inappropriate care.
Social justice	Physicians should work actively to eliminate discrimination in health care, whether based on race, gender, socioeconomic status, ethnicity, religion, or any other social category.
Professional Commitment	
Competence	Physicians must be committed to lifelong learning and to maintaining the medical knowledge and clinical and team skills necessary for the provision of quality care.
Honesty with patients	Obtain informed consent for treatment or research. Report and analyze medical errors in order to maintain trust, improve care, and provide appropriate compensation to injured parties.
Patient confidentiality	Privacy of information is essential to patient trust and even more pressing with electronic health records.
Appropriate patient relations	Given the inherent vulnerability and dependency of patients, physicians should never exploit patients for any sexual advantage, personal financial gain, or other private purpose.
Improve quality of care	Work collaboratively with other professionals to reduce medical errors, increase patient safety, minimize overuse of health care resources, and optimize the outcomes of care.
Improve access to care	Work to eliminate barriers to access based on education, laws, finances, geography, and social discrimination. Equity requires the promotion of public health and preventive medicine, as well as public advocacy, without concern for the self-interest of the physician or the profession.
Just distribution of resources	Work with other physicians, hospitals, and payers to develop guidelines for cost-effective care. Providing unnecessary services not only exposes one's patients to avoidable harm and expense but also diminishes the resources available for others.
Scientific knowledge	Uphold scientific standards, promote research, create new knowledge, and ensure its appropriate use.
Manage conflicts of interest	Medical professionals and their organizations have many opportunities to compromise their professional responsibilities by pursuing private gain or personal advantage. Such compromises are especially threatening with for-profit industries, including medical equipment manufacturers, insurance companies, and pharmaceutical firms. Physicians have an obligation to recognize, disclose to the general public, and deal with conflicts of interest that arise.
Professional responsibilities	Undergo self-assessment and external scrutiny of all aspects of one's performance. Participate in the processes of self-regulation, including remediation and discipline of members who have failed to meet professional standards.

Adapted with permission from ABIM Foundation; American Board of Internal Medicine; ACP-ASIM Foundation; American College of Physicians-American Society of Internal Medicine; European Federation of Internal Medicine. Medical professionalism in the new millennium: a physician charter. Ann Intern Med. 2002;136:243-6. [PMID: 11827500] Copyright 2002, American College of Physicians.

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(nonmaleficence). This is especially important in the context of the physician-patient relationship, given the inherent vulnerability of many patients. The altruism of serving the patient's interests before the physician's interests creates the trust that is essential to the physician-patient relationship.

Physicians must perform their duties irrespective of the health care setting or the patient's characteristics, including age, religion, gender, sexual orientation, decision-making capacity, insurance status, or immigration status. Care should be provided with respect, competence, compassion, and attention to the uniqueness of the patient and his or her circumstances.

Appropriate Patient Relationships

The physician-patient relationship should be based on mutual agreement. Once this relationship has been established, the physician should strive to understand the patient's health concerns, values, goals, and expectations to guide the provision of care.

Appropriate boundaries between the physician and patient must always be maintained. It is unethical for a physician to become sexually involved with a current patient, and sexual relationships with former patients should be avoided owing to concerns of continued vulnerability and transference (unconscious redirection of the feelings a person has about a second person to feelings that person has about a third person). Physicians must also maintain boundaries during the history, physical examination, and treatment maneuvers by communicating the planned actions in advance and effectively conveying the purpose of these actions (for example, "I will now lift the gown to examine your abdomen more closely"). During the examination of intimate areas, a chaperone should be present.

Physicians may be asked to care for persons with whom they have an existing nonprofessional relationship, including close friends and family members. Caring for these persons may be associated with impaired objectivity, insufficient history taking (for example, failure to obtain an adequate sexual history), incomplete examination, and incomplete or biased assessment. Physicians should weigh these considerations carefully and encourage alternative sources of care whenever feasible.

When communicating with patients online, physicians should conduct themselves according to the usual standards for professional interactions, including treating the patient with respect and maintaining privacy and confidentiality. Social media can lead to confusion over the boundaries between personal and professional interactions, and physicians should keep these spheres separate and behave professionally in both because their behavior reflects upon themselves and upon the profession as a whole. Importantly, all electronic physician-patient communications should be maintained in a secure electronic health record. Benefits, pitfalls, and recommended safeguards for online physician activities are described in **Table 25**.

Physician-patient relationships should generally be established based on an in-person professional encounter. Telemedicine, or the use of electronic communication and technologies to provide health care to patients at a distance, may improve physician-patient collaboration, access to care, and reduce costs. The American College of Physicians holds the position that a valid patient-physician relationship must be established for professionally responsible telemedicine services to occur; however, the patient-physician relationship may be formed during a telemedicine encounter through real-time audiovisual technology.

TABLE 25. Online Physician Activities: Benefits, Pitfalls, and Recommended Safeguards

Activity	Potential Benefits	Potential Pitfalls	Recommended Safeguards
Communications with patients using e-mail, text, and instant messaging	Greater accessibility Immediate answers to nonurgent issues	Confidentiality concerns Replacement of face-to-face or telephone interaction Ambiguity or misinterpretation of digital interactions	Establish guidelines for types of issues appropriate for digital communication Reserve digital communication only for patients who maintain face-to-face follow-up
Use of social media sites to gather information about patients	Observe and counsel patients on risk-taking or health-averse behaviors Intervene in emergency	Sensitivity to source of information Threaten trust in patient-physician relationship	Consider intent of search and application of findings Consider implications for ongoing care
Use of online educational resources and related information with patients	Encourage patient empowerment through self-education Supplement resource-poor environments	Non-peer-reviewed materials may provide inaccurate information Scam "patient" sites that misrepresent therapies and outcomes	Vet information to ensure accuracy of content Refer patients only to reputable sites and sources
Physician-produced blogs, microblogs, and physician posting of comments by others	Advocacy and public health enhancement Introduction of physician "voice" into such conversations	Negative online content, such as "venting" or ranting, that disparages patients and colleagues	"Pause before posting" Consider the content and the message it sends about a physician as an individual and the profession
Physician posting of physician personal information on public social media sites	Networking and communications	Blurring of professional and personal boundaries Impact on representation of the individual and the profession	Maintain separate personas, personal and professional, for online social behavior Scrutinize material available for public consumption
Physician use of digital venues (e.g., text and Web) for communicating with colleagues about patient care	Ease of communication with colleagues	Confidentiality concerns Unsecured networks and accessibility of protected health information	Implement health information technology solutions for secure messaging and information sharing Follow institutional practice and policy for remote and mobile access of protected health information

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Challenging Physician-Patient Relationships

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Conflicts between the physician and patient can arise for many reasons. Common causes of conflict include patient requests for inappropriate or nonindicated tests or treatments and patient refusal of a recommended course of treatment. Patients may disagree with the physician's recommendation because of a lack of understanding of the appropriate diagnostic or therapeutic approach, which can be exacerbated by a lack of trust or low health literacy. Other factors include financial or socioeconomic status, which can hinder patient participation in the recommended plan, and cultural considerations, which may lead to a divergent understanding of the cause of the health problem or appropriate approaches to treatment. In response to these conflicts, the physician should offer the rationale for the proposed intervention and explore the patient's reasoning. Physicians also should work to understand the social determinants of health for local communities and how these forces may affect the intersection of health and health care delivery. Furthermore, physicians have a responsibility to develop cultural responsiveness and to sensitively inquire and learn about how a patient's belief system can affect his or her understanding of the health condition. Physicians should consider cultural traditions, the specific social context, and communication standards when discussing care with patients and their families. A deeper understanding of the patient's background and rationale for decision making may allow for conflict resolution or prompt a search for more appropriate alternatives.

There are circumstances in which the physician-patient relationship becomes irreparably compromised because of lack of trust, lack of mutual goals, or failure to maintain an effective working relationship despite efforts to resolve differences. In these cases, the patient and physician can mutually terminate the relationship so long as the patient's health is stable enough for such a transition. The physician should provide formal, written documentation of the termination and provide the patient with information on obtaining a new provider. Patient abandonment (withdrawing from an established relationship without giving reasonable notice or providing a competent replacement) is unethical and may be a cause for legal action.

Requests for Interventions

Patients and their family members may request specific diagnostic or therapeutic interventions that challenge the physician's sense of what is best for the patient. Examples include requests for antibiotic therapy for a suspected viral infection and demands for aggressive chemotherapy in a debilitated patient with cancer. Although the physician needs to respect patient autonomy, this duty must be weighed against the physician's professional judgment and integrity, the potential harms of inappropriate interventions, possible secondary effects (for example, antimicrobial resistance caused by inappropriate antibiotic prescribing), and responsible stewardship of medical resources. When there is no evidence that the desired diagnostic or therapeutic intervention will provide clinical benefit, physicians are not obligated to provide these treatments.

Particularly difficult requests may occur in the setting of ambiguous or conflicting goals of care. For example, a physician may perceive that a patient with multiorgan failure will not achieve the goal of returning to his or her previous level of functioning and therefore conclude that continued intensive care is inappropriate. However, family members may have the goal of extending their loved one's life for as long as possible, regardless of the incurred risk and costs.

Effective communication regarding the preferences and goals of the patient and family members can often help adjudicate conflicts of values, clarify prognosis and uncertainties, and lead to conflict resolution. When resolution cannot be achieved, ethics consultation can be beneficial. Prompt transfer of care to a physician who concurs with the patient's or family's plan and is willing to provide the requested intervention may be necessary when resolution is not possible.

Conflicts of Interest

Conflicts of interest are financial, professional, or other personal concerns that have the potential to compromise the physician's objectivity. Real or potential conflicts threaten the physician's ability to ensure that the patient's welfare is the primary motivating factor in patient care and may undermine trust in the profession. Conflicts of interest may also exist in research and medical education.

Physicians should recognize, disclose, and manage all conflicts of interest. Researchers should disclose sources of funding and minimize opportunities for bias, and medical educators should disclose pertinent conflicts to learners. Disclosure of conflicts, however, may not be an adequate safeguard against bias in decision making, and potential conflicts should be removed if at all possible.

Physician acceptance of gifts, hospitality, and other items and services of value is also strongly discouraged, as even small and seemingly inconsequential gestures may lead to bias. To help guide decision making, physicians can consider whether they think it would be appropriate for their own physician to accept such an inducement and what the public or patient perception of the inducement might be. Other strategies for controlling conflicts of interest are listed in **Table 26**. Physicians should also recognize that the Physician Payments Sunshine Act requires medical product and pharmaceutical manufacturers to disclose payments and gifts to physicians and teaching hospitals, a list of which is published annually in a searchable database. H

KEY POINTS

- Patient abandonment, or withdrawing from an established relationship without giving reasonable notice or providing a competent replacement, is unethical and may be a cause for legal action.

(Continued)

TABLE 26. A Selection of Institute of Medicine Recommendations for Individual Physicians to Control Conflicts of Interest

Do not accept items of material value from pharmaceutical, medical device, and biotechnology companies, except when a transaction involves payment at fair market value for a legitimate service.
Do not make educational presentations or publish scientific articles that are controlled by industry or contain substantial portions written by someone who is not identified as an author or who is not properly acknowledged.
Do not enter into consulting arrangements unless they are based on written contracts for expert services to be paid for at fair market value.
Do not meet with pharmaceutical and medical device sales representatives except by documented appointment and at the physician's express invitation.
Do not accept drug samples except in certain situations for patients who lack financial access to medications.

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KEY POINTS ***(continued)***

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- If a patient requests diagnostic or therapeutic interventions for which there is no evidence of clinical benefit, physicians are not obligated to provide these interventions.
- Conflicts of interest threaten the physician's objectivity and the public's trust in the profession; physicians must avoid acceptance of financial, professional, or other personal inducements from health care companies and manufacturers.

H Respecting Patient Autonomy

Confidentiality

Physicians are required to protect the privacy and confidentiality of a patient's medical information. The promise of confidentiality fosters trust and encourages honest disclosure of sensitive personal details, thereby improving patient care.

Physicians must recognize that disclosure of medical information outside of the physician-patient relationship requires patient consent and that there is real risk for inadvertent disclosure. Physicians should be vigilant about protecting patient confidentiality in the era of electronic health records, e-mail, patient portals, and social media. Communication with and regarding patients should involve secure communication systems and storage, and physicians should follow best practices. Discussing patients outside of a clinical or educational setting, such as in a hospital cafeteria, violates confidentiality and may compromise trust in the physician and profession. Physicians must also be knowledgeable in the relevant state and federal statutes regarding confidentiality, including the Health Insurance Portability and Accountability Act of 1996 (HIPAA).

There are circumstances in which competing interests may conflict with the need for confidentiality, and disclosure becomes necessary to minimize a greater harm. For example, physicians may be required to breach confidentiality in situations of child or elder abuse, on behalf of public health concerns (for example, sexually transmitted infections), or when patients may be a threat to themselves or others. In these situations, the duty to the public good and other patients overrides the duty to maintain patient confidentiality.

Informed Consent and Refusal

Informed consent and refusal is the process of engaging the patient in meaningful dialogue about his or her health conditions, assessing the patient's understanding, and respecting the patient's autonomy to accept or refuse care. Informed consent requires that a patient be provided with all of the information necessary to determine the individual acceptability and appropriateness of the proposed treatment or intervention. Pertinent information includes the nature of the underlying condition; the goals of treatment; and the risks, benefits, and alternatives to treatment (including the option to forgo treatment). Information should be communicated in ways that are sensitive, appropriate for the patient's literacy level, and attentive to the cultural context. For informed consent to be considered valid, the patient must have decision-making capacity and be free from coercion. An exception to informed consent is a medical emergency in which a patient is unable to participate in the decision-making process; in these instances, consent for life-saving therapies should be presumed unless available information or directives suggest otherwise.

Therapeutic privilege, or the withholding of information due to concern that the disclosure will cause the patient harm, bypasses the process of informed consent and should rarely, if ever, be used. Therapeutic privilege may be used only after consultation with a colleague and a thorough weighing of the risks and benefits of the disclosure.

Advance Care Planning

Advance care planning is the process by which a patient articulates preferences, goals, and values regarding his or her future medical care. Advance care planning should consist of ongoing conversations between the patient, the physician, and loved ones to inform decisions and direct medical care in the event that the patient loses decision-making capacity. These conversations should be a routine component of care and ideally occur before an acute event or medical crisis. Advance care planning should include written documentation of the patient's preferences (advance directives) and be documented in the medical record.

Advance directives may include a living will or durable power of attorney for health care. In a living will, a patient can outline specific preferences for treatment decisions (for example, use of dialysis or mechanical ventilation). A durable power of attorney allows the patient to designate a surrogate to be the primary medical decision maker when the patient cannot make his or her own decisions.

The legal requirements for and implementation of advance directives vary by state, and physicians should be familiar with

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the laws pertaining to advance directives in the state in which they practice. State laws regarding the withdrawal of artificial nutrition and hydration may be particularly variable, and patients who have preferences regarding these interventions should clearly document these preferences in a living will.

Decision-Making Capacity

All adult patients should be presumed legally competent to make medical decisions unless found otherwise by judicial determination. However, in routine clinical care, physicians must frequently determine the patient's decision-making capacity, including the patient's ability to understand the relevant information, appreciate the medical consequences of the situation, consider various treatment options, and communicate a choice. Decision-making capacity should be evaluated for each decision to be made, and frequent reassessment is necessary to confirm previous determinations of capacity (Table 27). The presence of depression or early dementia may complicate the evaluation but

TABLE 27. Legally Relevant Criteria for Decision-Making Capacity and Approaches to Assessment of the Patient

Criterion	Patient's Task	Physician's Assessment Approach	Questions for Clinical Assessment[a]	Comments
Communicate a choice	Clearly indicate preferred treatment option	Ask patient to indicate a treatment choice	Have you decided whether to follow your doctor's (or my) recommendation for treatment? Can you tell me what the decision is? (If no decision) What is making it hard for you to decide?	Frequent reversals of choice because psychiatric or neurologic conditions may indicate lack of capacity
Understand the relevant information	Grasp the fundamental meaning of information communicated by the physician	Encourage patient to paraphrase disclosed information regarding medical condition and treatment	Please tell me in your own words what your doctor (or I) told you about: • The problem with your health now • The recommended treatment • The possible benefits and risks (or discomforts) of the treatment • Any alternative treatments and their risks and benefits • The risks and benefits of no treatment	Information to be understood includes nature of patient's condition, nature and purpose of proposed treatment, possible benefits and risks of that treatment, and alternating approaches (including no treatment) and their benefits and risks
Appreciate the situation and its consequences	Acknowledge medical condition and likely consequences of treatment options	Ask patient to describe views of medical condition, proposed treatment, and likely outcomes	What do you believe is wrong with your health now? Do you believe that you need some kind of treatment? What is treatment likely to do for you? What makes you believe it will have that effect? What do you believe will happen if you are not treated? Why do you think your doctor has (or I have) recommended this treatment?	Courts have recognized that patients who do not acknowledge their illnesses (often referred to as "lack of insight") cannot make valid decisions about treatment Delusions or pathologic levels of distortion or denial are the most common cause of impairment
Reason about treatment options	Engage in a rational process of manipulating the relevant information	Ask patient to compare treatment options and consequences and to offer reasons for selection of option	How did you decide to accept or reject the recommended treatment? What makes (chosen option) better than (alternative option)?	This criterion focuses on the process by which a decision is reached, not the outcome of the patient's choice, because patients have the right to make "unreasonable" choices

[a]Questions are adapted from Grisso T, Appelbaum PS. Assessing Competence to Consent to Treatment: A Guide for Physicians and Other Health Professionals. New York: Oxford University Press; 1998. Patients' responses to these questions need not be verbal.

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does not necessarily preclude the presence of decision-making capacity, highlighting the importance of an appropriate assessment. When a decision may result in serious consequences, determination of capacity is of even greater importance. Decisions are likely more valid when consistent with previously stated values, beliefs, and choices. Decisions that run counter to previously expressed preferences may be equally valid; however, when such changes occur, it must be clear that the patient maintains capacity and understands the ramifications of the decisions.

Surrogate Decision Making

In the absence of patient decision-making capacity, a surrogate is required to make health care decisions. The most appropriate surrogate is the person who has been legally appointed by the patient as a health care proxy. If the patient has not designated a surrogate, a person who is knowledgeable about the patient's preferences should serve as decision maker. Many states have laws that provide a hierarchy of preferred surrogates based upon relationship to the patient (typically in the sequence of spouse, adult child, parent, and adult sibling).

The surrogate should adhere to the instructions described in the living will, and physicians should assist surrogate decision makers in fulfilling these duties. If there is no living will, the surrogate should make decisions based on knowledge of the patient's preferences and values, also known as substituted judgment. If the surrogate does not have first-hand knowledge of the patient's preferences or values, he or she should make decisions based on what he or she perceives to be the patient's best interests.

Withholding or Withdrawing Treatment

When a patient with decision-making capacity refuses further treatment, even life-saving care, patient autonomy must be respected, and treatment should be stopped. If the patient lacks decision-making capacity but has articulated future wishes through an advance directive or surrogate, those preferences should guide the treatment decision. Ethically and legally, there is no distinction between withholding (not initiating) or withdrawing (removing) treatment. The decision to withdraw care can be fraught with guilt or concerns about suffering for some family members, and the physician can play an important role in explaining the process and ameliorating these concerns. An ethics committee or ethics consultation can also be helpful in assisting family members. If the patient or surrogate decides to withhold or withdraw life-sustaining treatment, other care (including symptom management and palliative care) should be continued.

Physician-Assisted Suicide

Physician-assisted suicide, or physician-assisted death, occurs when a physician provides a lethal prescription to a competent patient who has requested a means to end his or her life. The patient self-administers the drug with the intent to cause death. Physician-assisted suicide must be distinguished from euthanasia, in which a physician directly and intentionally administers an agent to cause death, and from interventions that are administered with the intent of relieving suffering but unintentionally hasten the patient's death.

Physician-assisted suicide raises profound legal, clinical, and social concerns. It may erode trust in the profession, cause harm to the most vulnerable, and hinder progress in improving end-of-life care. The American College of Physicians does not support legalization of physician-assisted suicide or euthanasia and instead emphasizes the need to provide palliative care, relief from suffering, and emotional support to the patient and family members during the end of life. Several states, however, have legalized physician-assisted suicide, and physicians may be asked to participate in discussions regarding the practice. H

KEY POINTS

- Physicians may be required to breach confidentiality in situations of child or elder abuse, on behalf of public health concerns, or when patients may be a threat to themselves or others.
- Informed consent requires that the patient be informed of the nature of the underlying condition; the goals of treatment; and the risks, benefits, and alternatives to treatment (including the option to forgo treatment).
- The presence of depression or early dementia does not necessarily preclude the presence of decision-making capacity, but these conditions increase the importance of an appropriate assessment.
- Surrogates and physicians are required to act in accordance with the patient's expressed preferences for medical care, and if these are not available, they should serve the patient's best interests.
- The American College of Physicians does not support legalization of physician-assisted suicide or euthanasia and instead emphasizes the need to provide palliative care, relief from suffering, and emotional support to the patient and family members during the end of life.

Justice

The principle of justice is predicated on fairness. Physicians have an obligation to promote and respect patients' rights and to justly allocate health care resources. Physicians should work to reduce disparities in the allocation of such resources based on patient characteristics, including sex, race, ethnicity, socioeconomic status, sexual orientation, or gender identify. However, resource allocation or rationing decisions should not be made at the bedside. Rather, these decisions are best made on the societal and policy levels; physicians should work at these levels (for example, through professional societies) to reduce disparities.

Physicians also have the responsibility to provide effective and efficient health care that uses health care resources responsibly (that is, high value care). At times, attention to just distribution of societal resources may seem contradictory to

H CONT. the principles of primacy of patient welfare and patient autonomy; however, physicians must weigh each of these considerations in a particular context to determine the appropriate course of action. By practicing high value care, physicians can ensure excellent care while also using resources wisely and ensuring that resources are equitably available.

Medical Error Disclosure

In the 1999 report *To Err Is Human: Building a Safer Health System*, the Institute of Medicine (now called the National Academy of Medicine) defined a medical error as "the failure of a planned action to be completed as intended or the use of a wrong plan to achieve an aim." Full disclosure of medical errors is recommended practice, and several states mandate such disclosures. Disclosure of errors is necessary to respect the patient's autonomy, promote trust through honesty, and promote justice through appropriate compensation. Disclosure may also benefit physicians by alleviating distress, improving physician-patient communication, and reducing litigation. Strategies that focus on early communication and response after an error have been associated with fewer malpractice lawsuits and lower litigation costs, although these outcomes are not the primary drivers of such initiatives.

The process of error disclosure should include an explanation of the course of events and how the error occurred, an apology by the physician, a description of how the effects of the error will be minimized or rectified, and steps the physician or system will take to reduce recurrences. Disclosure should be performed thoughtfully and sensitively, accounting for the emotional effect on both the patient and provider. H

KEY POINT

- Medical error disclosure should include an explanation of the course of events and how the error occurred, an apology by the physician, a description of how the effects of the error will be minimized or rectified, and steps the physician or system will take to reduce recurrences.

H Colleague Responsibility

Physicians have the responsibility to maintain professional competence, create and share new knowledge with colleagues and trainees, and work collaboratively to optimize patient care. These behaviors must be governed by self-regulation and mutual respect for the members of the health care team.

In accordance with these tenets of professionalism, physicians also have the responsibility to safeguard patients from impaired physicians and to assist impaired colleagues by identifying appropriate sources of help. Physicians have an individual obligation to report an impaired physician to the appropriate authorities and should also work collectively with institutions to develop methods for reporting, treating, and remediating impaired or disruptive colleagues.

Approaching Ethical Dilemmas

Clinical ethical dilemmas can often be resolved by analyzing (1) the patient's medical indications, including the medical condition, problems, and treatment options; (2) patient preferences, including a consideration of decision-making capacity and need for a surrogate; (3) patient quality of life, including the likelihood of restoring the patient to his or her previous state, possible harms to the patient with treatment, and patient and physician impressions of these considerations; and (4) contextual factors, including family, social, legal, religious, and other issues that might affect the decision. When ethical dilemmas are difficult to resolve, physicians may obtain assistance through an ethics consultation.

Providing Care as a Physician Bystander

Physicians' specialized knowledge creates a unique opportunity to intervene and benefit other citizens in emergency situations, and in this context, physicians may provide care outside of the clinical setting to persons who are not their patients. When physicians assist in emergency situations, patient consent to receive treatment is usually presumed or implied. If the treatment is provided in good faith, Good Samaritan laws usually protect the physician from liability, except in cases of gross negligence. Providing medical care as a bystander is typically voluntary; however, state laws vary on this point, and several states have "failure to act" laws that are not specific to physicians. H

Palliative Medicine

Introduction

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Palliative medicine improves quality of life for patients with a serious illness and their caregivers. It focuses on reducing pain, nonpain symptoms, and psychosocial stress associated with advanced disease. All physicians practice some degree of palliative medicine and should learn and use basic palliative medicine skills in patient care (**Table 28**). Specialty palliative medicine, which is palliative medicine delivered in conjunction with specialists in this field, involves an interdisciplinary team that coordinates with referring clinicians to align care with the patient's goals, preferences, and values. Notably, a palliative medicine team does not replace the primary care clinician, hospitalist, or specialist; rather, the team acts as an added layer of support, integrating key information from the referring clinician into goal-concordant care plans and attending to symptoms that affect quality of life.

Evidence has shown that specialty palliative medicine improves overall quality of life, physical symptom burden, mood, and caregiver satisfaction with patient care in the setting of serious or life-threatening illness. Although referral to palliative care historically occurred at the end of life, an

TABLE 28. Representative Skill Sets for Primary and Specialty Palliative Care

Primary Palliative Care
Basic management of pain and symptoms
Basic management of depression and anxiety
Basic discussions about:
Prognosis
Goals of treatment
Suffering
Code status
Specialty Palliative Care
Management of refractory pain or other symptoms
Management of more complex depression, anxiety, grief, and existential distress
Assistance with conflict resolution regarding goals or methods of treatment
Within families
Between staff and families
Among treatment teams
Assistance in addressing cases of near futility

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emerging consensus of research indicates that early initiation during a serious or life-threating illness is associated with substantial advantages. Much of the evidence on the benefits of subspecialty palliative care has involved patients with incurable cancer; however, numerous guidelines highlight the need for early palliative care in patients with advanced cardiac, pulmonary, or kidney disease; patients with advanced dementia; critically ill patients; and patients undergoing potentially curative interventions, such as hematopoietic stem cell transplantation.

KEY POINT

- HVC Specialty palliative medicine improves overall quality of life, physical symptom burden, mood, and caregiver satisfaction with patient care in the setting of serious or life-threatening illness.

Communicating with Patients with Serious Illness

For patients with serious illness, there are considerable disparities between the care that patients report they want and the care that they receive. Patients report a strong desire to have serious illness and end-of-life conversations and wish to have them with the clinicians they view as their primary physician contacts. Timely and skillful communication with patients, family members, and caregivers is essential to align care with patients' wishes. However, many clinicians report that they do not have the training for conversations about end-of-life care, and many conversations occur too late, with poor quality, and outside of the patient's primary clinician-patient relationship. Even among clinicians caring for populations for whom consistent advance care and end-of-life planning are considered to be standard care, it may be unclear who should facilitate end-of-life discussions, and such clinicians may feel ill equipped. One study of clinicians caring for patients with advanced heart failure found that primary care clinicians, cardiologists, and heart failure clinicians all felt unprepared for conversations related to advance care planning, despite guideline recommendations that such conversations should occur yearly.

Structured conversations are associated with improved goal-concordant care and reduced patient anxiety. One model for skilled conversations with patients facing a serious illness is outlined in **Table 29**. The Serious Illness Conversation Guide provides sample phrases that are designed to elicit a patient's goals, preferences, and values after the patient's illness understanding is assessed. In contrast to discussion techniques in which information is shared and patients are subsequently asked to choose from a list of medical interventions, the Serious Illness Conversation Guide encourages shared decision making and enables the physician to help patients understand the illness and prognosis, elicit important patient goals, and make recommendations for care. The output of these conversations should be communicated to the patient's family and surrogate decision maker. Institutional advance directives, commercial advance directive forms or electronic applications, physician orders for life-sustaining treatment (POLST) paradigm forms, and medical orders for life-sustaining treatment (MOLST) forms should be viewed as mechanisms to record the outcomes of these discussions rather than as conversation guides. For further discussion of advance care planning and advance directives, see Professionalism and Ethics.

KEY POINTS

- Patients report a strong desire to have serious illness and end-of-life conversations and wish to have them with the clinicians they view as their primary physician contact. HVC
- Structured conversations about serious illness are associated with improved goal-concordant care and reduced patient anxiety. HVC

Symptom Management

Effective and proactive symptom management is critical to the success of both basic and specialty palliative care interventions. Management of debilitating and distressing symptoms, such as pain or nausea, can markedly improve a patient's mood, sense of hope, and quality of life.

TABLE 29. Serious Illness Conversation Guide

Conversation Flow	Patient-Tested Language
1. Set up the conversation:	
Introduce the idea and benefits.	"I'm hoping we can talk about where things are with your illness and where they might be going. Is this okay?"
Ask permission.	
2. Assess illness understanding and information preferences.	"What is your understanding now of where you are with your illness?"
	"How much information about what is likely to be ahead with your illness would you like from me?"
3. Share prognosis:	
Tailor information to patient preference.	Prognosis: "I'm worried that time may be short."
	or "This may be as strong as you feel."
Allow silence; explore emotion.	
4. Explore key topics:	
Goals	"What are your most important goals if your health situation worsens?"
Fears and worries	"What are your biggest fears and worries about the future with your health?"
Sources of strength	"What gives you strength as you think about the future with your illness?"
Critical abilities	"What abilities are so critical to your life that you can't imagine living without them?"
Tradeoffs	"If you become sicker, how much are you willing to go through for the possibility of gaining more time?"
Family	"How much does your family know about your priorities and wishes?"
5. Close the conversation:	
Summarize what you've heard.	"It sounds like ______ is very important to you."
Make a recommendation.	"Given your goals and priorities and what we know about your illness at this stage, I recommend...."
Affirm your commitment to the patient.	"We're in this together."
6. Document your conversation.	

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Pain

H Although pain in advanced illness shares some features with chronic noncancer pain, pain management in palliative care has several unique attributes, which will be discussed in this section. For a discussion of pain mechanisms as well as the evaluation and initial treatment of patients with pain, refer to Common Symptoms.

Pain commonly occurs in patients with serious illness, and recognition and constant evaluation of pain are integral to effective management. Up to 90% of patients with advanced cancer have pain. Unfortunately, cancer pain remains undertreated, with about one third of patients with cancer receiving inadequate analgesia. The incidence of pain in patients with other serious illnesses is also underappreciated. Most patients with advanced COPD, severe heart failure, amyotrophic lateral sclerosis, or end-stage kidney disease undergoing hemodialysis have undertreated pain.

Many patients additionally face complex psychosocial and spiritual issues related to their illness and may experience total pain, defined as physical, social, psychological, and spiritual suffering. Engaging interdisciplinary team members, such as nurses, psychologists, chaplains, and social workers, is important in addressing the nonphysical components of pain.

The pharmacologic management of pain in patients with a serious illness requires a multimodal approach that uses both opioids and nonopioid analgesics, such as acetaminophen, NSAIDs, glucocorticoids, topical therapies, neuropathic agents, and antidepressants with analgesic properties. (See Common Symptoms for a discussion of common coanalgesic agents.) Current approaches eschew the use of opioid-acetaminophen combination medications because of the risk for acetaminophen overdose with titration of the opioid component, particularly when used concurrently with other acetaminophen-containing drugs. Additionally, the so-called "weak opioids" (codeine, tramadol) should be avoided in this population because of significant drug-drug interactions, marginal effectiveness, and wide variations in hepatic metabolism. For patients in whom nonopioid treatment is ineffective

or not tolerated, opioids are appropriate, with careful attention paid to dosing, frequency, and side effect profile. **Table 30** outlines the most commonly used opioids in the treatment of pain resulting from a serious illness, as well as specific patient population concerns.

Short-acting opioids should be titrated to achieve symptom relief. In patients using short-acting opioids who require longer-lasting relief, long-acting agents are appropriate; however, long-acting opioids should not be initiated in opioid-naive patients. Selection of a long-acting opioid should be based on underlying organ function and previous response to the equivalent short-acting formulation (for example, oxycodone immediate-release and controlled-release forms).

Fentanyl patches are commonly used for long-acting pain relief, although they have a more complex pharmacokinetic profile than oral agents and are less easily titrated. Fentanyl patches must be used with caution in patients with a serious illness, especially those who lack adipose tissue or are subject to recurrent infections. Absence of adipose tissue may result in irregular transdermal absorption, whereas fever may cause increased absorption with a greater potential for adverse events.

Orally administered transmucosal immediate-release fentanyl (TIRF) products are approved for the treatment of cancer-related pain. TIRF formulations are rapidly absorbed and offer immediate onset for patients who are not achieving adequate analgesia with high-dose morphine. Management of these medications is challenging because the dosing regimen, escalation, and frequency differ among brands. Additionally, clinicians require specialized education and certification (TIRF Risk Evaluation and Mitigation Strategy program) to initiate these medications. Methadone is another long-acting agent used to treat pain from a serious illness; however, its complex dosing and variable half-life restrict its general use. Owing to their complicated management, TIRF formulations and methadone should be prescribed in collaboration with an expert in pain management or a palliative medicine specialist with experience in their use. H

Medical cannabis has long been used in the management of symptoms associated with serious illness. It has been studied for numerous clinical indications and is approved in many states for the treatment of cancer symptoms or symptoms associated with other terminal illnesses. Cannabis extracts, predominantly those containing higher concentrations of cannabidiol, have shown a moderate degree of benefit in the treatment of patients with chronic pain and patients with pain symptoms from spasticity in the setting of neurodegenerative disorders. However, given the lack of data on medical cannabis in managing complex cancer pain and the need for multimodal analgesic therapy in seriously ill patients, the role of medical cannabis for this indication remains unclear.

Constipation

Constipation is a common symptom in patients with serious illness and negatively affects quality of life. Causes include opioids, dehydration, immobility, metabolic disturbances, and numerous nonopioid medications. More than 90% of patients with cancer who are receiving opioids experience constipation.

Patients with constipation in the setting of serious illness should be educated on increasing their intake of fluids and dietary fiber. Patients taking opioids, however, should not receive supplemental fiber, owing to concerns for worsening constipation in the setting of opioid-reduced gastrointestinal motility. Pharmacologic therapy for constipation and for all patients taking scheduled opioids should include a stimulant laxative, such as senna or bisacodyl. Osmotic laxatives, such as

TABLE 30. Opioids Commonly Used in Palliative Care

Opioid	Protein Binding	Metabolism	Comments
Hydrocodone	Low	Liver enzyme CYP2D6	Variable efficacy; combination with acetaminophen limits use Increased time to analgesic onset in liver failure
Hydromorphone	Low	Liver (glucuronidation)	Better choice if kidney disease is present Reduce dose and frequency in liver failure/cirrhosis
Tramadol	Low/moderate	Liver enzymes CYP2D6/CYP3A4	Variable time to onset and analgesic efficacy in liver failure Interactions with other serotonergic medications, potentially leading to serotonin syndrome (agitation, clonus, muscle rigidity, hyperreflexia)
Oxycodone	Moderate/high	Liver enzymes CYP2D6/CYP3A4	Increased half-life and variable onset in liver failure; if used, reduce dose and frequency
Morphine	Moderate/high	Liver (glucuronidation)	Avoid in liver failure/cirrhosis, kidney failure Increased bioavailability with liver failure Increased toxic metabolites with kidney failure
Fentanyl	High	Liver enzyme CYP3A4	Safest long-acting drug in kidney and liver failure Increased bioavailability with liver failure; start lower-dose patch in liver failure

CYP2D6 = cytochrome P-450 2D6; CYP3A4 = cytochrome P-450 3A4.

H CONT polyethylene glycol, are often added to achieve a regular bowel pattern. Docusate, alone or in combination, is no more effective than placebo for constipation in patients with a serious illness. Third-line therapy consists of rectal suppositories and/or enema preparations. Phosphate- or magnesium-containing enema preparations are contraindicated in seriously ill patients because of the potential for dangerous electrolyte shifts. If maximal medical therapy has failed to achieve laxation in patients taking opioids, peripheral opioid antagonists (such as methylnaltrexone) should be considered; these medications do not cross the blood-brain barrier and therefore do not affect analgesia.

Nausea

Nausea and vomiting are common and debilitating symptoms in patients with a serious illness, with many patients rating nausea as more distressing than unrelieved pain. Management of nausea should be tailored to address the underlying mechanism and associated neurotransmitter pathway (**Table 31**). More than one agent is frequently required for symptom relief. In hospitalized patients, parenteral forms should be administered on a scheduled basis to achieve symptom control and not just reduce the number of emesis events. H

Other Symptoms

Anorexia and weight loss frequently occur in patients at the end of life. Clinicians should identify and treat any reversible conditions that may contribute to anorexia to ease patient and family distress. Although some medications are marketed for patients with anorexia and weight loss, they are marginally effective in a minority of terminally ill patients and often have unacceptable side effects. The use of enteral or parenteral artificial nutritional support at the end of life does not improve survival, is invasive, and can cause side effects, including increased terminal secretions and painful edema. Discussing the dying process, including the common presence of weight loss and anorexia and the lack of effective treatment for these expected changes, can prepare patients and their family members and set realistic expectations.

H Audible oropharyngeal secretions at the end of life ("death rattle") are often distressing for families and clinicians alike and may occur in up to 50% of dying patients. However, these secretions rarely affect respiratory status or cause patient distress, and educating family members on the normal process of dying can ease concerns. Treatment is often initiated in anticipation of family distress but is generally ineffective. Current literature does not support the routine use of antimuscarinic drugs in the treatment of death rattle. There is also no evidence that scopolamine, glycopyrronium, hyoscine butylbromide, atropine, or octreotide are superior to no treatment. The use of anticholinergic agents in patients who are awake can lead to undesirable symptoms, such as dry mouth and urinary retention. Suctioning by catheter should be avoided unless secretions are causing obvious respiratory distress.

Although symptoms of anticipatory grief are common at the end of life, clinical depression is not experienced by most patients and should not be expected. Clinical depression worsens quality of life and should be aggressively treated if present. In contrast to neurovegetative symptoms that accompany terminal illness (such as poor appetite and low energy), symptoms of unrelenting helplessness, hopelessness, and lack of pleasure should raise concerns for clinical depression. If depression is diagnosed, pharmacotherapy consists of antidepressant agents that are appropriate for the patient's estimated prognosis. Selective serotonin reuptake inhibitors are effective and safe in patients with end-organ dysfunction; however, their therapeutic effects may not be reached for several weeks. In patients with an estimated life expectancy of less than 6 weeks, psychostimulants, such as methylphenidate, are favored.

Delirium is a common symptom in patients at the end of life. It can result from many potentially reversible causes (medication side effects, inadequate analgesia, urinary retention, constipation), although a cause is often not identified.

TABLE 31. Treatment of Nausea in the Palliative Care Patient

Cause of Nausea	Mediating Receptor Pathway	Treatment
Gut wall stretching or dilatation (constipation, bowel obstruction, ileus)	Dopamine type 2 (D_2) receptors in the gastrointestinal tract	Antidopaminergic antiemetics (metoclopramide, prochlorperazine, haloperidol)
Gut mucosal injury (radiation, chemotherapy, infection, inflammation, direct tumor invasion)	Serotonin (5-hydroxytryptamine-3 [5-HT_3]) receptors in the gastrointestinal tract	Serotonin antagonists (ondansetron, granisetron)
Drugs, metabolic by-products, bacterial toxins	D_2 receptors, 5-HT_3 receptors, and neurokinin type 1 receptors in the chemoreceptor trigger zone	Antidopaminergic antiemetics and serotonin antagonists
Motion sickness, labyrinthine disorders	Histamine type 1 (H_1) receptors and muscarinic acetylcholine receptors in the vestibular system	Anticholinergic antiemetics (scopolamine, diphenhydramine, promethazine)
Anticipatory nausea	Unknown, presumed cerebral cortex	Benzodiazepines
Increased intracranial pressure	Unknown	Glucocorticoids

Nonpharmacologic interventions remain standard care; however, for some patients, medications may be required to maintain patient and caregiver safety and to ensure relief from suffering. First-generation antipsychotics, such as haloperidol or chlorpromazine, are effective and have not been shown to be inferior to newer generation antipsychotics. The combination of benzodiazepines and antipsychotics may be more effective than antipsychotics alone in the treatment of delirium at the end of life.

Dyspnea can be a prominent and distressing symptom in patients with advanced illness and those at the end of life. The patient's subjective sensation of difficulty breathing should be measured on an iterative basis during evaluation and treatment. Although the initial goal of treatment is to address the underlying cause of dyspnea, many patients with advanced illness will have persistent dyspnea despite maximal medical management. In these patients, opioids are the treatment of choice. Opioids reduce the sensation of dyspnea and, when appropriately selected and dosed, do not cause respiratory depression. Refer to Common Symptoms for further discussion of the evaluation and management of dyspnea.

KEY POINTS

- The pharmacologic management of pain in patients with serious illness requires a multimodal approach that uses opioids and nonopioid analgesics such as acetaminophen, NSAIDs, glucocorticoids, topical therapies, neuropathic agents, and antidepressants with analgesic properties.
- For patients in whom nonopioid analgesic agents are ineffective or not tolerated, opioids are appropriate, with careful attention paid to dosing, frequency, and side effect profile.
- Pharmacologic therapy for patients with constipation and for all patients taking opioids should include a scheduled stimulant laxative, such as senna or bisacodyl.
- HVC Enteral or parenteral artificial nutritional support at the end of life does not improve survival, is invasive, and can cause side effects, such as increased terminal secretions and painful edema.
- Clinical depression should not be expected in patients at the end of life; if present, it should be aggressively treated.

Hospice

Hospice is a form of palliative medicine that delivers specialized interdisciplinary care to patients with an expected prognosis of 6 months or less. Hospice care can be provided to patients in multiple settings, including the home, skilled nursing facilities, and residential hospice homes. Hospice teams are skilled in managing the symptoms of advanced and terminal illness and improve overall satisfaction with care.

Common Symptoms

Introduction

Specific symptom concerns account for nearly half of all outpatient visits. Although most symptoms resolve in several weeks, they sometimes present clinicians with the challenge of how to best determine their significance and the role of testing in the diagnostic approach. Unnecessary testing accounts for nearly 30% of health care costs. Hence, when evaluating symptoms, physicians have a responsibility to use testing strategies that offer the highest value. Fortunately, a thorough history alone generates the highest diagnostic yield, up to 75% in some studies, with the physical examination contributing an additional 10% to 15%. In contrast, testing results in less than 10% of diagnoses. Although diagnostic testing may provide crucial information and justify the costs incurred, physicians should consider the value of diagnostic testing and the effects of test results on patient management.

This chapter focuses on high value approaches to the diagnosis and treatment of commonly encountered symptoms, including chronic noncancer pain, medically unexplained symptoms, dyspnea, cough, fatigue, dizziness, syncope, insomnia, and lower extremity edema. In addition, in-flight emergencies, a common event encountered by physicians, are reviewed.

Chronic Noncancer Pain

The classification, assessment, and management of chronic noncancer pain are discussed in this section. For a discussion of cancer-related pain and pain in the setting of advanced illness, refer to Palliative Medicine.

Chronic pain is defined as a painful sensation lasting for more than 3 months or beyond the time frame expected for normal healing. Chronic pain has substantial negative effects on patient quality of life and physical, social, financial, and functional status. More than 10% of the U.S. population has symptoms consistent with chronic pain.

The approach to the patient with chronic pain is guided by the type of pain the patient experiences. Classification of chronic pain as nociceptive or neuropathic can be helpful in designing a tailored therapeutic approach; however, many patients with chronic noncancer pain syndromes will experience both nociceptive and neuropathic pain from multiple sources.

Nociceptive pain syndromes are caused by involvement of either visceral or somatic nociceptors. Visceral pain syndromes classically result from injury to or abnormal firing of visceral pain fibers; patients typically report poorly localized cramping or aching. In contrast, somatic pain syndromes are more commonly associated with injury to somatic pain fibers that convey signals from muscles, bones, and joints. Types of somatic pain include musculoskeletal pain (see Musculoskeletal Pain) and inflammatory pain. Often described by patients as sharp

and stabbing pain, somatic nociception is easier to localize than visceral pain.

Neuropathic pain syndromes result from injury to peripheral nerve structures or central nervous system damage. Peripheral nerve syndromes, such as postherpetic neuralgia, are common and can be diagnosed by identifying sensory symptoms within the distribution of the affected peripheral nerve or nerves. Central neuropathic pain syndromes, such as those caused by cerebrovascular accidents or spinal cord injuries, often have widely varying presentations and symptom expression and can evade initial diagnostic approaches. A high index of suspicion is required because pain is often vaguely localized. Clinicians should look for key features, such as hyperalgesia (oversensitivity to a normally painful stimulus) or allodynia (pain from a normally nonpainful stimulus) occurring in the setting of underlying central nervous system injury.

In addition to nociceptive and neuropathic pain, pain induced by opioid therapy can occur paradoxically. Opioid-induced hyperalgesia is thought to result from repeated exposure to systemic opioids. Patients with this pain syndrome may experience a change in the character of their pain during the course of opioid therapy, a worsening of pain with increased opioid dosages, and a reduction in pain when opioid dosages are decreased.

Assessment

The first step in the assessment of chronic pain is a thorough history and physical examination. Determination of pain location, duration, severity, temporal nature, and responsiveness to treatment is crucial in identifying the pain generator and tailoring the diagnostic and therapeutic approaches. In most cases of chronic pain, additional testing and imaging are unlikely to produce further diagnostic yield.

A key component of the assessment is a thorough review of the patient's functional status, including physical functioning, ability to perform basic activities of daily living, and psycho-social-spiritual functioning. Psychological comorbidities influence and are influenced by experiences of chronic pain, and they affect response and adherence to a multimodal treatment strategy. Patients should be screened for mental health disorders, and if present, these disorders should be treated in conjunction with the patient's chronic pain whenever possible. Depending on severity, treatment of concomitant mental health conditions may take precedence over interventions targeting chronic pain.

Patients with chronic pain are up to four times more likely to have concomitant depression. Depression increases as pain symptoms magnify, and depression may also manifest as pain. Aggressive treatment of depression, with both pharmacologic and nonpharmacologic behaviorally based therapies, can lead to substantial improvement in both chronic pain and depressive symptoms. Iterative evaluation of depressive symptoms during chronic pain treatment is critical to ensuring that patients are able to sustain improvements.

Substance abuse screening is another essential part of the assessment of patients with chronic pain (see Routine Care of the Healthy Patient). Substance use disorders are more common in patients with chronic pain syndromes and increase the risk for opioid misuse.

In the setting of chronic pain without a treatable underlying cause, clinicians should monitor for significant changes in pain experience, new acute pain syndromes superimposed on chronic pain, and development of "red flag" symptoms. Red flags include pain occurring with constitutional symptoms (such as fever and involuntary weight loss), change in bowel or bladder function, and weakness or sensory deficits. These signs and symptoms should trigger further investigation.

Management

Management is determined by the cause of the patient's pain; the pain severity (as it relates to functional status); medical and psychosocial comorbid conditions; and barriers to treatment, such as health care access and concomitant mental health disorders. Developing a therapeutic relationship in which patients feel that their physician takes their pain seriously and in which patients, as well as family, friends, or other social supports, are active participants in the treatment strategy are important for success over time. Physical activity, engagement in work activities, and behavioral interventions should be encouraged regardless of pain score. Pharmacologic therapy should be viewed as adjunctive to nonpharmacologic therapy in the treatment of chronic pain. Patients receiving treatment should undergo periodic evaluation of pain, functional status, response to interventions, and quality of life.

Nonpharmacologic Therapy

All patients with chronic pain should be referred to a structured physical therapy program for evaluation and treatment. Physical therapy teaches patients safe, self-guided exercises to improve functional status. High-quality evidence suggests that physical therapy programs improve both pain and function in patients with debilitation due to pain symptoms. Continuation of physical therapy beyond 12 weeks should be based on iterative clinical assessments and documented gains. Like physical therapy, exercise programs improve pain and function in patients with chronic pain, although no specific regimen has proved superior. Low- to moderate-quality evidence supports the use of complementary and integrative therapies, such as massage and acupuncture, to manage chronic pain.

Cognitive behavioral techniques, including cognitive behavioral therapy (CBT), mindfulness practices, and biofeedback, have been associated with reduced pain and improved overall function and mood. Referral to practices or specialized pain centers that provide these therapies should be explored when available.

Interventional approaches may be appropriate for patients with pain syndromes that can be anatomically targeted with injection-based therapy. In addition, advanced therapies, such

as high-frequency neurostimulation, hold promise for appropriately selected patients. Patients may be referred to a pain specialist for consideration of these therapies.

Pharmacologic Therapy

Pharmacologic therapy should be used as adjunctive treatment for chronic pain when nonpharmacologic therapies have not achieved their desired effect. Clinicians should emphasize that pharmacologic therapies have limited efficacy in the long-term management of chronic pain and are intended to improve function and quality of life, not pain scores. Patients should be informed that adjuvant pharmacologic therapies may take weeks to be effective and that a combination of medications with differing mechanisms may be necessary to provide optimal benefit. When selecting pharmacologic therapies to add to a multimodal treatment regimen, attention to comorbid illness (particularly organ dysfunction) and concurrent medications is critical to limit side effects.

For chronic musculoskeletal or inflammatory nociceptive pain, trials of acetaminophen (≤3 g/d) or NSAIDs can be considered as initial pharmacologic therapy in patients without contraindications to their use. In cases of inflammatory nociceptive pain, NSAIDs can be given both orally and topically. NSAIDs are typically used for periodic pain flares or potentially while opioid therapy is being down-titrated but not for long-term therapy. Topical NSAIDs, such as topical diclofenac, have few systemic side effects, are generally well tolerated, and are effective for short-term treatment of musculoskeletal nociceptive conditions. Although short courses of muscle relaxants may be beneficial in some patients with acute pain, long-term use should be avoided because of the potential for side effects and drug-drug interactions.

In chronic neuropathic pain syndromes, gabapentinoids (such as gabapentin and pregabalin) and serotonin-norepinephrine reuptake inhibitors (such as duloxetine) are first-line therapy. When pain generators are topically located, capsaicin and topical lidocaine can be considered. Tricyclic antidepressants, such as nortriptyline and desipramine, are also effective for neuropathic pain syndromes, although titration to effective dosages is often limited by side effects and drug-drug interactions.

Medical cannabis is increasingly available for use in patients with chronic pain. Many states have passed laws legalizing the use of cannabis or allowing its use for medical conditions, although it is still classified by the U.S. Drug Enforcement Administration as a schedule I agent. Current data on the effectiveness of medical cannabis for chronic pain are characterized by significant heterogeneity in both patient populations and cannabis preparations, although recent systematic reviews have demonstrated that cannabis has some efficacy in the treatment of chronic noncancer pain. The most robust data originate from studies of compounds available outside the United States (such as nabiximols), which contain higher ratios of cannabidiol to tetrahydrocannabinol (THC) than the existing FDA-approved synthetic THC (dronabinol). Little is known about the comparative efficacy of cannabis preparations in states where medical cannabis is available.

Opioids

Patients who present to physicians' offices with chronic pain are frequently provided with prescriptions for opioids. Despite high prescribing rates, no evidence supports the use of long-term opioid therapy in patients with chronic noncancer pain. In fact, evidence demonstrates that long-term opioid use is associated with poorer overall functional status, worse quality of life, and worse pain (possibly mediated through opioid tolerance and hyperalgesic mechanisms). In addition, although often well intentioned, these prescribing patterns lead to substantial morbidity and mortality. From 1999 to 2015, more than 183,000 Americans died from overdose related to prescription opioids, and in 2011, an estimated 400,000 emergency department visits were attributable to opioid misuse or abuse. Importantly, most opioid-related overdoses occurred in patients taking opioids as prescribed. Opioids should not be considered first-line therapy in any patient with a chronic noncancer pain syndrome.

In patients in whom multimodal analgesic therapy has not improved function and quality of life or in patients already receiving opioids, the decision to initiate or continue opioids should include a thorough assessment of the benefits and burdens of therapy. In 2016, the Centers for Disease Control and Prevention (CDC) released a comprehensive guideline for prescribing opioids in patients with chronic pain syndromes, not including patients with active cancer, patients receiving palliative care, and patients at the end of life. Central to these guidelines are a robust discussion of risks and benefits, close monitoring, and use of risk mitigation strategies (**Table 32**). The CDC provides a checklist to assist clinicians in the prescribing of opioids in the setting of chronic noncancer pain, available at https://stacks.cdc.gov/view/cdc/38025.

When discussing opioid therapy with patients, it is important to emphasize the lack of evidence for long-term opioid therapy in chronic pain syndromes and the substantial risks associated with long-term use of these medications. **Table 33** summarizes some of the important risks associated with long-term opioid therapy.

Clear treatment goals based on functional improvement and quality-of-life considerations should be established to manage patient expectations and provide a means for measuring the success or failure of treatment. These goals can be incorporated into a patient-physician prescribing agreement, which can also be used to communicate expectations for follow-up, monitoring, and risk mitigation.

The CDC guideline recommends that before starting and periodically during continuation of opioid therapy, clinicians should evaluate risk factors for opioid-related harms. A commonly used risk assessment instrument, the Opioid Risk Tool, is available at https://www.drugabuse.gov/sites/default/files/files/OpioidRiskTool.pdf. Urine drug screening and surveillance of state prescription monitoring databases are important

TABLE 32. Centers for Disease Control and Prevention Recommendations for Prescribing Opioids for Chronic Pain Outside of Active Cancer, Palliative, and End-of-Life Care[a]

Determining When to Initiate or Continue Opioids for Chronic Pain
1. Nonpharmacologic therapy and nonopioid pharmacologic therapy are preferred for chronic pain. Clinicians should consider opioid therapy only if expected benefits for both pain and function are anticipated to outweigh risks to the patient. If opioids are used, they should be combined with nonpharmacologic therapy and nonopioid pharmacologic therapy, as appropriate.
2. Before starting opioid therapy for chronic pain, clinicians should establish treatment goals with all patients, including realistic goals for pain and function, and should consider how therapy will be discontinued if benefits do not outweigh risks. Clinicians should continue opioid therapy only if there is clinically meaningful improvement in pain and function that outweighs risks to patient safety.
3. Before starting and periodically during opioid therapy, clinicians should discuss with patients known risks and realistic benefits of opioid therapy and patient and clinician responsibilities for managing therapy.
Opioid Selection, Dosage, Duration, Follow-up, and Discontinuation
4. When starting opioid therapy for chronic pain, clinicians should prescribe immediate-release opioids instead of extended-release/long-acting (ER/LA) opioids.
5. When opioids are started, clinicians should prescribe the lowest effective dosage. Clinicians should use caution when prescribing opioids at any dosage, should carefully reassess evidence of individual benefits and risks when increasing dosage to ≥50 morphine milligram equivalents (MME)/day, and should avoid increasing dosage to ≥90 MME/day or carefully justify a decision to titrate dosage to ≥90 MME/day.
6. Long-term opioid use often begins with treatment of acute pain. When opioids are used for acute pain, clinicians should prescribe the lowest effective dosage of immediate-release opioids and should prescribe no greater quantity than needed for the expected duration of pain severe enough to require opioids. Three days or less will often be sufficient; more than 7 days will rarely be needed.
7. Clinicians should evaluate benefits and harms with patients within 1 to 4 weeks of starting opioid therapy for chronic pain or of dose escalation. Clinicians should evaluate benefits and harms of continued therapy with patients every 3 months or more frequently. If benefits do not outweigh harms of continued opioid therapy, clinicians should optimize other therapies and work with patients to taper opioids to lower dosages or to taper and discontinue opioids.
Assessing Risk and Addressing Harms of Opioid Use
8. Before starting and periodically during continuation of opioid therapy, clinicians should evaluate risk factors for opioid-related harms. Clinicians should incorporate into the management plan strategies to mitigate risk, including considering offering naloxone when factors that increase risk for opioid overdose, such as history of overdose, history of substance use disorder, higher opioid dosages (≥50 MME/day), or concurrent benzodiazepine use, are present.
9. Clinicians should review the patient's history of controlled substance prescriptions using state prescription drug monitoring program (PDMP) data to determine whether the patient is receiving opioid dosages or dangerous combinations that put him or her at high risk for overdose. Clinicians should review PDMP data when starting opioid therapy for chronic pain and periodically during opioid therapy for chronic pain, ranging from every prescription to every 3 months.
10. When prescribing opioids for chronic pain, clinicians should use urine drug testing before starting opioid therapy and consider urine drug testing at least annually to assess for prescribed medications as well as other controlled prescription drugs and illicit drugs.
11. Clinicians should avoid prescribing opioid pain medication and benzodiazepines concurrently whenever possible.
12. Clinicians should offer or arrange evidence-based treatment (usually medication-assisted treatment with buprenorphine or methadone in combination with behavioral therapies) for patients with opioid use disorder.

[a]All recommendations are category A (apply to all patients outside of active cancer treatment, palliative care, and end-of-life care) except recommendation 10 (designated category B, with individual decision making required); see full guideline at https://www.cdc.gov/mmwr/volumes/65/rr/rr6501e1.htm for evidence ratings.

Reproduced from Dowell D, Haegerich TM, Chou R. CDC guideline for prescribing opioids for chronic pain—United States, 2016. MMWR Recomm Rep. 2016;65:16. [PMID: 26987082] doi:10.15585/mmwr.rr6501e1

TABLE 33. Risks of Long-Term Opioid Therapy

Endocrinopathies (e.g., osteoporosis, hypogonadism)
Increased risk for opioid addiction
Increased risk for overdose and death
Increasing pain through mechanisms of opioid-induced hyperalgesia
Opioid tolerance resulting from adaptive central nervous system mechanisms

risk-mitigation strategies for patients receiving opioids in the setting of chronic pain. Although the optimal frequency of urine drug screening is unclear, patients taking long-term opioid therapy should undergo urine screening at least yearly to assess for adherence to the prescribed agent and for the presence of substances that could increase the risk for opioid overdose. More frequent screening may be recommended based on individual patient characteristics. State prescription monitoring databases (where available) should also be reviewed on a regular basis for adherence to the terms of the prescribing agreement.

The CDC guideline also provides recommendations on safe dosing. The risk for opioid-related overdose is dose dependent, with significantly increased risk for overdose in patients receiving dosages higher than 90 morphine milligram equivalents per day. The lowest possible dosage should be used to achieve the functional and quality-of-life goals established by the patient and prescriber. Given the risks and limited efficacy of opioid therapy in treating chronic noncancer pain, these dosages should not typically exceed more than 50 morphine milligram equivalents per day. Follow-up evaluation should occur at frequent intervals after therapy initiation or dosage changes and at least every 3 months. Dosages exceeding 50 morphine milligram equivalents per day should prompt re-evaluation and closer follow-up intervals. Dosages higher than 90 morphine milligram equivalents per day are considered high risk and should be prescribed only in consultation with pain specialists. Co-prescription of opioids and benzodiazepines is associated with an increased risk for death from overdose and should be avoided.

Evidence shows that naloxone, an opioid antagonist that reverses life-threatening respiratory depression, is effective in preventing opioid-related overdose death at the community level through community-based distribution. Primary care clinicians should consider offering naloxone kits and associated overdose prevention education to patients at increased risk for overdose, such as those receiving daily doses of 50 morphine milligram equivalents per day or more, concurrently taking a benzodiazepine, or with a history of substance use disorder, as well as to the patient's family members or caregivers. H

For patients who previously received prescriptions for opioids in the setting of chronic pain and present to a physician for referral or as a new patient, a discussion on opioid prescribing best practices should be framed by the CDC guideline recommendations. Discussions on tapering opioid therapy, incorporating a nonopioid multimodal pain strategy as the cornerstone of pain management, and setting appropriate goals are fundamental to these prescribing relationships.

For a discussion on the treatment of opioid use disorder, see Mental and Behavioral Health.

KEY POINTS

- HVC In patients with chronic pain, determining the pain location, duration, severity, temporal nature, and responsiveness to treatment is crucial in identifying the pain generator and tailoring the diagnostic and therapeutic approaches; in most cases of chronic pain, additional testing and imaging is unlikely to produce further diagnostic yield.
- In the setting of chronic pain without a treatable underlying cause, clinicians should monitor for significant changes in pain experience, new acute pain syndromes superimposed on chronic pain, and the development of red flag symptoms.

(Continued)

KEY POINTS *(continued)*

- Physical therapy improves both pain and function in patients with debilitation due to chronic pain. HVC
- Cognitive behavioral techniques, including cognitive behavioral therapy, mindfulness practices, and biofeedback, have been associated with reduced pain and improved overall function and mood in patients with chronic pain. HVC
- For chronic musculoskeletal or inflammatory nociceptive pain, trials of acetaminophen (≤3 g/d) or NSAIDs can be considered as initial pharmacologic therapy in patients without contraindications to their use. HVC
- In chronic neuropathic pain syndromes, gabapentinoids and serotonin-norepinephrine reuptake inhibitors are first-line therapy.
- No evidence supports long-term opioid therapy in patients with chronic noncancer pain, and evidence demonstrates that long-term opioid use is associated with poorer overall functional status, worse quality of life, and worse pain. HVC
- The decision to initiate opioid therapy in patients with chronic pain should involve a robust discussion of risks and benefits, close monitoring for benefits and harms, avoidance of long-acting opioid formulations, and use of risk mitigation strategies.
- Primary care clinicians should consider offering naloxone kits and associated overdose prevention education to patients at increased risk for overdose, such as those receiving daily doses of 50 morphine milligram equivalents per day or more, concurrently taking a benzodiazepine, or with a history of substance use disorder.

Medically Unexplained Symptoms

Medically unexplained symptoms (MUS) are symptoms that cannot be attributed to a specific medical cause after a thorough medical evaluation. The prevalence of MUS is high; a recent systematic review of 32 studies involving 70,085 patients determined that the prevalence of patients with at least one unexplained symptom ranges from 40% to 49%. Patients with MUS are frequently seen in both primary and subspecialty clinics, resulting in significantly increased health care utilization. The costs associated with MUS are estimated at more than $250 billion annually. Unsurprisingly, the high prevalence, increased resource utilization and frequency of visits, ongoing inexplicable symptoms, and looming fear of a missed diagnosis all contribute to patient and clinician dissatisfaction.

Many terms have been incorrectly and interchangeably used to describe and diagnose MUS, further complicating an already challenging scenario. Patients with MUS must be distinguished from those with somatic symptom and related disorders, which are psychiatric conditions with specific diagnostic criteria (see Mental and Behavioral Health). Although

many somatic symptom and related disorders involve MUS, most patients with MUS do not meet the diagnostic criteria for these disorders.

Clinical Presentation and Evaluation

Symptoms that are common in patients with MUS include fatigue, headache, abdominal pain, musculoskeletal pain (back pain, myalgia, and arthralgia), dizziness, paresthesia, generalized weakness, transient edema, insomnia, dyspnea, chest pain, chronic facial pain, chronic pelvic pain, and chemical sensitivities. MUS appear more frequently in women, persons with lower levels of education, and those with lower socioeconomic status.

There is no formal approach to the diagnostic evaluation of MUS; however, the initial evaluation should involve a thorough history and physical examination related to each symptom. Clinicians must approach each symptom in a focused manner and diligently review any previous diagnostic evaluations. Laboratory and radiographic studies should be guided by the findings on the history and physical examination, and subspecialty referrals should be used judiciously. Given the high comorbidity of mood disturbances in patients with MUS, patients with features concerning for an underlying mood disorder should be evaluated accordingly.

If an underlying medical cause cannot be identified after an appropriately thorough evaluation, it is imperative that clinicians have an open and honest discussion of the results with the patient, being mindful to acknowledge the patient's concerns and frustrations. Frequently, patients will request, or even demand, additional testing and consultations that may not be clinically indicated. Although doing so may be challenging, clinicians should limit additional evaluations to those deemed medically necessary, as unnecessary studies provide negligible reassurance, pose iatrogenic risks, and result in additional patient anxiety.

Management

The foundation of management of patients with MUS is an open, honest, and effective therapeutic relationship. Patients should be treated respectfully and cared for in a nonjudgmental manner. It is important to not only expect but to accept the patient's feelings of frustration; acknowledging these feelings early in the patient's management course can help to build and strengthen the therapeutic alliance.

Management of MUS requires a patient-focused, holistic, and multimodal approach. The goals of management are functional restoration, decreased symptom focus, and acquisition of coping mechanisms rather than abatement of symptoms. Office visits should be scheduled at regular intervals, allowing for additional discussion, educational opportunities, and longitudinal reassessment. Frequency of appointments can gradually be decreased over time as tolerated by the patient. It should be made clear to patients that the treatment of MUS will not likely be curative and that symptoms may persist. Patients should be encouraged to develop short-term and long-term goals with the recognition that many goals will change from a physical symptom focus to a psychosocial focus. If additional symptoms arise, clinicians should respond empathically and perform an appropriately thorough investigation.

Interventions that may benefit patients with MUS include CBT, physical therapy, occupational therapy, individual or group psychotherapy, social support, biofeedback therapy, graded exercise therapy, stress management activities, and training in coping mechanisms. Patients with comorbid mood conditions should be considered for a trial of antidepressant therapy and referral to a psychiatrist or psychologist. Given the wide-ranging effects of MUS, treatment should be focused on both physical and psychosocial aspects (**Table 34**).

Knowledge of barriers to the treatment of patients with MUS can help clinicians prevent unnecessary missteps and provide ongoing value-based care. Common barriers include a poor physician-patient relationship, the heterogeneity of symptoms, varying diagnostic labels, and ongoing changes in the health care system (insurance coverage, access to care, and value-based metrics).

KEY POINTS

- In patients with medically unexplained symptoms, clinicians should limit diagnostic tests to those deemed medically necessary because unrevealing studies provide negligible reassurance, pose iatrogenic risks, and result in additional patient anxiety. HVC
- The goals of management in patients with medically unexplained symptoms are functional restoration, decreased symptom focus, and acquisition of coping mechanisms rather than abatement of symptoms. HVC

Dyspnea

H

Dyspnea is a common symptom with a diverse pathophysiologic basis and substantial variation in patient experience. The American Thoracic Society defines dyspnea as "a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity." Patients may describe this symptom as breathlessness or tightness, an inability to catch their breath, or a feeling of drowning. The prevalence of dyspnea increases with age, with more than one third of those older than 70 years reporting sensations of dyspnea in an ambulatory setting. Dyspnea affects up to half of hospitalized patients and is a common reason for patients to seek care in urgent and emergent care settings.

Dyspnea results from multiple underlying neurophysiologic mechanisms, including greater work of breathing, air hunger, and airway irritation or damage. These mechanisms may be triggered by poor functional status, organ-specific pathology, medication effects, or physiologic stimuli (including hypoxia and hypercapnia).

TABLE 34. Follow-up Management of the Patient With Medically Unexplained Symptoms

Category	Issue	How?	How Often?	Notes
Nonpharmacologic therapy	Maintaining an effective relationship with the patient	Elicit and address the patient's emotional concerns; use a negotiated rather than a prescriptive approach; tailor care to patient's personality; address your own negative reactions to the patient.	Each visit	Monitor the provider-patient relationship regularly as you would, for example, monitor blood pressure in a patient with hypertension. Ask, "So how is all this going; how are you and I working together?" Examples of indicators of an effective relationship are adherence to the treatment plan, friendliness, improved eye contact, positive statements about the provider and the treatment.
	Dissociating treatment regimen from symptoms	Schedule regular, consistent, time-contingent visits rather than ad hoc (as-needed) visits; give all medications on a scheduled rather than on an as-needed basis.	Each visit	Titrate number of scheduled visits and amount of treatment to patient's needs and progress.
Pharmacologic therapy	MUS symptoms	Consider lowest effective dose of antidepressant and nonopioid analgesics.	Each visit	Minimize or avoid use of opioids and tranquilizers.
	Comorbid depression and anxiety	Treat depression as indicated.	As needed	
Patient education	Overall management	Review patient's diary and facilitate understanding of how his or her thoughts, emotions, and behaviors are related to symptoms.	Ongoing	
	Education and treatment plan	Educate the patient so that the patient understands the plan of care and its purpose.	Each visit	
	Reinforcing patient commitment to treatment	Give appropriate praise for commitment behavior, such as completing homework; address noncommittal behavior, such as not keeping appointments or visiting an acute care facility without prior discussion.	Each visit	
	Reviewing and revising patient goals	Reinforce previous short-term goals or negotiate new ones to operationalize patient's long-term goals.	Each visit	Help patient to identify solutions to roadblocks.
	Negotiating new plans	Negotiate plans to adjust physical activity; recommend relaxation techniques; refer for physical therapy.	Each visit	Continuously encourage the patient to add new healthy behaviors and to progress in what he or she is already doing.

MUS = medically unexplained symptoms.

Adapted with permission from Dwamena FC, Fortin AH, Smith RC. Medically unexplained symptoms. In ACP Smart Medicine [online database]. Philadelphia: American College of Physicians, 2015. Accessed June 25, 2015.

Evaluation

The history and physical examination are the most important components of the evaluation of dyspnea. A crucial aspect of the history is determining whether the patient's dyspnea is new in onset or an acute-on-chronic exacerbation of a known disease. Evaluation of the patient with acute-on-chronic symptoms should include an investigation for a potentially new generator of dyspnea (such as pleural effusion in the setting of existing lung malignancy) or progression of the underlying cause.

Dyspnea has many causes (**Table 35**). A cardiac or respiratory origin is most common, although some patients will have a mixed presentation. In the absence of an obvious cause, the initial evaluation in most patients will include measurement of oxygen saturation and hemoglobin, as well as electrocardiography and chest radiography. Depending on the results of these tests, further evaluation may entail measurement of B-type natriuretic peptide, D-dimer assay, pulmonary function testing, and advanced imaging of the cardiac or pulmonary systems. Such testing, however, should be pursued only when the

TABLE 35. Common Causes of Dyspnea
Acute Dyspnea
Decreased cardiac output/function
Ischemic heart disease
Pulmonary infection
Pneumothorax
Pleural effusion
Bronchospasm
Pulmonary vascular disease (e.g., pulmonary embolism or hemorrhage)
Chronic Dyspnea
Airflow obstruction (e.g., COPD)
Restrictive lung diseases
Decreased cardiac output/function
Deconditioning

H CONT.

initial evaluation reveals a reasonable likelihood of disease; scattershot testing should be avoided. Referral to a cardiologist or pulmonologist may be appropriate when the diagnosis remains elusive or when conditions require subspecialty input.

Dyspnea should be assessed on an iterative basis during the patient's care. Many validated dyspnea scoring systems are available; however, these instruments are lengthy, take significant time to complete, and may not account for contributing factors in the patient's experience of dyspnea. Standard measurement with a numeric scale akin to a pain-rating scale is advantageous for its ease of use, but it must be paired with a functional assessment of quality of life and dyspnea-related impairment.

Management

Initial treatment strategies are aimed at treating or modifying the patient's dyspnea generator and the underlying disease state responsible for causing the symptom. In patients with chronic conditions, the first step in reducing dyspnea is to maximize standard therapies, with regular assessment of symptomatic response.

In patients with persistent debilitating symptoms despite maximal medical therapy, there are nonpharmacologic and pharmacologic strategies to reduce dyspnea severity, with varying levels of evidence to support each one. Of these therapies, pursed-lip breathing, handheld fans, and devices that enhance air flow are the least invasive and easiest to administer. Studies examining the efficacy of guided relaxation training and acupuncture/acupressure have yielded mixed results, but these therapies are safe and may be reasonable for appropriately selected patients. Pulmonary rehabilitation can provide significant benefits for patients with chronic lung diseases and has been shown to improve subjective dyspnea in patients with severe COPD.

In patients with hypoxemia and COPD, oxygen therapy offers substantial benefits in survival, quality of life, and dyspnea reduction. However, the role of supplemental oxygen in other patient groups, including those with normoxemic dyspnea, is less clear. Data from a randomized controlled trial of palliative oxygen versus medical air in normoxemic patients demonstrated no improvement in quality of life or scores of subjective dyspnea with palliative oxygen therapy, supporting the hypothesis that movement of air is more important in reducing breathlessness in these patients. In patients with refractory dyspnea despite maximal therapy, a brief trial of supplemental oxygen is reasonable.

Opioids are an effective therapy for patients with dyspnea that is refractory to nonpharmacologic therapies and maximal medical management of the underlying disease. Opioids, both endogenous and exogenous, appear to exert an antidyspneic effect through modulation of central nervous system processing of sensory inputs, similar to their modulation of pain signaling. Although opioids affect respiratory mechanics and may blunt respiratory drive, appropriately dosed opioids should not cause respiratory depression if treatment is directed by symptoms. Patient selection and subsequent opioid selection should be based on symptom burden, underlying disease, comorbid organ dysfunction, and overall risk for respiratory depression. Although systemic opioids have shown clear benefit in treating refractory dyspnea, inhaled opioids have not shown significant efficacy in several placebo-controlled trials. H

KEY POINTS

- An important aspect of the evaluation of dyspnea is determining whether the patient's dyspnea is new in onset or an acute-on-chronic exacerbation of a known disease state.
- Pursed-lip breathing, handheld fans, and devices that enhance air flow are easy, noninvasive interventions to reduce dyspnea severity. HVC
- Opioids are an effective therapy for patients with dyspnea that is refractory to nonpharmacologic therapies and maximal medical management of the underlying disease.

Cough

Cough is another common symptom, resulting in roughly 30 million physician office visits and costing billions of dollars annually in the United States. An evidence-based approach to the evaluation of cough that ensures cost-effective care is framed around the duration of cough (acute, subacute, and chronic).

Acute Cough

Acute cough (<3 weeks' duration) is most often caused by viral respiratory tract infections, including upper respiratory tract infections (URIs) and bronchitis. Other conditions that may

present with acute cough include allergic rhinosinusitis, pneumonia, medication adverse reactions, and pulmonary edema.

The initial evaluation of the patient with acute cough focuses on identifying potentially life-threatening illnesses. Concomitant fever, dyspnea, chest pain, and abnormalities on lung or cardiovascular examination suggest a serious respiratory or cardiovascular disease as the source of cough, and further evaluation should be completed as appropriate. If signs and symptoms are primarily respiratory and constitutional, a lower respiratory tract infection is most likely, and chest radiography may be warranted. Pneumonia is an unlikely cause of acute cough, and chest radiography is not indicated in the absence of abnormal vital signs (heart rate >100/min, respiration rate >24/min, temperature >38 °C [100.4 °F]) or abnormal lung examination findings, unless there are other concerning clinical features (such as altered mental status).

Acute cough without evidence of lower respiratory tract infection or cardiovascular disease is most often caused by viral rhinosinusitis or acute bronchitis. Coronaviruses and rhinoviruses are the most common causative pathogens, but influenza virus should be highly suspected in patients presenting with fever and myalgia, especially during influenza season (between autumn and early spring). Bacterial infections can also cause acute sinusitis or bronchitis, although sinus imaging is not recommended unless a complication, such as spread of infection into contiguous structures, is suspected.

Another important cause of acute cough is ACE inhibitor therapy. Up to 20% of patients taking an ACE inhibitor develop a dry cough, usually within 1 to 2 weeks of therapy initiation. Onset of cough, however, may be delayed by months in a small percentage of patients, and cough may additionally persist for weeks after discontinuation of the offending agent. All ACE inhibitors may cause this side effect. Angiotensin receptor blockers typically do not cause cough and may be substituted if ACE inhibitor therapy is not tolerated.

Treatment of acute cough is primarily symptomatic and dependent on the underlying etiology. Antibiotics are not recommended in patients with acute bronchitis or URIs without clearly established bacterial infection, although most patients with acute bacterial sinusitis will improve without antibiotics. A meta-analysis of patients with acute rhinosinusitis found that use of intranasal glucocorticoids increased the rate of symptom response compared with placebo; there was a dose response curve, with higher doses offering greater relief. Analgesics, such as NSAIDs and acetaminophen, may provide pain relief. Only limited evidence supports saline irrigation in the relief of nasal symptoms; careful attention should be paid to the use of sterile or bottled water. Instructions for nasal saline irrigation are available online (https://www.fda.gov/ForConsumers/ConsumerUpdates/ucm316375.htm). First generation antihistamines may help dry nasal secretions; however, evidence supporting their efficacy is lacking, and sedation is a common side effect. Decongestants are of possible benefit in patients with evidence of eustachian tube dysfunction but should be used with caution in elderly patients and those with cardiovascular disease, hypertension, angle-closure glaucoma, or bladder neck obstruction. Antitussive agents are generally ineffective.

Subacute and Chronic Cough

Subacute cough (3-8 weeks' duration) is most often a postinfectious cough following an acute respiratory tract infection, particularly viral or *Mycoplasma* infection. Postinfectious cough is usually caused by postnasal drip or airway hyperreactivity. If postnasal drip is the primary problem, first-generation antihistamines may be beneficial. In patients with evidence of airway hyperreactivity, such as wheezing, therapies for asthma are usually effective. Patients with postinfectious cough not caused by postnasal drip or airway hyperreactivity may benefit from inhaled ipratropium. *Bordetella pertussis* infection should be considered in patients with subacute cough characterized by paroxysms of severe coughing and posttussive emesis. If infectious causes of subacute cough are excluded, the evaluation shifts to consideration of the causes of chronic cough.

Chronic cough (>8 weeks' duration) is most often caused by upper airway cough syndrome (UACS; formerly postnasal drip syndrome), gastroesophageal reflux disease (GERD), asthma, smoking, and ACE inhibitor use. Nonasthmatic eosinophilic bronchitis is another increasingly documented cause of chronic cough. Important but less common causes include chronic bronchitis, lung neoplasm, bronchiectasis, and chronic aspiration.

Evaluation of chronic cough begins with a thorough history, physical examination, and chest radiography (**Figure 4**). ACE inhibitor therapy and tobacco use should be discontinued. If an etiology is not determined after initial evaluation, a stepwise approach is pursued, beginning with a 2-week trial of empiric treatment for UACS. Allergic rhinitis-associated UACS is optimally treated with intranasal glucocorticoids, whereas UACS resulting from nonallergic rhinitis responds best to first-generation antihistamines (chlorpheniramine, brompheniramine, diphenhydramine) and decongestants (pseudoephedrine).

Asthma should be considered in patients with symptoms that do not respond to empiric treatment for UACS. Cough-variant asthma is diagnosed if spirometry and/or bronchial hyperresponsiveness testing results are abnormal and symptoms improve with standard therapy for asthma, including inhaled glucocorticoids.

In patients with normal findings on evaluation or failed empiric treatment for UACS and asthma, the most reasonable next step is to exclude nonasthmatic eosinophilic bronchitis with sputum analysis for eosinophils or exhaled nitric oxide testing. If test results are abnormal, therapy with inhaled glucocorticoids should be initiated.

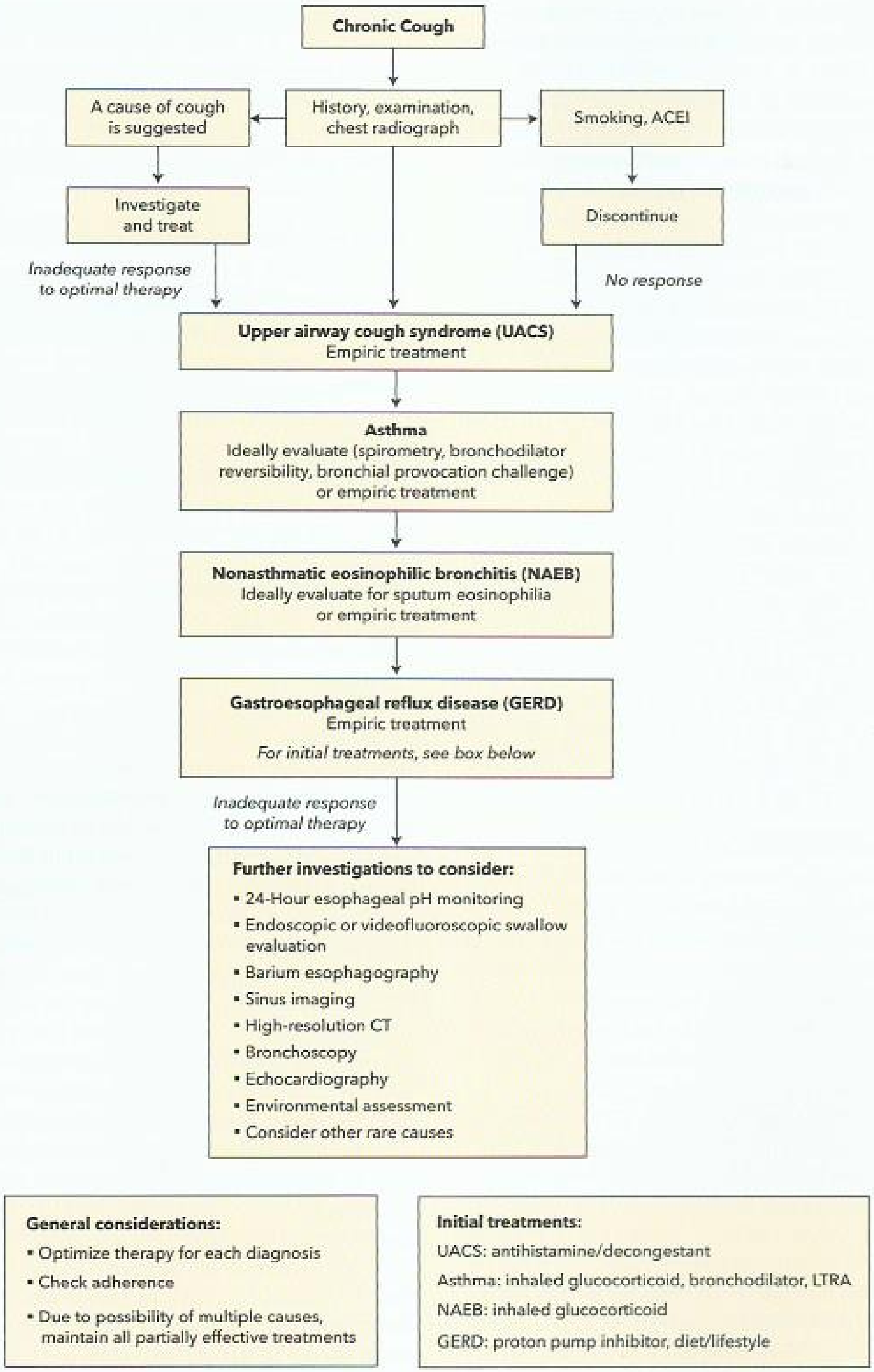

FIGURE 4. Evaluation of chronic cough. ACEI = ACE inhibitor; LTRA = leukotriene receptor antagonist.

Reproduced with permission of the American College of Chest Physicians from Irwin RS, Baumann MH, Bolser DC, et al; American College of Chest Physicians (ACCP). Diagnosis and management of cough executive summary ACCP evidence-based clinical practice guidelines. Chest. 2006;129(1 suppl):4S. [PMID: 16428686] Copyright 2006, American College of Chest Physicians.

Cough without a clear etiology that does not respond to the aforementioned empiric therapies should be treated with empiric proton pump inhibitor therapy and antireflux lifestyle changes to address possible GERD. Failure of empiric GERD treatment of 8 weeks' duration should prompt an advanced investigation (see Figure 4).

Persistent cough without an identifiable cause despite comprehensive evaluation is termed unexplained chronic cough.

Patients with unexplained chronic cough may benefit from other therapies for symptomatic relief. Antitussives, including dextromethorphan and topical anesthetics (benzonatate), have been shown to reduce cough and improve quality of life. Opioids, such as codeine, may have a similar effect but should be used with caution and only if other measures fail. Gabapentin can also be effective at controlling unexplained chronic cough and should be considered if the risk for adverse effects is acceptable. Protussives, such as guaifenesin, can improve mucus clearance and cough intensity in selected patients with excessive sputum production. Finally, multimodality speech pathology therapy may provide benefit and should be offered to all patients with chronic cough of undetermined cause.

Cough in the Immunocompromised Patient

Immunocompromised patients with cough require heightened suspicion for infections, particularly if immunosuppression is severe. In addition to common pathogens, other causes to consider include fungi, cytomegalovirus, varicella, herpesvirus, and *Pneumocystis jirovecii*. Clinicians should have a low threshold for initiating empiric antibiotic therapy while diagnostic testing is pursued.

Hemoptysis

Hemoptysis is expectoration of blood from the lower respiratory tract with coughing. Causes include bronchitis, bronchiectasis, malignancy, tuberculosis, pulmonary embolism, and left ventricular failure. Rare causes include anti–glomerular basement membrane antibody disease (Goodpasture syndrome) and granulomatosis with polyangiitis. Hemoptysis requires urgent evaluation, which begins with assessment to confirm the lower respiratory tract as the source of bleeding and exclude bleeding from the nasopharynx (nosebleed) or the gastrointestinal tract (hematemesis). Chest radiography should be performed, but most patients additionally require chest CT and/or bronchoscopy to accurately determine the cause.

KEY POINTS

HVC
- In patients with acute cough, chest radiography is not indicated in the absence of abnormal vital signs or abnormal lung examination findings, unless there are other concerning clinical features (such as altered mental status).

HVC
- Treatment of acute cough is primarily symptomatic; antibiotics are not recommended in patients with acute bronchitis or upper respiratory tract infection without a clear bacterial cause.
- Common causes of chronic cough include smoking, ACE inhibitor use, upper airway cough syndrome, gastroesophageal reflux disease, asthma, and nonasthmatic eosinophilic bronchitis.
- Patients with unexplained chronic cough may benefit from antitussives, gabapentin, and multimodality speech pathology therapy.

Fatigue and Systemic Exertion Intolerance Disease

Fatigue is generally defined as tiredness, exhaustion, or lack of energy precipitated by exertion or stress. It is a common symptom, occurring in one quarter to one third of patients in the primary care setting. Despite its high prevalence, the cause of fatigue is often elusive, leading to prolonged delays in diagnosis, substantial functional decline, and high direct and indirect societal costs. Chronic fatigue is defined as fatigue lasting longer than 6 months.

Fatigue is a truly subjective symptom with little to no corroborating objective measures. It can be classified as fatigue secondary to another cause (**Table 36**), secondary to multiple factors (termed chronic multifactorial fatigue [CMF]), or as a primary condition. In the past, the latter condition was termed chronic fatigue syndrome (CFS), myalgic encephalitis (ME), or neurasthenia. Each of these diagnoses had specific diagnostic criteria.

TABLE 36. Common Causes of Fatigue
Lifestyle
Alcohol
Drug dependency (overuse and withdrawal)
Extremes of activity
Night shift work
Sleep deprivation, poor sleep habits
Work/life imbalance
Medical
Anemia
Cancer
Chronic liver and kidney disease
Chronic lung disease, hypoxemia
Heart failure
HIV/AIDS
Hyperglycemia, uncontrolled diabetes mellitus
Medication side effects
Antidepressants
Antihistamines
Antipsychotics
β-Blockers
Benzodiazepines
Opioids
Obesity
Thyroid disorder (hyper- and hypothyroidism)
Psychological
Anxiety
Depression
Stress

creating inconsistencies in diagnosis and wide variability in treatment across providers and institutions. In 2015, the Institute of Medicine (IOM), now called the National Academy of Medicine, issued an extensive guideline aimed at developing validated, evidence-based clinical diagnostic criteria for this condition and using consensus building methods. The IOM recommended using the term systemic exertion intolerance disease (SEID) rather than CFS, ME, or other similar terms. Diagnosis of SEID requires the presence of all of the following three symptoms:

- A substantial reduction or impairment in the ability to engage in preillness levels of occupational, educational, social, or personal activities that persists for more than 6 months and is accompanied by fatigue, which is often profound, is of new or definite onset (not lifelong), is not the result of ongoing excessive exertion, and is not substantially alleviated by rest
- Postexertional malaise
- Unrefreshing sleep

In addition, the patient must have at least one of the following two manifestations:

- Cognitive impairment
- Orthostatic intolerance (symptoms such as lightheadedness, dizziness, and headache that worsen with upright posture and improve with recumbency)

An estimated 836,000 to 2.5 million U.S. adults have SEID; however, 84% to 91% of affected individuals are not yet diagnosed. In 2015, the economic cost associated with SEID was estimated to be between $17 billion and $24 billion annually.

Although the pathophysiology of SEID remains unclear, the phenomenon of central sensitization (the pathophysiologic dysregulation of the thalamus, hypothalamus, and amygdala) is gaining acceptance as a potential cause of SEID as well as of other highly prevalent comorbid conditions, including fibromyalgia, mood disturbances, irritable bowel syndrome, and interstitial cystitis. Central sensitization is often triggered by a prodromal event, such as infection, physical or emotional trauma, a motor vehicle accident, surgery, medical illness, or prolonged stress. Studies on central sensitization and its relationship to SEID and associated comorbid conditions are ongoing.

Evaluation

The diagnostic evaluation of acute or chronic fatigue begins with a careful history and physical examination. Clinicians should note the duration of fatigue, preceding factors, concomitant symptoms, prolonged deleterious lifestyle factors, medication use, and the presence of "red flag" signs or symptoms (fever, involuntary weight loss, persistent lymphadenopathy, muscle atrophy, and synovitis). Patients should also be assessed for an underlying sleep disturbance. Mood disorders are often comorbid in patients with SEID (approximately 70% of patients), and all patients with SEID should be screened for depression and anxiety. Clinicians should additionally ensure that all age-appropriate screenings have been performed.

The history and physical examination should guide the choice of diagnostic tests. In patients with fatigue without a clear cause, it is reasonable to obtain a complete blood count, electrolyte panel, thyroid-stimulating hormone level, fasting glucose level, and kidney and liver chemistry tests. Unnecessary laboratory, imaging, and invasive studies should be avoided because most patients will have unrevealing findings, which usually provide little reassurance.

Management

Treatment of fatigue should focus on correcting any underlying causes. In patients with SEID, the goals of treatment shift to functional rehabilitation and restoration. Patients benefit most from a structured, well-defined, multimodal approach that includes regularly scheduled office visits, which allow for discussion, educational opportunities, and longitudinal reassessment. There is evidence that CBT and graded exercise therapy may decrease fatigue and improve function, and these therapies should be offered to patients. Additionally, all patients should receive instruction on effective sleep hygiene. Other modalities that may be of benefit include physical therapy, occupational therapy, biofeedback therapy, massage therapy, acupuncture, yoga, tai chi, and stress management activities. In patients with comorbid mood conditions, treatment or referral to a psychiatrist or psychologist is reasonable.

There are no FDA-approved medications for the treatment of SEID. Medications play a very limited role in management, except in the treatment of comorbid conditions (such as depression). One small study found that methylphenidate increased concentration and decreased fatigue in 20% of patients, but its use is tempered by its addictive potential and adverse effects. There is no consistent evidence that opioids, glucocorticoids, pharmacologic sleep aids, prolonged antibiotics or antiviral agents, or immunotherapies improve symptoms or prognosis.

The prognosis for chronic fatigue varies and is often a source of frustration for patients and providers. The prognosis depends on many factors, including patient age, formal education level, severity of symptoms, duration of symptoms, decline in functional status relative to premorbid level of function, presence of other somatic (or medically unexplained) symptoms, comorbid mood disorders, availability of resources, and adherence to the treatment recommendations.

KEY POINTS

- In patients with fatigue without a clear cause, it is reasonable to obtain a complete blood count, electrolyte panel, thyroid-stimulating hormone level, fasting glucose level, and kidney and liver chemistry tests. HVC
- Patients with systemic exertion intolerance disease benefit most from a structured, well-defined, multimodal approach that includes regularly scheduled office visits; cognitive behavioral therapy and graded exercise therapy may decrease fatigue and improve function and should be offered. HVC

(Continued)

KEY POINTS *(continued)*

HVC
- There are no FDA-approved medications for the treatment of systemic exertion intolerance disease, and medications play a very limited role in management, except in the treatment of comorbid conditions.

Dizziness

Approach to the Patient with Dizziness

Dizziness is a common nonspecific symptom seen in inpatient and outpatient settings. Patients often interchangeably use the terms dizzy, lightheaded, woozy, cloudy, faint, or off-balance to describe the perception of dizziness. Owing to its subjective nature, the variability in symptom description, and broad differential diagnosis (which includes stroke and other life-threatening disorders), dizziness is a challenging symptom to assess and treat.

In patients with dizziness, a relevant history and physical examination should be performed to classify the symptom into one of four focused groupings: vertigo, presyncope, disequilibrium, and nonspecific dizziness. This classification facilitates establishing a formal diagnosis and treatment strategy.

Vertigo

Vertigo is the false perception of personal or environmental movement. Patients describe a spinning or whirling sensation, which is often associated with concomitant nausea, vomiting, and sudden-onset fatigue. Symptoms are typically episodic and brief and are usually triggered by positional changes of the head. Vertigo is classified as peripheral or central, depending on the specific etiology.

A thorough history and examination are crucial for differentiating between central and peripheral causes of vertigo, especially in patients with acute vertigo concerning for vertebrobasilar ischemia and other central causes. Examination should include an in-depth neurologic assessment as well as the HINTS (Head Impulse, Nystagmus, and Test of Skew) oculomotor assessment (**Table 37**). An abnormal result on any one of the three HINTS components suggests a central rather than peripheral cause of acute vertigo. Major causes of acute vertigo are presented in **Table 38**.

TABLE 37. HINTS (Head Impulse, Nystagmus, and Test of Skew) Examination

Maneuver	Method	Results
Head impulse test	With the patient focusing on the examiner, the examiner slowly moves the patient's head in either direction about 20 degrees and then rapidly rotates back to midline, while assessing for catch-up saccades	Reassuring: presence of catch-up saccades (consistent with peripheral cause of vertigo) Concerning: absence of catch-up saccades (consistent with central cause of vertigo)
Nystagmus assessment	Examiner observes for the presence and directionality of nystagmus on lateral gaze	Reassuring: unidirectional nystagmus Concerning: bidirectional nystagmus
Test of skew deviation	Examiner alternates covering and uncovering each eye and assesses for vertical adjustment or refixation	Reassuring: absence of vertical skew Concerning: presence of vertical skew

Peripheral Vertigo

Benign paroxysmal positional vertigo (BPPV) is the most common form of vertigo, with a lifetime prevalence of 2.4%. It is more common in women (female-to-male ratio of 2:1 to 3:1). BPPV is characterized by sudden-onset, recurrent, and brief (usually <1 minute) vertiginous symptoms, which are provoked and worsened with positional changes of the head. Patients report dizziness, imbalance, nausea, and vomiting that occur with positional changes; however, no focal neurologic findings are present. Symptoms lead to increased risk for falls and a decline in functional status. BPPV is caused by displacement and migration of otoconia (calcium carbonate crystals) within the semicircular canals. Up to 90% of all cases of BPPV involve the posterior semicircular canal because it is the most gravity-dependent semicircular canal.

The diagnostic test of choice for BPPV is the Dix-Hallpike maneuver (**Figure 5**), which can help differentiate between peripheral and central causes of vertigo (**Table 39**). In the setting of BPPV, a positive finding includes the presence of a mixed upbeat-torsional nystagmus toward the affected side. Brain imaging is not necessary for diagnosis. First-line therapy for BPPV is canalith repositioning with the Epley maneuver, which is effective in up to 85% of patients (**Figure 6** on p. 58).

Other common causes of peripheral vertigo include vestibular neuronitis, labyrinthitis, Meniere disease, medication effects (toxicity from aminoglycoside or diuretic use), Ramsay Hunt syndrome (herpes zoster involving cranial nerve VII), and vestibular schwannoma (acoustic neuroma). Vestibular neuronitis is most often preceded by a viral infection affecting the vestibular portion of cranial nerve VIII. Symptoms are generally more severe and of longer duration than in BPPV and may take longer to resolve. Labyrinthitis has a presentation similar to that of vestibular neuronitis, with the additional symptom of hearing loss. Meniere disease classically presents with the triad of vertigo, tinnitus, and hearing loss; symptoms are episodic and recurrent and may be severe.

Evidence supports the utility of diuretics in the treatment of Meniere disease, but pharmacologic therapy has not otherwise been shown to be significantly effective for peripheral vertigo. Rather, vestibular suppressants (antihistamines, benzodiazepines, and antiemetics) can be used in conjunction with other forms of therapy for temporary symptomatic relief.

TABLE 38. Differential Diagnosis of Acute Vertigo

Cause	Onset and Course	Nystagmus	Auditory Symptoms	Other Features
BPPV	Recurrent, transient, positional; usually provoked by turning over or getting in and out of bed	Positional, with mixed vertical torsional nystagmus in BPPV involving posterior canal and horizontal nystagmus in BPPV involving horizontal canal	None	Recent inciting event possible (e.g., recumbent position at dentist's office or hair salon, prolonged bed rest, head trauma); history of similar episodes
Stroke	Spontaneous, usually sustained; may be worsened by positional change	Spontaneous, with beating in various or changing directions	Occasional	Neurologic symptoms or signs often occur, but stroke may present as isolated vertigo; results of head impulse test are typically normal[a]
Vestibular neuronitis	Spontaneous, sustained; may be worsened by positional change	Spontaneous, predominantly horizontal	None	May be preceded by viral illness; results of head impulse test are abnormal[a]
Vestibular migraine	Recurrent, spontaneous; duration for minutes to hours; may be positional	Rare, but when present usually positional	Occasional	Migrainous headaches, motion sickness, family history
Meniere disease	Recurrent, spontaneous; typical duration for hours	Spontaneous, horizontal	Fluctuating hearing loss, tinnitus	Ear pain, sensation of fullness in ear

BPPV = benign paroxysmal positional vertigo.

[a]In the head impulse test, the result is considered abnormal when a corrective movement (saccade) is required to maintain straight-ahead fixation after the head has been rotated to the side.

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If vestibular suppressants are selected, it is imperative to limit the treatment duration because these agents can impede vestibular functioning, vestibular recovery, and centralized compensatory mechanism. Vestibular and balance rehabilitation therapy (VBRT) is also effective in the treatment of various forms of dizziness (vertigo, disequilibrium, and nonspecific dizziness). VBRT focuses on balance training, core stabilization, and desensitization exercises. It is often performed by physical and occupational therapists.

Central Vertigo

Central vertigo is a frequently missed and potentially life-threatening diagnosis. It may be caused by vertebrobasilar stroke (posterior circulation ischemic or hemorrhagic events), migraine, central nervous system infection, trauma (concussion, traumatic brain injury), demyelinating disease (multiple sclerosis), and chronic alcoholism.

Patients with central vertigo secondary to vertebrobasilar stroke frequently display concomitant neurologic findings in addition to vertigo, such as nystagmus, dysphagia, dysarthria, diplopia, ataxia, postural instability, hemiparesis, and mental status changes. A normal result on a head impulse test, direction changing nystagmus, or skew deviation in the HINTS assessment additionally suggest a central cause of vertigo. Roughly 20% of patients with vertebrobasilar stroke present with isolated vertigo, and studies have shown that up to one third of cases of vertebrobasilar stroke that manifest as isolated vertigo are misclassified as peripheral vertigo. Risk factors for posterior circulation stroke include advanced age, atrial fibrillation, diabetes, peripheral vascular disease, hypertension, and hyperlipidemia. To a lesser extent, neurologic findings may also be present in patients with other central processes, but they are not present in peripherally mediated forms of vertigo.

Advanced imaging should be performed in patients with central vertigo. MRI is more sensitive than CT in detecting ischemic stroke and can detect infarction in the posterior fossa on the first day. CT can provide an effective and expedited evaluation of hemorrhagic stroke, although hemorrhagic vertebrobasilar stroke accounts for a very small minority of cases of centrally mediated vertigo.

Presyncope

Presyncope is a temporary reduction in global cerebral perfusion, leading to symptoms of lightheadedness, dizziness, visual changes (tunnel vision), auditory changes, a sense of impending doom, warmth, nausea, and near loss of consciousness. Patients often report the sensation of "almost blacking out." Postural tone is retained. In contrast, syncope is transient reduction in global cerebral perfusion, leading to a true loss of consciousness and loss of postural tone. Notably, patients with presyncope do not have vertiginous symptoms. The differential diagnosis for presyncope is similar to that of syncope (see Syncope).

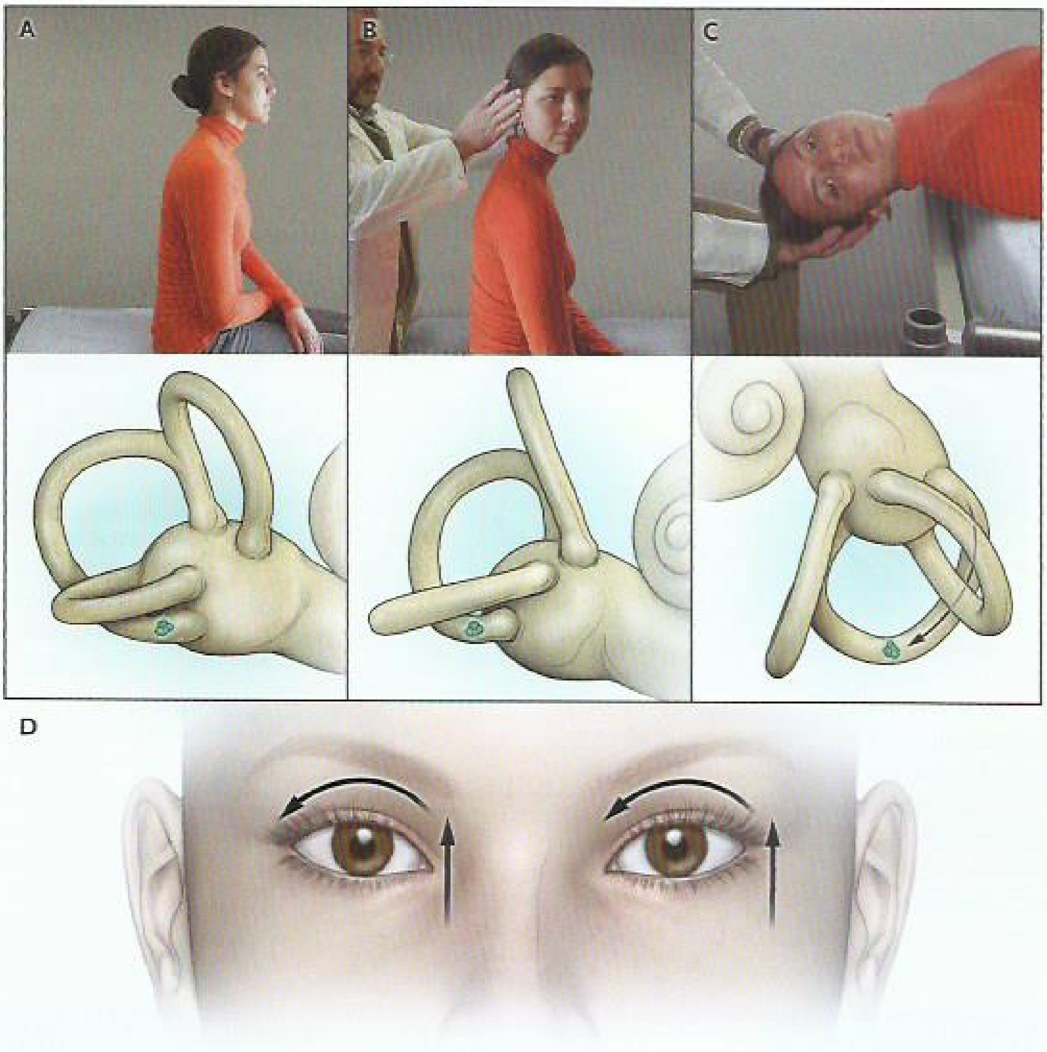

FIGURE 5. Use of the Dix-Hallpike maneuver to induce nystagmus in benign paroxysmal positional vertigo involving the right posterior semicircular canal. With the patient sitting upright (*A*), the head is turned 45 degrees to the patient's right (*B*). The patient is then moved from the sitting position to the supine position with the head hanging below the top end of the examination table at an angle of 20 degrees (*C*). The resulting nystagmus would be upbeat and torsional, with the top poles of the eyes beating toward the lower (right) ear (*D*).

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TABLE 39. Interpretation of the Dix-Hallpike Maneuver

Findings	Peripheral Disease	Central Disease
Latency of nystagmus[a]	Delayed	No delay
Duration of nystagmus	<1 min	>1 min
Fatigability of nystagmus[b]	Fatigable	Not fatigable
Direction of nystagmus	Unidirectional or mixed upbeat-torsional	Variable (vertical or horizontal)
Severity of symptoms	More severe	Less severe

[a]Time to onset of nystagmus after positioning the patient.

[b]Decrease in the intensity and duration of nystagmus with repeated maneuvers.

Disequilibrium

Disequilibrium refers to a sensation of imbalance or unsteadiness that is primarily experienced during positional changes, standing, or walking and is relieved with sitting or lying down. Disequilibrium predominantly affects older adults, and its prevalence increases with age. Falls are four times more likely in patients with disequilibrium and are, in turn, associated with significant morbidity, functional decline, and fear of future falls.

The etiology of disequilibrium is thought to be multifactorial, involving visual and auditory impairment; muscle weakness or atrophy; physical deconditioning; pain; and impairment in proprioception, balance, and gait. Brain imaging (MRI) studies of patients with disequilibrium have shown significantly more subcortical white matter lesions and frontal

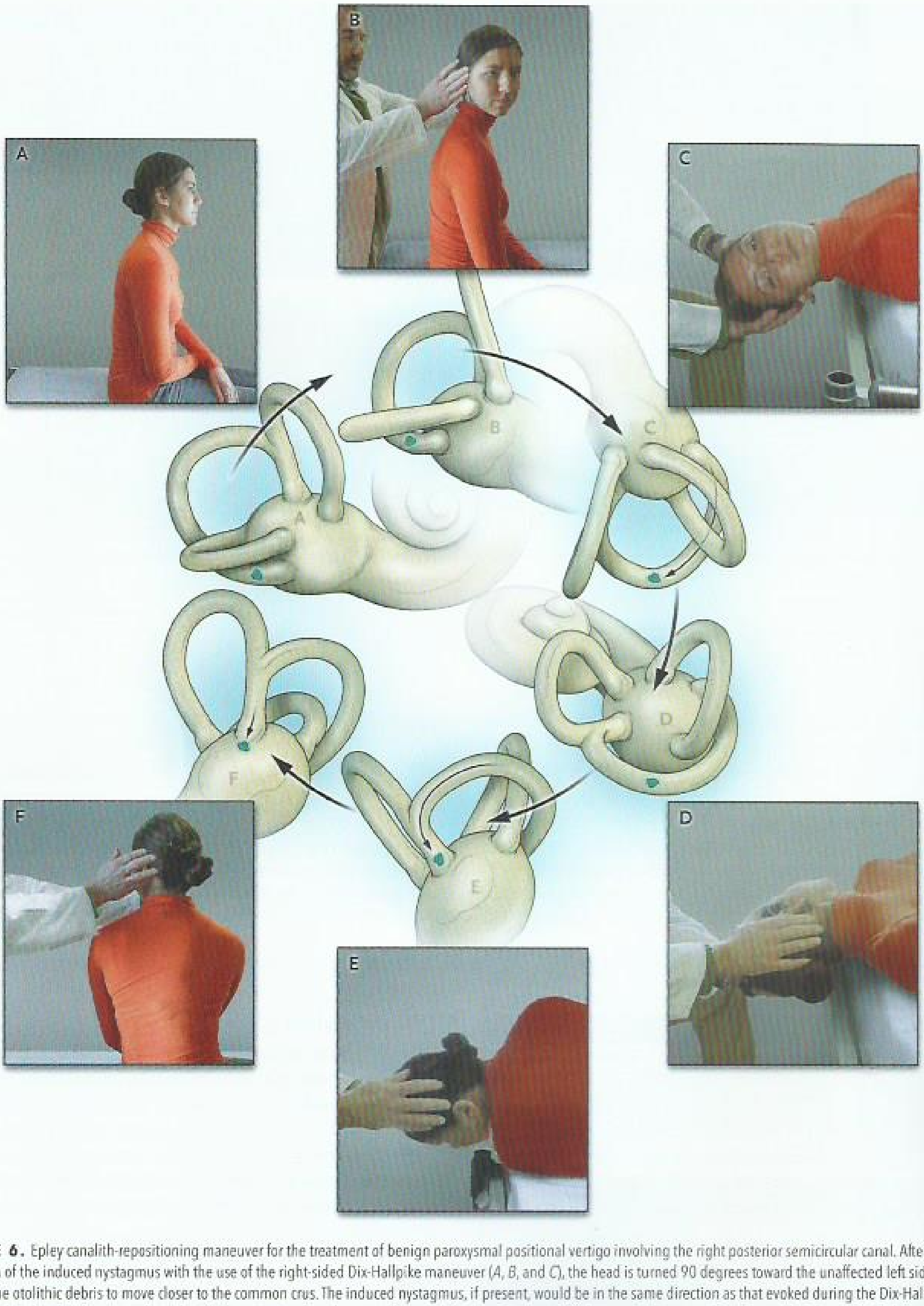

FIGURE 6. Epley canalith-repositioning maneuver for the treatment of benign paroxysmal positional vertigo involving the right posterior semicircular canal. After resolution of the induced nystagmus with the use of the right-sided Dix-Hallpike maneuver (*A*, *B*, and *C*), the head is turned 90 degrees toward the unaffected left side (*D*), causing the otolithic debris to move closer to the common crus. The induced nystagmus, if present, would be in the same direction as that evoked during the Dix-Hallpike maneuver. The head is then turned another 90 degrees, to a face-down position, and the trunk is turned 90 degrees in the same direction, so that the patient is lying on the unaffected side (*E*); the otolithic debris migrates in the same direction. The patient is then moved to the sitting position (*F*), and the otolithic debris falls into the vestibule through the common crus. Each position should be maintained until the induced nystagmus and vertigo resolve but always for a minimum of 30 seconds.

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atrophy than in patients without disequilibrium, although the significance of these findings is unclear.

Given the multifactorial nature of disequilibrium, treatment should be multifaceted. Treatment options include visual and auditory corrective measures (such as eye glasses and hearing aids), medication review (assessment of side effect profiles), mobility aids, physical therapy (balance and gait training), weight-bearing and resistive exercises, and fall prevention counseling.

Persistent Postural-Perceptual Dizziness

Dizziness that remains nonspecific despite a thorough history, examination, and evaluation is referred to as persistent postural-perceptual dizziness (PPPD, formerly chronic subjective dizziness). PPPD is described as persistent, nonvertiginous dizziness or imbalance that worsens with personal motion, upright positioning, and movement of objects in the surrounding environment. Symptoms must be present on most days for at least 3 months. It is most often preceded by another vestibular process (BPPV, vestibular neuronitis, vestibular migraine, or stroke), trauma (concussion or traumatic brain injury), infection, or certain psychiatric conditions (anxiety, panic disorder, or major depression). Approximately 75% of patients with PPPD have concomitant anxiety or depressive symptoms.

Treatment options for PPPD include pharmacologic therapies, such as selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors, and ongoing VBRT.

KEY POINTS

HVC • The diagnostic test of choice for benign paroxysmal positional vertigo is the Dix-Hallpike maneuver, which can help differentiate between peripheral and central causes of vertigo; routine imaging is not recommended.

HVC • First-line therapy for benign paroxysmal positional vertigo is canalith repositioning with the Epley maneuver; vestibular and balance rehabilitation therapy is also effective.

- Patients with central vertigo may display focal neurologic findings; however, approximately 20% of patients with vertebrobasilar stroke present with isolated vertigo.
- In acute vertigo, the examination should include an in-depth neurologic assessment as well as the HINTS (Head Impulse, Nystagmus, and Test of Skew) oculomotor assessment.

HVC • In patients with central vertigo, MRI is more sensitive than CT in detecting ischemic stroke, whereas CT provides an expedited, cost-effective assessment for hemorrhagic stroke.

- Treatment options for disequilibrium include visual and auditory corrective measures, medication review, mobility aids, physical therapy, weight-bearing and resistive exercises, and fall prevention counseling.

Syncope

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Syncope is complete and transient loss of consciousness and postural tone due to global cerebral hypoperfusion resulting from a decrease in cardiac output or systemic vascular resistance. The onset of syncope is sudden and abrupt, and recovery is rapid, with a complete return to the baseline level of functioning. Syncope is a very common medical condition, with a reported cumulative incidence of 3% to 6% over a 10-year period. Approximately 40% of adults have experienced a syncopal event, and 80% of these patients had a first episode before age 30 years. Although the Framingham Heart Study found that 44% of patients who experienced a syncopal event did not seek medical care, a recent 2014 financial analysis showed that the diagnostic and therapeutic costs associated with syncope exceed $4.1 billion annually in the United States.

Classification

Syncope can be classified according to the specific etiology of the event as neurally mediated (reflex), cardiovascular, orthostatic, neurologic, psychogenic, or idiopathic. These etiologies can be further subdivided according to the specific pathophysiologic mechanism. Approximately 40% of syncopal events are unexplained (idiopathic). Historical characteristics that are associated with increased probability of cardiac and noncardiac causes are detailed in **Table 40.**

Neurally mediated syncope, or reflex syncope, is the most common form of syncope and is seen primarily in younger adults. The underlying syncopal mechanism, termed the neurocardiogenic or vasodepressor reflex, is a response of vasodilation, bradycardia, and systemic hypotension, which leads to transient hypoperfusion of the brain. Neurally mediated syncope includes vasovagal syncope, which may be provoked by noxious stimuli, fear, stress, or heat overexposure; situational syncope, which is triggered by cough, micturition, defecation, or deglutition; and carotid sinus hypersensitivity, which is sometimes experienced during head rotation, shaving, or use of a tight-fitting neck collar. Prodromal symptoms, including nausea and diaphoresis, are classically present before the syncopal event, and fatigue and generalized weakness are typically present afterward.

Cardiovascular syncope is the second most common form of syncope and is associated with increased morbidity, mortality (including sudden death), and direct traumatic injury. Cardiovascular syncopal events often occur suddenly and usually without a significant prodrome, although chest pain and palpitations may be present. Causes of cardiovascular syncope include cardiac arrhythmia; coronary artery disease; and structural and obstructive disease, including aortic and pulmonary valve stenosis, obstructive hypertrophic cardiomyopathy, aortic dissection, and cardiac tamponade. Pulmonary embolism is increasingly appreciated as a cause of syncope, with a prevalence as high as 17% in some studies.

Orthostatic syncope is the third most common form of syncope and predominantly affects older adults. It classically

TABLE 40. Historical Characteristics Associated With Increased Probability of Cardiac and Noncardiac Causes of Syncope

More Often Associated With Cardiac Causes of Syncope
Older age (>60 y)
Male sex
Presence of known ischemic heart disease, structural heart disease, previous arrhythmias, or reduced ventricular function
Brief prodrome, such as palpitations, or sudden loss of consciousness without prodrome
Syncope during exertion
Syncope in the supine position
Low number of syncope episodes (one or two)
Abnormal cardiac examination
Family history of inheritable conditions or premature sudden cardiac death (<50 y of age)
Presence of known congenital heart disease
More Often Associated With Noncardiac Causes of Syncope
Younger age
No known cardiac disease
Syncope only in the standing position
Positional change from supine or sitting to standing
Presence of prodrome: nausea, vomiting, feeling of warmth
Presence of specific triggers: dehydration, pain, distressful stimulus, medical environment
Situational triggers: cough, laugh, micturition, defecation, deglutition
Frequent recurrence and prolonged history of syncope with similar characteristics

Reproduced with permission from Shen WK, Sheldon RS, Benditt DG, Cohen MI, Forman DE, Goldberger ZD, et al. 2017 ACC/AHA/HRS guideline for the evaluation and management of patients with syncope: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. Circulation. 2017;136:e32. [PMID: 28280232] doi:10.1161/CIR.0000000000000498. Copyright 2017, American Heart Association, Inc.

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occurs after changes in position and is typically associated with prodromal symptoms, such as lightheadedness. Orthostatic syncope is most commonly caused by hypovolemia, medications, and alcohol intoxication. Less commonly, primary autonomic failure (Parkinson disease, multiple system atrophy, multiple sclerosis) or secondary autonomic failure (diabetes, amyloidosis, connective tissue disease, spinal cord injury) can lead to neurogenic orthostatic syncope.

Neurologic conditions are a rare cause of syncope. Cerebrovascular events (transient ischemic attack, ischemic or hemorrhagic stroke), seizures, and direct head trauma may lead to transient loss of consciousness but should be distinguished from true syncope. Cerebrovascular events that lead to true syncope primarily involve the posterior (vertebrobasilar) circulation and usually present with concomitant symptoms of dizziness, vertigo, gait changes, and focal neurologic findings. Anterior circulation involvement rarely leads to syncope. Seizures can be confused with syncope, and bystander information can help distinguish between these two events. A prospective study demonstrated that the features most suggestive of a seizure in patients with loss of consciousness were witnessed abnormal posturing, involuntary head turning, and tongue laceration. Auras, incontinence, and prolonged postepisode confusion also favor a seizure.

Psychogenic syncope, which has also been referred to as pseudosyncope, generally occurs in younger patients with underlying anxiety, panic disorder, or depression.

Evaluation

The American Heart Association (AHA), American College of Cardiology (ACC), and Heart Rhythm Society (HRS) jointly conclude that the history and physical examination are the most important diagnostic tools in determining the underlying cause of a syncopal event. The history should focus on eliciting prodromal or postepisode symptoms, comorbid medical or psychiatric conditions, the psychosocial context of the event, and bystander information. A thorough review of the patient's prescription and over-the-counter medications should also be completed.

The physical examination should include an in-depth cardiovascular evaluation, including orthostatic (postural) blood pressure measurements, as well as a basic neurologic examination to evaluate for focal defects. Carotid hypersensitivity can be assessed in individuals older than 40 years with syncope of unknown cause with the use of carotid sinus massage; however, this technique is contraindicated in patients with known carotid disease or recent transient ischemic attack/stroke within the past 3 months.

The AHA/ACC/HRS syncope guideline recommends that electrocardiography be performed in all patients with syncope to identify an underlying arrhythmia, myocardial ischemia, or QT prolongation. Generally, additional studies have a low diagnostic yield; however, when there is a moderate to high pretest probability of a specific condition, these studies can help to identify or confirm a diagnosis (**Figure 7**). Echocardiography is indicated to detect suspected valvular heart disease, hypertrophic cardiomyopathy, and reduced left ventricular function. An exercise stress test is most likely to be helpful in patients with exercise-related syncope. Electrocardiographic monitoring (with an ambulatory monitor, event monitor, or implantable loop recorder) should be considered in selected patients with a probable arrhythmic cause; the choice of test is based on the frequency and nature of the syncopal event (see MKSAP 18 Cardiovascular Medicine). Targeted laboratory studies are guided by findings in the history and physical examination. Tilt-table testing is most commonly useful in patients suspected of having recurrent vasovagal syncope or when the initial evaluation of delayed orthostatic hypotension is not diagnostic. Cardiac imaging with CT or MRI is most useful when structural or infiltrative heart disease is suspected but initial diagnostic tests are inconclusive. CT angiography is

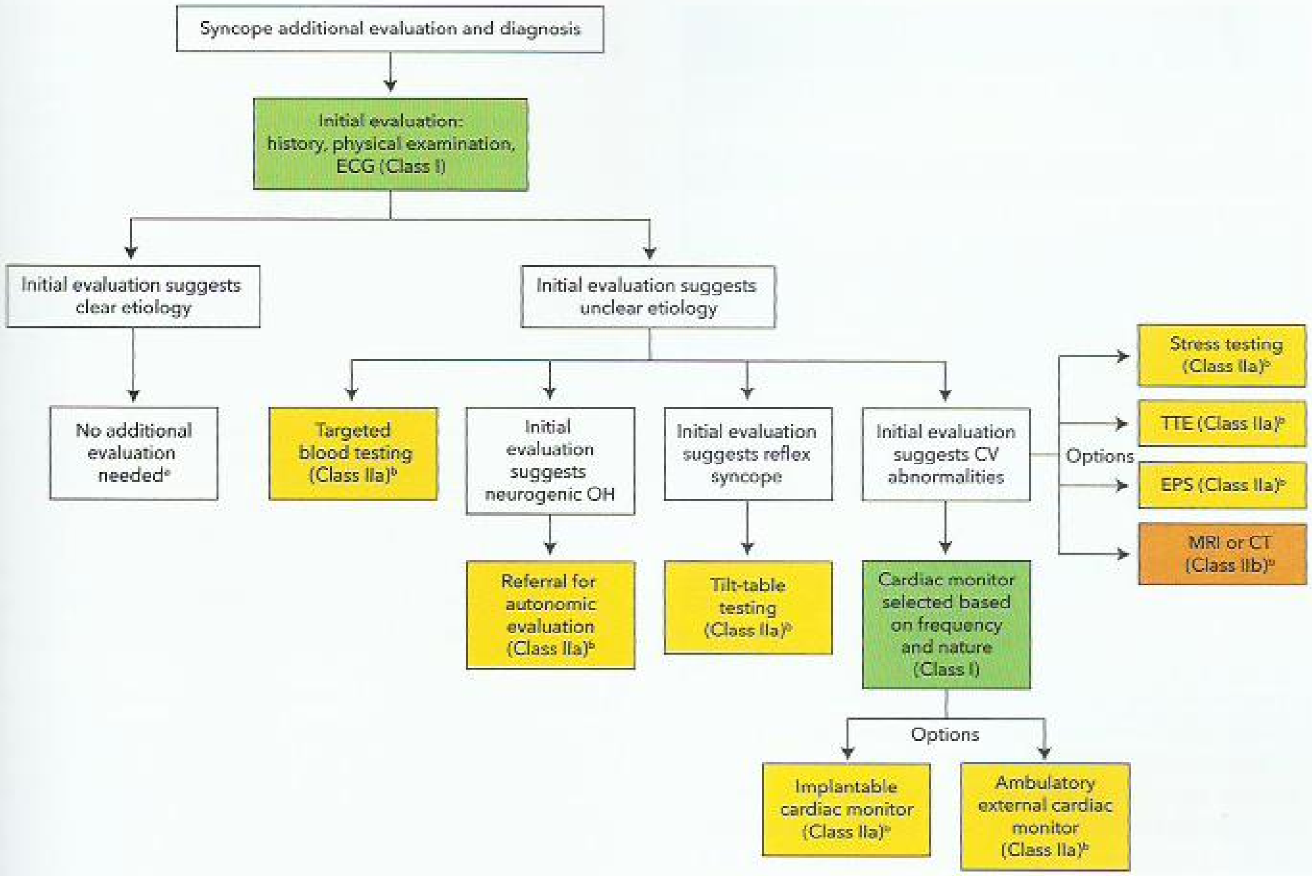

FIGURE 7. Additional evaluation and diagnosis of syncope. Colors correspond to class (strength) of recommendation, with green corresponding to a class I (strong) recommendation, yellow corresponding to a class IIa (moderate) recommendation, and orange corresponding to a class IIb (weak) recommendation. CV = cardiovascular; ECG = electrocardiography; EPS = electrophysiology study; OH = orthostatic hypotension; TTE = transthoracic echocardiography.

[a]Applies to patients after a normal initial evaluation without significant injury or cardiovascular morbidities; patients should be followed up by a primary care physician as needed.

[b]In selected patients.

Reproduced with permission from Shen WK, Sheldon RS, Benditt DG, Cohen MI, Forman DE, Goldberger ZD, et al. 2017 ACC/AHA/HRS guideline for the evaluation and management of patients with syncope: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. Circulation. 2017;136:e25-e59. [PMID: 28280232] doi:10.1161/CIR.0000000000000498. Copyright 2017, American Heart Association, Inc.

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indicated for patients with a high pretest probability of pulmonary embolism. Electrophysiology studies are reserved for patients suspected of having an arrhythmic cause of syncope, and electroencephalography should be based on the specific clinical scenario. The American College of Physicians (ACP) recommends against routinely obtaining brain imaging (CT or MRI) in cases of syncope that do not involve objective focal neurologic findings. Carotid duplex ultrasonography plays no role in the evaluation of a patient with syncope.

Risk Stratification and Decision for Hospital Admission

The AHA/ACC/HRS syncope guideline recommends evaluation to determine the cause of syncope and assessment of the patient's short- and long-term morbidity and mortality risk. Short-term adverse events and deaths are mainly determined by the underlying cause and the effectiveness of the treatment. Risk scores have been developed to assist in risk stratification and to guide patient disposition; however, they generally do not outperform unstructured clinical judgment. The presence of high-risk clinical characteristics should prompt consideration of hospitalization (**Table 41**). Patients with likely reflex-mediated syncope who do not have serious underlying medical conditions can usually be managed in the outpatient setting.

Management

The management of syncope depends on the underlying cause. In cases of neurally mediated syncope, clinicians should provide reassurance and counsel patients to avoid provoking measures. Physical counterpressure techniques, such as leg crossing, squatting, or handgrip maneuvers, can be beneficial in patients with neurally mediated syncope and a prolonged prodrome. The management of cardiovascular syncope should target the specific underlying cause. Orthostatic syncope may be treated with volume expansion (with salt liberalization, if appropriate), reconsideration of contributing medications, compression

TABLE 41. High-Risk Clinical Characteristics in the Patient With Syncope[a]
Syncope during exertion
Syncope in supine position
Symptoms of chest discomfort or palpitations before syncope
Family history of sudden death
History of heart failure, aortic stenosis, left ventricular outflow tract disease, dilated cardiomyopathy, hypertrophic cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy, ventricular arrhythmia, coronary artery disease, congenital heart disease, pulmonary hypertension, left ventricular ejection fraction <35%, implantable cardioverter-defibrillator placement
New or previously unknown left bundle branch block, bifascicular block, Brugada pattern, findings consistent with acute ischemia, nonsinus rhythm, prolonged QTc interval (>450 ms)
Hemoglobin <9 g/dL (90 g/L)
Systolic blood pressure <90 mm Hg
Sinus bradycardia <40/min

QTc = corrected QT interval.

[a]A patient is considered at high cardiac risk if any of the above risk factors are present.

Information from Costantino G, Sun BC, Barbic F, Bossi I, Casazza G, Dipaola F, et al. Syncope clinical management in the emergency department: a consensus from the first international workshop on syncope risk stratification in the emergency department. Eur Heart J. 2016;37:1493-8. [PMID: 26242712] doi:10.1093/eurheartj/ehv378

H CONT. stockings, and education on postural changes. Initiation of additional vasoactive agents, such as fludrocortisone or midodrine, can be considered; however, available evidence on their efficacy is limited and conflicting. In cases of psychogenic syncope, referral to a mental health specialist is appropriate.

Prognosis

The underlying cause of the syncopal event determines the prognosis. Patients with a syncopal episode are at increased risk for all-cause mortality (hazard ratio [HR], 1.3; 95% CI, 1.1-1.5) and cardiovascular events (HR, 1.3; 95% CI, 1.0-1.6). The risk for death is even greater in cases of cardiac syncope (HR, 2.0; 95% CI, 1.5-2.7). Neurally mediated and orthostatic syncope do not portend increased cardiovascular mortality. Syncope of any cause, especially if recurrent, can severely affect quality of life, functional independence, and self-confidence. Clinicians should assess for any ensuing mood changes, the need for skilled assistance, and the need for possible driving restrictions (which vary per state law). H

KEY POINTS

- HVC The history and physical examination, including orthostatic (postural) blood pressure measurement, are the most important diagnostic tools in determining the underlying cause of a syncopal event.
- All patients with syncope should undergo electrocardiography to identify underlying arrhythmia, ischemia, or QT prolongation.

(Continued)

KEY POINTS *(continued)*

- Echocardiography, ischemia evaluation, electrocardiographic monitoring, chest radiography, tilt-table testing, electroencephalography, and laboratory studies have low diagnostic yield for the cause of syncope and should be performed only when there is a moderate to high pretest probability of a specific underlying condition. HVC
- The American College of Physicians recommends against routinely obtaining brain imaging (CT or MRI) in cases of syncope that do not involve objective focal neurologic findings. HVC
- Neurally mediated syncope is treated with reassurance and avoidance of provoking measures; physical counterpressure techniques can be useful in patients with a prolonged prodrome. HVC
- Orthostatic syncope may be treated with volume expansion (with salt liberalization, if appropriate), reconsideration of contributing medications, compression stockings, and education on postural changes.

Insomnia

Insomnia is a complex health problem that affects many adults. Symptoms of insomnia vary and may include poor sleep quality, frustration with sleep quantity, difficulty initiating sleep, or an inability to return to sleep after awakening. The prevalence of insomnia increases with age, and women tend to be affected more than men. Medical disorders, including cardiopulmonary diseases, neurodegenerative disorders, and psychiatric disorders, are often implicated in sleep disruption. Medications and other substances also commonly contribute to symptoms of insomnia, and clinicians should screen for common culprits (such as caffeine, alcohol, glucocorticoids, diuretics, and antidepressants).

Chronic insomnia is diagnosed by the presence of symptoms that (1) cause substantial functional distress or impairment; (2) occur at least 3 nights per week for at least 3 months; and (3) are not associated with other sleep, medical, or mental disorders. Although 1 in 10 adults meet the diagnostic criteria for chronic insomnia, some studies have shown that up to 50% of adults report experiencing sleep symptoms.

Evaluation

Given the wide range of patients affected and the significant impact insufficient sleep can have on function, all patients should be asked about problems of sleep disruption. In patients with symptoms of insomnia, a thorough history and physical examination may point to potentially reversible causes, such as sleep apnea or restless legs syndrome. Eliciting an accurate medication history, including use of over-the-counter medications, herbal supplements, caffeine, alcohol, tobacco, and illicit drugs, is also an important part of the diagnostic approach. Physicians should obtain information on sleep pattern, including sleep difficulties (sleep initiation,

sleep maintenance, sleep quality) and environmental factors (work schedule). There is increasing evidence that screen time, such as smart phone and tablet use, before bed can alter circadian patterns and increase symptoms of insomnia, and use of electronics should be assessed. A sleep diary can facilitate collection of an accurate sleep history, and obtaining a collateral history from the patient's sleep partner may shed light on specific sleep-related disorders.

Diagnostic testing, such as polysomnography, is not a first-line approach unless guided by specific findings on the history and physical examination or directed by a sleep specialist.

Treatment

The goals of treatment of insomnia are to improve overall sleep and quality of life. Effective treatment programs are multimodal in their approach and include cognitive behavioral therapy for insomnia (CBT-I), sleep hygiene techniques, environmental changes, and, in poorly controlled cases, pharmacologic therapy.

Nonpharmacologic Treatments

The ACP recommends CBT-I as first-line therapy for insomnia. This multicomponent therapy includes cognitive therapy (to address maladaptive beliefs and expectations about sleep), educational interventions (such as sleep hygiene), and behavioral interventions (such as sleep restriction therapy, stimulus control therapy, and relaxation techniques). It may be delivered in various formats, such as individual or group therapy, web-based modules, or written materials. CBT-I provides significant value over pharmacologic-driven approaches and carries little risk for adverse effects.

Sleep hygiene strategies focus on optimizing environmental factors (instituting stable bed times and rising times); reducing stimuli (limiting screen time [television, laptop computers, and cell phones] and creating a dark environment) around bedtime; avoiding caffeine, alcohol, and nicotine before bedtime; reducing daytime naps; and limiting the bedroom activities to intimacy and sleep. Sleep restriction therapy, which entails limiting the amount of time in bed to increase sleep efficiency, may also be used.

Pharmacologic Therapy

The ACP recommends that physicians engage in a thorough shared decision-making process to decide whether to add pharmacologic therapies in patients with insomnia refractory to CBT-I. Several pharmacologic agents have been demonstrated to improve sleep latency and total sleep time (**Table 42**), but few studies have examined their overall impact on function and quality of life. Pharmacologic therapy is also associated with harms, including daytime drowsiness, increased risk for falls and hip fracture, and medication-related hallucinations. Factors that should be considered before initiating pharmacologic therapy for insomnia are included in **Table 43**. Medications ideally should be taken in short-term trials (no more than 4-5 weeks).

Patients frequently use over-the-counter medications, such as sedating antihistamines, for insomnia despite associated anticholinergic side effects and carry-over daytime sleepiness. Because of the risk for side effects, antihistamines are not recommended in the treatment of insomnia, especially in older adults, in whom the risk is magnified. Melatonin may be effective for circadian rhythm disruptions affecting sleep and has a more favorable side effect profile than antihistamines. Although melatonin is often recommended to older adults owing to the lower risk for side effects, there is insufficient evidence to support its use in this population.

Benzodiazepines induce sedation by activating inhibitory γ-aminobutyric acid (GABA) receptors. These drugs decrease sleep latency and have a sleep-promoting effect, although onset and effect differ between agents. The associated risk for rebound insomnia, addiction potential, and side effect profile make benzodiazepines poor candidates for treatment of insomnia, particularly in combination with other sedating agents (including opioids) and in geriatric populations.

Nonbenzodiazepine GABA receptor agonists are typically more selective in their activity at the GABA receptor and represent a large class of medications for insomnia. These agents (zolpidem, eszopiclone, and zaleplon) have a rapid onset of action and short half-life, making them better choices for patients with difficulty initiating sleep. Long-acting formulations and formulations meant for use with middle-of-the-night awakenings are also available. There is potential for prolonged impaired driving skills and somnolence with their use, and there are few data on the long-term safety or efficacy of these agents.

KEY POINTS

- Diagnostic testing, such as polysomnography, is usually unnecessary in the evaluation of insomnia, unless guided by specific findings on the history and physical examination or directed by a sleep specialist. **HVC**
- First-line therapy for insomnia is cognitive behavioral therapy, which includes cognitive therapy, educational interventions, and behavioral interventions. **HVC**
- Sleep hygiene strategies for insomnia focus on optimizing environmental factors; reducing stimuli around bedtime; avoiding caffeine, alcohol, and nicotine before bedtime; reducing daytime naps; and limiting the bedroom activities to intimacy and sleep. **HVC**
- Pharmacologic therapies for insomnia are associated with adverse effects and should only be initiated in patients with insomnia refractory to nonpharmacologic interventions. **HVC**

Lower Extremity Edema

Lower extremity edema is a common symptom in both the inpatient and outpatient settings. Resulting from accumulation of interstitial fluid in the most dependent part of the body, lower extremity edema may be secondary to several different

TABLE 42. FDA-Approved Prescription Drug Treatment for Insomnia

Agent[a]	Usual Dosage	Onset of Action[b]	Duration of Action[c]	Notes
Benzodiazepines (oral)				
Estazolam (generic)	1-2 mg	Slow	Intermediate	
Flurazepam (generic)	15-30 mg	Rapid	Long	
Quazepam (generic)	7.5-15 mg	Slow	Long	
Temazepam (generic)	7.5-30 mg	Slow	Intermediate	
Triazolam (generic)	0.125-0.5 mg	Rapid	Short	Short-acting benzodiazepines have been associated with an increased risk for anterograde amnesia
Nonbenzodiazepines				
Zolpidem				
Oral tablet (generic)	5-10 mg	Rapid	Short	
Extended-release oral tablet (generic)	6.25-12.5 mg	Rapid	Intermediate	
Sublingual				
Intermezzo	1.75-3.5 mg	Rapid	Ultra-short	Indicated for as-needed use for treatment of middle-of-the-night insomnia with ≥4 h of sleep time remaining
Edluar	10 mg	Rapid	Short	
Oral spray (Zolpimist)	10 mg	Rapid	Short	
Eszopiclone (generic)	1-3 mg	Rapid	Intermediate	The recommended initial dosage was reduced to 1 mg because of prolonged impaired driving skills, memory, and coordination at the previously recommended 3-mg dosage
Zaleplon (generic)	10-20 mg	Rapid	Short	
Orexin-Receptor Antagonist				
Suvorexant (Belsomra)	5-20 mg	Slow	Long	The recommended initial dosage is 10 mg; the daily dosage should not exceed 20 mg
Antidepressant				
Doxepin (Silenor)	3-6 mg	Rapid	Intermediate	
Melatonin Agonist				
Ramelteon (Rozerem)	8 mg	Rapid	Short	

[a]All agents classified as schedule C-IV by the Drug Enforcement Agency (DEA) except doxepin and ramelteon, which are not scheduled.

[b]Onset of action: rapid = 15-30 minutes; slow = 30-60 minutes.

[c]Based on elimination half life and preparation: short = 1-5 hours; intermediate = 5-12 hours; long = >12 hours.

Adapted with permission from Masters PA. In the clinic. Insomnia. Ann Intern Med. 2014;161:ITC9. [PMID: 25285559] doi:10.7326/0003-4819-161-7-201410070-01004. Copyright 2014, American College of Physicians.

pathophysiologic mechanisms, including increased capillary hydrostatic pressure, increased capillary permeability, and decreased plasma oncotic pressure. Obstruction of the lymphatic system is a less common mechanism of edema.

The most common causes of lower extremity edema include venous obstruction or insufficiency, heart failure (including right-sided heart failure secondary to pulmonary disease), cirrhosis, nephrotic syndrome and hypoalbuminemia of other etiologies, and use of certain medications (**Table 44**). If lower extremity edema is unilateral, it is usually the result of a mechanical obstruction to venous or lymphatic flow, such as venous thrombosis or malignancy.

A detailed history and physical examination will suggest the cause of lower extremity edema in most patients. Reasonable initial laboratory testing includes measurement of kidney and liver function, urinalysis (for detection of protein), and albumin measurement. The decision to pursue further testing, including echocardiography, lower extremity Doppler ultrasonography, and advanced imaging should be guided by the findings on the initial evaluation.

Chronic Venous Insufficiency

Chronic venous insufficiency is a condition in which the veins or valves in the lower extremities are incompetent, resulting in

TABLE 43. Factors to Consider When Prescribing Drugs to Treat Insomnia
Use the minimal effective dosage.
Avoid long-half-life medications, including long-half-life metabolites.
Be aware of potential interactions between drugs, including over-the-counter drugs.
Caution patients who are receiving these medications about interaction with alcohol.
Review potential side effects—in particular, daytime sleepiness.
Confer with the patient to determine an appropriate period of use.
Use a γ-aminobutyric acid agonist before other sedative-hypnotics for treatment of acute or short-term insomnia.
Look for rebound insomnia after discontinuation.
Consider intermittent or long-term use of hypnotic medications, depending on the clinical situation.
Consider consulting a sleep specialist before starting long-term therapy with hypnotic medication.

Adapted with permission from Masters PA. In the clinic. Insomnia. Ann Intern Med. 2014;161:ITC1-15; quiz ITC16. [PMID: 25285559] doi:10.7326/0003-4819-161-7-201410070-01004. Copyright 2014, American College of Physicians.

pooling of blood in the legs. It is most commonly caused by venous hypertension, but it may also be congenital. Symptoms include aching, itching, restlessness, leg heaviness, leg swelling, and pain.

A thorough history and physical examination should be performed. The examination may reveal edema, dilated veins (both varicosities and superficial telangiectasias), thin or hyperpigmented skin, and ulceration. Physical findings are best observed in the gravity-dependent upright position. Chronic venous insufficiency is a clinical diagnosis, but venous duplex Doppler ultrasonography can be used if the diagnosis is in doubt and in those considering intervention. Air plethysmography, which uses air displacement in a cuff surrounding the calf to measure venous outflow and filling, can be used when venous duplex ultrasonography is nondiagnostic or to guide therapy.

Conservative measures, including exercise, leg elevation, lifestyle changes (weight loss), and gradient compression stockings (20-50 mm Hg depending on the stage of disease) are first-line therapies. The presence of skin changes or ulceration should prompt at least 30 mm Hg of compression. To increase patient adherence, knee-length stockings are prescribed, and if used daily with an alternate pair, stockings should be replaced every 6 to 9 months. Skin care is also an important part of management, and daily use of topical moisturizers may reduce skin breakdown and prevent infection. Stasis dermatitis may require sparing use of a topical steroid (see MKSAP 18 Dermatology). Wound care, including use of hydrocolloids and foam dressings, is essential to control drainage from ulcers and to prevent maceration of the surrounding skin. Many drugs, including pentoxifylline and horse chestnut extracts, have been studied for chronic venous insufficiency; however, none are FDA approved for this condition. Patients with bothersome spider veins and small varicose veins can undergo sclerotherapy, thermocoagulation, or laser therapy. Patients with confirmed reflux and persistent symptoms despite conservative therapy may be treated with venous ablation, stripping or excision, or, in the case of stenosis and obstruction, stenting. Surgical options can be considered for those with symptoms refractory to medical and endovenous therapies.

KEY POINTS

- The most common causes of lower extremity edema include venous obstruction or insufficiency, heart failure, cirrhosis, nephrotic syndrome and hypoalbuminemia of other etiologies, and use of certain medications.
- Conservative measures, including exercise, leg elevation, lifestyle changes, and compression stockings, are first-line therapies for chronic venous insufficiency. HVC

Common In-Flight Emergencies

In-flight medical emergencies are relatively common during air travel, occurring in an estimated 1 in 600 flights. In the United States, physicians are not legally mandated to assist in the event of an in-flight emergency, although some countries do impose such obligations. The laws of the country in which the aircraft is registered usually prevail. Ethically, physicians should provide assistance as able. The Aviation Medical Assistance Act of 1998 includes a Good Samaritan provision that protects individuals who are medically qualified "from liability for rendering assistance unless that person is engaged in gross negligence or willful misconduct," such as providing care while intoxicated. Providers should practice within their scope of training, be mindful of patient privacy, and document the patient encounter.

Physicians who respond to an in-flight emergency typically have access to several medical resources. Most airlines have contracts with 24-hour call centers, and ground-based physicians trained in emergency or aerospace medicine can assist the on-board physician remotely and help direct care. Additionally, flight crews are required to receive cardiopulmonary resuscitation training, including training on the use of automated external defibrillators, and to be familiar with first aid equipment. If the patient's condition is critical, the physician can recommend diversion of the flight to the nearest airport, although the ultimate decision rests with the aircraft captain.

Airlines based in the United States are mandated by the Federal Aviation Administration to carry at least one automated external defibrillator, supplemental oxygen, and a medical kit that contains a stethoscope, sphygmomanometer, gloves, airway supplies, intravenous access supplies (needles, syringes, saline), and some basic medications (epinephrine, lidocaine,

TABLE 44. Differential Diagnosis of Lower Extremity Edema		
Condition or Cause	**Clinical Presentation**	**Diagnostic Testing**
Chronic venous insufficiency	Gradual-onset leg aching/heaviness that is more likely to improve with elevation/recumbency and walking (decreased venous pressure) Edema (most commonly bilateral but can be unilateral) that usually spares forefoot Hyperpigmentation (hemosiderin deposits); telangiectasias, reticular veins, varicose veins; eczematous dermatitis and lipodermatosclerosis leading to ulceration, especially over the medial malleolus	Duplex ultrasonography if considering intervention
Heart failure	Dyspnea, orthopnea, paroxysmal nocturnal dyspnea, elevated jugular venous pressure, lung crackles, ventricular gallop, symmetric pitting edema	Echocardiography
Kidney disease	Symmetric pitting edema	Urinalysis, random urine albumin-creatinine ratio, serum creatinine level
Liver disease	Symmetric pitting edema, ascites, spider angiomas, palmar erythema, jaundice/icterus	Liver chemistry tests, albumin level, INR
Hypothyroidism	Symptoms of hypothyroidism, nonpitting bilateral edema	Thyroid-stimulating hormone level, serum thyroxine
Lymphedema (bilateral)	Brawny induration; pitting edema present initially; nonpitting present late in process; involves feet (square toes) Kaposi-Stemmer sign (inability to pinch a fold of skin on the dorsal surface of the base of the second toe)	Can consider CT or the abdomen/pelvis, lymphoscintigraphy
Lipedema	Fatty tissue accumulation, nonpitting edema that spares the feet	
Pregnancy	Symmetric pitting edema	
Obstructive sleep apnea	Daytime sleepiness, snoring, witnessed apnea, neck circumference >43 cm (17 in), symmetric pitting edema	Polysomnography
Pulmonary hypertension	Exertional dyspnea, elevated jugular venous distention, prominent jugular venous *a* wave, widened split S_2	Echocardiography
Deep venous thrombosis	Unilateral, painful edema (most commonly) that may be tender on examination; typically pitting edema Should be strongly suspected with acute edema <72 h	D-dimer and/or lower extremity ultrasonography depending on pretest probability
Drugs (vasodilators, NSAIDs, gabapentinoids, hormones, antiestrogens, thiazolidinediones)	Gradual-onset, bilateral pitting edema that usually improves with recumbency; one side may be larger than the other, particularly if there is more pronounced venous disease	No diagnostic testing; symptoms resolve within days of discontinuing the offending agent

atropine, aspirin, nitroglycerin, antihistamines, bronchodilators, and dextrose). Many U.S. airlines augment their kits with additional supplies. The contents of international kits may vary. Other passengers may volunteer their own medical supplies, such as prescription medications, injectable epinephrine pens, or glucometers. The physician must weigh the benefits of using another passenger's glucometer against the potential harms, including transmission of blood-borne pathogens. Passengers may also be able to help with translation, although it is important to respect patient privacy.

In most in-flight medical emergencies, the physician's role involves assessing the patient, establishing a diagnosis when possible, administering basic medical treatments, providing reassurance as appropriate, and recommending flight diversion if necessary. The most common in-flight emergencies include presyncope or syncope (typically vasovagal), gastrointestinal disorders (diarrhea and vomiting), cardiovascular symptoms, and respiratory symptoms (asthma and hyperventilation). In-flight cardiac arrest is rare, accounting for approximately 0.3% of in-flight emergencies; however, it is responsible

for 86% of in-flight deaths. In the event of suspected acute myocardial infarction or stroke, immediate flight diversion should be recommended to the crew. Other frequently encountered issues include trauma caused by objects falling from overhead bins, hypoglycemia, psychiatric problems (most commonly anxiety or phobias), allergic reactions, seizures, headaches, and obstetric or gynecologic events. Several in-flight births occur each year.

KEY POINTS

- In the United States, physicians are not legally mandated to assist in the event of an in-flight emergency; however, physicians have an ethical obligation to provide assistance as able.
- The physician's role in in-flight emergencies involves assessing the patient, establishing a diagnosis when possible, administering basic medical treatments, providing reassurance as appropriate, and recommending flight diversion if necessary.

Musculoskeletal Pain

Low Back Pain

Diagnosis and Evaluation

Low back pain can be classified by duration as acute (<4 weeks), subacute (4-12 weeks), or chronic (>12 weeks). Approximately 90% of patients have nonspecific low back pain, in which no specific cause can be determined. The most common identifiable causes of low back pain are spinal stenosis, disk herniation, and compression fractures. Less common identifiable causes include cancer (vertebral metastases) and infection (diskitis, osteomyelitis, epidural abscess); visceral disease, such as nephrolithiasis, pyelonephritis, and abdominal aortic aneurysm, may also cause low back pain.

History and Physical Examination

Evaluation of patients with low back pain includes a detailed history directed toward factors that increase the likelihood of specific causes of pain (**Table 45**). Psychosocial factors may also affect the course of low back pain and should be assessed. Psychosocial distress; comorbid psychiatric conditions; somatization; and maladaptive coping strategies, such as avoiding work, are associated with poor clinical outcomes.

The physical examination should similarly search for evidence of an underlying disorder (see Table 45). Specific attention should be paid to "red flag" findings on examination, including fever and neurologic signs. A thorough neurologic examination, including strength, sensory, and reflex testing of the legs, in addition to performing both the ipsilateral and contralateral straight leg raise test (**Figure 8**), can identify patterns of deficits that point to lesions (most commonly disk herniation) at specific levels (**Table 46**). Similarly, decreased anal sphincter tone and perianal sensation raise concern for cauda equina syndrome. Many of the examination findings, however, are insensitive or nonspecific for the presence of a specific underlying disorder.

Further Diagnostic Testing

Clinicians should not routinely obtain imaging and other diagnostic tests in patients with nonspecific low back pain. Obtaining imaging studies in these patients is not associated with clinically meaningful outcomes. Notably, imaging abnormalities are commonly present in asymptomatic individuals. They are also common in patients with nonspecific low back pain, and their presence may lead to unhelpful and unnecessary interventions.

H In contrast, imaging is recommended when neurologic deficits are present or if serious underlying conditions are suspected. Plain radiography may be considered to evaluate for ankylosing spondylitis or vertebral compression fracture. When malignancy is suspected, the American College of Physicians recommends immediately obtaining plain radiography in addition to measuring the erythrocyte sedimentation rate. If results of these initial tests are negative and significant concern remains, MRI should then be obtained. Immediate MRI should be obtained when there are risk factors for spinal infection or concern for cord compression or cauda equina syndrome. In patients with persistent pain despite conservative measures, symptoms/signs of radiculopathy, or spinal stenosis, MRI or, less preferably, CT may be considered only if the patient is a potential candidate for surgical intervention or epidural glucocorticoid injection. H

Treatment

Patient education is a key component in the treatment of low back pain regardless of duration. Education includes providing information on the expected course of the back pain, promoting self-management, addressing misconceptions, and encouraging physical activity as appropriate. In all patients with low back pain, bed rest should be avoided, and depressive features should be appropriately assessed and managed.

In addition to education, treatment modalities for patients with low back pain may include nonpharmacologic and/or pharmacologic therapies and, rarely, surgery. The interventions chosen should be based on the patient's signs, symptoms, and comorbid conditions.

Nonpharmacologic Treatment

Clinical guidelines consistently emphasize nonpharmacologic therapies as a cornerstone of therapy for acute and chronic low back pain. For acute low back pain, potentially useful nonpharmacologic therapies include local heat, massage, acupuncture, and spinal manipulation, although the evidence supporting these approaches is generally weak.

Multiple nonpharmacologic options are available for chronic low back pain, including exercise therapy, manual and massage therapy, acupuncture, yoga, intensive interdisciplinary therapy, and cognitive behavioral therapy, with varying

TABLE 45. History and Examination Features and Suggested Diagnoses in Low Back Pain

Suggested Diagnosis	History Features	Examination Features
Cancer	Personal history of malignancy Unexplained weight loss Failure to improve after 1 mo No relief with bed rest	Vertebral tenderness
Infection	Fever Injection drug abuse Urinary tract infection Skin infection	Fever Vertebral tenderness
Inflammatory/ rheumatologic condition	Onset before age 40 y Gradual onset Presence of morning stiffness Pain not relieved when supine Pain persisting for >3 mo Involvement of other joints	
Nerve root irritation (radiculopathy)	Sciatica (pain that radiates from the back through the buttocks down into the leg[s]) Increased pain with cough, sneeze, or Valsalva maneuver	Positive ipsilateral SLR (LR+ of 3.7) Positive contralateral SLR (LR+ of 4.4)
Spinal stenosis	Severe leg pain No pain when seated Improvement in pain when bending forward Pseudoclaudication[a] (worsened pain with walking or standing and relief with sitting)	
Compression fracture	Advanced age Trauma Glucocorticoid use Osteoporosis	Vertebral tenderness
Cauda equina syndrome[b]	Bowel or bladder dysfunction Perineal (saddle) sensory loss Rapidly progressive neurologic deficits	Decreased anal sphincter tone Decreased perineal/perianal sensation

LR+ = positive likelihood ratio; SLR = straight leg raise.

[a]Lower extremity symptoms caused by lumbar spinal stenosis mimicking vascular ischemia; also termed neurogenic claudication.

[b]Compression of the lumbar and sacral nerves below the termination of the spinal cord (conus medullaris). Characterized by back pain; sensory changes in the S3 to S5 dermatomes (saddle anesthesia); bowel, bladder, and sexual dysfunction; and absent Achilles tendon reflexes bilaterally.

levels of predominantly weak evidence supporting these approaches. The 2016 National Institute for Health and Care Excellence (NICE) guidelines endorse self-management, exercise, manual therapy, psychological therapy, and return-to-work programs.

Pharmacologic Treatment

NSAIDs are considered first-line pharmacologic therapy for acute low back pain and should be used at the lowest effective dose for the shortest duration needed. A recent meta-analysis suggests that NSAIDs, compared with placebo, reduce pain and disability in patients with acute low back pain. Notably, another meta-analysis concluded that acetaminophen is ineffective for acute low back pain. Second-line agents include nonbenzodiazepine muscle relaxants. Opioids and tramadol should be avoided in acute low back pain if possible.

A similar approach is appropriate in patients with chronic low back pain. NSAIDs remain first-line pharmacologic therapy, and nonbenzodiazepine muscle relaxants may be used as second-line therapy. The serotonin-norepinephrine reuptake inhibitor duloxetine is approved by the FDA to treat chronic low back pain and may be useful in selected patients.

A 2018 randomized controlled trial demonstrated that opioids were not superior to nonopioid medications for improving pain-related function for chronic back pain or osteoarthritis-related hip or knee pain; pain intensity was

FIGURE 8. Straight leg raise test. With the patient lying supine on his or her back, the patient lifts the leg with the knee fully extended on the affected side (ipsilateral straight leg raise test) and then repeats on the opposite side (contralateral straight leg raise test). The test result is considered positive when pain radiates down the leg past the level of the knee when the hip is flexed between 30 and 70 degrees.

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TABLE 46. Patterns of Neurologic Deficits in Patients With Low Back Pain

Nerve Root Level	Motor Deficit	Sensory Deficit	Involved Reflex
L3	Hip flexion	Anteromedial thigh	Patella
L4	Knee extension	Anterior leg/ medial foot	Patella
L5	Great toe dorsiflexion	Lateral leg/ dorsal foot	N/A
S1	Plantar flexion of foot	Posterior leg/ lateral foot	Achilles

N/A = not applicable.

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significantly improved in the nonopioid group. The 2016 NICE guidelines recommend against the use of opioids for chronic back pain, and the 2016 Centers for Disease Control and Prevention guideline for prescribing opioids states that nonpharmacologic and nonopioid therapies are preferred over opioids.

Systemic glucocorticoids, tricyclic antidepressants, and neuromodulators (gabapentin and pregabalin) have not demonstrated effectiveness for chronic low back pain.

H Interventional and Surgical Treatment

Most patients with low back pain do not require surgery. Immediate surgery is indicated for most patients with suspected cord compression or cauda equina syndrome. Nonurgent surgery may be considered in patients with neurologic deficits, progressively worsening spinal stenosis, or chronic pain with corresponding abnormalities on imaging that has been refractory to conservative measures and has the potential to respond to surgery. Typical surgical approaches include diskectomy for disk herniation and posterior decompressive laminectomy for spinal stenosis.

Epidural glucocorticoid injections are frequently performed in patients with radiculopathy; however, available evidence suggests they offer only small, short-term benefits. H

KEY POINTS

- Evaluation of patients with low back pain includes a detailed history and physical examination to help distinguish nonspecific low back pain from pain attributable to a specific cause. **HVC**
- Most patients with nonspecific low back pain do not require imaging or other diagnostic testing. **HVC**
- Patient education for low back pain includes providing information on the expected course of the back pain, promoting self-management, addressing misconceptions, and encouraging physical activity as appropriate.
- Nonpharmacologic therapies are considered a cornerstone of treatment for both acute and chronic low back pain. **HVC**
- NSAIDs are considered first-line pharmacologic therapy for low back pain and should be used at the lowest effective dose for the shortest duration needed. **HVC**

Neck Pain

Diagnosis and Evaluation

As with low back pain, a priority in evaluating neck pain is differentiating nonspecific neck pain from other conditions that may result in serious complications or be amenable to specific therapy. Evaluation begins with a thorough history, including circumstances of the onset, presence of antecedent trauma, duration, progression, impact on daily activities, and accompanying symptoms. Examination includes inspection and palpation of the cervical spine and muscles, range of motion testing, and comprehensive neurologic assessment of the arms, including sensory, motor, and reflex testing.

The most common cause of neck pain is cervical sprain (nonspecific or axial neck pain), which is characterized by pain and stiffness in the paraspinal neck muscles frequently accompanied by neck and upper back muscle spasms. Examination findings include decreased cervical range of motion, muscle spasms, and absence of abnormal neurologic findings.

Whiplash-associated neck pain develops after trauma involving abrupt neck flexion or extension. Symptoms and signs are similar to those of cervical sprain.

Cervical radiculopathy is caused by nerve root compression as a result of disk herniation or adjacent bony degeneration. Several conditions can cause symptoms that may be mistaken for cervical radicular pain, including shingles,

entrapment syndromes (such as median or ulnar nerve entrapment, thoracic outlet syndrome), complex regional pain syndrome, and cardiac ischemia. Radiculopathy, however, usually causes neck pain accompanied by radiating arm pain and paresthesias that follow a dermatomal distribution. In some cases, pain may be limited to the shoulder girdle. On examination, the patient's symptoms may be reproduced with the Spurling test (sensitivity, 94%; specificity, 30%) (**Figure 9**) and improved by holding the patient's hand above the head (shoulder abduction test: variable sensitivity, 17%-78%; specificity, 75%-92%).

Cervical myelopathy (compression of the cervical spinal cord) can also cause neck pain. Symptoms are typically progressive and include difficulty with manual dexterity, fine object manipulation (buttoning a shirt), and gait disturbance. On examination, there are upper motor neuron signs such as increased muscle tone, hyperreflexia, and clonus.

Involvement of the cervical spine by malignancy should be considered in the presence of a history of malignancy or suggestive systemic symptoms such as weight loss. Infectious causes, such as an epidural abscess or osteomyelitis, should be considered in the presence of fevers and chills, a history of injection drug use, or a history of recent bacteremia.

Most patients with neck pain do not require imaging studies. Plain radiography should be obtained when evaluation suggests fracture, infection, or malignancy and can be considered in patients with cervical sprain that has been unresponsive to 6 to 8 weeks of conservative measures. MRI is recommended when suspicion for malignancy or infection remains high despite normal plain radiographs, when myelopathy is suspected, and in patients with progressive neurologic symptoms. In patients who cannot undergo MRI, CT myelography can be considered. Electrodiagnostic studies may be performed when there is diagnostic uncertainty about a patient's symptoms (for example, to help distinguish peripheral nerve entrapment or peripheral neuropathy from radiculopathy).

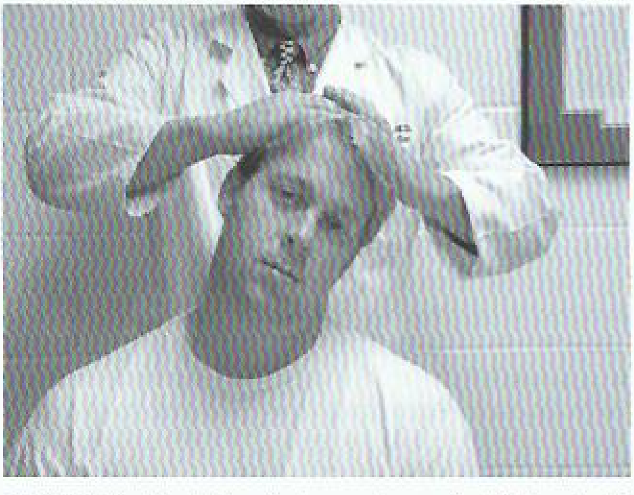

FIGURE 9. Spurling test for cervical nerve root compression. With the patient in a sitting position, the examiner extends the patient's head and then laterally flexes the neck. A downward pressure is then applied to the head in this position. A positive Spurling test reproduces the patient's pain, which radiates into the ipsilateral arm in a dermatomal distribution and supports the diagnosis of cervical radiculopathy (sensitivity, 94%; specificity, 30%).

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Treatment

Most patients with neck pain have resolution or near-resolution of their symptoms within 8 to 12 weeks of onset by using conservative measures. A multimodal approach that is tailored to the individual patient appears to work best and may include mobilization, exercise, physical therapy, and analgesic agents.

Stretching and strengthening exercises appear to provide intermediate-term relief of symptoms. Spinal manipulation, mobilization, and acupuncture may provide short-term pain relief. Although widely used, immobilization with a cervical collar appears to be no more effective than sham interventions. Immobilization for longer than 1 to 2 weeks may lead to atrophy of the neck muscles. The benefit of traction appears limited.

Oral and topical NSAIDs are considered first-line pharmacologic therapy for neck pain. Notably, a recent meta-analysis suggests that NSAIDs, compared with placebo, reduce pain in patients with neck pain. Because of its favorable side-effect profile, acetaminophen is also frequently used, although its effectiveness is not clearly established. Cyclobenzaprine, when used at intermediate or higher doses (≥15 mg/d), is more effective than placebo for treatment of acute neck pain associated with muscle spasm. For patients with chronic radicular symptoms, venlafaxine and neuromodulators, such as gabapentin and tricyclic antidepressants, may provide some pain relief. Because of abuse potential, opioids are generally avoided and, if used, should only be used on a short-term basis and restricted to persons with severe, intractable pain. No evidence supports the use of oral glucocorticoids. Epidural glucocorticoid injections may be considered in patients with cervical radiculopathy and significant symptoms that do not respond to other conservative measures, although the data supporting this practice are unconvincing.

Surgery is generally reserved for patients with structural disorders on imaging along with myelopathic findings and progressive neurologic symptoms, or for those with symptoms that do not respond to 6 months of conservative therapy.

For those with neck pain with a systemic cause, the underlying disorder should be appropriately treated.

KEY POINTS

- Most patients with neck pain do not require imaging studies; plain radiography should be obtained when evaluation suggests fracture, infection, or malignancy and can be considered in patients with cervical sprain that has been unresponsive to 6 to 8 weeks of conservative measures.
- Neck pain usually resolves with conservative measures, including mobilization, exercise, physical therapy, and analgesic agents.

Upper Extremity Disorders

Thoracic Outlet Syndrome

Diagnosis and Evaluation

The three subtypes of thoracic outlet syndrome (TOS) are differentiated according to the affected structure within the neurovascular bundle between the first rib and the clavicle. Neurogenic TOS, the most common type (>90% of cases), results from compression of the brachial plexus. Symptoms (arm paresthesias, pain, and weakness) worsen with repetitive arm use, especially overhead activities. Venous TOS is caused by axillary vein compression and usually thrombosis within the thoracic outlet. Symptoms (arm pain/fatigue, edema, and cyanosis) occur with repetitive arm use, especially overhead activities. Dilated collateral veins of the chest wall and shoulder may be present. Arterial TOS, due to subclavian artery compression (with or without thrombosis), usually occurs in the presence of an anomalous cervical rib; less commonly, it occurs with frequent and vigorous overhead activities, such as baseball pitching. Symptoms include arm pain (which may be exertional), weakness, paresthesias, coolness, and pallor.

Diagnosis of neurogenic TOS is clinical, although electrodiagnostic testing may be helpful in some patients. Vascular causes require imaging of the affected vessel, with ultrasonography being the most useful initial test.

Treatment

First-line therapy for neurogenic TOS includes improving posture and strengthening shoulder girdle muscles. Surgical decompression is reserved for progressive, disabling, or unresponsive symptoms. Treatment of both arterial and venous TOS involves catheter-directed thrombolysis followed by prompt surgical decompression of the thoracic outlet.

KEY POINT

- Neurogenic thoracic outlet syndrome (TOS), the most common type of TOS, results from compression of the brachial plexus; arm paresthesias, pain, and weakness worsen with repetitive arm use, especially overhead activities.

Shoulder Pain

Diagnosis and Evaluation

Shoulder pain assessment involves a detailed history with attention to the presence of antecedent trauma and relevant occupational or recreational activities. A comprehensive shoulder examination, performed with both shoulders fully exposed, includes inspection, palpation, range of motion assessment, and specialized maneuvers.

The initial step in evaluating shoulder pain is to determine whether the pain is arising from the shoulder (intrinsic) or is referred from another site (extrinsic), such as the cervical spine. Extrinsic pain is suggested by the inability to reproduce pain with shoulder movement, pain extending beyond the elbow, and pain with neck movement.

Rotator Cuff Disease

Rotator cuff disease, the most common cause of shoulder pain, refers to all symptomatic rotator cuff disorders, including rotator cuff tendinitis, rotator cuff tears, and subacromial bursitis. Pain from rotator cuff disease is frequently localized to the upper arm near the deltoid insertion, is worsened with overhead activities, and is often worse at night, particularly with lying on the affected side. Except for acute traumatic rotator cuff tears, onset of symptoms is usually insidious. Risk factors for rotator cuff disease include increasing age and participation in activities that require repetitive overhead arm use.

On examination, shoulder inspection may reveal infraspinatus muscle atrophy (positive likelihood ratio of 2.0 for rotator cuff disease). Many examination maneuvers are available for rotator cuff disease assessment; however, each is limited by test characteristics, and they are most useful in combination (**Table 47**). The combination of positive results on painful arc and drop arm tests in the setting of weakness in external rotation is particularly suggestive of a rotator cuff tear.

Most patients with rotator cuff disease do not require imaging studies. Ultrasonography or MRI should be reserved for patients with acute or progressive functional loss and for those who are unresponsive to conservative measures.

Patients with acute full-thickness tears should be referred for consideration of immediate repair. Treatment of other rotator cuff disorders should include education about the expected course, avoidance or modification of aggravating activities, and physical therapy. Immobilization with a sling should be avoided to prevent development of adhesive capsulitis. Pharmacologic treatment should begin with acetaminophen and, if ineffective, progress to oral or topical NSAIDs. Subacromial glucocorticoid injections may provide short-term pain relief in patients with subacromial bursitis in whom other measures have failed but should be limited to one or two courses to limit complications. Surgery is reserved for patients in whom 3 to 6 months of conservative therapy has failed or in physically active patients with functionally significant tears.

Adhesive Capsulitis

Adhesive capsulitis (frozen shoulder) usually occurs in patients aged 40 to 70 years. The cause is unclear but appears to involve glenohumeral joint capsular thickening and fibrosis. Adhesive capsulitis can be idiopathic but is also associated with prolonged immobilization, antecedent shoulder surgery or injury, diabetes mellitus, hypothyroidism, and autoimmune disorders. Patients describe shoulder pain that is often constant but is worse at night and in cold weather; shoulder stiffness is common. Both the degree of pain and stiffness may vary in an individual patient over time. On examination, patients have limited passive and active range of motion in all directions.

Treatment of adhesive capsulitis focuses on pain control and improved range of motion. Intra-articular glucocorticoid injections appear more effective than physical therapy alone, although evidence supports combining modalities. Acetaminophen and NSAIDs can be used as an adjunct for analgesia. Surgery is

TABLE 47. Physical Examination Maneuvers in Rotator Cuff Disease

Maneuver	Technique	Positive LR[a] (95% CI)	Negative LR[a] (95% CI)	Notes
Painful arc test	During full passive abduction of the affected arm, pain occurs between 60° and 120°.	3.7 (1.9-7.0)	0.36 (0.23-0.54)	Highest LR+ of all special RC maneuvers.
Drop arm test	The affected arm is fully passively abducted, and the patient is asked to slowly lower the arm. A sudden drop of the arm with reproduction of the patient's pain is a positive result.	3.3 (1.0-11)	0.82 (0.7-0.97)	An uncontrolled drop of the arm suggests a full tear of the supraspinatus.
Hawkins test	The arm is passively flexed to 90° with the elbow in 90° flexion. The examiner then internally rotates the shoulder. Reproduction of pain during internal rotation is a positive result.	1.5 (1.1-2.0)	0.51 (0.39-0.66)	Believed to maximize impingement of the supraspinatus tendon; if the painful arc test, Hawkins test, and resisted external rotation are positive, the LR+ for a full-thickness RC tear is 16.4.
Empty can test	The extended arm is passively abducted to 90° in the plane of the supraspinatus (30° anterior to the coronal plane) and internally rotated (as though pouring a glass of water onto the floor). The patient is asked to maintain the position while the examiner exerts downward force on the arm. Weakness or reproduction of pain is a positive result.	1.3 (0.97-1.6)	0.64 (0.33-1.3)	Inability to maintain the position before resistance is applied suggests a full tear of the supraspinatus.
Resisted external rotation	The arm is abducted to 0° with the elbow flexed to 90° and the thumb pointing upward. The examiner exerts an internal rotation force proximal to the wrist, which the patient is asked to resist. Weakness or reproduction of pain is a positive result.	2.6 (1.8-3.6)	0.49 (0.33-0.72)	Pain or weakness suggests infraspinatus pathology. Limitation in external rotation range of motion suggests glenohumeral disease or adhesive capsulitis.
Internal rotation lag sign	The patient places the dorsum of the hand on the lower back with the elbow flexed to 90°. The examiner lifts the hand off the back, further internally rotating the shoulder. Inability to maintain the hand away from the back is a positive result.	6.2 (1.9-12)	0.04 (0.0-0.58)	Subscapularis is the primary muscle of internal rotation; LRs are for a full tear of the subscapularis.

LR+ = positive likelihood ratio; RC = rotator cuff.

[a]LRs relate to the diagnosis of rotator cuff disease unless otherwise indicated.

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reserved for patients who do not respond to 12 weeks of conservative measures.

Acromioclavicular Joint Degeneration

Acromioclavicular joint degeneration is typically characterized by poorly localized pain on the superior shoulder, although pain may be throughout the shoulder region. On examination, pain may be elicited with palpation of the acromioclavicular joint. The crossed-arm adduction test often reproduces the pain, as does shoulder abduction beyond 120 degrees, but neither test is specific for acromioclavicular joint disease. Plain radiography is often completed to assess for other structural disease and usually reveals degenerative changes of the acromioclavicular joint.

First-line therapy consists of NSAIDs and activity modification. Glucocorticoid injections may provide short-term pain relief.

KEY POINTS

- Rotator cuff disease pain is frequently localized to the upper arm near the deltoid insertion, is worsened with overhead activities, and is often worse at night, particularly with lying on the affected side.
- Most patients with rotator cuff disease do not require imaging studies; treatment may include education, avoidance/modification of aggravating activities, physical therapy, and acetaminophen or NSAIDs.

(Continued)

KEY POINTS *(continued)*

- Treatment of adhesive capsulitis focuses on pain control and improved range of motion; intra-articular glucocorticoid injections appear more effective than physical therapy alone, although evidence supports combining both modalities.
- First-line therapy for acromioclavicular joint degeneration consists of NSAIDs and activity modification; glucocorticoid injections may provide short-term pain relief.

Elbow Pain

Diagnosis and Evaluation

Elbow pain may be caused by pathology within the elbow joint, surrounding tissues, or nerves. Diseases within the neck, shoulder, and wrist may also cause pain radiating to the elbow. Evaluation focuses on patient history and physical examination.

Epicondylitis

Epicondylitis (epicondylosis) refers to noninflammatory conditions of the tendons surrounding the elbow. Lateral epicondylitis (tennis elbow) is induced by activities with repetitive use of extensor tendons, such as computer use or tennis. Pain and tenderness are located over the lateral epicondyle and increase with resisted wrist extension. Medial epicondylitis (golfer's elbow) is less common and is caused by repetitive flexion of the wrist. Pain occurs over the medial elbow and ventral forearm and worsens with resisted wrist flexion. Diagnostic imaging is unnecessary if the clinical picture is consistent with medial or lateral epicondylitis.

There is little strong evidence regarding the optimal means of treatment. Initial management includes avoidance of pain-inducing activities and NSAIDs for analgesia. Physical therapy and counterforce braces may improve symptoms and prevent future exacerbations. Glucocorticoid injections may reduce pain in the short term, but they provide no long-term benefit and are used only as a temporizing measure. Surgery is rarely indicated for recalcitrant pain.

Olecranon Bursitis

Several conditions cause inflammation of the olecranon bursa, including trauma, gout, and infection. Posterior elbow swelling and tenderness with normal elbow range of motion are typical (**Figure 10**); swelling and pain on elbow extension suggest elbow joint effusion and an alternate cause. Aspiration with culture and fluid analysis should be performed for severe pain or suspicion of infection.

Noninfectious bursitis is treated by avoidance of bursal trauma and short-term use of NSAIDs. Glucocorticoid injections may provide short-term benefit but are associated with complications and should be considered only when conservative treatment fails. Surgery may be necessary for infectious or refractory bursitis.

FIGURE 10. Olecranon bursitis is characterized by warmth, redness, and swelling. The ability to extend and flex the elbow generally excludes an intra-articular process.

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Ulnar Nerve Entrapment

Ulnar nerve entrapment (cubital tunnel syndrome) results from ulnar nerve impingement at the elbow by fibrous scar tissue, ulnar nerve subluxation, ganglion cysts, or bone spurs. Characteristics include pain at the elbow that worsens with flexion, paresthesias and numbness of the fourth and fifth fingers, and weakness of the interosseous muscles. The diagnosis is usually clinical, but electromyography is often used for diagnostic confirmation; MRI or ultrasonography may be useful in some situations.

Initial treatment consists of avoidance of elbow trauma and nocturnal splinting. NSAIDs are beneficial for short-term pain relief. Surgery is an option when conservative measures fail in the setting of significant or progressive symptoms.

KEY POINTS

- Olecranon bursitis is characterized by posterior elbow swelling and tenderness with normal elbow range of motion; swelling and pain on elbow extension suggest elbow joint effusion and an alternate cause.
- Elbow pain is generally managed with avoidance of trauma and pain-inducing activities; NSAIDs may be effective for analgesia. **HVC**

Wrist and Hand Pain

Carpal Tunnel Syndrome

Carpal tunnel syndrome develops from increased pressure within the carpal tunnel causing median nerve compression. Diagnosis is usually established based on history. The syndrome presents with wrist pain that may radiate to the forearm and hand; paresthesias and weakness of the first three fingers and thenar eminence (median nerve distribution) may be present. Symptoms are often worse at night and with

repetitive wrist motion. Risk factors include obesity, female sex, hypothyroidism, pregnancy, and connective tissue disorders. Although keyboard use has been suggested as a risk factor, it has not been confirmed by studies.

Examination findings may include decreased sensation over the median nerve distribution, thenar muscle atrophy, and weakened thumb abduction. Examination is often normal early in the disease, and provocative testing with the Phalen maneuver (flexion of hands at wrists) or Tinel test (percussion of the median nerve on top of the carpal tunnel) is rarely useful. Electrodiagnostic testing is beneficial when the diagnosis is unclear, especially when cervical radiculopathy is possible.

Initial treatment includes activity modification and wrist splinting. Methylprednisolone injection or short-term oral glucocorticoids may also provide benefit as second-line therapy. Surgical treatment is necessary for patients who do not respond to conservative therapy or who have evidence of significant neurologic dysfunction.

Other Causes

Acute wrist or hand pain associated with trauma suggests fracture or dislocation and requires plain radiography for evaluation. Although multiple injuries are possible, special consideration for hamate and scaphoid fractures is necessary. Hamate hook fractures can occur from a fall onto an outstretched hand or activities with repetitive impact at the palm base (baseball hitting). Plain radiographs usually reveal the fracture. Scaphoid fractures are also commonly associated with falling onto an extended hand and are characterized by pain and tenderness in the anatomic snuffbox. Initial radiographs are normal in up to 20% of patients. If clinical suspicion is high and radiographs are normal, thumb splinting and repeat radiography in 1 to 2 weeks or immediate advanced imaging (MRI or CT) are recommended.

Wrist or hand pain lasting more than 2 weeks also has a wide differential diagnosis. De Quervain tendinopathy results from noninflammatory thickening of the thumb tendons. Pain occurs at the thumb base, radiates to the distal radius, and is elicited with making a fist over the thumb and ulnar deviation of the wrist (Finkelstein test). Initial management includes rest, NSAIDs, and splinting. When conservative measures fail, glucocorticoid injections provide symptomatic relief. Surgery may benefit patients with symptoms that do not respond to glucocorticoid injections.

Ganglion cysts are caused by herniated synovial tissue surrounding tendon sheaths or joints; they are often palpable on the ventral aspect of the wrist. Asymptomatic cysts require no treatment. Ganglion cysts causing pain may be treated with aspiration. The benefit of glucocorticoid or hyaluronidase injections is questionable; they are not indicated given the potential for complications. If cysts recur after aspiration, surgical resection is effective.

Ulnar neuropathy from ulnar nerve entrapment at the wrist presents with wrist pain and decreased hand strength and sensation. This condition can result from prolonged ulnar nerve compression in the Guyton canal, such as may occur with bicycling.

Osteoarthritis and inflammatory arthritis may affect the interphalangeal and carpometacarpal joints and cause hand and wrist pain (see MKSAP 18 Rheumatology).

KEY POINT

- Initial treatment of carpal tunnel syndrome includes activity modification, wrist splinting, and methylprednisolone injection or short-term oral glucocorticoid therapy if needed; surgical treatment is necessary for patients in whom conservative therapy fails or who have significant neurologic dysfunction. HVC

Lower Extremity Disorders

Hip Pain

Diagnosis and Evaluation

Evaluation of hip pain should be guided by location of the pain. Anterior hip and groin pain is caused by both intra- and extra-articular factors. Lateral hip pain is most commonly due to greater trochanteric pain syndrome (GTPS; formerly known as trochanteric bursitis) or meralgia paresthetica. Posterior hip pain is caused by sacroiliac joint dysfunction, lumbar radiculopathy, or vascular claudication.

Anterior hip pain that starts insidiously and worsens with standing and activity in older patients suggests osteoarthritis. The same pain characteristics in a younger person raise concern for a labral tear, especially when accompanied by painful clicking or catching. Gradual onset of anterior hip pain can also occur with avascular necrosis (or osteonecrosis), which should be considered in the presence of alcohol abuse, glucocorticoid use, systemic lupus erythematosus, or sickle cell anemia. Acute-onset, anteriorly located hip pain that interferes with weight bearing and is accompanied by fevers raises suspicion for infectious arthritis, whereas acute pain after a fall suggests fracture.

Lateral hip pain that worsens with lying on the affected side suggests GTPS; this pain may also radiate to the buttock or knee. Meralgia paresthetica is characterized by distal anterolateral thigh paresthesias associated with tight-fitting clothes and obesity.

Posterior or buttock pain associated with radiation down the leg suggests lumbar radiculopathy, whereas concomitant exertional leg pain or peripheral vascular disease suggests vascular claudication. Posterior pain without other features may be secondary to sacroiliac joint dysfunction.

Examination of patients with hip pain includes evaluation of the hip, abdomen, and back; neurologic and vascular assessments of the legs; and gait assessment. Pain with both passive and active hip movement suggests an intra-articular cause. The FABER (Flexion, ABduction, and External Rotation) test may cause posterior hip pain in the presence of sacroiliac joint dysfunction, groin pain with an intra-articular cause, and lateral hip pain with GTPS (**Figure 11**). The

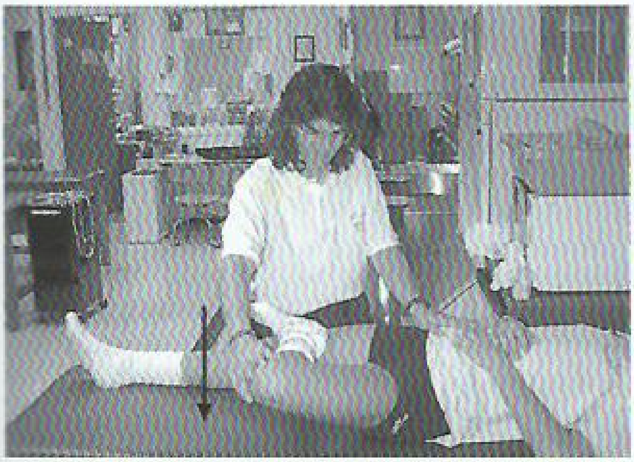

FIGURE 11. The FABER (Flexion, ABduction, and External Rotation) test. With the patient supine, the leg on the tested side is placed in the "figure 4" position (the knee of the tested side is flexed 90 degrees, and the lateral malleolus is placed on top of the opposite leg). The examiner then applies a posteriorly directed force with one hand while using the other hand to stabilize the patient's other hip. A positive test result occurs if groin pain or buttock pain is produced. Buttock pain suggests sacroiliac joint dysfunction, and groin pain suggests an intra-articular cause of pain.

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most common examination finding in GTPS is tenderness to palpation of the greater trochanter. A normal hip examination in a patient with groin pain suggests an extra-articular cause, such as an inguinal hernia. Pain reproduction on straight leg raise test (see Figure 8) supports lumbar radiculopathy.

Plain radiography (anteroposterior pelvic view and frog-leg lateral view) should be performed if intra-articular pathology, fracture, or dislocation is suspected. In patients with persistent anterior pain and normal plain radiographs, MRI of the hip can be performed; however, if suspicion is high for a labral tear, MR arthrography should be performed. Hip aspiration should be performed if infectious arthritis is suspected.

Treatment

Initial management of labral tears includes muscle strengthening and activity modification, with arthroscopic surgery reserved for those in whom conservative measures fail. Patients with advanced avascular necrosis often require total hip arthroplasty.

Initial GTPS management includes activity modification and analgesia with acetaminophen or NSAIDs. Glucocorticoid injection can be considered for persistently symptomatic GTPS, with surgery limited to recalcitrant cases. Primary treatment of meralgia paresthetica consists of reassurance, avoiding tight-fitting clothes, and weight loss. First-line therapy for sacroiliac joint dysfunction is physical therapy, with limited evidence existing for local glucocorticoid injection.

Management of osteoarthritis is discussed in MKSAP 18 Rheumatology.

KEY POINTS

- The FABER (Flexion, ABduction, and External Rotation) test may cause posterior hip pain in the presence of sacroiliac joint dysfunction, groin pain from an intra-articular cause, and lateral hip pain from greater trochanteric pain syndrome.
- Plain hip radiography (anteroposterior pelvic view and frog-leg lateral view) should be performed if an intra-articular pathology, fracture, or dislocation is suspected. **HVC**

Knee Pain

Diagnosis and Evaluation

The history obtained from patients with knee pain should focus on pain characteristics as well as history of knee injury or surgery, osteoarthritis, gout, and acute calcium pyrophosphate crystal arthritis (pseudogout).

Knee examination, performed with both knees fully exposed, includes inspection, palpation, range of motion testing, and special maneuvers (**Table 48**).

Plain radiography should be performed if fracture, bony pathology, or osteoarthritis is suspected. MRI can be performed if there is concern for meniscal or ligamentous injury and surgical therapy is being considered. Joint aspiration should be performed for suspicion of inflammatory or infectious arthritis.

Knee osteoarthritis is discussed in MKSAP 18 Rheumatology.

Ligament and Meniscal Tears

Acute, traumatic onset of knee pain, especially when associated with swelling, should raise concern for ligamentous and/or meniscal tears. Anterior cruciate ligament (ACL) tears usually involve noncontact twisting injuries. Patients may report a popping sound and frequently cannot immediately bear weight. Large effusions due to hemarthrosis frequently develop within 2 hours and may make initial examination challenging. The anterior drawer and Lachman tests frequently demonstrate increased ligamentous laxity, although the Lachman test may be most useful in the acute setting (see Table 48). Plain radiography should be obtained to evaluate for possible accompanying tibial avulsion fractures. ACL tears usually require surgical reconstruction, especially in active patients or those with an unstable knee. A nonoperative approach may be appropriate in older and less active patients. Medial collateral ligament (MCL) tears typically involve a lateral blow to the knee causing valgus stress, whereas posterior collateral ligament (PCL) tears involve a posteriorly directed force applied to the proximal anterior tibia with the knee flexed. Increased MCL laxity suggesting a tear may be detected by applying a medially directed force with the knee flexed at 30 degrees (valgus stress test), whereas increased PCL laxity may be detected by applying a posteriorly directed force to the proximal tibia with the knee flexed at 90 degrees. Most MCL and PCL tears can be managed conservatively.

TABLE 48. Knee Examination Maneuvers

Maneuver	Purpose	Description	Likelihood Ratios[a]
Anterior drawer	ACL integrity	Patient is supine with hip flexed to 45° and knee flexed to 90°. Examiner sits on dorsum of foot and places hands on proximal calf and then pulls anteriorly while assessing movement of tibia relative to femur. Positive result: Increased laxity with lack of firm end point (suggests ACL tear)	Positive likelihood ratio: 3.8[a] Negative likelihood ratio: 0.30[a]
Lachman	ACL integrity	Patient is supine with leg in slight external rotation and knee flexed 20° to 30° at examiner's side. Examiner stabilizes femur with one hand and grasps proximal calf with other. Calf is pulled forward while assessing movement of tibia relative to femur. Positive result: Increased laxity with lack of firm end point (suggests ACL tear)	Positive likelihood ratio: 42.0[b] Negative likelihood ratio: 0.1[b]
Posterior drawer	PCL integrity	Patient is supine with hip flexed to 45° and knee flexed to 90°. Examiner sits on dorsum of foot and places hands on proximal calf and then pushes posteriorly while assessing movement of tibia relative to femur. Positive result: Increased laxity with lack of firm end point (suggests PCL tear)	Positive likelihood ratio: 50.11[c] Negative likelihood ratio: 0.11[c]
Valgus stress	MCL integrity	Patient is supine with knee flexed to 30° and leg slightly abducted. Examiner places one hand on lateral knee and other hand on medial distal tibia and applies valgus force. Positive result: Increased laxity and pain (suggests MCL tear)	Positive likelihood ratio: 7.7 Negative likelihood ratio: 0.2
Varus stress	LCL integrity	Patient is supine with knee flexed to 30° and leg slightly abducted. Examiner places one hand on medial knee and other hand on lateral distal tibia and applies varus force. Positive result: Increased laxity and pain (suggests LCL tear)	Positive likelihood ratio: 16.2
Thessaly	Meniscal integrity	Examiner holds patient's outstretched hands while patient stands on one leg with knee flexed to 5° and with other knee flexed to 90° with foot off of floor. Patient rotates body internally and externally three times. Repeat with knee flexed to 20°. Always perform on uninvolved knee first. Positive result: Medial or lateral joint line pain (suggests meniscal tear)	Positive likelihood ratio: 1.37[d] Negative likelihood ratio: 0.68[d]
Medial-lateral grind	Meniscal integrity	With patient supine, examiner places calf in one hand and thumb and index finger of opposite hand over joint line and applies varus and valgus stress to tibia during extension and flexion. Positive result: Grinding sensation palpable over joint line (suggests meniscal injury)	Positive likelihood ratio: 4.8[b] Negative likelihood ratio: 0.4[b]
McMurray	Meniscal integrity	With patient supine, the examiner fully flexes the knee and rotates the tibia externally. The knee is then extended with the hand over the medial joint line. The maneuver is then repeated with the tibia internally rotated and the hand over the lateral joint line. Positive result: Snapping is detected over the joint line with extension on the knee	Positive likelihood ratio: 1.3[b] Negative likelihood ratio: 0.8[b]
Noble	Iliotibial band integrity	With patient supine, examiner repeatedly flexes and extends knee with examiner's thumb placed on lateral femoral epicondyle. Positive result: Reproduces patient's pain (suggests iliotibial band syndrome)	

ACL = anterior cruciate ligament; LCL = lateral collateral ligament; MCL = medial collateral ligament; PCL = posterior cruciate ligament.

[a]Data used to derive these values are of limited quality.

[b]Data from Solomon DH, Simel DL, Bates DW, Katz JN, Schaffer JL. The rational clinical examination. Does this patient have a torn meniscus or ligament of the knee? Value of the physical examination. JAMA. 2001;286:1610-20. [PMID: 11585485]

[c]Data from Rubinstein RA Jr, Shelbourne KD, McCarroll JR, VanMeter CD, Rettig AC. The accuracy of the clinical examination in the setting of posterior cruciate ligament injuries. Am J Sports Med. 1994;22:550-7. [PMID: 7943523]

[d]Data from Goossens P, Keijsers E, van Geenen RJ, Zijta A, van den Broek M, Verhagen AP, et al. Validity of the Thessaly test in evaluating meniscal tears compared with arthroscopy: a diagnostic accuracy study. J Orthop Sports Phys Ther. 2015;45:18-24, B1. [PMID: 25420009] doi:10.2519/jospt.2015.5215

Meniscal tears usually result from an acute twisting knee injury or can develop more insidiously as a result of chronic degeneration. Symptoms include pain, locking, catching, and grinding. Patients with acute meniscal tears are usually able to immediately bear weight. On examination, effusions, if present, are generally small to moderate in size. Results of specialized tests, such as the medial-lateral grind and Thessaly tests, are frequently positive (see Table 48). Initial management of both acute and chronic meniscal tears is conservative and consists of rest, ice, and strengthening the quadriceps and hamstring muscles. Surgery is reserved for patients with persistent (>4 weeks) mechanical symptoms.

Patellofemoral Pain Syndrome

Patellofemoral pain syndrome is caused by disordered patellar tracking with knee movement. It is characterized by anterior knee pain and/or stiffness with prolonged sitting, climbing, or descending stairs, and with running or squatting. On examination, applying pressure to the patella may reproduce pain. Patellar mobility can be assessed by medially and laterally displacing the patella, and abrupt patellar deviation may be noted during squatting and standing, although the utility of these findings is unclear.

Treatment is focused on identifying the underlying cause; activity modification, such as relative rest; cryotherapy (ice or cold water immersion); and physical therapy. NSAIDs, acetaminophen, and patellar taping and bracing are frequently used, although evidence for the effectiveness of these measures is limited.

KEY POINTS

HVC
- In patients with knee pain, plain radiography should be obtained if fracture, bony pathology, or osteoarthritis is suspected.
- Anterior cruciate ligament tears often require surgical reconstruction, whereas most medial collateral ligament and posterior collateral ligament tears can be managed conservatively.
- Patellofemoral pain syndrome is characterized by anterior knee pain and/or stiffness with prolonged sitting, climbing, or descending stairs, and with running or squatting; treatment may include activity modification, cryotherapy, and physical therapy.

Bursitis

Prepatellar bursitis presents as acute or chronic swelling anterior to the patella. Acute cases are often associated with tenderness, warmth, and erythema. Most cases of acute prepatellar bursitis are caused by infection with skin bacteria and less commonly by trauma and gout. Chronic prepatellar bursitis is usually caused by trauma, although gout and infection are possible. All patients with prepatellar bursitis regardless of duration should undergo fluid aspiration and analysis. Septic bursitis is managed with knee immobilization, systemic antibiotics, and re-aspiration if needed. Gouty bursitis is managed with appropriate gout therapy (see MKSAP 18 Rheumatology). Traumatic bursitis is managed by activity modification (avoidance of kneeling) and NSAIDs.

Pes anserine bursitis (pes anserine pain syndrome) classically presents with localized pain and swelling of the region overlying the proximal medial tibia several centimeters distal to the knee (**Figure 12**). It commonly occurs in athletes (especially runners) and in patients with knee osteoarthritis. First-line therapy includes quadriceps strengthening, local cryotherapy, activity modification, and NSAIDs.

Iliotibial Band Syndrome

Patients with iliotibial band syndrome (ITBS) report diffuse, poorly localized lateral knee and distal thigh pain. Pain is initially present at the end of exercise involving knee flexion and extension but may progress to occur earlier in exercise or with rest. Running outdoors or downhill may worsen symptoms. On examination, there is often tenderness approximately 2 to 3 cm proximal to the lateral femoral condyle. Patients also frequently have a positive result on a Noble test and weakness with hip abduction (see Table 48). Imaging is not usually required.

Initial treatment of ITBS centers on abstinence from inciting activity and use of ice, followed by gradual return to activity, stretching, strengthening, and local massage. NSAIDs appear effective when used as part of a multimodal approach. Local glucocorticoid injections may provide at least short-term relief.

Popliteal Cysts

A popliteal (Baker) cyst is a benign swelling of the synovial bursa behind the knee joint; synovial fluid fills the cyst. Popliteal cysts most commonly develop in the setting of knee trauma, osteoarthritis, or inflammatory arthritis. They are frequently asymptomatic but can present with posterior knee pain and swelling.

FIGURE 12. Location of the anserine bursa and pain associated with pes anserine bursitis.

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Ruptured cysts may mimic deep venous thromboses (pseudothrombophlebitis) and may be associated with ecchymosis from the popliteal fossa to the ankle. The "crescent sign" may be present, recognized as an ecchymotic area below the medial malleolus. In rare instances, cysts may cause compression of adjacent structures, leading to compression syndrome, posterior tibial nerve entrapment, or popliteal artery occlusion. In patients with asymptomatic popliteal cysts, no treatment is necessary. Symptomatic patients often experience relief with joint aspiration and intra-articular glucocorticoid injection. Pseudothrombophlebitis can be treated with rest, elevation, and NSAIDs. Surgical excision is reserved for severely symptomatic and functionally limited patients in whom conservative measures fail or who develop serious complications.

KEY POINTS

- All patients with prepatellar bursitis regardless of duration should undergo fluid aspiration and analysis.
- Iliotibial band syndrome is characterized by pain at the end of exercise involving knee flexion and extension but may progress to occur earlier in exercise or with rest; treatment is typically nonsurgical.
- HVC In patients with asymptomatic popliteal (Baker) cysts, no treatment is necessary; joint aspiration and intra-articular glucocorticoid injection may provide relief for those with symptoms.

Ankle and Foot Pain

Ankle Sprains

Acute ankle sprains are usually caused by excessive ankle inversion; ankle eversion injuries are rare. Common examination findings include overlying ecchymosis and swelling with tenderness of involved ankle ligaments. Weight-bearing ability and bony tenderness are components of Ottawa ankle rules, which help to determine the necessity of obtaining plain radiography to exclude fracture (**Figure 13**). Treatment includes intermittent cryotherapy and a lace-up support or air stirrup brace combined with elastic compression wrapping. Early mobilization should be encouraged with weight bearing as tolerated. Acetaminophen and oral or topical NSAIDs can be used for pain control. Patients with persistent ligamentous laxity 4 to 6 weeks after injury should be referred for proprioceptive training and strengthening therapy.

High ankle sprains (distal tibiofibular syndesmosis ligament injuries) occur when an externally rotated force is applied to a dorsiflexed ankle. Pain may be elicited by squeezing the leg at mid-calf (squeeze test) and by dorsiflexing and externally rotating the foot with the knee flexed (dorsiflexion-external rotation test). Treatment is similar to other ankle sprains, although recovery is usually delayed.

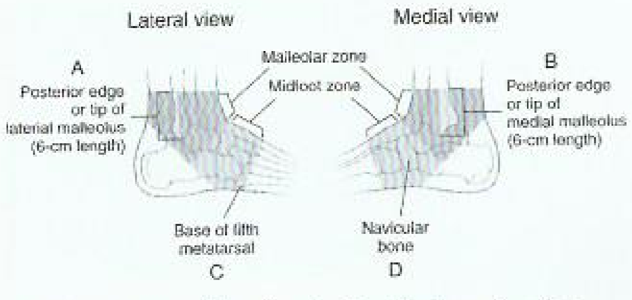

FIGURE 13. Ottawa ankle and foot rules. An ankle radiographic series is indicated if a patient has pain in the malleolar zone and any of the following findings: bone tenderness at *A*, bone tenderness at *B*, or inability to bear weight immediately and in the emergency department (or physician's office). A foot radiographic series is indicated if a patient has pain in the midfoot zone and any of the following findings: bone tenderness at *C*, bone tenderness at *D*, or inability to bear weight immediately and in the emergency department (or physician's office).

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Hindfoot Pain

Achilles tendinopathy typically develops in persons who initiate or abruptly increase activity. Patients report activity-related posterior heel pain and stiffness that improves with rest. On examination, there is usually tenderness of the Achilles tendon approximately 2 to 6 cm above the calcaneal insertion. Treatment includes activity modification, eccentric exercises (muscle lengthening in response to external resistance), and use of appropriate footwear. NSAIDs can be used for pain control.

Achilles tendon rupture commonly occurs during strenuous activities, although it may occur spontaneously in the elderly or with fluoroquinolone use. Patients usually have heel pain and may report hearing a "pop." On examination, a tendon defect may be palpable; a lack of plantar flexion with calf squeezing (Thompson test) suggests complete rupture (sensitivity, 93%; specificity, 96%) (**Figure 14**). Treatment is controversial and consists of surgery with immobilization or immobilization alone.

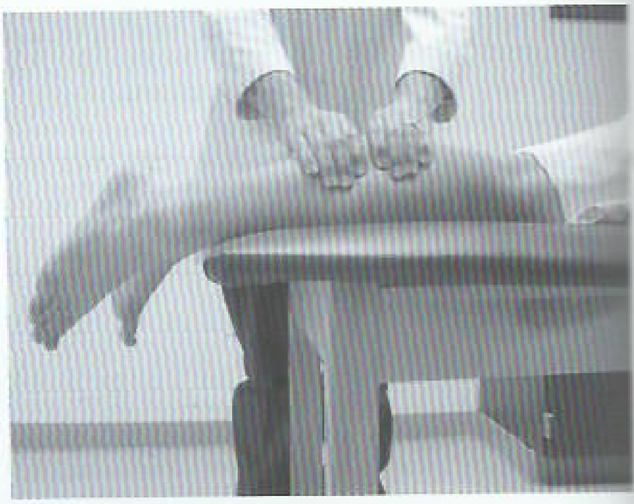

FIGURE 14. Thompson test. The patient is positioned in the prone position. The examiner squeezes mid-calf and observes for plantar flexion of the foot. When the patient has an intact Achilles tendon, plantar flexion will occur. When there is a complete Achilles tendon rupture, no plantar flexion is observed.

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Plantar fasciitis classically causes sharp, medial-inferior heel pain with the first morning steps and after prolonged rest. Pain usually improves with further walking but may persist in severe cases. On examination, the medial calcaneal tubercle is frequently tender. Passive toe dorsiflexion with standing (weight-bearing windlass test) may reproduce pain (sensitivity, 32%; specificity, 100%). Treatment includes weight loss, rest, calf/heel stretching, and arch supports (if pes planus is present). Because the underlying pathology is thought to be degenerative, use of NSAIDs is primarily for pain control. Patients should be educated that eventual resolution is expected but may take months. For recalcitrant cases, ultrasonography, extracorporeal shockwave therapy, night splints, and glucocorticoid injections can be considered. Surgery is reserved for patients who do not respond to these measures.

Heel pad syndrome causes inferior heel pain when walking barefoot and on hard surfaces. On examination, palpation may reproduce pain. Treatment consists of heel cushioning, rest, ice, and NSAIDs.

Midfoot Pain

Tarsal tunnel syndrome (posterior tibial nerve compression as it passes through the tarsal tunnel) causes posteromedial heel paresthesias that radiate distally into the plantar foot surface. On examination, pain may be reproduced with nerve tapping (Tinel sign) and with provocative measures that compress the nerve (plantar flexion-inversion and dorsiflexion-eversion tests). First-line treatment consists of activity modification, orthotics, NSAIDs, and neuromodulators.

Forefoot Pain

Morton neuromas (interdigital nerve injury) cause pain between the metatarsal heads and the sensation of walking on a pebble. First-line therapy consists of footwear modification and padding. Glucocorticoid injections may provide temporary relief. Interdigital nerve resection is reserved for those who do not respond to conservative measures.

Hammertoe deformities (proximal interphalangeal joint flexion deformity with distal interphalangeal joint extension and extended or neutral position of metatarsophalangeal [MTP] joint) occur with constricting footwear and increasing age. Treatment includes footwear modification, padding, and possibly surgery.

Hallux or bunion deformity (lateral deviation of great toe with medial bony deformity) can lead to pain, first MTP joint osteoarthritis, and overlying bursitis. Treatment includes orthotic devices, NSAIDs, and possibly surgery.

KEY POINTS

- Acute ankle sprains are usually caused by excessive ankle inversion; treatment includes intermittent cryotherapy, a lace-up support or air stirrup brace combined with elastic compression wrapping, early mobilization with weight bearing as tolerated, and acetaminophen and oral or topical NSAIDs.

(Continued)

KEY POINTS *(continued)*

- Achilles tendon rupture commonly occurs during strenuous activities, although it may occur spontaneously in the elderly or with fluoroquinolone use.
- Plantar fasciitis classically causes sharp, medial-inferior heel pain with the first morning steps and after prolonged rest; the medial calcaneal tubercle is frequently tender.
- Morton neuromas (interdigital nerve injury) cause pain between the metatarsal heads and the sensation of walking on pebbles.

Dyslipidemia

Evaluation of Lipid Levels

The U.S. Preventive Services Task Force (USPSTF) recommends universal lipid screening in adults aged 40 to 75 years to calculate risk for atherosclerotic cardiovascular disease (ASCVD) using the American College of Cardiology (ACC)/American Heart Association (AHA) Pooled Cohort Equations (see MKSAP 18 Cardiovascular Medicine). Lipid measurement may also be indicated to investigate for familial hypercholesterolemia; to determine therapy adherence and effectiveness; and to evaluate for complications of dyslipidemia, such as pancreatitis.

LDL Cholesterol

The association between high LDL cholesterol levels and increased risk for ASCVD is widely accepted. Historically, cholesterol treatment targeted specific LDL cholesterol goals, as LDL cholesterol is the most atherogenic lipoprotein. The 2013 ACC/AHA cholesterol treatment guideline recommends fixed statin dosing to reduce ASCVD risk and consideration of nonstatin drugs in patients who do not achieve adequate lipid lowering. Therefore, based on this guideline, the primary utility of LDL cholesterol measurement is to identify patients who will benefit from treatment with statin therapy and to assess response to therapy.

In patients with elevated LDL cholesterol levels, secondary causes, including hypothyroidism, poorly controlled diabetes mellitus, nephrotic syndrome, and medications (such as glucocorticoids, diuretics, and amiodarone), should be considered. Familial hypercholesterolemia should be considered in patients with an LDL cholesterol level of 190 mg/dL (4.92 mmol/L) or higher.

Triglycerides

Elevated triglyceride levels (>150 mg/dL [1.69 mmol/L]) are independently associated with increased ASCVD risk; however, it is uncertain whether reducing triglyceride levels decreases risk. Causes of hypertriglyceridemia include diabetes; excessive alcohol intake; hypothyroidism; and medications such as glucocorticoids, protease inhibitors, and

estrogens. Lifestyle factors, including obesity and concentrated sugar intake, are also implicated causes. Patients with triglyceride levels of 500 mg/dL (5.65 mmol/L) or more without an identifiable cause should be evaluated for familial hypertriglyceridemia.

Acute pancreatitis can be induced by triglyceride levels in excess of 1000 mg/dL (11.3 mmol/L), and triglyceride levels should be measured in selected patients with pancreatitis, especially in cases of pancreatitis without a clear cause (such as alcohol use or biliary disease).

HDL Cholesterol

HDL cholesterol is a protective factor against the development of ASCVD and is an important component in ASCVD risk assessment. However, a causative link between low HDL cholesterol levels and ASCVD has not been established, and pharmacologic treatment to raise HDL cholesterol levels is not recommended.

KEY POINTS

- The U.S. Preventive Services Task Force recommends universal lipid screening in adults aged 40 to 75 years to calculate risk for atherosclerotic cardiovascular disease.
- HVC The primary utility of LDL cholesterol measurement is to identify patients who will benefit from treatment with statin therapy and to assess response to therapy.
- Secondary causes of LDL cholesterol elevation include hypothyroidism, poorly controlled diabetes mellitus, nephrotic syndrome, and medication use (such as glucocorticoids, diuretics, and amiodarone).

Management of Dyslipidemia

Following assessment of ASCVD risk, treatment with therapeutic lifestyle changes and statin therapy may be indicated.

Therapeutic Lifestyle Changes

All patients at increased cardiovascular risk should be counseled regarding therapeutic lifestyle changes, including dietary modification, regular physical activity, weight loss, and smoking cessation.

Patients should be encouraged to adhere to a dietary pattern that focuses on consumption of fruits, vegetables, fiber, and monounsaturated fats and minimizes intake of saturated and *trans* fats, simple carbohydrates, and red meats. Replacing saturated fats with polyunsaturated fats has been shown to reduce LDL cholesterol levels and cardiovascular mortality. Examples of heart-healthy diets include the DASH (Dietary Approaches to Stop Hypertension) and Mediterranean diets. The DASH diet provides a suggested number of servings for each food group, with few servings of saturated fats, sweets, and red meat and a higher number of servings of grains, fruits, and vegetables; adherence to the DASH diet has been shown to decrease adverse cardiovascular events. The Mediterranean diet comprises high amounts of unsaturated fats, with ample intake of fruits, vegetables, fiber, seeds, nuts, and fatty fish and low consumption of red meat and dairy products. The ACC/AHA additionally recommend reducing the percentage of calories from saturated fat (<7% of calories from saturated fat; <6% of calories from saturated fat in patients at high cardiovascular risk) and the percentage of calories from *trans* fat. To facilitate these changes, clinicians should provide patients with educational resources and, when appropriate, refer them to a dietician.

Patients should also engage in 40 minutes of moderate to vigorous activity 3 to 4 days per week or 30 minutes on most days of the week. Small incremental changes to reduce sedentary behavior, such as increasing walking and time standing, are beneficial.

Drug Therapy

Statin therapy is the mainstay of pharmacotherapy for dyslipidemia. The ACC/AHA cholesterol treatment guideline defines four patient groups that benefit from statin therapy for primary or secondary prevention of ASCVD:

1. Patients aged 21 years and older with clinical ASCVD, defined as acute coronary syndrome, or a history of myocardial infarction, stable or unstable angina, coronary or other arterial revascularization, stroke/transient ischemic attack, or peripheral artery disease attributable to atherosclerosis (high-intensity statin therapy if aged ≤75 years; moderate-intensity statin therapy if aged >75 years)
2. Patients aged 21 years and older with an LDL cholesterol level of 190 mg/dL (4.92 mmol/L) or higher (high-intensity statin therapy)
3. Patients aged 40 to 75 years with diabetes and an LDL cholesterol level of 70 mg/dL to 189 mg/dL (1.81-4.90 mmol/L) (high-intensity statin therapy if 10-year ASCVD risk ≥7.5%; moderate-intensity statin therapy if 10-year ASCVD risk <7.5%)
4. Patients aged 40 to 75 years with no ASCVD or diabetes and a 10-year ASCVD risk of 7.5% or higher (moderate- or high-intensity statin therapy based on patient preferences, adverse effects, and expected ASCVD risk reduction)

These recommendations are summarized in **Figure 15**. Statin dosages for high- and moderate-intensity therapy are presented in **Table 49**.

A lipid panel should be obtained 4 to 12 weeks after initiation of therapy to determine treatment adherence and response. According to the 2013 ACC/AHA guideline, high-intensity statin therapy should decrease LDL cholesterol levels by at least 50% from baseline levels, whereas moderate-intensity statin therapy should decrease LDL cholesterol levels by 30% to 50%. All patients who do not achieve adequate reduction in LDL cholesterol levels should be assessed for medication adherence and should intensify lifestyle modifications. Additional medical therapy should be considered if the target effect is not realized. Once therapy goals have been achieved,

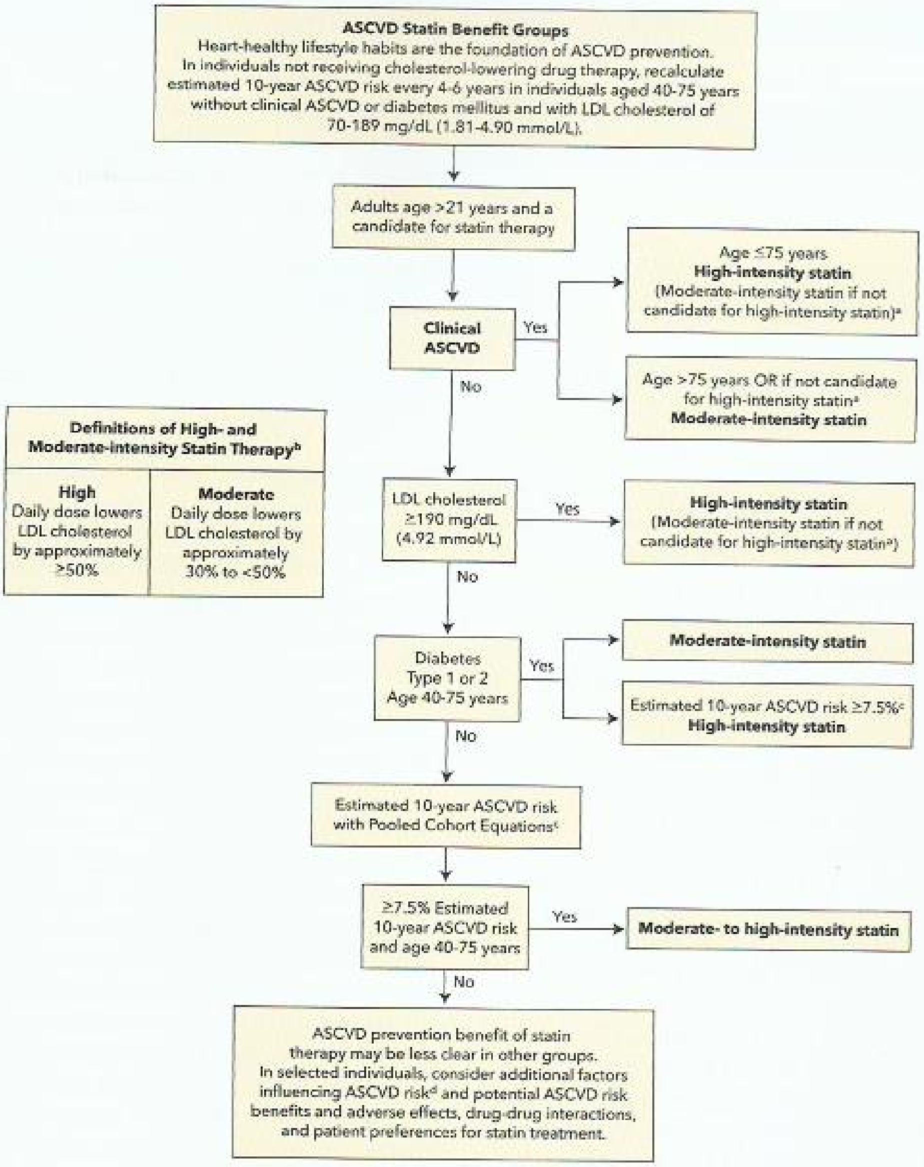

FIGURE 15. Major recommendations for statin therapy for ASCVD prevention. This flow diagram is intended to serve as an easy reference guide summarizing recommendations for ASCVD risk assessment and treatment. Assessment of the potential for benefit and risk from statin therapy for ASCVD prevention provides the framework for clinical decision making incorporating patient preferences. ASCVD = atherosclerotic cardiovascular disease.

[a]Moderate-intensity statin therapy should be used in individuals in whom high-intensity statin therapy would otherwise be recommended when high-intensity statin therapy is contraindicated or when characteristics predisposing them to statin-associated adverse effects are present.

Characteristics predisposing individuals to statin adverse effects include, but are not limited to:

- Multiple or serious comorbidities, including impaired kidney or liver function
- History of previous statin intolerance or muscle disorders
- Unexplained alanine aminotransferase elevations >3 times upper limit of normal
- Patient characteristics or concomitant use of drugs affecting statin metabolism
- >75 years of age

Additional characteristics that may modify the decision to use higher statin intensities may include, but are not limited to:

- History of hemorrhagic stroke
- Asian ancestry

[b]Percent reduction in LDL cholesterol can be used as an indication of response and adherence to therapy but is not in itself a treatment goal.

[c]*The Pooled Cohort Equations can be used to estimate 10-year ASCVD risk in individuals with and without diabetes mellitus. A downloadable* spreadsheet enabling estimation of 10-year and lifetime risk for ASCVD and a web-based calculator are available at http://my.americanheart.org/cvriskcalculator.

[d]Primary LDL cholesterol level ≥160 mg/dL (4.14 mmol/L) or other evidence of genetic hyperlipidemias; family history of premature ASCVD with onset <55 years of age in a first-degree male relative or <65 years of age in a first-degree female relative; high-sensitivity C-reactive protein ≥2 mg/L; coronary artery calcium score ≥300 Agatston units or ≥75th percentile for age, sex, and ethnicity; ankle-brachial index <0.90; or elevated lifetime risk of ASCVD.

Reproduced with permission from Stone NJ, Robinson JG, Lichtenstein AH, et al; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2013; Epub 2013 Nov 12. Copyright 2013, American Heart Association, Inc.

TABLE 49. High- and Moderate-Intensity Statin Therapy

Therapy Intensity	Drug and Dosage
High intensity	Atorvastatin, 40-80 mg/d
	Rosuvastatin, 20-40 mg/d
Moderate intensity	Atorvastatin, 10-20 mg/d
	Rosuvastatin, 5-10 mg/d
	Simvastatin, 20-40 mg/d
	Pravastatin, 40-80 mg/d
	Lovastatin, 40 mg/d
	Fluvastatin, 40 mg twice daily

lipid levels should be measured every 3 to 12 months as indicated.

The USPSTF recommendations for primary prevention statin therapy differ from those of the ACC/AHA in considering risk factors other than diabetes and the suggested intensity of statin therapy. In asymptomatic adults aged 40 to 75 years without ASCVD who have at least one ASCVD risk factor (dyslipidemia, diabetes, hypertension, or smoking), the USPSTF recommends low- to moderate-intensity statin therapy in those with a calculated 10-year ASCVD event risk of 10% or higher (grade B recommendation) and selective consideration of low- to moderate-intensity statin therapy in those with a calculated 10-year ASCVD event risk of 7.5% to 10% (grade C recommendation).

In contrast to the ACC/AHA guideline and USPSTF recommendations, the 2017 American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE) guidelines for management of dyslipidemia and prevention of cardiovascular disease recommend treating LDL cholesterol, non-HDL cholesterol, and apolipoprotein B levels to specific targets. On the basis of risk factors and calculated 10-year risk of ASCVD using the Framingham, MESA, Reynolds, or United Kingdom Prospective Diabetes Study risk scores, the AACE/ACE guideline classifies patients as low, moderate, high, very high, or extreme risk. Treatment goals are individualized according to the patient's level of risk, with LDL cholesterol targets of less than 130 mg/dL (3.37 mmol/L) for low-risk patients, less than 100 mg/dL (2.59 mmol/L) for moderate- and high-risk patients, less than 70 mg/dL (1.81 mmol/L) for very-high-risk patients, and less than 55 mg/dL (1.42 mmol/L) for extreme-risk patients. The category of extreme risk represents a new classification for dyslipidemia guidelines and includes patients with progressive ASCVD that persists after achieving an LDL cholesterol level below 70 mg/dL (1.81 mmol/L); patients with established ASCVD with concomitant diabetes mellitus, stage 3 or 4 chronic kidney disease, or hereditary heterozygous familial hypercholesterolemia; and patients with a history of premature ASCVD. The complete guideline, which provides 87 recommendations, is available at https://www.aace.com/files/lipid-guidelines.pdf.

Statins may infrequently cause liver dysfunction or myopathy. Liver chemistry tests should be obtained at baseline, but neither liver chemistry tests nor muscle enzyme studies should be routinely performed in the absence of suggestive symptoms. Statins may also cause memory problems in some patients, but this effect is reversible; evidence suggests that statins do not cause dementia. In patients with statin intolerance, switching to another statin is reasonable, as a patient's response to different statins can vary. Other options include decreasing the statin intensity (decreasing the dosage and/or dosing frequency) and, less preferably, discontinuing statin therapy and initiating nonstatin drugs.

Combination and Nonstatin Drug Therapy

Nonstatin drugs should be considered alone or in combination with statins in patients who do not achieve adequate LDL cholesterol reduction with statin therapy, especially in high-risk patients (those with clinical ASCVD, baseline LDL cholesterol level >190 mg/dL [4.92 mmol/L], or diabetes). Before nonstatin drugs are initiated, patient preferences as well as anticipated ASCVD risk reduction and adverse effects should be discussed. The most commonly used nonstatin drugs and their characteristics are described in **Table 50**.

Ezetimibe and the proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors are the preferred nonstatin drugs for high-risk patients who do not achieve goal LDL cholesterol reduction. The PCSK9 inhibitors are a relatively new class of lipid-lowering drugs. These monoclonal antibodies bind to serine protease PCSK9, a liver enzyme that degrades hepatocyte LDL receptors. Treatment with PCSK9 inhibitors produces a 50% to 60% reduction in LDL cholesterol. Barriers to the use of PCSK9 inhibitors include high cost and subcutaneous administration. Additional nonstatin options include bile acid sequestrants, fibrates, and phytosterols. Because of a lack of efficacy and potential harms, niacin is no longer routinely recommended.

In 2017, the ACC published a focused update on nonstatin therapies for LDL cholesterol lowering. Ezetimibe is the preferred nonstatin agent in patients with or without diabetes who have an LDL cholesterol level between 70 mg/dL (1.81 mmol/L) and 189 mg/dL (4.90 mmol/L) and are taking maximally tolerated statin therapy for primary prevention. Likewise, ezetimibe is preferred in patients with stable clinical ASCVD without comorbid conditions who require additional LDL cholesterol lowering. Ezetimibe or a PCSK9 inhibitor may be used in high-risk patients taking maximally tolerated statin therapy, including patients with LDL cholesterol levels greater than 190 mg/dL (4.92 mmol/L) and patients with clinical ASCVD with comorbidities. Factors that favor ezetimibe for these high-risk patients include the need for less than 25% LDL cholesterol reduction, recent myocardial infarction (within the last 3 months), present and future cost savings, and preference for oral administration.

Management of Hypertriglyceridemia

Therapeutic lifestyle changes are the cornerstone of management of elevated triglyceride levels. Patients should be counseled to lose weight (if appropriate); exercise regularly;

TABLE 50. Characteristics of Nonstatin Drugs

Medication	LDL-Cholesterol Lowering	ASCVD Risk Reduction	Adverse Effects	Approximate Cost
PCSK9 inhibitors	↓↓↓↓	↓↓↓	Nasopharyngitis, injection-site reactions, possible cognitive effects	$$$$
Ezetimibe	↓↓	↓↓↓	Diarrhea, arthralgia, abdominal pain, myositis, elevated liver aminotransferase levels when combined with statins	$$-$$$
Bile acid sequestrants	↓↓	↓ (cholestyramine)	Constipation, bloating, nausea, elevated liver aminotransferase levels, interference with drug absorption Increase triglyceride levels only if baseline levels are elevated	$$
Fibrates	↓	Not well determined	Myositis (especially if combined with statins), nausea, abdominal pain	$$
Phytosterols	↓	Not well determined	Mild bloating, diarrhea or constipation	$-$$

ASCVD = atherosclerotic cardiovascular disease; PCSK9 = proprotein convertase subtilisin/kexin type 9.

and avoid consumption of saturated fats, *trans* fats, and concentrated sugars. Although *trans* fats have been eliminated from many commercially prepared foods, some foods (such as creamers, margarine, and baked goods) may still contain *trans* fats, also called partially hydrogenated oil. The use of medications that increase triglyceride levels, such as estrogens, β-blockers, and glucocorticoids, should be avoided if possible.

Omega-3 fatty acids, which are found in many types of fish, reduce triglyceride levels and should be incorporated into the diet. Fibrates are the most effective pharmacotherapy for hypertriglyceridemia, resulting in a 30% to 50% reduction in triglyceride levels; these agents are indicated in patients with triglyceride levels of 500 mg/dL (5.65 mmol/L) or higher. Niacin and prescription omega-3 fatty acid supplements also lower triglyceride levels; however, omega-3 fatty acid supplements do not reduce heart disease, stroke, or death. According to the 2013 ACC/AHA guideline, baseline liver aminotransferase, hemoglobin A_{1c} or fasting plasma glucose, and uric acid levels should be obtained before and during niacin treatment. Niacin therapy should not be used in patients receiving statin therapy who have achieved adequate LDL cholesterol reduction.

Management of Dyslipidemia in Special Populations

In patients aged 75 years and older, there is insufficient evidence to guide the use of statin therapy for primary prevention; however, the ACC/AHA guideline suggests that it is reasonable to engage these patients in a discussion of the potential for ASCVD risk-reduction benefits, adverse effects, and drug-drug interactions, and to consider patient preferences for treatment. For secondary prevention of ASCVD in patients aged 75 years and older, it is reasonable to continue statins in patients who are already tolerating therapy; moderate-intensity therapy is beneficial and preferable to high-intensity therapy in these patients.

Owing to insufficient evidence, the ACC/AHA make no recommendations on the initiation or discontinuation of statin therapy in patients with heart failure (New York Heart Association functional class II-IV symptoms) or patients undergoing hemodialysis.

KEY POINTS

- All patients with elevated LDL cholesterol levels should be counseled regarding therapeutic lifestyle changes, including dietary modification, regular physical activity, weight loss, and smoking cessation. **HVC**
- The American College of Cardiology and American Heart Association recommend initiating statin therapy for primary or secondary prevention of atherosclerotic cardiovascular disease (ASCVD) in (1) patients with clinical ASCVD; (2) patients with an LDL cholesterol level of 190 mg/dL (4.92 mmol/L) or higher; (3) patients aged 40 to 75 years with diabetes mellitus, an LDL cholesterol level of 70 to 189 mg/dL (1.81-4.90 mmol/L), and no clinical ASCVD; and (4) patients aged 40 to 75 years with no ASCVD or diabetes and a 10-year ASCVD risk of 7.5% or higher.
- A lipid panel should be obtained 4 to 12 weeks after statin therapy initiation to determine treatment adherence and response to therapy.
- In patients treated with statin therapy, liver chemistry tests and muscle enzyme studies should not be routinely obtained in the absence of symptoms of liver dysfunction or myopathy. **HVC**
- Nonstatin drugs, such as ezetimibe and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, should be considered alone or in combination with statins in high-risk patients who do not achieve adequate LDL cholesterol reduction with statin therapy.

Metabolic Syndrome

Epidemiology and Pathophysiology

Metabolic syndrome, also referred to as insulin resistance syndrome, comprises a constellation of risk factors for cardiovascular disease and type 2 diabetes. It is a common condition, occurring in 20% to 35% of U.S. adults.

Although there are several definitions for metabolic syndrome, the diagnostic criteria proposed by the National Cholesterol Education Program Adult Treatment Panel III (with minor modifications by the AHA/National Heart, Lung, and Blood Institute) are the most widely used (**Table 51**). The presence of a pathophysiologic link between the components of the metabolic syndrome is controversial; however, insulin resistance and adipocyte cytokines associated with metabolic syndrome appear to play a central role in inducing inflammatory changes that contribute to ASCVD.

TABLE 51. Diagnostic Criteria for the Metabolic Syndrome

Measure (Any Three of Five Constitute Diagnosis of Metabolic Syndrome)	Categorical Cutpoints
Elevated waist circumference[a,b]	≥102 cm [40 in] in men; ≥88 cm [35 in] in women
Elevated triglycerides	≥150 mg/dL (1.7 mmol/L)
	or
	On drug treatment for elevated triglycerides
Reduced HDL cholesterol	<40 mg/dL (1.03 mmol/L) in men; <50 mg/dL (1.30 mmol/L) in women
	or
	On drug treatment for reduced HDL cholesterol[c]
Elevated blood pressure	≥130 mm Hg systolic blood pressure
	or
	≥85 mm Hg diastolic blood pressure
	or
	On antihypertensive drug treatment in a patient with a history of hypertension
Elevated fasting glucose	≥100 mg/dL (5.6 mmol/L)
	or
	On drug treatment for elevated glucose

[a]To measure waist circumference, locate top of right iliac crest. Place a measuring tape in a horizontal plane around abdomen at level of iliac crest. Before reading tape measure, ensure that tape is snug but does not compress the skin and is parallel to floor. Measurement is made at the end of a normal expiration.

[b]Some U.S. adults of non-Asian origin (e.g., white, black, Hispanic) with marginally increased waist circumference (e.g., 94-101 cm [37-39 inches] in men and 80-87 cm [31-34 inches] in women) may have strong genetic contribution to insulin resistance and should benefit from changes in lifestyle habits, similar to men with categorical increases in waist circumference. Lower waist circumference cutpoint (e.g., ≥90 cm [35 inches] in men and ≥80 cm [31 inches] in women) appears to be appropriate for Asian Americans.

[c]Fibrates and nicotinic acid are the most commonly used drugs for elevated triglycerides and reduced HDL cholesterol. Patients taking one of these drugs are presumed to have high triglycerides and low HDL cholesterol.

Reproduced with permission from Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA at al. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute scientific statement. Circulation. 2005;112(17):2735. [PMID: 16157765]

Management

Treatment of metabolic syndrome focuses on addressing each of the component risk factors. Lifestyle modifications, particularly weight loss and exercise, are the most important treatment interventions. Routine pharmacotherapy is not recommended in patients who do not meet treatment criteria for the individual risk factors. Aspirin is indicated for patients with metabolic syndrome and a 10-year ASCVD risk of 10% or greater, assuming there is not increased bleeding risk. In some studies, metformin has been shown to prevent progression to diabetes; however, it is inferior to lifestyle modifications, and its role in treating metabolic syndrome has not been established.

Obesity

Definition and Epidemiology

Obesity, defined as a BMI of 30 or greater, is associated with increased risk for type 2 diabetes mellitus, hypertension, dyslipidemia, cardiovascular disease, stroke, obstructive sleep apnea, osteoarthritis, and some cancers; risks for these conditions increase with increasing BMI. Waist circumference of 102 cm (40 in) or greater in men and 88 cm (35 in) or greater in women is additionally associated with increased risk for diabetes mellitus, cardiovascular disease, and all-cause mortality (**Table 52**).

Prevalence of obesity and extreme obesity (BMI ≥40) among adults in the United States increased from 35.1% to 37.7% and 6.5% to 7.7%, respectively, between 2011-2012 and 2013-2014. Prevalence of obesity varies by gender, ethnicity, education, and age, with the highest prevalence among women, non-Hispanic black persons, those with less education, and those aged 40 to 59 years.

The costs associated with providing care to patients with severe obesity are high (more than $69 billion in 2013).

KEY POINTS

- The prevalence of obesity (BMI >30) and extreme obesity (BMI ≥40) is increasing.
- Waist circumference of 102 cm (40 in) inches or greater in men and 88 cm (35 in) or greater in women is associated with increased risk for diabetes mellitus, cardiovascular disease, and all-cause mortality.

Screening and Evaluation

The U.S. Preventive Services Task Force recommends screening adults for obesity by measuring height and weight and

TABLE 52. Classification of Overweight and Obesity by BMI

Category	BMI	Obesity Class	Disease Risk[a] Relative to Normal Weight and Waist Circumference: Men: ≤102 cm (40 in) Women: ≤88 cm (35 in)	Men: >102 cm (40 in) Women: >88 cm (35 in)
Underweight	<18.5		—	—
Normal	18.5-24.9		—	—
Overweight	25.0-29.9		Increased	High
Obesity	30.0-34.9	I	High	Very high
	35.0-39.9	II	Very high	Very high
Extreme obesity	≥40	III	Extremely high	Extremely high

[a]Disease risk for type 2 diabetes mellitus, hypertension, and cardiovascular disease. Increased waist circumference also can be a marker for increased risk, even in persons of normal weight.

Reproduced from National Heart, Lung, and Blood Institute. Aim for a healthy weight. https://www.nhlbi.nih.gov/health/educational/lose_wt/BMI/bmi_dis.htm. Accessed June 25, 2018.

calculating BMI. Online BMI calculators are available (https://www.nhlbi.nih.gov/guidelines/obesity/BMI/bmicalc.htm). Clinicians should ask patients with obesity about their weight history, previous weight loss attempts, diet and physical activity patterns, social and emotional factors, and family history of obesity. A thorough medication history is recommended to identify medications that may contribute to weight gain (**Table 53**). Physicians should inquire about symptoms of obesity-related conditions, such as heart disease, obstructive sleep apnea, osteoarthritis, and erectile dysfunction.

Physical examination should include measurements of height, weight, waist circumference, and blood pressure. Examining patients with obesity is sometimes challenging and adaptations may be necessary, such as using a scale with an adequate weight limit, using an appropriately sized blood pressure cuff (bladder encircles 80% of the arm), and repositioning patients to optimize hearing of heart sounds. Many patients with obesity are deconditioned, and allowing the patient to sit quietly for 5 minutes after walking from the waiting area to the examination room before measuring heart rate and blood pressure may improve the reliability of these measurements.

TABLE 53. Medications That Promote Weight Gain

α-Blockers
β-Blockers
Glucocorticoids
Progestins (especially depot injections)
Antidiabetic drugs (insulin, sulfonylureas [especially glyburide and glipizide], thiazolidinediones)
Anticonvulsant drugs (carbamazepine, gabapentin, valproic acid)
Antidepressant drugs (amitriptyline, imipramine, doxepin, paroxetine, mirtazapine)
Antipsychotic drugs (clozapine, olanzapine, quetiapine, risperidone)

Laboratory evaluation should include fasting blood glucose and lipid levels. Requests for other laboratory tests should be based on patient-specific signs, symptoms, and risk factors. Although obesity is associated with higher risk for certain cancers, recommendations for cancer screening are the same as for patients without obesity. Screening for cardiovascular disease in asymptomatic patients with obesity is not indicated; testing is reserved for symptomatic patients.

KEY POINT

- The U.S. Preventive Services Task Force recommends screening all adults for obesity by calculating BMI. HVC

Treatment

Treatment options for obesity include lifestyle modification, pharmacotherapy, and bariatric surgery. Guidelines published by the American College of Cardiology/American Heart Association/The Obesity Society on the management of obesity recommend lifestyle modification that includes reduced calorie intake, increased physical activity, and behavioral therapy in all patients. Similarly, the U.S. Preventive Services Task Force recommends offering or referring obese patients to intensive, multicomponent behavioral interventions. For patients at highest risk who have tried lifestyle modification measures without success, pharmacotherapy or surgical intervention may be considered. Patients should be advised that weight loss is beneficial even without attaining a normal weight; loss of 3% to 5% of initial body weight is associated with improvement in glycemic control, blood pressure, and lipid levels.

Lifestyle Modification

Readiness to make lifestyle changes should be assessed. Engaging family members and other social supports may increase adherence to lifestyle change. Given the expected slow pace of weight loss, patients may benefit from encouragement to focus on other changes resulting from lifestyle modification, such as improved exercise tolerance.

Reduced Dietary Energy Intake

Typical dietary calorie intake ranges required to produce weight loss are 1200 to 1500 kcal/d for women and 1500 to 1800 kcal/d for men; the calorie intake required to achieve a calorie deficit for a given person varies. Clinicians can estimate basal energy expenditure in calories using the Harris-Benedict Equation (http://www.bmi-calculator.net/bmr-calculator/harris-benedict-equation/).

Any diet that achieves a calorie deficit will produce weight loss; this is true for low calorie, low-fat, low-carbohydrate, moderate/high-protein, low-glycemic-index, vegan (with or without a low-fat component), and Mediterranean-style diets, as well as commercial diet plans. Patients should be advised to use the diet to which they will most likely adhere.

Very-low-calorie diets (<800 kcal/d) produce accelerated weight loss but require medical supervision. They should be reserved for situations requiring rapid weight loss.

Exercise

Lifestyle interventions should include moderate- to vigorous-intensity physical activity (such as brisk walking) for at least 150 minutes per week. The main contribution of increased physical activity is to minimize the reduction in calories required to achieve a caloric deficit. Because patients are often initially deconditioned, gradual progression may be required. Long-term continuance of a similar program of physical activity is important for maintaining weight loss and improving cardiovascular fitness.

Behavioral Therapy

The Centers for Medicare & Medicaid Services have approved payment for "intensive behavioral weight loss counseling" by primary care providers. Content of this counseling in practice varies widely, as does its effectiveness. Specific components associated with increased effectiveness include a calorie deficit of at least 500 kcal/d, at least 150 minutes of moderate to vigorous physical activity per week, and the use of trained interventionists (nutritionists, behavioral therapists, or exercise therapists). Interventions should incorporate regular self-monitoring of weight and calorie intake as well as education on controlling or altering the environment to avoid excess calorie intake. Examples include removing calorie-dense snacks and beverages from the home or workplace, replacing them with lower-calorie options, and engaging in other behaviors (walking, chewing gum) for situations during which the patient might be tempted to eat for pleasure, for emotional solace, or because of boredom. Programs of high intensity (≥14 sessions over at least 6 months) delivered by trained interventionists are associated with successful weight loss. Comprehensive programs lasting longer than 1 year with at least monthly contact are associated with greater likelihood of maintaining lifestyle change.

Face-to-face interventions most reliably result in weight loss, but interventions delivered electronically or by telephone have also shown success.

Pharmacologic Therapy

Patients who do not achieve weight loss with lifestyle change alone should be considered for pharmacotherapy, especially patients at higher risk for complications (those with BMI ≥30, or with BMI ≥27 and at least one obesity-associated comorbid condition). Weight loss pharmacotherapy is effective but incurs risk for adverse events as well as increased cost, and these factors should be balanced against potential weight-loss benefit.

Table 54 describes the mechanism of action, expected weight loss, and side effects of commonly used agents; all have

TABLE 54. Medications for Weight Loss

Medication	Mechanism of Action	Weight Loss Versus Placebo at 52 Weeks in Meta-analysis of Randomized Controlled Trials	Common Side Effects (Odds Ratio for Discontinuation Versus Placebo)
Liraglutide	GLP-1 receptor activator, delays gastric emptying	5.2 kg (11.6 lb)	Gastrointestinal upset, headache, nasopharyngitis (2.82)
Lorcaserin	Selective serotonergic 5HT2C receptor agonist, suppresses appetite	3.3 kg (7.2 lb)	Headache, dizziness, fatigue, nausea, dry mouth, cough, constipation May cause hypoglycemia in patients with diabetes mellitus (1.40)
Naltrexone-bupropion	Opioid antagonist plus norepinephrine/dopamine uptake inhibitor, suppresses appetite	5 kg (10.9 lb)	Gastrointestinal upset, headache, dizziness, insomnia, dry mouth, tachycardia, hypertension, anxiety, tremor (2.60)
Orlistat	Lipase inhibitor, decreases triglyceride absorption	2.6 kg (5.8 lb)	Oily stools, increased defecation, fecal urgency/incontinence (1.84)
Phentermine-topiramate	Noradrenergic/GABA receptor activator plus AMPA glutamate receptor inhibitor, suppresses appetite	8.8 kg (19.4 lb)	Paresthesias, dizziness, taste alterations, insomnia, constipation, dry mouth, tachycardia, cognitive changes (2.32)

5HT2C = 5-hydroxytryptamine2C; AMPA = α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid; GABA = γ-aminobutyric acid; GLP-1 = glucagon-like peptide 1.

Data from Khera R, Murad MH, Chandar AK, Dulai PS, Wang Z, Prokop LJ, et al. Association of pharmacological treatments for obesity with weight loss and adverse events: a systematic review and meta-analysis. JAMA. 2016;315:2424-34. [PMID: 27299618] doi:10.1001/jama.2016.7602

demonstrated higher rates of achieving 5% to 10% weight loss and larger amounts of weight lost compared with placebo. Orlistat and lorcaserin had the lowest rates of discontinuation due to side effects. Orlistat also has long-term safety data. Liraglutide and phentermine-topiramate produced the greatest weight loss but had higher rates of discontinuation due to side effects.

Patients are inundated with advertisements for over-the-counter weight loss supplements, which often claim the supplements are safer and more effective than prescription medications. These claims and easy access have led to widespread use of weight loss supplements, but systematic reviews show little evidence that any over-the-counter weight loss supplements are effective. Moreover, some supplements, such as ma huang/ephedra and bitter orange, may also be associated with significant adverse effects. Physicians should be prepared to discuss the lack of effectiveness and potential for side effects of these supplements during weight loss counseling. Comprehensive information on supplements is available at https://medlineplus.gov/druginfo/herb_All.html.

As with all other comprehensive weight loss interventions, patients should be monitored regularly. Patients who do not show improved success with weight reduction after 12 weeks of therapy should not continue pharmacotherapy.

Bariatric Surgery

For patients at highest risk for obesity-related complications and for whom other measures have not resulted in the desired clinical end points, bariatric surgery should be considered. Guidelines recommend reserving surgery for patients with a BMI of 40 or greater or for those with a BMI of 35 or greater who have obesity-associated comorbid conditions.

The risks associated with bariatric surgery exceed those associated with nonsurgical treatments. Therefore, candidates for bariatric surgery should be selected carefully on the basis of harm-benefit analysis. Patients should have acceptable operative risk, understand the necessity of lifelong dietary and lifestyle measures for sustained weight loss, and be willing to adhere to lifelong follow-up. Candidates should not have psychological or psychiatric conditions that impede adherence to these requirements. Careful selection of patients in preparation for surgery and adherence to follow-up visits predict successful weight loss and maintenance, as well as avoidance of complications.

Techniques

The three most commonly performed bariatric surgical procedures include Roux-en-Y gastric bypass, sleeve gastrectomy, and gastric banding. Roux-en-Y gastric bypass involves detaching the proximal stomach and creating a small pouch, which is reattached to the Roux limb of the small intestine. Weight loss results from decrease in caloric intake because of the small stomach pouch, malabsorption due to bypassing much of the stomach and proximal small intestines, and appetite suppression due to changes in glucagon-like peptide-1 (GLP-1) and related hormones.

Sleeve gastrectomy is accomplished by excising the part of the stomach along the greater curvature, creating an approximately 85% reduction in size; similar to gastric bypass, it results in restriction of calorie intake via a smaller stomach and hormonal (GLP-1 and related hormones) appetite suppression. The smaller gastric surface area also results in less production of ghrelin, an appetite stimulant.

Gastric banding involves placement of a silicon fluid-filled band around the proximal stomach, creating a small stomach pouch with subsequent reduction in calorie intake by increasing satiety.

All procedures result in loss of excess weight in the short term, up to 70% with Roux-en-Y, 50% with sleeve gastrectomy, and 30% with gastric banding. Long-term (5-year) data are less robust but suggest sustained weight loss.

More recently, other alternative surgical and nonsurgical procedures have been developed. These include

TABLE 55. Nutrient Deficiencies and Replacement After Bariatric Surgery

Nutrient Deficiency	Replacement Therapy
Iron	MVI with iron, or elemental iron 40-80 mg/d orally
	If deficient, ferrous sulfate 325 mg/d orally
Vitamin B_{12}	Vitamin B_{12} 500-1000 µg/d orally, or 1000 µg IM monthly
Folic acid	MVI with folate
	If deficient, 400 µg/d orally
	For women of childbearing age, folate 1 mg/d orally
Calcium	Calcium citrate 1200 mg/d orally
Vitamin D	Vitamin D 400-1000 U/d orally
	If deficient, 50,000 U weekly orally for 3 mo, then reassess
Thiamine	25-50 mg/d orally
Vitamin A	MVI daily
	If deficient, 5000-10,000 U/d orally with ongoing monitoring
Vitamin E	MVI daily
	If deficient, 400 U/d orally
Vitamin K	MVI daily
	If deficient, 5-10 mg/d orally
Copper	MVI with minerals daily
	If deficient, 2-4 mg/d orally
Zinc	MVI with minerals daily
	If deficient, 220 mg/d orally

IM = intramuscularly; MVI = multivitamin.

Data from Marcotte E, Chand B. Management and prevention of surgical and nutritional complications after bariatric surgery. Surg Clin North Am. 2016;96:843-56. [PMID: 27473805] doi:10.1016/j.suc.2016.03.006

restrictive procedures (endoscopic suturing or stapling in a manner that replicates sleeve gastrectomy) or placement of space-occupying devices (intragastric balloons) or devices intended to decrease caloric absorption (duodenal-jejunal liners). These and other related techniques are less invasive and may carry less risk than surgical procedures, but more experience and data on long-term outcomes are needed.

Postoperative Care

H Rates of 30-day postoperative complications are low, ranging from 1.3% to 8.7%. Early complications include bleeding or leakage at the anastomosis (bypass procedures) or staple line (sleeve gastrectomy) and bowel obstruction. Later complications include anastomotic or marginal ulceration, leaks, bowel obstruction and slippage, or excessive tightness of gastric bands. Initial evaluation and management for bleeding or ulceration can be performed endoscopically. Leakage is evaluated with an upper gastrointestinal series or contrast CT scan and managed by laparoscopy. Symptoms of obstruction in patients with gastric band procedures are evaluated with an upper gastrointestinal series and managed by removing fluid from the band device. H

Weight should be monitored closely in the early postoperative period. As patients lose weight, frequent reassessment of prescription medications is required (for example, insulin dosage reduction).

Long-term postsurgical care focuses on preventing nutritional deficiencies, managing adherence to lifestyle modifications, and monitoring for behaviors that lead to weight regain. **Table 55** lists the anticipated nutritional deficiencies and recommended replacement strategies. **Table 56** describes post–bariatric surgery syndromes and their management.

TABLE 56. Post–Bariatric Surgery Syndromes

Syndrome	Cause	Monitoring/Therapy
Dumping syndrome/postprandial hypoglycemia (tachycardia, sweating, abdominal pain, nausea, vomiting, diarrhea)	Rapid transit of undigested food into small intestines Early symptoms (1 hour postprandial) caused by fluid shift into the GI tract (no hypoglycemia) Late symptoms (2-3 hours postprandial) hypoglycemia caused by insulin surge in response to hyperglycemia	Avoid foods high in simple sugar; replace with higher-fiber/high-protein foods Avoid sweetened beverages (including alcohol)
Chronic loose stool	May relate to rapid transit of food to small intestines, similar to dumping syndrome Consider small intestine bacterial overgrowth	Adherence to dietary modifications to avoid dumping syndrome Rifaximin if bacterial overgrowth is suspected
Kidney stones	Increased urinary oxalic acid related to fat malabsorption	Diet low in fat and oxalate, calcium supplementation, increased hydration
Gallstones	Bile stasis, increased biliary cholesterol saturation with rapid weight loss	Ultrasonography if symptomatic Cholecystectomy is definitive treatment Ursodeoxycholic acid shown to be effective prophylactically in meta-analysis of RCTs
Gastric or marginal ulceration	Often associated with NSAID use	Endoscopy to confirm Avoidance of NSAIDs
Hypotension, hypoglycemia	Improved blood pressure and insulin sensitivity with weight loss	Adjust medications as indicated; consider proactive reduction in dose (especially antidiabetic medications)
Chronic abdominal pain/nausea	Various, including nonadherence to diet recommendations, device slippage (gastric band procedures), bowel obstruction	Evaluate with endoscopy or CT Re-educate patient on diet modifications if no other cause is identified Consider low-dose antidepressant therapy
Gastroesophageal reflux	Incidence usually decreases after diversion procedures but may increase after sleeve gastrectomy	Evaluate with endoscopy PPI therapy, lifestyle modification
Regain of weight lost	Disordered eating, excess intake of high-calorie liquid/semisolid foods or supplements	Re-educate patient on diet modifications Refer to psychiatric care or counseling if indicated

GI = gastrointestinal; PPI = proton pump inhibitor; RCT = randomized controlled trial.

KEY POINTS

HVC • Lifestyle modifications that are effective for the treatment of obesity include a calorie deficit of at least 500 kcal/d, at least 150 minutes of moderate to vigorous physical activity per week, and the use of trained interventionists (nutritionists, behavioral therapists, or exercise therapists).

- Pharmacologic therapy may be used as an adjunct to lifestyle modifications in patients with a BMI of 30 or greater or in patients with a BMI of 27 or greater who have overweight- or obesity-associated comorbid conditions.

HVC • Systematic reviews show little evidence that over-the-counter weight loss supplements are effective.

- Bariatric surgery should be reserved for patients with a BMI of 40 or greater or for those with a BMI of 35 or greater who have obesity-associated comorbid conditions.
- Long-term postsurgical care focuses on preventing nutritional deficiencies, managing adherence to lifestyle modifications, and monitoring for behaviors that lead to weight regain.

Men's Health

Male Sexual Dysfunction

Erectile Dysfunction

The American Urological Association (AUA) defines erectile dysfunction as the "inability to achieve or maintain an erection sufficient for satisfactory sexual performance." Erectile dysfunction is a common medical condition, and prevalence increases with age between 18 and 69 years; up to 33% of men older than age 50 years are affected.

Numerous risk factors and conditions are associated with erectile dysfunction, including coronary artery disease, peripheral vascular disease, diabetes mellitus, hypertension, hyperlipidemia, metabolic syndrome, obesity, tobacco use, obstructive sleep apnea, hypothyroidism, hypogonadism (androgen deficiency), benign prostatic hyperplasia, neuropathy, central neurologic conditions (Parkinson disease, Alzheimer disease, and stroke), trauma, surgery, drug and alcohol abuse, depression, and anxiety. Furthermore, numerous medications have been linked to erectile dysfunction, particularly thiazide diuretics and selective serotonin reuptake inhibitors (**Table 57**).

Erectile dysfunction can be an isolated and independent presentation, or it can be an indication of another underlying condition. Erectile dysfunction, as compared with traditional cardiovascular risk factors, portends a similar, if not greater, predictive risk for a future cardiovascular event. As such, the evaluation of erectile dysfunction must include a thorough history and physical examination directed toward identifying any potentially treatable causative factors, including those associated with cardiovascular disease. The history should include medical, psychosocial, and sexual components and should focus on the timing of symptoms (whether gradual or sudden in onset) as well as the presence of early-morning and nocturnal spontaneous erections. It is also helpful to interview the patient's partner regarding sexual function and the relationship. Patients should be assessed for other concomitant disorders of sexual function, such as premature ejaculation and decreased libido.

TABLE 57. Drugs Commonly Associated With Erectile Dysfunction
Antidepressants (monoamine oxidase inhibitors, selective serotonin reuptake inhibitors, tricyclic antidepressants)
Benzodiazepines
Opioids, nicotine, alcohol, amphetamines, barbiturates, cocaine, marijuana, methadone
Anticonvulsants (phenytoin, phenobarbital)
Antihypertensives and diuretics (thiazide diuretics, loop diuretics, clonidine, spironolactone; possibly α-blockers, β-blockers, calcium channel blockers, ACE inhibitors)
5α-Reductase inhibitors (dutasteride, finasteride)
Antihistamines and H_2 blockers (dimenhydrinate, diphenhydramine, hydroxyzine, meclizine, promethazine, cimetidine, nizatidine, ranitidine)
NSAIDs (naproxen, indomethacin)
Parkinson disease medications (levodopa, bromocriptine, biperiden, trihexyphenidyl, benztropine, procyclidine)

Physical examination should include cardiovascular, genital, digital rectal, peripheral vascular, and neurologic evaluations. Clinicians should pay close attention for any alterations in secondary sexual characteristics suggestive of hypogonadism (reduced testicular volume, loss of normal body hair distribution, gynecomastia).

Laboratory assessment involves obtaining a fasting blood glucose level, lipid panel, 8:00 AM total testosterone level, and thyroid-stimulating hormone level. Additional testing is usually not warranted unless the history or physical examination suggests a separate process.

The treatment of erectile dysfunction has been shown to improve sexual performance, quality of life, and self-esteem and to strengthen interpersonal relationships. Before implementing any treatment strategies for erectile dysfunction, however, it is imperative for clinicians to fully evaluate patients in terms of cardiac risk associated with sexual activity (to determine whether it is safe for a patient to engage in sexual activities). The Princeton III Consensus recommendations provide specific guidelines on the safety of sexual activity based on the patient's cardiac risk level (**Table 58**).

Treatment options include lifestyle modifications, oral phosphodiesterase-5 inhibitor therapies, injectable and intraurethral prostaglandin E_1 therapies, penile device therapies, testosterone therapy, and psychotherapy (**Table 59**). All patients should undergo lifestyle modification as appropriate, including weight loss and tobacco cessation; the use of

TABLE 58. Third Princeton Consensus Conference Guidelines for Treatment of Erectile Dysfunction in Patients With Cardiovascular Disease or Cardiac Risk Factors

Risk Level	Treatment Recommendation
Low Risk	
Patients who are able to do moderate-intensity exercise without symptoms Successfully revascularized patients (e.g., coronary artery bypass grafting, coronary stenting, or angioplasty) Asymptomatic controlled hypertension Mild valvular disease Mild left ventricular dysfunction (NYHA functional class I or II) who can achieve 5 METs without ischemia as determined by recent exercise testing	Can initiate or resume sexual activity or treat for ED with PDE-5 inhibitor (if not using nitrates)
Intermediate/Indeterminate Risk	
Mild to moderate stable angina Recent MI (2-8 weeks) without intervention awaiting exercise ECG Heart failure (NYHA functional class III) Noncardiac atherosclerotic disease (clinically evident PAD, history of stroke/TIA)	Further cardiac evaluation and restratification before resumption of sexual activity or treatment for ED If the patient can complete 4 minutes of the standard Bruce treadmill protocol without symptoms, arrhythmias, or a decrease in blood pressure, treatment for ED can be safely initiated
High Risk	
Unstable or refractory angina Uncontrolled hypertension Moderate to severe heart failure (NYHA functional class IV) Recent MI (<2 weeks) without intervention High-risk arrhythmia (exercise-induced ventricular tachycardia, ICD with frequent shocks, poorly controlled atrial fibrillation) Obstructive hypertrophic cardiomyopathy with severe symptoms Moderate to severe valvular disease (particularly aortic stenosis)	Defer sexual activity or ED treatment until cardiac condition is stabilized and reassessed

ECG = electrocardiography; ED = erectile dysfunction; ICD = implantable cardioverter-defibrillator; METs = metabolic equivalents; MI = myocardial infarction; NYHA = New York Heart Association; PAD = peripheral artery disease; PDE = phosphodiesterase; TIA = transient ischemic attack.

Recommendations from Nehra A, Jackson G, Miner M, Billups KL, Burnett AL, Buvat J, et al. The Princeton III Consensus recommendations for the management of erectile dysfunction and cardiovascular disease. Mayo Clin Proc. 2012;87:766-78. [PMID: 22862865] doi:10.1016/j.mayocp.2012.06.015

medications that may contribute to erectile dysfunction should be reconsidered.

Oral phosphodiesterase-5 inhibitors are first-line medical therapy and are safe and effective in most patients. Their use is contraindicated in patients taking nitrates because of the risk for hypotension. Similarly, they should be used with caution in the setting of concomitant α-blocker therapy. Second-line medical therapy includes alprostadil (prostaglandin E_1), which has a mechanism of action similar to that of oral phosphodiesterase-5 inhibitors. Although efficacious, it is administered locally by intracavernous injection, transurethral injection, or transurethral suppository, making it inconvenient and less well tolerated. Testosterone therapy is indicated only in cases of confirmed androgen deficiency and has multiple contraindications.

Premature Ejaculation

The AUA defines premature ejaculation as ejaculation that occurs sooner than desired and is distressful to either or both partners. The diagnosis of premature ejaculation is solely based on history. Clinicians should obtain a thorough sexual history (frequency of premature ejaculation, antecedent sexual activities, aggravating and alleviating factors, the impact of premature ejaculation, and any concomitant erectile dysfunction). Assessment for an underlying mood condition is also imperative given the association between premature ejaculation and quality of life.

Treatment of premature ejaculation consists primarily of counseling and pharmacotherapy. According to the AUA, medication options include selective serotonin reuptake inhibitors (paroxetine, fluoxetine, sertraline) and tricyclic antidepressants (clomipramine) to delay ejaculation, as well as topical anesthetics (lidocaine, prilocaine) to reduce tactile stimulation.

Decreased Libido

Decreased libido is a common symptom and is defined as a reduced desire or inclination to engage in sexual activities, sexual thoughts, or fantasies. When associated with concomitant marked personal or interpersonal distress, the condition

TABLE 59. Treatment Strategies for Erectile Dysfunction

Treatment Option	Additional Information
Lifestyle modification	Recommended for all patients Weight loss, smoking cessation, exercise, stress management
Oral phosphodiesterase-5 inhibitor Sildenafil Tadalafil Vardenafil	Increases cGMP → vascular smooth muscle relaxation → increased penile blood flow Equally efficacious Side effects: headache, flushing, dizziness, hypotension, presyncope/syncope Visual disturbances: "blue haze," a benign finding due to inhibition of retinal phosphodiesterase-6; association with anterior ischemic optic neuropathy Use with care with drugs that inhibit cytochrome P-450 3A4 pathway (fluconazole, verapamil, erythromycin)
Injectable and intraurethral prostaglandin E_1 Alprostadil	Increases cAMP → vascular smooth muscle relaxation → increased penile blood flow Initial trial dose should be performed by or supervised by a clinician
Testosterone supplementation	Avoid in patients with breast or prostate cancer; prostate nodule; prostate-specific antigen >4 ng/mL (4 µg/L) or >3 ng/mL (3 µg/L) in patients with a first-degree relative with prostate cancer as well as black patients; poorly controlled heart failure; untreated severe obstructive sleep apnea; elevated hematocrit (>50%); severe lower urinary tract symptoms; and desire for future fertility
Psychotherapy	Management of potential underlying mood disorder and psychosocial/interpersonal aspects of erectile dysfunction via cognitive behavioral therapy, biofeedback therapy, and sensory awareness exercises
Penile devices and surgical interventions	Consider in patients with no response to oral/injectable agents Options include vacuum constriction devices, rings, and penile prostheses (malleable and inflatable) Penile venous reconstructive surgery (to limit venous outflow) is not recommended Penile arterial reconstructive surgery is appropriate only in otherwise healthy patients with recent focal occlusion of penile artery without concomitant peripheral vascular disease
Herbal and supplemental therapy	Not recommended given their lack of efficacy, potential side effects, and medication interactions

cAMP = cyclic adenosine monophosphate; cGMP = cyclic guanosine monophosphate.

is termed hypoactive sexual desire disorder. Although decreased libido is commonly experienced as part of normal aging, numerous medical and psychiatric conditions can cause decreased libido directly or indirectly. Common causes include alcohol use, mood disorders, and significant underlying systemic illness. Medications associated with erectile dysfunction similarly can induce decreased libido. Treatment involves addressing the underlying causative factor(s). Testosterone supplementation has no role in the absence of androgen deficiency.

KEY POINTS

- Before implementing any treatment strategies for erectile dysfunction, clinicians must fully evaluate patients in terms of cardiac risk associated with sexual activity (to determine whether it is safe for a patient to engage in sexual activities).
- Oral phosphodiesterase-5 inhibitors are first-line medical therapy for erectile dysfunction and are both safe and effective in most patients; however, they are contraindicated in patients taking nitrates.

Androgen Deficiency

Male hypogonadism is defined as the inability of the testes to produce physiologic levels of testosterone, ultimately leading to signs and symptoms suggestive of androgen deficiency (**Table 60**). Many of these signs and symptoms are nonspecific and can be manifestations of various other common medical conditions. Thus, it is imperative to obtain a thorough history, including medical comorbidities, recent illness, eating disorders, mood disorders, and medication use (including glucocorticoids and opioids).

The Endocrine Society recommends against screening for androgen deficiency in the general population. In patients with clinical features suggestive of androgen deficiency, a morning (ideally, 8:00 AM to 9:00 AM) serum total testosterone level should be measured as an initial diagnostic test, which should not take place during times of acute illness. If low, the total testosterone level should be confirmed with a repeat morning measurement. Hypogonadism should be diagnosed only in men with consistent findings and unequivocally and consistently low serum total testosterone levels. Free and bioavailable testosterone measurements should be reserved for patients with total testosterone

TABLE 60. Symptoms and Signs Suggestive of Androgen Deficiency in Men

More Specific Symptoms and Signs
Incomplete or delayed sexual development, eunuchoidism
Reduced sexual desire (libido) and activity
Decreased spontaneous erections
Breast discomfort, gynecomastia
Loss of body (axillary and pubic) hair, reduced shaving
Very small (especially <5 mL) or shrinking testes
Inability to father children, low or zero sperm count
Height loss, low-trauma fracture, low bone mineral density
Hot flushes, sweats
Other Less Specific Symptoms and Signs
Decreased energy, motivation, initiative, and self-confidence
Feeling sad or blue, depressed mood, dysthymia
Poor concentration and memory
Sleep disturbance, increased sleepiness
Mild anemia (normochromic, normocytic, in the female range)
Reduced muscle bulk and strength
Increased body fat, BMI
Diminished physical or work performance

Reproduced from Bhasin S, Cunningham GR, Hayes FJ, et al; Task Force, Endocrine Society. Testosterone therapy in men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2010;95(6):2537. [PMID: 20525905] Copyright 2010, The Endocrine Society. Licensed under the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License (https://creativecommons.org/licenses/by-nc-nd/4.0/).

levels in the low-normal range and for patients suspected of having alterations in sex hormone–binding globulin (SHBG) levels. Total testosterone levels may be unreliable in patients with increased SHBG levels (advanced age, liver disease) and decreased SHBG levels (obesity, diabetes/insulin resistance, glucocorticoid use), necessitating measurement of free and bioavailable testosterone in these patient populations.

The decision to treat for androgen deficiency is complex and should be individualized after a thorough discussion of the risks (cardiovascular disease, prostate cancer, benign prostatic hyperplasia) and benefits (improvements in sexual function, sense of well-being, bone health, and male sexual characteristics). A careful assessment for contraindications to testosterone must be completed. Treatment is not indicated in patients with low testosterone levels only; it should be reserved for patients with a low testosterone level associated with symptoms. Furthermore, randomized, double-blind, placebo-controlled trials aimed at determining the benefit of testosterone supplementation in men aged 65 years and older showed that testosterone supplementation improved sexual function (sexual activity, desire, and erectile function) but did not improve physical function or vitality.

See MKSAP 18 Endocrinology and Metabolism for details on the evaluation of hypogonadism and testosterone treatment.

KEY POINTS

- In patients with clinical features suggestive of androgen deficiency, morning serum total testosterone level should be measured as an initial diagnostic test, and if low, confirmed with a repeat measurement.
- A careful screening for the multiple contraindications to testosterone therapy must be completed before testosterone supplementation is initiated.
- Treatment is not indicated in patients with low testosterone levels only; it should be reserved for patients with a low testosterone level associated with symptoms. HVC

Benign Prostatic Hyperplasia

Benign prostatic hyperplasia (BPH) is a very common condition and the most common cause of lower urinary tract symptoms (LUTS) in men. LUTS can be divided into obstructive (hesitancy, weakened stream, straining, incomplete emptying, urinary retention, overflow incontinence) and irritative (frequency, urgency, nocturia) symptoms. The AUA estimates that 90% of men aged 45 to 80 years experience some form of LUTS. The prevalence of BPH and the reported severity of LUTS both increase with age.

From an anatomic perspective, BPH generally begins at the central transition zone of the prostate, running adjacent to the course of the prostatic urethra. LUTS occur as a combined result of direct bladder outlet obstruction with increased resistance to urinary flow and increased smooth muscle tone within the prostate gland. In time, detrusor muscle dysfunction can also develop.

Clinicians should be mindful of the many potential causes of LUTS (**Table 61**). A thorough history should be taken to assess for any "red flag" symptoms (fever, hematuria, weight loss), recent urinary tract infection, and recent or distant pelvic trauma or surgery, and to assess for the presence of other causes. BPH symptoms can be classified as mild, moderate, or severe by using the AUA Symptom Index (AUA-SI), a validated clinical survey that quantifies and stratifies patients based on their symptoms (available at https://www.hiv.va.gov/provider/manual-primary-care/urology-tool1.asp). A digital rectal examination may be performed to assess for prostate size, symmetry, and nodularity. Physical examination should also assess for bladder distention, reduction in perineal sensation, and adequacy of rectal tone. Although recommended by the AUA, digital rectal examination has a low sensitivity (59%) and low positive predictive value (28%) for BPH and is subject to significant interexaminer variability.

The AUA recommends obtaining a serum prostate-specific antigen (PSA) level in all patients with LUTS and a life expectancy greater than 10 years. An elevated PSA level commonly occurs in BPH, and the finding is less specific for prostate cancer in this population. The decision to obtain a serum PSA level should be individualized to each patient, after an in-depth discussion of risks and benefits. Urinalysis is recommended for all patients to assess for the presence of infection

TABLE 61. Causes of Lower Urinary Tract Symptoms in Men
Benign prostatic hyperplasia
Medications (diuretics, anticholinergics, sympathomimetics, antihistamines, opioids)
Bladder irritants (caffeine, alcohol, spicy and acid-rich foods, carbonated beverages)
Overactive bladder/detrusor dysfunction
Urethral strictures
Bladder stones
Urinary tract infections
Urethritis
Prostatitis
Prostate cancer
Bladder cancer
Polydipsia
Diabetes mellitus
Hypercalcemia
Spinal cord injury
Parkinson disease
Neurogenic bladder
Obstructive sleep apnea

and hematuria. A postvoid residual study is reserved for patients with a history suggesting urinary retention, whereas a uroflow/urodynamic study can be used in ambiguous cases. Other studies, such as serum creatinine measurement, ultrasonography, and endoscopy, are not recommended in the absence of other symptoms.

Treatment of BPH should be guided by the severity of symptoms (by using the AUA-SI) and is aimed at improving quality of life. The AUA suggests that if a patient has mild symptoms (AUA-SI score of 0 to 7) or moderate (AUA-SI score of 8 to 19) to severe (AUA-SI score of 20 to 35) symptoms that are not bothersome, no specific treatment is required beyond reassurance. Conversely, if a patient has bothersome moderate to severe symptoms, treatment should be considered. Treatment options include lifestyle modifications, medications, and surgical interventions.

Lifestyle modifications should be offered to patients as first-line therapy with or without medications. Helpful measures may include weight loss, decreasing nocturnal fluid intake, and timed voiding. The diuretic effects of caffeine and alcohol may worsen symptoms, and intake should be limited.

Medical therapies for BPH should be offered in a systematic approach. The most commonly used classes of medications for BPH include α-blockers, 5α-reductase inhibitors, and anticholinergic agents.

α-Blockers (tamsulosin, terazosin, doxazosin, alfuzosin, silodosin) work by blocking α-receptors in the prostatic urethra and bladder neck, thereby decreasing smooth muscle tone within the gland and leading to reduction in LUTS. Effects are usually reported in approximately 4 weeks, with studies demonstrating roughly equal efficacy among different α-blockers. Patients should be counseled on potential side effects, including hypotension (especially with terazosin and doxazosin), orthostasis, and sexual dysfunction. α-Blockers should also be avoided or discontinued in patients undergoing cataract surgery because of the risk for floppy iris syndrome (intractable intraoperative iris prolapse). In patients taking a phosphodiesterase-5 inhibitor for erectile dysfunction, α-blockers can lead to significant hypotension. Tadalafil, a phosphodiesterase-5 inhibitor useful in the treatment of erectile dysfunction, improves LUTS and may be a reasonable option in patients with concomitant BPH and erectile dysfunction.

5α-Reductase inhibitors (finasteride and dutasteride) block the conversion of testosterone to dihydrotestosterone; this leads to a reduction in prostatic size and thus improvement in LUTS. The AUA recommends the addition of 5α-reductase inhibitors in patients with BPH refractory to α-blocker monotherapy who have an enlarged prostate on examination. Unlike α-blockers, which work relatively quickly, 5α-reductase inhibitors take approximately 6 months to improve symptoms. Side effects include erectile and ejaculatory dysfunction and decreased libido. The reduction in prostatic size causes a reduction in serum PSA levels (up to 50%); knowledge of this effect is important for patients undergoing routine monitoring of serum PSA levels.

Anticholinergic agents (oxybutynin, tolterodine, solifenacin) can be offered to patients with significant irritative symptoms. Studies have shown that combination anticholinergic and α-blocker therapy is more effective than α-blocker monotherapy. Patients should be counseled on potential side effects, including urinary retention, constipation, dry mouth, and dry eyes.

Various herbs, supplements (including saw palmetto), and alternative therapies (such as acupuncture) have been studied to assess for efficacy in improving LUTS associated with BPH but are not recommended because of a lack of clear benefit.

Referral to a urologist for a potential surgical intervention (transurethral resection of the prostate, transurethral needle ablation, transurethral vaporization, transurethral microwave thermotherapy, and various laser techniques) is warranted in patients with medically refractory symptoms or with BPH-mediated complications. BPH-related complications include recurrent urinary tract infection, bladder stone, obstructive nephropathy, persistent hematuria, and urinary retention.

KEY POINTS

- Lifestyle modifications such as weight loss, decreasing nocturnal fluid intake, timed voiding, and avoidance of common diuretics (for example, caffeine and alcohol) is first-line therapy for benign prostatic hyperplasia. **HVC**
- The most commonly used classes of medications for benign prostatic hyperplasia include α-blockers, 5α-reductase inhibitors, and anticholinergic agents (for irritative symptoms).

Acute Testicular and Scrotal Pain

Acute testicular and scrotal pain are common concerns; overall, they account for approximately 1% of all emergency department visits. Causes of acute testicular and scrotal pain include testicular torsion, epididymitis, and orchitis. Several other conditions, including inguinal hernia, nephrolithiasis, and spinal nerve root impingement, can lead to referred pain to the scrotum.

Epididymitis (and epididymo-orchitis when a testicle is also involved) is the most common cause of acute scrotal pain in adults. Noninfectious causes include trauma and connective tissue diseases, but infection is the most frequent cause. In younger patients, gonorrhea and chlamydia are the most likely causes, whereas gram-negative rods are the most likely cause in older patients and in patients engaging in insertive anal intercourse. Epididymitis presents as acute to subacute unilateral pain and swelling in the superolateral aspect of the testicle, sometimes with LUTS (dysuria, urgency, frequency) and fever. Pain relief with lifting of the affected testicle may be present (Prehn sign). Increased blood flow on Doppler ultrasound and an elevated C-reactive protein level (>0.24 mg/dL [2.4 mg/L]) are typically present. Supportive care, including scrotal support, ice, and pain control, is sufficient treatment for noninfectious causes. For infectious epididymitis in patients younger than 35 years, ceftriaxone and doxycycline (or azithromycin) are indicated; ceftriaxone and a fluoroquinolone are recommended in older patients and those engaging in insertive anal intercourse.

Testicular torsion results from a twisting of the testicle on the spermatic cord, eventually leading to ischemia and testicular infarction. It is most common in children and young adults and presents as acute, unilateral, severe scrotal pain and swelling. Examination reveals a "high-riding hemiscrotum" and an absent cremasteric reflex (failure of the testis to pull up when the ipsilateral inner thigh is stroked). Decreased blood flow on Doppler ultrasound is typical, and because this is a mechanical rather than inflammatory process, the C-reactive protein level is normal (<0.24 mg/dL [24 mg/L]). Testicular torsion is a surgical emergency; if repaired within 6 hours, testicular salvage rate is 80% to 100%.

KEY POINTS

- For infectious epididymitis in patients younger than 35 years, ceftriaxone and doxycycline (or azithromycin) are indicated; ceftriaxone and a fluoroquinolone are recommended in older patients and those engaging in insertive anal intercourse.
- Testicular torsion presents as acute, unilateral, severe scrotal pain and swelling with a "high-riding hemiscrotum" on examination and absent cremasteric reflex; it is a surgical emergency with high testicular salvage rates if decompressed within 6 hours.

Hydrocele, Varicocele, and Epididymal Cyst

Hydrocele, varicocele, epididymal cyst/spermatocele, and testicular malignancy most frequently present with chronic symptoms such as scrotal discomfort or swelling. They may also be noted incidentally by the patient. The key differences in the presentation, examination, appropriate diagnostic measures, and indications for treatment are presented in **Table 62**.

KEY POINT

- Hydroceles, varicoceles, and epididymal cysts (spermatoceles) present with scrotal discomfort or swelling and are all treated conservatively, with surgery reserved for worsening pain or enlarging size.

Acute and Chronic Prostatitis and Pelvic Pain

Prostatitis encompasses several disparate disorders, including acute bacterial prostatitis, chronic bacterial prostatitis, chronic pelvic pain syndrome, and asymptomatic prostatitis. It is a common problem with a reported prevalence of approximately 8%, accounting for approximately 8% of all urology visits and 1% of all primary care visits.

Acute bacterial prostatitis is characterized by irritative voiding symptoms; perineal pain; systemic symptoms of fever, chills, myalgia, and malaise; and potentially features of sepsis. Chronic bacterial prostatitis causes irritative voiding symptoms and perineal pain, but patients are not systemically ill. Bacterial prostatitis is most commonly caused by *Escherichia coli*, *Klebsiella*, *Proteus*, *Pseudomonas*, *Enterococci*, *Neisseria*, and *Chlamydia*. Chronic pelvic pain syndrome is associated with chronic pelvic pain and intermittent voiding symptoms without evidence of infection. It may be inflammatory or noninflammatory and may be idiopathic or associated with trauma, surgery, lumbosacral neuropathy, and pelvic floor dysfunction. Asymptomatic prostatitis is usually discovered incidentally.

When encountering a patient with signs and symptoms concerning for prostatitis, it is imperative to exclude other causes, including testicular, epididymal, urethral, rectal, or urinary tract conditions. The history and physical examination should attempt to address each of these potential causative sources. Evaluation should include examination of the prostate, which often is tender, enlarged, boggy, and edematous in acute bacterial prostatitis; mild tenderness or a normal prostate examination may be present with the other causes of prostatitis. Additional diagnostic measures should include a urinalysis with Gram stain and culture, as well as expressed prostatic secretion culture (by prostatic massage). However, prostatic massage is contraindicated in acute bacterial prostatitis, given concern for possible abscess, bacteremia, and sepsis. Tests such as semen analysis, PSA level, prostatic imaging (ultrasonography or CT), and prostate biopsy are not routinely performed.

TABLE 62. Causes of Chronic Testicular and Scrotal Pain or Swelling

Cause	Presentation	Diagnosis	Treatment	Additional Information
Epididymal cyst/ spermatocele	Small, benign, nontender mass along the epididymis and spermatic cord Asymptomatic; usually an incidental finding	Examination Ultrasonography	Reassurance Surgery (rarely; only if painful or enlarging)	Cysts >2 cm in diameter are referred to as spermatocele
Hydrocele	Asymptomatic to painful swelling Small to large tense, smooth scrotal mass	Examination Transillumination Ultrasonography	Conservative (pain control [analgesics]; scrotal support) Surgery (worsening pain or enlarging size)	Fluid collection between the layers of the tunica vaginalis Common (1% of men)
Varicocele	Asymptomatic to dull ache with scrotal fullness Increased fullness/pain with standing and Valsalva maneuver; improves with support and while supine	Examination ("bag of worms") No transillumination Ultrasonography	Conservative (pain control [analgesics]; scrotal support) Surgery (worsening pain, refractory to conservative methods, infertility)	Dilated testicular vein/ pampiniform plexus Common (15% of men) Left-sided (90%) Associated infertility Consider obstruction of inferior vena cava with right-sided varicocele
Testicular malignancy	Firm, unilateral mass/ nodule adherent to the testicle	Examination Ultrasonography Tumor markers (α-fetoprotein, β-human chorionic gonadotropin, lactate dehydrogenase)	Surgery/chemotherapy	Approximately 15% of testicular cancers present with pain; most are asymptomatic Patients often younger than those with hydrocele, spermatocele, or varicocele

H In acute bacterial prostatitis, mild to moderately ill patients are treated with an antimicrobial agent with good prostate tissue penetration, such as ciprofloxacin or trimethoprim-sulfamethoxazole, for approximately 6 weeks. In severely ill patients, hospitalization and parenteral antibiotics may be necessary. H

Chronic bacterial prostatitis is treated similarly with an antimicrobial agent for approximately 6 weeks. First-line therapy is a fluoroquinolone or trimethoprim-sulfamethoxazole; second-line therapy is doxycycline or azithromycin. Some patients might require a prolonged antibiotic course of up to 12 weeks to minimize the risk for recurrent episodes.

Chronic pelvic pain syndrome is best managed with a multimodal approach that includes an antimicrobial agent (6 weeks' duration) and an α-blocker such as tamsulosin. Other treatment options include 5α-reductase inhibitors, anti-inflammatory analgesics, neuromodulating agents (pregabalin, gabapentin, nortriptyline), and nonpharmacologic strategies such as cognitive behavioral therapy, biofeedback therapy, and physical therapy. Asymptomatic prostatitis requires no specific treatment.

KEY POINTS

- In acute bacterial prostatitis, mild to moderately ill patients are treated with an antimicrobial agent with good prostate tissue penetration, such as ciprofloxacin or trimethoprim-sulfamethoxazole, for approximately 6 weeks; severely ill patients may require hospitalization and parenteral antibiotics.

(Continued)

KEY POINTS *(continued)*

- Prostatic massage is contraindicated in acute bacterial prostatitis, given concern for possible abscess, bacteremia, and sepsis.
- Chronic pelvic pain syndrome is best managed with a multimodal approach including an antimicrobial agent (6 weeks' duration) and an α-blocker such as tamsulosin.

Hernia

Hernia is defined as a condition in which a portion of an organ protrudes through the wall of the cavity that contains it. This usually occurs at a weakened muscular or connective tissue site and can be congenital or acquired. Hernias most commonly occur in the abdominopelvic region, including ventral (protrusion through the anterior abdominal wall), umbilical (protrusion through the umbilicus), incisional (protrusion through previous surgical scars), femoral (protrusion inferior to inguinal ligament, near the femoral vessels at the femoral canal), and inguinal hernias. Hernias are typically noticeable during times of increased intra-abdominal pressure, such as coughing, sneezing, laughing, heavy lifting, and straining.

Inguinal hernias can be divided into direct or indirect based on their anatomic characteristics. A direct hernia is an intra-abdominal protrusion that occurs outside of the inguinal canal, between the abdominal musculature and the inguinal ligament. It does not involve the internal or external inguinal rings and does not traverse the inguinal canal. Conversely, an

indirect inguinal hernia is an intra-abdominal protrusion through the internal inguinal ring that can traverse (partly or entirely) the inguinal canal potentially through the external inguinal ring and into the scrotum. Indirect inguinal hernias are far more common than direct inguinal hernias.

Symptoms from hernias can range from an asymptomatic bulge, to a mildly dull aching sensation, to acute severe pain with concomitant nausea and vomiting. Asymptomatic to mildly symptomatic hernias are generally spontaneously or self-reducible. Conversely, acute and severe symptoms usually occur in the setting of bowel or omental incarceration and strangulation, which if not treated expeditiously could lead to tissue ischemia and necrosis. All patients should be educated on the variability of symptoms and when to seek emergent medical care (signs of bowel incarceration).

Diagnosis is usually made solely based on history and physical examination with provocative maneuvers (Valsalva). Treatment depends on the severity of symptoms and location of the hernia. Whereas surgical repair is recommended for most femoral hernias, given the high incidence of complications, asymptomatic inguinal and umbilical hernias can often be monitored. Symptomatic inguinal hernias usually require surgical repair (options include laparoscopic or open repair techniques with or without mesh). In the case of a strangulated or incarcerated hernia, immediate surgical repair is of critical importance.

KEY POINTS

- HVC Most asymptomatic hernias can be monitored; symptomatic hernias may require surgical consultation and possible repair.
- Surgical repair is recommended for most femoral hernias given the high incidence of complications.

Women's Health

Breast Symptoms

Breast Mass

A palpable breast mass that differs from the surrounding breast tissue and the corresponding area in the contralateral breast and persists throughout the menstrual cycle warrants evaluation. Although breast cancer should be considered in all patients, most breast masses are benign conditions, such as cysts, fibroadenomas, fat necrosis, or lipomas.

Evaluation requires consideration of breast cancer risk factors, including family history of breast or ovarian cancer and a detailed history of the mass, including onset, changes with the menstrual cycle, associated symptoms, and overlying skin/nipple changes. Examination of the breast includes assessment of the features of the mass, which can be well-defined with smooth margins (cyst or fibroadenoma) or ill-defined (malignancy). The axilla and supraclavicular regions should be examined to assess for lymphadenopathy. Although a detailed history and examination provide useful information, the determination of whether a discrete mass is benign or malignant often requires further evaluation with breast imaging and/or biopsy.

Imaging of a breast mass may include diagnostic mammography and/or targeted ultrasonography of the mass. Mammography is the first test performed in most patients aged 30 years or older with a breast mass. The sensitivity of mammography is lower in women with dense breasts. The mammogram may demonstrate a mass, asymmetric density, and abnormal/pleomorphic calcifications potentially indicating breast cancer. For patients with a focal abnormality noted on clinical examination or mammogram, targeted ultrasonography can clarify the size of the mass, determine whether the mass is solid or cystic, and identify the margins as smooth or irregular. Ultrasonography is the preferred method of evaluation for women younger than 30 years, in whom mammography has low sensitivity due to dense breasts. It is also the test of choice in pregnant patients. When breast imaging is completed, results are categorized by using BI-RADS (Breast Imaging Reporting and Data System) (**Table 63**). Biopsy is recommended for category 4 and 5 breast findings. About one fifth of palpable breast masses are not identified on mammogram or ultrasound, and a normal mammogram in a patient with a discrete breast mass does not rule out malignancy; therefore, a suspicious breast mass should be evaluated with a biopsy even if the mammogram and ultrasound findings are negative.

TABLE 63. Breast Imaging Reporting and Data System (BI-RADS) Assessment Categories

Category 0	Mammography: Incomplete—Need additional imaging evaluation and/or prior mammograms for comparison Ultrasound and MRI: Incomplete—Need additional imaging evaluation
Category 1	Negative
Category 2	Benign
Category 3	Probably benign
Category 4	Suspicious Mammography and ultrasound: Category 4A: Low suspicion for malignancy Category 4B: Moderate suspicion for malignancy Category 4C: High suspicion for malignancy
Category 5	Highly suggestive of malignancy
Category 6	Known biopsy-proven malignancy

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Breast biopsy can be performed with fine-needle aspiration, image-guided core-needle biopsy, or surgical/excisional biopsy. Fine-needle aspiration is done for cystic lesions; benign cysts that completely resolve with aspiration require no further work-up. Image-guided core-needle biopsy can be a stereotactic biopsy when the lesion is seen only on mammogram, ultrasound-guided biopsy when the lesion can be seen on ultrasound, or an MRI-guided biopsy when the mass is seen only on a breast MRI. Management of an abnormal finding requires a consultation with a breast surgeon. A surgical biopsy is performed when the core-needle biopsy is technically challenging due to location of the lesion, when atypical hyperplasia is seen on core-needle biopsy specimens, or when the pathology report and breast imaging findings are discordant.

Breast Pain

Breast pain (mastalgia) is common and may be cyclic or noncyclic in relation to the menstrual cycle. Cyclic breast pain often occurs in the premenstrual phase, tends to be bilateral, and resolves with onset of menstruation; it is usually associated with hormonal changes and is typically benign. Noncyclic breast pain is usually related to underlying breast conditions, such as fibrocystic breasts, hormone therapy, and stretching of Cooper ligaments (connective tissue that maintains breast structural integrity) with large breast size. Noncyclic breast pain may also result from breast infection or mastitis, breast trauma, or thrombophlebitis of the thoracoepigastric vein (Mondor disease). Non-breast causes of breast pain include costochondritis, coronary artery disease, gastroesophageal reflux disease, and intercostal nerve pain.

Evaluation includes a detailed history of breast pain to identify characteristics of the pain and relationship to menses, along with a careful physical examination to rule out palpable masses or anatomic causes. Women evaluated for breast pain with no obvious abnormal findings should be up to date with routine age- and risk-appropriate breast screening. Patients with noncyclic mastalgia with focal breast pain and no palpable mass should undergo targeted breast ultrasonography because approximately 1% of such patients may have breast cancer at the site of pain. Any palpable breast masses should be evaluated with diagnostic imaging (see Breast Mass).

For women with cyclic breast pain and negative clinical findings, conservative management (education, reassurance of the absence of malignancy, and advice regarding adequate breast support) is recommended as cyclic pain usually resolves spontaneously. There is a lack of evidence to support limiting caffeine intake or using vitamin E as a means of mitigating the pain. Medical management may be offered for patients with severe pain that persists despite conservative management. Danazol is the only FDA-approved agent for cyclic breast pain, but its use is limited because of side effects, including amenorrhea, hirsutism, and adverse changes in lipid profile. Low-dose tamoxifen, although not FDA approved for this indication, has been shown to have benefit with fewer side effects; however, hot flushes, menstrual irregularities, and the need for contraception must be considered. Treatment of noncyclic breast pain depends on the underlying cause.

KEY POINTS

- Mammography is the first test performed in most women aged 30 years or older with a breast mass; the sensitivity of mammography is lower in women with dense breasts.
- Ultrasonography is the preferred method of evaluation of a breast mass in women younger than 30 years, in whom mammography has low sensitivity due to dense breasts. **HVC**
- A suspicious breast mass should be evaluated with a biopsy even if the mammogram and ultrasound results are negative.
- Cyclic breast pain often occurs in the premenstrual phase, tends to be bilateral, and resolves with onset of menstruation and conservative management (education, reassurance of the absence of malignancy, and advice regarding adequate breast support). **HVC**
- Noncyclic breast pain is usually related to underlying breast conditions; patients with noncyclic focal breast pain and no palpable mass should undergo targeted breast ultrasonography to exclude breast cancer.

Reproductive Health

The Centers for Disease Control and Prevention provides information and recommendations on reproductive health (https://www.cdc.gov/reproductivehealth/index.html).

Contraception

Approximately 50% of pregnancies in the United States are unintended, with a higher prevalence in women with low socioeconomic status, younger women, and those who cohabit. Contraception counseling to reduce unintended pregnancy involves an understanding of the risk for pregnancy, assessing contraceptive options, identifying the appropriate agent based on benefits and risks, and educating the patient on appropriate use of the contraceptive. Contraceptive options include hormonal contraception, barrier methods, sterilization, and emergency contraception (**Table 64**).

Hormonal Contraception

Hormonal contraceptive options include oral contraceptive pills (combination estrogen-progesterone or progesterone-only pills), long-acting reversible contraceptives, transdermal patches, and vaginal rings. Patient factors influencing choice include hypertension, history of breast cancer, obesity, thrombotic disorders, migraines, and tobacco use. Before initiation of hormonal contraception, a negative pregnancy test result must be documented if 7 days have passed since the first day of the patient's last menstrual period.

TABLE 64. Comparison of Contraceptive Options

Agent	Women Experiencing Unintended Pregnancy Within the First Year of Use (%)		Advantages	Disadvantages
	Typical Use[a]	Perfect Use[a]		
Hormonal Agents				
Oral contraceptives				
Combination estrogen-progestin preparations	9	0.3	Easy to use Rapidly reversible Decreased risk for endometrial and ovarian cancers Decreased dysmenorrhea, menorrhagia, symptomatic ovarian cysts Less iron deficiency anemia	Daily use may affect adherence Increased risk for myocardial infarction, ischemic stroke, VTE, hypertension Increased risk for cancers of the cervix, liver, and breast Breakthrough bleeding May exacerbate migraine
Progestin-only preparations ("mini-pill")	9	0.3	Use when estrogen is contraindicated	Irregular bleeding, breakthrough bleeding; must maintain precise daily dosing schedule
Long-acting reversible preparations				
Depot medroxyprogesterone acetate (IM or SQ)	6	0.2	Administered every 3 months Decreased risk for endometrial cancer, PID Improves endometriosis Decreased menstrual frequency	Delayed return to ovulation (6-10 months) Irregular bleeding, amenorrhea, decreased bone mineral density (especially in adolescents)
Progestin implants	0.05	0.05	Effective up to 3 years	
Intrauterine devices				
Copper	0.8	0.6	Nonhormonal Effective up to 10 years	Bleeding, pain Requires placement and removal in office Expulsion rates up to 5% in first year No protection from STIs
Levonorgestrel	6	0.2	Decreased menstrual flow Effective up to 3-5 years, depending on formulation	
Other hormonal agents				
Patch (combination estrogen-progestin)	9	0.3	Easier adherence Change weekly	Local skin reaction Increased estrogen dose, thus higher VTE risk
Vaginal ring (combination estrogen-progestin)	9	0.3	Easier adherence Change monthly Lowest level of systemic estrogen	Requires self-insertion
Barrier Methods				
Cervical cap	16-32	9-26	-	User dependent, requires spermicide
Diaphragm	12	6	-	Requires spermicide
Male condom	18	2	Protection from STIs	-
Female condom	21	5	Protection from STIs	-
Vaginal sponge	12-24	9-20	-	-
Sterilization				
Female (tubal ligation)	0.5	0.5	May reduce ovarian cancer risk	Surgical complications (rare) Regret Increased risk for ectopic pregnancy
Male (vasectomy)	0.15	0.10	Lower costs, fewer complications, and more effective than tubal ligation	Surgical complications (rare)

IM = intramuscular; PID = pelvic inflammatory disease; SQ = subcutaneous; STI = sexually transmitted infection; VTE = venous thromboembolism.

[a]Perfect use implies correct and consistent use exactly as directed/intended. Typical use reflects rates in actual practice with patients.

Oral Contraceptive Pills

Oral contraceptive pills include combination estrogen-progesterone pills and progesterone-only pills. The combination pills vary in the type and strength of estrogen and the type of progestin. They inhibit ovulation, alter the cervical mucus to prevent migration of the sperm, inhibit endometrial thickening, and prevent implantation. Although all agents are equivalent in terms of the contraceptive efficacy, they vary in terms of side effects. Contraindications to combination pills include breast cancer, venous thromboembolism, uncontrolled hypertension, liver disease, and migraine with aura.

Women who smoke more than 15 cigarettes per day and are older than 35 years should not use estrogen-containing preparations because of the increased risk for thrombotic disorders. Progesterone-only pills can be used for women with a contraindication to estrogen.

Long-Acting Reversible Contraception

Long-acting reversible contraceptives are progestin-only forms of contraception that include depot medroxyprogesterone acetate injections, progestin implants, and intrauterine devices (IUDs). Patients can receive these contraceptives in the outpatient office setting.

An IUD is a small, T-shaped device (copper or levonorgestrel) that is placed inside the uterus. The copper IUD induces a local reaction that impairs implantation of the fertilized ovum, whereas the levonorgestrel IUD releases a low dose of progestin that leads to endometrial atrophy and also prevents implantation. Complications include uterine perforation with approximately 1 per 1000 insertions. Risk factors for perforation include breastfeeding at the time of insertion or insertion within 36 weeks after the last childbirth. Risk for pelvic infection with IUD placement is low, and prophylactic antibiotics are not recommended during the procedure. If a woman with a sexually transmitted infection (STI) has an IUD in place, she should be treated with antibiotics, and the IUD does not need to be removed. Contraindications to IUD placement include pregnancy; anatomic uterine abnormalities with distortion of the uterine cavity; and acute untreated pelvic infection, gonorrhea, or chlamydia.

Barrier Contraception

Barrier contraceptive methods such as diaphragms and condoms are among the least effective of all the modes of contraception. Their efficacy is improved when combined with a spermicidal agent. Use of condoms reduces the risk for STIs.

Sterilization

Female sterilization is a safe and permanent form of sterilization that is associated with a low complication rate. The fallopian tube lumen may be occluded by techniques such as clip or cautery. Preprocedure counseling includes a detailed discussion of the permanence of the procedure, the risk for regret after surgery, the complex nature and poor success rates of reversal procedures, and the availability of alternative long-acting contraceptive methods.

Emergency Contraception

Emergency contraception refers to postcoital contraception using a device or medication to prevent pregnancy after unprotected or inadequately protected intercourse. The most effective form of emergency contraception is the placement of a copper IUD within 5 days of intercourse. The IUD is also the preferred option in obese women because they experience higher failure rates with oral emergency contraception.

FDA-approved medications include levonorgestrel, which is most effective within 3 days of intercourse, and ulipristal, which has a 5-day window.

Preconception Care

Preconception counseling refers to education provided before pregnancy, aimed at reducing the risk for preterm birth and congenital anomalies. Optimizing health before pregnancy reduces exposures to factors that can potentially compromise a healthy pregnancy, as organogenesis starts as early as the third to fifth week of gestation. This differs from prenatal counseling, which occurs after pregnancy is diagnosed.

Any primary care visit for a woman of reproductive age is an opportunity to routinely ask if she could become pregnant or is considering pregnancy. For women who are not interested in pregnancy, contraception should be discussed to reduce the risk for unintended pregnancy. For women considering pregnancy, a comprehensive risk assessment should be completed (**Table 65**). An obstetric history of pregnancy-induced hypertension, preeclampsia, or gestational diabetes is particularly predictive of future risk.

All medications should be reviewed to reduce or avoid exposure to potential teratogens (**Table 66**). The pregnancy letter categories that have been used by the FDA to characterize the safety of drugs in pregnancy are provided in **Table 67**. In 2015, the FDA published changes in pregnancy and lactation labeling for prescription drugs (https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm). The pregnancy letter categories will be discontinued with the new labeling requirements; however, for prescription drugs that were previously approved, these changes will be phased in gradually. Labeling will include information relevant to the use of the drug in pregnant women (such as dosing and potential risks to the developing fetus), information about using the drug while breastfeeding (such as the amount of drug in breast milk and potential effects on the breastfed infant), and information regarding potential risks to females and males of reproductive potential who take the drug.

Physical examination includes assessment of blood pressure and BMI. Pelvic examination may include screening cervical cytology. Testing for STIs and hepatitis is indicated in high-risk patients. HIV counseling and screening are recommended for all women planning pregnancy.

Intervention to prevent complications depends on the results of the risk assessment. All women should be encouraged to follow a healthy lifestyle, with emphasis on complete

TABLE 65. Preconception Risk Assessment

Risk Category	Specific Items to Assess
Reproductive awareness	Desire for pregnancy, number and timing of desired pregnancies, age-related changes in fertility, sexuality, contraception
Environmental hazards and toxins	Exposure to radiation, lead, and mercury
Nutrition and folic acid consumption	Healthy diet; daily consumption of folic acid; low-dose iron supplementation; restricting consumption of shark, swordfish, king mackerel, and tilefish to <2 servings weekly (owing to high mercury content)
Genetics	Family history of genetic disorders
Substance use	Use of tobacco, alcohol, and illicit drugs
Medical conditions	Seizure disorder, diabetes mellitus, hypertension, thyroid disease, asthma, HIV infection, systemic lupus erythematosus
Obstetric history	Pregnancy-induced hypertension, preeclampsia, gestational diabetes
Medications	Over-the-counter and prescription medications, potential teratogens
Infectious diseases and vaccinations	Vaccinations up to date; immunity to varicella and rubella; risk for hepatitis B infection
Psychosocial concerns	Depression, interpersonal/family relationships, risk for abuse (physical, sexual, emotional)

Information from Johnson K, Posner SF, Biermann J, et al; CDC/ATSDR Preconception Care Work Group; Select Panel on Preconception Care. Recommendations to improve preconception health and health care—United States. A report of the CDC/ATSDR Preconception Care Work Group and the Select Panel on Preconception Care. MMWR Recomm Rep. 2006;55:1-23. [PMID: 16617292]

TABLE 66. Commonly Used Medications With Potential for Teratogenic Effects

Class/Type	Examples
Antibiotics	Tetracycline, doxycycline, sulfonamides, trimethoprim, para-aminosalicylate
Anticoagulants	Warfarin
Antidepressants	Selective serotonin reuptake inhibitors, lithium
Antihypertensive agents	ACE inhibitors, angiotensin receptor blockers, direct renin inhibitors
Antiepileptic drugs	Valproic acid, phenytoin, carbamazepine
Antithyroid medications	Propylthiouracil, carbimazole, methimazole
Hormones	Androgens, testosterone derivatives
Immunosuppressant/chemotherapeutic agents	Folate antagonists, cyclophosphamide, methotrexate
Others	Vitamin A derivatives, statins, NSAIDs, isotretinoin

TABLE 67. FDA Classification of Drugs in Pregnancy[a]

Class	Fetal Effect of Drug During Pregnancy
A	No disclosed fetal effects
B	Animal studies failed to demonstrate fetal risk
C	Animal studies suggest adverse fetal effects
D	Evidence of human fetal risk
X	Documented fetal abnormalities

[a]In 2015, the FDA published changes in pregnancy and lactation labeling for prescription drugs. A summary of these changes is available at https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm. The pregnancy letter categories will be removed with the new labeling requirements; however, for prescription drugs that were previously approved, these changes will be phased in gradually.

cessation of tobacco, alcohol, or illicit drugs before conception and education on the consequences of not doing so.

Women should be up to date with immunizations. Women who are considering pregnancy should be assessed for immunity to varicella and rubella. For women who are not immune, varicella and rubella vaccination should be administered with the advice that pregnancy be avoided for at least 4 weeks after the vaccine is administered to reduce risk to the fetus. Immunizations to be avoided during pregnancy, in addition to varicella and rubella, include human papillomavirus, measles, mumps, live attenuated influenza, and live attenuated herpes zoster.

Consultation with a genetics counselor may be helpful if there is a personal or family history of genetic disorders.

Patients should also be counseled about new infections, such as Zika virus and its risk for adverse fetal outcomes (for example, microcephaly), and be educated on the risks of travel to endemic areas and modes of transmission, including mosquito bite, sexual intercourse, and blood transfusion. Appropriate preventive measures should be addressed.

Interventions that optimize pregnancy outcomes include daily intake of folic acid (0.4-0.8 mg/d [400-800 µg/d]) to reduce the risk for neural tube defects. Low-dose oral iron supplements can reduce the risk for maternal anemia. Prenatal multivitamins that contain sufficient folic acid are a reasonable option for women contemplating pregnancy.

KEY POINTS

- Contraception counseling involves an understanding of the risk for pregnancy, assessing contraceptive options, identifying the appropriate agent based on benefits and risks, and educating the patient on appropriate use of contraceptives.
- Contraindications to oral combination estrogen-progesterone contraceptive pills include breast cancer, venous thromboembolism, uncontrolled hypertension, liver disease, and migraine with aura; progesterone-only pills can be used for women with a contraindication to estrogen.

(Continued)

KEY POINTS *(continued)*

- Women who smoke more than 15 cigarettes per day and are older than 35 years should not use estrogen-containing contraceptive preparations.
- Long-acting reversible contraceptives are progestin-only forms of contraception that include depot medroxyprogesterone acetate injections, progestin implants, and intrauterine devices.
- Women considering pregnancy should undergo a comprehensive assessment of risk factors for adverse pregnancy outcomes and begin folic acid supplementation.

Menstrual Disorders

Abnormal Uterine Bleeding

Evaluation

Abnormal uterine bleeding is defined as excessive bleeding in terms of flow volume, frequency, and duration. Among nonpregnant women of reproductive age, abnormal uterine bleeding is classified according to etiology by using the International Federation of Obstetrics and Gynecology system with the acronym PALM-COEIN (polyp, adenomyosis, leiomyoma, malignancy and hyperplasia, coagulopathy, ovulation dysfunction, endometrial, iatrogenic, and not yet classified). Abnormal uterine bleeding in this population can be further classified as ovulatory or anovulatory. Ovulatory bleeding occurs at regular intervals, but the menstrual flow is excessive. This may be related to thyroid disease; bleeding disorders; or structural abnormalities, such as uterine fibroids or polyps. Anovulatory cycles are characteristically irregular in terms of flow and cycle duration, as lack of ovulation and the resultant lack of cyclic progesterone cause endometrial hyperplasia and irregular bleeding. Anovulation occurs with polycystic ovary syndrome, hypothyroidism or hyperthyroidism, hyperprolactinemia, chronic liver or kidney disease, and medications (such as antidepressant and antipsychotic agents, chemotherapy, and tamoxifen). Anovulatory causes of bleeding in the patient of reproductive age increase the risk for endometrial cancer because of the lack of cyclic progesterone-induced withdrawal bleeding and resultant endometrial hyperplasia.

Causes of abnormal uterine bleeding in the postmenopausal patient are similar to those in women of reproductive age, although there is an increased risk for endometrial cancer. Risk factors for endometrial cancer other than age older than 50 years and anovulatory causes of bleeding include such conditions as Lynch or Cowden syndrome; obesity; and reproductive factors, such as nulliparity and late menopause.

Evaluation of abnormal uterine bleeding in the premenopausal woman includes assessment of menstrual cycle length, regularity, intermenstrual bleeding, volume of menstrual flow (including passage of clots), association with pain, presence of an intrauterine device, and postcoital bleeding. Assessment for thyroid disease, liver or kidney disease, and bleeding disorders is also indicated. Pelvic examination is performed to determine whether the source of bleeding is from the vulva, vagina, cervix, or uterus. Pregnancy testing is recommended for all premenopausal women with abnormal uterine bleeding because bleeding may occur with pregnancy-related conditions, such as placenta previa and ectopic gestation. Pelvic ultrasonography is indicated to assess for structural abnormalities in the uterus and to determine endometrial thickness. Endometrial thickness greater than 4 mm in postmenopausal women may indicate endometrial hyperplasia or malignancy. In premenopausal women, endometrial thickness is not a reliable indicator because thickness varies according to the phase of the menstrual cycle.

Evaluation of the postmenopausal patient is similar to that of the premenopausal patient. Because of the increased risk for endometrial cancer, however, any vaginal bleeding occurring in peri- and postmenopausal women warrants evaluation to rule out malignancy, usually with endometrial biopsy.

Management

Management of abnormal uterine bleeding is aimed at the underlying cause. Structural abnormalities, such as endometrial polyps or submucosal fibroids, may be surgically resected. Treatment of underlying endocrine disorders (thyroid disease, polycystic ovary disease) may result in improvement.

For women with anovulatory cycles, treatment is aimed at providing adequate progestin to maintain endometrial stability. The type of therapy depends on the patient's plans for contraception. For women who wish to preserve fertility, medroxyprogesterone acetate used for the second half of the menstrual cycle will restore cyclic withdrawal bleeding. For women interested in contraception, oral contraceptive pills containing estrogen and progesterone or the levonorgestrel intrauterine device may be used. Additionally, NSAIDs may be used because these drugs reduce synthesis of prostaglandins in the endometrium, leading to vasoconstriction and reduced bleeding. Tranexamic acid, an antithrombolytic agent, stabilizes clots and may be used for treatment of heavy vaginal bleeding. For women experiencing acute and severe bleeding, agents such as gonadotropin-releasing hormone or intravenous administration of high-dose estrogens may be used. For women who do not respond to medical therapy, operative procedures such as endometrial ablation or hysterectomy may be performed.

Dysmenorrhea

Dysmenorrhea is characterized by pain during menstruation; it may also be associated with low back pain, headache, nausea, vomiting, and diarrhea. Dysmenorrhea is classified as primary or secondary. Primary dysmenorrhea involves cramping lower abdominal and pelvic pain that occurs during menstrual cycles without an identifiable cause. Secondary dysmenorrhea may result from pelvic conditions, such as endometriosis, inflammatory disease, or uterine fibroids.

A detailed history is necessary to assess the timing of pain and relationship to the menstrual cycle. Sexual history is important to assess for infection and risk for abuse. Primary dysmenorrhea can be treated with NSAIDs and cyclooxygenase-2 inhibitors; persistent symptoms can be treated with oral contraceptive pills. Secondary dysmenorrhea requires treatment of the underlying condition.

KEY POINTS

- Evaluation of all patients with abnormal uterine bleeding includes a detailed history, physical and pelvic examinations, pregnancy testing, and pelvic ultrasonography.
- Risk factors for endometrial cancer include age older than 50 years; anovulatory causes of bleeding; such conditions as Lynch or Cowden syndrome; obesity; and reproductive factors, such as nulliparity and late menopause.
- Any vaginal bleeding occurring in peri- and postmenopausal women warrants evaluation to rule out malignancy, usually with endometrial biopsy.
- Primary dysmenorrhea can be treated with NSAIDs and cyclooxygenase-2 inhibitors, and persistent symptoms can be treated with oral contraceptive pills; secondary dysmenorrhea requires treatment of the underlying condition.

Menopause

Diagnosis

Menopause is the permanent cessation of menses that is diagnosed retrospectively after a woman has not experienced a menstrual period for 12 months. Menopause may be natural, surgical following bilateral oophorectomies, or medical as a result of medications such as chemotherapy. Menopause occurring before age 40 years is considered premature menopause or premature ovarian insufficiency. Perimenopause refers to the phase of menopause transition, extending into early postmenopause; it varies in length and may be associated with irregular menstrual cycles, fluctuating hormone levels, and intermittent hot flushes.

Symptoms of menopause include vasomotor symptoms (hot flushes, night sweats), depression, difficulties with memory and concentration, sleep disturbances, and genitourinary symptoms (vaginal dryness, dyspareunia). Up to 50% of women experience hot flushes during perimenopause, but symptoms generally resolve spontaneously in a few years. Genitourinary syndrome of menopause is the result of estrogen deficiency and is characterized by vaginal symptoms, such as vaginal burning or irritation; sexual symptoms, such as dyspareunia or sexual dysfunction; or urinary symptoms, such as dysuria or recurrent urinary infections. Pelvic examination findings include a pale, dry vaginal lining with reduction in rugae. Increases in LDL cholesterol and bone loss are also associated with menopause.

Routine laboratory testing for the diagnosis of menopause is not recommended. Patients with possible early menopause should have pregnancy excluded and undergo measurement of follicle-stimulating hormone, thyroid-stimulating hormone, and prolactin. Younger patients should undergo evaluation for amenorrhea (see MKSAP 18 Endocrinology and Metabolism).

Management

Management of menopausal symptoms is recommended to improve quality of life. Pregnancy is possible even if menstrual cycles are irregular, and contraception should be discussed if pregnancy is not desired. The U.S. Preventive Services Task Force recommends against the use of combined estrogen and progestin for the primary prevention of chronic conditions (coronary artery disease, dementia, stroke, and fractures) in postmenopausal women and against the use of estrogen alone for the primary prevention of chronic conditions in postmenopausal women who have had a hysterectomy.

Vasomotor Symptoms

The approach to starting menopausal hormone therapy for women aged 50 to 59 years, or within 10 years of menopause onset, who are experiencing menopause symptoms is outlined in **Table 68**. Estrogen is the most effective therapy for vasomotor symptoms; the lowest dose of estrogen to manage symptoms should be used. Contraindications to hormone therapy include pregnancy, unexplained vaginal bleeding, coronary artery disease, stroke, thromboembolic disease, breast cancer, and endometrial cancer.

Transdermal estrogen is preferable to oral estrogen because it may be associated with less thromboembolic risk, but some patients may prefer oral therapy.

For women who experience menopausal symptoms and have an intact uterus, estrogen should be combined with progestin to avoid unopposed estrogen-related endometrial proliferation. Continuous daily estrogen with progestin does not result in cyclic vaginal bleeding and may be a preferred option for many women. Women must be informed that estrogen with cyclic progestin will result in withdrawal bleeding.

Use of hormone therapy in menopause should be reassessed every year to determine benefits and risks and determine the appropriate time to discontinue the medication. Treatment duration is based on continued presence of vasomotor symptoms. Postmenopausal hormone use with combined estrogen-progestin therapy taken for more than 5 years is associated with increased risk for breast cancer and requires that women receive individualized breast cancer risk assessment and counseling.

Nonhormonal drugs can help modulate vasomotor symptoms in women with contraindications to hormone therapy or who wish to avoid the associated risks. Antidepressant agents, including selective serotonin reuptake inhibitors (such as citalopram, escitalopram, and paroxetine) and serotonin-norepinephrine reuptake inhibitors (such as

TABLE 68. Initiating Systemic Hormone Therapy in Women Aged 50 to 59 Years or Within 10 Years of Menopause Onset for Vasomotor Symptoms[a]

Step 1: Confirm that hot flushes/night sweats are moderate to severe in intensity and refractory to lifestyle modifications and/or vaginal symptoms have been refractory to local therapies.
Step 2: Assess for contraindications to systemic hormone therapy.
Step 3: Assess the patient's baseline risk for stroke, cardiovascular disease, and breast cancer (consider using the 10-year ASCVD risk calculator, Framingham stroke risk score, Framingham CHD risk score, and Gail model risk score to quantify this risk). If the Framingham stroke or CHD risk score is >10% or Gail model risk score is elevated, consider alternatives to systemic hormone therapy.[b,c]
Step 4: Use the lowest dose of estrogen that relieves menopausal symptoms.
Step 5: Add systemic progesterone therapy to estrogen therapy in women who have an intact uterus.
Step 6: Assess symptoms and side effects after initiating therapy and adjust the dose of estrogen if symptoms are persistent.
Step 7: Reassess symptoms and risk factors for cardiovascular disease, stroke, and breast cancer annually.
Step 8: Discontinue systemic hormone therapy if the risks of treatment outweigh the benefits.

ASCVD = atherosclerotic cardiovascular disease; CHD = coronary heart disease.

[a]According to the 2017 hormone therapy position statement of The North American Menopause Society, the safety profile of hormone therapy in women who initiate therapy more than 10 or 20 years after menopause onset or at age 60 years or older is not as favorable as for younger women, owing to greater absolute risks for coronary heart disease, stroke, venous thromboembolism, and dementia.

[b]Some experts indicate that systemic hormone therapy is safe in women who have experienced menopause within the last 5 years and have a Framingham CHD risk score of 10% to 20%.

[c]Most participants in the Women's Health Initiative (a set of two hormone therapy trials) had a Gail model risk score of less than 2%.

venlafaxine, desvenlafaxine, and duloxetine), and gabapentin are effective. Research is inconclusive regarding supplements such as soy, black cohosh, and other phytoestrogens for vasomotor symptoms.

Genitourinary Syndrome of Menopause

Management of genitourinary syndrome of menopause (GSM) includes topical nonhormonal and hormonal preparations to relieve symptoms. Nonhormonal approaches include as-needed vaginal lubricants for intercourse and vaginal moisturizers that can alleviate vaginal dryness and irritation when used regularly. The North American Menopause Society recommends nonhormonal vaginal therapies as first-line treatment for GSM.

Hormonal preparations include estradiol or conjugated estrogen in tablet, cream, or ring forms. Low-dose vaginal estrogen is recommended for the management of vaginal atrophy because it builds the vaginal epithelium and restores the acidic pH and microenvironment. Moreover, improving the lining of the lower urethra reduces dysuria and recurrent urinary tract infection. For women with breast cancer, current or past, low-dose vaginal therapy should be given only with the approval of the treating oncologist. Vaginal dehydroepiandrosterone and the selective estrogen receptor modulator ospemifene are both approved by the FDA for management of dyspareunia associated with GSM; most experts consider these treatment modalities second-line therapies because of their side effects and limited safety experience.

KEY POINTS

- Routine laboratory testing for the diagnosis of menopause is not recommended; patients with possible early menopause should have pregnancy excluded and undergo measurement of follicle-stimulating hormone, thyroid-stimulating hormone, and prolactin levels. **HVC**
- Pregnancy is possible even if menstrual cycles are irregular, and contraception should be discussed if pregnancy is not desired.
- Estrogen is the most effective therapy for vasomotor symptoms of menopause.
- Nonhormonal options for vasomotor symptoms of menopause include antidepressant agents and gabapentin.
- Management of genitourinary syndrome of menopause includes topical nonhormonal and hormonal preparations to achieve symptom relief.

Chronic Pelvic Pain

Chronic pelvic pain (CPP) refers to a syndrome of intermittent or persistent pain below the level of the umbilicus or in the pelvis of at least 6 months' duration that is severe enough to result in functional disability or require medical care. Evaluation and diagnosis of CPP are challenging; CPP may be secondary to a single underlying cause, multiple concurrent disorders, or no clear cause. The identifiable causes can be classified as gynecologic (endometriosis, pelvic inflammatory disease), urologic (recurrent urinary tract infection, interstitial cystitis), gastrointestinal (pelvic adhesions, irritable bowel syndrome), musculoskeletal (myofascial pain, hernia), psychological (depression, sexual abuse), or neurologic (pudendal neuralgia).

Risk factors for CPP include physical, sexual, and/or emotional abuse; pelvic inflammatory disease; history of abdominopelvic surgery; chronic pain syndromes; and psychological conditions, such as anxiety or depression.

Evaluation includes a detailed history to determine characteristics of the pain, including association with menstrual cycle, urination, or bowel movement, as well as assessment for risk factors and known causes of CPP. Physical examination includes detailed abdominal and gynecologic examinations. Laboratory testing is of limited value unless specific disorders are suggested by the history and clinical examination (urinalysis for urinary tract infection, testing for STI). Transvaginal ultrasonography is used to identify

anatomic pathology, such as a pelvic mass. In the absence of an abnormality noted on clinical examination or ultrasound, laparoscopy may be helpful for the evaluation of severe symptoms of unclear cause.

Treatment is aimed at the underlying cause and may be challenging if no clear cause is identified. For patients without a clearly identified cause, treatment is aimed at pain management. NSAIDs may be helpful for patients with moderate CPP. Additional therapies include antidepressant agents, physical therapy, cognitive behavioral therapy, biofeedback, acupuncture, hypnosis, and stress reduction therapies.

KEY POINTS

- Risk factors for chronic pelvic pain include physical, sexual, and/or emotional abuse; pelvic inflammatory disease; history of abdominopelvic surgery; chronic pain syndromes; and psychological conditions, such as anxiety or depression.
- NSAIDs may be helpful for patients with moderate chronic pelvic pain without a clearly identified cause.

Female Sexual Dysfunction

Female sexual dysfunction is characterized by persistent or recurrent distressing sexual concerns or difficulties and is likely underappreciated; it affects more than one third of sexually active women. A sexual health history is an important part of the medical evaluation; open-ended questions regarding sexual activity and possible concerns, such as pain with intercourse, are appropriate and may uncover a previously unidentified disorder.

According to the DSM-5, female sexual dysfunction is divided into three categories: female orgasmic disorder, sexual interest/arousal disorder, and genitopelvic pain/penetration disorder. Female orgasmic disorder is the persistent or recurrent delay, infrequency, reduced intensity, or absence of orgasm following a normal excitement phase. Female sexual interest/arousal disorder includes hypoactive sexual desire or arousal dysfunction and is diagnosed if the patient reports at least three of the following symptoms: lack of sexual interest, lack of sexual thoughts or fantasies, decreased initiation of sexual activity or decreased responsiveness to the partner's initiation attempts, reduced excitement or pleasure during sexual activity, reduced response to sexual cues, or decreased genital or nongenital sensations during sexual activity. Genitopelvic pain/penetration disorder is diagnosed when there is persistent or recurrent difficulty in vaginal penetration during intercourse, marked vulvovaginal or pelvic pain during penetration, fear of pain or anxiety about pain in anticipation of or during penetration, or tightening or tensing of pelvic floor muscles during attempted penetration. Diagnosis of a sexual disorder requires that the aforementioned symptoms occur more than 75% of the time for at least 6 months and cause clinically significant distress.

Sexual functioning involves multiple components, including emotions, relationships, past experiences, physiologic responses, overall health, and personal beliefs; therefore, a comprehensive approach is needed to evaluate and treat the condition.

Assessment of female sexual dysfunction includes a detailed sexual history of symptom duration, whether acute or gradual onset, if related to a specific partner or a generalized concern; association with pain; precipitating events; life stressors; medical and surgical history; medications; and history of physical, emotional, and/or sexual abuse. Screening for concurrent depression is indicated. The Female Sexual Function Index questionnaire, a brief validated self-report questionnaire, can be used for clinical assessment of symptoms. Pelvic examination is aimed at assessing for specific sites of pain or tenderness, vaginal dryness, or atrophy suggestive of genitourinary symptoms of menopause. Laboratory testing is of limited value and performed only if an underlying cause is suspected.

Therapy is aimed at treating the underlying cause of female sexual dysfunction, which is often multifactorial. Vaginal dryness and atrophy from genitourinary symptoms of menopause may warrant use of vaginal moisturizers and vaginal estrogen therapy. Lubricants can be used as needed for intercourse, and deep muscle relaxation therapies and objects, such as dilators, to increase the diameter of the vagina may be used for patients with vulvovaginal pain. Systemic hormone therapy in postmenopausal women may help sexual function. Ospemifene is a selective estrogen receptor modulator approved by the FDA for treatment of dyspareunia associated with vulvovaginal atrophy.

Flibanserin is the only drug approved by the FDA for premenopausal women with female sexual interest/arousal disorder. However, caution is warranted when this medication is prescribed because of side effects (dizziness, syncope, hypotension, somnolence) and lack of safety data when flibanserin is combined with alcohol or certain medications (antidepressants). Low-dose testosterone treatment (off-label) increases sexual function scores, but side effects must be discussed. Phosphodiesterase inhibitors, such as sildenafil, have shown inconsistent results in women.

Treatment strategies must also address psychological and behavioral aspects of female sexual dysfunction. Cognitive behavioral therapy can help minimize negative attitudes and help with anxiety. Couples therapy may be beneficial. Sex therapy includes counseling; cognitive behavioral therapy; and treatment of concomitant mental health conditions, such as depression and anxiety.

KEY POINT

- A sexual health history is an important part of the medical evaluation; open-ended questions regarding sexual activity and possible concerns, such as pain with intercourse, are appropriate and may uncover a previously unidentified disorder.

Vaginitis

Vaginitis describes conditions associated with vulvovaginal symptoms that may include vaginal discharge, burning, itching, or odor. Vaginal discharge can be physiologic, related to ovulation or pregnancy, or infectious, most commonly bacterial vaginosis, candidiasis, or trichomoniasis (**Table 69**). Other causes of vaginal discharge include irritation from use of douches, atrophic vaginitis, malignancy, or a foreign body.

History should include details about the type of vaginal discharge (volume, color, odor), timing related to menstrual cycle, use of douches, at-risk sexual behavior, dysuria, and dyspareunia. Physical examination includes assessment of the

TABLE 69. Clinical Presentation, Evaluation, and Management of Vaginitis

Cause of Vaginitis	Clinical Presentation	Evaluation	Management
Bacterial vaginosis	Malodorous or "fishy" vaginal discharge, often most noticeable after intercourse Increased thin white or gray discharge Symptoms other than malodor may be minimal	pH >4.5 KOH amine whiff test result positive Saline wet mount with >20% epithelial clue cells	Metronidazole: 500 mg orally twice daily for 7 days[a] (avoid alcohol during treatment and for 24 hours after last dose); or vaginal gel (0.75%) 5 g into vagina at bedtime for 5 nights Clindamycin: 300 mg orally twice daily for 7 days; or vaginal cream (2%) 5 g into vagina for 7 nights Note: Use oral regimens in pregnancy.
Vulvovaginal candidiasis	Itching, irritation, dysuria, dyspareunia, vulvodynia, excoriation, erythema, fissures Increased thick white discharge (although may be normal)	pH ≤4.5 KOH amine whiff test result negative KOH wet mount shows hyphae, pseudohyphae, or yeast	**Uncomplicated[b]** Fluconazole: 150 mg orally as a single dose Butoconazole vaginal: (2% cream) 5 g into vagina at bedtime for 3 nights Clotrimazole vaginal: (1% cream) 5 g into vagina at bedtime for 7-14 nights; or 100-mg vaginal tablet into vagina at bedtime for 7 nights; or 200 mg (two vaginal tablets) into vagina once daily at bedtime for 3 nights Miconazole vaginal: (2% cream) 5 g into vagina at bedtime for 7 nights; or 100-mg vaginal suppository into vagina at bedtime for 7 nights; or 200-mg vaginal suppository into vagina at bedtime for 3 nights Note: Single-dose vaginal preparations and non-imidazoles are available but less effective. **Complicated[c]** Longer duration of initial oral or topical treatment, followed by maintenance therapy: Fluconazole: 150 mg orally every 3 days for a total of three doses; or topical imidazole therapy for 7-14 nights Following this, maintenance therapy is based on refractory or recurrent symptoms: Fluconazole: 150 mg orally weekly for 6 months; or 200 mg orally weekly for 8 weeks; or 200 mg orally twice weekly for 4 months; or 200 mg orally once monthly for 6 months
Trichomoniasis	Increased discolored discharge (yellowish, gray, and/or frothy) Dyspareunia, dysuria, itch, erythema, postcoital bleeding, abdominal pain Punctate cervical hemorrhages ("strawberry" cervix)	pH ≥4.5 KOH amine whiff test result negative Saline wet mount with trichomonads, leukocytes NAAT or rapid assay result positive	Metronidazole[a]: 2 g orally as a single dose; treatment failure with 2-g metronidazole is treated with 500 mg orally twice daily for 7 days Note: Avoid alcohol during treatment and for 24 hours after last dose.

KOH = potassium hydroxide; NAAT = nucleic acid amplification test.

[a]Safe in pregnancy.

[b]Uncomplicated vulvovaginal candidiasis: *Candida albicans*, mild to moderate symptom severity, healthy nonpregnant women, four or fewer episodes per year.

[c]Complicated vulvovaginal candidiasis: Severe symptoms, suspected or proven non-albicans *Candida* species, more than four episodes per year, uncontrolled diabetes mellitus, or immunosuppression.

vulva and vagina for erythema, edema, excoriation, papillomas, and the type of discharge. However, clinical findings do not sufficiently distinguish between the common causes of vaginitis, and laboratory testing is necessary to establish a diagnosis. Diagnostic testing includes assessment of vaginal wall secretions for pH, amine (whiff) test, and microscopic evaluation with saline potassium hydroxide (KOH) wet mounts, or specific testing for trichomoniasis.

Bacterial Vaginosis

Bacterial vaginosis is the most common cause of vaginal discharge. It results from the loss of the normal hydrogen peroxide-producing lactobacilli in the vagina with an increase in the vaginal pH that contributes to an overgrowth of *Gardnerella vaginalis* and other anaerobes. Anaerobic overgrowth results in the production of amines, causing the characteristically malodorous discharge. Patients with bacterial vaginosis are at increased risk for STIs, including HIV infection, and for preterm delivery.

More than half of patients with bacterial vaginosis are asymptomatic. Symptomatic patients report a thin, vaginal discharge with a fishy odor. Clinical diagnosis includes the presence of at least three of four features: vaginal pH greater than 4.5, thin and homogeneous vaginal discharge, a positive whiff test result in which application of 10% KOH to vaginal secretions results in a fishy odor, and the finding of at least 20% clue cells on saline wet mount preparation. Clue cells are vaginal epithelial cells that on microscopy have ill-defined cell borders due to adherent coccobacilli (**Figure 16**).

Asymptomatic bacterial vaginosis does not require treatment. See Table 69 for treatment options for symptomatic bacterial vaginosis.

Vulvovaginal Candidiasis

Vulvovaginal candidiasis is the second most common cause of vaginitis; it is usually caused by *Candida albicans* and less commonly by non-albicans *Candida*. Unlike pharyngeal candidiasis, it frequently occurs in immunocompetent women with no risk factors. Factors that may increase the risk for vulvovaginal candidiasis include diabetes mellitus; pregnancy; and use of oral contraceptives, glucocorticoids, or antibiotics. Recurrent vulvovaginal candidiasis, characterized by infections occurring four or more times per year, is also caused by *C. albicans*, but up to 20% may be caused by *Candida glabrata* and other non-albicans *Candida* species.

Vulvovaginal candidiasis is typically characterized by vaginal itching, irritation, and discharge and may be associated with dysuria and dyspareunia. Examination reveals vulvar edema and excoriation, with thick, white, curdy vaginal discharge. Diagnostic testing involves a saline or 10% KOH wet mount of the discharge showing yeast, hyphae, or pseudohyphae (**Figure 17**). Women with negative wet mount results but signs and symptoms of candidiasis should have vaginal cultures for *Candida* performed and should be treated if results are positive. If cultures cannot be performed, empiric treatment is recommended.

Asymptomatic patients should not receive treatment. See Table 69 for treatment options of symptomatic uncomplicated and complicated vulvovaginal candidiasis. Recurrent symptoms after treatment warrant an evaluation for the presence of underlying predisposing factors. No evidence supports treatment of sexual partners of patients with vulvovaginal candidiasis.

Trichomoniasis

Trichomoniasis is a vaginal infection caused by *Trichomonas vaginalis*, a flagellated protozoan. It is a common STI, with a high prevalence among patients in STI clinics and incarcerated individuals. It is associated with increased risk for preterm labor in pregnancy as well as increased risk for HIV transmission.

Women may be asymptomatic or present with copious vaginal discharge that is malodorous, pale yellow or gray, frothy, and associated with vulval itching and burning. Vaginal pH is often elevated but is not helpful diagnostically. Testing may include microscopy, nucleic acid amplification testing (NAAT),

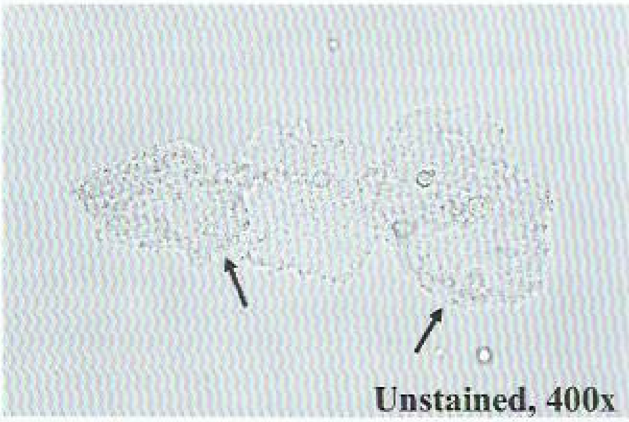

FIGURE 16. Clue cells are vaginal epithelial cells whose surface is studded with adherent coccobacilli bacteria (*arrows*), often obscuring the border of the epithelial cells; they are characteristic of bacterial vaginosis.

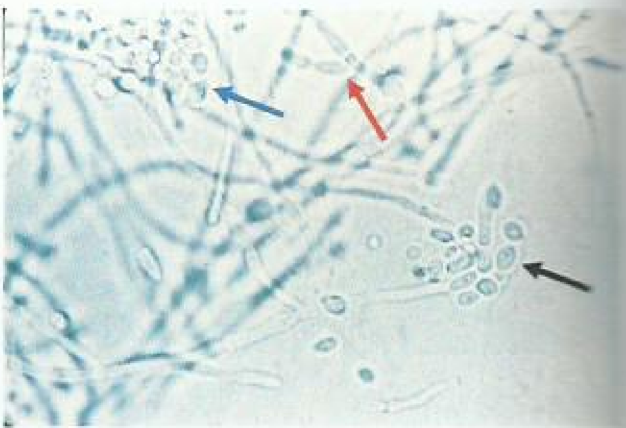

FIGURE 17. *Candida* vaginitis showing budding yeast (*blue arrow*), spores (*black arrow*), and elongated spores appearing as pseudohyphae (*red arrow*) with potassium hydroxide.

rapid antigen testing, and culture; choice of diagnostic testing is largely driven by availability. Microscopy with examination of a wet mount of the vaginal fluid showing motile trichomonads can establish the diagnosis when positive, but false-negative test results are common. NAAT or rapid antigen testing may be used as the primary diagnostic test or if the suspicion of trichomoniasis is high but the wet mount result is negative. When *Trichomonas* is identified, testing for other STIs should be considered. See Table 69 for treatment of trichomoniasis. Women should be retested within 3 months of treatment. Treatment of sexual partners is recommended to prevent reinfection.

KEY POINTS

- HVC Clinical findings do not sufficiently distinguish between the common causes of vaginitis, and laboratory testing is necessary to establish a diagnosis.
- HVC Clinical diagnosis of bacterial vaginosis includes the presence of at least three of four features: vaginal pH greater than 4.5, thin and homogeneous vaginal discharge, a positive whiff test result, and at least 20% clue cells on saline wet mount preparation.
- Diagnostic testing for vulvovaginal candidiasis involves a saline or 10% potassium hydroxide wet mount of the discharge showing yeast, hyphae, or pseudohyphae.
- Testing for trichomoniasis may include microscopy, nucleic acid amplification testing, rapid antigen testing, and culture; choice of diagnostic testing is largely driven by availability.

Eye Disorders

Eye Emergencies

H

Acute vision loss requires immediate ophthalmology evaluation. Selected conditions that can cause acute vision loss are listed in **Table 70**.

Trauma or chemical injury to the globe, eyelid, or nasolacrimal system also warrants urgent evaluation by an ophthalmologist. Patients with chemical injury to the eye should immediately receive eye irrigation to neutralize the ocular surface while awaiting ophthalmologic evaluation.

Vision-threatening eye infections requiring immediate intravenous antibiotics and ophthalmology evaluation include endophthalmitis (particularly bacterial infection of the aqueous and vitreous humors) and orbital cellulitis (infection of the fat and muscle cells of the orbit). Periorbital and preseptal cellulitis (infection anterior to the orbital septum) are less of a threat to sight. H

KEY POINT

- Eye emergencies requiring immediate ophthalmology evaluation include acute vision loss; trauma or chemical injury to the globe, eyelid, or nasolacrimal system; and vision-threatening eye infections.

TABLE 70. Selected Conditions Requiring Immediate Ophthalmologic Evaluation
Acute angle-closure glaucoma
Central retinal artery occlusion
Central retinal vein occlusion
Chemical injury
Corneal ulcers
Endophthalmitis
Keratitis
Optic neuritis
Orbital cellulitis
Retinal detachment
Scleritis
Trauma
Uveitis

Red Eye

Cardinal features of conditions that cause red eye are listed in **Table 71**.

Conjunctivitis

H

Conjunctivitis is the most common cause of red eye and is categorized as infectious (viral [**Figure 18**], bacterial [**Figure 19**]) or noninfectious (irritants, allergic). Factors favoring a bacterial cause include glued eyes in the morning, redness completely obscuring the tarsal vessels, purulent discharge, a red eye observed at 20 feet, and occurrence in the winter or spring. Lack of discharge decreases the likelihood of a bacterial cause. Bacterial conjunctivitis is often caused by *Staphylococcus aureus* and usually resolves within a week; however, topical antimicrobial treatment (erythromycin ophthalmic 0.5% ointment, trimethoprim-polymyxin B ophthalmic ointment) shortens the duration of symptoms by up to 1.5 days. Topical fluoroquinolones (such as levofloxacin) are not first-line therapy for routine bacterial conjunctivitis; however, they are indicated for conjunctivitis in contact lens wearers because of the high incidence of *Pseudomonas* infection. The threshold to treat with antibiotics is lowered in health care workers; patients in health care facilities; or patients with immunocompromise, including those with diabetes mellitus. Treatment of viral conjunctivitis is supportive, including cold compresses. Patients with viral conjunctivitis are considered contagious for as long as the eye continues to tear and produce discharge, usually 3 to 7 days. H

Keratitis

Keratitis represents infection and inflammation of the cornea. It most commonly results from bacterial infection (especially with *Pseudomonas* species) in contact lens wearers or in those with herpes simplex virus infection. Keratitis is an ocular emergency and requires urgent ophthalmology evaluation.

TABLE 71. Cardinal Features of Conditions That Cause Red Eye

Cause	Pain	Visual Symptoms	Examination Findings	Associated Systemic Conditions	Immediate Ophthalmologic Evaluation?
Conjunctivitis	Irritation only; associated with discharge and crusting	None unless discharge clouds vision	Diffuse erythema of conjunctiva, also involving inner aspect of eyelids	Usually limited to eye	No
Keratitis	Present, often with foreign body sensation	Blurred vision	Corneal stromal infiltrates or, in the case of herpes, corneal dendritic branching; circumferential redness around the border of the sclera and cornea (ciliary flush)	Usually limited to the eye	Yes
Episcleritis	Minimal	None	Superficial redness of episcleral vessels and episclera; may be localized	Minority of patients have underlying disease (rheumatoid arthritis, inflammatory bowel disease)	No
Scleritis	Severe, often worse with eye movement; associated tearing and photophobia	Decreased vision; may be complete loss	Scleral edema with diffuse deep red/violaceous discoloration; globe tenderness	>50% with rheumatologic disease (rheumatoid arthritis, vasculitis)	Yes
Uveitis/iritis	None to moderate	Variable; may include floaters	Ciliary flush; hypopyon (suppurative fluid seen in the dependent portion of the anterior chamber)	Common; infection (HSV, CMV); inflammatory disorders (spondyloarthritis, sarcoidosis)	Yes
Subconjunctival hemorrhage	Mild or none	None	Discrete bright red confluent region without hyperemia	Spontaneous; anticoagulation; trauma; increased pressure (coughing)	No

CMV = cytomegalovirus; HSV = herpes simplex virus.

FIGURE 18. Diffuse conjunctival injection and erythema, usually with a watery or mucoserous discharge, are characteristic of viral conjunctivitis.

Reproduced from Joyhill09. Eye with viral conjunctivitis. Digital image. http://commons.wikimedia.org/wiki/File:An_eye_with_viral_conjunctivitis.jpg. February 1, 2010. Accessed July 10, 2018. Licensed under the Creative Commons Attribution-ShareAlike 3.0 Unported (CC BY-SA 3.0) International License (https://creativecommons.org/licenses/by-sa/3.0/deed.en).

FIGURE 19. In patients with bacterial conjunctivitis, eye discharge is thick and may be yellow or green.

Reproduced from Tanalai. Swollen eye with conjunctivitis. Digital image. http://commons.wikimedia.org/wiki/File:Swollen_eye_with_conjunctivitis.jpg. January 22, 2008. Accessed July 10, 2018. Licensed under the Creative Commons Attribution 3.0 Unported (CC BY 3.0) International License (https://creativecommons.org/licenses/by/3.0/deed.en).

Episcleritis and Scleritis

Episcleritis is a focal, acute area of inflammation involving the superficial layers of the episclera. It is usually self-limited, resolving in a few weeks. Treatment is symptomatic and includes artificial tears; anti-inflammatory agents, such as topical NSAIDs and glucocorticoids, may be needed.

Scleritis is an inflammatory disorder of the sclera, which lies beneath the episcleral and conjunctival layers (**Figure 20**). Scleritis is an acute threat to vision and requires urgent evaluation by an ophthalmologist.

Uveitis

Anterior uveitis (iritis) is characterized by inflammation of the middle eye, including the iris, ciliary body, and choroid. In addition to pain, photophobia, vision impairment, and circumferential redness around the border of the sclera and cornea (ciliary flush), the pupil may have an irregular shape because it has become attached to the anterior surface of the lens or the posterior surface of the cornea. Uveitis requires urgent evaluation by an ophthalmologist.

Subconjunctival Hemorrhage

Subconjunctival hemorrhage is common and not a threat to vision (**Figure 21**). When symptoms are present, warm compresses or ophthalmic lubricants may provide relief. Symptoms should resolve gradually but may recur in patients receiving anticoagulants.

Blepharitis

Blepharitis is a common inflammatory condition of the eyelid margin and may be associated with rosacea. Treatment includes warm compresses, application of diluted shampoo with a cotton-tip applicator, topical antibiotics (for staphylococcal infections), and oral tetracyclines (for infections associated with rosacea).

FIGURE 20. The cardinal sign of scleritis is edema of the sclera often associated with a violaceous discoloration of the globe (*red arrow*). Tenderness is invariably present. Typically, there is intense dilation of episcleral blood vessels (*yellow arrow*). Scleral inflammation may be focal or diffuse.

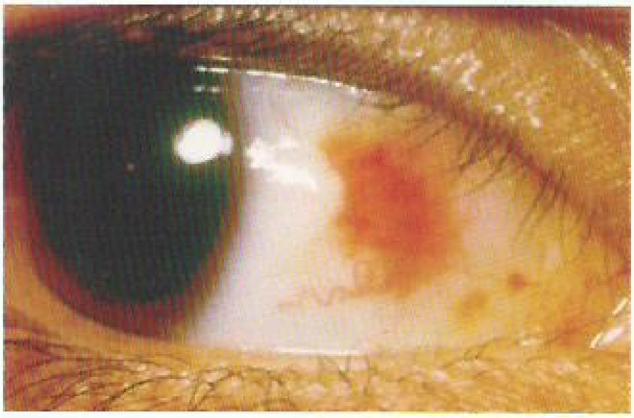

FIGURE 21. Subconjunctival hemorrhage is characterized by unilateral, localized, and sharply circumscribed redness without discharge or pain.

KEY POINTS

- Conjunctivitis is the most common cause of red eye and is associated with ocular irritation (not pain), discharge, and no impairment of vision.
- Keratitis is an ocular emergency that represents infection and inflammation of the cornea and is characterized by ocular redness, pain, and impaired vision.
- Episcleritis is a focal, acute area of typically asymptomatic inflammation involving the superficial layers of the episclera that is usually self-limited, whereas scleritis is a painful inflammatory disorder of the sclera associated with tearing and photophobia and is an acute threat to vision.

Dry Eye

Dry eye (keratoconjunctivitis sicca) is a multifactorial inflammatory disorder involving the tears and ocular surface. Symptoms may include eye dryness, a sensation of a foreign body in the eye, blurred vision, and light sensitivity. Examination may show decreased tearing, malposition of the lids, conjunctival erythema, blepharitis, or reduced blink rate. Validated symptom questionnaires may be diagnostically helpful. Ophthalmologists can perform more specific lacrimal function testing. Treatment includes artificial tears, environmental strategies (for example, increased humidification), and topical cyclosporine. Oral omega-3 fatty acid supplements may alleviate the symptoms of dry eye syndrome.

KEY POINT

- Treatment of dry eye includes artificial tears, environmental strategies, and topical cyclosporine.

Corneal Abrasion and Ulcer

Corneal abrasions are often caused by trauma from a foreign body. Pain, sensation of a foreign body, watery eyes, red eye, photophobia, and reactive miosis may be present. Corneal examination involves fluorescein dye and a Wood lamp or slit lamp. Management of uncomplicated abrasions includes topical NSAIDs. Current evidence does not support the use of topical antibiotics or eye patching. Topical anesthetics may decrease rate of healing and should be avoided. The presence of a corneal ulcer requires prompt evaluation by an ophthalmologist.

Cataracts

Cataracts are opacifications of the lens and should be suspected in patients presenting with painless gradual worsening of visual acuity. Direct ophthalmoscopy shows lens opacification, a diminished red reflex, and obscured funduscopic examination. Surgery is indicated when vision impairment interferes with the patient's activities of daily living.

Glaucoma

Glaucoma is the leading cause of permanent blindness in the world. It is typically characterized by increased intraocular pressure (IOP) as a result of decreased outflow of aqueous humor from the anterior chamber. However, according to the U.S. Preventive Services Task Force, there is insufficient evidence to recommend screening for glaucoma in adults.

Primary Open-Angle Glaucoma

Primary open-angle glaucoma accounts for more than 80% of glaucoma cases in the United States. Increased resistance to aqueous outflow through the trabecular meshwork leads to increased IOP and vision loss through retinal cell death. Patients may present with bilateral peripheral visual loss that is gradual and painless. Funduscopic examination may demonstrate increased cup-to-disc ratio (CDR) (**Figure 22**), CDR asymmetry, and disc hemorrhage. Treatment is directed by an ophthalmologist and involves medications (topical prostaglandins, β-blockers, and α-adrenergic agonists) to decrease IOP and, when refractory, surgery.

Angle-Closure Glaucoma

Angle-closure glaucoma is caused by mechanical obstruction of the aqueous humor drainage at the angle of the anterior chamber, leading to increased IOP. Blockage is usually secondary to the positioning of the lens on the iris; if blockage is present chronically, patients may be asymptomatic until advanced vision loss has occurred. Acute blockage may occur with exposure to sympathomimetic or anticholinergic medications or with pupillary dilation.

Patients with acute blockage present with severe eye pain, headache, nausea, and blurred vision or halos around lights.

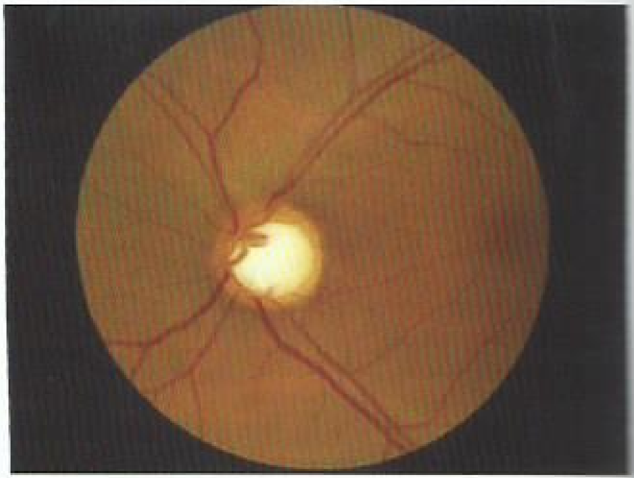

FIGURE 22. A relatively large cup-to-disc ratio and cupping identified by the disappearance of vessels over the edge of the attenuated optic rim are characteristic of glaucoma.

Examination may demonstrate severe conjunctive hyperemia, corneal edema, a mid-dilated (4-6 mm) nonreactive pupil, and severe elevation in IOP. Because of the immediate threat to vision, urgent evaluation by an ophthalmologist is required.

KEY POINTS

- Primary open-angle glaucoma is characterized by increased intraocular pressure, increased cup-to-disc ratio (CDR), CDR asymmetry, and bilateral peripheral visual loss that is gradual and painless.
- Patients with acute angle-closure glaucoma present with severe eye pain, headache, nausea, and blurred vision or halos around lights, and examination may demonstrate severe conjunctive hyperemia, corneal edema, a mid-dilated (4-6 mm) nonreactive pupil, and severe elevation in intraocular pressure; urgent evaluation by an ophthalmologist is required because of the immediate threat to vision.

Age-Related Macular Degeneration

Age-related macular degeneration (AMD) is a progressive chronic disease involving the central retina. Patients with early AMD are often asymptomatic, although yellow drusen may be visible underneath retinal pigment epithelium (**Figure 23**). Patients with atrophic (dry) AMD, which accounts for 80% to 90% of AMD cases, note slowly progressive vision loss over years. About 10% to 20% of patients with atrophic AMD progress to neovascular (wet) AMD, which often presents with more rapid visual loss and may be accompanied by a sudden worsening of central vision associated with straight-line distortion (metamorphopsia), scotoma, or both.

Smoking cessation decreases the risk for developing AMD and should be recommended to all patients who smoke. There

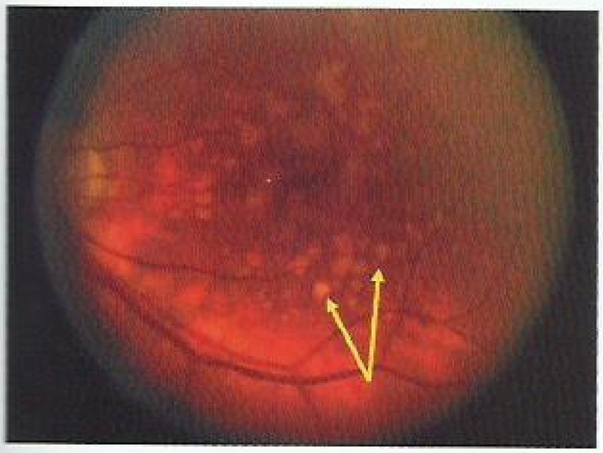

FIGURE 23. Atrophic (dry) age-related macular degeneration showing distinct yellow-white lesions called drusen (*arrows*) surrounding the macular area and areas of pigment mottling.

FIGURE 24. Optic nerve papillitis is characterized by hyperemia and swelling of the disc, blurring of disc margins, and distended veins (*arrow*). The normal arteriole-to-venous ratio is approximately 4:5.

is no cure for atrophic AMD; however, dietary supplementation with high-dose antioxidants, vitamins, and zinc can delay the progression of AMD. First-line treatment for neovascular AMD is anti–vascular endothelial growth factor (VEGF) therapies. The treatment burden of the intravitreal injections, however, is high, and the long-term risk for systemic absorption of VEGF inhibitors is unknown.

KEY POINT

- Smoking cessation decreases the risk for age-related macular degeneration and should be recommended to all patients who smoke.

Optic Neuritis

Optic neuritis is characterized by inflammation and demyelination of the optic nerve. Usually unilateral in onset, it presents with visual loss occurring over hours to days. It is associated with acute pain, particularly with eye movement, as well as loss of color vision. Examination may demonstrate an afferent pupillary defect (paradoxical dilation of the affected pupil when the examining light is rapidly shifted from the unaffected to the affected eye); papillitis (swollen disc with blurred margin) may be seen on funduscopy in one third of patients (**Figure 24**). Two thirds of patients will have retrobulbar neuritis and a normal funduscopic examination. Urgent evaluation by an ophthalmologist is required. Although the diagnosis is clinical, MRI usually reveals demyelination of the optic nerve. Treatment with high-dose intravenous glucocorticoids improves the rate of visual recovery.

Retinal Detachment

Patients with retinal detachment may present with a unilateral increase in floaters followed by a sudden, peripheral visual field defect that resembles a black curtain and may progress across the entire visual field. A retinal tear and elevation of the surrounding retina may be visible on dilated funduscopy. Immediate evaluation by an ophthalmologist is indicated for surgical treatment.

Retinal Vascular Occlusion

Retinal Artery Occlusion

Patients with central retinal artery occlusion present with acute, profound, and painless loss of monocular vision. It is most commonly associated with carotid artery atherosclerosis but may be associated with cardiogenic embolism, thrombophilia, or giant cell arteritis. Examination usually shows an afferent pupillary defect; funduscopic examination may show a "cherry red spot" at the fovea surrounded by retinal pallor. Emergent evaluation by an ophthalmologist is necessary.

Retinal Vein Occlusion

Central retinal vein occlusion (CRVO) is usually associated with thrombus formation in the central retinal vein, whereas branch retinal vein occlusion (BRVO) appears related to compression of the branch vein by nearby crossing arterioles. Both are associated with cardiovascular risk factors, including hypertension, diabetes, and tobacco use. CRVO often presents with acute onset of painless blurred monocular vision. BRVO may be asymptomatic but may present with scotoma or focal field defects of blurriness corresponding to the area of retinal vein occlusion.

Examination may reveal an afferent pupillary defect (particularly in CRVO), retinal vein congestion, retinal hemorrhage, and cotton-wool spots (**Figure 25**). A patient whose presentation suggests CRVO requires immediate evaluation by an ophthalmologist.

FIGURE 25. Central retinal vein occlusion is characterized by optic disc swelling, dilated and tortuous veins, as well as flame-shaped retinal hemorrhages (*white arrow*) and cotton-wool spots (*yellow arrow*) ("blood and thunder").

KEY POINTS

- Central retinal artery occlusion may present with acute, profound, and painless loss of monocular vision and is most commonly associated with carotid artery atherosclerosis.

(Continued)

KEY POINTS *(continued)*

- Central retinal vein occlusion is usually associated with thrombus formation in the central retinal vein and often presents with acute onset of painless blurred monocular vision; immediate evaluation by an ophthalmologist is required.

Ear, Nose, Mouth, and Throat Disorders

Hearing Loss

Hearing loss is common. It is associated with depression and functional decline but underrecognized by patients and physicians. The U.S. Preventive Services Task Force has concluded that there is insufficient evidence to assess the benefits and harms of screening for hearing loss in asymptomatic older adults.

Hearing loss is categorized according to the anatomic deficit: conductive, sensorineural, or mixed (Table 72). Conductive hearing loss is more often associated with pain or ear drainage, whereas sensorineural hearing loss is more often accompanied by tinnitus or vertigo.

TABLE 72. Causes of Hearing Loss

Cause	Description
Conductive Hearing Loss[a]	
Cerumen impaction	May completely obstruct ear canal
Otosclerosis	Associated with overgrowth of bone in the middle ear
Tympanic membrane perforation	Often heals without intervention
Cholesteatoma	Abnormal growth of keratinized squamous epithelium in the middle ear
Sensorineural Hearing Loss[b]	
Presbycusis	Age-related hearing loss; often symmetric, high-frequency loss
Sudden sensorineural hearing loss	Often idiopathic, more often unilateral
Meniere disease	Classically, triad of sensorineural hearing loss, tinnitus, and vertigo; not all are necessarily present at once, may fluctuate
Acoustic neuroma	Benign tumor of Schwann cell sheath surrounding vestibular or cochlear nerve
Noise	May be related to chronic noise exposure or sudden, short noise blast exposure
Ototoxic drugs	Antibiotics (aminoglycosides, erythromycin, vancomycin) Chemotherapeutic agents (cisplatin, carboplatin, vincristine) Loop diuretics Anti-inflammatory agents (aspirin, NSAIDs, quinine)
Mixed or Causing Either Conductive or Sensorineural Hearing Loss	
Infection	Labyrinthitis, otitis media, chronic otitis
Head trauma	May be caused by ossicular disruption leading to conductive hearing loss or by auditory nerve injury causing sensorineural hearing loss

[a]Conductive hearing loss is inadequate mechanical transmission of sound through the tympanic membrane and ossicles of the middle ear.

[b]Sensorineural hearing loss is deficit or injury of the vestibulocochlear nerve.

Assessment of hearing may begin with asking the patient about perceived hearing loss (for example, "Do you have difficulty hearing?"). More formal screening can also be performed (Table 73).

In patients with hearing loss, physical examination should include otoscopic examination as well as the Weber and Rinne tests (Table 74), which can help differentiate sensorineural from conductive hearing loss. Referral to an audiologist is indicated when hearing loss is identified. Imaging (typically MRI) is rarely required unless the hearing loss is acute, unilateral, progressive, or associated with other neurologic changes. Patients should be evaluated urgently by an otolaryngologist when there is sudden sensorineural hearing loss, hearing loss with vertigo, or hearing loss associated with head trauma. Vertigo is discussed in Common Symptoms.

Treatment options for hearing loss include assistive listening devices, hearing aids, and cochlear implants. Treatment of sudden sensorineural hearing loss involves oral glucocorticoids, although strong evidence of efficacy is lacking.

TABLE 73. Screening Maneuvers to Assess Hearing

Screening Maneuver	Technique
Patient Self-Assessment	
Single-item screening	Patient answers yes or no to the following question: "Do you feel you have hearing loss?"
Hearing Handicap Inventory for the Elderly-Screening Version	Patient answers 10-item question set, with options of yes, no, or sometimes.
Clinician Examination	
Finger rub test	The examiner gently rubs two fingers together at a distance of 15 cm (6 in) from patient's ear. A positive test result is failure to identify rub in more than two of six attempts.
Whispered voice test	The examiner stands an arm's length behind the patient and masks the untested ear by occluding the canal and rubbing the tragus. The examiner whispers six sets of three letter or number combinations. Failure to repeat at least three sets correctly is a positive test result.
Handheld audiometer	The examiner holds the device in the patient's ear while the patient indicates awareness of each tone. A positive test result is a failure to identify the 1000-Hz or 2000-Hz frequency in both ears or the 1000-Hz and 2000-Hz frequency in one ear.

TABLE 74. Distinguishing Between Conductive and Sensorineural Hearing Loss With the Weber and Rinne Tests

Condition	Weber Test[a] Result	Rinne Test[b] Result
Conductive hearing loss	Louder in the affected ear	Decreased in the affected ear (bone conduction > air conduction)
Sensorineural hearing loss	Louder in the unaffected ear	As loud or louder in the affected ear (air conduction > bone conduction)

[a]A 256-Hz vibrating tuning fork (although a 512-Hz tuning fork may be used) is applied to the forehead or scalp at the midline, and the patient is asked if the sound is louder in one ear or the other; a normal test result shows no lateralization.

[b]A 512-Hz vibrating tuning fork is applied to the mastoid process of the affected ear until it is no longer heard. The fork is then repositioned outside of the external auditory canal, and the patient is asked if he or she can again hear the tuning fork; with a normal test result, air conduction is greater than bone conduction, and the tuning fork can be heard.

KEY POINTS

- Assessment of hearing may begin with asking the patient about perceived hearing loss (for example, "Do you have difficulty hearing?"). HVC
- Patients should be evaluated urgently by an otolaryngologist when there is sudden sensorineural hearing loss, hearing loss with vertigo, or hearing loss associated with head trauma.

Tinnitus

Tinnitus is the conscious perception of an auditory sensation (for example, buzzing or ringing) without an external stimulus. Evaluation should include assessment for hearing loss and cardiovascular, cerebrovascular, and neurologic disease, including examination of the carotid arteries and temporal bone for bruits. Patients with unilateral tinnitus should undergo prompt audiologic assessment and, if hearing loss is confirmed, MRI to examine for acoustic neuroma. Patients should be evaluated urgently by an otolaryngologist when tinnitus is associated with sudden hearing loss, otorrhea, vestibular dysfunction, focal neurologic deficits, or pulsatile tinnitus (particularly if tinnitus is sudden in onset, which may suggest a vascular cause).

Treatment involves addressing the underlying condition. Medications have not been shown to be of benefit, but antidepressants may reduce associated distress. Cognitive behavioral therapy, relaxation therapy, and tinnitus retraining therapy may also be helpful.

KEY POINT

- Medications have not been shown to be of benefit for tinnitus, but antidepressants may reduce associated distress. HVC

Otitis Media and Otitis Externa

Patients with acute otitis media have ear pain along with bulging or intense erythema of the tympanic membrane or new

onset of otorrhea not associated with otitis externa. Few published studies guide management in adults. In children, guidelines suggest use of antibiotics when there is otorrhea or severe signs and symptoms (including moderate to severe otalgia lasting for >48 hours or temperature >39 °C [102.2 °F]). In milder cases, management may consist of observation first with antibiotics for worsening or persistent symptoms. An otolaryngologist should evaluate adults with recurrent acute or persistent otitis media with effusion.

Acute otitis externa is cellulitis of the ear canal with associated inflammation and edema. Bacterial infection, usually with *Pseudomonas* or *Staphylococcus aureus*, causes most cases (90%). Topical treatments, including antibiotics, glucocorticoids, antiseptics, and combination therapies, are first-line management for uncomplicated acute otitis externa; aminoglycosides should be avoided if tympanic membrane perforation is present or possible. Pseudomonal infections, especially in patients with diabetes mellitus, may be aggressive and result in spread to contiguous structures, including bone (malignant otitis externa); treatment requires systemic antipseudomonal antibiotics and urgent referral to an otolaryngologist.

KEY POINT

- Malignant otitis externa requires systemic antipseudomonal antibiotics and urgent referral to an otolaryngologist.

Cerumen Impaction

Cerumen has protective, emollient, and bactericidal properties. However, its normal expulsion, assisted by jaw movement, is sometimes hindered, and cerumen accumulation may cause pain, itching, tinnitus, or hearing loss. When symptomatic, cerumen can be removed by irrigation, manual removal, or topical preparations. No topical agent has demonstrated superiority. Irrigation in the presence of a perforated tympanic membrane may cause vertiginous symptoms; mechanical removal is preferred in these instances.

Upper Respiratory Tract Infection

Sinusitis

Acute rhinosinusitis presents with nasal congestion, purulent nasal discharge, facial pain/pressure, fever, or cough. Most cases are caused by viruses, allergies, or irritants. It is usually self-limited; decongestants and mucolytics may alleviate symptoms. Avoidance of unnecessary antibiotics represents high value care. Indications for antibiotic treatment and regimens are described in **Table 75**. Patients who are seriously ill, deteriorate despite appropriate antibiotic therapy, or have recurrent episodes should be evaluated by an otolaryngologist.

Chronic sinusitis manifests with at least 12 weeks of nasal congestion with purulent drainage, diminished sense of smell, or facial pain/pressure. It may be associated with nasal polyposis (with a strong association with asthma). Demonstration of mucosal involvement by nasal endoscopy or imaging (typically CT) is necessary for diagnosis. Treatment includes glucocorticoids and antibiotics.

TABLE 75. Acute Sinusitis Treatment[a]

Indications for Antibiotic Treatment	First-Line Therapy[b]	Penicillin Allergy
Persistent symptoms of >10 days' duration Onset of severe symptoms or signs of high fever >39 °C (102.2 °F) with purulent nasal discharge or facial pain lasting for at least 3 consecutive days Onset of worsening symptoms following a typical viral illness that lasted 5 days after initially improving ("double sickening")	Amoxicillin-clavulanate or amoxicillin	Doxycycline (adults only) or Levofloxacin or moxifloxacin or Clindamycin

[a]There is limited evidence to guide therapy, particularly in adults, and guidelines from major professional societies differ.

[b]Adjunctive therapy, such as intranasal saline irrigation or intranasal glucocorticoids, has been shown to alleviate symptoms and potentially decrease antibiotic use.

Rhinitis

Allergic rhinitis involves sneezing, congestion, and rhinorrhea often linked to a season or exposure. Nonallergic rhinitis occurs in response to nonallergic stimuli, such as spicy foods and irritants. First-line treatment of allergic and nonallergic rhinitis consists of avoiding precipitating factors and monotherapy with intranasal glucocorticoids (rather than an intranasal glucocorticoid in combination with an oral antihistamine or a leukotriene receptor antagonist). Rhinitis medicamentosa is chronic rhinitis resulting from the inappropriate long term use of topical nasal decongestants. Treatment consists of cessation of the decongestant and intranasal glucocorticoids when needed.

Pharyngitis

Pharyngitis presents as sore throat that may worsen with swallowing. Symptoms typically last less than 1 week. Features suggesting the more common viral cause include cough, conjunctivitis, coryza, hoarseness, and oral ulcers. Only 5% to 15% of pharyngitis cases are caused by bacteria, most often group A *Streptococcus pyogenes*. In these cases, appropriate antibiotic treatment reduces the risk for rheumatic fever, suppurative complications (such as peritonsillar or retropharyngeal abscess), duration of symptoms, and transmission. Patients with fewer than three of the four Centor criteria (fever by history, tonsillar exudates, tender anterior cervical lymphadenopathy, and absence of cough) do not need to be tested or treated for group A *Streptococcus*. These patients should be treated conservatively with symptom control (such as analgesics [NSAIDs or acetaminophen], lozenges or topical sprays,

and increased environmental humidity). Patients with three or more Centor criteria should be tested by using a rapid antigen detection test. Throat culture should be considered in patients who are at high risk for complications (immunocompromised state) in the setting of high clinical suspicion but negative results on rapid antigen detection testing. Antibiotic treatment is reserved for patients with positive test results; penicillin and amoxicillin are first-line therapies.

Fusobacterium necrophorum infection can cause Lemierre syndrome, a rare suppurative complication of pharyngitis caused by local spread of infection with resultant septic thrombosis of the internal jugular vein. Clinicians should suspect Lemierre syndrome in patients with severe pharyngitis and neck pain that do not respond to appropriate antibiotics. Diagnosis is made with contrast CT of the neck.

KEY POINTS

- Acute rhinosinusitis is usually caused by viruses, allergies, or irritants, and avoidance of unnecessary antibiotics represents high value care.
- Patients with pharyngitis who present with fewer than three of the four Centor criteria do not need to be tested or treated for group A *Streptococcus* infection.

Epistaxis

Ninety percent of epistaxis cases occur in the anterior nasal septum. Cases that occur in the posterior nasopharynx are more common in older patients. The history should include local trauma, nose picking, nasal medications, insufficient humidification, infection, drug use, and coagulopathies.

Anterior bleeds can be managed with compression for at least 15 minutes. Concomitant use of topical vasoconstrictors, such as oxymetazoline, may be useful. Refractory bleeding may require cautery or nasal packing and, rarely, embolization or surgical ligation. Posterior bleeds may cause substantial blood loss; most patients will require hospitalization and otolaryngology consultation. Patients with recurrent unilateral epistaxis should undergo CT or MRI imaging and nasal endoscopy.

KEY POINT

- Anterior epistaxis can usually be managed with compression and concomitant administration of topical vasoconstrictors, such as oxymetazoline.

Oral Health

Oral Infection and Ulcers

Oral mucosal findings are discussed in MKSAP 18 Dermatology.

Dental Infections

Dental infections may involve the gingiva, tooth, or supportive bony structures. Infection of the tooth is often asymptomatic until the pulp cavity is involved, which leads to abscess. Abscess often necessitates root canal (removal of the diseased pulp).

Dental caries (**Figure 26**) is caused by bacteria that destroy enamel and dentin, resulting in tooth sensitivity or pain and stained pits and fissures on tooth surfaces. Caries may lead to odontogenic infection and tooth loss.

Periodontal infections are caused by bacteria in subgingival dental plaque, leading to gingivitis (inflamed gums) (**Figure 27**) or periodontitis (loss of supportive bone structure from chronic gingivitis). Chronic periodontal disease is associated with increased risk for cardiovascular disease. Fluoride and good dental hygiene are essential for prevention and treatment.

The presence of dental caries or periodontal disease should prompt dental consultation.

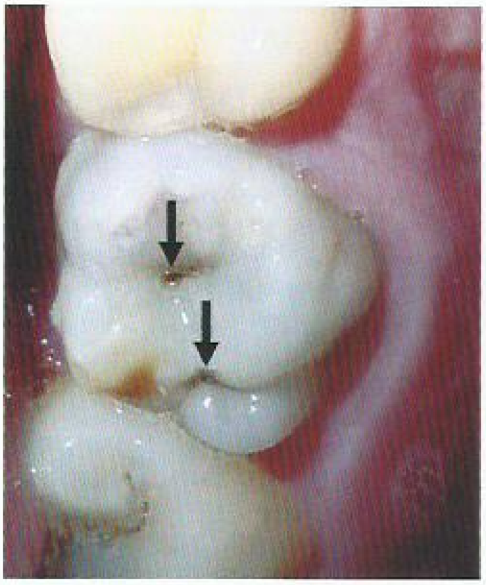

FIGURE 26. Dental caries (cavities or tooth decay) represents localized destruction of dental hard tissues and appears as black or brown spots on the surface of the tooth.

Modified from Nerval. Tooth with extensive evidence of dental caries. Digital image. https://commons.wikimedia.org/wiki/File:Toothdecay_(1).jpg. January 21, 2004. Accessed July 10, 2018. Licensed under the Creative Commons Attribution-ShareAlike 3.0 Unported (CC BY-SA 3.0) International License (https://creativecommons.org/licenses/by-sa/3.0/deed.en).

FIGURE 27. Red and swollen gingival tissue (*blue arrows*) that typically bleeds with brushing or flossing is characteristic of gingivitis. Also seen is abundant yellow dental plaque at the gum line and between teeth (*green arrows*).

Reproduced from Wikimedia Commons. Gingivitis before treatment. Digital image. https://commons.wikimedia.org/wiki/Category:Gingivitis#/media/File:Gingivitis-before.JPG. August 8, 2013. Accessed July 10, 2018.

Mental and Behavioral Health

Mood Disorders

Mood disorders are characterized by elevation or depression of mood associated with psychomotor, cognitive, and/or vegetative symptoms that cause significant functional impairment. The two main groups of mood disorders are depressive disorders and bipolar disorder.

Depressive Disorders

The lifetime prevalence of depressive disorders in developed countries is approximately 20%, and women are affected almost twice as often as men. The peak onset is in the fifth decade of life, and incidence decreases in the elderly population. Depression is the leading cause of disability in the United States among individuals aged 15 to 44 years and is a major risk factor for suicide.

Depressive disorders most often initially present in the primary care setting but are underdiagnosed. Depressive symptoms are frequently encountered in patients with chronic medical disease either as a result of the illness itself (such as hypothyroidism) or as a response to the disability caused by the illness. Depression commonly accompanies many medical conditions, including cancer, neurologic diseases (Parkinson disease), heart failure, and HIV infection. Medications, including glucocorticoids and interferon, may also trigger depressive symptoms. Clinicians must exclude these potential causes of depressive symptoms during the evaluation of any patient for depression.

Screening for depression is underperformed, and the U.S. Preventive Services Task Force advises screening all patients for depression during primary care visits, with adequate systems in place to ensure accurate diagnosis, effective treatment, and appropriate follow-up. For such general-population screening, the PHQ-2 is effective and easy to use. If a patient provides a positive response to either of the two questions ("Over the past 2 weeks, have you felt down, depressed, or hopeless?" and "Over the past 2 weeks, have you felt little interest or pleasure in doing things?"), further investigation for depression is warranted.

Diagnosis

Major Depressive Disorder

The DSM-5 criteria for diagnosis of major depressive disorder require at least five of the following symptoms (at least one of which must be depressed mood or anhedonia) during the same 2-week period:

- Depressed mood most of the day, almost every day
- Anhedonia (loss of interest or pleasure in nearly all activities), almost all the time
- Insomnia or hypersomnia almost every day
- Significant change in weight (gain or loss) or appetite (increase or decrease) nearly every day
- Fatigue or decreased energy nearly every day
- Psychomotor agitation or retardation almost every day
- Decreased ability to concentrate almost all the time
- Feelings of worthlessness or of excessive or inappropriate guilt nearly every day
- Recurrent thoughts of death or suicidal ideation (with or without a specific plan), or a suicide attempt

For a diagnosis of major depressive disorder, the symptoms cannot be attributable to a medical condition, medication, or substance use and must cause significant functional impairment. Clinicians must assess patients with depression for any history of elevated mood, which would suggest bipolar disorder; prescribing antidepressant monotherapy to a patient with bipolar disorder may precipitate a manic episode.

Persistent Depressive Disorder

Previously known as dysthymia, persistent depressive disorder is characterized by depressed mood most of the time for at least 2 years with at least two of the following symptoms while depressed: appetite change (increased or decreased), fatigue or low energy, decreased self-esteem, insomnia or hypersomnia, poor concentration, and feelings of hopelessness. These symptoms are milder than in major depressive disorder but still cause impairment of social or occupational functioning. Symptoms can temporarily resolve but do not abate for more than 2 months at a time.

Seasonal Affective Disorder

Seasonal affective disorder (SAD) is defined as major depressive disorder, mania, or hypomania with recurrent seasonal onset and resolution. SAD is not a separate diagnostic entity; rather, it is a subtype of each of these mood disorders (with the specifier "with seasonal pattern"). The most common form of SAD is major depressive disorder in which symptoms arise during autumn or winter and subside the following spring for at least 2 consecutive years (major depressive disorder with seasonal pattern). Seasonal episodes of depression substantially outnumber nonseasonal episodes. The diagnostic criteria are otherwise the same as for major depressive disorder.

Premenstrual Dysphoric Disorder

Premenstrual dysphoric disorder consists of symptoms of mood disturbance that develop the week before menses, remit within a week after menses, and occur with most menstrual cycles during a given year. Diagnosis requires the presence of at least one primary symptom: mood swings, irritability or anger, feelings of hopelessness or depressed mood, and anxiety. Additionally, a patient must have a total of at least five symptoms, which may also include appetite changes, decreased interest in usual activities, fatigue, difficulty concentrating, feelings of loss of control, sleep disturbance, and physical symptoms (breast tenderness, weight gain, bloating, myalgia).

Peripartum Depression

Peripartum depression affects 7% of pregnant or postpartum women and is characterized as a major depressive disorder occurring during pregnancy or within 4 weeks after delivery. It is not considered a separate mood disorder; instead, it is a subtype of major depressive disorder with the specifier "with peripartum onset." Risk factors include previous depression, anxiety, low socioeconomic status, lack of social support, previous physical abuse, and unintended pregnancy. Treatment is similar to that used for other forms of depression but with close attention to drug safety in pregnancy and breastfeeding.

Persistent Complex Bereavement Disorder

Grief is a normal response to interpersonal loss (such as death of a loved one) and may include symptoms of labile emotions, sadness, loneliness, and even fleeting hallucinations of deceased loved ones. The grief process varies, but most patients functionally adapt to loss within 12 months. Pathologic grieving persists longer and is accompanied by intense longing for and preoccupation with the deceased, along with feelings of emptiness and inability to live after the loss. This response to grief is termed "complicated grief," or "persistent complex bereavement disorder" (as proposed in DSM-5 as a future diagnostic classification). Up to 10% of bereaved patients develop persistent complex bereavement disorder, but the incidence is doubled in patients with other mood disorders. Other risk factors include older age, loss of a spouse or child, and sudden death of loved one. A major life loss can induce other mood disorders; therefore, clinicians should maintain a high index of suspicion for these disorders in the bereaved patient.

Management

Most patients with major depressive disorder can be successfully managed in the primary care setting. Referral to a psychiatrist is indicated for patients with severe depression, failure of initial therapy, complex psychiatric comorbidities, and high suicide risk. Before initiating therapy, clinicians must assess medical comorbidities, other medical treatments, and substance use, which may contribute to depression. For initial acute therapy, a 2016 clinical practice guideline from the American College of Physicians recommends either cognitive behavioral therapy (CBT) or second-generation antidepressants (SGAs) after discussing treatment and side effects, cost, accessibility, and patient preferences. It is unclear whether combination therapy with both CBT and medication therapy is more efficacious than either treatment modality alone. Other psychologic therapies are available as second-line options (**Table 76**).

Four classes of SGAs are available: selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), serotonin modulators, and atypical antidepressants (**Table 77**). Drug selection should be based on side effect profiles and patient-specific characteristics. Side effects are common, and patient education regarding adverse effects can improve adherence. SSRIs are generally well tolerated but can cause reduced sexual desire, anorgasmia, and delayed orgasm. Bupropion causes fewer sexual side effects but is contraindicated in patients with seizure disorders. SSRIs, SNRIs, bupropion, and monoamine oxidase inhibitors all have the potential to cause serotonin syndrome, particularly if used in combination or with other specific medications (including metoclopramide, tramadol, and linezolid).

After starting with a low dosage, the medication should be gradually titrated to achieve a clinical response while monitoring for adverse effects. Therapeutic response can be objectively measured with the PHQ-9 (https://www.integration.samhsa.gov/images/res/PHQ%20-%20Questions.pdf) by comparing scores before and during treatment. A decrease in the score of at least 50% indicates a response to treatment; a decrease to a score of less than 5 indicates remission. If initial monotherapy fails to achieve an adequate response within 6 to 12 weeks, potential next therapeutic steps are guided by the initial choice of therapy and the presence of any response. If a partial response occurs, increasing the dosage of the chosen medication or adding psychotherapy (if not already used) may be appropriate. If no response is seen, switching to another SGA or adding a second agent with or without psychotherapy is indicated. A second-line approach is the addition of an antipsychotic drug. FDA-approved antidepressant-antipsychotic combinations include olanzapine with fluoxetine and aripiprazole or quetiapine with any antidepressant. In cases of resistant depression, electroconvulsive therapy is also safe and effective.

Approximately half of patients who respond to appropriate initial therapy (CBT or SGA monotherapy) develop recurrent depression after 1 year without continued treatment. The American Psychiatric Association recommends continuation

TABLE 76. Common Psychological Interventions to Treat Depression

Intervention	Description
Acceptance and commitment therapy	Uses mindfulness techniques to overcome negative thoughts and accept difficulties
Cognitive therapy	Helps patients correct false self-beliefs and negative thoughts
Cognitive behavioral therapy	Includes a behavioral component in cognitive therapy, such as activity scheduling and homework
Interpersonal therapy	Focuses on relationships and how to address issues related to them
Psychodynamic therapy	Focuses on conscious and unconscious feelings and experiences
Third-wave cognitive behavioral therapy	Targets thought processes to help persons with awareness and acceptance

Reproduced with permission from Qaseem A, Barry MJ, Kansagara D; Clinical Guidelines Committee of the American College of Physicians. Nonpharmacologic versus pharmacologic treatment of adult patients with major depressive disorder: a clinical practice guideline from the American College of Physicians. Ann Intern Med. 2016;164:351. [PMID: 26857948] doi:10.7326/M15-2570. Copyright 2016, American College of Physicians.

TABLE 77. Dosages and Comparative Adverse Effects of Second-Generation Antidepressants

Drug	Dosage (mg/d)	Comparative or Drug-Specific Adverse Effects[a]
Selective serotonin reuptake inhibitors (SSRIs)		
Citalopram	20-40	Possible increased risk for QT interval prolongation and torsade de pointes (dosages >40 mg/d)
Escitalopram	10-20	N/A
Fluoxetine	10-80	Lowest rates of discontinuation syndrome compared with other SSRIs
Paroxetine	20-60	Highest rates of sexual dysfunction among SSRIs; higher rates of weight gain; highest rates of discontinuation syndrome
Sertraline	50-200	Higher incidence of diarrhea syndrome
Fluvoxamine	40-120	N/A
Serotonin-norepinephrine reuptake inhibitors (SNRIs)		
Venlafaxine	75-375	Higher rates of nausea and vomiting; higher rates of discontinuations due to adverse events than SSRIs as a class; highest rates of discontinuation syndrome; duloxetine has lower rates of adverse events and discontinuation syndrome than other SNRIs
Venlafaxine XR	75-225	
Desvenlafaxine	50-100	Same as venlafaxine
Duloxetine	60-120	Same as venlafaxine
Serotonin modulators		
Nefazodone	200-600	N/A
Atypical antidepressants		
Bupropion	200-450	Lower rate of sexual adverse events than escitalopram, fluoxetine, paroxetine, and sertraline
Bupropion SR	150-400	

N/A = not available; SR = sustained release; XR = extended release.

[a]Common adverse effects associated with second-generation antidepressants include constipation, diarrhea, dizziness, headache, insomnia, nausea, sexual adverse events, and somnolence.

Adapted with permission from Qaseem A, Barry MJ, Kansagara D; Clinical Guidelines Committee of the American College of Physicians. Nonpharmacologic versus pharmacologic treatment of adult patients with major depressive disorder: a clinical practice guideline from the American College of Physicians. Ann Intern Med. 2016;164:350-9. [PMID: 26857948] doi:10.7326/M15-2570. Copyright 2016, American College of Physicians.

therapy (treatment after resolution of a major depressive episode) for 4 to 9 months in patients who responded to acute therapy. The antidepressant dosage that was effective in acute treatment should be maintained in the continuation phase, and if psychotherapy was used, it should also be continued. Patients with three or more previous major depressive episodes, persistent depressive disorder, or residual depressive symptoms should receive long-term maintenance therapy at a similar dosage. When long-term drug therapy is not indicated or must be stopped for other reasons, antidepressant medications should be gradually tapered to avoid discontinuation syndrome. The most common symptoms associated with discontinuation syndrome are dizziness, fatigue, headache, and nausea typically occurring within 1 to 7 days of abruptly stopping or rapidly discontinuing antidepressants.

Special Populations

Persistent complex bereavement disorder may respond to both psychotherapy and pharmacologic therapy, which should be targeted to specific symptoms. SSRIs and SNRIs have demonstrated benefit in patients with depressive symptoms.

Premenstrual and peripartum depression are treated similarly to other forms of depression but with additional attention paid to drug safety during pregnancy. SSRIs and SNRIs are FDA pregnancy category C, except for paroxetine, which is category D. All antidepressant medications are safe with breastfeeding.

Major depressive disorder with seasonal pattern can be effectively treated with CBT and SGAs. However, daily exposure to 10,000 lux of visible light for 30 to 60 minutes is also beneficial.

Patients with concomitant pain syndromes may derive additional analgesic benefit from the use of SNRIs.

Bipolar Disorder

Bipolar disorder is characterized by major depressive episodes and periods of mania or hypomania. The prevalence is 1% to 3%, and women are affected slightly more often than men. Onset typically occurs in early adulthood, and more than half of patients initially present with a major depressive episode. Bipolar disorder is the most expensive mental health problem and carries a high lifetime suicide risk.

Bipolar disorder is divided into two main categories: bipolar 1 and bipolar 2. Diagnosis of bipolar 1 disorder requires at least one episode of mania that is not explained by a medication effect, substance use, or a medical condition. DSM-5 defines mania as an episode of at least 7 consecutive days of irritable, expansive, or elevated mood that interferes with social or occupational functioning and has at least three of the following characteristics (four if the patient reports irritable mood only): inflated self-esteem (grandiosity), increased talkativeness, flight of ideas, distractibility, decreased sleep need, increased goal-directed activity, and excessive risk-taking behaviors (promiscuity, spending sprees). Most patients with bipolar 1 disorder also experience major depressive episodes, and many experience periods of hypomania. Hypomania is defined by the same criteria as mania except the duration is at least 4 consecutive days and symptoms do not cause severe functional impairment.

Patients with bipolar 2 disorder have periods of both hypomania and major depression but never mania. Cyclothymic disorder is a related disorder characterized by multiple episodes of hypomanic and depressive symptoms that do not meet criteria for hypomania or major depression.

Treatment of bipolar disorder should be directed by a psychiatrist. First-line medications include lithium, valproic acid, carbamazepine, and lamotrigine; psychotherapy plays an adjunctive role. Patients with acute mania typically require one of the aforementioned medications plus an atypical antipsychotic agent (aripiprazole, olanzapine, quetiapine). Severe bipolar depression may require a combination of first-line medications or adjunctive antidepressants (fluoxetine plus olanzapine). Quetiapine is also effective as monotherapy for bipolar depression.

KEY POINTS

- The U.S. Preventive Services Task Force advises screening all patients for depression at primary care visits.
- For initial acute treatment of major depressive disorder, options include cognitive behavioral therapy or second-generation antidepressants after consideration and discussion of side effects, cost, accessibility, and patient preferences.
- Peripartum depression may occur during pregnancy or within 4 weeks after delivery; treatment is similar to that for other forms of depression but with close attention paid to drug safety in pregnancy.
- Referral to a psychiatrist is indicated for patients with severe depression, failure of initial therapy, complex psychiatric comorbidities, and high suicide risk.
- Clinicians must assess patients with depression for any history of elevated mood, which would suggest bipolar disorder; prescribing antidepressant monotherapy to a patient with bipolar disorder may precipitate a manic episode.

Anxiety Disorders

Generalized Anxiety Disorder

Generalized anxiety disorder (GAD) is characterized by excessive anxiety about activities or events (occupation, school) that occurs more days than not for at least 6 months and causes significant distress or functional impairment. Patients with GAD typically worry more than expected about minor matters and recognize that this anxiety is difficult to control. DSM-5 diagnostic criteria also require that a patient have at least three of the following symptoms: restlessness, fatigue, irritability, muscle tension, sleep disturbance, or difficulty concentrating. Patients often have comorbid mood and anxiety disorders, including depression, panic disorder, and social anxiety disorder, and clinicians must investigate for other psychiatric illnesses as the source of symptoms. In addition, patients with GAD frequently report various other physical symptoms, including headaches, palpitations, dizziness, and chest and abdominal pain; these may be the presenting symptoms and often prompt evaluation for medical illness. The lifetime prevalence of GAD is 5% to 10%, and women are affected more often than men.

Patients with significant anxiety or multiple unexplained physical symptoms should be screened for GAD using the GAD-7 screening tool (http://www.adaa.org/sites/default/files/GAD-7_Anxiety-updated_0.pdf). The GAD-7 can also be useful for monitoring the severity of the illness during treatment. CBT and pharmacotherapy are equally effective in the treatment of GAD, but patients with comorbid mood disorders are best treated with a medication that targets their concomitant illnesses. SSRIs, SNRIs, buspirone, and tricyclic antidepressants are all effective in the treatment of GAD. SSRIs and SNRIs are preferred first-line drugs because they have fewer side effects than tricyclic antidepressants and effectively treat comorbid behavioral disorders (unlike buspirone). Benzodiazepines are useful for rapidly controlling severe symptoms, especially during initial treatment, while patients await CBT and/or titration of antidepressant dosage. However, benzodiazepines should be used only short term (<4-6 weeks) to avoid dependence and long-term side effects, such as impaired psychomotor performance and amnesia.

Panic Disorder

Panic disorder is commonly encountered in the primary care setting and has a lifetime prevalence of 2%. Panic attacks are a key feature of panic disorder but are not pathognomonic; up to one third of all adults will experience a panic attack during their lifetimes. Depression and other anxiety disorders are frequent comorbidities with panic disorder.

Panic attacks are characterized by sudden onset and rapid escalation (within minutes) of extreme fear or anxiety along with at least four of the following: fear of dying, fear of losing control, palpitations, diaphoresis, tremor, dyspnea, sensation of choking, chest pain, nausea, dizziness, chills or heat sensations, paresthesia, and derealization (the perception that the

perceived world is not real). DSM-5 diagnostic criteria for panic disorder include the following: (1) recurrent, unexpected panic attacks and (2) at least one attack followed by 1 or more months of persistent concern about additional panic attacks along with maladaptive behavior changes (for example, avoiding unfamiliar situations). The paroxysmal onset of dyspnea and chest pain may prompt significant medical evaluation. Rarely, panic attacks have a medical cause (hyperthyroidism, pheochromocytoma), and these diagnoses should be considered when other diagnostic findings suggest these conditions.

Treatment of panic disorder involves CBT, pharmacotherapy, or both. SSRIs and SNRIs are first-line medications because of their favorable side effect profile and efficacy. Short courses of benzodiazepines can be used for symptom control, but long-term use is discouraged. Treatment should be continued for at least 1 year after remission is achieved.

Social Anxiety Disorder

Previously known as social phobia, social anxiety disorder is associated with excessive anxiety or fear of criticism or humiliation in social or performance situations. In these situations, patients with social anxiety disorder may experience palpitations, flushing, dyspnea, chest pain, or even panic attacks. To meet DSM-5 diagnostic criteria, these symptoms must be present for at least 6 months and cause significant functional impairment. Patients usually understand that their anxiety is excessive but continue to avoid social situations that trigger anxiety. Both CBT and pharmacotherapy with SSRIs and SNRIs are effective for treatment of social anxiety disorder. For patients with social anxiety disorder restricted to performance situations, CBT is preferred.

Posttraumatic Stress Disorder

Posttraumatic stress disorder (PTSD) is an increasingly recognized anxiety disorder triggered by at least one of the following: direct experience of or witnessing a traumatic situation, learning that a loved one experienced a violent or accidental event, or repeated or excessive exposure to details of a traumatic event (for example, a social worker repeatedly exposed to cases of child abuse). Diagnostic criteria for PTSD also include at least 1 month of intrusive memories of the event (nightmares or flashbacks), avoidance of reminders of the event, adverse changes in cognition or mood related to the event (impaired memory of the event, generalized distrust, anhedonia), and significantly altered arousal and activity (irritability, hypervigilance, sleep disturbance, self-destructive behavior). Risk factors for development of PTSD include greater severity of trauma, poor social support, comorbid psychiatric illness, refugee status, and traumatic brain injury (particularly among military veterans). The symptoms of PTSD typically begin within 4 weeks of the traumatic event. Diagnosis can be challenging because of the patient's desire to avoid discussing the event and the frequency of concomitant psychiatric disorders, including depression, anxiety, substance use disorder, and personality disorders.

Treatment of PTSD generally requires psychotherapy from a specialist with experience in treating the disorder. Antidepressants, including SSRIs and SNRIs, are useful adjunctive therapies. Benzodiazepines are not effective and are not recommended because of the high prevalence of substance use disorders.

Obsessive-Compulsive Disorder

Obsessive-compulsive disorder (OCD) has a lifetime prevalence of approximately 2% and often is accompanied by other mental health disorders. Patients with OCD experience obsessions (recurrent, intrusive thoughts, images, or impulses causing distress) and compulsions (repetitive behaviors [hand washing, counting] done to alleviate obsession-related anxiety). These behaviors cause significant functional impairment through wasted time and disrupted social interactions.

CBT is first-line treatment for OCD. CBT is more effective than pharmacotherapy alone, but SSRIs may be beneficial as adjunct therapy in patients with severe symptoms or inadequate response to CBT. For patients treated with medication, the American Psychiatric Association recommends continued treatment for at least 1 to 2 years.

KEY POINTS

- Cognitive behavioral therapy and pharmacotherapy are equally effective in the treatment of generalized anxiety disorder, but patients with comorbid mood disorders are best treated with a medication that targets their concomitant illnesses.
- Cognitive behavioral therapy and pharmacotherapy with selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors are effective for treatment of social anxiety disorder and panic disorder.
- Risk factors for development of posttraumatic stress disorder include greater severity of trauma, poor social support, comorbid psychiatric illness, refugee status, and traumatic brain injury (particularly among military veterans); treatment generally requires psychotherapy from a specialist.
- Cognitive behavioral therapy is first-line treatment for obsessive-compulsive disorder.

Substance Use Disorders

Tobacco

Tobacco use remains the most common cause of preventable death in the United States. It is implicated in the development of multiple malignancies, pulmonary diseases, and cardiovascular conditions, and all-cause mortality is three to five times higher in smokers than nonsmokers. Tobacco use has been associated with an increased risk for several cancers, reproductive disorders, peptic ulcer disease, osteoporosis, certain pulmonary infections, diabetes mellitus, and age-related macular degeneration. The benefits of quitting tobacco use begin

immediately, and over decades, risks for many of the associated conditions decrease substantially.

The U.S. Preventive Services Task Force recommends that clinicians ask all adults about tobacco use, advise them to stop using tobacco, and provide behavioral interventions and approved pharmacotherapy to adult tobacco users (**Table 78**). Abrupt cessation of tobacco use may result in higher long-term abstinence rates than gradually decreasing use. Combining behavioral counseling with pharmacotherapy is more effective than either modality alone. Effective counseling and behavioral resources include problem-solving guidance (such as developing a quit plan and overcoming barriers), motivational interviewing, social support, and telephone quit lines. There is a dose-response relationship between the intensity and frequency of counseling and quit rates, which seem to plateau after 90 minutes of total counseling.

All smokers without contraindications should additionally receive at least one of seven FDA-approved treatments for smoking cessation (**Table 79**). Varenicline is superior to single forms of nicotine replacement therapy and bupropion; combining more than one type of nicotine replacement therapy (short-acting and long-acting) is more effective than monotherapy.

Although tobacco use has decreased overall in the United States, increasing use of electronic nicotine delivery systems (also known as e-cigarettes and vaping), particularly among young people, is creating new health concerns because their long-term health risks are not yet fully understood. Although e-cigarettes may have a benefit of harm reduction for established smokers, the nicotine-containing aerosol also includes other chemicals (such as formaldehyde, propylene glycol, and heavy metals), which may be harmful. Use of e-cigarettes may also act as a "gateway" for young people, leading toward smoking more traditional tobacco products. The National Academy of Sciences has concluded that e-cigarettes are not without biological effects, including dependence, although not to the extent of combustible tobacco cigarettes. The implications for long-term effects on morbidity and mortality remain unclear.

TABLE 78. Tobacco Cessation: The 5 As

ASK about tobacco use at every encounter
Identify and document tobacco use
Consider systematic process (such as asking about tobacco use when taking vital signs)
ADVISE patients to quit tobacco use
Strong, clear, personalized message
ASSESS willingness to quit
Not everyone is ready to try to quit
If not ready, offer motivational counseling
ASSIST in quitting
Set a quit date
Behavioral changes: alternatives, skills
Pharmacotherapy
Support: environment, triggers
ARRANGE follow-up
In person, telephone, electronic
Monitor progress, side effects, withdrawal

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Alcohol

Unhealthy alcohol use is the third leading cause of preventable death in the United States. Individuals with disordered alcohol use often interact with the health care system but rarely receive appropriate treatment. The U.S. Preventive Services Task Force recommends routine screening for unhealthy alcohol use. Recommended screening tools include the Alcohol Use Disorders Identification Test (AUDIT) (available at https://pubs.niaaa.nih.gov/publications/Audit.pdf), the abbreviated AUDIT-Consumption (AUDIT-C) (available at https://www.integration.samhsa.gov/images/res/tool_auditc.pdf), and the single-question screen "How many times in the past year have you had five [four for women and adults older than age 65 years] or more drinks in 1 day?" (see Routine Care of the Healthy Patient).

Patients with a positive screening result should be assessed for the presence of an alcohol use disorder, the severity of the disorder, and related health consequences, including hepatic, cardiac, and neurologic sequelae. Comorbid psychiatric, chronic pain, and substance use disorders are often present and complicate treatment. Treatment should be tailored to the risk level (**Table 80**).

For patients with at-risk or harmful drinking behavior, brief (6-15 minutes) multicontact behavioral counseling has the best evidence for reducing episodes of heavy drinking and weekly alcohol consumption and improving adherence to recommended drinking levels.

Patients diagnosed with alcohol use disorder often require a multipronged approach with both psychotherapy and medication to ensure safety and minimize relapse. Psychotherapeutic interventions are a key component of effective treatment and may include CBT or 12-step facilitation. Pharmacotherapy for relapse prevention should be considered; naltrexone and acamprosate are the most effective medications (**Table 81**). Naltrexone is preferred because some studies have demonstrated acamprosate to be no more effective than placebo. When at-risk patients do not respond to brief interventions or when patients with alcohol use disorder do not respond to office-based therapies, they should be referred to addiction specialists.

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Alcohol withdrawal is a common complication of alcohol use disorder. Alcoholic hallucinosis (hallucinations without clouding of the sensorium) and withdrawal seizures are typically seen within 24 to 48 hours of cessation of alcohol use and are treated expectantly, although a significant percentage of patients will progress to severe withdrawal (delirium tremens). Delirium tremens usually has onset at least 48 hours after the last drink and manifests as autonomic activation (hypertension, tachycardia, fever) and altered mental status. It

TABLE 81. Pharmacotherapy for Patients With an Alcohol Use Disorder

Medication (Typical Dosage)[a]	Indication	Mechanism	Side Effects	Notes
Benzodiazepines Symptom-triggered: chlordiazepoxide, 50-100 mg; diazepam, 10-20 mg; or lorazepam, 2-4 mg every 1-2 hours until symptoms subside	Treatment or prophylaxis for alcohol withdrawal syndrome	Enhance GABA inhibition of neuronal excitability	Oversedation, paradoxical hyperactivity, depression Addictive potential	Caution in patients with respiratory or hepatic impairment
Naltrexone Oral, 50-100 mg daily Injectable, 380 mg monthly	Relapse prevention	Opioid antagonist that may reduce the subjective reward associated with alcohol use	Nausea, indigestion, headache, fatigue Depressive symptoms Rarely, medication-associated hepatitis Potential for precipitated opioid withdrawal with opioid use	Contraindicated with opioid use Avoid in patients with decompensated cirrhosis; use with caution with hepatitis, compensated cirrhosis
Acamprosate 666 mg three times daily	Relapse prevention	May antagonize glutamate-mediated neuronal hyperexcitability and reduce prolonged (but not acute) withdrawal symptoms	Diarrhea, nausea/vomiting, myalgia, rash, dizziness, palpitations Rarely associated with kidney impairment	Reduce dosage with kidney insufficiency May be used with naltrexone Medication adherence may be challenging
Disulfiram 250-500 mg daily	Prevention of drinking and relapse prevention	Aldehyde dehydrogenase inhibition results in acetaldehyde accumulation with alcohol use, leading to unpleasant symptoms (alcohol-disulfiram reaction)	Drowsiness, rash Rarely, medication-associated severe hepatotoxicity, optic neuritis, peripheral neuropathy	Potential for many drug-drug interactions Patient must be abstinent at least 12 hours before medication administration Avoid in patients with hepatic impairment or cardiovascular disease Most appropriate for patients with strong motivation to be abstinent and with support to promote medication adherence

GABA = γ-aminobutyric acid.

[a]Naltrexone, disulfiram, and acamprosate are all FDA pregnancy category C (animal studies indicate potential fetal risk or have not been conducted, and no or insufficient human studies have been done; drugs in this category should be used in pregnant or lactating women only when potential benefits justify potential risk to the fetus or infant). Benzodiazepines are category X (contraindicated in pregnancy) or D (positive evidence of risk).

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examination, or risk profile suggest drug use (see Routine Care of the Healthy Patient for discussion of other screening tools). Internists play a central role in prevention, diagnosis, and management of substance use disorders, including identifying and managing medical comorbidities and reducing harm.

Treatment primarily involves psychotherapeutic support. Internists may also play a role in harm reduction, ensuring that at-risk patients (such as injection drug users) receive appropriate vaccinations and referrals to needle exchange services.

Prescription opioid use has emerged as a major cause of morbidity and mortality, necessitating coordinated medical and policy responses (see Common Symptoms). The risk for overdose is increased with higher doses and with concurrent benzodiazepine prescription. A notable study of trends in benzodiazepine use found that increased prescriptions and the mortality rate associated with overdose increased by a factor of five since 1996. Although nonfatal prescription opioid overdose presents an opportunity for intervention, most of these patients continued to receive opioids, and those receiving the highest dosage had the highest risk for repeated overdose. The nonmedical use of prescription opioids appears to be a strong risk factor for heroin use, although the transition to heroin occurs at a low rate and is influenced by cost and availability of drugs when it occurs.

Internists are increasingly treating opioid use disorder with pharmacotherapy in the office (**Table 82**). Most patients with opioid use disorder will require extended treatment consisting of both psychosocial support and medication-assisted treatment.

Intranasal naloxone is an important adjunct therapy in opioid use disorder, with evidence demonstrating a reduction in overdose death when used. Patients at risk for overdose, including those prescribed high-dose opioids for chronic pain (>50 morphine milligram equivalents per day) and those being

TABLE 82. Medical Treatment for Opioid Use Disorder

Medication	Uses	Side Effects and Risks	Precautions	Notes
Methadone	Inpatient withdrawal management; maintenance	Sedation, prolongation of the QTc interval, nausea, constipation, weight gain, edema, amenorrhea, decreased bone density, decreased libido Risk for respiratory depression and overdose	Prolonged, variable half-life with incomplete cross-tolerance with other opioids; requires low initiation dose and slow titration Potential for drug interactions with inducers or inhibitors of P-450 system	U.S. schedule II For outpatient addiction treatment, only available through state-licensed programs For pain treatment, available from licensed prescribers
Buprenorphine-naloxone	Inpatient withdrawal management; maintenance	Nausea, constipation, headache, insomnia Rarely associated with overdose, usually in combination with other sedating agents	Risk for precipitated opioid withdrawal if initiated too soon in opioid-tolerant patient after last use of full opioid agonist May be less effective in severe liver disease due to increased bioavailability of naloxone; periodic monitoring of liver enzymes is recommended	U.S. schedule III Requires federal waiver
Buprenorphine	Inpatient withdrawal management; maintenance, particularly for pregnant women	Nausea, constipation, headache, insomnia Rarely associated with overdose, usually in combination with other sedating agents	Risk for precipitated opioid withdrawal if initiated too soon after last use of full opioid agonist Periodic monitoring of liver enzymes is recommended	U.S. schedule III Requires federal waiver Once-monthly injection formulation approved in 2017
Naltrexone				
IM	Maintenance	Nausea, fatigue, dizziness, injection site reaction	Risk for precipitated withdrawal if taken soon after last opioid dose Risk for overdose if dose is missed and patient relapses Periodic monitoring of liver enzymes is recommended; impaired metabolism in liver disease	Some variability in length of time for full opioid blockade
Oral	Bridge before IM naltrexone; maintenance in highly supervised settings	Nausea, headache, dizziness, elevated aminotransferase levels	Periodic monitoring of liver enzymes is recommended; impaired metabolism in liver disease	

IM = intramuscular; QTc = corrected QT interval.

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treated for or in recovery from opioid use disorders, should be offered naloxone. Friends and family members may also receive prescriptions and training in naloxone use.

KEY POINTS

- In tobacco cessation, combining behavioral counseling with pharmacotherapy is more effective than either modality alone, and combining more than one type of nicotine replacement therapy (short- and long-acting) is more effective than monotherapy.
- For patients with at-risk or harmful drinking behavior, brief (6-15 minutes) multicontact behavioral counseling has the best evidence for improving adherence to recommended drinking levels.
- Patients diagnosed with alcohol use disorder often require both psychotherapeutic and pharmacologic approaches to ensure safety and minimize relapse.
- Patients at risk for opioid overdose, including those prescribed high-dose opioids for chronic pain and those being treated for or in recovery from opioid use disorders, should be offered naloxone.
- Most patients with opioid use disorder will require extended treatment consisting of both psychosocial support and medication-assisted treatment.

Personality Disorders

Personality disorders involve consistent patterns of interpersonal behavior and perceptions that are inflexible, diverge significantly from the behavioral standards of the person's culture, and cause substantial functional impairment and emotional distress. Development of these disorders usually occurs in adolescence, and the prevalence in the United States is estimated at 10% to 15%. Comorbid psychiatric illness is common. Three clusters of personality disorders are based on symptoms (**Table 83**).

Personality disorders add challenges to patient care and can serve as a substantial barrier to care. Physicians should have open, yet sensitive, discussion of the personality disorder diagnosis with the patient and emphasize the purpose of providing the best possible care. Such discussion may also make the patient more receptive to referral to a mental health professional. Establishing a relationship based on trust and clear boundaries can also help facilitate care. No pharmacotherapy specifically treats personality disorders, but medications may be used for improving specific symptoms (for example, mood stabilizers for impulsivity). Psychotherapy can help patients improve coping mechanisms.

TABLE 83. Personality Disorders

Cluster A: Odd or Eccentric Thinking and Behaviors
Paranoid: pervasive distrust of others; unjustified suspicion of others; unjustified suspicions regarding their partners or spouses; overly hostile reactions to perceived insults
Schizoid: prefer to be alone and lack interest in relationships; seem indifferent, cold, and unresponsive to social cues; take pleasure in few activities
Schizotypal: manifest odd thinking, beliefs (e.g., their thoughts are magical and can influence others, events have hidden meaning), dress, and other behaviors
Cluster B: Dramatic or Unpredictable Thinking and Behaviors, Emotional
Antisocial: engage in behaviors such as lying, stealing, and other aggressive and violent behaviors; disregard others' feelings, rights, and safety; lack remorse for these behaviors; often experience recurrent legal problems
Borderline: have chaotic relationships (idealized and devalued) and a fragile self-image; fear abandonment; experience labile and intense emotions (e.g., anger), sense of emptiness; engage in impulsive and risky behaviors (e.g., gambling, sex); may manifest self-injury and suicidality
Histrionic: excessive emotionality and attention-seeking behavior; dramatic; often seductive or sexually provocative; melodramatic
Narcissistic: grandiose and inflated self-perceptions; desire attention
Cluster C: Anxious and Fearful Thinking and Behaviors
Avoidant: feel inadequate and are sensitive to criticism; extremely shy and socially inhibited and avoid activities that involve interactions with others, especially strangers
Dependent: excessively dependent on others ("clingy") and fear being alone; lack self-confidence and tolerate poor treatment by others
Obsessive-compulsive: perfectionistic and preoccupied with orderliness and rules; controlling of situations and others; rigid regarding values; not the same as obsessive-compulsive disorder, which is an anxiety disorder

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Somatic Symptom and Related Disorders

Previously known as somatoform disorders, somatic symptom and related disorders are characterized by medically unexplained symptoms causing emotional distress and psychosocial impairment. Prevalence is as high as 4%, and primary care is a common setting for presentation. Patients with these disorders have very high use of health care resources yet are dissatisfied with their care. Before diagnosing any of these disorders, clinicians should thoroughly evaluate for and optimize treatment of medical disease and other psychiatric disorders (such as depression and generalized anxiety). Many unexplained medical problems are related to unidentified organic pathology, and patients with known medical disease may have a concurrent somatic symptom or related disorder.

Types

Somatic symptom disorder (previously called somatization disorder) is characterized by one or more somatic symptoms present for at least 6 months causing significant distress or

interference with life and associated with excessive thoughts, behaviors, and feelings related to the symptoms. When the main symptom is pain, the specifier "with predominant pain" is applied (previously referred to as pain disorder).

Illness anxiety disorder (formerly known as hypochondriasis) is characterized by excessive concern about health and preoccupation with health-related activities (for example, measuring pulse). In contrast to somatic symptom disorder, no or only mild somatic symptoms are present in illness anxiety disorder.

Conversion disorder involves at least one symptom of neurologic dysfunction (abnormal sensation or motor function) that is unexplained by a medical condition and not consistent with examination findings. Conversion disorder does not represent fabrication of symptoms but rather unexplained symptoms that do not have a pathophysiologic basis. These symptoms, which are functionally limiting, occur during times of substantial physical, emotional, or psychological stress.

Somatic symptom and related disorders must be differentiated from factitious disorder and malingering. Factitious disorder is an intentional fabrication of symptoms or injury to oneself or another without clear external benefit. Malingering occurs when a patient feigns medical problems for gain; thus, malingering is not a psychiatric diagnosis.

Management

Clinicians should acknowledge the patient's symptoms in somatic symptom and related disorders and focus on coping mechanisms and regularly scheduled visits. Diagnostic testing and referral to specialists should not be requested solely to provide reassurance. For somatic symptom disorder, CBT is effective for patients willing to undergo psychotherapy; antidepressant drugs also have demonstrated benefit. Illness anxiety disorder may respond to CBT, whereas disease education is the primary treatment for conversion disorder.

KEY POINT

HVC
- Clinicians should acknowledge the patient's symptoms in somatic symptom and related disorders and focus on coping mechanisms and regularly scheduled visits.

Eating Disorders

Types

Approximately 3% of the U.S. population has an eating disorder. Disorders most likely to be encountered by internists include anorexia nervosa, bulimia nervosa, and binge eating disorder.

Anorexia nervosa is characterized by restriction of caloric intake relative to requirements that leads to below-normal body weight and is also associated with fear of weight gain and a distorted body image. DSM-5 further divides the disorder by subtypes: restricting type (no episodes of food binges or purging) and binge eating/purging type. Women are affected three to four times more often than men, and onset most often occurs in adolescence.

In bulimia nervosa, patients engage in binge eating followed by compensatory behaviors to prevent weight gain, including self-induced vomiting, laxative abuse, fasting, and excessive exercise, at least once weekly for 3 months. Binge eating is defined as eating substantially more food than most people would consume within a period of time. The key difference between the binge eating/purging type of anorexia nervosa and bulimia nervosa is that patients with anorexia have significant weight loss. Similar to anorexia nervosa, patients with bulimia nervosa have a distorted body image. Prevalence is three times greater among women, and the median age at onset is 18 years.

Binge eating disorder is more common than anorexia and bulimia nervosa and is characterized by binge eating and feelings of loss of control that occur an average of at least once weekly for 3 months. Binging episodes include at least three of the following characteristics: abnormally rapid consumption, eating until uncomfortably full, consuming large amounts of food when not hungry, eating alone due to embarrassment, and feelings of guilt related to overconsumption. These characteristics distinguish binge eating disorder from overeating. The lack of compensatory behaviors to avoid weight gain differentiates binge eating disorder from bulimia nervosa. Concurrent psychiatric disease, including personality, mood, and substance use disorders, is common.

Clues to the presence of an eating disorder on physical examination include findings suggesting malnutrition (muscle wasting, xerosis, and lanugo) and/or self-induced vomiting (erosion of dental enamel, parotid gland enlargement, and scarring or calluses on the hand dorsum).

Medical Complications

Multiple medical problems can develop in patients with anorexia nervosa as a result of malnutrition. Patients often exhibit signs of a hypometabolic state, including bradycardia, hypotension, hypothermia, and decreased gastrointestinal mobility. Electrolyte abnormalities (hypokalemia, hypomagnesemia, and hypophosphatemia) can cause dysrhythmia and contribute to increased mortality. Refeeding syndrome can worsen these electrolyte disturbances, and prevention requires gradual, carefully monitored increase of nutritional intake. Osteopenia and osteoporosis are common and may not be fully reversible if anorexia occurred during peak bone development in adolescence. Amenorrhea, anemia, and peripheral edema also occur frequently and usually resolve with recovery from anorexia nervosa.

Purging behaviors may also lead to electrolyte abnormalities. Additionally, upper gastrointestinal problems (esophagitis, esophageal tears) may develop from self-induced vomiting, and laxative abuse may cause colonic dysmotility.

Treatment

The main goal of treatment is reestablishing normal weight and eating behaviors. Psychotherapy and monitored dietary intake are the mainstays of treatment for anorexia nervosa. In

some circumstances, this may require hospitalization to ensure adequate emotional support, appropriate intake, and monitoring for refeeding syndrome. Antidepressant therapy has not proved effective in treating anorexia nervosa, although olanzapine may be considered for patients not responding to psychotherapy and nutritional interventions. CBT is the most effective intervention for bulimia nervosa and binge eating disorder; antidepressant therapy may be beneficial. Topiramate has also shown promise as an adjunctive therapy with CBT in patients with binge eating disorder. Bupropion should be avoided because of increased risk for seizures in patients with eating disorders.

KEY POINTS

- Psychotherapy and monitored dietary intake are the mainstays of treatment for anorexia nervosa; antidepressant therapy has not proved effective.
- Cognitive behavioral therapy is the most effective intervention for bulimia nervosa and binge eating disorder; antidepressant therapy and topiramate may also be beneficial.

Schizophrenia

Schizophrenia is a heterogeneous psychiatric disorder composed of both positive symptoms (hallucinations, disorganized thought, and delusions) and negative symptoms (flattened affect, decreased activity). Worldwide prevalence is approximately 1%, with a slight male predominance. The pathogenesis of schizophrenia is unclear.

DSM-5 diagnostic criteria for schizophrenia require the presence at least two of the following: delusions, hallucinations, disorganized speech, disorganized or catatonic behavior, and negative symptoms. Diagnosis also requires at least one area of functional impairment (occupation, social interactions, or self-care) and duration of at least 6 months (including 1 month of active symptoms).

Schizophrenia is associated with an increased risk for diabetes, cardiovascular disease, and obesity, and these coexisting conditions may be exacerbated by the metabolic complications of antipsychotic therapy. Undertreatment of medical disease is also common in this population. Mortality is significantly increased in patients with schizophrenia due to these conditions along with concurrent behavioral disorders and substance use; approximately 5% of patients with schizophrenia commit suicide.

Schizophrenia is usually co-managed with a psychiatrist. Antipsychotic medications are highly effective at controlling positive symptoms of schizophrenia, but some degree of negative symptoms usually persists. Because the effectiveness of different antipsychotics is relatively similar, choice of therapy is based primarily on patient comorbidities and the adverse effect profile of medications. Typical or first-generation antipsychotic agents have a higher risk for extrapyramidal symptoms (parkinsonism, akathisia), tardive dyskinesia, and hyperprolactinemia than second-generation or atypical antipsychotic agents (**Table 84**). Some newer antipsychotic agents may also cause less sedation and anticholinergic side effects but carry an increased risk for weight gain and metabolic syndrome (particularly olanzapine and quetiapine). Clozapine may be particularly effective for refractory schizophrenia but is associated with significant adverse effects, including agranulocytosis. Close monitoring for common adverse effects is extremely important with use of any antipsychotic agent.

TABLE 84. Adverse Effects of Common Antipsychotic Medications

Medication	EPS	Elevated Prolactin	Anticholinergic Symptoms	Sedation	Weight Gain	Hyperlipidemia
First-Generation Antipsychotics						
Fluphenazine	++	++	+/–	+	+	+
Haloperidol	++	++	+/–	++	+	+
Thiothixene	++	++	+	+	++	–
Chlorpromazine	+	++	++	++	++	++
Thioridazine	+	++	++	++	++	–
Second-Generation Antipsychotics						
Clozapine[a]	+/–	+/–	++	++	+++	+++
Risperidone	++	++	++	+	++	+
Olanzapine	+	+	+	++	+++	+++
Quetiapine	+/–	+/–	+/–	++	++	++
Aripiprazole	+	–	–	+	+	–

EPS = extrapyramidal symptoms.

[a]Clozapine can also cause agranulocytosis and requires routine monitoring of blood counts.

KEY POINTS

- Mortality is significantly increased in patients with schizophrenia because of concurrent cardiovascular disease, behavioral disorders, and substance use; approximately 5% of patients with schizophrenia commit suicide.
- Antipsychotic medications are highly effective at controlling positive symptoms of schizophrenia, but some degree of negative symptoms usually persists; the effectiveness of different antipsychotic agents is relatively similar, and choice of therapy is based primarily on patient comorbidities and the adverse effect profile of medications.

Attention-Deficit/Hyperactivity Disorder

Attention-deficit/hyperactivity disorder (ADHD) is characterized by persistent inattention and/or hyperactivity-impulsivity that disrupts functioning or development. Symptoms must interfere with at least two different settings (such as home and work), and some must be present since age 12 years. ADHD is most frequently recognized in childhood, but the diagnosis may be delayed until adulthood. Most patients diagnosed early in life continue to meet diagnostic criteria as adults. Common manifestations in adults include inattention, disorganization, distractibility, emotional dysregulation, and restlessness. The diagnosis is clinical, and rating scales may be useful; anxiety, mood, and substance use disorders should be considered in the differential diagnosis but may also exist concurrently.

Pharmacologic therapy is similar in adults and children, with stimulants (methylphenidate, amphetamine) as first-line therapy. Close monitoring for cardiovascular side effects (hypertension, arrhythmia) is necessary. Given the potential for abuse, these drugs should not be prescribed to patients with a history of substance use; atomoxetine may be preferred in such patients. Bupropion and tricyclic antidepressants are also beneficial in patients with contraindications to stimulants or with concurrent depression. CBT is beneficial alone or in combination with pharmacotherapy for improving executive functioning.

KEY POINTS

- For diagnosis of attention-deficit/hyperactivity disorder, symptoms must interfere with at least two different settings (such as home and work) and be present since age 12 years.
- Stimulants should not be prescribed to patients with a history of substance use; atomoxetine may be preferred in such patients.

Autism Spectrum Disorder

Autism spectrum disorder (ASD) is a heterogeneous group of developmental disorders that feature repetitive behaviors and significant deficiencies in communication and social interaction. The exact prevalence is debated but ranges from 0.5% to 1%. Pathogenesis remains uncertain but is most likely genetic. Diagnosis requires that symptoms be present since early childhood; however, these may be masked until adulthood. Half of patients have intellectual disability, and many have concurrent seizure and sleep disorders. Early intervention with behavioral and educational interventions improves long-term functioning. Complementary therapies, including specialized diets and music therapy, are also commonly used but lack evidence of efficacy. Pharmacotherapy is reserved for targeted symptoms, such as melatonin for sleep disturbance. Even with intervention, most patients require lifelong assistance with functioning.

Clinicians should understand what communication methods a patient uses and incorporate caregivers into health care visits. Consistency in the health care team can prevent confusion and anxiety, and extra time should be allowed for explanation of procedures. Medical causes of acute behavioral changes should always be considered.

Geriatric Medicine

Comprehensive Geriatric Assessment

Comprehensive geriatric assessment is a multidisciplinary diagnostic process to ascertain the physical, cognitive, psychological, environmental, and functional capabilities of older persons in order to develop a plan for preserving function and maximizing independence and quality of life. Common health issues in older adults include impaired mobility and physical functioning, deficits in sensory function (particularly vision and hearing), and cognitive decline. Additionally, polypharmacy and the cumulative effects of chronic diseases may contribute to decreased functional status and loss of independence. Identifying these issues requires a systematic and multidimensional evaluation, which may be performed in the office, in the patient's home, or upon hospital admission or discharge. When completed in the home or in a dedicated inpatient geriatric unit, comprehensive geriatric assessment may reduce mortality and decrease the need for long-term institutional or nursing home placement.

Functional Status

Functional status assessment is evaluation of a patient's ability to perform activities required for basic self-care (activities of daily living [ADLs]) or to live independently (instrumental activities of daily living [IADLs]). ADLs include bathing, grooming, dressing, toileting, feeding, walking, and transferring. IADLs comprise tasks such as managing finances, performing housework, shopping, self-administering medications, using transportation, preparing meals, and communicating by telephone. Standardized screening

instruments for assessment of functional status are presented in **Table 85**. Functional assessment may help determine the need for specific services or the appropriate level of care for the patient.

Vision

Older patients are at increased risk for many conditions that cause vision loss, including cataracts, macular degeneration, presbyopia, glaucoma, and disease-related retinopathy (such as diabetic retinopathy). Reduced visual acuity decreases functional status and quality of life and increases risk for falls, depression, and cognitive impairment.

Screening tests and examination techniques to assess vision in the primary care setting include standardized questionnaires, the Snellen eye chart, and direct ophthalmoscopic examination; however, these tests may not detect such disorders as glaucoma and macular degeneration. The U.S. Preventive Services Task Force (USPSTF) concluded that evidence is insufficient to assess the balance of benefits and harms of screening for impaired visual acuity in asymptomatic adults aged 65 years and older. Nonetheless, given the risks associated with decreased vision coupled with the increased risk for common treatable eye conditions in older adults, it is reasonable to ask about changes in vision and refer the patient to an eye specialist when changes are present. In contrast to the USPSTF recommendations, the American Ophthalmologic Association recommends performing a comprehensive eye examination in older adults every 1 to 2 years.

Hearing

Hearing loss is common in older adults, affecting more than 80% of adults by age 80 years. As with vision loss, hearing loss contributes to increased morbidity and decreased quality of life. The inability to hear is also socially isolating, perhaps more so than other sensory losses. Because of the impaired communication abilities inherent to hearing loss, it may be misdiagnosed as cognitive dysfunction.

Diagnostic tests that reliably screen for hearing loss include assessing whether the patient can hear a whispered voice, fingers rubbing together, or a watch ticking. These tests and single-question screening (that is, asking "Do you have difficulty hearing?") perform as well as more complex questionnaires or handheld audiometry in detecting hearing loss, although there is no evidence that identifying hearing loss translates to better hearing-related quality of life. As such, routine screening for hearing loss in asymptomatic patients is not recommended by the USPSTF. Patients with symptoms, however, should be referred to an otologist or audiologist for formal hearing testing and evaluation to determine whether hearing aids would be beneficial.

Depression

The prevalence of depression in adults older than 60 years is as high as 15%. Chronic illness, grief associated with the loss of loved ones, social isolation due to decreased physical and cognitive function, and the need for institutionalization may all contribute to depression. Common symptoms of depression, such as low energy and somatic symptoms, are often mistakenly attributed to aging and chronic illness. Depression in older adults may also be confused with cognitive dysfunction and is itself a risk factor for cognitive dysfunction.

The USPSTF recommends screening for depression in all adults. The PHQ-2 has been validated as a screening instrument in older adults, with similar sensitivity and specificity in this population compared with its performance in younger adults (see Routine Care of the Healthy Patient). In all age

TABLE 85. Indices to Assess Basic and Instrumental Activities of Daily Living

Index	Assessed Functional Activity	Scoring	Comments
Katz Index of Independence in Activities of Daily Living	Bathing Dressing Toileting Transferring Continence Feeding	Assign 1 point for each activity if it can be performed independently, which is defined as requiring no supervision, direction, or personal assistance; scores are then added for a range of 0 to 6 (6 = fully functional; 4 = moderately impaired; 2 = severely impaired)	Simple to use/score; brief, takes only a few minutes to complete Less discriminative at low levels of disability
Lawton and Brody Instrumental Activities of Daily Living (IADL) Scale	Ability to use telephone Shopping Food preparation Housekeeping Laundry Transportation Medication management Ability to handle finances	Assign 1 point for each activity if it can be performed at all; scores are then added for a range of 0 to 8, with a score of 8 representing independence and 0 representing total dependence for IADLs	Simple to use; brief, takes only a few minutes to complete

groups, the PHQ-2 has a lower specificity than more comprehensive screening instruments, which may result in overdiagnosis of depression. A positive screening result should therefore prompt further assessment. The PHQ-9 and Geriatric Depression Scale (https://integrationacademy.ahrq.gov/sites/default/files/Update_Geriatric_Depression_Scale-15_0.pdf) have similar sensitivity and specificity in older adults. The Geriatric Depression Scale, with its yes-or-no answer format, may be easier to administer in patients with cognitive impairment.

Older adults with depression are most commonly treated with pharmacotherapy, and antidepressants protect against suicide attempts in this population. Selective serotonin reuptake inhibitors are the most widely studied antidepressants and are considered first-line therapy. Psychotherapy, including cognitive behavioral therapy, may also be considered as primary treatment or as an adjunct to pharmacotherapy.

Cognitive Function

Cognitive impairment is defined as a progressive decline in at least two cognitive domains (memory, attention, language, visual-spatial function, executive function) that negatively affects patient functioning. The strongest risk factor for cognitive impairment is increasing age. In the absence of symptoms, routine screening is not recommended owing to a lack of evidence that screening leads to effective intervention. However, because cognitive impairment is a risk factor for falls, loss of independence, and poor control of chronic diseases, clinicians should have a low threshold for assessing cognitive decline.

The most widely studied instrument for evaluating cognitive function is the Mini-Mental State Examination (MMSE). The proprietary nature of the MMSE and the time required to administer the test (approximately 7 minutes) may preclude its use for routine outpatient screening. The Montreal Cognitive Assessment (MoCA) takes a similar amount of time to complete and is sensitive for detecting cognitive impairment. The Mini-Cog assessment includes a three-item recall test (similar to elements of the MMSE) followed by a clock-drawing test if any one of the three recall items is missed. The Mini-Cog has acceptable sensitivity and specificity in identifying dementia and is available to clinicians without charge, although it is copyright protected.

Evaluation and treatment of mild cognitive impairment (impaired cognition in the absence of impaired function) and dementia are further discussed in MKSAP 18 Neurology.

Fall Prevention

Thirty percent to 40% of adults older than 65 years fall every year, making falls the leading cause of injury in this age group. Modifiable risk factors for falls include chronic musculoskeletal or neurologic conditions, visual impairment, cognitive impairment, frailty, and polypharmacy.

Screening older adults for fall risk is recommended by the USPSTF and is an element of the Medicare annual wellness visit. Patients should be asked about falls and unsteadiness with walking; those who report falls or balance issues should be evaluated with the Timed Up and Go test, in which the patient is asked to rise from a chair with armrests, walk 10 feet (with their usual assistive devices, if applicable), turn, return to the chair, and sit down. A time of more than 12 seconds is considered abnormal. Patients with prolonged times on the Timed Up and Go test may be referred for more comprehensive assessment or formal gait and balance assessment and therapy. An algorithm for fall risk assessment and prevention is presented in **Figure 28**.

The USPSTF recommends exercise to prevent falls in community-dwelling adults aged 65 years or older who are at increased risk for falls. Exercise interventions include supervised individual and group classes as well as physical therapy. The USPSTF also recommends multifactorial interventions to prevent falls. This process typically involves an initial assessment of modifiable risk factors for falls and subsequent customized interventions. The USPSTF acknowledges that the overall benefit of routinely offering multifactorial interventions to prevent falls is small and should take into account the balance of benefits and harms based on the circumstances of previous falls, presence of comorbid medical conditions, and the patient's values and preferences. The USPSTF recommends against vitamin D supplementation to prevent falls in community-dwelling adults aged 65 years or older who are not known to have osteoporosis or vitamin D deficiency.

Assessment of the Older Driver

Driving is one of the most valued IADLs for older adults, and cessation of driving in this population is associated with negative health consequences. However, drivers older than 65 years are responsible for more traffic fatalities than any other group of drivers other than those younger than 25 years. Decreased visual acuity, decreased cognitive abilities, use of centrally acting medications (including alcohol), conditions that increase the risk for loss of consciousness, and mobility issues of the extremities or neck all increase the risk for motor vehicle crashes in older adults. Caregiver or family concern for driving safety, history of traffic citations, self-restricted driving, and impulsive behaviors are also associated with increased risk for crashes. The decision to advise an older driver to "retire from driving," which is the preferred terminology, is qualitative, complex, and largely dependent on clinician judgment. The evaluation should consider the known risk factors and underlying medical conditions.

Physician advice to retire from driving is associated with older drivers appropriately stopping driving; however, given the risk for depression and social isolation associated with driving retirement, this advice should be coupled with support, suggestions for alternate forms of transportation, and follow-up assessment of mood and quality of life. When patients are resistant to retiring from driving or when the appropriate decision is less clear, formal occupational therapy driving assessment may be helpful.

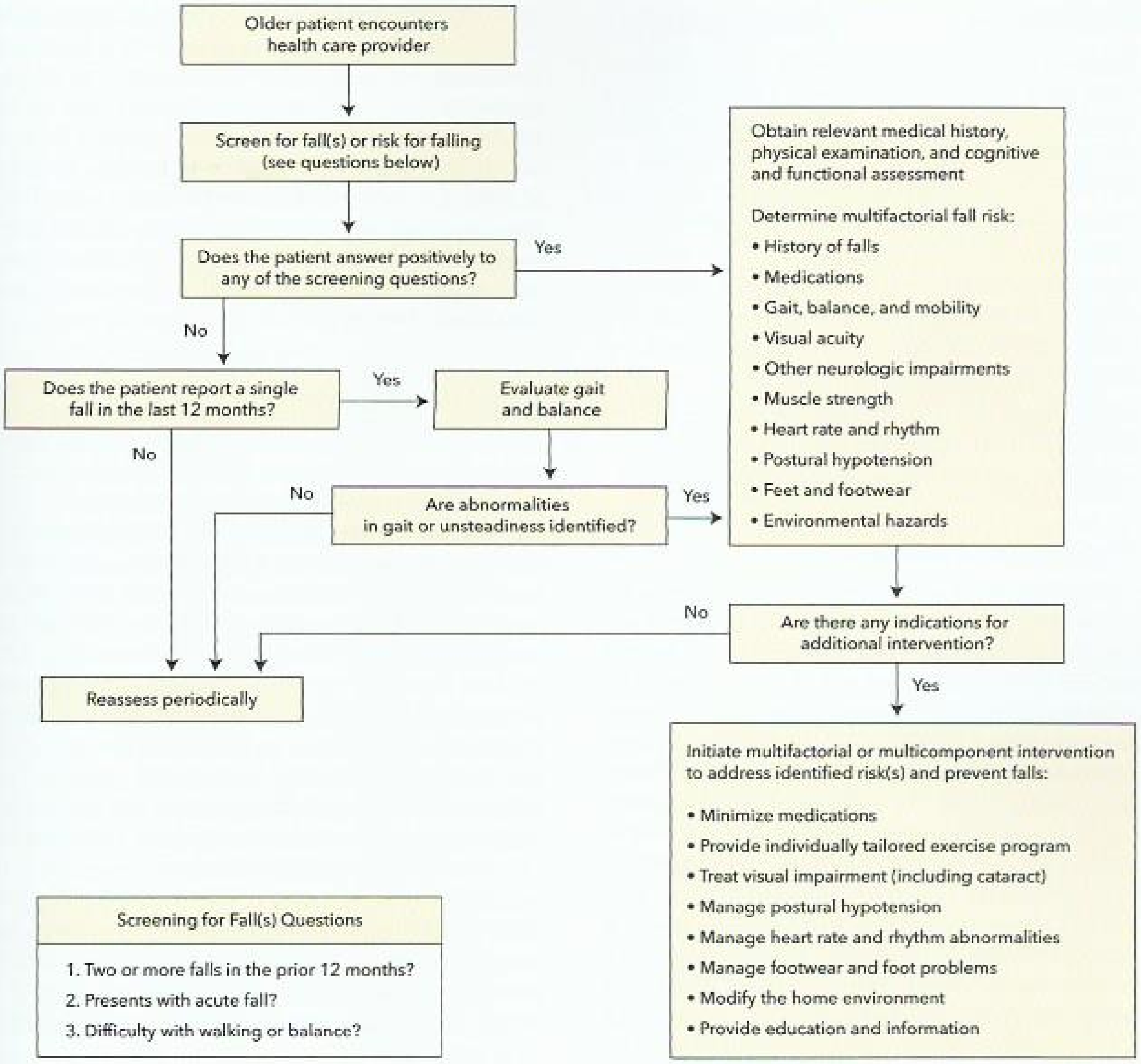

FIGURE 28. Prevention of falls in older persons living in a community.

Adapted with permission from Panel on Prevention of Falls in Older Persons, American Geriatrics Society and British Geriatrics Society. Summary of the updated American Geriatrics Society/British Geriatrics Society clinical practice guideline for prevention of falls in older persons. J Am Geriatr Soc. 2011;59:148-57. [PMID: 21226685] doi:10.1111/j.1532-5415.2010.03234.x. Copyright 2011, John Wiley & Sons, Inc.

Screening for Mistreatment

Older adults are at increased risk for mistreatment, including abuse (infliction of harm), neglect, or financial exploitation, owing to decreased functioning that leads to dependence on others. The prevalence of elder mistreatment is estimated to be roughly 10%. Victims are high utilizers of emergency services, hospital care, and nursing homes and have a higher mortality rate.

There is uncertainty regarding whether screening for elder mistreatment should be routine. The USPSTF concluded that screening cannot be universally recommended for asymptomatic adults; however, screening should be considered in adults with vulnerability for or signs of abuse. Simple screening instruments, such as the Hwalek-Sengstock Elder Abuse Screening Test and the Vulnerability to Abuse Screening Scale, are available but require self-reporting; this complicates assessment in cognitively impaired individuals who cannot independently provide information. Screening may also not occur because of unawareness of these instruments and how to use them, confusion regarding legal and reporting implications (which vary from state to state), and fear of potential harms to the patient and family members that result from false-positive and false-negative screening results.

KEY POINTS

- Comprehensive geriatric assessment is a multidisciplinary diagnostic process to ascertain the physical, cognitive, psychological, environmental, and functional capabilities of older persons in order to develop a plan for preserving function and maximizing independence and quality of life.

(Continued)

KEY POINTS (continued)

- Although routine screening for hearing loss in asymptomatic patients is not recommended, patients with symptoms of hearing loss should be referred to an otologist or audiologist for formal testing and hearing aid placement, if appropriate.
- All older adults should be screened for depression, such as with the PHQ-2.
- HVC • Cognitive impairment is a risk factor for falls, loss of independence, and poor control of chronic diseases; clinicians should inquire about symptoms and perform further evaluation when symptoms are present.
- HVC • The U.S. Preventive Services Task Force recommends exercise to prevent falls in community-dwelling adults aged 65 years or older who are at increased risk for falls.

Frailty Assessment

Frailty is a multifactorial geriatric syndrome characterized by unintentional weight loss, low energy and activity levels, weakness, and slow walking speed. It is important to note that advanced age is not synonymous with frailty. Assessment of frailty may be used to predict response to certain treatments as well as morbidity and mortality in patients with chronic illness. Standardized indices to objectively measure frailty include the Frailty Index, the frailty phenotype, the FRAIL (Fatigue, Resistance, Ambulation, Illness, and Loss of weight) scale, and the Osteoporotic Fractures Frailty Scale. The Frailty Index, a comprehensive assessment of chronic conditions and functioning, has been in use for a longer time than other indices; however, its length and complexity limit its usefulness in routine care. The five-item frailty phenotype was originally validated in the Cardiovascular Health Study of more than 5000 patients aged 65 years and older; it requires measurement of gait speed and grip strength (with a dynamometer), which may not be feasible in primary care. The FRAIL scale consists of five self-reported measures and is easy to administer and score. The Osteoporotic Fractures Frailty Scale, which was developed and validated in an all-female cohort, consists of three elements and is also easy to administer. The rapid screening tools are most easily incorporated into a primary care practice and are useful in the identification of patients who might require more formal comprehensive geriatric assessment (**Table 86**).

Levels of Care

As the population ages, medical complexity and care needs also increase, necessitating a variety of care delivery models, including home-based and facility-based options.

Several resources are available for older adults who wish to remain in their homes but need medical assistance. Home health agencies offer skilled assistance with medication management, wound care, and physical therapy. These services are provided on an intermittent basis (usually no more than two to three times per week) and are covered by Medicare and Medicaid if the patient is homebound with a documented skilled care need. Patients requiring assistance with ADLs can use custodial care services for help with dressing, bathing, toileting, and cooking; these services are not covered by Medicare but may be paid for by Medicaid. Visiting physicians can also provide outpatient medical care.

For patients who are cared for by family members but require additional resources for gaps in care, adult day care can provide part-time assistance when a patient's primary caregiver is unavailable. If supervision is needed for a longer time, respite care is available at many senior living

TABLE 86. Examples of Frailty Indices

Instrument	Description	Scoring
FRAIL (Fatigue, Resistance, Ambulation, Illness, and Loss of weight) scale	Measures presence (1) or absence (0) of: Fatigue: Feeling fatigued most or all of the time over the past 4 weeks Resistance: Difficulty walking up 10 steps alone without resting or assistance Ambulation: Difficulty walking several hundred yards without assistance Illness: Presence of more than five illnesses Loss of weight: Weight loss >5% in the past year	Each item scored dichotomously as 0 for normal or 1 for abnormal 1-2 = Prefrail 3-5 = Frail
Osteoporotic Fractures Frailty Scale	Measures three items: Ability to rise from an armless chair five times (inability = 1) Response to the question "Do you feel full of energy?" (answer of "no" = 1) Weight loss >5% in the past year (presence of weight loss = 1)	Each item scored dichotomously as 0 for normal or 1 for abnormal 1 = Prefrail 2-3 = Frail

communities (assisted living facilities and nursing homes). Adult day care and respite care are not typically covered by Medicare or Medicaid.

When long-term daily care needs exceed those that can be provided in a patient's home, three different levels of care are available: independent living, assisted living, and nursing homes. Independent living is suitable only for patients who can independently perform ADLs and simply provides patients with the benefits of living in a community. Assisted living offers a home-like environment but provides varying levels of assistance with medications, ADLs, housekeeping, and meals. For patients requiring additional help with ADLs or medical management, nursing homes provide 24-hour nursing care as well as rehabilitation services. A residential care home (or group home) is a variation of assisted living or the nursing home. Residential care homes use a smaller, home-like environment in the care of patients with similar needs (such as patients with chronic mental illness); however, services provided vary. Independent and assisted living are typically paid for with private funds, or "private pay." Medicare does not usually cover long-term nursing home or residential home care; Medicaid may pay for long-term care depending on patient eligibility and state regulations.

Acute medical care is almost always provided in a hospital setting. Infrequently, serious acute illnesses may be treated in the patient's living environment; however, home hospital care typically occurs only when significant home health resources are available and avoidance of hospitalization has been established as a primary goal in care-planning discussions.

Post-hospitalization care is available in multiple forms. Safe return to a patient's previous living situation can be facilitated with outpatient physical, occupational, and speech therapies in the home or clinic. If a patient requires functional improvement before returning home, rehabilitation can be performed in an acute rehabilitation program or skilled nursing facility (that is, subacute rehabilitation). Acute rehabilitation is provided in a free-standing rehabilitation hospital or a designated hospital unit, and it requires that the patient be able to participate in 3 hours of therapy at least 5 days per week. In patients who cannot tolerate this level of therapy, subacute rehabilitation is appropriate. Medicare covers the costs of both options for up to 100 days, provided that the patient had an inpatient hospitalization of at least 3 days and continues to make progress with goals. Some patients require longer-term, high-intensity medical care, including mechanical ventilation or multiple parenteral therapies, and long-term acute care hospitals are an appropriate option for these patients.

[illegible] the patient be able to [illegible] at least 5 days per [illegible]

Polypharmacy

The percentage of patients older than 65 years who take five or more prescription medications increased from 24% to 39% between 1999 and 2012. Studies estimate that nursing home patients take eight different medications on average, and medication errors occur in two thirds of such patients. Polypharmacy in older patients is associated with increased health care utilization, costs, medication nonadherence, and functional decline. Patients transitioning between levels of care are particularly vulnerable to inappropriate medication additions, omissions, and dosage changes; the risk for these mistakes increases with the number of medications prescribed. Hazards of polypharmacy include overtreatment or undertreatment of disease, serious drug-drug interactions, and adverse reactions.

Although treatment of comorbid health conditions in older adults often necessitates the use of several medications, clinicians can minimize the potential for adverse effects from polypharmacy. During medication review, clinicians should specifically assess for and reduce medications that should be avoided in older patients, including tricyclic antidepressants, antipsychotics, and benzodiazepines. Drug dosage adjustment is also crucial in older adult patients, given the wide variability in drug metabolism resulting from decreased kidney and liver function as well as the potential for drug interactions. Frequent review of patient medications to confirm their necessity and proper dosing is paramount, especially during care transitions. The 2015 Beers Criteria for Potentially Inappropriate Medication Use in Older Adults from the American Geriatrics Society provides lists of medications that are problematic for elderly patients, as well as recommendations regarding drug interactions to avoid (available at https://geriatricscareonline.org/ProductAbstract/american-geriatrics-society-updated-beers-criteria-for-potentially-inappropriate-medication-use-in-older-adults/CL001).

KEY POINT

- Adverse effects from polypharmacy can be minimized with frequent review of the patient's current medications, discontinuation of drugs that are unnecessary or should be avoided, and adjustment of drug dosages as appropriate. **HVC**

Urinary Incontinence

Epidemiology

Urinary incontinence (UI) is common in older adults, occurring in at least one third of community-dwelling adults older than 65 years and about two thirds of those in nursing homes. Prevalence increases with age in both women and men; however, incidence is higher in women. UI increases risk for falls, depression, and social isolation and reduces health-related quality of life. UI is also a major factor leading to loss of inde-

diabetes, heart failure, cerebrovascular disease, Parkinson disease, osteoarthritis, and dementia) as well as the medications used in their treatment. Other risk factors are pelvic surgery (including hysterectomy and prostate surgery), pelvic irradiation, pelvic trauma, and obesity.

There are four main classifications of UI: urgency, stress, overflow, and mixed. Functional incontinence, which occurs in patients who cannot reach and use the toilet in a timely manner, may result from cognitive or mobility impairment. Disorders that predispose patients to specific types of incontinence are presented in **Table 87**. Urgency UI and stress UI are the two most common forms, although mixed presentations frequently occur. Urgency UI is associated with intrinsic detrusor muscle instability and is characterized by urine leakage preceded by a sudden urge to void. Urgency UI occurs at increased rates in older patients, with higher rates in women. Stress UI is characterized by urine leakage associated with activities that cause increased intra-abdominal pressure, such as coughing, laughing, or sneezing. Changes in the pelvic floor musculature can contribute to both urgency and stress incontinence. Overflow UI is less common and is associated with comorbidities that alter neurologic control of the bladder and bladder outlet obstruction.

Evaluation

A comprehensive history, including specific questions about the presence and nature of incontinence, should be included in the routine care of the geriatric patient. Because of the social implications of incontinence, patients may be hesitant to volunteer information about symptoms. Validated questionnaires can be used to obtain details on the type of incontinence and the degree of interference with the patient's quality of life, as well as to monitor response to treatment. The 3 Incontinence Questions (3IQ) questionnaire is straightforward and easy to administer in an office setting; however, several other validated instruments are available.

TABLE 87. Conditions Commonly Associated With Urinary Incontinence

Incontinence Type	Associated Conditions
Stress	Multiparous state, radical prostatectomy
Urgency	Spinal cord injury, stroke, Parkinson disease
	Often idiopathic
Overflow	Diabetes mellitus with neurogenic bladder
	Neurologic disorders (lumbosacral degenerative joint disease, spinal cord injury)
	Prostate hypertrophy with bladder outlet obstruction
Functional	Dementia
	Mobility issues (osteoarthritis, residual deficits from cerebrovascular disease, Parkinson disease)
Mixed	All conditions associated with stress and urgency urinary incontinence

During the history, female patients should be questioned about pregnancies and gynecologic procedures, and male patients should be asked about symptoms suggestive of prostate enlargement. Additionally, all patients should be screened for chronic conditions associated with increased risk for incontinence (see Table 87). A comprehensive medication history should be obtained, with special attention paid to the use of diuretics and medications with cholinergic or anticholinergic effects, including over-the-counter medications.

The physical examination should incorporate a genitourinary examination, including evaluation of the pelvis in women and the prostate in men. Urinalysis is recommended because transient incontinence may be explained by the presence of urinary tract infection. Additional laboratory investigation or diagnostic testing is usually unnecessary. Postvoid bladder residual volume assessment, which is performed with ultrasonography after spontaneous voiding, may be considered in patients in whom overflow incontinence is suspected. Urodynamic studies are required only for complex cases in which neurologic disease is suspected and surgical intervention is being considered.

Treatment

The American College of Physicians (ACP) recommends nonpharmacologic therapy as the preferred first-line treatment for all types of UI. In cases of urgency UI, pharmacologic therapy may be considered when symptoms are not adequately improved with behavioral therapy. Devices and surgical interventions are third-line therapy. Treatment strategies for UI are listed in **Table 88**.

Behavioral Therapy

Validated behavioral therapy measures include pelvic floor muscle training for stress UI and mixed UI, bladder training with timed voiding for urgency UI, and exercise and weight loss in obese patients with any form of UI.

Pelvic floor muscle training, in which the patient performs sets of contractions of the pelvic floor, is five times more effective than no treatment for stress UI. Patients should be instructed to contract the pelvic floor as if attempting to avoid urination and sustain the contraction for 10 seconds. Contractions should be performed in three or four sets of 10 daily. Patients should be counseled that symptom improvement may not be noticeable until pelvic floor muscle training is consistently performed for several months. Some studies have demonstrated benefits when biofeedback therapy (using a vaginal electromyography probe to provide direct confirmation that the patient is correctly contracting the pelvic floor muscles) is included with these exercises.

Timed voiding or bladder training comprises scheduled voiding attempts at intervals shorter than the usual time between incontinence episodes, regardless of the urge to void.

TABLE 88. Treatment Strategies for Urinary Incontinence

Incontinence Type	Behavioral Therapy	Pharmacologic Therapy	Other Therapies
Stress	Pelvic floor muscle training +/− biofeedback	No recommended pharmacologic therapies	Pessaries, injectable bulking agents, sling cystourethropexy
Urgency	Bladder training/timed voiding	Antimuscarinics (oxybutynin, darifenacin, solifenacin, tolterodine, fesoterodine, trospium) Mirabegron	Spinal neuromodulators, botulinum toxin injections
Overflow	Double voiding (remaining on the toilet for a few minutes after voiding and then attempting to void again) Triggered voiding (maneuvers to stimulate voiding, including massaging the pubic bone and tugging on pubic hairs)	α-Blocker and 5α-reductase inhibitors for BPH-related symptoms	Transurethral prostatectomy can be considered for BPH-related symptoms Scheduled in-and-out catheterization
Functional	Caregiver-prompted timed voiding	No recommended pharmacologic therapies	None routinely recommended
Mixed	Pelvic floor muscle training +/− biofeedback Bladder training/timed voiding	Consider antimuscarinics or mirabegron	Consider therapies for stress or urgency incontinence depending on predominant symptoms

BPH = benign prostatic hyperplasia.

with a gradual increase in the time between voids. If an episode of urgency occurs before the designated voiding time, patients are encouraged to use pelvic floor muscle contraction until the urge passes and then proceed with voiding directly afterward. In patients with cognitive impairment–related functional UI, timed voiding with prompting by the caregiver may be useful.

Pharmacologic Therapy

No pharmacologic therapies are recommended for the treatment of stress UI. Trials of systemic and vaginal estrogen therapy for stress UI in women generally have been of low quality and yielded mixed results. Vaginal estrogen has been shown to improve symptoms compared with placebo; however, the risks associated with estrogen therapy may outweigh the benefits, especially in patients with breast cancer. Current guidelines do not recommend the use of estrogen therapy for women with continued symptoms of stress UI despite behavioral therapy.

Several classes of pharmacologic agents are available for the treatment of urgency and mixed UI, although medications are recommended only when symptoms persist despite behavioral therapy (see Table 88). No one agent or class of agents has been shown to be superior in head-to-head comparisons. The risk for adverse effects with pharmacologic treatment is low but higher than with behavioral therapies. Anticholinergic and antimuscarinic side effects (dry mouth, constipation, blurred vision) predominate with agents other than mirabegron (a β_3-agonist), whereas mirabegron is associated with gastrointestinal upset and nasopharyngitis. Anticholinergic agents are contraindicated in patients with angle-closure glaucoma and should be used with caution in men with benign prostatic hyperplasia due to the risk for urinary retention.

Pharmacologic treatment of urgency or overflow UI associated with prostatic hyperplasia is discussed in Men's Health. The pharmacologic agents recommended for female patients with urgency UI are also approved for use in men.

Devices, Injectable Agents, and Surgery

Patients with continued symptoms and reduced quality of life despite behavioral and/or pharmacologic therapies should be considered for third-line treatments, including device therapy, injectable agents, and surgery. Ideally, patients should be referred to a urologist or urogynecologist in order to match their clinical symptoms, overall functional status, and personal preferences to an appropriate therapy.

In patients with stress UI, pessary devices are a low-risk treatment option. However, in a systematic review of comparative effectiveness of stress UI treatments, no definitive benefit was demonstrated with pessary devices, vaginal cones, or other intrauterine/intravaginal devices. Limited high-quality evidence supports cystoscopically guided injection of bulking agents into the urethral mucosa at the bladder neck. Injection therapy requires repeat administration in upwards of 70% of patients whose symptoms initially improve. Surgical treatment of stress UI is reserved for patients who do not respond to other therapies and typically consists of sling cystourethropexy. Postoperative adverse effects include increased urinary retention, urgency incontinence, and increased incidence of urinary tract infection.

Resistant urgency UI may be treated with botulinum toxin injections into the detrusor muscle. Repeat dosing is usually performed every 6 to 12 months. Adverse effects include urinary retention requiring self-catheterization. Surgically implanted sacral nerve root neurostimulation

devices may be used in combination with behavioral therapy and pharmacotherapy for resistant urgency UI. Although sacral neuromodulation is associated with symptom improvement, widespread use of these devices is not indicated because of the required surgical intervention, complex programming, high costs, and potential for infection.

Indwelling urinary catheters are not recommended for any type of incontinence, owing to an unacceptably high risk for infection associated with their use.

KEY POINTS

HVC • First-line therapy for urinary incontinence (UI) includes pelvic floor muscle training for stress UI and mixed UI, bladder training with timed voiding for urgency UI, and exercise and weight loss in obese patients with any form of UI.

HVC • No pharmacologic therapies are recommended for the treatment of stress urinary incontinence or functional incontinence.

• Urgency and mixed urinary incontinence may be treated with pharmacologic therapy, including anticholinergic and antimuscarinic agents, when symptoms persist despite behavioral therapy.

H Pressure Injuries

Pressure injuries (or pressure ulcers) represent damage to the skin and underlying tissue caused by unrelieved pressure. The most important risk factors for pressure injury are immobility, malnutrition, sensory loss, and reduced skin perfusion, such as occurs with hypovolemia, hypotension, and systemic vasoconstriction. An estimated 2.5 to 3 million pressure injuries are treated each year in acute care facilities in the United States. Among hospitalized patients, prevalence rates range from 3% to 17%; however, rates are much higher in some high-risk groups, approaching 50% in long-term ICU patients. Patients who develop pressure injuries during an acute care stay are much more likely to be discharged to a long-term care facility.

Prevention

Pressure injury prevention is a cost-effective intervention that can positively affect health status. Improved understanding of ulcer pathogenesis and changes in reimbursement have increased the focus on identifying patients at risk and allocating resources to prevention efforts. The Centers for Medicare & Medicaid Services (CMS) has identified pressure ulcer development as a sentinel event (unexpected and preventable occurrence that results in serious patient injury) for health care facilities. As of October 2008, guidelines from CMS dictate that hospitals no longer receive additional payment when a patient has developed a stage III or IV pressure ulcer.

Risk assessment, including a comprehensive history and physical examination, is the first step in pressure injury prevention. In a 2015 clinical practice guideline, the ACP recommends regular, structured risk assessment to identify at-risk patients. Standardized risk assessment tools include the Braden, Cubbin and Jackson, Norton, and Waterlow scales. Clinical validation studies have found these instruments to have fairly low positive predictive values (60%-70%); therefore, bedside clinical assessment remains an important part of risk evaluation.

After identification of at-risk patients, pressure redistribution is of paramount importance in the prevention of pressure injuries and may be accomplished with pressure-reducing equipment and proper patient positioning. In patients at increased risk, the ACP recommends using advanced static mattresses or overlays (for example, medical sheepskin overlay) for prevention. Evidence of the efficacy of repositioning, nutritional interventions, and local care (silicone foam dressings or creams) in preventing pressure ulcers is limited. The ACP recommends against the use of alternating air mattresses, primarily based on cost considerations and lack of data demonstrating a clear advantage. There are insufficient data to recommend the routine use of dietary supplements for pressure injury prevention.

Management

Pressure injuries may be classified with the use of a staging system (**Table 89**); advancing stages are characterized by increasing tissue loss, depth, and ulcer size. Successful treatment of established pressure injuries requires interdisciplinary management involving nutrition, pressure-reducing surfaces (including air-fluidized beds), wound care, surgical debridement and repair, and in some cases, vacuum-assisted closure. On the basis of moderate-quality evidence, the ACP

TABLE 89. Classification of Pressure Injuries

Stage	Description
I	Intact skin with nonblanchable redness
II	Partial-thickness loss of dermis. Shallow open ulcer with red-pink wound bed without slough. May also present as intact or ruptured serum-filled blister
III	Full-thickness tissue loss. Visible subcutaneous fat but not bone, tendon, or muscle. May include undermining or tunneling
IV	Full-thickness tissue loss with exposed bone, tendon, or muscle
Unstageable	Full-thickness tissue loss in which the base of the ulcer is covered by slough or eschar
Suspected deep-tissue injury	Purple or maroon localized area of discolored but intact skin or a blood-filled blister due to damage of underlying soft tissue from pressure or shear

Adapted from National Pressure Ulcer Advisory Panel. National Pressure Ulcer Advisory Panel, European Pressure Ulcer Advisory Panel, and Pan Pacific Pressure Injury Alliance. Prevention and Treatment of Pressure Ulcers: Quick Reference Guide. Cambridge Media: Perth, Australia; 2014.

recommends protein-containing supplements to improve wound healing. Moderate-quality evidence has also shown a reduction in pressure injury size with air-fluidized beds compared with other support surfaces. Hydrocolloid and foam dressings are recommended treatments because they have been shown to reduce ulcer size compared with gauze dressings in low-quality studies. Wound electrical stimulation has been demonstrated to be effective as adjunctive therapy to improve healing. Evidence is insufficient to support the use of platelet-derived growth factor dressings, hydrotherapy, hyperbaric oxygen, or maggot therapy. H

KEY POINTS

- Pressure redistribution, such as with advanced static mattresses or overlays, is of paramount importance in the prevention of pressure injuries.
- Protein-containing supplements and hydrocolloid or foam dressings are recommended in the treatment of established pressure injuries.

Perioperative Medicine

General Recommendations

Perioperative medicine comprises preoperative risk assessment, preoperative testing, medical optimization of surgical patients, and postoperative medical care. The role of the internist in the perioperative setting is not to provide surgical clearance but to determine and communicate operative risk to patients and surgical and anesthesia colleagues and to suggest strategies that may mitigate this risk.

Decisions regarding the modality of anesthesia, such as whether to pursue regional or general anesthesia, are best deferred to the anesthesiologist and surgeon, owing to a lack of high-quality evidence that anesthetic choice significantly affects medical outcomes. A recent Cochrane review showed no differences in outcomes, including 30-day mortality, myocardial infarction, pneumonia, and hospital length of stay, with regional anesthesia compared with general anesthesia.

Preoperative Laboratory Testing

Preoperative laboratory testing should be performed on the basis of the patient's medical conditions, physical examination findings, and preoperative symptoms (**Table 90**). Routine laboratory panels expose patients to unnecessary testing and are not recommended.

Perioperative Medication Management

Perioperative medication management begins with eliciting a complete preoperative medication history, including herbal preparations, supplements, and over-the-counter medications. Careful medication reconciliation should be performed to rectify any discrepancies and to prevent medication errors.

TABLE 90. Selected Indications for Preoperative Laboratory Testing

Laboratory Test	Preoperative Indications
Hemoglobin	History of anemia
	Underlying disease that predisposes to anemia (such as kidney disease)
	Suggestive physical examination
	Expected substantial operative blood loss
Platelet count	History of thrombocytopenia or cirrhosis; the presence of signs or symptoms of thrombocytopenia or liver disease
Coagulation studies	Anticoagulant use
	History of abnormal bleeding
	Medical conditions that predispose to coagulopathy (such as liver disease or hemophilia)
Electrolytes	Diseases that predispose to electrolyte derangements (such as kidney disease)
	Use of medications that can cause electrolyte abnormalities (such as diuretics, ACE inhibitors, and angiotensin receptor blockers)
Creatinine	Kidney disease; creatinine is also used in preoperative cardiovascular risk calculators and for calculation of the MELD score
Liver chemistry tests (including bilirubin)	Cirrhosis, history of abnormal liver chemistry test results, or the presence of signs or symptoms of liver disease
	Examination findings suggestive of liver disease
Fasting glucose and hemoglobin A_{1c}	Hyperglycemia suspected based on history and physical examination findings
Urinalysis	Suspected urinary tract infection
	Planned urologic procedures
	Planned implantation of prosthetic devices

MELD = Model for End-stage Liver Disease.

There is a paucity of high-quality evidence to guide perioperative medication management. Most medications are tolerated throughout the perioperative period, with some important exceptions. **Table 91** provides perioperative recommendations for medications with potential surgery-related risk. Patients should be provided with clear instructions on which medications to withhold preoperatively and for what duration.

Postoperative Care

Promotion of patient mobilization, use of lung expansion modalities (see later discussion), improvement in patient nutrition, and enhanced recovery after surgery (ERAS) programs may all decrease the likelihood of postoperative complications. Early mobilization and physical therapy (as necessary) are important components of the postoperative care plan and

TABLE 91. Perioperative Medication Management[a]

Medication	Perioperative Recommendation	Special Considerations
Cardiovascular Agents		
α_1-Blockers	Continue	Risk for intraoperative floppy iris syndrome in cataract surgery; notify surgeon if ocular surgery is planned
α_2-Blockers	Continue	Do not initiate clonidine for preoperative cardiovascular risk reduction (increases risk for perioperative hypotension)
β-Blockers	Continue	Consider initiating preoperatively in patients with ≥3 RCRI risk factors and those with intermediate- or high-risk myocardial ischemia on preoperative stress testing
		Begin β-blocker with enough time to assess tolerability; β-blocker should not be started on the day of surgery (2-7 days before surgery is preferred)
Calcium channel blockers	Continue	Withhold for preoperative hypotension
ACE inhibitors and ARBs	Individualize	Consider withholding if large fluid shifts expected intraoperatively, or if preoperative hypotension, hyperkalemia, or acute kidney injury is present; restart as soon as possible postoperatively
Diuretics	Withhold	Monitor volume status closely if heart failure is present and restart as soon as possible
Nitrates	Continue	Withhold for preoperative hypotension; remove patch and paste formulations
Vasodilators	Continue	Withhold for preoperative hypotension
Statins	Continue	Thought to have beneficial pleiotropic effects in addition to lipid-lowering properties
		Reasonable to start in patients undergoing vascular surgery and those undergoing elevated-risk noncardiac surgery with indication for statin
		Withhold all other lipid-lowering medications
Analgesic Agents		
NSAIDs	Withhold	If possible, withhold 3 days before surgery, especially if increased bleeding risk
Opioids	Individualize	If surgery is elective, may consider preoperative pain rehabilitation and opioid taper
		Continue in most patients receiving long-term opioid therapy
		Risk for poorly controlled postoperative pain and respiratory depression
Acetaminophen	Continue	
Gastrointestinal Agents		
Antacid medications (including H_2 blockers and proton pump inhibitors)	Continue	
Hyoscyamine	Withhold	Risk for anticholinergic side effects
Rheumatologic Agents		
Hydroxychloroquine	Continue	
Methotrexate	Individualize	Limited high-quality evidence
		Likely safe to continue in most situations; withhold if significant concern for infection or history of septic complications; dose adjust in cases of kidney injury
TNF-α inhibitors	Withhold	No definitive evidence or guideline recommendations
		Reasonable to withhold one to two half-lives preoperatively
Psychiatric Agents		
Selective serotonin reuptake inhibitors	Usually continue	May increase risk for bleeding, especially in conjunction with antiplatelet agents; risk for withdrawal symptoms with abrupt cessation
Benzodiazepines	Continue	Risk for withdrawal with abrupt cessation; monitor for respiratory depression
Antipsychotics	Continue	Potential for QT prolongation
Supplements		
Herbal preparations	Withhold	Withhold 1 week preoperatively
Vitamins and supplements	Withhold	

ARB = angiotensin receptor blocker; RCRI = Revised Cardiac Risk Index; TNF = tumor necrosis factor.

[a]Perioperative management of antiplatelet agents, anticoagulants, antiepileptic drugs, glucocorticoids, and diabetes medications are discussed later in this chapter.

Information from Fleisher LA, Fleischmann KE, Auerbach AD, Barnason SA, Beckman JA, Bozkurt B, et al; American College of Cardiology. 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines. J Am Coll Cardiol. 2014;64:e77-137. [PMID: 25091544] doi:10.1016/j.jacc.2014.07.944 and Devereaux PJ, Sessler DI, Leslie K, Kurz A, Mrkobrada M, Alonso-Coello P, et al; POISE-2 Investigators. Clonidine in patients undergoing noncardiac surgery. N Engl J Med. 2014;370:1504-13. [PMID: 24679061] doi:10.1056/NEJMoa1401106

may decrease the probability of postoperative pneumonia and venous thromboembolism (VTE).

Malnutrition is a risk factor for perioperative morbidity, including infection and poor wound healing, and several nutrition risk stratification tools are available to identify patients at risk for postoperative complications related to malnutrition. The Subjective Global Assessment of Nutritional Status tool incorporates history of calorie intake and physical examination findings, whereas the Nutritional Risk Screening Tool relies on age, BMI and weight loss, and severity of the current medical condition. Serum protein markers, including albumin and prealbumin, are also predictive of postoperative complications. Loss of 15% of body weight over 6 months and a serum albumin level less than 3.0 g/dL (30 g/L) are the most predictive factors of poor surgical outcomes related to malnutrition. Notably, increased enteral calorie intake is effective in reducing postoperative complications.

ERAS programs use evidence-based protocols to standardize care, improve outcomes, and reduce costs in postoperative patients. Best studied in patients undergoing colorectal surgery, ERAS interventions include optimization of nutritional status, physical conditioning, abstinence from alcohol and tobacco, postoperative mobilization, and early removal of urinary catheters. ERAS programs have been demonstrated to decrease length of hospital stay and result in earlier mobilization and return of bowel function in colorectal surgery populations. They are currently being implemented and studied in other surgical populations.

Common complications in the postoperative setting include postoperative urinary retention (POUR), postoperative ileus, and postoperative nausea and vomiting (PONV). POUR is characterized by incomplete bladder emptying after surgery, resulting in increased postvoid residual urine volume. Risk factors include type of surgery (incontinence and anorectal surgery, hernia repair, joint arthroplasty), longer surgery, use of regional anesthesia, administration of more than 750 mL of intraoperative fluids, use of certain postoperative medications (opioids, anticholinergic agents), older age, constipation, pelvic organ prolapse, neurologic disease, history of urinary retention, and history of pelvic surgery. POUR is a urologic emergency. Reversible causes of POUR, such as medication use, should be addressed. In patients with benign prostatic hyperplasia, α_1-blockers should be continued, whereas medications with associated anticholinergic effects, such as oxybutynin, should be withheld. Early removal of indwelling catheters and voiding trials are recommended. For patients in whom a voiding trial is unsuccessful, clean intermittent catheterization is indicated. Urinary tract obstruction should be excluded if POUR is persistent.

Postoperative ileus, or gastrointestinal hypomotility after surgery, is associated with increased length of hospital stay. Ileus is often a physiologic response related to sympathetic nervous system activation, although it can also be caused by activation of inflammatory mediators or the use of medications, such as anesthetics and opioids. Risk factors for the development of postoperative ileus include abdominal and pelvic surgery, open surgical technique, and the presence of other postoperative complications, such as pneumonia. Treatment of ileus includes minimization of postoperative opioids, adequate hydration, bowel rest, electrolyte repletion, postoperative ambulation, and use of chewing gum. Preventive measures for ileus include an appropriate postoperative bowel regimen, which may comprise fiber, stool softeners, osmotic laxatives, and stimulant laxatives. Few data from well-designed clinical trials are available to guide therapy for prolonged postoperative ileus, typically defined as ileus lasting longer than 3 to 5 days. In these patients, it is important to distinguish postoperative ileus from mechanical bowel obstruction.

The prevention and treatment of PONV, a common postoperative event that results in significant patient distress, require a multifaceted approach that involves identifying at-risk patients, reducing baseline risk factors, providing prophylaxis, and treating symptoms. Risk factors for PONV include female sex; young age; nonsmoking status; and use of general anesthesia, postoperative opioids, or volatile anesthetics. Although many risk-mitigation strategies include intraoperative and immediate postoperative care, the internist plays an important role in ensuring adequate postoperative hydration, minimizing the use of opioids, and providing pharmacologic antiemetic therapy. H

KEY POINTS

- Preoperative laboratory testing should be performed based on the patient's medical conditions, physical examination findings, and preoperative symptoms; routine laboratory panels expose patients to unnecessary testing and are not recommended. **HVC**
- There is a paucity of high-quality evidence to guide perioperative medication management; in general, most medications are tolerated throughout the perioperative period.
- Optimization of nutritional status, early mobilization, use of lung expansion modalities, and enhanced recovery after surgery programs are important components of the postoperative care plan. **HVC**
- Treatment of postoperative ileus includes minimization of postoperative opioids, adequate hydration, bowel rest, electrolyte repletion, postoperative ambulation, and use of chewing gum.

Cardiovascular Perioperative Management H

Cardiovascular Risk Assessment

Preoperative cardiac evaluation entails assessment of patient-specific risk, surgery-specific risk, and urgency of surgery (emergent, urgent, or time sensitive). The approach recommended by the American College of Cardiology (ACC)/American Heart Association (AHA) for perioperative cardiovascular

H CONT.

evaluation in patients undergoing noncardiac surgery is presented in **Figure 29**.

Risk calculators, including the Revised Cardiac Risk Index (**Table 92**) and American College of Surgeons National Surgical Quality Improvement Program myocardial infarction and cardiac arrest calculator (https://riskcalculator.facs.org/RiskCalculator), can be used to determine the risk for a perioperative major adverse cardiac event (MACE). Both risk calculators incorporate patient- and surgery-specific risk factors.

Patients with low risk (<1% risk of perioperative MACE) may proceed to surgery without preoperative cardiac stress testing, whereas patients with elevated risk (≥1% risk for perioperative MACE) should undergo assessment of functional capacity. Metabolic equivalents (METs) are used to represent the patient's functional capacity based on the intensity of activity able to be performed. If the patient's functional capacity exceeds 4 METs, the patient may proceed to surgery without further testing. Examples of activities that require 4 METs include walking 4 miles per hour on a flat surface; climbing one to two flights of stairs without stopping; or performing vigorous housework, such as vacuuming. Cardiac stress testing should be considered in patients at elevated risk for MACE with a functional capacity of less than 4 METs or if functional capacity cannot be determined, but only if the results of stress testing will change perioperative management.

Preoperative electrocardiography (ECG) is reasonable in patients with known coronary artery disease, arrhythmia, peripheral artery disease, cerebrovascular disease, or structural heart disease undergoing moderate- to high-risk surgeries. Preoperative ECG may be considered for other asymptomatic patients except those undergoing low-risk procedures. ECG may not alter preoperative decision making, but it provides a useful baseline to guide postoperative management in the event of complications.

Echocardiography to evaluate left ventricular function should not be routinely performed preoperatively. Echocardiography is recommended in certain clinical scenarios, such as in the presence of dyspnea of unknown origin, heart failure with worsening dyspnea or overall change in clinical status, known left ventricular dysfunction without echocardiographic assessment in the last year, and known or suspected moderate to severe valvular stenosis or regurgitation without echocardiographic assessment in the last year or with a change in clinical status.

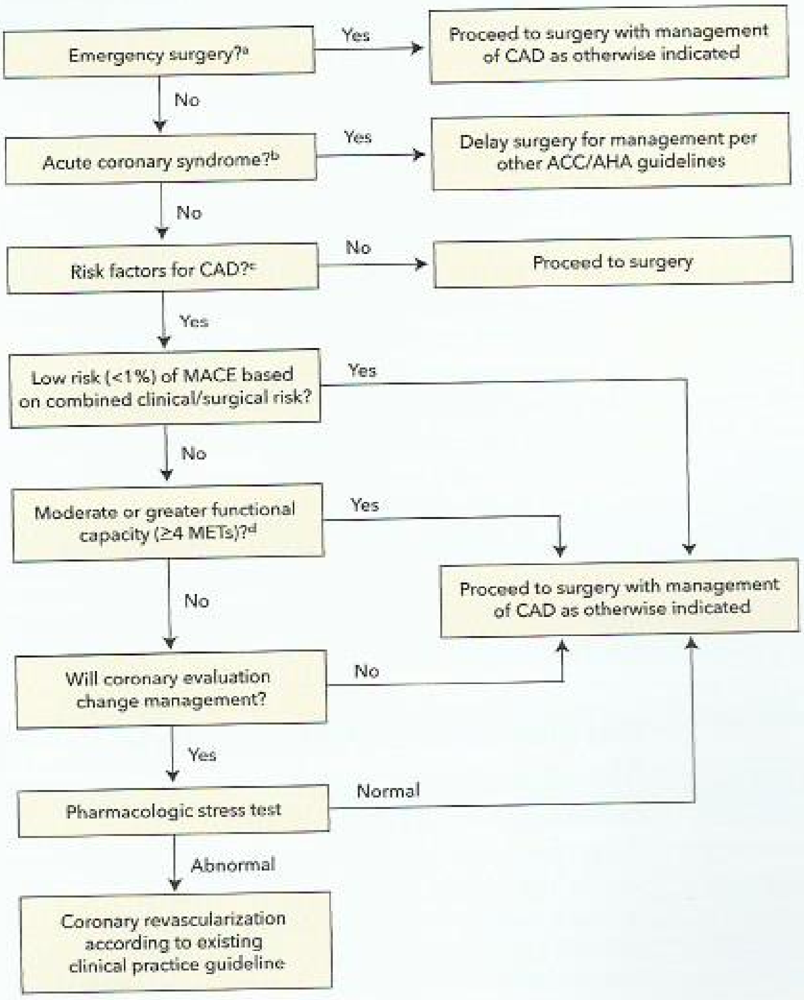

FIGURE 29. Perioperative ischemic cardiac disease evaluation for noncardiac surgery.

ACC = American College of Cardiology; AHA = American Heart Association; CAD = coronary artery disease; MACE = major adverse cardiac event; METs = metabolic equivalents.

[a]Emergency surgery required within 6 hours to avoid loss of life or limb.

[b]Acute coronary syndromes: myocardial infarction <30 days ago, unstable or severe angina.

[c]Risk factors for CAD: not specifically defined in ACC/AHA guidelines; examples include known CAD, cerebrovascular disease (i.e., stroke or transient ischemic attack), chronic kidney disease, diabetes mellitus, and heart failure.

[d]Examples of activities requiring ≥4 METs include climbing a flight of stairs, walking up a hill, walking on level ground at 4 miles per hour, running for a short distance, and playing tennis.

Recommendations from Fleisher LA, Fleischmann KE, Auerbach AD, Barnason SA, Beckman JA, Bozkurt B, et al; American College of Cardiology. 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines. J Am Coll Cardiol. 2014;64:e77-137. [PMID: 25091544] doi:10.1016/j.jacc.2014.07.944

TABLE 92. Revised Cardiac Risk Index and Predicted Rate of Major Cardiac Complications Perioperatively

Risk Factor (1 point for each)
High-risk surgery (intrathoracic, intraperitoneal, suprainguinal vascular)
Ischemic heart disease
Heart failure (compensated)
Diabetes mellitus (requiring insulin)
Cerebrovascular disease
Chronic kidney disease (serum creatinine >2.0 mg/dL [176.8 µmol/L])[a]

Number of Points	Risk for Major Cardiac Complications[b]
0	0.4% (95% CI, 0.1-0.8)
1	1.0% (95% CI, 0.5-1.4)
2	2.4% (95% CI, 1.3-3.5)
≥3	5.4% (95% CI, 2.8-7.9)

[a]Estimated glomerular filtration rate <30 mL/min/1.73 m^2 also shown to predict cardiovascular risk.

[b]Defined as cardiac death, nonfatal myocardial infarction, and nonfatal cardiac arrest.

Data from Lee TH, Marcantonio ER, Mangione CM, et al. Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. Circulation. 1999;100(10):1043-9. [PMID: 10477528] and Devereaux PJ, Goldman L, Cook DJ, Gilbert K, Leslie K, Guyatt GH. Perioperative cardiac events in patients undergoing noncardiac surgery: a review of the magnitude of the problem, the pathophysiology of the events and methods to estimate and communicate risk. CMAJ. 2005;173:627-34. [PMID: 16157727]

Cardiovascular Risk Management

Coronary Artery Disease

Patients with coronary artery disease (CAD) should not undergo routine coronary angiography or revascularization exclusively to reduce perioperative events. These procedures should be reserved for patients with recognized indications based on existing clinical practice guidelines. In patients who meet the criteria for intervention and in whom noncardiac surgery is time sensitive, balloon angioplasty or bare metal stent implantation should be considered over use of a drug-eluting stent. Elective noncardiac surgery should be delayed 14 days after balloon angioplasty, 30 days after bare metal stent implantation, and optimally 6 to 12 months after drug-eluting stent placement. However, if the risk of surgical delay outweighs the risk for ischemia and stent thrombosis, surgery may be considered 90 days after drug-eluting stent placement.

Patients taking β-blockers, statins, and many antihypertensive medications should continue these medications throughout the perioperative period, unless prohibited by hypotension. In hypotensive patients, dosage reduction is preferred to β-blocker discontinuation. There are also circumstances in which β-blocker or statin therapy should be initiated preoperatively (see Table 91). Postoperative β-blocker administration should be guided by clinical circumstances.

The ACC/AHA perioperative evaluation and management guideline does not recommend routinely obtaining postoperative troponin levels and an ECG in asymptomatic patients. However, these tests are recommended in patients with signs or symptoms of myocardial ischemia, which often presents atypically in the postoperative period (including as delirium in the elderly, hyperglycemia, and blood pressure fluctuations).

Heart Failure

Medical management of decompensated heart failure should be optimized before surgery and may involve diuresis, fluid restriction, and medication adjustments (see MKSAP 18 Cardiovascular Medicine).

Cardiac Arrhythmias

Risk management strategies for patients with a cardiac arrhythmia who are undergoing surgery include continuation of antiarrhythmic medications and, for some patients, continuous cardiac monitoring.

Patients with atrial fibrillation are at risk for rapid ventricular rate due to surgical stress, fluid shifts, and postoperative pain. Maintaining euvolemia, optimizing postoperative pain management, and controlling rates with medications are all appropriate strategies in stable patients. Hemodynamically unstable patients should undergo direct-current cardioversion.

A cardiologist should be consulted in patients with an implantable cardioverter-defibrillator who are undergoing surgery. Patients in whom a device has been deactivated for surgery should undergo continuous cardiac monitoring until the device is reprogrammed.

Valvular Heart Disease

The ACC/AHA guideline states that it is reasonable to perform elevated-risk elective noncardiac surgery in patients with severe asymptomatic aortic stenosis, mitral regurgitation, or aortic regurgitation with preserved left ventricular function. In patients who are candidates for valvular intervention due to symptoms or severity of disease, valvular intervention should be performed before elective noncardiac surgery.

Pulmonary Hypertension

Preoperative evaluation by a pulmonary hypertension specialist is advised for patients with pulmonary hypertension with high-risk features, including group 1 pulmonary hypertension (pulmonary arterial hypertension), pulmonary arterial systolic pressure greater than 70 mm Hg, moderate or severe right ventricular systolic dysfunction, and New York Heart Association functional class III or IV symptoms attributable to pulmonary hypertension. Patients with pulmonary hypertension undergoing noncardiac surgery should be continued on pulmonary vascular targeted therapies, such as phosphodiesterase-5 inhibitors.

Primary Hypertension

In patients with hypertension, urgent blood pressure lowering is not mandatory preoperatively unless there is evidence of

H CONT end-organ dysfunction, in which case surgery should be delayed and blood pressure treated. Deferral of surgery may also be considered in patients with a systolic blood pressure of 180 mm Hg or higher or diastolic blood pressure of 110 mm Hg or higher. Moderate preoperative hypertension has not been linked to adverse perioperative outcomes, although evidence is lacking regarding a specific blood pressure threshold. The perioperative use of specific antihypertensive agents is outlined in Table 91. H

KEY POINTS

- HVC Patients with low cardiovascular risk (<1% risk for perioperative major adverse cardiac event [MACE]) may proceed to surgery without preoperative cardiac stress testing, whereas patients with elevated risk (≥1% risk for perioperative MACE) should undergo assessment of functional capacity to determine necessity for cardiac stress testing.
- HVC Routine electrocardiography is not indicated in asymptomatic patients undergoing low-risk surgical procedures.
- HVC In patients with coronary artery disease, routine coronary angiography or revascularization should be performed for recognized indications based on existing clinical practice guidelines and should not be performed exclusively to reduce perioperative cardiovascular events.
- Patients with hypertension who are undergoing surgery do not require urgent blood pressure lowering preoperatively unless there is evidence of end-organ dysfunction.

TABLE 93. Pulmonary Risk Factors

Patient-Specific Risk Factors
Age
COPD
Cigarette use
ASA class ≥2[a]
Functional dependence
Obstructive sleep apnea
Heart failure
Poor nutritional status
Procedure-Specific Risk Factors
Surgery in close proximity to the diaphragm (aortic, thoracic, abdominal)
Head and neck surgery
Neurosurgery
Major vascular surgery
Procedure duration >3-4 hours
Emergency surgery

ASA = American Society of Anesthesiologists.

[a]ASA classes are as follows: class 1, normal healthy patient; class 2, patient with mild systemic disease; class 3, patient with severe systemic disease; class 4, patient with systemic disease that is a constant threat to life; and class 5, moribund patient who is not expected to survive for 24 hours with or without operation.

Adapted with permission from Smetana GW, Lawrence VA, Cornell JE; American College of Physicians. Preoperative pulmonary risk stratification for noncardiothoracic surgery: systematic review for the American College of Physicians. Ann Intern Med. 2006;144:584, 587. [PMID: 16618956] Copyright 2006, American College of Physicians.

H Pulmonary Perioperative Management

Perioperative pulmonary complications include pneumonia, respiratory failure, and exacerbation of underlying lung disease. Pulmonary perioperative management involves pulmonary risk assessment, including screening for obstructive sleep apnea (OSA), assessment of any underlying lung disease with optimization of treatment, and optimization of perioperative risk-reduction strategies.

Pulmonary Risk Assessment

Pulmonary risk factors can be categorized as patient-related risk factors or procedure-related risk factors (**Table 93**). Obesity and well-controlled asthma have not been shown to be independently associated with perioperative pulmonary complications. Risk calculators that include many of the important risk factors as well as other predictors, such as low oxygen saturation and the presence of preoperative sepsis, are available to help determine postoperative risk for respiratory failure, pneumonia, and overall pulmonary complications. The Postoperative Respiratory Failure Risk Calculator is available at www.surgicalriskcalculator.com/prf-risk-calculator, and the Postoperative Pneumonia Risk Calculator is available at www.surgicalriskcalculator.com/postoperative-pneumonia-risk-calculator. These calculators do not consider important pulmonary comorbid conditions, such as COPD and OSA, but they are useful in planning for surgery and establishing informed consent.

Spirometry is not useful for predicting risk and should not be routinely ordered for preoperative evaluation, including in patients with COPD. Furthermore, evidence does not support a spirometric threshold below which the risk of surgery is unacceptable. Spirometry is indicated in patients undergoing lung resection, however, to help predict postoperative lung function. Chest radiography is not required in most patients but is indicated in patients with signs or symptoms of pulmonary disease and in patients with underlying cardiac or pulmonary disease and new or unstable symptoms.

All patients should be screened for OSA, which is associated with adverse perioperative outcomes, including cardiac events, pulmonary complications, and ICU admissions. A commonly used screening tool for OSA is the STOP-BANG score (**Table 94**). In high-risk patients undergoing elective surgery, the American Society of Anesthesiologists recommends further evaluation with polysomnography.

Assessment of Underlying Lung Disease

COPD is the most commonly identified risk factor for postoperative pulmonary complications. Patients should be

TABLE 94. STOP-BANG Obstructive Sleep Apnea Screening Tool

Survey Items (1 point for each)	
Snoring	
Tiredness or sleepiness during the day	
Observed apnea during sleep	
Pressure, high blood	
BMI >35	
Age >50 years	
Neck circumference >40 cm (15.7 in)	
Gender = male	
STOP-BANG Score	**Risk Correlation**
0-2	Low risk for OSA
≥3	Increased risk for OSA
≥5	Increased risk for moderate-severe OSA

OSA = obstructive sleep apnea.

Adapted with permission from Chung F, Yegneswaran B, Liao P, et al. STOP questionnaire: a tool to screen patients for obstructive sleep apnea. Anesthesiology. 2008 May;108(5):812-21. [PMID: 18431116] and Chung F, Subramanyam R, Liao P, Sasaki E, Shapiro C, Sun Y. High STOP-Bang score indicates a high probability of obstructive sleep apnoea. Br J Anaesth. 2012 May;108(5):768-75. [PMID: 22401881]

screened preoperatively for signs and symptoms of COPD exacerbation and instructed to take prescribed inhaled medications on the morning of surgery. In patients with an exacerbation, surgery should be postponed, and treatment should be initiated.

Perioperative Risk-Reduction Strategies

Risk for pulmonary complications should be mitigated with perioperative risk-reduction interventions, including preoperative initiation of lung expansion maneuvers (deep breathing exercises and incentive spirometry), limiting use of nasogastric tubes in abdominal surgery for nausea or abdominal distention, and aspiration precautions. A recent multicenter randomized trial demonstrated that a 30-minute preoperative education and breathing exercise training session can reduce postoperative pulmonary complication rates by 50%. Smoking cessation has been shown to reduce pulmonary risk and should be encouraged as far in advance of surgery as possible. Patients with pulmonary disease should continue outpatient medications.

In patients diagnosed with OSA, continuous positive airway pressure (CPAP) should be initiated preoperatively. Patients at high risk for OSA undergoing nonelective surgery should be placed on continuous pulse oximetry and monitored for oxygen desaturation, apneas, reduced respiration rate, and oversedation in the postanesthesia care unit (PACU); patients with recurrent respiratory events in the PACU benefit from additional monitoring postoperatively. All patients with known OSA should bring their CPAP device to the hospital for use in the perioperative period. H

KEY POINTS

- Preoperative chest radiography is indicated only in patients with signs or symptoms of pulmonary disease and in patients with underlying cardiac or pulmonary disease and new or unstable symptoms. HVC
- Spirometry should not be routinely performed preoperatively except in patients undergoing lung resection. HVC
- All patients undergoing surgery should be screened for obstructive sleep apnea, which is associated with adverse perioperative outcomes, including cardiac events, pulmonary complications, and ICU admissions.

Hematologic Perioperative Management

H

Venous Thromboembolism Prophylaxis

The American College of Chest Physicians (ACCP) antithrombotic guideline provides recommendations for VTE prophylaxis for both orthopedic and nonorthopedic surgery populations (**Table 95**). In patients undergoing general surgery or abdominal-pelvic surgery, the ACCP recommends using the Caprini score to estimate the patient's risk for postoperative thrombosis (**Table 96**).

Hip fracture surgery, total knee arthroplasty, and total hip arthroplasty pose a high risk for VTE, and both mechanical (nonpharmacologic) and pharmacologic VTE prophylaxis are recommended. Mechanical prophylaxis is provided with an intermittent pneumatic compression device. For pharmacologic prophylaxis, the ACCP recommends low-molecular-weight heparin in preference to other pharmacologic agents. The minimum recommended duration of pharmacologic VTE prophylaxis in patients undergoing orthopedic surgery is 10 to 14 days; however, in patients without increased bleeding risk, extended-duration postoperative prophylaxis (up to 35 days) is preferred over shorter-duration prophylaxis. Intermittent pneumatic compression devices and pharmacologic VTE prophylaxis are recommended during the entire hospital stay. If bleeding risk is especially high, mechanical prophylaxis is recommended over no prophylaxis. In patients who decline or are unable to tolerate low-molecular-weight heparin, the ACCP recommends apixaban, rivaroxaban, dabigatran,[*] or a vitamin K antagonist over alternate forms of prophylaxis.

The ACCP recommends against the routine placement of inferior vena cava filters for VTE prophylaxis. Routine surveillance for VTE with venous compression ultrasonography is also not recommended in patients undergoing orthopedic surgery, general surgery, abdominal-pelvic surgery, and trauma surgery.

Perioperative Management of Anticoagulant Therapy

Anticoagulant therapy increases the risk for perioperative hemorrhage and should be discontinued in most patients before surgery. Minor surgery, including dental extractions

TABLE 95. Postoperative Venous Thromboembolism Prophylaxis Recommendations for Common Noncardiothoracic Surgeries

	Surgery and Risks		Recommended Prophylaxis[a]
General, abdominal-pelvic, urologic, plastic, vascular	Caprini[b] score 0		Early ambulation
	Caprini score 1-2		IPC
	Caprini score 3-4	Average bleeding risk	LMWH, LDUH, IPC
		High bleeding risk[c]	IPC
	Caprini score ≥5	Average bleeding risk	LMWH or LDUH (+ IPC)
		High bleeding risk[c]	IPC
	Cancer surgery		LMWH for 4 wk
Orthopedic	Hip or knee arthroplasty[d]		IPC + LMWH, LDUH, aspirin, NOAC, fondaparinux, warfarin, or IPC alone if high bleeding risk; continue for 10-35 d
	Hip fracture repair[d]		IPC + LMWH, LDUH, warfarin, fondaparinux, or IPC alone if high bleeding risk; continue for 10-35 d
	Isolated lower leg fracture repairs		None
	Knee arthroscopy with no previous VTE		Early ambulation
Spine (elective)	Average VTE risk		IPC
	High VTE risk (e.g., malignancy, anterior-posterior approach)		IPC + LMWH (when bleeding risk sufficiently low)
Major trauma	Average VTE risk		LMWH, LDUH, IPC
	High VTE risk (e.g., spinal cord or brain injury)		LMWH or LDUH (+ IPC)
	High bleeding risk[c]		IPC
Intracranial	Average VTE risk		IPC
	High VTE risk (e.g., malignancy)		LMWH or LDUH (+ IPC)

IPC = intermittent pneumatic compression; LDUH = low-dose unfractionated heparin; LMWH = low-molecular-weight heparin; NOAC = non-vitamin K antagonist oral anticoagulant (dabigatran, rivaroxaban, apixaban); VTE = venous thromboembolism.

[a]Duration is for postoperative hospitalization unless noted otherwise.

[b]See Table 96 for the Caprini Risk Assessment Scoring method.

[c]Risk factors suggesting high bleeding risk: concurrent antithrombotic therapy (e.g., aspirin for cardiac disease), known or suspected bleeding disorder, active bleeding, liver or kidney disease, and sepsis.

[d]LMWH is preferred.

Recommendations from Gould MK, Garcia DA, Wren SM, Karanicolas PJ, Arcelus JI, Heit JA, et al. Prevention of VTE in nonorthopedic surgical patients: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2012;141:e227S-e277S. [PMID: 22315263] doi:10.1378/chest.11-2297 *and* Falck-Ytter Y, Francis CW, Johanson NA, Curley C, Dahl OE, Schulman S, et al. Prevention of VTE in orthopedic surgery patients: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2012;141:e278S-e325S. [PMID: 22315265] doi:10.1378/chest.11-2404

H CONT.

and minor skin surgery, can be completed while a patient is anticoagulated. Vitamin K antagonist (warfarin) therapy may also be continued in some patients undergoing cardiac device implantation, although the best approach to these procedures in patients receiving non-vitamin K antagonist oral anticoagulants (NOACs), including direct thrombin and factor Xa inhibitors, is unclear. In any case, collaboration with the surgeon or proceduralist is crucial to ensure that it is safe for the patient to remain anticoagulated. When it is necessary to discontinue anticoagulation, vitamin K antagonists should be discontinued at least 5 days before surgery; most procedures can be safely performed with an INR of less than 1.5. The duration for which NOACs are discontinued before surgery depends on the bleeding risk of the procedure, the patient's kidney function, and the medication half-life; generally, NOACs can be stopped 2 to 3 days preoperatively because of their shorter half-lives.

Bridging anticoagulation is the administration of therapeutic doses of short-acting parenteral therapy, usually heparin, when oral anticoagulant therapy is being withheld during the perioperative period in patients with elevated thromboembolic risk. Bridging is most commonly indicated in patients taking vitamin K antagonists. It is not indicated in patients taking NOACs because of the rapid onset and short half-life associated with these drugs, but it may be needed when patients are unable to take oral medications for an extended time after surgery, such as with gastrointestinal surgery.

TABLE 96. Caprini Venous Thromboembolism Risk Assessment Scoring Method

Number of Points for Each Risk Factor	Risk Factors
1	Age 41-60 y; minor surgery; BMI >25; leg edema; varicose veins; recent or current pregnancy; estrogen use; recurrent spontaneous abortion; recent sepsis (<1 mo)/pneumonia (<1 mo); severe lung disease; abnormal pulmonary function; inflammatory bowel disease; acute MI; recent HF (<1 mo); medical patient at bed rest
2	Age 61-74 y; arthroscopic surgery; major surgery lasting >45 min; malignancy; bed rest for >72 h; immobilizing cast; central venous access
3	Age ≥75 y; personal history of VTE; family history of VTE; congenital or acquired thrombophilia; HIT
5	Stroke or spinal cord injury within 1 mo; elective arthroplasty; hip, pelvis, or leg fracture

HF = heart failure; HIT = heparin-induced thrombocytopenia; MI = myocardial infarction; VTE = venous thromboembolism.

Adapted from Bahl V, Hu HM, Henke PK, Wakefield TW, Campbell DA Jr, Caprini JA. A validation study of a retrospective venous thromboembolism risk scoring method. Ann Surg. 2010;251:344-50. [PMID: 19779324] doi:10.1097/SLA.0b013e3181b7fca6

TABLE 97. Annual Stroke Risk Based on $CHADS_2$ Score

$CHADS_2$ Score[a]	Unadjusted Annual Stroke Rate in Patients Not Treated With Anticoagulation (per 100 Patient-Years)[b]
0	0.6
1	3.0
2	4.2
3	7.1
4	11.1
5	12.5
6	13.0

[a]One point is given for heart failure, hypertension, age ≥75 years, and diabetes mellitus. Two points are given for previous stroke or transient ischemic attack.

[b]Data from Friberg L, Rosenqvist M, Lip GY. Evaluation of risk stratification schemes for ischaemic stroke and bleeding in 182 678 patients with atrial fibrillation: the Swedish Atrial Fibrillation cohort study. Eur Heart J. 2012;33:1500-10. [PMID: 22246443] doi:10.1093/eurheartj/ehr488

Postprocedural management of anticoagulation is based on thrombotic and bleeding risk, and close collaboration with the surgeon is essential. In patients taking a vitamin K antagonist, bridging anticoagulation may be deferred if thrombotic risk is low; the first dose of a vitamin K antagonist is typically administered 12 to 24 hours after surgery. If bridging is needed and the bleeding risk is low, bridging anticoagulation may be started as soon as 24 hours after the procedure; in the case of high bleeding risk, initiation of bridging anticoagulation is delayed 48 to 72 hours or possibly longer. Postoperative timing of NOAC reinstitution depends on bleeding risk, as NOACs reach therapeutic levels in 1 to 3 hours, at which point the patient is presumed to be fully anticoagulated. NOACs may be resumed once adequate hemostasis is ensured, usually 48 to 72 hours after surgery.

Because of the risk for spinal epidural hematoma, anticoagulant use with concomitant neuraxial (spinal and epidural) anesthesia should be avoided.

Atrial Fibrillation

The decision to initiate bridging anticoagulation in patients with atrial fibrillation is based on bleeding risk and thrombotic risk. Procedures with an intermediate or high risk for bleeding almost always require interruption of anticoagulation, and the $CHADS_2$ score (**Table 97**) and CHA_2DS_2-VASc score may be used to determine thrombotic risk and the need for bridging anticoagulation in patients with nonvalvular atrial fibrillation. Although use of the CHA_2DS_2-VASc score for risk stratification is advocated in several guidelines, it has not been validated in the perioperative setting (see MKSAP 18 Cardiovascular Medicine).

The landmark BRIDGE trial has shifted clinical practice toward a more conservative approach to bridging anticoagulation in patients with nonvalvular atrial fibrillation. This randomized controlled trial determined bleeding and thrombotic outcomes in patients who received bridging anticoagulation compared with those who did not. An increased risk for bleeding was identified in patients who received bridging anticoagulation, and those who received no bridging anticoagulation did not demonstrate an increased risk for thrombosis. Only a small proportion of patients with a higher thrombotic risk ($CHADS_2$ score of 5 and 6) were included in the study, limiting the applicability in this population. Additionally, most patients underwent minor procedures, which likely carry lower thrombotic risk.

Recommendations from the ACCP and ACC on bridging anticoagulation in patients with atrial fibrillation are provided in **Table 98**.

Prosthetic Heart Valves and Venous Thromboembolic Disease

In patients receiving warfarin anticoagulant therapy for a mechanical prosthetic heart valve, continuation of anticoagulation is recommended when the surgical procedure is minor and bleeding can be managed. In patients undergoing surgery with a higher risk for bleeding, the 2017 ACC/AHA guideline on valvular heart disease suggests that bridging should be considered on an individualized basis in patients with a mechanical mitral valve, a mechanical aortic valve with thromboembolic risk factors, or an older-generation mechanical aortic valve. Bridging is not necessary in patients with a bileaflet mechanical aortic valve and no other risk factors for thrombosis. The ACCP provides similar recommendations for bridging anticoagulation in patients with prosthetic heart valves (**Table 99**).

TABLE 98. American College of Chest Physicians and American College of Cardiology Recommendations for Perioperative Bridging in Patients With Atrial Fibrillation

Risk for Thromboembolism	Patient History and Risk Stratification Score	Bridging Anticoagulation Recommendation
High (annual risk >10%)		
ACCP	$CHADS_2$ score of 5 or 6 Recent stroke or TIA Rheumatic valvular heart disease Patient with history of stroke with warfarin interruption	Bridging
ACC	CHA_2DS_2-VASc score of 7-9 Ischemic stroke, TIA, or systemic embolism within the last 3 mo	Bridging
Moderate (annual risk of 5%-10%)		
ACCP	$CHADS_2$ score of 3 or 4	Bridging unless procedure is associated with a high bleeding risk
ACC	CHA_2DS_2-VASc of 5 or 6 History of ischemic stroke, TIA, or systemic embolism ≥3 mo ago	Increased risk for bleeding: interrupt VKA without bridging No significant bleeding risk: Stroke, TIA, or systemic embolism history: consider bridging[a] No stroke, TIA, or systemic embolism history: no bridging[a]
Low (annual risk <5%)		
ACCP	$CHADS_2$ score of 0-2 No stroke or TIA history	No bridging
ACC	CHA_2DS_2-VASc score ≤4 No history of ischemic stroke, TIA, or systemic embolism	No bridging

ACC = American College of Cardiology; ACCP = American College of Chest Physicians; TIA = transient ischemic attack; VKA = vitamin K antagonist.

[a]Clinical judgment is required.

Information from Douketis JD, Spyropoulos AC, Spencer FA, Mayr M, Jaffer AK, Eckman MH, et al. Perioperative management of antithrombotic therapy: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2012;141:e326S-e350S. [PMID: 22315266] doi:10.1378/chest.11-2298 and Doherty JU, Gluckman TJ, Hucker WJ, Januzzi JL Jr, Ortel TL, Saxonhouse SJ, et al. 2017 ACC expert consensus decision pathway for periprocedural management of anticoagulation in patients with nonvalvular atrial fibrillation: a report of the American College of Cardiology Clinical Expert Consensus Document Task Force. J Am Coll Cardiol. 2017;69:871-898. [PMID: 28081965] doi: 10.1016/j.jacc.2016.11.024

TABLE 99. American College of Chest Physicians Recommendations for Perioperative Bridging in Patients With a Prosthetic Heart Valve

Risk for Thromboembolism	Patient History	Bridging Anticoagulation Recommendation
High (annual risk >10%)	Any mitral valve prosthesis Any caged-ball or tilting disc aortic valve prosthesis Recent (within 6 mo) stroke or TIA	Bridging
Moderate (annual risk of 5%-10%)	Bileaflet aortic valve prosthesis and one or more of the of following risk factors: atrial fibrillation, previous stroke or TIA, hypertension, diabetes mellitus, heart failure, age >75 y	Bridging unless procedure is associated with a high bleeding risk
Low (annual risk <5%)	Bileaflet aortic valve prosthesis without atrial fibrillation and no other risk factors for stroke	No bridging

TIA = transient ischemic attack.

Recommendations from Douketis JD, Spyropoulos AC, Spencer FA, Mayr M, Jaffer AK, Eckman MH, et al. Perioperative management of antithrombotic therapy: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2012;141:e326S-e350S. [PMID: 22315266] doi:10.1378/chest.11-2298

ACCP recommendations for bridging anticoagulation in those with a history of venous thromboembolism, including patients with thrombophilias, are included in **Table 100**.

Perioperative Management of Antiplatelet Medications

The perioperative management of dual antiplatelet therapy (DAPT), comprising aspirin plus a $P2Y_{12}$ inhibitor (clopidogrel, ticagrelor, or prasugrel), in patients with CAD depends on the presence of a bare metal or drug-eluting coronary stent, time since stent placement, and, to some degree, the indication for DAPT (stable ischemic heart disease [SIHD] or acute coronary syndrome [ACS] within the last year).

In patients who have a stent placed for SIHD, DAPT should be continued uninterrupted for at least 30 days after bare metal stent placement and a minimum of 6 months after drug-eluting stent placement. Elective surgery should be postponed during these time frames. However, if the risk of surgical delay exceeds the risk for stent thrombosis, discontinuation of the $P2Y_{12}$ inhibitor can be considered after a minimum of 3 months in patients with a drug-eluting stent. Aspirin should be continued if at all possible, and DAPT should be restarted as soon as bleeding risk has sufficiency diminished.

In patients with recent ACS, the ACC and AHA recommend continuing DAPT for at least 1 year regardless of whether the ACS was managed with medical therapy or coronary stent placement. If surgery must be performed within this time frame, DAPT should optimally be maintained for a minimum of 6 months. If more than 3 months have passed and the patient cannot be continued on DAPT because of bleeding risk, proceeding with surgery can be considered if the risk of surgical delay is greater than the risk for stent thrombosis.

In patients with recent percutaneous coronary intervention with stent placement for ACS in whom surgery mandates discontinuation of DAPT, aspirin should be continued. In patients with recent ACS treated medically who must undergo surgery for which DAPT must be discontinued, it is similarly reasonable to continue aspirin when the risk for cardiac events outweighs the risk for bleeding.

In most patients receiving long term aspirin monotherapy for both primary and secondary prevention of cardiovascular events (in the absence of a coronary stent), aspirin should be discontinued at least 5 days before surgery and restarted postoperatively once bleeding risk has decreased. This recommendation is based on the POISE 2 trial, which found that continued perioperative aspirin resulted in increased bleeding without a decrease in cardiac events.

Perioperative Management of Anemia, Coagulopathies, and Thrombocytopenia

In all patients undergoing surgery, a careful preoperative bleeding history, including a family history, should be obtained to evaluate for underlying bleeding disorders and anemia. Laboratory testing should be reserved for patients with a suggestive history. Patients with known factor deficiencies, platelet function defects, and other coagulopathies should be managed by a hematologist.

In orthopedic and cardiac surgery patients and those with a history of stable CAD, the American Association of Blood Banks recommends a restrictive transfusion threshold (hemoglobin level of 8 g/dL [80 g/L]), as studies indicate that a restrictive threshold results in equivalent or improved patient outcomes. Similarly, in hospitalized hemodynamically stable patients, a transfusion threshold of 7 g/dL (70 g/L) is recommended.

The American Association of Blood Banks recommends a platelet transfusion threshold of 50,000/µL (50×10^9/L) for patients undergoing major non-neurologic surgery or lumbar puncture. Patients with mild thrombocytopenia due to

TABLE 100. American College of Chest Physicians Recommendations for Perioperative Bridging in Patients With Venous Thromboembolism

Risk for Thromboembolism	Patient History	Bridging Anticoagulation Recommendation
High (annual risk >10%)	Recent (within 3 mo) VTE	Bridging
	Severe thrombophilia (e.g., deficiency of protein C, protein S, or antithrombin; antiphospholipid antibodies; multiple abnormalities)	
Moderate (annual risk of 5%-10%)	VTE within the past 3-12 mo	Bridging unless procedure is associated with a high bleeding risk
	Nonsevere thrombophilia (e.g., heterozygous factor V Leiden or prothrombin gene mutation)	
	Recurrent VTE	
	Active cancer (treated within 6 mo or palliative)	
Low (annual risk <5%)	VTE >12 mo ago and no other risk factors	No bridging

VTE = venous thromboembolism.

Recommendations from Douketis JD, Spyropoulos AC, Spencer FA, Mayr M, Jaffer AK, Eckman MH, et al. Perioperative management of antithrombotic therapy: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2012;141:e326S-e350S. [PMID: 22315266] doi:10.1378/chest.11-2298

H CONT. immune thrombocytopenia are typically able to proceed to surgery at the recommended threshold. Postoperative thrombocytopenia warrants further evaluation, especially in patients with heparin exposure owing to the risk for heparin-induced thrombocytopenia. See MKSAP 18 Hematology and Oncology for a discussion of heparin-induced thrombocytopenia. H

KEY POINTS

- Patients undergoing general surgery or abdominal-pelvic surgery who are at high risk for venous thromboembolism should receive pharmacologic prophylaxis (with low-molecular-weight heparin or low-dose unfractionated heparin) in combination with mechanical prophylaxis.
- The minimum recommended duration of pharmacologic venous thromboembolism prophylaxis in patients undergoing orthopedic surgery is 10 to 14 days; however, in patients without increased bleeding risk, extended-duration postoperative prophylaxis (up to 35 days) is preferred.
- In patients with atrial fibrillation undergoing a procedure with an intermediate or high risk for bleeding, interruption of anticoagulation is almost always required, and the $CHADS_2$ and CHA_2DS_2-VASc scores may be used to determine thrombotic risk and the need for bridging anticoagulation.
- In patients treated with percutaneous coronary intervention who are undergoing elective noncardiac surgery, dual antiplatelet therapy should be continued uninterrupted for at least 30 days after bare metal stent placement and a minimum of 6 months after drug-eluting stent placement.
- HVC In orthopedic and cardiac surgery patients and those with a history of CAD, the American Association of Blood Banks recommends a restrictive transfusion threshold (hemoglobin level of 8 g/dL [80 g/L]).

H Perioperative Management of Endocrine Diseases

Diabetes Mellitus

Evidence demonstrates that patients with uncontrolled diabetes are at increased risk for perioperative complications, including surgical and nonsurgical infections, and postoperative mortality. Patients at high risk for diabetes, such as those with a history of impaired fasting glucose, should be evaluated for diabetes before elective surgery. In patients with established diabetes, it is reasonable to measure hemoglobin A_{1c} within 3 months of surgery. There is not high-quality evidence on whether delaying surgery to improve glycemic control improves outcomes, although efforts should be made to optimize glycemic control before major elective surgery.

Oral and injectable noninsulin medications should be withheld 12 to 72 hours before surgery, replaced with supplemental insulin, and resumed at hospital discharge or when the patient has resumed a full diet. In patients taking insulin therapy, basal insulin should be continued perioperatively. The basal insulin dosage should not be reduced in patients with type 1 diabetes. Preoperative dosage reduction (often 25%-50%) may be considered in patients with type 2 diabetes who have a history of hypoglycemia with skipped or delayed meals.

Postoperatively, if the patient is eating, the ideal insulin regimen is a basal-bolus regimen, with prandial coverage and correction boluses for premeal hyperglycemia. For a discussion of the management of hyperglycemia in the hospital setting, see MKSAP 18 Endocrinology and Metabolism.

Thyroid Disease

Preoperative screening for thyroid disease is not recommended in the absence of symptoms. In patients with symptoms suggestive of thyroid disease or patients with hypothyroidism and a recent change in levothyroxine dosage, it is reasonable to obtain a preoperative thyroid-stimulating hormone level, although there are no guidelines to support such an approach.

In patients with hypothyroidism treated with levothyroxine, therapy should continue uninterrupted. Patients with untreated, asymptomatic mild hypothyroidism may proceed to surgery. A recent retrospective cohort study demonstrated that mild hypothyroidism (median thyroid-stimulating hormone level of 8.6 µU/mL [8.6 mU/L]) was not associated with an increase in perioperative mortality, cardiovascular morbidity, or infectious morbidity. In the presence of severe hypothyroidism, elective surgery should be postponed to prevent myxedema coma, arrhythmias, perioperative hypotension, and other complications.

Patients with well-controlled hyperthyroidism should be continued on therapy, including β-blockers and thionamides. Patients with uncontrolled hyperthyroidism are at risk for thyroid storm in the perioperative period, and surgery should be deferred until thyroid disease can be controlled.

Consultation with an endocrinologist is advised if emergent surgery is required in patients with severe thyroid disease.

Adrenal Insufficiency

Patients with adrenal insufficiency should be evaluated for the need for perioperative supplemental glucocorticoid dosing, known as stress dosing. The decision to initiate perioperative stress dosing is guided by limited evidence, although one strategy uses patient characteristics and the degree of surgical stress to determine management (Table 101). Perioperative supplemental glucocorticoid dosing recommendations are provided in Table 102.

TABLE 101. Stress Dosing Strategies in Patients at Risk for Adrenal Insufficiency

Patient Risk	Patient Characteristics	Management
High risk	Primary adrenal insufficiency	Stress dosing
	Hypothalamic-pituitary-adrenal axis disease	
	Cushingoid features	
	Equivalent of >5 mg/d of prednisone for >3 wk during the previous 3 mo	
	High-dose inhaled glucocorticoid therapy	
Moderate risk	Equivalent of >5 mg/d of prednisone for <3 wk during the previous 3 mo	Stress dosing may be indicated[a]
	High-dose topical glucocorticoid therapy	Perform preoperative adrenal axis testing
	Injectable glucocorticoid therapy in the last 3 mo	
Low risk	Equivalent of <5 mg/d of prednisone for any duration	No stress dosing
	Low-dose inhaled or topical glucocorticoid therapy	

[a]In patients at moderate risk who require emergent or urgent surgery, no further testing is recommended, and stress-dose glucocorticoids should be administered. In other patients, it is reasonable to measure morning serum cortisol preoperatively to test the hypothalamic pituitary-adrenal axis.

TABLE 102. Perioperative Supplemental Glucocorticoid Dosing

Surgical Stress Anticipated	Daily Intravenous Hydrocortisone Dose	Duration of Stress Dosing (in Days)
Minor (e.g., ambulatory procedures)	25 mg	1
Moderate (e.g., orthopedic surgery)	50-75 mg	1-2
High (e.g., cardiac bypass graft surgery)	100 mg, followed by 50 mg every 6 hours	2-3

KEY POINTS

- In patients with diabetes mellitus who are undergoing surgery, oral and injectable noninsulin medications should be withheld, replaced with supplemental insulin, and resumed at hospital discharge or when the patient has resumed a full diet.
- Patients with untreated, asymptomatic mild hypothyroidism may proceed to surgery without further testing or treatment.
- Surgery should be deferred in patients with severe uncontrolled hypo- or hyperthyroidism.

Perioperative Management of Kidney Disease

H

Patients with chronic kidney disease (CKD) are at increased perioperative risk for fluid and electrolyte imbalance, metabolic acidosis, anemia, bleeding diathesis, and cardiac events, depending on the severity of the underlying disease. For patients undergoing hemodialysis, it is advisable to consult a nephrologist for review of the dialysate prescription, adjustment of fluid removal, and management of peridialysis heparin. Patients with less advanced CKD require correction of electrolyte abnormalities and optimization of volume status preoperatively. In all patients with kidney disease undergoing surgery, it is important to avoid iodinated contrast dye and other nephrotoxic agents and minimize perioperative hypotension.

Perioperative acute kidney injury portends an increased risk for postoperative CKD and, in those with underlying CKD, end-stage kidney disease. The two most important means of mitigating the risk for acute kidney injury are maintenance of renal blood flow and avoidance of further insults to the kidneys. Renal blood flow is maintained by avoiding renal hypoperfusion; effectively managing diuresis and antihypertensive medications; and treating anemia, which may impair peripheral vasodilation. Careful medication review is also warranted to ensure appropriate dosing based on renal clearance. H

KEY POINT

- The two most important means of mitigating the risk for acute kidney injury in the perioperative period are maintenance of renal blood flow and avoidance of further insults to the kidneys.

Perioperative Management of Liver Disease

H

Liver disease increases risk for perioperative infection, encephalopathy, bleeding, fluid retention, and acute kidney and liver decompensation. Patients with chronic liver disease require careful preoperative evaluation and risk stratification using the Model for End-stage Liver Disease (MELD) score and Child-Turcotte-Pugh classification. Patients with compensated liver disease, including those with a MELD score of less than 8 to 10, are often able to proceed with surgery with optimal medical management. In patients with intermediate risk, referral to a hepatologist is reasonable before proceeding with surgery. Those with severe liver disease are at increased and often prohibitive risk for perioperative complications and death; patients with Child-Turcotte-Pugh class C disease and a MELD score greater than 15 are generally advised to avoid elective surgery and should be referred for transplant evaluation if appropriate.

Complications of liver disease should be optimally managed in all patients; however, the American Association for the Study of Liver Diseases recommends against perioperative

H CONT.

transjugular intrahepatic portosystemic shunt placement because of a lack of evidence that the procedure improves outcomes.

In general, patients with liver disease should be advised to abstain from alcohol consumption for at least 12 weeks before elective surgery.

Perioperative Management of Neurologic Disease

Patients with neurologic disease are at increased perioperative risk for loss of disease control, among other complications. In patients with epilepsy, perioperative seizure risk is thought to be driven by the severity of the underlying disease and seizure frequency, rather than by anesthesia or surgery type; an important exception is intracranial surgery, which may provoke seizures depending on the location of the surgery, underlying pathologic conditions, and required degree of brain manipulation. Antiepileptic medications should be continued uninterrupted. In patients who are unable to tolerate oral intake, alternate formulations should be used.

Patients with Parkinson disease are predisposed to perioperative delirium, hallucinations, orthostatic hypotension, and complications related to dysphagia. It is essential that patients maintain their normal treatment regimen. Surgery should be scheduled for as early in the day as possible to minimize missed doses, and antidopaminergic antiemetics should be avoided. Parkinson-hyperpyrexia syndrome is a potentially life-threatening complication resulting from withdrawal of or reduction in the dosage of dopamine agonists; it is characterized by rigidity, fever, altered mental status, and autonomic instability.

Asymptomatic carotid bruit is a common finding in older adults but is not predictive of perioperative stroke and therefore requires no preoperative evaluation. Perioperative stroke is discussed in MKSAP 18 Neurology.

Delirium commonly occurs in the postoperative setting, especially in the elderly. Risk factors and treatment are similar to those for delirium in the general hospital setting (see MKSAP 18 Neurology). H

KEY POINTS

- Patients with Parkinson disease should continue antiparkinson agents through surgery, and surgery should be scheduled for as early in the day as possible to minimize missed doses.
- HVC Asymptomatic carotid bruit is a common finding in older adults but is not predictive of perioperative stroke and therefore requires no preoperative evaluation.

H Perioperative Management of the Pregnant Patient

In women of child-bearing age, an accurate menstrual history should be obtained, and pregnancy testing should be performed if pregnancy is suspected. Many institutions require preoperative pregnancy testing in this population.

Elective surgery should be delayed until after pregnancy. Pregnant patients who require surgery should undergo the same preoperative medical evaluation as nonpregnant patients; additional diagnostic testing is unnecessary unless directed by the obstetrician. Modifications to surgical and anesthetic techniques may be required because of the anatomic and physiologic changes of pregnancy. Close collaboration among the obstetrician, surgeon, anesthesiologist, and internist is essential. Notably, pregnancy is considered a hypercoagulable state, and the ACCP recommends perioperative mechanical or pharmacologic VTE prophylaxis for pregnant patients. Although high-quality evidence is lacking, the current body of evidence suggests that surgery does not negatively affect obstetric or maternal outcomes. H

KEY POINT

- Pregnant patients who require surgery should undergo the same preoperative medical evaluation as nonpregnant patients; additional diagnostic testing is unnecessary, but close collaboration with the patient's obstetrician is advised.

Bibliography

High Value Care in Internal Medicine

The Commonwealth Fund. U.S. spends more on health care than other high-income nations but has lower life expectancy, worse health [Press release]. October 8, 2015. Retrieved from http://www.commonwealthfund.org/~/media/files/news/news-releases/2015/oct/oecd_spending_release_10_6_15_links-ds.pdf.

Qaseem A, Alguire P, Dallas P, Feinberg LE, Fitzgerald FT, Horwitch C, et al. Appropriate use of screening and diagnostic tests to foster high-value, cost-conscious care. Ann Intern Med. 2012;156:147-9. [PMID: 22250146] doi:10.7326/0003-4819-156-2-201201170-00011

Interpretation of the Medical Literature

Barratt A, Wyer PC, Hatala R, McGinn T, Dans AL, Keitz S, et al; Evidence-Based Medicine Teaching Tips Working Group. Tips for learners of evidence-based medicine: 1. Relative risk reduction, absolute risk reduction and number needed to treat. CMAJ. 2004;171:353-8. [PMID: 15313996]

Centre for Evidence Based Medicine. Study designs. http://www.cebm.net/study-designs/. Accessed January 23, 2018.

Citrome L, Ketter TA. When does a difference make a difference? Interpretation of number needed to treat, number needed to harm, and likelihood to be helped or harmed. Int J Clin Pract. 2013;67:407-11. [PMID: 23574101] doi:10.1111/ijcp.12142

Howick J, Chalmers I, Glasziou P, Greenhalgh G, Heneghan C, Liberati A, et al. Explanation of the 2011 Oxford Centre for Evidence-Based Medicine (OCEBM) levels of evidence (background document). Oxford Centre for Evidence-Based Medicine. https://www.cebm.net/wp-content/uploads/2014/06/CEBM-Levels-of-Evidence-Background-Document-2.1.pdf. Accessed January 23, 2018.

Richardson WS, Wilson MC, Keitz SA, Wyer PC; EBM Teaching Scripts Working Group. Tips for teachers of evidence-based medicine: making sense of diagnostic test results using likelihood ratios. J Gen Intern Med. 2008;23:87-92. [PMID: 18064524]

Uman LS. Systematic reviews and meta-analyses. J Can Acad Child Adolesc Psychiatry. 2011;20:57-9. [PMID: 21286370]

Routine Care of the Healthy Patient

Bibbins-Domingo K, Grossman DC, Curry SJ, Davidson KW, Epling JW Jr, García FAR, et al; US Preventive Services Task Force. Screening for colorectal cancer: US Preventive Services Task Force recommendation statement. JAMA. 2016;315:2564-2575. [PMID: 27304597] doi:10.1001/jama.2016.5989

Bibbins-Domingo K, Grossman DC, Curry SJ, Davidson KW, Epling JW Jr, García FA, et al; US Preventive Services Task Force. Screening for obstructive sleep apnea in adults: US Preventive Services Task Force recommendation statement. JAMA. 2017;317:407-414. [PMID: 28118461] doi:10.1001/jama.2016.20325

Bibbins-Domingo K; U.S. Preventive Services Task Force. Aspirin use for the primary prevention of cardiovascular disease and colorectal cancer: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2016;164:836-45. [PMID: 27064677] doi:10.7326/M16-0577

Crowley RA; Health and Public Policy Committee of the American College of Physicians. Climate change and health: a position paper of the American College of Physicians. Ann Intern Med. 2016;164:608-10. [PMID: 27089232] doi:10.7326/M15-2766

Curry SJ, Krist AH, Owens DK, Barry MJ, Caughey AB, Davidson KW, et al; US Preventive Services Task Force. Screening for cervical cancer: US Preventive Services Task Force recommendation statement. JAMA. 2018;320:674-686. [PMID: 30140884] doi:10.1001/jama.2018.10897

Curry SJ, Krist AH, Owens DK, Barry MJ, Caughey AB, Davidson KW, et al; US Preventive Services Task Force. Screening for osteoporosis to prevent fractures: US Preventive Services Task Force recommendation statement. JAMA. 2018;319:2521-2531. [PMID: 29946735] doi:10.1001/jama.2018.7498

DiazGranados CA, Dunning AJ, Kimmel M, Kirby D, Treanor J, Collins A, et al. Efficacy of high-dose versus standard-dose influenza vaccine in older adults. N Engl J Med. 2014;371:635-45. [PMID: 25119609] doi:10.1056/NEJMoa1315727

Grossman DC, Curry SJ, Owens DK, Bibbins-Domingo K, Caughey AB, Davidson KW, et al; US Preventive Services Task Force. Screening for prostate cancer: US Preventive Services Task Force recommendation statement. JAMA. 2018;319:1901-1913. [PMID: 29801017] doi:10.1001/jama.2018.3710

Ikeda Y, Shimada K, Teramoto T, Uchiyama S, Yamazaki T, Oikawa S, et al. Low-dose aspirin for primary prevention of cardiovascular events in Japanese patients 60 years or older with atherosclerotic risk factors: a randomized clinical trial. JAMA. 2014;312:2510-20. [PMID: 25401325] doi:10.1001/jama.2014.15690

Jørgensen T, Jacobsen RK, Toft U, Aadahl M, Glümer C, Pisinger C. Effect of screening and lifestyle counselling on incidence of ischaemic heart disease in general population: Inter99 randomised trial. BMJ. 2014;348:g3617. [PMID: 24912589] doi:10.1136/bmj.g3617

Kim DK, Riley LE, Hunter P. Advisory Committee on Immunization Practices recommended immunization schedule for adults aged 19 years or older - United States, 2018. MMWR Morb Mortal Wkly Rep. 2018;67:158-160. [PMID: 29420462] doi:10.15585/mmwr.mm6705e3

Krogsbøll LT, Jørgensen KJ, Grønhøj Larsen C, Gøtzsche PC. General health checks in adults for reducing morbidity and mortality from disease: Cochrane systematic review and meta-analysis. BMJ. 2012;345:e7191. [PMID: 23169868] doi:10.1136/bmj.e7191

LeFevre ML; U.S. Preventive Services Task Force. Screening for abdominal aortic aneurysm: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2014;161:281-90. [PMID: 24957320] doi:10.7326/M14-1204

Moyer VA; U.S. Preventive Services Task Force. Risk assessment, genetic counseling, and genetic testing for BRCA-related cancer in women: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2014;160:271-81. [PMID: 24366376]

Oeffinger KC, Fontham ET, Etzioni R, Herzig A, Michaelson JS, Shih YC, et al; American Cancer Society. Breast cancer screening for women at average risk: 2015 guideline update from the American Cancer Society. JAMA. 2015;314:1599-614. [PMID: 26501536] doi:10.1001/jama.2015.12783

Saito Y, Okada S, Ogawa H, Soejima H, Sakuma M, Nakayama M, et al; JPAD Trial Investigators. Low-dose aspirin for primary prevention of cardiovascular events in patients with type 2 diabetes mellitus: 10-year follow-up of a randomized controlled trial. Circulation. 2017;135:659-670. [PMID: 27881565] doi:10.1161/CIRCULATIONAHA.116.025760

Siu AL, Bibbins-Domingo K, Grossman DC, Baumann LC, Davidson KW, Ebell M, et al; US Preventive Services Task Force (USPSTF). Screening for depression in adults: US Preventive Services Task Force recommendation statement. JAMA. 2016;315:380-7. [PMID: 26813211] doi:10.1001/jama.2015.18392

Siu AL; U.S. Preventive Services Task Force. Screening for abnormal blood glucose and type 2 diabetes mellitus: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2015;163:861-8. [PMID: 26501513] doi:10.7326/M15-2345

Siu AL; U.S. Preventive Services Task Force. Screening for breast cancer: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2016;164:279-96. [PMID: 26757170] doi:10.7326/M15-2886

Siu AL; U.S. Preventive Services Task Force. Screening for high blood pressure in adults: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2015;163:778-86. [PMID: 26458123] doi:10.7326/M15-2223

Teng K, Acheson LS. Genomics in primary care practice. Prim Care. 2014;41:421-35. [PMID: 24830615] doi:10.1016/j.pop.2014.02.012

van der Wouden CH, Carere DA, Maitland-van der Zee AH, Ruffin MT 4th, Roberts JS, Green RC; Impact of Personal Genomics Study Group. Consumer perceptions of interactions with primary care providers after direct-to-consumer personal genomic testing. Ann Intern Med. 2016;164:513-22. [PMID: 26928821] doi:10.7326/M15-0995

Patient Safety and Quality Improvement

The Joint Commission. Patient safety systems. Comprehensive Accreditation Manual for Hospitals. Update 2, January 2016; PS 1-53. www.jointcommission.org/assets/1/18/PSC_for_Web.pdf. Accessed May 23, 2018.

National Academies of Sciences, Engineering, and Medicine. Improving Diagnosis in Health Care. Washington, DC: The National Academies Press; 2015.

U.S. Department of Health and Human Services, Health Resources and Services Administration. Quality improvement. www.hrsa.gov/quality/toolbox/508pdfs/qualityimprovement.pdf. Published April 2011. Accessed May 23, 2018.

U.S. Department of Health and Human Services, Office of Disease Prevention and Health Promotion. National action plan to improve health literacy. https://health.gov/communication/hlactionplan/pdf/Health_Literacy_Action_Plan.pdf. Published May 2010. Accessed May 23, 2018.

Professionalism and Ethics

ABIM Foundation. American Board of Internal Medicine. Medical professionalism in the new millennium: a physician charter. Ann Intern Med. 2002;136:243-6. [PMID: 11827500]

Appelbaum PS. Clinical practice. Assessment of patients' competence to consent to treatment. N Engl J Med. 2007;357:1834-40. [PMID: 17978292]

Daniel H, Sulmasy LS; Health and Public Policy Committee of the American College of Physicians. Policy recommendations to guide the use of telemedicine in primary care settings: an American College of Physicians position paper. Ann Intern Med. 2015;163:787-9. [PMID: 26344925] doi:10.7326/M15-0498

DeMartino ES, Dudzinski DM, Doyle CK, Sperry BP, Gregory SE, Siegler M, et al. Who Decides When a Patient Can't? Statutes on Alternate Decision Makers. N Engl J Med. 2017;376:1478-1482. [PMID: 28402767] doi:10.1056/NEJMms1611497

Farnan JM, Snyder Sulmasy L, Worster BK, Chaudhry HJ, Rhyne JA, Arora VM; American College of Physicians Ethics, Professionalism and Human Rights Committee. Online medical professionalism: patient and public relationships: policy statement from the American College of Physicians and the Federation of State Medical Boards. Ann Intern Med. 2013;158:620-7. [PMID: 23579867] doi:10.7326/0003-4819-158-8-201304160-00100

Halpern SD, Emanuel EJ. Can the United States buy better advance care planning? Ann Intern Med. 2015;162:224-5. [PMID: 25486099] doi:10.7326/M14-2476

Owens DK, Qaseem A, Chou R, Shekelle P; Clinical Guidelines Committee of the American College of Physicians. High-value, cost-conscious health care: concepts for clinicians to evaluate the benefits, harms, and costs of medical interventions. Ann Intern Med. 2011;154:174-80. [PMID: 21282697] doi:10.7326/0003-4819-154-3-201102010-00007

Snyder Sulmasy L, Mueller PS; Ethics, Professionalism and Human Rights Committee of the American College of Physicians. Ethics and the legalization of physician-assisted suicide: an American College of Physicians position paper. Ann Intern Med. 2017;167(8):576-578. [PMID: 28975242] doi: 10.7326/M17-0938

Palliative Medicine

Bernacki RE, Block SD; American College of Physicians High Value Care Task Force. Communication about serious illness care goals: a review and synthesis of best practices. JAMA Intern Med. 2014;174:1994-2003. [PMID: 25330167] doi:10.1001/jamainternmed.2014.5271

Kavalieratos D, Corbelli J, Zhang D, Dionne-Odom JN, Ernecoff NC, Hanmer J, et al. Association between palliative care and patient and caregiver outcomes: a systematic review and meta-analysis. JAMA. 2016;316:2104-2114. [PMID: 27893131] doi:10.1001/jama.2016.16840

Quill TE, Abernethy AP. Generalist plus specialist palliative care–creating a more sustainable model. N Engl J Med. 2013;368:1173-5. [PMID: 23465068] doi:10.1056/NEJMp1215620

Strand JJ, Kamdar MM, Carey EC. Top 10 things palliative care clinicians wished everyone knew about palliative care. Mayo Clin Proc. 2013;88:859-65. [PMID: 23910412] doi:10.1016/j.mayocp.2013.05.020

Swetz KM, Kamal AH. Palliative care. Ann Intern Med. 2018;168:ITC33-ITC48. [PMID: 29507970] doi:10.7326/AITC201803060

Temel JS, Greer JA, Muzikansky A, Gallagher ER, Admane S, Jackson VA, et al. Early palliative care for patients with metastatic non-small-cell lung cancer. N Engl J Med. 2010;363:733-42. [PMID: 20818875] doi:10.1056/NEJMoa1000678

Common Symptoms

Abernethy AP, McDonald CF, Frith PA, Clark K, Herndon JE 2nd, Marcello J, et al. Effect of palliative oxygen versus room air in relief of breathlessness in patients with refractory dyspnoea: a double-blind, randomised controlled trial. Lancet. 2010;376:784-93. [PMID: 20816546] doi:10.1016/S0140-6736(10)61115-4

Chow AW, Benninger MS, Brook I, Brozek JL, Goldstein EJ, Hicks LA, et al; Infectious Diseases Society of America. IDSA clinical practice guideline for acute bacterial rhinosinusitis in children and adults. Clin Infect Dis. 2012;54:e72-e112. [PMID: 22438350] doi:10.1093/cid/cir1043

Committee on the Diagnostic Criteria for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome, Board on the Health of Select Populations, Institute of Medicine. Beyond Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Redefining an Illness. Washington (DC): National Academies Press (US); 2015 Feb 10. [PMID: 25695122]

Costantino G, Sun BC, Barbic F, Bossi I, Casazza G, Dipaola F, et al. Syncope clinical management in the emergency department: a consensus from the first international workshop on syncope risk stratification in the emergency department. Eur Heart J. 2016;37:1493-8. [PMID: 26242712] doi:10.1093/eurheartj/ehv378

Dowell D, Haegerich TM, Chou R. CDC guideline for prescribing opioids for chronic pain-United States, 2016. JAMA. 2016;315:1624-45. [PMID: 26977696] doi:10.1001/jama.2016.1464

Evens A, Vendetta L, Krebs K, Herath P. Medically unexplained neurologic symptoms: a primer for physicians who make the initial encounter. Am J Med. 2015;128:1059-64. [PMID: 25910791] doi:10.1016/j.amjmed.2015.03.030

Gibson P, Wang G, McGarvey L, Vertigan AE, Altman KW, Birring SS; CHEST Expert Cough Panel. Treatment of unexplained chronic cough: CHEST guideline and expert panel report. Chest. 2016;149:27-44. [PMID: 26426314] doi:10.1378/chest.15-1496

Hallenbeck J. Pathophysiologies of dyspnea explained: why might opioids relieve dyspnea and not hasten death? J Palliat Med. 2012;15:848-53. [PMID: 22594628] doi:10.1089/jpm.2011.0167

Haller H, Cramer H, Lauche R, Dobos G. Somatoform disorders and medically unexplained symptoms in primary care. Dtsch Arztebl Int. 2015;112:279-87. [PMID: 25939319] doi:10.3238/arztebl.2015.0279

Hooten M, Thorson D, Bianco J, Bonte B, Clavel Jr A, Hora J, et al. Pain: assessment, non-opioid treatment approaches and opioid management. Bloomington (MN): Institute for Clinical Systems Improvement (ICSI); 2016 Sep. 160 p. Available at https://www.icsi.org/guidelines_more/catalog_guidelines_and_more/catalog_guidelines/catalog_neurological_guidelines/pain/.

Kim JS, Zee DS. Clinical practice. Benign paroxysmal positional vertigo. N Engl J Med. 2014;370:1138-47. [PMID: 24645946] doi:10.1056/NEJMcp1309481

Lipsitt DR, Joseph R, Meyer D, Notman MT. Medically unexplained symptoms: barriers to effective treatment when nothing is the matter. Harv Rev Psychiatry. 2015;23:438-48. [PMID: 26378814] doi:10.1097/HRP.0000000000000055

Masters PA. In the clinic. Insomnia. Ann Intern Med. 2014;161:ITC1-15; quiz ITC16. [PMID: 25285559] doi:10.7326/0003-4819-161-7-201410070-01004

Nable JV, Tupe CL, Gehle BD, Brady WJ. In-flight medical emergencies during commercial travel. N Engl J Med. 2015;373:939-45. [PMID: 26332548] doi:10.1056/NEJMra1409213

Parshall MB, Schwartzstein RM, Adams L, Banzett RB, Manning HL, Bourbeau J, et al; American Thoracic Society Committee on Dyspnea. An official American Thoracic Society statement: update on the mechanisms, assessment, and management of dyspnea. Am J Respir Crit Care Med. 2012;185:435-52. [PMID: 22336677] doi:10.1164/rccm.201111-2042ST

Prandoni P, Lensing AW, Prins MH, Ciammaichella M, Perlati M, Mumoli N, et al; PESIT Investigators. Prevalence of pulmonary embolism among patients hospitalized for syncope. N Engl J Med. 2016;375:1524-1531. [PMID: 27797317]

Qaseem A, Kansagara D, Forciea MA, Cooke M, Denberg TD; Clinical Guidelines Committee of the American College of Physicians. Management of chronic insomnia disorder in adults: a clinical practice guideline from the American College of Physicians. Ann Intern Med. 2016;165:125-33. [PMID: 27136449] doi:10.7326/M15-2175

Sharon JD, Trevino C, Schubert MC, Carey JP. Treatment of Menière's disease. Curr Treat Options Neurol. 2015;17:341. [PMID: 25749846] doi:10.1007/s11940-015-0341-x

Shen WK, Sheldon RS, Benditt DG, Cohen MI, Forman DE, Goldberger ZD, et al. 2017 ACC/AHA/HRS guideline for the evaluation and management of patients with syncope: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. Circulation. 2017;136:e25-e59. [PMID: 28280232] doi:10.1161/CIR.0000000000000498

Sun BC. Quality-of-life, health service use, and costs associated with syncope. Prog Cardiovasc Dis. 2013;55:370-5. [PMID: 23472773] doi:10.1016/j.pcad.2012.10.009

Trauer JM, Qian MY, Doyle JS, Rajaratnam SM, Cunnington D. Cognitive behavioral therapy for chronic insomnia: a systematic review and meta-analysis. Ann Intern Med. 2015;163:191-204. [PMID: 26054060] doi:10.7326/M14-2841

Venhovens J, Meulstee J, Verhagen WI. Acute vestibular syndrome: a critical review and diagnostic algorithm concerning the clinical differentiation of peripheral versus central aetiologies in the emergency department. J Neurol. 2016;263:2151-2157. [PMID: 26984607]

Whiting PF, Wolff RF, Deshpande S, Di Nisio M, Duffy S, Hernandez AV, et al. Cannabinoids for medical use: a systematic review and meta-analysis. JAMA. 2015;313:2456-73. [PMID: 26103030] doi:10.1001/jama.2015.6358

Musculoskeletal Pain

Abdel Shaheed C, Maher CG, Williams KA, Day R, McLachlan AJ. Efficacy, tolerability, and dose-dependent effects of opioid analgesics for low back pain: a systematic review and meta-analysis. JAMA Intern Med. 2016;176:958-68. [PMID: 27213267] doi:10.1001/jamainternmed.2016.1251

Buller LT, Jose J, Baraga M, Lesniak B. Thoracic outlet syndrome: current concepts, imaging features, and therapeutic strategies. Am J Orthop (Belle Mead NJ). 2015;44:376-82. [PMID: 26251937]

Chou R. In the clinic. Low back pain. Ann Intern Med. 2014;160:ITC6-1. [PMID: 25009837]

Cohen SP. Epidemiology, diagnosis, and treatment of neck pain. Mayo Clin Proc. 2015;90:284-99. [PMID: 25659245] doi:10.1016/j.mayocp.2014.09.008

Deyo RA, Mirza SK. Clinical practice. Herniated lumbar intervertebral disk. N Engl J Med. 2016;374:1763-72. [PMID: 27144851] doi:10.1056/NEJMcp1512658

Goossens P, Keijsers E, van Geenen RJ, Zijta A, van den Broek M, Verhagen AP, et al. Validity of the Thessaly test in evaluating meniscal tears compared with arthroscopy: a diagnostic accuracy study. J Orthop Sports Phys Ther. 2015;45:18-24, B1. [PMID: 25420009] doi:10.2519/jospt.2015.5215

Gross AR, Paquin JP, Dupont G, Blanchette S, Lalonde P, Cristie T, et al; Cervical Overview Group. Exercises for mechanical neck disorders: A Cochrane review update. Man Ther. 2016;24:25-45. [PMID: 27317503] doi:10.1016/j.math.2016.04.005

Hong E, Kraft MC. Evaluating anterior knee pain. Med Clin North Am. 2014;98:697-717, xi. [PMID: 24994047] doi:10.1016/j.mcna.2014.03.001

Iyer S, Kim HJ. Cervical radiculopathy. Curr Rev Musculoskelet Med. 2016;9:272-80. [PMID: 27250042] doi:10.1007/s12178-016-9349-4

Krebs EE, Gravely A, Nugent S, Jensen AC, DeRonne B, Goldsmith ES, et al. Effect of opioid vs nonopioid medications on pain-related function in patients with chronic back pain or hip or knee osteoarthritis pain: the SPACE randomized clinical trial. JAMA. 2018;319:872-882. [PMID: 29509867] doi:10.1001/jama.2018.0899

Li HY, Hua YH. Achilles tendinopathy: current concepts about the basic science and clinical treatments. Biomed Res Int. 2016;2016:6492597. [PMID: 27885357]

Maher C, Underwood M, Buchbinder R. Non-specific low back pain. Lancet. 2017;389:736-747. [PMID: 27745712] doi:10.1016/S0140-6736(16)30970-9

Olaussen M, Holmedal O, Lindback M, Brage S, Solvang H. Treating lateral epicondylitis with corticosteroid injections or non-electrotherapeutical physiotherapy: a systematic review. BMJ Open. 2013;3:e003564. [PMID: 24171937] doi:10.1136/bmjopen-2013-003564

Page MJ, Green S, Kramer S, Johnston RV, McBain B, Chau M, et al. Manual therapy and exercise for adhesive capsulitis (frozen shoulder). Cochrane Database Syst Rev. 2014:CD011275. [PMID: 25157702] doi:10.1002/14651858.CD011275

Qaseem A, Wilt TJ, McLean RM, Forciea MA; Clinical Guidelines Committee of the American College of Physicians. Noninvasive treatments for acute, subacute, and chronic low back pain: a clinical practice guideline from the American College of Physicians. Ann Intern Med. 2017;166:514-530. [PMID: 28192789] doi:10.7326/M16-2367

Tenforde AS, Yin A, Hunt KJ. Foot and ankle injuries in runners. Phys Med Rehabil Clin N Am. 2016;27:121-37. [PMID: 26616180] doi:10.1016/j.pmr.2015.08.007

Verdugo RJ, Salinas RA, Castillo JL, Cea JG. Surgical versus non-surgical treatment for carpal tunnel syndrome. Cochrane Database Syst Rev. 2008:CD001552. [PMID: 18843618] doi:10.1002/14651858.CD001552.pub2

Wilson JJ, Furukawa M. Evaluation of the patient with hip pain. Am Fam Physician. 2014;89:27–34. [PMID: 24444505]

Dyslipidemia

Bibbins-Domingo K, Grossman DC, Curry SJ, Davidson KW, Epling JW Jr, García FA, et al; US Preventive Services Task Force. Statin use for the primary prevention of cardiovascular disease in adults: US Preventive Services Task Force recommendation statement. JAMA. 2016;316:1997–2007. [PMID: 27838723] doi:10.1001/jama.2016.15450

Eckel RH, Jakicic JM, Ard JD, de Jesus JM, Houston Miller N, Hubbard VS, et al; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2013 AHA/ACC guideline on lifestyle management to reduce cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014;129:S76–99. [PMID: 24222015] doi:10.1161/01.cir.0000437740.48606.d1

Jellinger PS, Handelsman Y, Rosenblit PD, Bloomgarden ZT, Fonseca VA, Garber AJ, et al. American Association of Clinical Endocrinologists and American College of Endocrinology guidelines for management of dyslipidemia and prevention of cardiovascular disease. Endocr Pract. 2017;23:1–87. [PMID: 28437620] doi:10.4158/EP171764.APPGL

Lloyd-Jones DM, Morris PB, Ballantyne CM, Birtcher KK, Daly DD Jr, DePalma SM, et al. 2017 Focused update of the 2016 ACC expert consensus decision pathway on the role of non-statin therapies for LDL-cholesterol lowering in the management of atherosclerotic cardiovascular disease risk: a report of the American College of Cardiology Task Force on Expert Consensus Decision Pathways. J Am Coll Cardiol. 2017;70:1785–1822. [PMID: 28886926] doi:10.1016/j.jacc.2017.07.745

Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, et al; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014;129:S1–45. [PMID: 24222016] doi:10.1161/01.cir.0000437738.63853.7a

Van Horn L, Carson JA, Appel LJ, Burke LE, Economos C, Karmally W, et al; American Heart Association Nutrition Committee of the Council on Lifestyle and Cardiometabolic Health; Council on Cardiovascular Disease in the Young; Council on Cardiovascular and Stroke Nursing; Council on Clinical Cardiology; and Stroke Council. Recommended dietary pattern to achieve adherence to the American Heart Association/American College of Cardiology (AHA/ACC) guidelines: a scientific statement from the American Heart Association. Circulation. 2016;134:e505–e529. [PMID: 27789558]

Obesity

Behary J, Kumbhari V. Advances in the endoscopic management of obesity. Gastroenterol Res Pract. 2015;2015:757821. [PMID: 26106413] doi:10.1155/2015/757821

Chang SH, Stoll CR, Song J, Varela JE, Eagon CJ, Colditz GA. The effectiveness and risks of bariatric surgery: an updated systematic review and meta-analysis, 2003–2012. JAMA Surg. 2014;149:275–87. [PMID: 24352617] doi:10.1001/jamasurg.2013.3654

Flegal KM, Kruszon-Moran D, Carroll MD, Fryar CD, Ogden CL. Trends in obesity among adults in the United States, 2005 to 2014. JAMA. 2016;315:2284–91. [PMID: 27272580] doi:10.1001/jama.2016.6458

Jacob JA. Obesity-related medical care costs Medicaid $8 billion a year. Health agencies update. JAMA 2015;314(24):2607. doi:10.1001/jama.2015.16829

Jensen MD, Ryan DH, Apovian CM, Ard JD, Comuzzie AG, Donato KA, et al; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society. Circulation. 2014;129:S102–38. [PMID: 24222017] doi:10.1161/01.cir.0000437739.71477.ee

Johnston BC, Kanters S, Bandayrel K, Wu P, Naji F, Siemieniuk RA, et al. Comparison of weight loss among named diet programs in overweight and obese adults: a meta-analysis. JAMA. 2014;312:923–33. [PMID: 25182101] doi:10.1001/jama.2014.10397

Khera R, Murad MH, Chandar AK, Dulai PS, Wang Z, Prokop LJ, et al. Association of pharmacological treatments for obesity with weight loss and adverse events: a systematic review and meta-analysis. JAMA. 2016;315:2424–34. [PMID: 27299618] doi:10.1001/jama.2016.7602

Marcotte E, Chand B. Management and prevention of surgical and nutritional complications after bariatric surgery. Surg Clin North Am. 2016;96:843–56. [PMID: 27473805] doi:10.1016/j.suc.2016.03.006

Moyer VA; U.S. Preventive Services Task Force. Screening for and management of obesity in adults: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2012;157:373–8. [PMID: 22733087]

Men's Health

Crawford P, Crop JA. Evaluation of scrotal masses. Am Fam Physician. 2014;89:723–7. [PMID: 24784335]

McVary KT, Roehrborn CG, Avins AL, et al. American Urological Association guideline: management of benign prostatic hyperplasia (BPH). Linthicum, MD: American Urological Association; 2010. https://www.auanet.org/education/guidelines/benign-prostatic-hyperplasia.cfm. Accessed January 20, 2017.

Nehra A, Jackson G, Miner M, Billups KL, Burnett AL, Buvat J, et al. The Princeton III Consensus recommendations for the management of erectile dysfunction and cardiovascular disease. Mayo Clin Proc. 2012;87:766–78. [PMID: 22862865] doi:10.1016/j.mayocp.2012.06.015

Pearson R, Williams PM. Common questions about the diagnosis and management of benign prostatic hyperplasia. Am Fam Physician. 2014;90:769–74. [PMID: 25611711]

Sharp VJ, Takacs EB, Powell CR. Prostatitis: diagnosis and treatment. Am Fam Physician. 2010;82:397–406. [PMID: 20704171]

Snyder PJ, Bhasin S, Cunningham GR, Matsumoto AM, Stephens-Shields AJ, Cauley JA, et al; Testosterone Trials Investigators. Effects of testosterone treatment in older men. N Engl J Med. 2016;374:611–24. [PMID: 26886521] doi:10.1056/NEJMoa1506119

Women's Health

American College of Radiology. ACR Appropriateness Criteria. Palpable breast masses. Available at https://acsearch.acr.org/docs/69495/Narrative/. Accessed March 15, 2018.

Goyal A. Breast pain. Am Fam Physician. 2016;93:872–3. [PMID: 27175723]

Grossman DC, Curry SJ, Owens DK, Barry MJ, Davidson KW, Doubeni CA, et al; US Preventive Services Task Force. Hormone therapy for the primary prevention of chronic conditions in postmenopausal women: US Preventive Services Task Force recommendation statement. JAMA. 2017;318:2224–2233. [PMID: 29234814]

Joffe HV, Chang C, Sewell C, Easley O, Nguyen C, Dunn S, et al. FDA approval of flibanserin–treating hypoactive sexual desire disorder. N Engl J Med. 2016;374:101–4. [PMID: 26649985]

Mitchell CM, Reed SD, Diem S, Larson JC, Newton KM, Ensrud KE, et al. Efficacy of vaginal estradiol or vaginal moisturizer vs placebo for treating postmenopausal vulvovaginal symptoms: a randomized clinical trial. JAMA Intern Med. 2018;178:681–690. [PMID: 29554173] doi:10.1001/jamainternmed.2018.0116

Munro MG, Critchley HO, Broder MS, Fraser IS; FIGO Working Group on Menstrual Disorders. FIGO classification system (PALM-COEIN) for causes of abnormal uterine bleeding in nongravid women of reproductive age. Int J Gynaecol Obstet. 2011;113:3–13. [PMID: 21345435]

The NAMS 2017 Hormone Therapy Position Statement Advisory Panel. The 2017 hormone therapy position statement of The North American Menopause Society. Menopause. 2017;24:728–753. [PMID: 28650869]

Neal L, Sandhu NP, Hieken TJ, Glazebrook KN, Mac Bride MB, Dilaveri CA, et al. Diagnosis and management of benign, atypical, and indeterminate breast lesions detected on core needle biopsy. Mayo Clin Proc. 2014;89:536–47. [PMID: 24684875]

Portman DJ, Gass ML; Vulvovaginal Atrophy Terminology Consensus Conference Panel. Genitourinary syndrome of menopause: new terminology for vulvovaginal atrophy from the International Society for the Study of Women's Sexual Health and the North American Menopause Society. Menopause. 2014;21:1063–8. [PMID: 25160739]

Steege JF, Siedhoff MT. Chronic pelvic pain. Obstet Gynecol. 2014;124:616–29. [PMID: 25162265]

Workowski KA, Bolan GA; Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2015. MMWR Recomm Rep. 2015;64:1–137. [PMID: 26042815]

Eye Disorders

Azari AA, Barney NP. Conjunctivitis: a systematic review of diagnosis and treatment. JAMA. 2013;310:1721–9. [PMID: 24150468] doi:10.1001/jama.2013.280318

Gelston CD. Common eye emergencies. Am Fam Physician. 2013;88:515–9. [PMID: 24364572]

Lim LS, Mitchell P, Seddon JM, Holz FG, Wong TY. Age-related macular degeneration. Lancet. 2012;379:1728–38. [PMID: 22559899] doi:10.1016/S0140-6736(12)60282-7

Moyer VA; U.S. Preventive Services Task Force. Screening for glaucoma: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2013;159:484–9. [PMID: 24325017]

Narayana S, McGee S. Bedside diagnosis of the 'red eye': a systematic review. Am J Med. 2015;128:1220–1224.e1. [PMID: 26169885] doi:10.1016/j.amjmed.2015.06.026

Weinreb RN, Aung T, Medeiros FA. The pathophysiology and treatment of glaucoma: a review. JAMA. 2014;311:1901-11. [PMID: 24825645] doi:10.1001/jama.2014.3192

Ear, Nose, Mouth, and Throat Disorders

Baguley D, McFerran D, Hall D. Tinnitus. Lancet. 2013;382:1600-7. [PMID: 23827090] doi:10.1016/S0140-6736(13)60142-7

Gauer RL, Semidey MJ. Diagnosis and treatment of temporomandibular disorders. Am Fam Physician. 2015;91:378-86. [PMID: 25822556]

Harris AM, Hicks LA, Qaseem A; High Value Care Task Force of the American College of Physicians and for the Centers for Disease Control and Prevention. Appropriate antibiotic use for acute respiratory tract infection in adults: advice for high-value care from the American College of Physicians and the Centers for Disease Control and Prevention. Ann Intern Med. 2016;164:425-34. [PMID: 26785402] doi:10.7326/M15-1840

Kociolek LK, Shulman ST. In the clinic. Pharyngitis. Ann Intern Med. 2012;157:ITC3-1 - ITC3-16. [PMID: 22944886] doi:10.7326/0003-4819-157-5-201209040-01003

Moyer VA; U.S. Preventive Services Task Force. Screening for hearing loss in older adults: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2012;157:655-61. [PMID: 22893115]

Uy J, Forciea MA. In the clinic. Hearing loss. Ann Intern Med. 2013;158:ITC4-1; quiz ITC4-16. [PMID: 23546583] doi:10.7326/0003-4819-158-7-201304020-01004

Wilson JF. In the clinic. Acute sinusitis. Ann Intern Med. 2010;153:ITC31-15; quiz ITC316. [PMID: 20820036] doi:10.7326/0003-4819-153-5-201009070-01003

Mental and Behavioral Health

Bachhuber MA, Hennessy S, Cunningham CO, Starrels JL. Increasing benzodiazepine prescriptions and overdose mortality in the United States, 1996-2013. Am J Public Health. 2016;106:686-8. [PMID: 26890165] doi:10.2105/AJPH.2016.303061

Dickstein LP, Franco KN, Rome ES, Auron M. Recognizing, managing medical consequences of eating disorders in primary care. Cleve Clin J Med. 2014;81:255-63. [PMID: 24692444] doi:10.3949/ccjm.81a.12132

Edelman EJ, Fiellin DA. In the clinic. Alcohol use. Ann Intern Med. 2016;164:ITC1-16. [PMID: 26747315] doi:10.7326/AITC201601050

Larochelle MR, Liebschutz JM, Zhang F, Ross-Degnan D, Wharam JF. Opioid prescribing after nonfatal overdose and association with repeated overdose: a cohort study. Ann Intern Med. 2016;164:1-9. [PMID: 26720742] doi:10.7326/M15-0038

Lindson-Hawley N, Banting M, West R, Michie S, Shinkins B, Aveyard P. Gradual versus abrupt smoking cessation: a randomized, controlled noninferiority trial. Ann Intern Med. 2016;164:585-92. [PMID: 26975007] doi:10.7326/M14-2805

Moyer VA; Preventive Services Task Force. Screening and behavioral counseling interventions in primary care to reduce alcohol misuse: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2013;159:210-8. [PMID: 23698791] doi:10.7326/0003-4819-159-3-201308060-00652

Pace CA, Samet JH. In the clinic. Substance use disorders. Ann Intern Med. 2016;164:ITC49-ITC64. [PMID: 27043992] doi:10.7326/AITC201604050

Patel MS, Steinberg MB. In the clinic. Smoking cessation. Ann Intern Med. 2016;164:ITC33-ITC48. [PMID: 26926702] doi:10.7326/AITC201603010

Qaseem A, Barry MJ, Kansagara D; Clinical Guidelines Committee of the American College of Physicians. Nonpharmacologic versus pharmacologic treatment of adult patients with major depressive disorder: a clinical practice guideline from the American College of Physicians. Ann Intern Med. 2016;164:350-9. [PMID: 26857948] doi:10.7326/M15-2570

Schuckit MA. Treatment of opioid-use disorders. N Engl J Med. 2016;375:357-68. [PMID: 27464203] doi:10.1056/NEJMra1604339

Siu AL; U.S. Preventive Services Task Force. Behavioral and pharmacotherapy interventions for tobacco smoking cessation in adults, including pregnant women: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2015;163:622-34. [PMID: 26389730] doi:10.7326/M15-2023

Geriatric Medicine

Buta BJ, Walston JD, Godino JG, Park M, Kalyani RR, Xue QL, et al. Frailty assessment instruments: systematic characterization of the uses and contexts of highly-cited instruments. Ageing Res Rev. 2016;26:53-61. [PMID: 26674984] doi:10.1016/j.arr.2015.12.003

Carlson C, Merel SE, Yukawa M. Geriatric syndromes and geriatric assessment for the generalist. Med Clin North Am. 2015;99:263-79. [PMID: 25700583] doi:10.1016/j.mcna.2014.11.003

Chou R, Dana T, Bougatsos C, Grusing S, Blazina I. Screening for impaired visual acuity in older adults: updated evidence report and systematic review for the US Preventive Services Task Force. JAMA. 2016;315:915-33. [PMID: 26934261] doi:10.1001/jama.2016.0783

Dong X. Screening for elder abuse in healthcare settings: why should we care, and is it a missed quality indicator? J Am Geriatr Soc. 2015;63:1686-8. [PMID: 26277299] doi:10.1111/jgs.13538

Gormley EA, Lightner DJ, Faraday M, Vasavada SP; American Urological Association. Diagnosis and treatment of overactive bladder (non-neurogenic) in adults: AUA/SUFU guideline amendment. J Urol. 2015;193:1572-80. [PMID: 25623739] doi:10.1016/j.juro.2015.01.087

Lin JS, O'Connor E, Rossom RC, Perdue LA, Eckstrom E. Screening for cognitive impairment in older adults: a systematic review for the U.S. Preventive Services Task Force. Ann Intern Med. 2013;159:601-12. [PMID: 24145578]

Martin AJ, Marottoli R, O'Neill D. Driving assessment for maintaining mobility and safety in drivers with dementia. Cochrane Database Syst Rev. 2013:CD006222. [PMID: 23990315] doi:10.1002/14651858.CD006222.pub4

Moyer VA; U.S. Preventive Services Task Force. Screening for hearing loss in older adults: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2012;157:655-61. [PMID: 22893115]

Moyer VA; U.S. Preventive Services Task Force. Screening for intimate partner violence and abuse of elderly and vulnerable adults: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2013;158:478-86. [PMID: 23338828] doi:10.7326/0003-4819-158-6-201303190-00588

Qaseem A, Dallas P, Forciea MA, Starkey M, Denberg TD, Shekelle P; Clinical Guidelines Committee of the American College of Physicians. Nonsurgical management of urinary incontinence in women: a clinical practice guideline from the American College of Physicians. Ann Intern Med. 2014;161:429-40. [PMID: 25222388] doi:10.7326/M13-2410

Qaseem A, Humphrey LL, Forciea MA, Starkey M, Denberg TD; Clinical Guidelines Committee of the American College of Physicians. Treatment of pressure ulcers: a clinical practice guideline from the American College of Physicians. Ann Intern Med. 2015;162:370-9. [PMID: 25732279] doi:10.7326/M14-1568

Qaseem A, Mir TP, Starkey M, Denberg TD; Clinical Guidelines Committee of the American College of Physicians. Risk assessment and prevention of pressure ulcers: a clinical practice guideline from the American College of Physicians. Ann Intern Med. 2015;162:359-69. [PMID: 25732278] doi:10.7326/M14-1567

Siu AL, Bibbins-Domingo K, Grossman DC, Baumann LC, Davidson KW, Ebell M, et al; US Preventive Services Task Force (USPSTF). Screening for depression in adults: US Preventive Services Task Force recommendation statement. JAMA. 2016;315:380-7. [PMID: 26813211] doi:10.1001/jama.2015.18392

Perioperative Medicine

Apfelbaum JL, Connis RT, Nickinovich DG, Pasternak LR, Arens JF, Caplan RA, et al; Committee on Standards and Practice Parameters. Practice advisory for preanesthesia evaluation: an updated report by the American Society of Anesthesiologists Task Force on Preanesthesia Evaluation. Anesthesiology. 2012;116:522-38. [PMID: 22273990] doi:10.1097/ALN.0b013e31823c1067

Botto F, Alonso-Coello P, Chan MT, Villar JC, Xavier D, Srinathan S, et al; Vascular events In noncardiac Surgery patIents cOhort evaluatioN (VISION) Writing Group, on behalf of The Vascular events In noncardiac Surgery patIents cOhort evaluatioN (VISION) Investigators. Myocardial injury after noncardiac surgery: a large, international, prospective cohort study establishing diagnostic criteria, characteristics, predictors, and 30-day outcomes. Anesthesiology. 2014;120:564-78. [PMID: 24534856] doi:10.1097/ALN.0000000000000113

Daniels PR. Peri-procedural management of patients taking oral anticoagulants. BMJ. 2015;351:h2391. [PMID: 26174061] doi:10.1136/bmj.h2391

Devereaux PJ, Mrkobrada M, Sessler DI, Leslie K, Alonso-Coello P, Kurz A, et al; POISE-2 Investigators. Aspirin in patients undergoing noncardiac surgery. N Engl J Med. 2014;370:1494-503. [PMID: 24679062] doi:10.1056/NEJMoa1401105

Doherty JU, Gluckman TJ, Hucker WJ, Januzzi JL Jr, Ortel TL, Saxonhouse SJ, et al. 2017 ACC expert consensus decision pathway for periprocedural management of anticoagulation in patients with nonvalvular atrial fibrillation: a report of the American College of Cardiology Clinical Expert Consensus Document Task Force. J Am Coll Cardiol. 2017;69:871-898. [PMID: 28081965] doi:10.1016/j.jacc.2016.11.024

Douketis JD, Spyropoulos AC, Kaatz S, Becker RC, Caprini JA, Dunn AS, et al; BRIDGE Investigators. Perioperative bridging anticoagulation in patients with atrial fibrillation. N Engl J Med. 2015;373:823-33. [PMID: 26095867] doi:10.1056/NEJMoa1501035

Douketis JD, Spyropoulos AC, Spencer FA, Mayr M, Jaffer AK, Eckman MH, et al. Perioperative management of antithrombotic therapy: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2012;141:e326S-e350S. [PMID: 22315266] doi:10.1378/chest.11-2298

Falck-Ytter Y, Francis CW, Johanson NA, Curley C, Dahl OE, Schulman S, et al. Prevention of VTE in orthopedic surgery patients: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2012;141:e278S-e325S. [PMID: 22315265] doi:10.1378/chest.11-2404

Fleisher LA, Fleischmann KE, Auerbach AD, Barnason SA, Beckman JA, Bozkurt B, et al; American College of Cardiology. 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines. J Am Coll Cardiol. 2014;64:e77-137. [PMID: 25091544] doi:10.1016/j.jacc.2014.07.944

Gould MK, Garcia DA, Wren SM, Karanicolas PJ, Arcelus JI, Heit JA, et al. Prevention of VTE in nonorthopedic surgical patients: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2012;141:e227S-e277S. [PMID: 22315263] doi:10.1378/chest.11-2297

Kaufman RM, Djulbegovic B, Gernsheimer T, Kleinman S, Tinmouth AT, Capocelli KE, et al; AABB. Platelet transfusion: a clinical practice guideline from the AABB. Ann Intern Med. 2015;162:205-13. [PMID: 25383671] doi:10.7326/M14-1589

Kaw R, Chung F, Pasupuleti V, Mehta J, Gay PC, Hernandez AV. Meta-analysis of the association between obstructive sleep apnoea and postoperative outcome. Br J Anaesth. 2012;109:897-906. [PMID: 22956642] doi:10.1093/bja/aes308

Levine GN, Bates ER, Bittl JA, Brindis RG, Fihn SD, Fleisher LA, et al. 2016 ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2016;68:1082-115. [PMID: 27036918] doi:10.1016/j.jacc.2016.03.513

Whelton PK, Carey RM, Aronow WS, Casey DE Jr, Collins KJ, Dennison Himmelfarb C, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2017. [PMID: 29146535] doi:10.1016/j.jacc.2017.11.006

Zielsdorf SM, Kubasiak JC, Janssen I, Myers JA, Luu MB. A NSQIP analysis of MELD and perioperative outcomes in general surgery. Am Surg. 2015;81:755-9. [PMID: 26215235]

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CME credits and MOC points are available from the publication date of December 31, 2018, until December 31, 2021. You may submit your answer sheet or enter your answers online at any time during this period.

Directions

Each of the numbered items is followed by lettered answers. Select the ***ONE*** *lettered answer that is* ***BEST*** *in each case.*

Item 1

A 35-year-old woman is evaluated after laboratory test results showed an elevated LDL cholesterol level during routine screening. Family history is remarkable for myocardial infarction in her father at age 45 years. She takes no medications.

On physical examination, vital signs are normal. BMI is 30. The remainder of the examination is unremarkable.

Laboratory studies:

Alanine aminotransferase	30 U/L
Thyroid-stimulating hormone	Normal
Total cholesterol	294 mg/dL (7.61 mmol/L)
LDL cholesterol	195 mg/dL (5.05 mmol/L)
HDL cholesterol	55 mg/dL (1.42 mmol/L)
Triglycerides	220 mg/dL (2.49 mmol/L)

The patient is instructed in therapeutic lifestyle changes to lower her risk for atherosclerotic cardiovascular disease (ASCVD).

According to the American College of Cardiology/American Heart Association cholesterol treatment guideline, which of the following is the most appropriate additional treatment for primary prevention of ASCVD in this patient?

(A) Evolocumab
(B) High-intensity rosuvastatin
(C) Moderate-intensity atorvastatin
(D) No additional treatment is necessary

Item 2

A 40-year-old woman seeks advice on whether she should undergo breast cancer screening with mammography. Her family history is negative for breast and ovarian cancers, and she has no other risk factors for breast cancer.

On physical examination, vital signs and the remainder of the examination are normal.

The patient is engaged in a discussion of the potential benefits and harms of initiating mammography now, including the potential for false-positive results and overdiagnosis. After the discussion, she states that she is not overly concerned about her risk for breast cancer but is anxious about the potential harms associated with screening.

Which of the following is the most appropriate screening test for this patient?

(A) Breast self-examination
(B) Breast tomosynthesis
(C) Screening mammography
(D) No testing

H

Item 3

A 49-year-old man is scheduled for total right knee arthroplasty. Medical history is otherwise unremarkable. He takes no medications.

On physical examination, vital signs are normal. The right knee demonstrates bony hypertrophy and crepitus with passive movement.

Low-molecular-weight heparin and intermittent pneumatic compression will be initiated and continued during the hospital stay.

Which of the following is the recommended duration of low-molecular-weight heparin prophylaxis for this patient?

(A) Total of 10 days
(B) Total of 14 days
(C) Total of 35 days
(D) Until fully ambulatory
(E) Until hospital discharge

Item 4

A 67-year-old man is evaluated for a 2-year history of worsening pain in his feet. He describes the pain as long-standing aching and burning. The pain is persistent, sometimes waking him from sleep. Medical history is otherwise significant for type 2 diabetes mellitus, hypertension, and hyperlipidemia. Medications are insulin glargine, insulin aspart, valsartan, aspirin, and simvastatin.

On physical examination, vital signs are normal. The feet are insensate to monofilament testing, and vibratory sensation is absent in the feet and ankles. No evidence of skin breakdown is noted.

Which of the following is the most appropriate treatment?

(A) Oral duloxetine
(B) Oral hydromorphone
(C) Oral lamotrigine
(D) Oral tramadol
(E) Topical diclofenac

Item 5

H

A 23-year-old woman is evaluated for depression as she prepares for discharge from the hospital to home hospice care. She was diagnosed with metastatic ovarian cancer 2 years ago, and she progressed through four lines of chemotherapy, a trial of immunotherapy, and a failed attempt at a phase 1 clinical trial. Her life expectancy is measured in weeks. She is currently hospitalized with volume depletion, and after consultation with her oncologist and palliative care team, she has decided to be discharged home with hospice care.

On physical examination, the patient exhibits substantial fatigue and poor concentration. She has a flat affect except when intermittently tearful. Previously upbeat despite all of the setbacks, she is now withdrawn and describes feeling hopeless. She has pervasive guilt over the burden she believes she has caused her family. Medications are a fentanyl patch, oxycodone, ondansetron, polyethylene glycol, senna, and zolpidem.

H CONT.

Which of the following is the most appropriate treatment?

(A) Citalopram
(B) Cognitive behavioral therapy
(C) Methylphenidate
(D) Sertraline

Item 6

A 52-year-old man is evaluated for a 2-day history of painless red eye, which began on the right side and quickly spread to the left. He reports that his eyes have a thin mucopurulent discharge and that his eyelids are matted shut in the morning upon waking. He has had no photophobia, change in visual acuity, or itching in the eyes, but he has experienced some mild rhinorrhea. He does not use contact lenses. He is sexually monogamous. Medical history is significant for type 2 diabetes mellitus treated with metformin.

On physical examination, vital signs are normal. There is redness of the sclerae bilaterally, with a white crust-like residue along the edges of the eyelids. The tarsal vessels are obscured by the conjunctival erythema. Visual acuity is intact, and there is no tenderness around the globes.

Which of the following is the most appropriate treatment?

(A) Ceftriaxone
(B) Levofloxacin ophthalmic drops
(C) Olopatadine ophthalmic drops
(D) Trimethoprim-polymyxin B ophthalmic drops

Item 7

Two new treatments for patients with heart failure with preserved ejection fraction were compared in a randomized controlled trial. The primary outcome was reduction in heart failure–related hospitalizations.

Compared with treatment B, treatment A was associated with a statistically significant absolute risk reduction of 6%, and the number needed to treat to prevent one hospitalization was 17.

Which of the following is needed to conclude that treatment A is superior to treatment B?

(A) Confidence interval
(B) Harms and cost of treatment
(C) *P* value
(D) Relative risk reduction

H

Item 8

A 68-year-old man is evaluated for fever, perineal pain, dysuria, frequency, and intermittent straining that began yesterday. Symptoms began 48 hours after a prostate biopsy due to an elevated prostate-specific antigen level detected during routine screening.

On physical examination, temperature is 38.7 °C (101.7 °F), blood pressure is 145/82 mm Hg, pulse rate is 105/min, and respiration rate is normal. The prostate is enlarged and boggy, and it is tender to gentle palpation. There is no penile discharge, and no scrotal pain occurs with palpation.

Dipstick urinalysis is positive for leukocyte esterase and nitrates. Urine Gram stain reveals gram-negative rods. Urine culture is pending.

Which of the following is the most appropriate treatment?

(A) Amoxicillin
(B) Ceftriaxone and doxycycline
(C) Cephalexin
(D) Trimethoprim-sulfamethoxazole

Item 9

A 22-year-old man is evaluated during a pre-employment examination. The patient is starting a new job as a registered nurse. He is asymptomatic. He received the tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap) vaccine 7 years ago and the influenza vaccine during the last influenza season. Approximately 6 months ago, he received one dose of the measles, mumps, and rubella (MMR) vaccine because of lack of documented immunity on serologic testing. Medical history is negative for chronic medical conditions. He is a nonsmoker, and he does not plan to travel outside of the United States in the near future. He takes no medications.

Physical examination is normal.

Laboratory studies are significant for a positive result on a hepatitis B surface antibody test. Hepatitis B surface antigen, hepatitis B core antibody, and hepatitis A IgG antibody levels are undetectable.

Which of the following is the most appropriate vaccination strategy for this health care worker?

(A) Administer a second dose of MMR vaccine
(B) Administer the hepatitis A vaccine
(C) Administer the hepatitis B vaccine
(D) Administer the 23-valent pneumococcal polysaccharide vaccine
(E) No vaccination at this time

Item 10

A 32-year-old woman is evaluated during a domestic airline flight for an episode of weakness and lightheadedness. She is pregnant at 35 weeks' gestation. She has had several contractions since take-off but without regularity. She reports no abdominal pain. She has no medical problems, and her only medication is a prenatal vitamin.

On physical examination, the patient appears weak. Temperature is normal, blood pressure is 105/60 mm Hg, pulse rate is 99/min, and respiration rate is 14/min. Her skin is clammy. Cardiovascular examination is unremarkable. Lungs are clear to auscultation. On abdominal examination, she has a gravid uterus.

Oxygen, 2 L/min by nasal cannula, is started. An intravenous line is placed, and fluids are initiated.

Which of the following is the most appropriate next step in management?

(A) Ask the pilot to descend to a lower altitude
(B) Connect with the ground-based physician
(C) Recommend flight diversion
(D) No further management

Item 11

An 82-year-old man is evaluated during a routine evaluation. He is accompanied to the visit by his son. The patient lives alone, and his son expresses reservations about his father continuing to drive. The patient no longer drives after dark or on the interstate highway. He limits his driving to within a 10-mile radius of his home and mainly drives for local errands and to church on Sundays. He has had no traffic accidents, but he had two recent incidents in which he misjudged the angle of his car in the grocery store parking lot and ran into the shopping cart stand. Medical history is significant for coronary artery disease, hypertension, and mild cognitive impairment. Medications are atorvastatin, aspirin, hydrochlorothiazide, lisinopril, and metoprolol.

On physical examination, blood pressure is 132/82 mm Hg, and pulse rate is 64/min; other vital signs are normal. The patient appears frail with a pleasant demeanor. He wears eyeglasses and hearing aids, and he has impaired hearing as measured by the whispered voice test. On musculoskeletal examination, limited mobility of the cervical spine is noted. He scores 26/30 on the Mini-Mental State Examination. The remainder of the examination is unremarkable.

Which of the following is the most appropriate management regarding this patient's driving?

(A) Advise the patient to retire from driving
(B) Obtain neuropsychological testing
(C) Obtain occupational therapy driving evaluation
(D) Reassure the patient he is competent to drive with self-imposed limitations

Item 12

A 36-year-old woman is evaluated for a 3-year history of fatigue that worsens after activity and does not improve with rest. She also notes intermittent diffuse myalgia and arthralgia, constipation, dizziness, headaches, urinary urgency, memory problems, and paresthesias. Her musculoskeletal symptoms, dizziness, and headache worsen in the upright position and improve when she lies back down. She has almost entirely eliminated social activities. Medical history is significant for episodic migraine and irritable bowel syndrome. Medications are sumatriptan, polyethylene glycol, and hyoscyamine.

On physical examination, vital signs are normal. BMI is 24. Neck circumference is 36 cm (14 in). The remainder of the examination is normal.

Laboratory studies obtained 6 months ago showed a normal complete blood count, electrolyte levels, kidney function test results, liver chemistry test results, fasting glucose level, serum creatine kinase level, and serum thyroid-stimulating hormone level.

Which of the following is the most appropriate diagnostic test to perform next?

(A) Antinuclear antibody assay
(B) Polysomnography
(C) Serum cortisol level measurement
(D) No further testing is recommended

Item 13

A 62-year-old man is evaluated for severe low back pain that began 2 days ago and is progressively worsening. The pain began when he was lifting concrete blocks at his job. The pain is located in his lower back and radiates into the lateral aspects of his legs bilaterally. He also has numbness and tingling in the groin. His last bowel movement was 2 days ago, and he has not urinated for the last 24 hours. Prior to the onset of the pain, the patient felt well.

On physical examination, vital signs are normal. There is decreased pinprick sensation surrounding the anus, decreased anal sphincter tone, and decreased ankle reflexes bilaterally; knee reflexes are normal. Bilateral dorsiflexion and plantar flexion weakness are present. Straight leg raise test reproduces pain bilaterally. There is no spinal tenderness.

Which of the following is the most appropriate diagnostic test to perform next?

(A) CT of the lumbosacral spine
(B) MRI of the lumbosacral spine
(C) Plain radiography of the lumbosacral spine
(D) No imaging studies are indicated

Item 14

A 24-year-old woman is evaluated for a breast lump. She has had no breast trauma or discharge from the nipples. She is nulliparous and has regular menstrual cycles. Medical history is otherwise unremarkable. The patient's mother was recently diagnosed with breast cancer at age 58 years; no other family members have breast or ovarian cancer. Her only medication is an oral contraceptive pill.

On physical examination, vital signs are normal. BMI is 25. A breast examination reveals no skin changes, with dense breast tissue bilaterally. She has a firm, 2-cm, nontender, mobile mass with well-defined margins in the upper outer quadrant of the left breast. There is no evidence of axillary, cervical, or supraclavicular lymphadenopathy.

Which of the following is the most appropriate test to perform in this patient?

(A) Biopsy
(B) Mammography
(C) Mammography and ultrasonography
(D) Ultrasonography

Item 15

A 24-year-old man is evaluated for a 6-week history of severely depressed mood and loss of interest in work, family, and friends. During this time period, he has been sleeping more than usual (up to 11 hours per day) but still feels like he has no energy. He feels that he is a burden to his family and coworkers and admits to sometimes thinking about suicide. He had similar symptoms 2 years ago, for which he was treated with escitalopram. He remained on this therapy for only 2 weeks because his symptoms rapidly abated, and he had a "surge of energy." One year ago, he had a 4-week period during which he had a similar increase in energy level. During that time, he slept only 4 hours per night and

decided that he would become a competitive triathlete. He used most of his money to start a boot camp fitness business, which closed within 2 months. He has never had hallucinations. He takes no medications and does not use alcohol or recreational drugs.

Which of the following is the most likely diagnosis?

(A) Bipolar disorder
(B) Generalized anxiety disorder
(C) Major depressive disorder
(D) Schizophrenia

Item 16

A 27-year-old man is evaluated during a routine follow-up visit for obesity. On his previous two visits, he had a BMI of 38. Despite enrollment in a 6-month comprehensive supervised weight loss program that included nutritional counseling, he has gained 2.3 kg (5.0 lb). He briefly tried orlistat but discontinued this medication because of gastrointestinal side effects. Medical history is significant for type 2 diabetes mellitus and hypertension. Medications are liraglutide, lisinopril, and metformin.

On physical examination, blood pressure is 146/91 mm Hg; other vital signs are normal. BMI is 39. The remainder of the physical examination is unremarkable.

Laboratory studies reveal a hemoglobin A_{1c} value of 8.2%.

Which of the following is the most appropriate management?

(A) Bariatric surgery
(B) Lorcaserin
(C) Referral to a dietician
(D) Very-low-calorie diet

Item 17

A 39-year-old man is evaluated for a 3-month history of dry, intermittent cough. He reports no other associated symptoms and has had no unusual environmental exposures. He is a lifelong nonsmoker. Medical history is significant for hypertension, for which he was started on lisinopril and hydrochlorothiazide 4 months ago. He has no known allergies.

On physical examination, vital signs are normal. There is no pharyngeal erythema or exudate. Lungs are clear to auscultation.

A chest radiograph is normal.

Which of the following is the most appropriate management?

(A) Discontinue lisinopril
(B) Initiate intranasal glucocorticoid therapy
(C) Obtain spirometry
(D) Start proton pump inhibitor therapy

Item 18

A 46-year-old man seeks advice on whether he should undergo prostate cancer screening. He recently underwent direct-to-consumer genetic testing, which revealed that his risk for prostate cancer is 33% higher than that of the average person. He is asymptomatic. Medical history is unremarkable. Family history is significant for prostate cancer diagnosed in his paternal grandfather at age 72 years. He takes no medications.

On physical examination, vital signs and the remainder of the examination are normal.

Which of the following is the most appropriate management?

(A) Digital rectal examination (DRE)
(B) Serum prostate-specific antigen level measurement
(C) Serum prostate-specific antigen level measurement and DRE
(D) Patient education and no further testing

Item 19

A 55-year-old woman is evaluated for left-sided tinnitus that has gradually emerged over the last 6 months. She describes the tinnitus as a high-pitched continuous (nonpulsatile) buzzing. The patient reports no hearing loss, balance difficulties, dizziness, or headaches. Her medical history is otherwise unremarkable.

On physical examination, vital signs are normal. Direct visualization of the external ear canals and tympanic membranes is unremarkable. Findings on Weber and Rinne testing suggest left sensorineural hearing loss. The whispered voice test suggests hearing loss on the left side. Results of the Romberg, cerebellar, and cranial nerve tests are all normal. Audiologic tests confirm mild to moderate left sensorineural hearing loss.

Which of the following is the most appropriate management?

(A) CT angiography of the posterior fossa
(B) MRI of the internal auditory canal
(C) Referral for hearing aid placement
(D) Urgent referral to an otolaryngologist

Item 20

An 82-year-old woman is evaluated for severe and progressive shortness of breath on ambulation. She has COPD and has been hospitalized only once in the past 18 months for an acute exacerbation. She has not experienced an acute worsening of her symptoms, and she has minimal nonproductive cough. She stopped smoking 15 years ago. She notes that her dyspnea is a substantial impediment to her quality of life. Medical history is otherwise significant for heart failure with preserved ejection fraction. Medications are umeclidinium/vilanterol and albuterol inhalers, lisinopril, and chlorthalidone.

On physical examination, temperature is 37.0 °C (98.6 °F), blood pressure is 128/78 mm Hg, pulse rate is 74/min, and respiration rate is 20/min. Oxygen saturation is 96% breathing 1 L/min of oxygen by nasal cannula and is maintained at 96% during a 6-minute walk test. Pulmonary examination reveals a prolonged expiratory phase and intermittent scattered rhonchi throughout her lung fields, with hyperresonance to percussion. Cardiac examination reveals an S_4 but no murmur or jugular venous distention.

Spirometry performed 2 months ago showed an FEV_1 of 42% of predicted.

Which of the following is the most appropriate treatment?

(A) Furosemide
(B) Oxygen at 2 L/min by nasal cannula
(C) Prednisone
(D) Pulmonary rehabilitation

Item 21

A 50-year-old man is seen for preoperative medical evaluation before left shoulder arthroplasty. History is significant for alcohol-related cirrhosis and osteoarthritis. Medications are lactulose, furosemide, and spironolactone. The patient stopped drinking alcohol 5 months ago but has difficulty with medication adherence. He reports increasing ascites and lower extremity edema.

On physical examination, vital signs are normal. There is no jaundice or scleral icterus. Spider telangiectasias are noted on the face and chest. The abdomen is distended with flank dullness. There is 1+ pitting edema to the knees bilaterally. Mental status examination is normal.

The calculated Model for End-stage Liver Disease (MELD) score is 22.

The patient is instructed to increase his furosemide.

Which of the following is the most appropriate preoperative management?

(A) Cancel surgery and refer for liver transplant evaluation
(B) Delay surgery until after patient achieves 1 year of sobriety
(C) Delay surgery until after placement of a transjugular intrahepatic portosystemic shunt
(D) Proceed to surgery

Item 22

A 24-year-old person is evaluated as an add-on patient for a 1-week history of nasal congestion, watery eyes, and cough productive of yellow sputum. The patient is new to the practice and has indicated on the intake form that his gender is transmale. He responds to questioning that he would prefer to be addressed as "he" or "him," but he seems nervous. He reports no fevers, chills, shortness of breath, or rash. He takes no medications.

On physical examination, vital signs are normal. There is oropharyngeal erythema, and nasal turbinates are boggy. No tonsillar exudate or cervical lymphadenopathy is noted. Lungs are clear to auscultation bilaterally.

Which of the following is the most appropriate next step in management at this visit?

(A) Obtain a hormonal and surgical history
(B) Obtain a social and sexual history
(C) Perform a genital examination
(D) Screen for sexually transmitted infections
(E) Symptomatic treatment

Item 23

A 75-year-old man is being discharged following treatment for acute decompensated heart failure. The patient and his wife are alerted to symptoms that indicate acute worsening of his heart failure and are informed of when he should seek immediate medical assistance. The discharge medication list and the side effects of these medications are reviewed, and the patient and his wife acknowledge an understanding. A nursing education visit regarding the hospital stay and evaluations is completed. A copy of the discharge summary is given to the patient, and a follow-up appointment is scheduled with his internist in 7 days.

Which of the following is also recommended to improve patient safety and reduce rehospitalization in this patient?

(A) Follow-up telephone call and one home nursing visitation
(B) Home telemonitoring
(C) Postdischarge patient education
(D) Timely discharge summary for the primary care physician

Item 24

A 54-year-old man is evaluated for a 6-month history of right shoulder pain. He describes the pain as moderately severe aching that is diffusely localized over the shoulder without radiation to the arm. The pain is constant, although it is worse at night and with any shoulder movement. The pain was insidious in onset and has been progressively worsening. He has had no neurologic or constitutional symptoms. Ibuprofen provides some pain relief.

On physical examination, vital signs are normal. Pain and limited range of motion are noted with both active and passive movement in all planes of motion, as is diffuse tenderness over the anterior and posterior areas of the right shoulder. There is no tenderness to palpation of the bony or soft tissue structures, nor is there cervical spine tenderness. There are no neck symptoms or findings.

Which of the following is the most likely diagnosis?

(A) Acromioclavicular joint degeneration
(B) Adhesive capsulitis
(C) Bicipital tendinitis
(D) Rotator cuff disease

Item 25

A 32-year-old man is evaluated for ongoing intermittent premature ejaculation of 3 years' duration, which he describes as distressing to him and his spouse. He reports no other symptoms. The patient also has depression, which is currently well controlled with amitriptyline. A previous trial of sertraline caused mood instability, prompting its discontinuation. He takes no other medications.

On physical examination, vital signs are normal. Growth and pattern of body hair and testicular size are normal. No gynecomastia is noted.

Laboratory studies show a normal 8:00 AM serum total testosterone level.

Which of the following is the most appropriate additional treatment?

(A) Paroxetine
(B) Testosterone gel
(C) Topical lidocaine
(D) No additional treatment is indicated

Item 26

A 67-year-old woman is evaluated for urinary incontinence that has progressively worsened over the past 2 years. She experiences incontinence when she laughs or sneezes but reports no dysuria, hematuria, or loss of continence at night. She has been postmenopausal for 12 years. She had four spontaneous term vaginal deliveries between age 24 and 32 years. She has no other problems and takes no medications.

On physical examination, all vital signs are normal. BMI is 20. Pelvic examination reveals vaginal atrophy. The remainder of the examination is normal.

Which of the following is the most appropriate treatment?

(A) Bladder training
(B) Oral estradiol
(C) Oxybutynin
(D) Pelvic floor muscle training (Kegel exercises)
(E) Weight loss

Item 27

An 81-year-old woman was admitted to the ICU 8 days ago for multisystem organ failure associated with a severe episode of multilobar pneumonia. She has required mechanical ventilation since admission. Efforts to wean the patient from mechanical ventilation have not succeeded, and the patient remains somnolent and unresponsive to verbal stimuli. Medical history is significant for dementia, diabetes mellitus, COPD, chronic kidney disease, and heart failure.

The care team concludes and shares with the patient's family that she will not have a meaningful recovery; however, the patient's children request continued ICU-level care. The patient does not have an advance directive, and her wishes are unknown. After a family meeting with the care team to discuss the patient's prognosis, the children continue to request all treatment.

Which of the following is the most appropriate management?

(A) Consult with the hospital ethics committee
(B) Discontinue ICU care in 48 hours if there is no improvement
(C) Transfer the patient to another institution
(D) Continue current level of care

Item 28

A 54-year-old woman is evaluated for a 9-month history of vaginal irritation and itching. She also has pain during intercourse and uses vaginal lubricants without much relief. At age 50 years, she developed severe menopause-related vasomotor symptoms that responded to a 2-year course of estrogen replacement therapy; she currently has no vasomotor symptoms. Family history is significant for breast cancer. She takes no medications.

On physical examination, vital signs are normal. Pelvic examination shows diminished elasticity of the vulvar skin; thinning of the labia minora; introital narrowing; and dry, pale-colored vaginal lining with decreased rugae.

Which of the following is the most appropriate treatment?

(A) Clobetasol
(B) Ospemifene
(C) Systemic estrogen therapy
(D) Vaginal estrogen therapy

Item 29

A 30-year-old woman is evaluated for a 1-year history of severe anxiety about multiple aspects of her life, including her marriage, work, and health. She also reports irritability, poor sleep, and difficulty concentrating, and she finds it difficult to complete her daily home and occupational tasks. She has had multiple visits with her internist for various symptoms, including atypical chest pain, shortness of breath, palpitations, and intermittent diarrhea. She does not use alcohol, tobacco, or recreational drugs. She drinks one cup of coffee every morning. Her Generalized Anxiety Disorder 7-item scale score is 15, corresponding to severe anxiety.

Laboratory studies reveal a normal serum thyroid-stimulating hormone level.

Which of the following is the most appropriate long-term pharmacologic treatment?

(A) Amitriptyline
(B) Clonazepam
(C) Lithium
(D) Sertraline

Item 30

A 66-year-old woman is evaluated during a follow-up visit for a 5-year history of chronic autoimmune pancreatitis. She has constant, severe, aching midabdominal pain that radiates to the back. Her only surgical option is a pancreaticojejunostomy, a procedure that she is not ready to accept. She has previously tried several tricyclic antidepressants, venlafaxine, gabapentin, oral morphine, and tramadol. A fentanyl patch was substituted for oral morphine during a recent hospitalization, and over the past 6 weeks, she has noted reduced pain and improved function with its use. She lives with her husband and oldest daughter at her home. She does not smoke, drink alcohol, or use illicit drugs. Her only medications are a fentanyl patch, 25 µg/h changed every 72 hours (approximately 75 morphine milligram equivalents/day); prednisone; and pancreatic enzyme replacement.

On physical examination, the patient is frail appearing. Vital signs are normal. BMI is 21. The abdomen is scaphoid; bowel sounds are present. Midepigastric palpation reveals tenderness.

H

Which of the following is the most appropriate next step in management?

(A) Add lorazepam

(B) Prescribe naloxone and provide caregiver education on its use

(C) Recommend weekly nursing visits before each opioid prescription

(D) Switch the fentanyl patch to short-acting hydromorphone

Item 31

A 60-year-old man is evaluated for abdominal cramping and diarrhea that began after starting ezetimibe. The patient has had persistently elevated LDL cholesterol levels while taking maximally tolerated statin therapy. One year ago, he began receiving atorvastatin, 80 mg/d, with an initial LDL cholesterol level of 180 mg/dL (4.66 mmol/L). However, he developed severe muscle pain, and the dosage was decreased to 40 mg/d and ultimately 20 mg/d. Three months ago, his LDL cholesterol was 140 mg/dL (3.63 mmol/L), at which time ezetimibe was added. Medical history is otherwise significant for myocardial infarction treated with drug-eluting stent placement 1 year ago. Medications are aspirin, clopidogrel, atorvastatin, ezetimibe, metoprolol, and lisinopril.

On physical examination, vital signs are normal. BMI is 27. There is mild, diffuse abdominal tenderness to palpation without rebound or guarding. The remainder of the examination is unremarkable.

In addition to discontinuing ezetimibe, which of the following is the most appropriate management?

(A) Add alirocumab

(B) Add cholestyramine

(C) Add niacin

(D) No further intervention

Item 32

A 65-year-old man is evaluated during a visit to establish care. He is interested in colorectal cancer screening; however, he adamantly refuses to undergo colon preparation, and he does not want to modify his diet for screening. He has never undergone colorectal cancer screening. Medical and family histories are unremarkable. He takes no medications.

Physical examination, including vital signs, is normal.

After discussing the colon preparation process and dietary restrictions with the patient and exploring his concerns, he is steadfast in his refusal.

Which of the following is the most appropriate screening test for this patient?

(A) Circulating methylated *SEPT9* DNA test

(B) CT colonography

(C) Fecal immunochemical test

(D) Sensitive guaiac-based fecal occult blood test

Item 33

A 35-year-old woman is evaluated during a follow-up visit for anxiety. Her symptoms have been well controlled with cognitive behavioral therapy, and she has been drinking kava tea every morning and practicing mindfulness daily. Medical history is significant for nonalcoholic steatohepatitis. Other supplements are folic acid and echinacea.

On physical examination, vital signs are normal. BMI is 36. The remainder of the examination is unremarkable.

Which of the following is the most appropriate recommendation for this patient?

(A) Discontinue echinacea

(B) Discontinue folic acid

(C) Discontinue kava tea

(D) No changes to current therapy

Item 34

H

A 70-year-old man is seen for a preoperative medical evaluation before laminectomy for spinal stenosis. History is also significant for coronary artery disease and a non-ST-elevation myocardial infarction that occurred 5 years ago. He swims for 30 minutes every other day. He reports no chest pain with activity. Medications are aspirin, simvastatin, metoprolol, and lisinopril.

Physical examination, including vital signs, is normal.

Electrocardiogram performed 2 years ago demonstrated a left anterior fascicular block, several premature atrial contractions, and sinus rhythm.

Which of the following is the most appropriate preoperative cardiac testing for this patient?

(A) Dobutamine stress echocardiography

(B) Electrocardiography

(C) Exercise stress testing

(D) No further testing

Item 35

A 44-year-old man is evaluated for right medial elbow pain that began 2 months ago with a dull ache and has gradually worsened. The pain is worse with elbow flexion, and his right fourth and fifth fingers are numb.

On physical examination, vital signs are normal. Decreased sensation over the volar aspect of the right fourth and fifth fingers is noted, with adduction and abduction weakness of the fingers. The right elbow has full range of motion and no notable erythema, swelling, or tenderness.

Which of the following is the most likely diagnosis?

(A) Carpal tunnel syndrome

(B) Medial epicondylitis

(C) Olecranon bursitis

(D) Ulnar nerve entrapment

Item 36

H

A 63-year-old woman is evaluated in the emergency department after an unwitnessed syncopal event. She

H CONT.

recalls feeling a sensation of warmth and generalized weakness prior to the event but had no chest pain, dyspnea, or palpitations. Medical history is significant for hypertension, hyperlipidemia, and carotid artery stenosis treated with endarterectomy. Medications are lisinopril, hydrochlorothiazide, atorvastatin, and aspirin.

Vital signs and screening cardiovascular and neurologic examinations are normal.

Which of the following tests should be included in the initial evaluation of this patient?

(A) Ambulatory electrocardiographic monitoring and echocardiography
(B) B-type natriuretic peptide and cardiac enzyme measurement
(C) Magnetic resonance carotid angiography and MRI of the brain
(D) Orthostatic blood pressure measurement and electrocardiography

Item 37

A 37-year old woman is evaluated for contraceptive advice. She is married and has a 1-year old child. The patient describes the conception of this child as an "accident" because she often missed taking her previous oral contraceptive. Her menstrual periods have resumed and are regular but heavy and, in that regard, bothersome to her. Medical history is unremarkable. She drinks a glass of wine every night and smokes a pack of cigarettes daily. She has no other health issues and takes no medications.

The result of a pregnancy test performed today is negative.

The patient is provided with a brief smoking cessation intervention. She is not ready to stop smoking but will consider it again at a later time.

Which of the following is the most appropriate female contraceptive option for this patient?

(A) Estrogen-progestin oral contraceptive
(B) Estrogen-progestin vaginal ring
(C) Progesterone-containing intrauterine device
(D) Progesterone-only "mini pill"

Item 38

A 43-year old woman is evaluated during a follow-up appointment for obesity. She has been following a reduced-calorie, low-fat diet and participating in a 45-minute aerobic exercise class three times weekly for the past 6 months. After her last follow-up appointment 1 month ago, she added 30 minutes of brisk walking on the weekend to her exercise regimen. She brings a food diary and weekly weight records to her appointment. She lost an average of 0.2 kg (0.5 lb) per week over the first 3 to 4 weeks, but her weight loss tapered thereafter and her weight has increased by 0.5 kg (1 lb) since her last visit. The total amount of weight lost over the past 8 months is 2.7 kg (6 lb), or 3% of her original weight. The patient reports that she is unable to achieve the calorie reduction recommended, stating that she is "hungry all the time." Medical history is also significant for type 2 diabetes mellitus and hypertension. Medications are amlodipine, lisinopril, and metformin.

On physical examination, blood pressure is 141/92 mm Hg, and other vital signs are normal. BMI is 31. The remainder of the examination is unremarkable.

Which of the following is the most appropriate next step in treatment?

(A) Bariatric surgery
(B) Liraglutide
(C) Switch to a low-carbohydrate diet
(D) Switch to a very-low-calorie diet

Item 39

H

A 37-year-old man inquires about palliative medicine referral during a follow-up visit after hospital discharge. He was recently diagnosed with metastatic non-small cell lung cancer, and 1.5 L of fluid was removed with therapeutic thoracentesis, with substantial relief of dyspnea. He has met with his medical oncologist, with plans to initiate disease-directed treatment soon. Medications are dexamethasone, hydromorphone, and senna.

When is the most appropriate time for palliative medicine referral?

(A) Now
(B) At initiation of chemotherapy
(C) At onset of symptoms
(D) Palliative medicine is not indicated for patients undergoing active cancer treatment

Item 40

A 51-year-old woman is evaluated during a routine follow-up visit for diabetes mellitus. She also has hypertension and hyperlipidemia. Medications are metformin, enalapril, chlorthalidone, and high-intensity rosuvastatin. She has no drug allergies.

On physical examination, blood pressure is 126/74 mm Hg. The remainder of the examination is unremarkable.

Her 10-year risk for atherosclerotic cardiovascular disease is 11% according to the Pooled Cohort Equations. She has been instructed in intensive lifestyle modifications.

Which of the following is the most appropriate preventive measure to reduce this patient's cardiovascular risk?

(A) Clopidogrel
(B) Low-dose aspirin
(C) Low-dose aspirin and clopidogrel
(D) Regular-dose aspirin
(E) No additional therapy

Item 41

A 37-year-old woman is evaluated for a 6-year history of difficulty initiating sleep and significant daytime sleepiness. She works as a registered nurse, and she notes that

her daytime sleepiness is exacerbated when she works several night shifts in a row at the hospital. She does not drink alcohol, use tobacco, or consume caffeinated products. She recently initiated a new exercise program and exercises three to four mornings each week. She has no other symptoms and takes no medications.

On physical examination, vital signs are normal. BMI is 30. Oxygen saturation breathing ambient air is 97%. The remainder of the physical examination is normal.

Which of the following is the most appropriate next step in management?

(A) Multiple sleep latency testing
(B) Overnight oximetry
(C) Polysomnography
(D) Serum ferritin level measurement
(E) Two-week sleep diary

Item 42

A 32-year-old man emails to request an opinion on his medical conditions. He is not an established patient but decided to contact the physician after viewing an online profile. His message indicates that he has a several-year history of abdominal pain with intermittent diarrhea and constipation, for which he takes polyethylene glycol, fiber, and dicyclomine. He notes that he has seen a primary care physician and gastroenterologist and undergone extensive testing, including an endoscopy and colonoscopy. He requests a recommendation for a new test or treatment.

Which of the following is the most appropriate management?

(A) Advise the patient to obtain celiac disease assessment
(B) Ask the patient to email his medical records before providing advice
(C) Request that the patient call the office to establish care
(D) Do not respond to the patient's email

Item 43

A 38-year-old woman is evaluated for a 2-day history of worsening eye pain and decreasing visual acuity in her left eye. The pain is worse with eye movement. She reports no fever or trauma. Vision loss is mostly central, and her ability to distinguish colors has diminished. She does not feel the sensation of a foreign body in the eyes. She wears contact lenses. Her medical history is otherwise unremarkable.

On physical examination, vital signs are normal. Eye movement is intact but painful, with visual acuity of 20/20 in the right eye and 20/60 in the left. Afferent pupillary defect is noted in the left eye. There is no corneal injection or discharge, and the optic discs appear normal.

Which of the following is the most likely diagnosis?

(A) Corneal abrasion
(B) Herpes simplex keratitis
(C) Optic neuritis
(D) Orbital cellulitis

Item 44

During a routine health examination, a patient asks about an article that recommended avoiding statin therapy because of the risk for memory loss. The findings were based on cross-sectional data analysis of a well-validated national health survey, which was conducted by random sampling of patients according to zip code of residence. The analysis showed that patients who self-reported memory loss were more likely to also report having taken statin drugs (odds ratio, 1.8; 95% CI, 1.2-2.7; $P = 0.046$).

Which of the following is the most likely threat to the validity of this study?

(A) Confounding
(B) Selection bias
(C) Self-reported data
(D) Statistical significance

Item 45

H

A 75-year-old woman underwent total hip arthroplasty 4 hours ago and is now evaluated because she has been unable to void since the operation. Bladder ultrasound reveals 900 mL of urine. Other than manageable postoperative pain, she has no symptoms. Current medications are acetaminophen, oxycodone, and enoxaparin.

Which of the following is the most appropriate management?

(A) Suprapubic catheter placement
(B) Suprapubic warm wet gauze application
(C) Tamsulosin administration
(D) Urethral bladder catheterization

Item 46

A 66-year-old woman is transitioning care after her previous physician retired and undergoes a new patient evaluation. She is asymptomatic. She is unclear when her last Pap smear was performed or the result. Medical history is unremarkable, and she takes no medications.

The physical examination, including vital signs, is normal.

Which of the following is the most appropriate cervical cancer screening strategy for this patient?

(A) Obtain high-risk human papillomavirus (hrHPV) testing now
(B) Obtain Pap smear and hrHPV testing now
(C) Obtain Pap smear now
(D) Obtain results of last cervical cancer screening examination
(E) No further screening

Item 47

A 51-year-old woman is referred for evaluation. She has a 10-year history of chronic pain that she describes as head-to-toe aching, twisting, and sometimes burning that involves several large muscle groups. The pain is constant, and she

rates the severity as a 6 on a 10-point scale. She is able to work despite the pain but is constantly fatigued. Her current regimen of oxycodone provides minimal relief. She has tried three other opioid medications as well as gabapentin and milnacipran, all of which provided only minimal improvement in her pain. Medical history is also significant for generalized anxiety disorder treated with sertraline.

On physical examination, vital signs are normal. There is tenderness in multiple large muscle groups. The remainder of the physical examination is normal.

In addition to slow tapering of oxycodone, which of the following is the most appropriate next step in treatment?

(A) Lorazepam
(B) Physical therapy
(C) Transcutaneous electrical nerve stimulation
(D) Transdermal fentanyl

Item 48

A 79-year-old woman is accompanied to the office by her son for an evaluation of her memory. The patient forgot to attend her last two scheduled appointments. The patient lives alone; her son visits her daily and sets up a weekly pill box with her medications. The son reports that on several occasions lately, pills that his mother should have taken have been left in the compartments. The patient admits that she sometimes gets confused as to which section of the pill box is the correct one for that day. Medical history is significant for hypothyroidism, hypertension, gastroesophageal reflux disease, and osteoarthritis. Medications are levothyroxine, amlodipine, omeprazole, vitamin D, and acetaminophen.

On physical examination, vital signs are normal. The patient is pleasant and interactive. The physical examination is normal, including neurologic and gait assessment. Depression screening with PHQ-2 is negative.

Which of the following is the most appropriate test to perform next?

(A) Apolipoprotein E (*APOE*-ε4) genotyping
(B) Fluorodeoxyglucose-PET brain imaging
(C) Formal neurocognitive testing
(D) Mini-Cog testing

Item 49

A 36-year-old woman is evaluated for posterior neck pain and stiffness that began 1 week ago while she was doing sit-ups. The pain is worse with movement of the head. She has limited range of motion of the neck in all directions. The pain does not radiate down her arms, and she has not had arm weakness, parethesias, or other neurologic symptoms. She reports no systemic symptoms. The pain is lessened with ibuprofen.

On physical examination, vital signs are normal. On palpation, tenderness of the cervical paraspinal muscles is noted. There is no cervical spine tenderness. Symptoms are not reproduced when the examiner bends the patient's head to either side while also extending the neck and applying a downward axial load (Spurling test). Neurologic examination is normal.

Which of the following is the most likely diagnosis?

(A) Cervical myelopathy
(B) Cervical radiculopathy
(C) Cervical sprain
(D) Whiplash-associated neck pain

Item 50

A 32-year-old woman is evaluated for bothersome vaginal discharge of 2 weeks' duration. Her last Pap smear was obtained 15 months ago and was normal. Nucleic acid amplification test results confirm *Trichomonas vaginalis* infection. Treatment of the patient is initiated.

Which of the following is the most appropriate additional management?

(A) Pap testing
(B) Test sexual partner for trichomoniasis
(C) Treat sexual partner for trichomoniasis
(D) No further testing or intervention is necessary

Item 51

A 46-year-old woman is evaluated for a 3-day history of paresthesia of the right lateral nipple. She has experienced this symptom approximately three times per year for the past 7 years. The paresthesia generally lasts 7 to 10 days. She has no other right breast concerns and reports no milky or bloody discharge, fever, chills, or antecedent trauma. She has undergone extensive evaluation, including laboratory testing, mammography, breast ultrasonography, and dermatologic and neurologic examinations; all results have been normal. She has no other medical problems and takes no medications. She works full time, and her symptom has not limited her functioning.

On physical examination, vital signs are normal. Breast examination is normal bilaterally.

Which of the following is the most likely diagnosis?

(A) Conversion disorder
(B) Illness anxiety disorder
(C) Medically unexplained symptom
(D) Somatic symptom disorder

Item 52

A 45-year-old woman is evaluated for a 2-month history of bothersome lower extremity edema. The edema does not vary with time of day or activity level. Medical history is notable for fibromyalgia treated with pregabalin. She otherwise feels well and is active in a physical therapy program.

On physical examination, vital signs are normal. Pitting edema is present to just above the ankles bilaterally without evidence of calf swelling, varicosities, or hyperpigmentation. There is no tenderness to palpation of the lower extremities. No jugular venous distention, extracardiac sounds, or pulmonary crackles are noted.

Which of the following is the most appropriate next step in management?

(A) Begin hydrochlorothiazide
(B) Perform lower extremity duplex Doppler ultrasonography
(C) Prescribe compression stockings
(D) Switch pregabalin to duloxetine

Item 53

A 40-year-old woman is evaluated for a 6-month history of poor sleep, lack of energy, constant feelings of sadness, and difficulty concentrating at work. These symptoms began shortly after she was passed over for a promotion at work. She has lost interest in her usual hobbies of running and gardening and has withdrawn from her family and friends. She reports feeling like she is "not worth anything" and sometimes thinks about "ending it all." She says she has never felt like this before; she was previously a positive and optimistic person. She reports never having periods of increased energy, decreased need for sleep, or drastically elevated mood. She has had no hallucinations. She does not use alcohol, tobacco, or recreational drugs.

Laboratory studies reveal a normal serum thyroid-stimulating hormone level.

Which of the following is the most likely diagnosis?

(A) Bipolar disorder
(B) Generalized anxiety disorder
(C) Major depressive disorder
(D) Persistent depressive disorder

Item 54

A 24-year old woman is evaluated for an 8-month history of chronic fatigue, unrefreshing sleep, short-term memory loss, and postexertional malaise. She also has symptoms of lightheadedness and dizziness that worsen with upright posture and improve after lying down. Her symptoms do not improve with rest and began suddenly 1 month after being diagnosed with early localized Lyme disease, for which she received a 14-day course of doxycycline. As a result of her symptoms, she has had to curtail many of her social activities and has taken numerous days off work. She takes no medications and has no known allergies.

On physical examination, vital signs are normal. The remainder of the examination is unremarkable.

Laboratory studies reveal a normal complete blood count, electrolyte levels, kidney function test results, liver chemistry test results, and serum thyroid-stimulating hormone level. A pregnancy test result is negative.

Her PHQ-9 score and her Generalized Anxiety Disorder 7-item scale score are both normal.

Which of the following is the most likely diagnosis?

(A) Chronic multifactorial fatigue
(B) Mood disorder
(C) Post-Lyme disease syndrome
(D) Systemic exertion intolerance disease

Item 55

A 29-year-old man is evaluated in an urgent care center for a 2-day history of pain and swelling of the right hemiscrotum. The pain is stable in intensity, neither worsening nor improving. Other symptoms include low-grade fever and dysuria. He reports no abdominal pain, nausea, or vomiting.

On physical examination, temperature is 38.3 °C (100.9 °F), and pulse rate is 103/min. Blood pressure and respiration rate are normal. There are erythema and swelling of the right hemiscrotum and moderate tenderness to palpation of the superolateral aspect of the right hemiscrotum. The hemiscrotum is not elevated, and there is no scrotal mass, rash, or penile discharge.

Which of the following tests is most likely to have a positive finding?

(A) Cremasteric reflex test
(B) Pain relief with testicular elevation
(C) Scrotal examination in standing and supine positions
(D) Transillumination study

Item 56

A 44-year-old man is evaluated during a follow-up visit for a 6-month history of low back pain. The pain worsens with standing and is relieved by lying down. He describes the pain as moderate aching. The pain does not radiate down the legs, and he has not had bowel or bladder dysfunction, fevers, leg weakness, night sweats, saddle anesthesia, or weight loss. The pain has been interfering with his ability to work. He participated in acupuncture, mindfulness-based stress reduction, and spinal manipulation, all of which provided only minimal relief.

On physical examination, vital signs are normal. On palpation, bilateral paraspinal muscle tenderness is noted. The musculoskeletal and neurologic examinations are otherwise normal.

Which of the following is the most appropriate pharmacologic option for this patient?

(A) Acetaminophen
(B) Duloxetine
(C) Hydrocodone
(D) Ibuprofen
(E) Tramadol

Item 57

A 59-year old man is evaluated for recurring epistaxis over the last several months, usually on the right side. He has been able to stop the bleeding by applying pressure to the nares, but on one occasion, he required treatment in the emergency department. Typically, blood loss has been minimal. He does not use intranasal medications and reports no substance use. He has otherwise been well. There is no family history of epistaxis or rheumatologic or bleeding disorders. His only medication is low-dose aspirin.

On physical examination, vital signs are normal. On nasal examination, there are no clear lesions, erythema, petechiae, scabs, telangiectasias, ulcers, or visible bleeding.

Which of the following is the most appropriate management?

(A) Discontinue aspirin
(B) Obtain coagulation studies
(C) Obtain complete blood count
(D) Perform nasal endoscopy

H

Item 58

A hospital system is attempting to reduce the number of hospital-acquired infections, including catheter-related urinary tract infections, bloodstream infections, *Clostridium difficile* infections, and ventilator-associated pneumonia. A common possible factor appears to be the low rate of hand hygiene (78%) documented among hospital staff.

Which of the following measures is most likely to improve hand hygiene rates at this hospital?

(A) Create a spaghetti diagram
(B) Implement the Lean model and create a value stream map
(C) Reiterate the importance of hand hygiene in an email to the hospital staff
(D) Use a Plan-Do-Study-Act cycle

Item 59

A 91-year-old woman is evaluated to establish care following discharge from a hospital to a skilled nursing facility. She had been living in her own home until 2 weeks ago when she fell and sustained a left intertrochanteric femur fracture. Her fracture was surgically stabilized, and her postoperative course was complicated by delirium and urinary tract infection. Since discharge, she has had no major medical problems. Left hip pain is controlled with acetaminophen as needed. Medical history is otherwise significant for hypertension and type 2 diabetes mellitus. Medications before hospital admission were amlodipine, lisinopril, and metformin. In the hospital, acetaminophen was added for pain and quetiapine for agitated postoperative delirium.

On physical examination, blood pressure is 148/78 mm Hg without orthostatic changes; other vital signs are normal. She has mildly antalgic gait. Cardiac, neurologic, and pulmonary examinations are normal.

Which of the patient's prescribed medications should be discontinued to prevent adverse effects?

(A) Acetaminophen
(B) Amlodipine
(C) Lisinopril
(D) Quetiapine

Item 60

A 59-year-old woman is evaluated during a follow-up visit for mouth pain of 2 years' duration. Her mouth pain was previously localized to the tongue and floor of the mouth; however, it is now diffuse, burning, and constant. The pain has also worsened over the past year despite continued dosage escalation of a transdermal fentanyl patch and oral hydromorphone. She has no pain with swallowing. Medical history is significant for squamous cell carcinoma of the tongue treated with chemotherapy and radiation therapy; her treatment course was complicated by severe mucositis. She has been without evidence of disease for the past 2 years.

On physical examination, vital signs are normal. The patient is alert and oriented but inattentive and slow to answer questions. Reflexes are exaggerated in the upper and lower extremities, and myoclonic jerking of the legs and clonus at the ankles are noted. Strength is normal. Mouth examination reveals erythematous oral mucosa with no focal areas of erosion or masses.

A CT scan of the head and neck shows no evidence of recurrent disease.

Which of the following is the most likely diagnosis?

(A) Malingering
(B) Opioid-induced hyperalgesia
(C) Opioid withdrawal
(D) Pseudoaddiction

H

Item 61

A 61-year-old man is seen for medical evaluation before a pancreaticoduodenectomy for suspected pancreatic cancer scheduled in 7 days. He reports no recent chest pain or bleeding complications after undergoing drug-eluting stent placement to the left anterior descending artery for an ST-elevation myocardial infarction 5 months ago. He has been riding his bike 10 miles daily since recovering from the myocardial infarction. Medications are aspirin, clopidogrel, losartan, atorvastatin, and atenolol.

On physical examination, vital signs are normal. Scleral icterus and jaundice are noted. Cardiac examination is normal, the lungs are clear, and the abdomen is nontender. There is no lower extremity edema.

Which of the following is the most appropriate perioperative management of this patient's antiplatelet therapy?

(A) Continue clopidogrel and aspirin
(B) Withhold aspirin and clopidogrel now
(C) Withhold aspirin now; continue clopidogrel
(D) Withhold clopidogrel now; continue aspirin

Item 62

A 55-year-old man is seen for a general wellness visit. He is asymptomatic. Family history is significant for prostate cancer diagnosed in his father at age 85 years.

The physical examination is normal.

Which of the following is the most appropriate action regarding prostate cancer screening?

(A) Discuss the benefits and harms of screening
(B) Obtain a serum prostate-specific antigen level
(C) Perform a digital rectal examination
(D) Recommend against screening

H

Item 63

An 84-year-old woman in hospice care is evaluated for "death rattle" that is disturbing to family members. She is in the active phases of dying, and her family is distressed by her noisy respiratory secretions; they are worried that she is choking. Medications are haloperidol, hydromorphone, lactulose, and acetaminophen.

On physical examination, respiration rate is 12/min. She is not responsive but does not appear uncomfortable. Extremities are cool. There are oropharyngeal secretions that produce a rattling and gurgling sound with inspiration.

Which of the following is the most appropriate initial management?

(A) Atropine ophthalmic drops given sublingually
(B) Glycopyrronium
(C) Scopolamine patch
(D) Suctioning by catheter
(E) Symptom explanation and reassurance

Item 64

A 48-year-old man is evaluated during a follow-up visit for hypertension. He has no symptoms. He received the tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine 9 years ago and the influenza vaccine during the most recent influenza season. He is a current smoker with a 25-pack-year history. His only medication is chlorthalidone.

On physical examination, vital signs are normal, and the remainder of the examination is unremarkable.

Which of the following is the most appropriate vaccine to administer to this patient?

(A) Recombinant zoster vaccine
(B) Tetanus and diphtheria toxoids booster
(C) 13-Valent pneumococcal conjugate vaccine
(D) 23-Valent pneumococcal polysaccharide vaccine
(E) No vaccines are indicated

Item 65

A 17-year-old girl is seen for a health maintenance evaluation. She reports no health issues. In discussing dietary habits, she states that she frequently eats very large amounts of food until she is uncomfortably full. These episodes have occurred at least twice per week for the past year; during them, she feels a loss of control over her eating and guilt about her overconsumption. She often eats large amounts of food despite not being hungry, and she prefers eating alone because she is embarrassed of her eating. She does not take laxatives or induce vomiting after such episodes. She rarely exercises. BMI is 30.

Which of the following is the most likely diagnosis?

(A) Anorexia nervosa, binging subtype
(B) Binge eating disorder
(C) Bulimia nervosa
(D) Overeating

Item 66

A 33-year-old woman is evaluated for a 10-month history of bilateral diffuse breast pain. The pain is severe in intensity, occurring about a week before her menstrual cycle and resolving afterward. She has generally lumpy breasts without a dominant mass and no nipple discharge. Her menstrual cycles are regular. She drinks a cup of coffee in the morning and another at noon. Medical history is otherwise unremarkable. She has no family history of breast cancer.

On physical examination, vital signs are normal. BMI is 29. Examination of the breasts shows dense nodularity in the upper outer quadrant of both breasts and no skin changes. Tenderness is elicited on examination of the upper outer quadrants of the breasts. There is no evidence of cervical, supraclavicular, or axillary lymphadenopathy.

Which of the following is the most appropriate next step in management?

(A) Advise avoidance of caffeine
(B) Advise use of a well-fitting bra
(C) Breast ultrasonography
(D) Diagnostic mammography
(E) Initiate danazol

Item 67

H

A 67-year-old man is evaluated for a 3-hour history of episodic dizziness. He notes a room-spinning sensation started suddenly without antecedent trauma and has been accompanied by nausea. Medical history is significant for hypertension, hyperlipidemia, and type 2 diabetes mellitus. Medications are lisinopril, atorvastatin, and metformin.

On physical examination, temperature is normal, blood pressure is 174/88 mm Hg, pulse rate is 101/min, and respiration rate is normal. The Dix-Hallpike maneuver evokes immediate nystagmus with no fatigability. The nystagmus is vertical without a torsional component, but the direction varies depending on the direction of the patient's gaze. The neurologic examination is limited but grossly nonfocal.

Which of the following is the most likely diagnosis?

(A) Acoustic neuroma
(B) Acute labyrinthitis
(C) Benign paroxysmal positional vertigo
(D) Vertebrobasilar ischemia
(E) Vestibular neuronitis

Item 68

A 46-year-old man is evaluated for a 2-month history of right anterior knee swelling. The swelling began insidiously and has gradually worsened. It is now the size of a golf ball and interferes with his ability to kneel, which is vital to his job as a carpet layer. The knee is painful only when he kneels; he has no problems with knee motion or stability. He feels well otherwise.

On physical examination, vital signs are normal. He has a 4-cm swelling on the anterior aspect of the right knee. The overlying skin is erythematous and warm. The knee exhibits full range of motion. There is no medial or lateral

joint tenderness; knee joint effusion; or laxity with anterior, posterior, valgus, or varus forces.

Which of the following is the most appropriate initial management?

(A) Activity modification
(B) Fluid aspiration
(C) Ibuprofen
(D) Plain radiography
(E) Serum uric acid measurement

H Item 69

A 49-year-old man was admitted to the ICU 3 days ago with sepsis secondary to health care–associated pneumonia. He is now being transferred to the general medical floor. Medical history is significant for spinal cord injury with associated lower extremity paralysis and neurogenic bladder. He is able to perform intermittent bladder catheterization. Medications are baclofen, enoxaparin, and levofloxacin.

On physical examination, vital signs are normal. BMI is 19. Left lower lobe crackles are present on lung auscultation. There is flaccid paralysis of the lower extremities. Skin is intact without erythema over pressure points.

Which of the following is the most appropriate intervention to prevent the development of a pressure injury?

(A) Advanced static mattress
(B) Alternating air mattress
(C) Frequent repositioning
(D) Zinc supplementation

Item 70

A 24-year-old man is evaluated during a routine examination. He is asymptomatic. He is sexually active with men and has had multiple partners in the past year. He reports using condoms half of the time. Medical history is unremarkable. He takes no medications.

On physical examination, vital signs and the remainder of the examination are normal.

Results of combination HIV antibody immunoassay/p24 antigen testing are negative.

Which of the following is the most appropriate interval for HIV screening in this patient?

(A) At least annually
(B) Every 2 years
(C) Every 3 years
(D) Every 5 years
(E) No further screening

Item 71

A 65-year-old woman is evaluated during a wellness visit. She has no symptoms. Medical history is significant for hypertension and impaired fasting glucose. She has never smoked cigarettes. Medications are hydrochlorothiazide and metformin.

On physical examination, blood pressure is 130/80 mm Hg; other vital signs are normal. BMI is 26. The remainder of the physical examination is normal.

Laboratory studies:

Total cholesterol	271 mg/dL (7.02 mmol/L)
LDL cholesterol	155 mg/dL (4.01 mmol/L)
HDL cholesterol	50 mg/dL (1.29 mmol/L)
Triglycerides	330 mg/dL (3.73 mmol/L)

Her estimated 10-year risk for atherosclerotic cardiovascular disease (ASCVD) using the Pooled Cohort Equations is 11.1%.

In addition to therapeutic lifestyle changes, which of the following is the most appropriate therapy for primary prevention of ASCVD in this patient?

(A) Alirocumab
(B) Ezetimibe
(C) Gemfibrozil
(D) Simvastatin

Item 72

A 72-year-old woman is evaluated for a 2-week history of intermittent dizziness. She has had no falls. Medical history is notable for hypertension and diabetes mellitus, for which she takes amlodipine, lisinopril, and metformin. A review of the patient's medical record reveals that the dosage of amlodipine was increased 3 weeks ago by a colleague's order. The patient's documented blood pressure was normal 3 weeks ago, and the care plan notes that the dosage of the antihypertensive agents should remain the same.

On physical examination, blood pressure is 115/70 mm Hg supine and 90/55 mm Hg standing, and pulse rate is 85/min supine and 105/min standing.

Which of the following is the most appropriate management?

(A) Explain that a colleague committed an error and steps will be taken to reduce the chance of recurrence
(B) Explain that the pharmacy committed an error by providing the incorrect dosage
(C) Report the error to the National Practitioner Data Bank without further patient disclosure
(D) Restore the previous dose of amlodipine without further patient disclosure

Item 73

A 68-year-old woman is evaluated for a 6-month history of incontinence typified by continuous leakage and dribbling. She reports no back pain, dysuria, or fever. Medical history is significant for a 30-year history of type 2 diabetes mellitus and a 10-year history of hypertension and hyperlipidemia. Medications include benazepril, metformin, and rosuvastatin.

On physical examination, blood pressure is 147/76 mm Hg and pulse rate is 92/min. On abdominal examination, the bladder is palpable just above the pubic symphysis. Foot examination demonstrates dry feet, loss of sensation to monofilament testing, and vibration up to the ankles. Lower extremity tendon reflexes are absent.

Urinalysis results are normal.

Which of the following is the most appropriate management?

(A) Botulinum toxin injection
(B) Oxybutynin
(C) Postvoid residual urine volume measurement
(D) Urodynamic testing

Item 74

A 44-year-old man is evaluated for a 6-year history of constant low-grade perineal pain with intermittent exacerbations and intermittent urinary symptoms of dysuria, frequency, and urgency. He had a documented case of acute bacterial prostatitis 6 years ago; since then, he has undergone extensive urologic evaluation during many of his exacerbations, all with negative findings. He has been treated numerous times with antibiotics, anti-inflammatory agents, and α-blockers without symptomatic benefit. He has no other medical problems and currently takes no medications.

On physical examination, vital signs are normal. Prostate examination yields mild and poorly localized tenderness without masses or nodules. There is no penile discharge or scrotal pain on palpation.

Results of previous laboratory studies reveal a normal erythrocyte sedimentation rate, C-reactive protein level, leukocyte count, serum creatinine level, electrolyte levels, and serum prostate-specific antigen level. A postvoid residual ultrasound was normal.

Which of the following is the most appropriate pharmacologic treatment?

(A) Lidocaine-hydrocortisone suppository
(B) Pregabalin
(C) Tamsulosin
(D) Trimethoprim-sulfamethoxazole

Item 75

A 51-year-old woman is evaluated for a 2-year history of intermittent chest pain that lasts up to 6 hours. The chest pain is not triggered by exertion, stress, or other inciting factors and is not accompanied by other symptoms. The patient also reports cramping lower abdominal and pelvic pain of 4 years' duration without nausea or bowel habit changes. She has undergone evaluation by four different physicians for these symptoms. Over the past year, she has undergone electrocardiography, chest radiography, mammography, exercise stress testing, echocardiography, CT of the abdomen and chest, upper endoscopy, and colonoscopy; all findings were normal. Recent complete blood count, comprehensive metabolic panel, and C-reactive protein level were also normal. She is unhappy with the medical care she has received and spends much of her free time reading articles related to her symptoms. She is afraid that she has a life-threatening illness that no one has been able to diagnose. Medications are acetaminophen, a multivitamin, and probiotics.

On physical examination, vital signs and all other findings are normal.

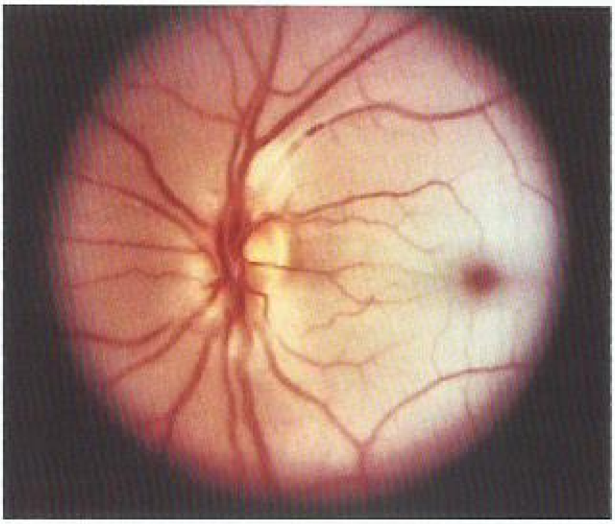
Which of the following is the most appropriate next step in management?

(A) Cognitive behavioral therapy
(B) *MEFV* gene analysis
(C) Pregabalin
(D) Whole-body PET

Item 76

A 64-year-old man is evaluated in the emergency department for acute onset of vision loss in the right eye, which began 1 hour ago. He can barely see his own hands in front of his eye. He has no eye pain. One week ago, he had an episode of monocular vision loss in the right eye that resolved after 5 minutes. He has had no other recent medical concerns. He has no history of floaters, headaches, jaw claudication, muscular weakness, or weight loss. Medical history is significant for hyperlipidemia and hypertension. Medications are atorvastatin and lisinopril.

On physical examination, vital signs are normal. There is loss of visual acuity in the right eye, and pupillary examination reveals an afferent pupillary defect. The optic disc is shown. There is no conjunctival erythema or scalp tenderness.



Laboratory studies reveal an erythrocyte sedimentation rate of 22 mm/h.

Which of the following is the most likely diagnosis?

(A) Acute angle-closure glaucoma
(B) Central retinal artery occlusion
(C) Idiopathic intracranial hypertension
(D) Retinal detachment

Item 77

H

A 74-year-old man is evaluated for severe chronic shortness of breath. Medical history is significant for New York Heart Association functional class III heart failure and severe COPD. He was hospitalized 3 weeks ago for an exacerbation

H CONT.

of his COPD. He has returned to his baseline oxygen requirements, but his continued shortness of breath is a significant impediment to his quality of life. The patient's goal is comfort. He does not desire any additional interventions for his heart failure or COPD. Medications are tiotropium, fluticasone propionate/salmeterol, albuterol, amlodipine, lisinopril, hydrochlorothiazide, and oxygen by nasal cannula.

On physical examination, the patient is comfortable at rest but develops dyspnea while ambulating, with associated anxiety. Temperature is 36.9 °C (98.4 °F), blood pressure is 124/68 mm Hg, pulse rate is 98/min, and respiration rate is 32/min. Oxygen saturation is 93% breathing 4 L/min of oxygen by nasal cannula. Pulmonary examination reveals distant breath sounds and a prolonged expiratory phase; the lungs are otherwise clear to auscultation. The estimated central venous pressure is 6 cm H_2O. Cardiac examination reveals an S_4 but is otherwise normal. There is no peripheral edema.

Chest radiograph shows evidence of hyperinflation but no signs of heart failure, pneumonia, or pneumothorax.

Which of the following is the most appropriate treatment of this patient's dyspnea?

(A) Oral furosemide
(B) Oral hydromorphone
(C) Oral lorazepam
(D) Nebulized morphine

Item 78

A 69-year-old man is evaluated during a routine visit. He is asymptomatic. Medical history is remarkable for hypertension, atrial fibrillation, and type 2 diabetes mellitus. He has a 25-pack-year smoking history but quit smoking 3 years ago. Medications are amlodipine, metoprolol, rivaroxaban, and atorvastatin.

Physical examination, including vital signs, is normal.

His estimated 10-year risk for atherosclerotic cardiovascular disease (ASCVD) according to the Pooled Cohort Equations is 14.6%.

Which of the following is most appropriate for primary prevention of ASCVD in this patient?

(A) Add aspirin
(B) Add fish oil
(C) Switch rivaroxaban to aspirin
(D) No further intervention

Item 79

A 28-year-old man is evaluated in the emergency department for a right ankle sprain that occurred earlier in the day while he was refereeing a soccer game. When running down the field, his right cleat stuck in the turf, and his foot rotated laterally. He was able to bear weight immediately after the injury, but he had to leave the game. The ankle has begun to swell, making it difficult for the patient to ambulate.

On physical examination, vital signs are normal. The patient walks with antalgic gait, although he is able to bear weight. Swelling is present over the anterior and lateral distal leg above the right ankle. Pain is reproduced both by squeezing the leg at mid-calf level and by having the patient cross his right leg with the lateral malleolus resting on the left knee. There is no tenderness to palpation over the malleoli, the navicular bone, or the fifth metatarsal base.

Which of the following is the most likely diagnosis?

(A) Achilles tendon rupture
(B) Ankle fracture
(C) High ankle sprain
(D) Lateral ankle sprain

Item 80

A 23-year-old woman is evaluated for a 2-week history of persistent thick, white vaginal discharge; burning in the vulvar and vaginal regions; and vaginal itching. She has never had these symptoms before. She is in a monogamous sexual relationship. Medical history is otherwise unremarkable, and she takes no medications.

On physical examination, vital signs are normal. Pelvic examination reveals vulvar edema with a few excoriations. Speculum examination demonstrates thick, white, curdy vaginal discharge. The remainder of the examination is unremarkable.

Laboratory studies reveal a vaginal pH of 4.4; whiff test result is negative. Potassium hydroxide microscopy shows hyphae. Results of tests for *Chlamydia trachomatis* and *Neisseria gonorrhoeae* are negative.

Which of the following is the most appropriate treatment?

(A) Intravaginal clotrimazole
(B) Intravaginal nystatin
(C) Oral metronidazole
(D) Oral voriconazole

Item 81

A 53-year-old man is evaluated for possible opioid therapy initiation for a several-year history of chest and back pain. Both types of pain significantly impair his ability to sleep, and he has not been able to work for the last 6 months. Over the past few years, he has undergone extensive evaluation, and no modifiable cause of the pain has been discovered. The patient has tried various nonpharmacologic interventions (acupuncture, cognitive behavioral therapy, exercise) and nonopioid pharmacologic therapies (duloxetine, gabapentin, ibuprofen), but he continues to have poor quality of life. These interventions are ongoing. He has no history of anxiety, depression, or substance use disorder. Results of screening tests for depression and anxiety disorders performed today are negative. His only medications are duloxetine, gabapentin, and ibuprofen.

The risks and known benefits of long-term opioid therapy are reviewed with the patient. Treatment goals are discussed, and there is an understanding that opioid therapy will be stopped if the goals are not achieved or the risks exceed the benefit. A check with the state's prescription drug monitoring program confirms that the patient is not receiving opioids or benzodiazepine therapy.

Which of the following is recommended before starting opioid therapy in this patient?

(A) Baseline urine drug screening
(B) Discontinuation of all other pain medications
(C) Discontinuation of all nonpharmacologic therapies
(D) Psychiatric evaluation

H

Item 82

A 60-year-old woman is seen for a preoperative medical evaluation before elective total left knee arthroplasty. She experiences occasional dizziness after swimming for 30 minutes. History is also significant for benign paroxysmal positional vertigo. She has no other medical problems or symptoms and takes no medications.

On physical examination, temperature is normal, blood pressure is 130/75 mm Hg, pulse rate is 75/min, and respiration rate is 16/min. Cardiac examination reveals a grade 3/6 late peaking harsh systolic murmur heard throughout the precordium, with radiation to the bilateral carotid arteries. The lungs are clear. There is no lower extremity edema.

Transthoracic echocardiogram obtained 2 years ago demonstrated moderate aortic stenosis with a valve area of 1.3 cm^2 and gradient of 25 mm Hg.

In addition to electrocardiography, which of the following is the most appropriate preoperative testing for this patient?

(A) B-type natriuretic peptide level measurement
(B) Dobutamine stress echocardiography
(C) Transthoracic echocardiography
(D) No further testing

Item 83

A 29-year-old man is evaluated during a new patient visit. He is concerned about gradual weight gain over the last several years. He does not pay much attention to his diet and describes his lifestyle as generally sedentary. He does not use tobacco products and does not drink more than one to two alcoholic drinks per week. He reports no problems with nonrestorative sleep or daytime hypersomnolence. He takes no medications.

On physical examination, blood pressure is 149/90 mm Hg, and pulse rate is 87/min. BMI is 35. His waist circumference is 107 cm (42 in). The remainder of the physical examination is normal.

Which of the following is the most appropriate test to perform next?

(A) Exercise stress test
(B) Hepatic ultrasonography
(C) Overnight polysomnography
(D) Serum lipid panel
(E) Thyroid function studies

Item 84

A 59-year-old woman is evaluated for an 8-month history of minimally productive cough. Her cough has persisted despite empiric treatment with intranasal and inhaled glucocorticoids, inhaled bronchodilators, a proton pump inhibitor, antihistamines, and decongestants. She reports no wheezing, heartburn, or nasal discharge. She is a lifelong nonsmoker and has no history of unusual environmental exposures. She has no known allergies and currently takes no medications.

On physical examination, vital signs are normal. Tympanic membranes are clear. The remainder of the examination is unremarkable.

Chest radiograph, spirometry, bronchial hyperresponsiveness testing, sinus CT scan, and esophageal pH monitoring are normal. Sputum analysis is negative for eosinophils.

Which of the following is the most appropriate treatment?

(A) Azithromycin
(B) Inhaled ipratropium
(C) Morphine
(D) Multimodal speech therapy

Item 85

A 47-year-old woman is evaluated during a follow-up visit for major depressive disorder that was diagnosed 2 months ago. At that time, she reported a 4-month history of anhedonia, depressed mood, decreased energy, insomnia, and weight loss. Her PHQ-9 score was 14, indicating moderate depression. She was prescribed sertraline, and her symptoms improved; her PHQ-9 score is now 9 (mild depression). However, she is distressed because she has had anorgasmia since starting sertraline.

Which of the following is the most appropriate next step in management?

(A) Continue sertraline and initiate cognitive behavioral therapy
(B) Discontinue sertraline and initiate bupropion
(C) Discontinue sertraline and initiate paroxetine
(D) Discontinue sertraline and refer for electroconvulsive therapy

Item 86

A 53-year-old woman is evaluated during follow-up for several chronic medical problems without a medical explanation despite extensive evaluation. Symptoms include nonpositional lightheadedness, difficulty concentrating, and total body numbness. Her symptoms have been stable for the past 2 years. She has a history of anxiety and depression, and her mood is well controlled with medical therapy. Medications are sertraline and acetaminophen as needed.

The physical examination, including vital signs, is normal. Findings on brain MRI obtained 2 years ago were normal.

Which of the following is the most appropriate management?

(A) Anti-Hu antibody assay
(B) Anti-*N*-methyl-D-aspartate receptor antibody assay
(C) Cognitive behavioral therapy
(D) No further management

Item 87

A 42-year-old man is evaluated for low back pain that began 4 days ago after he shoveled snow. The pain is mild to moderate in severity and does not radiate. He has not had any fevers, leg weakness, night sweats, or bowel or bladder dysfunction. Ibuprofen lessens the pain, as does a heating pad. He has no history of illicit substance use, and his medical history is unremarkable. He takes no additional medications.

On physical examination, vital signs are normal. Bilateral lumbar paraspinal muscle tenderness is noted; the musculoskeletal and neurologic examinations are otherwise normal.

Which of the following is the most appropriate test to perform next?

(A) CT of the lumbar spine
(B) Erythrocyte sedimentation rate measurement
(C) MRI of the lumbar spine
(D) Plain radiography of the lumbar spine
(E) No additional testing

Item 88

A 26-year-old man requests genetic testing for familial adenomatous polyposis. He is asymptomatic. Medical history is unremarkable. His 34-year-old brother recently underwent genetic testing, which revealed a mutation of the adenomatous polyposis coli (*APC*) gene. His father died of colon cancer at age 45 years, and two paternal uncles died of colon cancer at age 46 years and age 47 years. There is no family history of colon cancer in his maternal family members. He takes no medications.

Which of the following is the most appropriate management?

(A) Begin sulindac
(B) Obtain colonoscopy at age 40 years
(C) Obtain genetic testing
(D) Refer for genetic counseling

H Item 89

A 70-year-old man is evaluated before discharge from the hospital after treatment for community-acquired pneumonia. Medical history is significant for mild dementia. The patient lives alone and has a daughter who lives nearby. Remaining in his home is very important to him.

The care team recommends that the patient be discharged to a short-term rehabilitation facility to gain strength and prepare him to safely return to his home. The patient refuses. Decision-making capacity is assessed; he is able to articulate the risks, benefits, and alternatives to short-term rehabilitation as well as an understanding of his current medical condition.

Which of the following is the most appropriate management?

(A) Administer the Mini-Mental State Examination
(B) Ask the patient's daughter to make a decision on his behalf
(C) Discharge the patient home with home care services
(D) Obtain a court order for the patient to be discharged to a rehabilitation facility
(E) Refer the patient to a psychiatrist for a capacity assessment

Item 90

A 55-year-old woman is evaluated during a routine examination. Medical history is significant for hypertension, hyperlipidemia, diabetes mellitus, and a non–ST-elevation myocardial infarction 2 weeks ago. She is a current smoker with a 35-pack-year smoking history. She is ready to stop smoking. Medications are metformin, rosuvastatin, aspirin, clopidogrel, metoprolol, and lisinopril.

On physical examination, vital signs and other findings are normal.

Which of the following is the most effective smoking cessation therapy for this patient?

(A) Bupropion
(B) Electronic cigarettes
(C) Nicotine replacement therapy
(D) Varenicline

Item 91

A 69-year-old man is evaluated during a routine examination. The patient reports being healthy and has no symptoms. He has a 10-pack-year smoking history but quit smoking at age 42 years. Medical history is otherwise unremarkable. He takes no medications.

On physical examination, vital signs are normal. BMI is 22. The remainder of the examination is normal.

Which of the following is the most appropriate screening test for this patient?

(A) Abdominal duplex ultrasonography
(B) Chest radiography
(C) Dual-energy x-ray absorptiometry
(D) Low-dose lung CT
(E) No screening is recommended

Item 92

A 62-year-old woman is admitted to the hospital for pneumonia. Her medical history is significant for stage I estrogen receptor–positive invasive breast cancer, for which she was treated with breast-conserving surgery and radiation therapy and then started on tamoxifen. During her hospital stay, antibiotic therapy is initiated, and tamoxifen is withheld. Following discharge, the patient is evaluated in the office and it is noted that she is no longer taking tamoxifen.

Which of the following measures would have most likely prevented this medication error?

(A) Computerized physician order entry
(B) Electronic medication administration record use
(C) Improved medication labeling
(D) Medication reconciliation

Item 93

An 87-year-old woman is evaluated during a follow-up visit after a recent diagnosis of breast cancer. In the 18 months before her diagnosis, she noted a generalized decline in her energy level and appetite. She no longer is able keep up with others when walking any distance, and she now requires some assistance with dressing because of generalized weakness. She has unintentionally lost 3.6 kg (8 lb) in the last 6 months. Medical history is significant for breast cancer, coronary artery bypass graft surgery at age 74 years, COPD, and hypertension. Medications are albuterol, tiotropium, salmeterol, atorvastatin, aspirin, lisinopril, and metoprolol.

On physical examination, vital signs are normal. BMI is 19. The remainder of the examination is unremarkable.

Which of the following is most likely to predict the patient's overall morbidity, mortality, and response to breast cancer treatment?

(A) FRAIL scale score
(B) Pharmacologic cardiac stress test
(C) Six-minute walk test
(D) Timed Up and Go test

Item 94

A 30-year-old man is evaluated for feeling "moody" and having persistent difficulty staying focused and keeping track of tasks. He reports often feeling restless and catching himself jumping between tasks before completing them. He describes himself as "hopelessly disorganized." As a result, he has lost or not paid home utility bills and has not always completed work tasks to the satisfaction of his supervisor. He recalls having these problems since childhood. He is otherwise well. He does not use coffee, alcohol, tobacco, or recreational drugs and does not take any medications.

In addition to cognitive behavioral therapy, which of the following is the most appropriate treatment?

(A) Clonazepam
(B) Escitalopram
(C) Methylphenidate
(D) Ropinirole

Item 95

A 26-year-old woman is evaluated for left lateral knee and distal thigh pain that began 6 weeks ago. She is a long-distance runner who trains 6 days per week. The pain began insidiously and has slowly worsened over time. The pain is worst when she is running downhill. She experiences no pain while resting. She has not had any knee trauma and reports no catching, grinding, or locking.

On physical examination, vital signs are normal. On palpation, tenderness is noted 2 cm proximal to the lateral femoral condyle. With the patient supine, pain is reproduced with repeated flexion and extension of the knee as thumb pressure is applied to the lateral femoral epicondyle. There is weakness with left hip abduction. There is no joint line tenderness, joint effusion, or ligament laxity with applied stress.

Which of the following is the most likely diagnosis?

(A) Iliotibial band syndrome
(B) Lateral collateral ligament tear
(C) Lateral meniscal tear
(D) Meralgia paresthetica

Item 96

A 28-year-old woman is evaluated for persistent pain in the left upper outer breast of 9 weeks' duration. The pain is nonradiating and is not associated with aggravating factors or trauma. She has not noted breast lumps, fever, nipple discharge, or skin changes. Medical history is unremarkable, and she has no family history of breast or ovarian cancer. She takes no medications.

On physical examination, vital signs are normal. BMI is 24. The breast tissue is dense, with no overlying skin changes or underlying masses. Focal tenderness is elicited on palpation of the upper quadrant of the left breast, but no mass or chest wall tenderness is present. There is no evidence of axillary, cervical, or supraclavicular lymphadenopathy. The remainder of the examination is unremarkable.

Which of the following is the most appropriate management?

(A) Advise elimination of caffeine
(B) Breast ultrasonography
(C) Initiate danazol
(D) Mammography and breast ultrasonography
(E) Reassurance

Item 97

A 52-year-old man is evaluated for substernal chest pain. The pain is not consistently associated with exertion, nor is it always relieved by rest; it sometimes occurs when he is eating or when he is anxious. He has a 30-pack-year smoking history, but he quit smoking 2 years ago. Medical history is significant for hypertension and hyperlipidemia, for which he takes lisinopril and rosuvastatin, respectively.

On physical examination, vital signs and cardiovascular examination are normal.

An electrocardiogram reveals left ventricular hypertrophy with associated ST-T-wave changes, findings that are unchanged from an electrocardiogram obtained 2 years ago.

The patient's pretest probability of ischemic coronary artery disease is estimated to be 50%. Treadmill stress echocardiography is performed. This test has a positive likelihood ratio of 10.0 and a negative likelihood ratio of 0.1. The patient's stress test result is positive.

Which of the following best approximates the patient's posttest probability of ischemic coronary artery disease?

(A) 65%
(B) 75%
(C) 85%
(D) 95%

Item 98

A 34-year-old woman is hospitalized for a small bowel resection due to multiple strictures. She has a 10-year history of Crohn disease. History is also significant for a provoked pulmonary embolism that occurred 5 years ago. Medications are azathioprine and certolizumab.

On physical examination, vital signs are normal. The abdomen is soft. Mild diffuse pain without rebound or guarding is noted.

The patient's Caprini risk score for venous thromboembolism is 6 (high risk).

Which of the following is the most appropriate postoperative venous thromboembolism prophylaxis for this patient?

(A) Graduated compression stockings
(B) Graduated compression stockings and low-molecular-weight heparin
(C) Intermittent pneumatic compression
(D) Low-molecular-weight heparin
(E) Low-molecular-weight heparin and intermittent pneumatic compression

Item 99

A 49-year-old man is hospitalized for a 4-day history of poorly controlled nausea, vomiting, fatigue, and volume depletion. He has locally advanced esophageal adenocarcinoma and is undergoing neoadjuvant chemoradiation therapy. Radiation therapy is administered daily, and chemotherapy with low-dose carboplatin plus paclitaxel is administered weekly. His nausea and vomiting are temporally related to the radiation therapy. Medical history is otherwise significant for previous tobacco use. Other medications are acetaminophen, docusate sodium, bisacodyl, oxycodone, and prochlorperazine.

On physical examination, the patient appears fatigued. Blood pressure is 110/68 mm Hg, and pulse rate is 96/min; the remaining vital signs are normal. Pain is elicited with deep palpation of the epigastrium.

Which of the following is the most appropriate initial treatment of this patient's nausea?

(A) Haloperidol
(B) Olanzapine
(C) Ondansetron
(D) Synthetic oral cannabinoids

Item 100

A 30-year-old woman is evaluated for a 2-day history of sore throat and fatigue. She reports anorexia, chills, fever, rhinorrhea, and a dry persistent cough that keeps her awake at night. She works as a school bus driver. She has tried over-the-counter cough and cold products without benefit. Medical history is unremarkable, and she takes no medications.

On physical examination, temperature is 37.2 °C (99.0 °F); all other vital signs are normal. She has nasal and pharyngeal erythema with sparse whitish exudate. There is no lymphadenopathy or rash. The remainder of the examination is normal.

Which of the following is the most appropriate management?

(A) Amoxicillin
(B) Streptococcal rapid antigen detection test
(C) Symptom control
(D) Throat culture

Item 101

A 22-year-old woman is evaluated in the emergency department after an episode of syncope. She experienced a prodrome of nausea, diaphoresis, and warmth while waiting in line to attend a concert in a crowded, warm corridor. Her boyfriend reports that she recovered quickly and was not confused after the event. Before the episode, she had skipped dinner to arrive at the concert early. She experienced a similar episode of syncope at age 14 years when she had venipuncture for routine laboratory testing. She describes no other symptoms at the time of the episode, and her only reported symptom at this time is fatigue. She takes no medications.

On physical examination, blood pressure is 118/65 mm Hg sitting and 108/60 mm Hg after standing for 3 minutes, and pulse rate is 78/min sitting and 82/min after standing for 3 minutes. Other vital signs and the remainder of the examination are normal.

An electrocardiogram is normal.

Which of the following is the most likely diagnosis?

(A) Hypoglycemia-induced syncope
(B) Neurally mediated syncope
(C) Orthostatic syncope
(D) Postural orthostatic tachycardia syndrome

Item 102

A 67-year-old man is evaluated in follow-up for urinary incontinence. Six months ago, he began tamsulosin for occasional nocturia, frequency, and urgency related to benign prostatic hyperplasia. Tamsulosin decreased the frequency of nocturia, but he continued to have daytime urinary urgency with a few occasions of urine leakage. He attempted to control his symptoms with behavioral modification, including bladder training and scheduled voiding, but he still has episodes of urgency and leakage. He prefers not to undergo any surgical intervention. Medical history is otherwise significant for heart failure with preserved ejection fraction. Medications include benazepril, carvedilol, furosemide, spironolactone, tamsulosin, and aspirin.

On physical examination, blood pressure is 102/60 mm Hg, and pulse rate is 72/min. Other vital signs and the remainder of the physical examination are normal.

Bladder ultrasonography shows a postvoid residual urine volume of 30 mL.

Which of the following is the most appropriate treatment?

(A) Dutasteride
(B) Intermittent bladder catheterization
(C) Mirabegron
(D) Sacral nerve root neurostimulation

Item 103

A 29-year old woman is evaluated during a routine examination. She is asymptomatic. Her last Pap smear was obtained 3 years ago and was normal. She completed the human papillomavirus (HPV) vaccine series at age 26 years. Medical and family histories are unremarkable. She takes no medications.

Which of the following is the most appropriate cervical cancer screening strategy at this time?

(A) Cervical cytology
(B) Cervical cytology and HPV testing
(C) High-risk HPV testing
(D) No further testing

Item 104

A 31-year old man is evaluated for dull, aching, left sided scrotal discomfort and fullness with intermittent swelling. His symptoms began 6 months ago. He is sexually inactive.

On physical examination, vital signs are normal. Testicular size is normal bilaterally. On his left hemiscrotum, there are tenderness to palpation in the superolateral region and soft, compressible swelling along the spermatic cord, which increases with standing and the Valsalva maneuver. Transillumination and the Prehn sign (diminished scrotal discomfort with elevation) are negative.

Which of the following is the most appropriate treatment?

(A) Ceftriaxone plus doxycycline
(B) Ibuprofen and scrotal support
(C) Ligation of the left gonadal vein
(D) Topical lidocaine

Item 105

A 60-year old woman is evaluated for left wrist pain that began 3 months ago. She describes the pain as aching, with an intermittent tingling sensation over her left thumb, index, and middle fingers. Symptoms are worse at night and with repetitive motion of the wrist. She types frequently during her work as an administrative assistant.

On physical examination, vital signs are normal. The left wrist exhibits full range of motion, with no visible swelling. There is no evidence of sensory loss, muscle atrophy, or weakness.

Which of the following is the most appropriate initial management?

(A) Electromyography
(B) Glucocorticoid injection
(C) Splinting of the wrist
(D) Surgical decompression of the median nerve

Item 106

A 45 year-old woman is evaluated for a 2 day history of deep boring pain in the right eye. She also describes eye redness and photophobia but no recent trauma to the eye. She has a 10-year history of rheumatoid arthritis, treated with etanercept.

On physical examination, vital signs are normal. Diffuse right eye redness is noted, and there is pain on extraocular movement testing. Gentle pressure over the eye with the lid closed results in pain. There is no scleromalacia in either eye. There is diminished visual acuity of the right eye.

Which of the following is the most likely diagnosis?

(A) Episcleritis
(B) Scleritis
(C) Subconjunctival hemorrhage
(D) Viral conjunctivitis

Item 107

H

A 57-year-old man is evaluated prior to a right partial nephrectomy for renal cell carcinoma. He is asymptomatic. Medical history is significant for stage 3 chronic kidney disease, hypertension, hyperlipidemia, and degenerative joint disease. He has no history of abnormal bleeding and tolerated left knee arthroplasty 3 years ago without complications. Family history is negative for bleeding diatheses. Medications are lisinopril, hydrochlorothiazide, and simvastatin.

On physical examination, temperature is normal, blood pressure is 125/75 mm Hg, pulse rate is 63/min, and respiration rate is 18/min. BMI is 29. Cardiac examination reveals a regular rate and rhythm with no murmurs. Lungs are clear to auscultation. There is no lower extremity edema, conjunctival pallor, abdominal mass or tenderness, or hepatomegaly.

Which of the following is the most appropriate preoperative testing for this patient?

(A) Alanine aminotransferase and aspartate aminotransferase levels
(B) Prothrombin time and activated partial thromboplastin time
(C) Serum creatinine and electrolyte levels
(D) No preoperative testing

Item 108

A 46 year-old woman is evaluated for knee pain. Seven months ago, she underwent sleeve gastrectomy for obesity. Before the procedure, her BMI was 36. She recently initiated a running program to enhance her weight loss and is now experiencing knee pain, which she treats with ibuprofen as needed. Medical history is significant for hypertension, obesity, and type 2 diabetes mellitus. Medications are atorvastatin, ibuprofen, lisinopril, and metformin.

On physical examination, blood pressure is 118/64 mm Hg; other vital signs are normal. Knee examination is remarkable for tenderness with compression of the patella. There is no joint instability or tenderness along the medial or lateral joint lines.

Which of the following medications should be discontinued in this patient?

(A) Atorvastatin
(B) Ibuprofen
(C) Lisinopril
(D) Metformin

Item 109

A 38-year-old man is evaluated for an 8-week history of insomnia and irritability. He previously saw another physician in the practice, whom he describes as a "terrible doctor." He was treated for depression for several years and has a history of several low-lethality suicide attempts, usually related to interpersonal conflicts. He also reports having turbulent relationships with his parents and siblings.

During the appointment, he makes several compliments about your bedside manner and calls you the best doctor he has ever had. In discussing his symptoms, he attributes many of them to the break-up with his previous girlfriend. After the break-up, he engaged in a 3-day drinking and gambling binge. The patient says he is doing great now because he is in a new relationship with "the perfect woman."

Which of the following is the most likely diagnosis?

(A) Bipolar disorder
(B) Borderline personality disorder
(C) Generalized anxiety disorder
(D) Histrionic personality disorder

Item 110

A 33-year-old woman is evaluated for a 16-month history of chronic fatigue, unrefreshing sleep, difficulty concentrating, and postexertional malaise. As a result of her symptoms, she has become isolated, restricting her social and personal activities. She has also taken sick days from work with increasing frequency in recent months. Medical and family histories are unremarkable. She takes no medications.

On physical examination, the patient has depressed mood. Vital signs are normal. Neurologic examination and the remainder of the examination are normal.

Her PHQ-9 score is 6, consistent with mild depression.

After a careful evaluation, the patient is diagnosed with systemic exertion intolerance disease.

In addition to a graded exercise program, which of the following is the most appropriate treatment?

(A) Cognitive behavioral therapy
(B) Methylphenidate
(C) Mirtazapine
(D) Prednisone
(E) Sertraline

Item 111

A 35-year-old woman is evaluated during a routine follow-up examination for hypothyroidism and requests a prescription for birth control pills. She is in a new sexual relationship. She has regular menstrual cycles, and her last menstrual period was 4 weeks ago. Her most recent Pap smear was obtained 2 years ago and was normal. Her only medical problem is hypothyroidism treated with levothyroxine. Her mother had breast cancer at age 67 years.

On physical examination, vital signs are normal. BMI is 25. The remainder of the examination is unremarkable.

Which of the following is the most appropriate next step in her management?

(A) Advise against hormonal contraception
(B) Mammography
(C) Pelvic examination and Pap test
(D) Pregnancy test

Item 112

A 38-year-old woman is evaluated for low back pain that began 7 days ago when she bent over to pick up a piece of paper. She describes the pain as moderate aching that is localized to the right lower back. A sharp pain intermittently radiates down the lateral aspect of the right leg. She has not had bowel or bladder dysfunction, fevers, leg weakness, night sweats, saddle anesthesia, or weight loss. She has no history of trauma, and she does not use intravenous drugs.

On physical examination, vital signs are normal. BMI is 21. Musculoskeletal and neurologic examinations are normal.

Which of the following is the most appropriate initial treatment?

(A) Acetaminophen
(B) Duloxetine
(C) Nonpharmacologic modalities
(D) Oxycodone

Item 113

A 59-year-old man is evaluated following recent diagnoses of type 2 diabetes mellitus and hypertension. He is asymptomatic. He has never smoked cigarettes. Medications are metformin, chlorthalidone, and low-dose aspirin.

On physical examination, blood pressure is 130/80 mm Hg; other vital signs are normal. BMI is 36. The remainder of the physical examination is unremarkable.

Laboratory studies:

Total cholesterol	243 mg/dL (6.29 mmol/L)
LDL cholesterol	140 mg/dL (3.63 mmol/L)
HDL cholesterol	45 mg/dL (1.17 mmol/L)
Triglycerides	290 mg/dL (3.28 mmol/L)

His 10-year risk for atherosclerotic cardiovascular disease (ASCVD) based on the Pooled Cohort Equations is 22.4%.

The patient is instructed in therapeutic lifestyle changes to lower his risk for ASCVD.

Which of the following is the most appropriate additional treatment for primary prevention of ASCVD in this patient?

(A) Fenofibrate
(B) Fish oil supplementation
(C) Moderate- or high-intensity atorvastatin
(D) No additional treatment is required

Item 114

A 49-year-old man is evaluated for a 2-year history of poor sleep with associated daytime fatigue and sleepiness that

often interfere with his performance at work. He recorded a sleep diary, which reveals difficulty with sleep initiation and multiple awakenings throughout the night. He has no other physical symptoms that affect his sleep, and his partner does not notice him snoring or gasping.

Physical examination, including vital signs, is normal.

Which of the following is the most appropriate next step in management?

(A) Cognitive behavioral therapy
(B) Diphenhydramine
(C) Melatonin
(D) Mirtazapine
(E) Zolpidem

Item 115

A 52-year-old man fails to attend a scheduled appointment. He was initially evaluated for bilateral knee osteoarthritis 1 year ago, and treatment with weight loss, NSAIDs, and physical therapy was recommended. Over the past year, the patient missed three scheduled appointments, did not attend physical therapy, arrived for urgent care assessment twice with requests for stronger pain medications, and did not complete sufficient trials of oral nonopioid pharmacologic agents. Attempts to reach the patient by phone to discuss adherence to his care plan have not been successful. The visit today was scheduled to discuss the difficulties in his treatment and assess his barriers to care. Medical history is significant for bipolar disorder. In past visits, he has not appeared manic or suicidal.

Which of the following is the most appropriate management?

(A) Refer the patient to a psychiatrist
(B) Report the patient to the local mental health crisis team
(C) Send the patient a letter warning that the relationship may be terminated
(D) Terminate the patient relationship immediately

Item 116

A 35-year-old woman is evaluated for numbness, tingling, and weakness in her left arm that radiates from the shoulder to the fingers. Her symptoms began 3 months ago and appear to be worsening. They occur with repetitive use of the arm, especially with overhead activities. She has been painting a ceiling mural for the past 6 months. She has no history of arm or shoulder trauma. She takes no medications.

On physical examination, vital signs are normal. When the patient holds her arms above her head for several minutes during the examination, the symptoms are reproduced. The neck demonstrates full range of motion, and muscle bulk and tone in the upper extremities are normal bilaterally. Neurologic examination is normal, and all upper extremity pulses are full and equal.

Results of electrodiagnostic studies are normal.

Which is the most appropriate therapy for this patient?

(A) Gabapentin
(B) Interscalene injection of botulinum toxin type A
(C) Physical therapy
(D) Surgical decompression

Item 117

A 52-year-old woman is evaluated for acute onset of right-sided hearing loss that began yesterday. Soon afterward, she also noted a sensation of ear fullness and ringing in the same ear. She has no other focal neurologic symptoms. She reports no rhinorrhea, fever, pharyngitis, or ear pain. Medical history is significant for hypertension. She takes chlorthalidone. She has had no other exposures to medications or supplements.

On physical examination, vital signs are normal. There is decreased hearing in the right ear; the Weber test lateralizes to the left ear, and air conduction is louder than bone conduction bilaterally. The ear canals are unobstructed, and the tympanic membranes are normal appearing. The neurologic examination is unremarkable.

Which of the following is the most likely diagnosis?

(A) Meniere disease
(B) Otosclerosis
(C) Ototoxicity
(D) Sudden sensorineural hearing loss

Item 118

H

A 60-year-old man is evaluated in the hospital for a pressure injury. The pressure injury developed during a prolonged hospitalization after a motor vehicle accident that resulted in a closed head injury and pelvic and spinal fractures. Medications are heparin, oxycodone, and ibuprofen or acetaminophen as needed.

On physical examination, vital signs are normal. A painful 4-cm sacral ulcer with full-thickness loss of skin and adipose tissue is present (stage III). The ulcer has no purulence or surrounding induration.

Which of the following is the most appropriate treatment?

(A) Hydrocolloid dressing
(B) Platelet-derived growth factor dressing
(C) Standard gauze dressing
(D) Zinc-infused dressing

Item 119

A 25-year-old man is evaluated during a new patient visit. He is experiencing severe anxiety about the start of a new job next month. Specifically, he is concerned about his ability to arrive on time because every morning before leaving his apartment, he feels compelled to perform multiple checks to ensure that all electronic devices are turned off and all windows and doors are locked. These activities consume approximately 1 hour of time. He performs these same activities each night before going to bed and often repeats them several times because of overwhelming feelings that he has forgotten something and his apartment will catch fire or be robbed. As a result of his anxieties, the patient rarely socializes outside of his home. When he is away from home,

he uses a surveillance application to monitor his apartment 11 minutes after every hour.

Which of the following is the most appropriate management?

(A) Buspirone
(B) Clonazepam
(C) Cognitive behavioral therapy
(D) Risperidone

Item 120

A 58 year old man is evaluated in an urgent care center for a 3 day history of right-sided scrotal swelling, pain, and dysuria. He reports no antecedent trauma, nausea, or vomiting. He is sexually active with both men and women and uses condoms intermittently. He does not take any medications.

On physical examination, temperature is 38.5 °C (101.3 °F), pulse rate is 101/min, and other vital signs are normal. The right hemiscrotum is edematous, with tenderness to palpation of the superolateral aspect. The scrotal pain lessens with elevation of the scrotum. There is no penile discharge.

Results of nucleic acid amplification testing for chlamydia and gonorrhea are pending.

Which of the following is the most appropriate treatment?

(A) Ceftriaxone
(B) Ceftriaxone and doxycycline
(C) Ceftriaxone and levofloxacin
(D) Ibuprofen and scrotal support

Item 121

A 44 year old woman is evaluated for a breast lump she noticed 1 week ago. There is no nipple discharge. She birthed two children, the first at age 25 years, and her menstrual cycles are regular. She has no family members with breast or ovarian cancer. She has no other medical problems and takes no medications.

On physical examination, vital signs are normal. BMI is 28. Examination of the breasts reveals dense tissue bilaterally and no skin changes. A mass is noted in the upper inner area of the right breast, measuring 1.8 cm; it is firm, mobile, and nontender, with ill defined margins. There is no evidence of axillary, cervical, or supraclavicular lymphadenopathy. The remainder of the examination is unremarkable.

Which of the following is the most appropriate diagnostic test to perform next?

(A) Breast MRI
(B) Core-needle biopsy
(C) Diagnostic mammography and ultrasonography
(D) Ultrasonography

Item 122

A 34-year-old woman is evaluated during a follow up visit for blood pressure control. She states that she hopes to become pregnant and would like to stop her oral contraceptive. She does not smoke, drink alcohol, or use illicit drugs. She is in a monogamous sexual relationship and has had no sexually transmitted infections. Medical history is significant for hypertension, type 2 diabetes mellitus, and depression since childhood. Medications are an oral contraceptive, lisinopril, metformin, citalopram, and acetaminophen as needed.

On physical examination, vital signs are normal. The remainder of the examination is unremarkable.

In addition to starting folic acid, which of the following medications should be stopped at this time?

(A) Acetaminophen
(B) Citalopram
(C) Lisinopril
(D) Metformin

Item 123

H

A 77-year-old woman is seen for a preoperative medical evaluation before resection of the sigmoid colon for recurrent diverticulitis scheduled 5 days from now. She has nonvalvular atrial fibrillation and is receiving long-term warfarin, without a history of bleeding complications. She has no history of stroke, transient ischemic attack, or intracardiac thrombus. History is also significant for hypertension. Medications are warfarin, chlorthalidone, and metoprolol.

The physical examination, including vital signs, is normal.

The INR measurement is 2.3. Calculated $CHADS_2$ score is 2, and CHA_2DS_2-VASc score is 4.

In addition to withholding warfarin before surgery, which of the following is the most appropriate management of this patient's perioperative anticoagulation?

(A) Begin aspirin, 81 mg/d
(B) Begin enoxaparin when the INR drops below 2.0
(C) Begin unfractionated heparin when the INR drops below 2.0
(D) No additional interventions

Item 124

A 26 year old man is evaluated during a routine examination. He is asymptomatic. The patient is sexually active with men and has had multiple partners in the past year. He engages in both oral and anal sex, and he reports using condoms most of the time. He does not use illicit drugs. He is unsure about his vaccination status and has never been tested for HIV infection, syphilis, or infectious hepatitis. Medical history is unremarkable. He takes no medications.

The physical examination, including vital signs, is normal.

Screening is arranged for HIV infection, syphilis, and hepatitis A and B.

Which of the following additional screening tests is most appropriate, as recommended by the Centers for Disease Control and Prevention?

(A) Anal cytology
(B) Hepatitis C antibody assay

(C) Nucleic acid amplification test for chlamydia and gonorrhea
(D) No additional tests are indicated

Item 125

A 31-year-old man is evaluated during a follow-up visit for depression. He previously experienced two episodes of major depressive disorder that were effectively treated with fluoxetine. Three months ago, he presented with recurrent symptoms of depression. His PHQ-9 score was 14, indicating moderate depression. Fluoxetine was initiated and uptitrated to an effective dosage. The patient now reports significant improvement in his symptoms. His PHQ-9 score is 6, indicating mild depression; he reports no adverse effects from the medication.

Which of the following is the most appropriate next step in management?

(A) Complete 8 months of fluoxetine therapy
(B) Complete 8 months of fluoxetine, then switch to bupropion for long-term maintenance therapy
(C) Continue fluoxetine as long-term maintenance therapy
(D) Discontinue fluoxetine

Item 126

A 38-year-old man is evaluated during a new-patient visit for a 5-year history of fatigue, dizziness, nonexertional chest pain, intermittent and transient abdominal swelling, insomnia, and fleeting numbness of the extremities. He has been evaluated by two different internal medicine physicians, a gastroenterologist, a rheumatologist, and a pulmonologist. Despite extensive blood testing and imaging, a unifying diagnosis has never been established. Medical history is significant for depression, migraine, and cholecystectomy. He does not use tobacco, alcohol, or illicit drugs. Current medications are ibuprofen and sumatriptan as needed, acetaminophen, and citalopram.

Physical examination, including vital signs, is normal.

In addition to eliciting the patient's concerns, which of the following is the most appropriate initial management?

(A) Comprehensive metabolic profile and C-reactive protein level
(B) *MEFV1* genetic testing
(C) Obtain all previous medical records
(D) Psychiatry consultation
(E) Rheumatoid factor and antinuclear antibody titer

Item 127

A 49-year-old man is evaluated for a 2-day history of posterior neck stiffness and pain that radiates down his left arm and into the fourth and fifth fingers of his left hand. He is left-handed and works as a roofer. The pain worsens when he turns his head to the left and improves when he lies down, although he sometimes has pain when rising from a prone position. He has not had any arm or hand weakness or problems writing. He has no systemic symptoms.

On physical examination, vital signs are normal. On palpation, the pain is reproduced when the examiner applies downward pressure with the patient's head bent to the left and extended (Spurling test). Pain is relieved when the patient holds his left arm above the plane of his shoulder. Neck range of motion is limited with both left and right lateral rotation. There is no cervical spine tenderness to palpation. The neurologic examination is normal.

Which of the following is the most appropriate management?

(A) Cervical collar
(B) Cervical MRI
(C) Electrodiagnostic testing
(D) Gabapentin
(E) Neck exercises

Item 128

A 25-year-old woman is evaluated during a routine wellness visit. She received the tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap) vaccine at age 18 years; the meningococcal conjugate vaccine at age 11 years with a booster dose at age 16 years; and an influenza vaccine during the most recent influenza season. She is single, lives in an apartment with a roommate, and is a nonsmoker. She has no upcoming travel plans. She has no medical problems and takes no medications.

Physical examination, including vital signs, is normal.

Which of the following vaccinations should be offered to this patient?

(A) Human papillomavirus vaccine
(B) Quadrivalent meningococcal conjugate vaccine
(C) Tdap vaccine
(D) 23-Valent pneumococcal polysaccharide vaccine

Item 129

A 49-year-old woman is seeking therapy for a 6-month history of increasing hot flushes, now occurring six to eight times per day. She also has night sweats that occur three to five times per night and result in disrupted sleep and daytime fatigue. Her last menstrual period was 14 months ago. She has no personal or family history of breast or ovarian malignancies. She takes no medications.

On physical examination, vital signs are normal, as are pelvic and breast examinations.

Which of the following is the most appropriate management?

(A) Hormone therapy with estrogen alone
(B) Hormone therapy with estrogen and progesterone
(C) Ospemifene
(D) Vaginal estrogen therapy

Item 130

A 55-year-old man is evaluated in the emergency department for a 2-day history of dizziness accompanied by nausea and vomiting. He works as an electrician, and his symptoms started suddenly while installing an overhead light

fixture with his head tilted back for a prolonged period. He describes the dizziness as a constant whirling sensation that is unaffected by changes in position. He also reports symptoms of a recent upper respiratory tract infection but no fever. He has no other medical problems and takes no medications.

On physical examination, temperature is normal, blood pressure is 155/84 mm Hg, pulse rate is 99/min, and respiration rate is normal. Hearing is diminished on the left side. Spontaneous combined horizontal and torsional nystagmus is noted but lessens with a fixed gaze. The patient declines further examination because of severe nausea.

Which of the following is the most likely diagnosis?

(A) Benign paroxysmal positional vertigo
(B) Labyrinthitis
(C) Meniere disease
(D) Posterior circulation stroke
(E) Vestibular neuronitis

Item 131

A 47-year-old man is evaluated for a 2-day history of cough productive of small amounts of yellow sputum, as well as sinus congestion, frontal headache, rhinorrhea, and malaise. He has had no fevers, chest pain, or shortness of breath. Medical history is otherwise unremarkable.

On physical examination, vital signs are normal. There is tenderness over the maxillary sinuses bilaterally. The nasal mucosa is diffusely edematous with moderate amounts of clear discharge. Pharyngeal examination reveals erythema without tonsillar exudate. The tympanic membranes appear normal. No cervical lymphadenopathy is noted. The remainder of the examination is normal.

Which of the following is the most appropriate treatment?

(A) Amoxicillin
(B) Codeine
(C) Inhaled albuterol
(D) Intranasal fluticasone

H Item 132

A 67-year-old woman with multiple myeloma is evaluated for back pain. The pain began several months ago but has dramatically worsened in the past 2 weeks. It is located in the lumbar and thoracic spine with associated paraspinal muscle spasms. The pain does not radiate into the buttocks or legs, and there has been no change in gait or bowel or bladder function. She rates the pain as an 8 on a 10-point scale at its worst. Medical history is significant for multiple myeloma and end-stage kidney disease on hemodialysis. Medications are acetaminophen, amlodipine, aspirin, metoprolol, sertraline, bortezomib, dexamethasone, and lenalidomide.

On physical examination, vital signs are normal. Palpation elicits tenderness over the thoracic and lumbar spine. The abdomen is not distended, and there are no palpable masses. Neurologic examination is normal.

Restaging CT scans from 2 months ago reveal lytic lesions in the lumbar spine and left iliac crest.

Spine MRI is scheduled.

Which of the following is the most appropriate treatment of this patient's pain?

(A) Fentanyl patch
(B) Gabapentin
(C) Hydromorphone
(D) Morphine
(E) Tramadol

Item 133 H

A 68-year-old man is evaluated before elective left total hip arthroplasty. He reports left groin pain and new fatigue and dyspnea that limit ambulation to one flight of stairs and one block. Medical history is significant for type 2 diabetes mellitus, ischemic stroke, hypertension, hyperlipidemia, peripheral artery disease, degenerative joint disease, and chronic kidney disease. Medications are insulin glargine, insulin lispro, aspirin, lisinopril, simvastatin, and tramadol.

On physical examination, temperature is normal, blood pressure is 145/85 mm Hg, pulse rate is 89/min, and respiration rate is 18/min. BMI is 35. Cardiopulmonary examination is normal. There is no lower extremity edema.

Laboratory studies are notable for a serum creatinine level of 2.1 mg/dL (185.6 µmol/L).

An electrocardiogram demonstrates Q waves in leads II and III.

Which of the following is the most appropriate diagnostic test to perform next?

(A) Dobutamine stress echocardiography
(B) Exercise electrocardiography
(C) Transthoracic echocardiography
(D) No further testing

Item 134

A physician has noticed that a 67-year-old colleague in the medical practice has been increasingly forgetful in recent months. The colleague has had more difficulty remembering the names of her new patients and the medical students who are doing rotations in the practice, and she has also frequently missed meetings because of scheduling mix-ups. She admits that she cannot keep track of all of the new medications for diabetes mellitus without using a reference. The physician is unaware of the colleague's personal medical history but is concerned about her memory and cognitive status.

Which of the following is the most appropriate management?

(A) Continue to monitor the colleague
(B) Directly approach the colleague and help her plan for confidential evaluation
(C) Offer to confidentially evaluate the colleague
(D) Report the colleague to the state medical board

Item 135

A 64-year-old man is evaluated for a 5-year history of intermittent erectile dysfunction. He experiences nocturnal and

early-morning penile tumescence, and he is able to achieve and maintain an erection sufficient for sexual activity approximately 50% of the time. Medical history is significant for coronary artery disease, depression, hyperlipidemia, hypertension, obstructive sleep apnea, peripheral vascular disease, and type 2 diabetes mellitus. Medications are aspirin, atorvastatin, isosorbide mononitrate, lisinopril, metformin, metoprolol, and sertraline. He does not use continuous positive airway pressure.

On physical examination, all vital signs are normal. BMI is 26. He has normal body hair growth and pattern, normal testicular size, and no gynecomastia.

Laboratory studies reveal an 8:00 AM serum fasting total testosterone level of 380 ng/dL (13.2 nmol/L).

Which of the following is the most appropriate treatment?

(A) Alprostadil
(B) Psychotherapy
(C) Sildenafil
(D) Testosterone gel

Item 136

A 42-year-old woman is evaluated for a 2-month history of left foot pain between the third and fourth toes, accompanied by a burning sensation and the sensation of walking on a pebble. She has not experienced any trauma in the area, and she does not have edema or erythema. Symptom onset was insidious, and the pain only occurs when she is standing or walking. She works as a restaurant hostess and wears high-heeled shoes for her job.

On physical examination, vital signs are normal. The left foot appears normal, with no palpable abnormalities or tenderness between the third and fourth toes. Sensation is intact throughout the foot, and posterior tibial and dorsalis pedis pulses are palpable.

Which of the following is the most likely diagnosis?

(A) Bunion deformity
(B) Hammertoe deformity
(C) Morton neuroma
(D) Plantar fasciitis

Item 137

A hospital system's initial analysis of costs related to prolonged hospital stays revealed that surgical wound infections account for a large proportion of costs. Assessment of the surgical data for the hospital showed that the postoperative wound infection rate is 19%.

Which of the following is the most appropriate tool to assist in reducing postoperative wound sepsis at this institution?

(A) Clinical audit
(B) Control chart
(C) Lean model
(D) Model for Improvement

Item 138

A 92-year-old woman is evaluated for urinary incontinence. Six months ago, the patient occasionally lost control of small amounts of urine, which was managed with an adult diaper. At present, the patient seems to have lost the ability to recognize that she needs to urinate until it is too late to reach the bathroom. There have been no recent noticeable changes in cognition. Medical history is significant for dementia treated with donepezil.

On physical examination, vital signs are normal. The patient appears frail. She is not oriented to place or time. Gait is stable and narrow based. She is slow to rise from a chair, and she requires the arm rests to get up.

Which of the following is the most appropriate treatment?

(A) Oxybutynin
(B) Pelvic floor muscle training (Kegel exercises)
(C) Prompted voiding
(D) Sling cystourethropexy

Item 139

A 23-year-old man is evaluated during a new patient visit. He was honorably discharged from the Army 2 months ago after serving two tours of duty in Afghanistan. Four months ago, his platoon's vehicle was struck by an improvised explosive device. He sustained a severe concussion and multiple lacerations, and three members of his platoon were killed. For the last 3 months, the patient has had daily nightmares in which he relives the event and can see his comrades being killed. He has also experienced flashbacks of the event when he hears loud noises, such as fireworks and thunder. He has had great difficulty sleeping and is increasingly irritable.

The patient has been unable to find employment because he avoids social situations. He has also withdrawn from family and friends because he is afraid they will ask about his military service, and he does not wish to discuss the events he experienced. He has been drinking alcohol more frequently, having up to four beers before bedtime to induce sleep. He does not use tobacco or recreational drugs.

Medical history is otherwise unremarkable, and physical examination is normal.

Which of the following is the most appropriate treatment?

(A) Clonazepam
(B) Propranolol
(C) Psychotherapy
(D) Topiramate

Item 140

A 61-year-old man is evaluated in an urgent care center for acute frontal headache and pain in the right eye that began a few hours earlier while he was watching his grandson's basketball game. The pain extends through the anterior scalp and downward across the nose. The patient is also nauseated and vomiting acutely. He has photophobia and notes that lights appear "fuzzy." Medical history is significant for hypertension and anxiety. Medications are hydrochlorothiazide and citalopram.

H CONT.

On physical examination, blood pressure is 150/90 mm Hg; other vital signs are normal. Severe conjunctival erythema; photophobia; a mid-dilated, nonreactive pupil on the right side; and corneal cloudiness are noted. Upon gentle palpation of the eyes, tenderness and increased firmness are noted over the right globe compared with the left. Right eye visual acuity is grossly decreased. No discharge is noted.

Which of the following is the most likely diagnosis?

(A) Acute angle-closure glaucoma
(B) Bacterial endophthalmitis
(C) Central retinal vein occlusion
(D) Scleritis

Item 141

A 31-year-old woman requests genetic testing for Huntington disease. She has a close friend who recently had a positive genetic test result for the *huntingtin* gene mutation, and she would like to undergo testing for assurance that she is without the disease. She is asymptomatic. Medical history is unremarkable. She takes no medications.

On physical examination, vital signs are normal. Neurologic examination and the remainder of the examination are normal.

Which of the following is the most appropriate management?

(A) Obtain a brain MRI
(B) Obtain a three-generation family history
(C) Obtain genetic testing
(D) Refer for genetic counseling

Item 142

A 45-year-old woman is evaluated for heavy menstrual bleeding. She reports having heavy unpredictable bleeding of variable flow and duration for the past year. Her last period was 12 days ago. She has a history of provoked deep venous thrombosis 3 years ago following an intercontinental flight. She is a current smoker with a 10-pack-year history and does not wish to quit smoking at this time. She has never been pregnant and does not wish to become pregnant in the future.

On physical examination, vital signs are normal. BMI is 24. Breast and pelvic examinations are normal.

Laboratory studies reveal a hemoglobin level of 10.2 g/dL (102 g/L) and mean corpuscular volume of 68 fL. Pregnancy test result is negative.

A subsequent evaluation for secondary causes of abnormal uterine bleeding, including endometrial cancer, was negative.

In addition to oral iron supplements, which of the following is the most appropriate management?

(A) Combination oral contraceptive pill
(B) Endometrial ablation
(C) Levonorgestrel-containing intrauterine device
(D) Medroxyprogesterone acetate for the second half of the menstrual cycle

Item 143

A 28-year-old man is evaluated for a 10-month history of dizziness. He describes the dizziness as a sense of nonvertiginous imbalance and notes that it worsens with personal motion, movement of objects around him, and sitting or standing upright. The dizziness has persisted since he experienced a concussion without loss of consciousness while playing soccer 10 months ago. He reports no focal neurologic symptoms. He takes no medications.

On physical examination, vital signs are normal. On neurologic examination, cranial nerve examination findings are normal, motor strength is intact, and deep tendon reflexes are normal. Romberg test result is negative. Gait is normal.

Findings on a brain MRI are normal.

In addition to vestibular and balance rehabilitation therapy, which of the following is the most appropriate treatment?

(A) Amitriptyline
(B) Canalith repositioning maneuver (Epley maneuver)
(C) Lorazepam
(D) Sertraline

Item 144

H

An 82-year-old man is evaluated for discharge planning. He was hospitalized with community-acquired pneumonia complicated by respiratory failure and sepsis, which required prolonged mechanical ventilation. He eventually required a tracheostomy and remains on mechanical ventilation, but his respiratory status is otherwise stable. He is severely deconditioned and has been unable to participate even minimally in physical therapy. Although he is expected to require mechanical ventilation for at least several more weeks, he is medically stable for discharge. Medical history is significant for chronic kidney disease, heart failure, hypertension, and type 2 diabetes mellitus. Medications are insulin aspart, insulin glargine, carvedilol, furosemide, and lisinopril.

On physical examination, the patient is alert and cooperative but appears frail on mechanical ventilation. Vital signs and the remainder of the examination are normal.

Which of the following is the most appropriate discharge disposition for this patient?

(A) Acute rehabilitation facility
(B) In-home rehabilitation services
(C) Rehabilitation at a long-term acute care hospital
(D) Skilled nursing facility

Item 145

A proposed new screening protocol for ovarian cancer involves universal pelvic ultrasonography for asymptomatic women starting at age 30 years. The protocol is based on a national study of randomly selected 30-year-old women. The authors of the study note that unilateral oophorectomy performed for suspicious lesions resulted in longer survival than oophorectomy performed for patients with symptoms.

based on historical data. The study authors conclude that the screening protocol will reduce ovarian cancer-related deaths.

Which of the following is most likely to threaten the validity of the authors' conclusions?

(A) Lead-time bias
(B) Length-time bias
(C) Recall bias
(D) Selection bias

Item 146

A 42-year-old woman is approaching discharge from the hospital for alcohol withdrawal. She has had severe alcohol use disorder for several years but says she is willing to do whatever it takes to quit. Medical history is also significant for hypertension and chronic kidney disease. Medications are amlodipine and chlorthalidone.

Physical examination, including vital signs, is normal.

A complete blood count and comprehensive metabolic profile are normal. The estimated glomerular filtration rate is 50 mL/min/1.73 m^2.

Which of the following is the most appropriate pharmacologic treatment?

(A) Acamprosate
(B) Chlordiazepoxide
(C) Disulfiram
(D) Naltrexone

H

Item 147

A 72-year-old man is hospitalized for the third time in 3 months for shortness of breath. He has stage 3 chronic kidney disease, end-stage COPD, and New York Heart Association functional class III heart failure. The patient does not have an advance directive, and the resuscitation preference most recently noted from a visit 6 months ago is "full code." Medications are acetaminophen, aspirin, lisinopril, metoprolol, and torsemide.

Which of the following is the most appropriate initial strategy to develop goals of care?

(A) Ask about hospice referral timing
(B) Ask about resuscitation preferences
(C) Ask what he understands about his illnesses
(D) Provide information about prognosis

Item 148

A 50-year-old woman is evaluated in the hospital following a non-ST-elevation myocardial infarction treated with drug-eluting stent placement. She is currently asymptomatic. Medical history is significant only for hypertension. Medications are clopidogrel, aspirin, lisinopril, and metoprolol.

Physical examination, including vital signs, is normal. BMI is 29.

Laboratory studies:

Total cholesterol	239 mg/dL (6.19 mmol/L)
LDL cholesterol	155 mg/dL (4.01 mmol/L)
HDL cholesterol	45 mg/dL (1.17 mmol/L)
Triglycerides	195 mg/dL (2.20 mmol/L)

Which of the following is the most appropriate additional diagnostic testing to perform before initiating high-intensity statin therapy in this patient?

(A) Alanine aminotransferase level measurement
(B) Alanine aminotransferase and creatine kinase level measurement
(C) Creatine kinase level measurement
(D) No further laboratory studies are indicated

Item 149

A 40-year-old man is evaluated during a routine examination. He is healthy and asymptomatic, although he leads a sedentary lifestyle. Family history is noncontributory. He takes no medications.

On physical examination, temperature is normal, blood pressure is 120/74 mm Hg, pulse rate is 68/min, and respiration rate is normal. BMI is 32. The remainder of the physical examination is unremarkable.

When should this patient be screened for diabetes mellitus?

(A) At age 45 years
(B) At this visit
(C) If he develops an additional risk factor for diabetes
(D) No screening is indicated

Item 150

A 19-year-old man is evaluated in the emergency department after his roommate became concerned about his behavior. The patient began college 7 months ago, and since then, his roommate has watched the patient become increasingly isolated from others and lacking in emotion. The patient has frequently expressed concerns that the government is tracking his movements and even his thoughts. In the past 2 months, he has stopped attending classes and spends long periods in bed. The roommate called the patient's parents after the patient sealed up the ventilation in their room because he believed government agents were injecting gas into the building. The patient says he does not feel depressed. He had no behavioral problems before starting college, and he does not use alcohol, recreational drugs, or over-the-counter medications.

Which of the following is the most likely diagnosis?

(A) Bipolar disorder
(B) Major depressive disorder
(C) Paranoid personality disorder
(D) Schizophrenia

Item 151

A 39-year-old woman is evaluated for a 3-week history of malodorous vaginal discharge. She was treated with antibiotics for a urinary tract infection 3 weeks before the onset

of symptoms. She is in a monogamous sexual relationship. Medical history is unremarkable. Her only medication is an oral contraceptive.

On physical examination, vital signs are normal. Pelvic examination reveals thin, homogenous, grayish vaginal discharge. There is no adnexal or cervical motion tenderness. The rest of the examination is unremarkable.

Laboratory testing reveals a vaginal pH of 5.6; whiff test result is negative.

Which of the following is the most appropriate test to confirm the diagnosis?

(A) Culture for *Gardnerella vaginalis*
(B) Nucleic acid amplification test for trichomoniasis
(C) Potassium hydroxide wet mount study for yeast
(D) Saline microscopy for clue cells

Item 152

A 60-year-old man is evaluated for a 6-month history of worsening urinary frequency, urgency, hesitancy, incomplete emptying, nocturia, and weakened stream. He reports no dysuria, incontinence, or acute urinary retention. Medical history is also significant for erectile dysfunction. He takes no medications.

On physical examination, vital signs are normal. Rectal examination reveals a diffusely enlarged prostate that is nontender to palpation, with no masses or nodules noted. Testicular size is normal. A comprehensive metabolic profile and urinalysis are normal; an 8:00 AM total testosterone level is also normal.

Which of the following is the most appropriate treatment?

(A) Finasteride
(B) Oxybutynin
(C) Tadalafil
(D) Tamsulosin

H Item 153

A 55-year-old man is hospitalized after he was injured at a construction site structure collapse. He has a fractured pelvis, a shoulder dislocation, a mild concussion, and multiple abrasions. He is scheduled to undergo surgery for the fractured pelvis tomorrow morning. History is significant for hyperlipidemia, hypertension, coronary artery disease, and a non–ST-elevation myocardial infarction 2 years ago treated with drug-eluting stent placement. Current medications are atorvastatin, metoprolol, amlodipine, and aspirin.

On physical examination, temperature is normal, blood pressure is 170/90 mm Hg, pulse rate is 102/min, and respiration rate is 20/min. Oxygen saturation is 96% breathing ambient air. Multiple abrasions and ecchymosis are noted. Cardiac examination reveals tachycardia but is otherwise normal.

Which of the following is the most appropriate management of this patient's medications before surgery?

(A) Continue amlodipine, aspirin, and metoprolol; withhold atorvastatin
(B) Continue amlodipine, atorvastatin, and metoprolol; withhold aspirin
(C) Continue atorvastatin, metoprolol, and aspirin; withhold amlodipine
(D) Continue all medications

Item 154

A 50-year-old woman is seen following screening digital mammography. She is asymptomatic and has no medical problems. Other than her age and sex, she has no additional risk factors for breast cancer and no family history of breast cancer. The mammogram report notes no suspicious lesions but indicates that the breasts are heterogeneously dense (density category C).

On previous physical examination, vital signs and breast examination were normal.

In addition to education on breast density, which of the following is the most appropriate adjunctive breast cancer screening?

(A) Breast MRI
(B) Digital breast tomosynthesis
(C) Repeat digital mammography in 6 months
(D) No further testing

Item 155

A 49-year-old woman is evaluated for a 3-year history of pelvic pain. An extensive evaluation has not found a clearly defined pathophysiologic or anatomic cause, and therapy has been targeted to general pain management lately. She has been a willing and cooperative participant in biofeedback, cognitive behavioral therapy, physical therapy, hypnosis, acupuncture, meditation, and stress-reduction techniques without significant pain relief. Her pain has been unresponsive to multiple trials of nonopioid analgesics and antidepressants, and she has tried oral tapentadol and tramadol, which were also ineffective. She currently takes acetaminophen and gabapentin. Medical history is significant for end-stage kidney disease, for which she receives hemodialysis, and hypertension. Other medications are metoprolol succinate, amlodipine, intravenous iron, and an erythropoiesis-stimulating agent.

Which of the following is the most reasonable treatment option for this patient's chronic pain?

(A) Oral immediate-release morphine sulfate
(B) Oral medical cannabis oil
(C) Oral methadone
(D) Topical lidocaine

Item 156

A 66-year-old man is evaluated for right posterior knee swelling that began 3 days ago. The knee is not painful, unstable, warm, or red. He has no systemic symptoms. History is significant for bilateral knee osteoarthritis. His only medication is aspirin, which adequately controls his osteoarthritis pain.

On physical examination, vital signs are normal. A large bulge is visible on the posterior aspect of the right knee, without erythema, tenderness, or warmth. Crepitus of the knees is noted bilaterally. There is no joint instability or increased laxity with stress forces.

Which of the following is the most appropriate management?

(A) Aspiration of fluid
(B) Glucocorticoid injection
(C) Ibuprofen
(D) Plain radiography of the knee
(E) No treatment

Item 157

A 56-year-old woman is evaluated during a wellness examination. She reports no vaginal bleeding, discharge, or other symptoms since reaching menopause at age 52 years. Over the past 3 months, she has noted a lack of interest in sexual activity that has been occasionally distressing for her. She uses vaginal lubricant for intercourse, which reduces the mild discomfort with sexual activity. She has no history of pelvic surgery, sexually transmitted infections, or sexual trauma. Results of screening tests for anxiety and depression are negative. Medical history is otherwise unremarkable, and she takes no medications.

On physical examination, the external genitalia are normal. Pelvic examination reveals pale vaginal walls and a decrease in vaginal lubrication. The remainder of the examination is unremarkable.

Which of the following is the most likely female sexual disorder diagnosis?

(A) Female orgasmic disorder
(B) Genitopelvic pain/penetration disorder
(C) Sexual interest/arousal disorder
(D) No female sexual disorder

H Item 158

A 78-year-old man is evaluated in the emergency department for a 1-day history of worsening dizziness. The patient describes the dizziness as a room-spinning sensation and notes that he has some accompanying nausea and imbalance. He reports no other symptoms. Medical history is notable for hypertension, hyperlipidemia, and type 2 diabetes mellitus. Medications are aspirin, lisinopril, atorvastatin, and metformin.

On physical examination, blood pressure is 172/88 mm Hg; other vital signs are normal. The patient has difficulty with tandem walking. With extraocular movement testing, the patient has vertical nystagmus. The neurologic examination is otherwise nonfocal and without mental status changes.

Which of the following is the most appropriate diagnostic test to perform next?

(A) CT of the head
(B) MRI of the brain
(C) Vestibular laboratory testing
(D) No further testing

Item 159

A 27-year-old woman is evaluated for help with weight loss. After a visit 3 months ago, she enrolled in an online weight loss program and began a walking program. She currently walks 30 minutes per session 5 days per week. She admits that she has difficulty adhering to the diet restrictions. She avoids weighing herself because she finds it discouraging. She has lost 0.2 kg (0.5 lb) since her visit 3 months ago. Medical history is unremarkable, and she takes no medications.

On physical examination, vital signs are normal. BMI is 32. The remainder of the examination is unremarkable.

Which of the following is the most appropriate management?

(A) Bariatric surgery
(B) Behavioral therapy
(C) Exercise for 45 minutes/day
(D) Low-carbohydrate diet
(E) Phentermine-topiramate

Item 160 H

A 45-year-old man was hospitalized following a head-on motor vehicle crash. On day 4, he survived cardiac arrest but experienced anoxic brain injury. The care team concludes that he has a poor neurologic prognosis and is unlikely to regain consciousness or interact with his environment.

A family meeting is planned to discuss the decision to perform a tracheostomy and percutaneous endoscopic gastrostomy for enteral feeding. His wife reports that the patient has previously stated that he would not want to be kept alive if he could not interact with her or their children. The patient does not have an advance directive.

Which of the following should be the basis for the decision regarding this patient's management?

(A) Patient's best interests
(B) Patient's medical condition
(C) Patient's previously expressed wishes
(D) Risk management

Item 161 H

A 58-year-old man is admitted to the hospital for a 2-week history of worsening constipation. He has end-stage heart failure (New York Heart Association functional class IV) and stage 3 chronic kidney disease. Medications include bisoprolol, furosemide, losartan, spironolactone, hydromorphone (for dyspnea palliation), bisacodyl, lactulose, senna, docusate, and tap water enema.

On physical examination, respiration rate is 20/min; other vital signs are normal. Oxygen saturation is 92% breathing ambient air. Cardiac examination reveals an S_3, jugular venous distention, and peripheral edema. Crackles are auscultated at the lung bases. Moderate abdominal distention is noted, with tenderness to palpation.

H CONT.

Which of the following is the most appropriate treatment of this patient's constipation?

(A) Lubiprostone
(B) Methylnaltrexone
(C) Polyethylene glycol
(D) Sodium phosphate enema

Item 162

An 18-year-old man is brought to the office by his mother, who is concerned about his behavior in school. Since age 6 years, the patient has had difficulty interacting with people and exhibits several unusual, repetitive behaviors, including tapping his fork three times with each bite of food. He has scored well on aptitude tests but has struggled in classroom activities that require working with other students. He has no friends, and his parents find it difficult to engage in conversation with him.

On physical examination, the patient exhibits paucity of speech; he answers yes-or-no questions appropriately. There is no evidence of disordered thinking.

Which of the following is the most likely diagnosis?

(A) Antisocial personality disorder
(B) Autism spectrum disorder
(C) Obsessive-compulsive disorder
(D) Social anxiety disorder

Item 163

A 42-year-old man is seen to discuss recent test results. He is asymptomatic. He has no known medical problems and takes no medications. He does not use tobacco products.

On physical examination, blood pressure is 128/74 mm Hg; other vital signs are also normal. BMI is 24. The remainder of the examination is unremarkable.

Laboratory studies:

Total cholesterol	270 mg/dL (6.99 mmol/L)
LDL cholesterol	170 mg/dL (4.40 mmol/L)
HDL cholesterol	40 mg/dL (1.04 mmol/L)
Triglycerides	300 mg/dL (3.39 mmol/L)

His 10-year risk for atherosclerotic cardiovascular disease based on the Pooled Cohort Equations is 3.4%.

Which of the following is the most appropriate treatment of this patient's hyperlipidemia?

(A) Low-intensity statin therapy
(B) Moderate-intensity statin therapy
(C) High-intensity statin therapy
(D) Therapeutic lifestyle changes

Item 164

A 58-year-old woman is evaluated for a 4-week history of left lateral hip pain. She describes the pain as a moderate ache that intermittently radiates down the lateral aspect of the left leg. It began insidiously and has gradually worsened. The pain worsens when she is climbing stairs or lying on the affected side. She reports no previous trauma to the area. She has not had any leg weakness or swelling or any constitutional symptoms. She has not taken any analgesics for the pain.

On physical examination, vital signs are normal. On palpation, there is tenderness over the left greater trochanter. There is painless full range of motion with abduction, flexion, and external rotation of the left hip. The remainder of the examination is normal.

In addition to activity modification, which of the following is the most appropriate management?

(A) Ibuprofen
(B) Glucocorticoid injection
(C) Hydrocodone/acetaminophen
(D) Plain radiography of the left hip

Item 165

A 56-year-old woman is evaluated for severe vaginal itching and discomfort. Her symptoms have progressively worsened over the last 4 months. There is no associated vaginal discharge or vaginal odor. She is experiencing significant vaginal dryness, and intercourse has become painful despite the use of lubricants. She has been menopausal since age 53 years. She takes no medications.

On physical examination, vital signs are normal. Physical examination reveals dry vaginal epithelium that is smooth and shiny. Blood vessels are visible beneath the pale vaginal mucosa, and increased friability is evident.

Vaginal pH is 6.0. Wet mount shows occasional leukocytes. Whiff test result is negative. There are no clue cells and no hyphae on potassium hydroxide preparation.

Which of the following is the most likely diagnosis?

(A) Acute allergic contact dermatitis
(B) Genitourinary syndrome of menopause
(C) Vulvar lichen planus
(D) Vulvar lichen sclerosus

Item 166

A 64-year-old man is evaluated to establish care. Medical history is significant for long-standing low back pain secondary to traumatic vertebral compression fractures. He has chronic pain that partially responds to heat and relaxation, but he also has several acute exacerbations of pain daily that "immobilize" him and prevent him from working. These episodes do not respond to nonpharmacologic therapy. He has tried multiple nonopioid analgesic agents but discontinued these drugs because of lack of efficacy or side effects. He works from his home as an editor for a sports magazine.

Long-term opioid therapy is considered. Treatment goals, as well as the possibility of discontinuing therapy in the absence of meaningful improvements or if the risks exceed the benefits, are discussed with the patient.

Which of the following is also recommended before prescribing opioid therapy to this patient?

(A) Current Opioid Misuse Measure survey
(B) Naloxone prescription and education

(C) Opioid risk assessment
(D) Psychiatry referral

H

Item 167

A 55-year-old woman is evaluated before partial colectomy for recurrent episodes of diverticulitis. Medical history is otherwise significant for atrial fibrillation and hypertension. Medications are apixaban, hydrochlorothiazide, and metoprolol.

On physical examination, vital signs are normal. BMI is 25. Cardiac examination reveals an irregularly irregular rhythm. Pulmonary examination is normal.

Laboratory studies demonstrate a serum creatinine level of 1.0 mg/dL (88.4 µmol/L), an estimated glomerular filtration rate greater than 60 mL/min/1.73 m², and a hemoglobin level of 13.0 g/dL (130 g/L).

When should this patient's anticoagulant therapy be discontinued before surgery?

(A) 1 Day
(B) 3 Days
(C) 5 Days
(D) 7 Days

Item 168

A 36-year-old man is evaluated for a 3-month history of severely depressed mood; hypersomnia; poor appetite; 6.8-kg (15-lb) weight loss; and loss of interest in family, hobbies, and work. He has not had thoughts of suicide. He has never had similar problems and does not use alcohol, tobacco, or recreational drugs. He wants help but is concerned about the side effects of psychotropic medications. His PHQ-9 score is 13, indicating moderate depression.

Laboratory studies reveal a normal serum thyroid-stimulating hormone level.

Which of the following is the most appropriate treatment?

(A) Amitriptyline
(B) Cognitive behavioral therapy
(C) Paroxetine
(D) Quetiapine

Answers and Critiques

Item 1 Answer: B

Educational Objective: Treat a patient with an LDL cholesterol level higher than 190 mg/dL (4.92 mmol/L).

The most appropriate treatment for primary prevention of atherosclerotic cardiovascular disease (ASCVD) in this patient is high-intensity statin therapy with rosuvastatin or atorvastatin. According to the American College of Cardiology (ACC)/American Heart Association (AHA) cholesterol treatment guideline, patients aged 21 years or older with severe LDL cholesterol elevation (≥190 mg/dL [4.92 mmol/L]) should receive the maximum tolerated statin therapy for primary prevention of ASCVD, regardless of 10-year risk for ASCVD. High-intensity statin therapy is recommended unless there are contraindications to its use. It is reasonable to intensify statin therapy as tolerated to achieve an LDL cholesterol reduction of at least 50%. In contrast to the ACC/AHA recommendation, the U.S. Preventive Services Task Force recommends initiating low- to moderate-intensity statin therapy in adults aged 40 to 75 years without a history of ASCVD who have one or more ASCVD risk factors (dyslipidemia, diabetes mellitus, hypertension, or smoking) and a calculated 10-year ASCVD event risk of 10% or higher.

In the absence of familial hypercholesterolemia, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, such as alirocumab and evolocumab, are not indicated in primary prevention of ASCVD. Cost, treatment burden (injections), and absence of long-term safety data argue against their use in primary prevention. Such treatment might be considered if the patient cannot tolerate statin therapy or if LDL cholesterol cannot be sufficiently reduced in the highest-risk patients.

In patients with an LDL cholesterol level of 190 mg/dL (4.92 mmol/L) or higher, initial treatment with a moderate-intensity statin is less preferred; however, if the patient is unable to tolerate high-intensity therapy, down-titration to moderate-intensity therapy could be considered, especially if adequate LDL cholesterol reduction can be achieved.

An evaluation for secondary causes of hyperlipidemia is also indicated in patients with an LDL cholesterol level of 190 mg/dL (4.92 mmol/L) or higher. The most common secondary causes are obesity, hypothyroidism, biliary obstruction, and nephrotic syndrome. Medications can also increase LDL cholesterol level, and some of the most commonly implicated drugs include cyclosporine, HIV medications (such as protease inhibitors), glucocorticoids, and amiodarone. If a secondary cause is not identified, LDL cholesterol level elevation is considered primary, and family members should undergo screening because severe hypercholesterolemia is often genetically determined, as may be the case with this patient who has a first-degree relative with premature ASCVD.

KEY POINT

- The American College of Cardiology and American Heart Association recommend that patients aged 21 years or older with an LDL cholesterol level of 190 mg/dL (4.92 mmol/L) or higher should receive high-intensity statin therapy for primary prevention of atherosclerotic cardiovascular disease.

Bibliography

Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, et al; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014;129:S1-45. [PMID: 24222016] doi:10.1161/01.cir.0000437738.63853.7a

Item 2 Answer: D

Educational Objective: Use a shared decision-making approach to guide the initiation of breast cancer screening in a younger woman.

This patient should not be screened for breast cancer at this time. In women aged 50 to 74 years, there is a clear benefit to screening mammography, and all breast cancer guidelines recommend screening mammography in this age group. Biennial screening mammography imparts most of the benefit of annual screening mammography with fewer harms, although the recommended screening frequency differs between guidelines. In women younger than 50 years or aged 75 years or older, the balance of benefits and harms is less clear, and screening recommendations vary widely. Most guidelines, including the recommendation statement of the U.S. Preventive Services Task Force (USPSTF), recommend individualized screening decisions for women aged 40 to 49 years based on patient context and values regarding specific benefits and harms. Compared with screening mammography in older women, the USPSTF concludes that, for women in their 40s, the number of women who benefit from screening mammography is smaller, and the harm is higher; however, the benefit still outweighs the harm. Therefore, the value the patient places on averting death from breast cancer compared with the importance she places on avoiding potential harms (false-positive results, anxiety, and overdiagnosis) can help guide her decision. This patient places more importance on avoiding potential harms and therefore should not pursue screening mammography or breast tomosynthesis at this time; no further testing is the best option.

The USPSTF recommends against teaching breast self-examination (BSE), as BSE does not reduce breast cancer mortality and is associated with increased rates of breast biopsy.

The USPSTF found insufficient evidence to assess the balance of benefits and harms of using breast tomosynthesis, or three-dimensional mammography, as a primary screening method for breast cancer; however, National Comprehensive Cancer Network guidelines indicate that breast tomosynthesis can be considered as an initial screening strategy for average-risk women. In studies, breast tomosynthesis is often associated with double the rate of radiation but lower recall rates.

As women progress through their 40s, the number of women who benefit from screening mammography increases, while the chance for harms slightly decreases. A woman's values and preferences may also shift over time; therefore, breast cancer screening should be periodically discussed.

KEY POINT

- The decision to initiate breast cancer screening in women aged 40 to 49 years should be an individualized one based on patient context and values regarding specific benefits and harms.

Bibliography

Nelson HD, Pappas M, Cantor A, Griffin J, Daeges M, Humphrey L. Harms of breast cancer screening: systematic review to update the 2009 U.S. Preventive Services Task Force recommendation. Ann Intern Med. 2016;164:256-67. [PMID: 26756737] doi:10.7326/M15-0970

H Item 3 Answer: C

Educational Objective: Provide extended-duration postoperative pharmacologic venous thromboembolism prophylaxis in a patient undergoing major orthopedic surgery.

The recommended postoperative duration of venous thromboembolism (VTE) prophylaxis with low-molecular-weight heparin (LMWH) following major orthopedic surgery is 35 days in patients who are not at increased bleeding risk and have not experienced perioperative bleeding complications. The American College of Chest Physicians (ACCP) antithrombotic guideline provides recommendations for VTE prophylaxis for both orthopedic and nonorthopedic surgery populations. The ACCP guideline identifies hip arthroplasty, knee arthroplasty, and hip fracture surgery as major orthopedic surgeries. These surgeries pose a high VTE risk, and both pharmacologic and mechanical VTE prophylaxis are recommended during hospitalization. The ACCP recommends LMWH over other pharmacologic agents, although there are other acceptable agents, including aspirin for those unable or unwilling to take heparin. For patients without increased bleeding risk, extended duration of postoperative prophylaxis for up to 35 days is recommended over shorter-duration prophylaxis of 10 to 14 days, which is the minimum recommended duration of pharmacologic VTE prophylaxis in orthopedic surgery. Randomized trials, systematic reviews, and meta-analyses have shown that compared with placebo, aspirin, and warfarin, extended prophylaxis up to 35 days with LMWH reduces the rate of VTE disease without excess bleeding in patients who undergo major orthopedic surgery. If bleeding risk is especially high, mechanical prophylaxis is recommended over no prophylaxis. In patients who decline LMWH injections or who are unable to tolerate LMWH, the oral direct thrombin inhibitor dabigatran, a factor Xa inhibitor (apixaban, rivaroxaban, edoxaban), or a vitamin K antagonist (warfarin) is recommended over alternate forms of prophylaxis. For this patient undergoing major orthopedic surgery, dual perioperative VTE prophylaxis with LMWH and intermittent pneumatic compression is recommended during hospitalization, with LMWH continued for up to 35 days.

Because of the elevated risk for VTE in many patients undergoing orthopedic surgery, a short course of VTE prophylaxis, such as 10 or 14 days, is insufficient because thrombotic risk remains elevated beyond this time frame.

KEY POINT

- For patients undergoing orthopedic surgery without increased bleeding risk, postoperative dual venous thromboembolism prophylaxis with intermittent pneumatic compression and low-molecular-weight heparin is recommended during hospitalization; low-molecular-weight heparin should be continued for up to 35 days.

Bibliography

Falck-Ytter Y, Francis CW, Johanson NA, Curley C, Dahl OE, Schulman S, et al. Prevention of VTE in orthopedic surgery patients: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2012;141:e278S-e325S. [PMID: 22315265]

Item 4 Answer: A

Educational Objective: Treat a patient with neuropathic pain with duloxetine.

The most appropriate treatment for this patient with evidence of painful diabetic peripheral neuropathy and substantial neuropathic pain is initiation of oral duloxetine. Diabetes mellitus can cause various types of neuropathy. The most common pattern is symmetric distal sensory or sensorimotor. It is characterized by a stocking glove distribution that ascends proximally. Diabetic sensorimotor neuropathy frequently presents as a sensation of numbness, tingling, burning, heaviness, pain, or sensitivity to light touch. The pain may worsen at night and with walking. Glycemic control and minimizing cardiovascular risk factors can slow the progression and improve the symptoms of diabetic neuropathy. Treatment of painful neuropathies is symptomatic. Tricyclic antidepressants (amitriptyline, nortriptyline), serotonin-norepinephrine reuptake inhibitors (venlafaxine, duloxetine), antiepileptic drugs (pregabalin, gabapentin, valproic acid), opioids (tapentadol), and topical capsaicin are commonly used. However, only pregabalin, duloxetine, and tapentadol (extended release) have FDA approval for

painful diabetic neuropathy. Although duloxetine and gabapentinoids are considered first-line therapy, they are costly. The dosage of duloxetine is started at 20 mg/d or 30 mg/d and increased to a goal dosage of 60 mg/d. Dosages higher than 60 mg/d have not been shown to be more effective for analgesia.

Hydromorphone is a potent opioid agonist that is typically used in the treatment of cancer-associated pain, whereas tramadol is a weak opioid agonist with analgesic activity that is influenced by inhibition of serotonin and norepinephrine reuptake. Although potentially effective in the treatment of neuropathic pain syndromes, opioids are considered third-line therapy after maximization and combination of neuropathic agents. Studies have shown that most patients with peripheral neuropathies are not treated with appropriate neuropathic agents or adequate dosages of these drugs, and dosages should be maximized before initiating opioids.

The effectiveness of lamotrigine for chronic neuropathic pain was evaluated in a systematic review. The studies included patients with central poststroke pain, diabetic neuropathy, HIV-related neuropathy, intractable neuropathic pain, spinal cord injury–related pain, and trigeminal neuralgia. Only one study of patients with HIV-related neuropathy had a statistically significant result, which was restricted to patients receiving antiretroviral therapy. The authors concluded that there is no role for lamotrigine in the treatment of chronic neuropathic pain.

Topical NSAIDs such as diclofenac (available as a solution, spray, gel, or patch) provide similar pain relief for inflammatory conditions as oral medications with fewer gastrointestinal effects. However, they are significantly more expensive than oral NSAIDs. More importantly, anti-inflammatory agents have not been shown to be effective in the treatment of peripheral neuropathies and would not be indicated in this patient with a neuropathic pain syndrome.

KEY POINT

- Gabapentinoids and serotonin-norepinephrine reuptake inhibitors are first-line therapy for neuropathic pain syndromes.

Bibliography

Watson JC, Dyck PJ. Peripheral neuropathy: a practical approach to diagnosis and symptom management. Mayo Clin Proc. 2015;90:940-51. [PMID: 26141332]

H

Item 5 Answer: C

Educational Objective: Treat depression at the end of life with methylphenidate.

The most appropriate treatment for this patient's depression is methylphenidate. Patients with a serious, life-threatening illness and untreated depression have poorer quality of life, which can lead to increased caregiver stress and burden. Diagnosing depression in terminally ill patients, however, is challenging. Although anticipatory grief is common in patients at the end of life and is considered a normal part of most end-of-life experiences, it can be distinguished from clinical depression by the patient's ability to find enjoyment and a fluctuating mood. Patients with depression at the end of life have symptoms that include hopelessness, pervasive guilt, and worthlessness. Depression in terminally ill patients responds well to both pharmacologic and nonpharmacologic treatments. Tricyclic antidepressants, selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, and mirtazapine are all effective agents. Prognosis should be taken into account because these medications take weeks to reach peak effect. This patient has symptoms consistent with clinical depression as well as a limited life expectancy. Methylphenidate is a rapid-acting psychostimulant that is well tolerated and effective in the treatment of depression; once initiated, results can be seen within 24 to 48 hours. Methylphenidate may also have the benefit of improving cancer-associated fatigue.

Selective serotonin reuptake inhibitors, such as citalopram and sertraline, are effective in the treatment of depression; however, they can take many weeks and dose titration to reach effectiveness. Given this patient's limited life expectancy, a more rapid-acting agent is needed.

Cognitive behavioral therapy, when available, is an effective therapy for patients with depression and a serious medical illness. However, most trials showing benefit are centered on multiweek, if not several-months-long, interventions and are of limited availability for patients on home hospice.

KEY POINT

- Methylphenidate is a rapid-acting psychostimulant that is well tolerated and effective in the treatment of depression at the end of life; results can be seen as quickly as 24 to 48 hours after initiation.

Bibliography

Swetz KM, Kamal AH. Palliative care. Ann Intern Med. 2018;168:ITC33-ITC48. [PMID: 29507970] doi:10.7326/AITC201803060

Item 6 Answer: D

Educational Objective: Treat bacterial conjunctivitis.

The most appropriate treatment is *trimethoprim-polymyxin B ophthalmic drops*. This patient has acute, painless eye redness and several other signs of bacterial conjunctivitis. Studies have identified features that increase the probability of a bacterial cause of conjunctivitis, including redness of the conjunctival membrane obscuring the tarsal vessels, matting of both eyes in the morning, and purulent discharge. Inability to see redness of the eyes at 20 feet decreases the likelihood of a bacterial cause. Antibiotic treatment of bacterial conjunctivitis with topical trimethoprim-polymyxin B or erythromycin can shorten the duration of symptoms, but overall, bacterial conjunctivitis is a self-limited condition from which most patients recover within 2 weeks. Antibiotics should be enlisted when there

is a higher risk for complications, such as in patients who wear contact lenses; immunocompromised patients, such as those with diabetes mellitus; and patients with copious, hyperpurulent discharge of the eye.

Ceftriaxone is used to treat gonococcal infection. Typical patients with gonococcal conjunctivitis are young men with copious purulent discharge and marked conjunctival inflammation. Periocular edema and tenderness, gaze restriction, and preauricular lymphadenopathy are common with gonococcal conjunctivitis.

Because of concerns about antimicrobial resistance and cost, topical fluoroquinolones (such as levofloxacin) are not first-line therapy for routine cases of bacterial conjunctivitis. Topical fluoroquinolones are indicated for conjunctivitis in contact lens wearers as a result of the high incidence of *Pseudomonas* infection.

Olopatadine ophthalmic drops are used for seasonal allergies; the mucopurulent discharge, morning matting of the eyes, and lack of itching make allergic conjunctivitis a less likely cause of this patient's symptoms.

KEY POINT

- Bacterial conjunctivitis is characterized by redness of the conjunctival membrane obscuring the tarsal vessels, matting of both eyes in the morning, and thin mucopurulent discharge; treatment may include topical antibiotics, such as trimethoprim–polymyxin B or erythromycin.

Bibliography

Narayana S, McGee S. Bedside diagnosis of the 'red eye': a systematic review. Am J Med. 2015;128:1220-1224.e1. [PMID: 26169885] doi:10.1016/j.amjmed.2015.06.026

Item 7 Answer: B

Educational Objective: Understand the limitations of the number needed to treat to inform clinical decision making.

The harms and cost of treatment are needed to conclude that treatment A is superior to treatment B. When assessing the clinical impact of an intervention, the number needed to treat (NNT) provides a quantifiable measure of the treatment effect that is easily understood by physicians and patients: it represents the number of patients who must receive a treatment to cause one additional patient to benefit. The acceptability of the NNT as a means of comparing one treatment with another depends on the risks associated with the condition, the cost and side effects of the treatment, and other treatments available. When comparing one treatment with another, head-to-head comparisons provide the best evidence of superiority. In this head-to-head comparison of two treatments, the absolute risk reduction for heart failure–related hospitalizations is 6% with treatment A compared with treatment B. This translates to 17 patients (NNT = 1/absolute risk reduction) who need to receive treatment A to result in 1 less heart failure–related hospitalization compared with treatment B. Although this information is informative, other data, such as cost and harms, must be evaluated before a conclusion that treatment A is superior to treatment B can be reached. If harms are more frequent or more severe with treatment A, the reduction in hospitalization for heart failure may become clinically meaningless.

Confidence intervals (CIs) are a method for indicating the range in which a value derived from a study is likely to lie; narrower ranges imply greater confidence, or certainty, that the reported value is closer to the true value. The *P* value expresses the probability that the findings in a study can be explained by chance alone and represents the level of statistical significance. *P* values offer less information than do CIs because CIs can demonstrate the plausible range of values for an event or outcome, whereas *P* values indicate only statistical significance. Although CIs provide more precise information about the range of expected benefit, the *P* value and CI are of less importance than understanding the harms, costs, and alternative therapies that might be available.

A disadvantage of relative comparisons, including relative risk, is the potential for exaggerated outcomes. For instance, interventions that reduce the rate of an outcome from 40% to 20% or from 4% to 2% have a relative risk reduction of 50%. However, the absolute risk reduction for the first case is 20%, whereas the absolute risk reduction for the second case is 2%.

KEY POINT

- The acceptability of the number needed to treat as a means of comparing one treatment with another depends on the risks associated with the condition, the cost and side effects of the treatment, and other treatments available.

Bibliography

Citrome L, Ketter TA. When does a difference make a difference? Interpretation of number needed to treat, number needed to harm, and likelihood to be helped or harmed. Int J Clin Pract. 2013;67:407-11. [PMID: 23574101] doi: 10.1111/ijcp.12142

Item 8 Answer: D

Educational Objective: Treat acute bacterial prostatitis after a urologic procedure.

This patient's history and physical examination findings indicate acute bacterial prostatitis, and the most appropriate treatment regimen is trimethoprim-sulfamethoxazole. Patient groups at high risk for acute bacterial prostatitis include those with diabetes mellitus, immunosuppression, or cirrhosis. Risk factors include unprotected sexual intercourse, urogenital instrumentation (chronic indwelling bladder catheterization, intermittent bladder catheterization, prostate biopsy), urinary tract manipulation (prostate resection), urinary stasis (obstruction), and benign prostatic hyperplasia. The most common infectious cause for acute bacterial prostatitis is *Escherichia coli* or other gram-negative bacilli. Diagnosis is typically established with

urine Gram stain and culture in patients with a compatible history. The treatment of choice for acute bacterial prostatitis is a prolonged course of trimethoprim-sulfamethoxazole or ciprofloxacin. Data on treatment duration are sparse, but 6 weeks is reasonable and recommended by experts. Given the prolonged duration of antimicrobial therapy required in cases of acute bacterial prostatitis, it is most prudent to select an antibiotic with appropriate coverage, while also attempting to minimize the potential for serious adverse effects. Prolonged ciprofloxacin use has been associated with QT prolongation as well as tendinopathy/tendon rupture, especially in older adults. As such, given the treatment duration needed for acute bacterial prostatitis, trimethoprim-sulfamethoxazole would be the most appropriate choice.

Amoxicillin would be an appropriate choice for patients with acute prostatitis and gram-positive cocci in chains. This finding would suggest an enterococcal infection, and treatment with amoxicillin or ampicillin would be appropriate. Neither of these antibiotics would be effective for acute bacterial prostatitis caused by *E. coli* or other gram-negative bacilli.

Men younger than 35 years who are sexually active and men older than 35 years who engage in high-risk sexual behavior should be treated with regimens that cover *Neisseria gonorrhoeae* and *Chlamydia trachomatis*. Ceftriaxone and doxycycline, or ceftriaxone and azithromycin, would be appropriate treatment choices in cases of acute epididymitis, specifically targeting *C. trachomatis* or *N. gonorrhoeae*. Neither regimen would be appropriate in this case.

Cephalexin would be an appropriate choice for patients with acute prostatitis and gram-positive cocci in clusters suggesting infection with *Staphylococcus aureus* or coagulase-negative staphylococci (*Staphylococcus epidermidis* or *Staphylococcus saprophyticus*).

KEY POINT

- The most common infectious cause of acute bacterial prostatitis is *Escherichia coli* or other gram-negative bacilli; the treatment of choice is a prolonged course of trimethoprim-sulfamethoxazole or ciprofloxacin.

Bibliography

Gill BC, Shoskes DA. Bacterial prostatitis. Curr Opin Infect Dis. 2016;29:86-91. [PMID: 26555038] doi:10.1097/QCO.0000000000000222

Item 9 Answer: A

Educational Objective: Manage vaccination of a health care worker.

This patient should receive a second dose of the measles, mumps, and rubella (MMR) vaccine. In all immunocompetent adults who lack documented immunity against measles, mumps, and rubella, at least one dose of the MMR vaccine should be administered. Health care workers are at increased risk for acquiring and transmitting measles, mumps, and rubella and should receive a second dose of the MMR vaccine at least 28 days after the first dose. A second dose should also be administered to postsecondary students and international travelers. For persons who have been previously vaccinated with two doses of a mumps virus-containing vaccine but are at increased risk because of an outbreak, the Advisory Committee on Immunization Practices recommends administering a third dose of mumps virus-containing vaccine to improve protection.

This patient's status as a health care worker does not necessitate administration of the hepatitis A vaccine, despite serologic tests indicating that he lacks immunity. The hepatitis A vaccine should be administered to patients who are at increased risk for infection or complications of infection, such as those who work or travel to endemic areas, men who have sex with men, individuals with chronic liver disease, illicit drug users, persons with clotting disorders, persons who conduct hepatitis A-related research, and household or close contacts of adopted children from endemic areas. Hepatitis A vaccination is also indicated in persons who desire vaccination and could be administered to this patient if he wishes.

Hepatitis B vaccination is indicated in all health care workers who lack immunity. This patient has a positive hepatitis B surface antibody test result, whereas his surface antigen and core antibody levels are undetectable. This pattern is consistent with prior vaccination with an appropriate immune response. As such, hepatitis B vaccination is unnecessary in this patient.

Pneumococcal vaccination is recommended in all adults aged 65 years and older and adults aged 19 to 64 years with certain high-risk conditions. This patient does not have any chronic medical conditions and is also a nonsmoker; therefore, vaccination with the 23-valent pneumococcal polysaccharide vaccine is not indicated.

KEY POINT

- Health care workers are at increased risk for acquiring and transmitting measles, mumps, and rubella and should receive a second dose of the MMR (measles, mumps, and rubella) vaccine.

Bibliography

Kim DK, Riley LE, Hunter P; Advisory Committee on Immunization Practices. Recommended immunization schedule for adults aged 19 years or older, United States, 2018. Ann Intern Med. 2018;168:210-220. [PMID: 29404596] doi:10.7326/M17-3439

Item 10 Answer: B

Educational Objective: Manage an in-flight medical emergency by connecting to the ground-based physician.

The most appropriate next step in management is to connect with the ground-based physician. In-flight medical emergencies are relatively common during air travel, occurring in an estimated 1 of 600 flights. Airlines based in the United States are mandated by the Federal Aviation Administration to carry at least one automated external defibrillator; supplemental oxygen; and a medical kit that contains a stethoscope, sphygmomanometer, gloves, airway supplies, intravenous access supplies, and some basic medications. In the case of an in-flight emergency, the physician's role generally

involves assessing the patient, establishing a diagnosis when possible, administering basic medical treatments, providing reassurance as appropriate, and recommending flight diversion if necessary. Physicians should practice within their scope of training, be mindful of patient privacy, and document the patient encounter. Although not a Federal Aviation Administration requirement, most airlines have contracts with 24-hour call centers with a ground-based physician to aid in the event of an in-flight emergency. Often, ground-based physicians trained in emergency or aerospace medicine can assist the on-board physician remotely and help direct care, which can be particularly helpful when the medical problem is outside the scope of the physician's practice.

The principles of hypobaric hypoxia apply to commercial airplanes, in which cabins are pressurized to the equivalent of 1500 to 2500 meters (approximately 5000 to 8200 feet) in altitude, resulting in an inspired oxygen tension between 110 and 120 mm Hg (about 70% of the levels encountered at sea level). Although this correlates with an arterial Po_2 of approximately 60 mm Hg (8.0 kPa) in healthy individuals, those with underlying pulmonary disease are at risk for significant hypoxemia during a flight. This patient will have no difficulty maintaining her oxyhemoglobin saturation above 90%, and asking the pilot to descend to a lower altitude will serve no useful purpose. A better strategy is to contact the ground-based physician.

Although this patient is dizzy and weak, her clinical status and vital signs appear stable. She needs further medical evaluation and management; however, flight diversion is probably not indicated at this time. Furthermore, the ground-based medical team can also help determine whether flight diversion is needed.

KEY POINT

- In most in-flight medical emergencies, the physician's role involves assessing the patient, establishing a diagnosis when possible, administering basic medical treatments, providing reassurance as appropriate, and recommending flight diversion if necessary.

Bibliography

Nable JV, Tupe CL, Gehle BD, Brady WJ. In-flight medical emergencies during commercial travel. N Engl J Med. 2015;373:939-45. [PMID: 26332548] doi:10.1056/NEJMra1409213

Item 11 Answer: A

Educational Objective: Counsel an older patient with risk factors for a motor vehicle accident.

This patient should be advised to retire from driving. Driving assessments are qualitative and rely heavily on clinical judgment. The more risk factors for a motor vehicle accident that an older driver has, the higher the risk for an adverse event while driving. Drivers at highest risk should be counseled to retire from driving. This patient has multiple risk factors for unsafe driving, including cognitive impairment, self-restrictions in driving (does not drive after dark or on the interstate highway, drives within a 10 mile radius of home), minor accidents, and concerns from family members about driving safety. His other risk factors include impaired mobility, hearing decline, and medical conditions with increased risk for loss of consciousness. Physician advice to retire from driving is associated with older drivers appropriately discontinuing driving. Given the risk for depression and social isolation associated with driving retirement, however, this advice should be coupled with suggestions for alternate forms of transportation and follow-up assessment of his mood and quality of life.

Detailed neuropsychological testing is especially useful for the following patients: (1) those with milder cognitive symptoms to determine whether cognitive difficulties are within the realm of normal age-associated cognitive decline versus mild cognitive impairment; (2) those with definite dementia, diagnosed on the basis of clinical impression and results of screening cognitive tests, who have clinical features overlapping two or more underlying pathologic processes; and (3) those with cognitive symptoms whose clinical picture is confounded by significant depression. The results of neuropsychological testing are unlikely to change the recommendation to retire from driving considering this patient's multiple risk factors.

If a patient is resistant to advice to retire from driving, a formal occupational therapy driving evaluation may be helpful.

Given his numerous observable risk factors, this patient should not be reassured that he is competent to drive.

KEY POINT

- The more risk factors for a motor vehicle accident that an older driver has, the higher the risk for an adverse event while driving.

Bibliography

Martin AJ, Marottoli R, O'Neill D. Driving assessment for maintaining mobility and safety in drivers with dementia. Cochrane Database Syst Rev. 2013:CD006222. [PMID: 23990315] doi:10.1002/14651858.CD006222.pub4

Item 12 Answer: D

Educational Objective: Evaluate a patient with symptoms of systemic exertion intolerance disease.

No further diagnostic testing is required in this patient. She meets the diagnostic criteria for systemic exertion intolerance disease (SEID), with fatigue of at least 6 months' duration accompanied by substantial reduction in preillness activities, postexertional malaise, unrefreshing sleep, and either cognitive impairment or orthostatic intolerance. Although the pathophysiology of SEID remains unclear, the phenomenon of central sensitization (the pathophysiologic dysregulation of the thalamus, hypothalamus, and amygdala) is gaining acceptance as a potential cause of SEID as well as of other highly prevalent comorbid conditions.

including fibromyalgia, mood disturbances, irritable bowel syndrome, and interstitial cystitis. This patient's history, examination, and previous diagnostic test results point to central sensitization, as demonstrated by the constellation of such symptoms as diffuse arthralgia and myalgia, chronic fatigue, bowel and bladder irritability, chronic headaches, brain fog, paresthesias, and unrefreshing sleep. In patients with SEID, the history and physical examination should guide the choice of diagnostic tests. It is reasonable to obtain a complete blood count, creatine kinase (for myalgia), electrolyte panel, thyroid-stimulating hormone level, fasting glucose level, and kidney and liver chemistry tests; however, unnecessary laboratory, imaging, and invasive studies should be avoided because most patients will have unrevealing findings, which provide no lasting reassurance to patients. In this case, the diagnostic evaluation should be limited unless there is compelling new information to warrant further testing.

Antinuclear antibody testing is an effective screening tool for systemic lupus erythematosus; however, myalgia, arthralgia, and fatigue are insufficient reasons to test for antinuclear antibodies unless accompanied by objective findings of systemic lupus erythematosus.

Patients at moderate to high risk for obstructive sleep apnea should undergo further testing, including a home sleep study or polysomnography. On the basis of this patient's presentation (female, young, normal BMI and neck circumference, lack of daytime sleepiness), she is considered to be at low risk for obstructive sleep apnea, and further sleep testing is not warranted.

Serum cortisol testing is unnecessary in this patient who is not manifesting findings that are suggestive of adrenal failure or insufficiency, such as hypotension, tachycardia, hyponatremia, and hyperkalemia.

KEY POINT

- In patients with fatigue without a clear cause, it is reasonable to obtain a complete blood count, electrolyte panel, thyroid-stimulating hormone level, fasting glucose level, and kidney and liver chemistry tests; unnecessary laboratory, imaging, and invasive studies should be avoided.

Bibliography

Committee on the Diagnostic Criteria for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome, Board on the Health of Select Populations, Institute of Medicine. Beyond Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Redefining an Illness. Washington, DC: National Academies Press; 2015. [PMID: 25695122]

Item 13 Answer: B

Educational Objective: **Evaluate a patient suspected of having cauda equina syndrome.**

This patient should undergo emergent MRI of the lumbosacral spine. His history and physical examination findings are concerning for cauda equina syndrome, which is a surgical emergency. Cauda equina syndrome is most commonly caused by a large disk herniation, but it can also result from direct trauma, infection, or malignancy. Symptoms include low back pain with radiation to the legs, saddle anesthesia, bowel and/or bladder dysfunction, erectile dysfunction, and leg weakness. On physical examination, absent or decreased perianal sensation, diminished anal sphincter tone, hypoactive or absent ankle reflexes, and focal sensory and muscle weakness are commonly present. MRI is considered the gold standard for diagnosing cauda equina syndrome.

CT can be obtained in patients suspected of having cauda equina syndrome who are unable to undergo MRI. However, MRI is considered to be better at visualizing the soft tissue structures of the cauda equina than CT and is therefore the preferred imaging modality in patients who can undergo either procedure, such as this one.

Although plain radiography can be performed when there is concern for metastatic cancer to the vertebral bodies, it has no value in visualizing the soft tissue structures of the cauda equina and therefore is not the preferred imaging modality in cases of suspected cauda equina syndrome.

Signs that urgent surgical intervention may be necessary include bowel- or bladder-sphincter dysfunction, particularly urine retention or urinary incontinence; diminished perineal sensation, sciatica, or sensory motor deficits; and bilateral or unilateral motor deficits that are severe and progressive. Forgoing imaging in this patient and failing to provide definitive surgical intervention could result in permanent neurologic deficits.

KEY POINT

- Nerve root involvement of the cauda equina requires immediate imaging, preferably with MRI, and surgical intervention to prevent permanent neurologic damage.

Bibliography

Chou R. In the clinic. Low back pain. Ann Intern Med. 2014;160:ITC6-1. [PMID: 25009837]

Item 14 Answer: D

Educational Objective: **Evaluate a breast mass in a woman younger than 30 years.**

The most appropriate diagnostic test for this young woman with a breast mass is ultrasonography. A breast mass is characterized by a lesion that persists throughout the menstrual cycle and differs from the surrounding breast tissue and the corresponding area in the contralateral breast. The differential diagnosis of a palpable breast mass includes abscess, cyst, fat necrosis, fibroadenoma, and neoplasm. Evaluation of a palpable breast mass varies based on the patient's age and risk factors and the degree of clinical suspicion. Mammography and ultrasonography are the initial imaging modalities. Ultrasonography is often preferred in women younger than 30 years because increased breast tissue density in younger women limits the usefulness of mammography. Ultrasonography may also be a better choice for young women and

pregnant patients in order to avoid radiation exposure. The main utility of ultrasonography is its ability to differentiate cystic from solid lesions. A cyst is likely to be benign if it has symmetric, round borders with no internal echoes. A solid lesion with uniform borders and uniformly sized internal echoes is consistent with a benign fibroadenoma. In this patient with relatively low-risk clinical symptoms, ultrasonography is preferred. The description of the mass (firm, nontender, mobile mass with well-defined margins and no lymphadenopathy) suggests a benign finding, such as a fibroadenoma or cyst. If the ultrasound shows a simple cyst, no further evaluation is necessary, unless the patient is symptomatic. If the ultrasound reveals a solid lesion, it must be evaluated completely with biopsy.

An image-directed core-needle biopsy of a breast mass would be recommended if an ultrasound shows a solid-appearing, suspicious (Breast Imaging Reporting and Data System [BI-RADS] category 4) or highly suspicious (BI-RADS category 5) mass. This patient must undergo ultrasonography to determine the BI-RADS category of the mass before a decision on whether to perform a biopsy can be made.

The dense breast tissue often found in young women limits the sensitivity, and hence the effectiveness, of mammography. Therefore, mammography is generally not needed for young women with a low-risk breast mass.

For women aged 30 years or older with a palpable breast abnormality, both diagnostic mammography and ultrasonography would be recommended. Because this patient is younger than 30 years, only ultrasonography is warranted at this time.

KEY POINT

- For women younger than 30 years with a low-risk breast mass, ultrasonography is usually the only imaging required.

Bibliography

Lehman CD, Lee AY, Lee CI. Imaging management of palpable breast abnormalities. AJR Am J Roentgenol. 2014;203:1142-53. [PMID: 25341156] doi:10.2214/AJR.14.12725

Item 15 Answer: A

Educational Objective: Diagnose bipolar disorder.

The most likely diagnosis is bipolar disorder. This patient exhibits multiple symptoms of depression (anhedonia, sleep disturbance, feelings of worthlessness, suicidal ideation), but he also has a history of at least one previous manic episode, manifested by increased energy, decreased need for sleep, grandiose thinking, and risky behavior. This patient's clinical picture of depression and one or more episodes of mania is most consistent with a diagnosis of bipolar disorder. In patients with bipolar disorder, dysfunction is often extreme, and the associated lifetime risk for suicide is high (6%-15%). Referral to a psychiatrist should be strongly considered when resources are available.

Generalized anxiety disorder is characterized by excessive anxiety about activities or events occurring more days than not for at least 6 months and causing significant distress or functional impairment. Patients with this disorder often experience fatigue and sleep disturbance but do not have a history of mania or meet diagnostic criteria for a major depressive disorder.

More than half of patients with bipolar disorder initially present with a depressive episode. However, presence of manic episodes in this patient excludes major depressive disorder as the diagnosis. Recognition of previous manic or hypomanic episodes is crucial because the treatment of depression in bipolar disorder requires mood stabilizers (such as carbamazepine, lithium, or valproic acid), either alone or in combination with antidepressants. Treatment with antidepressants alone may increase the risk for mania and hypomania.

Patients with schizophrenia have negative symptoms, such as flattened affect and decreased activity, in combination with positive symptoms, including hallucinations and disorganized thought. This patient has no positive symptoms.

KEY POINT

- More than half of patients with bipolar disorder initially present with a depressive episode; however, recognition of previous manic or hypomanic episodes is crucial because the treatment of bipolar disorder requires mood stabilizers, either alone or in combination with antidepressants.

Bibliography

Frye MA. Clinical practice. Bipolar disorder—a focus on depression. N Engl J Med. 2011;364:51-9. [PMID: 21208108] doi:10.1056/NEJMcp1000402

Item 16 Answer: A

Educational Objective: Treat an obese patient with bariatric surgery.

This patient with obesity-related comorbid conditions and no weight loss success after a trial of comprehensive lifestyle modifications meets the criteria for referral for bariatric surgery. Bariatric surgery should be considered for patients who do not lose weight with lifestyle modifications, with or without pharmacologic therapy, and have a BMI of 40 or greater or a BMI of 35 or greater with obesity-related comorbid conditions, such as type 2 diabetes mellitus, coronary artery disease, obstructive sleep apnea, or osteoarthritis. Studies comparing bariatric surgery with nonsurgical treatment (diet, exercise, behavioral modification, and medications) have shown that participants randomly assigned to bariatric surgery lost more weight and were more likely to experience remission of type 2 diabetes and metabolic syndrome, improved quality of life, and reduced medication use. Evidence suggests that bariatric surgery is also associated with reduced mortality and improvement of obstructive sleep apnea, osteoarthritis, and other conditions.

Lorcaserin is approved as adjunctive therapy to comprehensive lifestyle modification in the treatment of overweight

and obesity. This patient is already taking liraglutide, another approved pharmacologic agent for obesity, and has tried but not responded to a third approved agent, orlistat. He is unlikely to benefit from the addition of lorcaserin to his medication regimen.

Behavioral therapy for obesity may include the use of a trained interventionist, such as a nutritionist or dietician. This patient is already participating in a comprehensive behavioral therapy plan that includes nutritional counseling; a separate referral to a dietician is unnecessary. Behavioral therapy is also less likely than bariatric surgery to be successful in this patient.

Very-low-calorie diets are recommended when rapid weight loss is medically indicated. Their use requires close medical supervision with frequent office visits and laboratory monitoring. In this patient, there is no indication for rapid weight loss that would warrant the use of a very-low-calorie diet.

KEY POINT

- Bariatric surgery should be considered in patients who do not lose weight with lifestyle modifications and have a BMI of 40 or greater, or a BMI of 35 or greater with obesity-related comorbid conditions, such as type 2 diabetes mellitus, coronary artery disease, obstructive sleep apnea, or osteoarthritis.

Bibliography

Jensen MD, Ryan DH, Apovian CM, Ard JD, Comuzzie AG, Donato KA, et al; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society. Circulation. 2014;129:S102-38. [PMID: 24222017] doi:10.1161/01.cir.0000437739.71477.ee

Item 17 Answer: A

Educational Objective: Treat ACE inhibitor–induced chronic cough.

The most appropriate management is discontinuation of lisinopril. This patient has chronic cough, defined as cough lasting more than 8 weeks. When smoking and use of an ACE inhibitor are eliminated, the most common causes of chronic cough are upper airway cough syndrome (UACS), gastroesophageal reflux disease, and asthma. Evaluation of chronic cough begins with a thorough history, physical examination, and chest radiography. If the initial evaluation is unrevealing and the patient is taking ACE inhibitor therapy, discontinuation of the ACE inhibitor is the most appropriate first step in management. Up to 20% of patients taking an ACE inhibitor develop a dry cough, usually within 1 to 2 weeks of therapy initiation. Onset of cough, however, may be delayed by months in a small percentage of patients. Cessation of ACE inhibitor therapy usually results in resolution of the cough within 2 weeks. Rechallenge with an ACE inhibitor will result in return of the cough in two thirds of patients and is not recommended. In patients whose blood pressure responded to ACE inhibitor therapy or who require renin-angiotensin system inhibition, an angiotensin receptor blocker can be tried because this class of drugs is associated with a lower incidence of cough.

If a cause of chronic cough is not determined after initial evaluation, and smoking and ACE inhibitor therapy have been discontinued, a stepwise approach is pursued, beginning with a 2-week trial of empiric treatment for UACS. UACS related to allergic rhinitis is best treated with intranasal glucocorticoids, whereas UACS due to nonallergic rhinitis should be treated with first-generation antihistamines and decongestants. This patient has no findings suggestive of allergic rhinitis and has not yet discontinued ACE inhibitor therapy; therefore, an intranasal glucocorticoid should not be initiated.

If chronic cough does not respond to empiric treatment for UACS, evaluation of asthma with spirometry (or empiric treatment) is warranted. If results of spirometry are negative for asthma, bronchial hyperresponsiveness testing should be pursued.

Proton pump inhibitor therapy is indicated in patients with chronic cough when symptoms of gastroesophageal reflux are present or when chronic cough persists despite empiric therapy for UACS or empiric treatment for asthma and nonasthmatic eosinophilic bronchitis with inhaled glucocorticoids.

KEY POINT

- In patients with chronic cough who have a normal chest radiograph and are taking an ACE inhibitor, the first intervention is discontinuation of the ACE inhibitor.

Bibliography

Irwin RS, Baumann MH, Bolser DC, Boulet LP, Braman SS, Brightling CE, et al. Diagnosis and management of cough executive summary: ACCP evidence-based clinical practice guidelines. Chest. 2006;129:1S-23S. [PMID: 16428686] doi:10.1378/chest.129.1_suppl.1S

Item 18 Answer: D

Educational Objective: Manage a patient who has undergone direct-to-consumer genetic testing.

This patient should be advised that no further testing is necessary and should be educated on the limitations of direct-to-consumer (DTC) genetic testing. DTC genetic testing is a commercial service that allows patients to obtain genetic information for a low cost and without referral from a physician. These tests estimate the risk for many common medical conditions by genotyping polymorphic nucleotides. Single-nucleotide polymorphisms (SNPs) that are disproportionately found in affected individuals are identified, and odds ratios for each SNP are determined. The SNPs are usually common but have low penetrance (that is, most people with an SNP do not develop disease). Individually, SNPs contribute very little to overall disease risk; most SNPs have an odds ratio of less than 1.5. Because

counseling or education is not typically provided before or after the DTC genetic test is obtained, patients are generally unable to accurately interpret the results and may request guidance or additional testing from their physicians. This patient's absolute risk for developing prostate cancer based on the test results is extremely small; therefore, no further testing is required.

Screening for prostate cancer in asymptomatic, average-risk men is controversial, and recommendations vary among professional organizations and frequently change. However, no guidelines support performing a digital rectal examination (DRE) to screen for prostate cancer. The overall sensitivity of DRE does not exceed 60%, whereas the specificity is greater than 90%; the positive predictive value of an abnormal DRE is 28%. As such, there is no indication for this test either alone or in combination with serum prostate-specific antigen (PSA) level measurement.

The U.S. Preventive Services Task Force recommends that clinicians discuss potential benefits and harms of PSA-based screening for prostate cancer in men aged 55 to 69 years. The decision to proceed with PSA level measurement should be individualized based on the patient's beliefs and values. In this 46-year-old patient, obtaining a serum PSA level is not indicated. The patient's family history of prostate cancer at an advanced age does not significantly increase his risk for cancer. He has a low pretest probability of prostate cancer, and a positive test result will likely be false positive. Nevertheless, patients with positive test results often undergo biopsy with the attendant risks of infection, bleeding, pain, and anxiety.

KEY POINT

- Patients who undergo direct-to-consumer genetic testing should be advised of the risks and limitations of these tests, including the possibility for misinterpretation.

Bibliography

Burke W, Trinidad SB. The deceptive appeal of direct-to-consumer genetics. Ann Intern Med. 2016;164:564-5. [PMID: 26925528] doi:10.7326/M16-0257

Item 19 Answer: B

Educational Objective: Evaluate unilateral tinnitus and hearing loss.

The most appropriate management is MRI of the internal auditory canal. The assessment of tinnitus must differentiate more dangerous causes (such as neoplasms or cerebrovascular conditions) from more benign causes (such as infections or drugs). Most commonly, tinnitus is bilateral; unilateral tinnitus may indicate more serious pathology. Patients with unilateral tinnitus should undergo prompt hearing testing; if hearing loss is documented, as in this case, the patient should undergo MRI of the internal auditory canal to rule out an acoustic neuroma. It is important to note that patients who present with tinnitus may not report hearing loss that is subsequently revealed on audiologic testing.

The type of tinnitus is an important factor in the evaluation. Pulsatile tinnitus, when synchronous with the heartbeat, may suggest a vascular anomaly, including atherosclerotic disease, arteriovenous fistulas, or paragangliomas, most commonly in the jugular bulb or tympanic arteries of the middle ear. A patient with pulsatile tinnitus should be examined for bruits over the neck, periauricular area, temple, orbit, and mastoid areas. If the physical examination findings do not explain the pulsatile tinnitus, noninvasive intracranial imaging, including CT angiography or MR angiography, should be performed. This patient does not have pulsatile tinnitus but does have unilateral hearing loss. Therefore, imaging of the internal auditory canal for acoustic neuroma will be of higher diagnostic yield than vascular imaging.

This patient's primary symptom is tinnitus, with accompanying asymptomatic hearing loss. A hearing aid is more likely to be of use in a patient with symptomatic hearing loss. More importantly, the priority in this patient is excluding an acoustic neuroma, not hearing aid placement.

This patient's tinnitus is gradual in onset and requires further evaluation. However, the patient does not need urgent referral to an otolaryngologist. Patients should be urgently referred when tinnitus is associated with symptoms suggesting serious, reversible underlying pathology, including sudden sensorineural hearing loss, pulsatile tinnitus, vestibular symptoms, ear pain, or drainage or malodor that fails to resolve.

KEY POINT

- Tinnitus associated with unilateral sensorineural hearing loss suggests acoustic neuroma and requires advanced imaging with MRI.

Bibliography

Baguley D, McFerran D, Hall D. Tinnitus. Lancet. 2013;382:1600-7. [PMID: 23827090] doi:10.1016/S0140-6736(13)60142-7

Item 20 Answer: D

Educational Objective: Treat severe dyspnea.

The most appropriate treatment for this patient is pulmonary rehabilitation. Pulmonary rehabilitation is recommended for all symptomatic patients with an FEV_1 less than 50% of predicted and specifically for those hospitalized with an acute exacerbation of COPD. These programs include education, functional assessment, nutrition counseling, and follow-up to reinforce behavioral techniques for change. They also include an exercise training component that has been shown to improve endurance, flexibility, and upper and lower body strength. Exercise training can provide sustained benefit for postexacerbation symptoms (such as breathlessness) following the completion of even a single rehabilitation program. When combined with other forms of therapy (medical therapy, smoking cessation, nutrition counseling, and education), pulmonary rehabilitation decreases patients' perceived intensity of breathlessness,

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reduces dyspnea and fatigue, facilitates increased participation in daily activities, and enhances health-related quality of life, including improvements in anxiety and depression.

This patient has heart failure with preserved ejection fraction but no physical examination findings that suggest volume overload. Thus, initiation of furosemide is not indicated at this time.

Although this patient has severe dyspnea in the setting of advanced COPD, her oxygen saturation is preserved with 1 L/min oxygen by nasal cannula at rest and during a 6-minute walk test. Additional oxygen therapy will not relieve dyspnea or improve clinical outcomes.

Glucocorticoids, such as prednisone, can be an effective treatment in the setting of a COPD exacerbation, which is defined as a sustained worsening of a patient's COPD. Exacerbations are marked by increased breathlessness and are usually accompanied by increased cough and sputum production. This patient has stable chronic dyspnea on exertion and no other findings that would suggest an exacerbation.

KEY POINT

- Pulmonary rehabilitation can provide significant benefits for patients with chronic lung disease and has been shown to improve subjective dyspnea in patients with severe COPD and following an acute exacerbation of COPD.

Bibliography

Cortopassi F, Gurung P, Pinto-Plata V. Chronic obstructive pulmonary disease in elderly patients. Clin Geriatr Med. 2017;33:539-552. [PMID: 28991649]

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Item 21 Answer: A

Educational Objective: Evaluate a patient with decompensated liver disease who is scheduled for elective surgery.

The most appropriate preoperative management is to cancel surgery and refer the patient for liver transplant evaluation. Patients with cirrhosis but no complications are referred to as having compensated cirrhosis; they may be asymptomatic or may have nonspecific symptoms, such as fatigue, poor sleep, muscle cramps, feeling cold, or itching. Patients with complications of cirrhosis (hepatic encephalopathy, variceal hemorrhage, ascites, spontaneous bacterial peritonitis, hepatorenal syndrome, jaundice, or hepatocellular carcinoma) are referred to as having decompensated cirrhosis. Referral to a transplant center is indicated for patients with decompensation or a Model for End-stage Liver Disease (MELD) score of greater than 15. The MELD score is an equation that incorporates bilirubin, INR, and serum creatinine levels, and it accurately predicts 3-month survival. This patient, who has decompensated liver disease with a MELD score of 22, which confers a 30-day surgical mortality risk of more than 50%, should avoid elective surgery. Patients with decompensated liver disease have not only a higher perioperative mortality rate but also a significantly increased risk for other complications, including encephalopathy, electrolyte derangements, fluid imbalance, coagulopathy, infection, acute kidney injury, and hepatorenal syndrome. It is reasonable to refer patients at intermediate risk to a hepatologist before proceeding with surgery. Patients with compensated liver disease are often able to proceed with surgery with optimal medical management.

The deciding factor in this case is not the patient's duration of sobriety but the presence of decompensated liver disease and an unacceptably high MELD score. Elective surgery should be avoided until these risks are mitigated with liver transplantation.

The American Association for the Study of Liver Diseases recommends against perioperative transjugular intrahepatic portosystemic shunts, stating that there is no reliable perioperative evidence of improved clinical outcomes.

KEY POINT

- Patients with decompensated liver disease should avoid elective surgery and be referred for liver transplant evaluation.

Bibliography

Rai R, Nagral S, Nagral A. Surgery in a patient with liver disease. J Clin Exp Hepatol. 2012;2:238-46. [PMID: 25755440]

Item 22 Answer: E

Educational Objective: Provide culturally sensitive care to a transgender patient.

This patient requires symptomatic treatment of his viral upper respiratory tract symptoms. In general, examination of an organ system should be related to the patient's symptoms. This patient's gender identity is not relevant to the reason for the visit; therefore, obtaining a detailed gender-related history (hormonal, surgical, social, and sexual) and performing a genital examination are unnecessary. Additionally, these interventions may make this nervous patient feel more uncomfortable and potentially dissuade him from returning for important ongoing health care.

A comprehensive history of a transgender person is usually not possible to obtain in one visit; it is best obtained over time in order to build rapport with the patient. In general, history taking is similar in transgender and nontransgender patients and should include family, reproductive, sexual, psychiatric, and social histories. Elements of the history that are unique to the transgender population are hormonal and surgical therapies related to gender transition.

Recommendations for sexually transmitted infection (STI) screening are the same for transgender patients as for nontransgender patients. Screening should take into account the patient's anatomy and sexual history. As it would be inappropriate to perform STI screening in a nontransgender patient during a first-time visit for unrelated episodic care, it would also be inappropriate to screen this patient today. STI screening is important and should be performed; however, it can wait until patient rapport

has been established and a more detailed history has been obtained to guide screening.

Many online resources are available for learning about transgender persons and providing culturally sensitive medical care. The University of California, San Francisco, has published guidelines for primary and gender-affirming care of transgender and gender nonbinary persons at http://transhealth.ucsf.edu/protocols. Additionally, the National Lesbian, Gay, Bisexual, and Transgender (LGBT) Health Education Center, a program of the Fenway Institute, provides learning modules at www.lgbthealtheducation.org/lgbt-education/learning-modules/.

KEY POINT

- Irrespective of gender presentation, physicians should provide care for all patients in a sensitive, respectful, and affirming manner.

Bibliography

Lewis EB, Vincent B, Brett A, Gibson S, Walsh RJ. I am your trans patient. BMJ. 2017;357:j2963. [PMID: 28667010] doi:10.1136/bmj.j2963

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Item 23 Answer: D

Educational Objective: **Use a discharge summary to improve patient safety at transitions of care.**

Communicating with and sharing the discharge summary with the primary care physician is recommended to improve patient safety and reduce rehospitalization in this patient. The evidence to support a reduction in hospital readmissions with completion of a discharge summary is mixed, most likely because of many complex factors that are difficult to control, such as timeliness, completeness, and quality of the discharge summary. However, the Institute for Healthcare Improvement identifies the lack of a timely discharge summary as a barrier to patient safety and prevention of early hospital readmission and therefore recommends a timely discharge summary as a key element in improving the transition of care from hospital to home. A discharge summary should include the evaluations performed, medication reconciliation, pending test results, required follow-up tests, and follow-up appointments and should be shared with the follow-up clinician. Timely follow-up with the primary care clinician is also important in ensuring that the transition goes smoothly. Another approach that has been successful in reducing hospitalization is the use of multiple team members, such as a nurse and pharmacist, to provide components of care.

A systematic review found that implementation of an intensive home visitation program reduced the risk for hospital readmission for heart failure at 3 to 6 months. This intervention included a series of eight planned home visits, the first within 24 hours of discharge. A medium-intensity intervention that included one telephone call within 7 days of discharge and one planned home visit within 10 days of discharge found no statistically significant reduction in all-cause readmissions or mortality.

Home telemonitoring of patients with heart failure had no impact on hospital readmission or mortality. Post-discharge heart failure patient education programs also failed to result in reduced readmission rates or lower mortality.

KEY POINT

- A discharge summary that includes the evaluations performed, medication reconciliation, pending test results, required follow-up tests, and follow-up appointments is an important tool in the communication between the hospital and the follow-up clinician.

Bibliography

Rattray NA, Sico JJ, Cox LM, Russ AL, Matthias MS, Frankel RM. Crossing the communication chasm: challenges and opportunities in transitions of care from the hospital to the primary care clinic. Jt Comm J Qual Patient Saf. 2017;43:127-137. [PMID: 28334591] doi:10.1016/j.jcjq.2016.11.007

Item 24 Answer: B

Educational Objective: **Diagnose adhesive capsulitis.**

This patient's clinical presentation is most consistent with adhesive capsulitis, also known as frozen shoulder. Adhesive capsulitis commonly presents as poorly localized, progressive pain described as a deep aching with an insidious onset. Pain is also frequently worse at night and in cold weather. In addition to pain, patients with adhesive capsulitis frequently develop decreased shoulder mobility as the disease progresses. Range of motion (both active and passive) is decreased in all planes of motion. Adhesive capsulitis may be idiopathic (primary adhesive capsulitis) or secondary to several conditions (secondary adhesive capsulitis). Secondary conditions include diabetes mellitus, hypothyroidism, prior surgery or trauma, prolonged immobilization, autoimmune disorders, and stroke.

Acromioclavicular joint degeneration is unlikely to be responsible for this patient's clinical presentation. Patients with acromioclavicular joint degeneration typically report pain localized to the acromioclavicular joint. Physical examination findings include tenderness to palpation of the joint, pain with shoulder abduction beyond 120 degrees, and pain with passive shoulder adduction (a positive cross-arm test).

Bicipital tendinitis typically results in pain localized to the anterior shoulder that may radiate toward the deltoid and into the arm. Pain classically worsens with overhead activity. On examination, tenderness may be elicited by palpating the bicipital groove. Pain also can be reproduced by placing the patient's ipsilateral arm at his or her side while flexing the elbow to 90 degrees and supinating against resistance (Yergason test).

Rotator cuff disease would not be expected to cause pain with both active and passive movement of

the shoulder; therefore, it would not account for this patient's presentation.

KEY POINT

- Adhesive capsulitis is characterized by loss of shoulder movement accompanied by pain; examination discloses significant loss of both active and passive range of motion.

Bibliography

Le HV, Lee SJ, Nazarian A, Rodriguez EK. Adhesive capsulitis of the shoulder: review of pathophysiology and current clinical treatments. Shoulder Elbow. 2017;9:75-84. [PMID: 28405218] doi:10.1177/1758573216676786

Item 25 Answer: C

Educational Objective: Treat premature ejaculation.

Topical lidocaine is the most appropriate treatment for this patient's premature ejaculation. Premature ejaculation is defined as ejaculation that occurs sooner than desired and is distressful to either or both partners. The mainstays of therapy include counseling and pharmacotherapy (oral and topical agents). According to the American Urological Association, pharmacologic options include selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants, and topical anesthetic agents. Oral medications (fluoxetine, paroxetine, sertraline) are effective because they tend to cause delayed ejaculation as a side effect. This patient is currently taking a tricyclic antidepressant and has had previous mood instability with an SSRI; therefore, the most appropriate treatment is a regimen of topical lidocaine to help reduce tactile stimulation and thus prolong the time to ejaculation. Topical medications (lidocaine, prilocaine) may be used with or without a condom.

Paroxetine therapy is an effective treatment strategy for premature ejaculation. However, it is not appropriate in this case because of the patient's previously reported mood instability when exposed to sertraline. Both sertraline and paroxetine are SSRIs, which can cause deleterious mood changes (a class effect). In a patient with depression that is currently well controlled, adding an additional psychoactive medication is not warranted.

Testosterone gel, which is used in the treatment of hypogonadism, is not appropriate for this patient. Hypogonadism (androgen deficiency) can lead to decreased libido and erectile dysfunction, but it has not been shown to be a causative or correlative factor in premature ejaculation. Furthermore, this patient has no examination findings that would raise concern for hypogonadism, such as body hair growth and pattern changes, reduced testicular size, or gynecomastia, and his 8:00 AM serum total testosterone level was normal.

Given that the patient's premature ejaculation is distressing to both the patient and his spouse, offering no treatment options could lead to worsening self-confidence, mood, and quality of life.

KEY POINT

- Pharmacologic options for the treatment of premature ejaculation include selective serotonin reuptake inhibitors, tricyclic antidepressants, and topical anesthetic agents.

Bibliography

Martin C, Nolen H, Podolnick J, Wang R. Current and emerging therapies in premature ejaculation: Where we are coming from, where we are going. Int J Urol. 2017;24:40-50. [PMID: 27704632] doi:10.1111/iju.13202

Item 26 Answer: D

Educational Objective: Treat a woman with stress urinary incontinence.

The most appropriate treatment for this patient is pelvic floor muscle training (PFMT; also known as Kegel exercises). This multiparous, postmenopausal woman describes classic stress urinary incontinence, which is characterized by urine leakage associated with activities that cause increased intra-abdominal pressure, such as coughing, laughing, or sneezing. The American College of Physicians (ACP) recommends PFMT as first-line therapy for women with stress incontinence. PFMT may also be of benefit in patients with mixed urge and stress incontinence. If performed correctly and diligently, PFMT exercises may strengthen the pelvic floor muscles and enhance urinary retention. The patient is advised to tighten the pelvic muscles as if trying to interrupt urination. Best results require three or four sets of 10 contractions daily, with contractions lasting 10 seconds. The regimen should be continued for a minimum of 15 to 20 weeks. The ACP recommends against pharmacotherapy for this condition.

Bladder training and suppressive therapy are recommended by the ACP for urgency and mixed incontinence. With bladder training, patients are instructed to void regularly throughout the day, regardless of urge, and progressively increase the interval between voids. Suppression techniques are used to manage urge to void outside of the schedule. The patient is instructed to contract pelvic floor muscles quickly three or four times, use a distraction technique (counting backwards from 100), and, when the urge passes, walk to the bathroom to urinate.

The risks and benefits of systemic hormone replacement therapy, such as oral estradiol, in postmenopausal women must be carefully considered. Its use should be reserved for vasomotor symptoms of menopause at the lowest effective dosage. Estrogen replacement therapy is not recommended for chronic medical problems. Trials of topical estrogen therapy for stress urinary incontinence in patients with vaginal atrophy are of mixed quality at best, and its use is not routinely recommended.

Oxybutynin is a treatment for urgency urinary incontinence when bladder training is only partially successful or has failed. It is not recommended for the treatment of stress urinary incontinence.

The ACP recommends exercise and weight loss for all obese women with urinary incontinence. This patient is not overweight, and her incontinence would likely not benefit from exercise and weight loss.

KEY POINT

- Stress urinary incontinence is characterized by urine leakage associated with activities that cause increased intra-abdominal pressure, such as coughing, laughing, or sneezing; it is best managed with pelvic floor muscle training exercises.

Bibliography

Qaseem A, Dallas P, Forciea MA, Starkey M, Denberg TD, Shekelle P; Clinical Guidelines Committee of the American College of Physicians. Nonsurgical management of urinary incontinence in women: a clinical practice guideline from the American College of Physicians. Ann Intern Med. 2014;161:429-40. [PMID: 25222388] doi:10.7326/M13-2410

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Item 27 Answer: A

Educational Objective: Manage a request for potentially inappropriate treatment.

The most appropriate management is consultation with the hospital ethics committee. A recent policy statement from the Society of Critical Care Medicine recommends that appropriate treatment goals of ICU care include treatment that provides a reasonable expectation of survival outside of the acute care setting with sufficient cognitive ability to perceive benefits of treatment, or palliative care through the dying process in the ICU. Because conflicts between the desire to provide benefit to the patient and the desire to minimize the burden of treatment can be very difficult, one of the most important skills of the physician is the ability to communicate and negotiate a reasonable treatment plan with the patient's family. If these situations become intractable, many organizations recommend initiating a process to resolve the disagreement, including notifying surrogates of the process, seeking a second medical opinion, obtaining review by an interdisciplinary ethics committee, offering the surrogate the opportunity to seek care at another institution, and implementing the decision of the resolution process. This patient's family is requesting treatment that the care team does not think will achieve reasonable goals, and an ethics consultation may lead to conflict resolution.

In some situations, the physician and the patient's family may mutually establish a time frame in which care will be withdrawn if there is no improvement; however, these decisions should not be made unilaterally by the care team.

A physician should not provide treatment that conflicts with professional obligations and will not meet the goals of care. However, often by communicating his or her concerns, a physician is able to help a family understand the burden of continued, ineffective treatment. If resolution is not possible, family members may seek transfer to another institution; however, the physician is not obliged to initiate such arrangements.

KEY POINT

- A physician should not provide treatment that conflicts with professional obligations and will not meet the goals of care; when the physician and the patient (or family members) have conflicting goals of care, an ethics consultation may be beneficial.

Bibliography

Kon AA, Shepard EK, Sederstrom NO, Swoboda SM, Marshall MF, Birriel B, et al. Defining futile and potentially inappropriate interventions: a policy statement from the Society of Critical Care Medicine Ethics Committee. Crit Care Med. 2016;44:1769-74. [PMID: 27525995] doi: 10.1097/CCM.0000000000001965

Item 28 Answer: D

Educational Objective: Treat genitourinary syndrome of menopause.

Vaginal estrogen therapy is the most appropriate treatment for this patient with genitourinary syndrome of menopause (GSM), also known as vaginal atrophy. GSM is a common condition in postmenopausal women that is characterized by dryness, inflammation, and thinning of the vaginal walls due to decreased estrogen. Other symptoms include dyspareunia, itching, and vulvovaginal irritation. The associated dyspareunia may lead to avoidance of sexual activity because of discomfort. This patient's pelvic examination features are classic for GSM, including a pale and dry vaginal lining with reduction in rugae. For severe symptoms or symptoms not responsive to moisturizers and lubricants, topical estrogen therapy has numerous beneficial effects, including restoration of the acidic vaginal pH, thickening of the epithelium, and increase in vaginal secretions. Available preparations include estradiol or conjugated estrogen in tablet, cream, or ring forms. Low-dose vaginal estradiol tablets and the estradiol vaginal ring have minimal systemic estrogen absorption. Because estradiol absorption is insufficient to cause endometrial proliferation, concurrent progestin is typically not indicated when low-dose local estrogen is used to treat GSM. The dose and duration of topical estrogen therapy are individualized according to symptom severity. Family history of breast cancer is not a contraindication to use.

A potent topical glucocorticoid, such as clobetasol, is used to treat vulvar lichen sclerosus. This inflammatory condition often presents as white, atrophic patches on the genital and perianal skin. It is associated with dyspareunia, pain, and pruritus. Prepubertal girls and postmenopausal women appear to be at highest risk. The intense itching and plaque-like involvement of the labia, introitus, and perianal region are clinical clues that distinguish vulvar lichen sclerosus from the generalized thinning and drying associated with GSM.

Ospemifene is an estrogen agonist/antagonist used to reduce the severity of moderate to severe dyspareunia in postmenopausal women. It is recommended that women with an intact uterus also take a progestin. How ospemifene compares to vaginal estrogens in terms of efficacy and safety is

unknown. Because topical estrogen therapy has a long history of safety, experts recommend that ospemifene be reserved for women who cannot or will not use topical estrogens.

Although systemic estrogen therapy may help with symptoms of vaginal atrophy, use of vaginal estrogen is most effective for treatment of GSM in a patient with no other menopausal symptoms, such as hot flushes, night sweats, or mood concerns.

Recent evidence suggests that vaginal estrogen therapy may be as effective as vaginal lubricants for treating postmenopausal vaginal symptoms. However, in this patient with symptoms that have not responded to vaginal lubricants, vaginal estrogen is the most reasonable option.

KEY POINT

- Vaginal estrogen therapy is appropriate treatment for patients with moderate to severe genitourinary syndrome of menopause that has not responded to moisturizers and lubricants.

Bibliography

The NAMS 2017 Hormone Therapy Position Statement Advisory Panel. The 2017 hormone therapy position statement of The North American Menopause Society. Menopause. 2017;24:728-753. [PMID: 28650869] doi:10.1097/GME.0000000000000921

Item 29 Answer: D

Educational Objective: Treat generalized anxiety disorder with pharmacologic therapy.

The most appropriate long-term pharmacologic treatment for this patient with generalized anxiety disorder (GAD) is sertraline. GAD is characterized by excessive anxiety about activities or events (occupation, school) occurring more days than not for at least 6 months and causing significant functional impairment. Patients with GAD also experience difficulty concentrating, irritability, muscle tension, restlessness, and sleep disturbance. A useful tool for identifying and assessing the severity of GAD is the Generalized Anxiety Disorder 7-item scale (GAD-7), which asks patients to rate seven items on a scale of 0 to 3 based on increasing severity (https://www.integration.samhsa.gov/clinical-practice/GAD708.19.08Cartwright.pdf). A score of 5 to 9 indicates mild anxiety, 10 to 14 moderate anxiety, and 15 to 21 severe anxiety. The GAD-7 can be used to monitor symptom severity over time, allowing clinicians to monitor treatment effectiveness.

Treatment options for GAD include cognitive behavioral therapy (CBT) and pharmacologic therapy, such as with a selective serotonin reuptake inhibitor (SSRI) or serotonin-norepinephrine reuptake inhibitor (SNRI). Patients with GAD often have comorbid mood and anxiety disorders, which often make SSRIs (such as sertraline) and SNRIs (such as venlafaxine) preferred because of their broad therapeutic applicability. CBT is the most effective psychotherapy for GAD; trials have shown it is as effective as pharmacologic therapy and can be used as monotherapy or in combination with drugs. The choice between pharmacologic therapy and CBT is often based on patient preference and the presence of comorbid disorders. Another consideration may be costs of treatment, both direct and indirect (due to time away from work or school). Depending on the particular agent, antidepressant therapy costs $100 to $300 per year, with low indirect costs. On average, annual costs for CBT are three to four times higher than for antidepressant therapy and also require significant time away from work or school to attend therapy.

Tricyclic antidepressants, such as amitriptyline, are considered second-line therapy for GAD because of a higher incidence of side effects with their use.

Benzodiazepines, such as clonazepam, are useful for controlling severe anxiety symptoms, especially before the benefits of CBT or other pharmacologic therapy take effect. These agents should be used only for short periods (<4-6 weeks) because of the potential for dependency.

Lithium and other mood stabilizers are appropriate treatment for bipolar disorder but are not indicated for the treatment of anxiety disorders.

KEY POINT

- Treatment options for generalized anxiety disorder include cognitive behavioral therapy and pharmacologic therapy with a selective serotonin reuptake inhibitor or serotonin-norepinephrine reuptake inhibitor.

Bibliography

Patel G, Fancher TL. In the clinic. Generalized anxiety disorder. Ann Intern Med. 2013;159:ITC6-1-ITC6-11; quiz ITC6-12. [PMID: 24297210] doi:10.7326/0003-4819-159-11-201312030-01006

Item 30 Answer: B

H

Educational Objective: Implement risk mitigation strategies for patients at high risk for opioid overdose.

The most appropriate next step before continued prescription of this patient's long-term opioid therapy is to prescribe naloxone and provide caregiver education on its use. Naloxone, a pure opioid antagonist that acts as a competitive inhibitor at opioid receptors, can be a life-saving reversal agent for patients with opioid overdose, and evidence shows that naloxone is effective in preventing opioid-related overdose death at the community level through community-based distribution. The Centers for Disease Control and Prevention Guideline for Prescribing Opioids for Chronic Pain recommends that physicians consider offering naloxone to patients with a high risk for overdose (history of overdose or substance use disorder, high opioid dosage [≥50 morphine milligram equivalents/day], or concurrent benzodiazepine use). When naloxone is prescribed, patients and patients' household members should be educated on its use and on ways to prevent overdose. This patient is currently taking approximately 75 morphine milligram equivalents/day and using a long-acting formulation; therefore, she is considered at high risk for overdose and should be considered for naloxone prescription.

H CONT.

Coprescription of opioids and benzodiazepines is associated with an increased risk for death from overdose and should be avoided when prescribing medications for patients with chronic pain.

Close monitoring, including review of prescription monitoring databases (where available), urine drug screening, and ongoing functional assessment, are all appropriate tools in the safe prescribing of long-term opioid therapy; however, weekly nursing visits are not currently recommended as a risk-mitigation strategy.

Although current guidelines recommend avoiding the use of extended-release opioids, this patient's pain and quality of life improved with substitution of a short-acting regimen for a transdermal fentanyl patch. If the benefits outweigh the risks and the patient has provided informed consent and received appropriate education, continued extended-release opioid therapy (with implementation of appropriate safety mechanisms) could be considered in this patient with chronic, irreversible pain.

KEY POINT

- Physicians should consider offering naloxone to patients receiving long-term opioid therapy with a high risk for overdose (history of overdose or substance use disorder, high opioid dosage [≥50 morphine milligram equivalents/day], or concurrent benzodiazepine use).

Bibliography

Dowell D, Haegerich TM, Chou R. CDC guideline for prescribing opioids for chronic pain—United States, 2016. JAMA. 2016;315:1624-45. [PMID: 26977696] doi:10.1001/jama.2016.1464

Item 31 Answer: A

Educational Objective: Treat a patient with clinical atherosclerotic cardiovascular disease who has not achieved target LDL cholesterol reduction with statin therapy.

In addition to discontinuing ezetimibe, the most appropriate management of this patient with clinical atherosclerotic cardiovascular disease (ASCVD) is to initiate alirocumab. For patients with clinical ASCVD, high-intensity statin therapy is recommended, with a goal of at least 50% LDL cholesterol reduction. Nonstatin drugs, preferably ezetimibe or a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor, should be considered alone or in combination with statins in patients who do not achieve target LDL cholesterol reduction. PCSK9 inhibitors, such as alirocumab, are monoclonal antibodies that bind to serine protease PCSK9, a liver enzyme that degrades hepatocyte LDL receptors. Treatment with PCSK9 inhibitors produces a 50% to 60% reduction in LDL cholesterol. ASCVD risk reduction has also been demonstrated with PCSK9 inhibitors, although studies have included a relatively small number of patients with limited follow-up. A modest reduction in triglyceride level and increase in HDL cholesterol level have also been observed with their use. Limitations include high cost and the need for subcutaneous injections every 2 to 4 weeks. Common side effects include injection-site reactions, fatigue, and limb pain. This patient with clinical ASCVD has not achieved the goal LDL cholesterol reduction on maximally tolerated statin therapy and did not tolerate ezetimibe. Therefore, alirocumab should be initiated. In addition to starting a PCSK9 inhibitor, intensification of therapeutic lifestyle changes, such as weight loss and regular exercise, should be encouraged.

A bile acid sequestrant, such as cholestyramine, may be considered as an optional alternative agent for patients with ezetimibe intolerance and a triglyceride level less than 300 mg/dL (3.39 mmol/L) or because of patient preference, but there is no evidence of a net cardiovascular risk reduction benefit with bile acid sequestrants in combination with statins.

Niacin is no longer routinely recommended for treatment of hyperlipidemia based on lack of efficacy and potential harms.

Continuing atorvastatin without additional intervention is unlikely to result in further LDL cholesterol reduction.

KEY POINT

- Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors and ezetimibe are the preferred nonstatin drugs for patients with clinical atherosclerotic cardiovascular disease who do not achieve goal LDL cholesterol reduction with maximally tolerated statin therapy.

Bibliography

Lloyd-Jones DM, Morris PB, Ballantyne CM, Birtcher KK, Daly DD Jr, DePalma SM, et al. 2017 focused update of the 2016 ACC expert consensus decision pathway on the role of non-statin therapies for LDL-Cholesterol lowering in the management of atherosclerotic cardiovascular disease risk: a report of the American College of Cardiology Task Force on Expert Consensus Decision Pathways. J Am Coll Cardiol. 2017;70:1785-1822. [PMID: 28886926] doi:10.1016/j.jacc.2017.07.745

Item 32 Answer: C

Educational Objective: Screen for colorectal cancer in an average-risk patient with fecal immunochemical testing.

The most appropriate screening test for this patient is a fecal immunochemical test (FIT). The U.S. Preventive Services Task Force (USPSTF) recommends screening for colorectal cancer in asymptomatic adults aged 50 to 75 years. For patients with average risk for colorectal cancer, several screening strategies are available, including fecal occult blood testing, direct endoscopic visualization, radiologic examination, and testing the blood for molecular markers of cancer. There is little head-to-head comparative evidence that any one recommended screening modality provides a greater benefit than the others. In addition, despite unequivocal evidence that colon cancer screening reduces mortality, an estimated one in three U.S. adults who are eligible for

colon cancer screening has not been screened. Therefore, the USPSTF supports using the test that is most likely to result in completion of screening. Test selection should be guided by evidence, patient preferences, and local availability. Two fecal blood detection tests are available: a sensitive guaiac-based fecal occult blood test (gFOBT) and an FIT that uses antibodies to detect human hemoglobin. Sensitive gFOBT requires dietary restriction in order to reduce false-positive results, whereas FIT does not. The FDA has approved a third stool-based screening test that is combined with FIT and detects cancer DNA in the stool (the multitargeted stool DNA test). Mortality data for this screening strategy are not available. Because this patient would prefer not to modify his diet, FIT is the most appropriate screening option.

The plasma circulating methylated *SEPT9* DNA test is an FDA-approved colorectal cancer screening test that holds promise, as blood tests may result in increased screening adherence. However, its sensitivity for detecting colorectal cancer is suboptimal at 48%, and mortality data are lacking.

Endoscopic tests include flexible sigmoidoscopy and colonoscopy. The mortality benefit of flexible sigmoidoscopy is limited to cancers of the distal bowel. Colonoscopy can visualize the entire bowel but requires colon preparation, which can be a barrier to completing the study. CT colonography is a radiologic technique that also requires colon preparation, which this patient has refused.

Major guidelines differ in their recommendations regarding screening strategy and frequency. The 2016 USPSTF guideline recommends sensitive gFOBT or FIT annually or multitargeted stool DNA testing every 3 years. Flexible sigmoidoscopy is recommended every 5 years, but if combined with FIT (or possibly gFOBT), the interval can be increased to every 10 years, the same interval recommended for colonoscopy. CT colonography can be performed every 5 years.

KEY POINT

- The U.S. Preventive Services Task Force recommends screening for colorectal cancer in asymptomatic adults aged 50 to 75 years; the choice of screening test should be guided by evidence, patient preferences, and local availability.

Bibliography

Inadomi JM. Screening for colorectal neoplasia. N Engl J Med. 2017;376:149-156. [PMID: 28076720] doi:10.1056/NEJMcp1512286

Item 33 Answer: C

Educational Objective: Counsel a patient on the use of herbal supplements.

This patient should be advised to discontinue drinking kava tea. Patients take dietary supplements for various reasons, such as to prevent illness, enhance health, and correct perceived deficiencies. In the United States, approximately 50% of adults report using vitamins or dietary supplements, with total consumer spending of more than $20 billion each year. Despite their prevalent use, the U.S. Preventive Services Task Force does not recommend multivitamins or herbal supplements for the prevention of cardiovascular disease or cancer. In addition to questionable efficacy, supplement use is associated with risk for considerable harms, including side effects; interactions with other drugs; and harms related to inclusion of unadvertised additives, compounds, or toxins. Despite the risks, many patients strongly believe in supplement use, and the role of the physician is to inform these patients of harmful supplements and suggest safer alternatives. This patient is taking kava, which is derived from *Piper methysticum*, a plant native to the western Pacific islands. It is often used to relieve stress and anxiety but has been associated with liver damage. In 2002, the FDA issued a consumer advisory regarding the potential risk for severe liver injury with kava use, especially in patients with liver disease or at risk for liver disease. Therefore, advising this patient with nonalcoholic steatohepatitis to discontinue kava tea would be the best management option.

Echinacea may be slightly effective for prevention but not treatment of the common cold. The most common side effects are gastrointestinal upset and nausea. Although this patient does not need to take echinacea, this herb has a relatively safe side effect profile, and she may continue it if she wishes.

The U.S. Preventive Services Task Force recommends daily folic acid supplementation (400 to 800 µg) for women of child-bearing age to prevent fetal neural tube defects; therefore, folic acid should be continued in this 35-year-old patient.

This patient has diagnoses of nonalcoholic steatohepatitis and obesity, and continuing an herbal supplement that is associated with known hepatotoxicity may cause harms.

KEY POINT

- Dietary and herbal supplements have questionable efficacy and may be associated with considerable harms; physicians must inform patients of harmful supplements and suggest safer alternatives.

Bibliography

Teschke R, Wolff A, Frenzel C, Schulze J, Eickhoff A. Herbal hepatotoxicity: a tabular compilation of reported cases. Liver Int. 2012;32:1543-56. [PMID: 22928722] doi: 10.1111/j.1478-3231.2012.02864.x

Item 34 Answer: B

H

Educational Objective: Evaluate preoperative cardiac risk using electrocardiography in a patient with known cardiovascular disease.

The most appropriate preoperative cardiac testing for this patient is electrocardiography (ECG). The 2014 American College of Cardiology/American Heart Association guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery states that preoperative ECG is reasonable for patients with known atherosclerotic cardiovascular disease (including coronary artery disease, arrhythmia,

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CONT.

peripheral artery disease, cerebrovascular disease, or significant structural heart disease) who are undergoing moderate- to high-risk surgeries. Preoperative ECG also may be considered for other asymptomatic patients, except for those undergoing low-risk procedures. This patient has known coronary artery disease and has not undergone ECG in 2 years. It is reasonable to obtain ECG preoperatively because certain interval findings (for example, new Q waves), additional evidence of conduction disease, or arrhythmia may result in changes in perioperative management.

Risk calculators, including the Revised Cardiac Risk Index and the American College of Surgeons National Surgical Quality Improvement Program myocardial infarction and cardiac arrest calculator, can be used to determine the risk for a perioperative major adverse cardiac event (MACE). Patients with low risk (<1% risk for perioperative MACE) may proceed to surgery without preoperative cardiac stress testing, whereas patients with elevated risk (≥1% risk for perioperative MACE) should undergo assessment of functional capacity. Metabolic equivalents (METs) are used to represent the patient's functional capacity based on the intensity of activity able to be performed. If the patient's functional capacity exceeds 4 METs, the patient may proceed to surgery without further testing. Examples of 4 METs of activity include the ability to walk 4 miles per hour on a flat surface, climb one to two flights of stairs without stopping, or perform vigorous housework such as vacuuming. Swimming for 30 minutes also exceeds this threshold. Cardiac stress testing should generally be reserved for patients at elevated risk for MACE with a functional capacity less than 4 METs, but only if the results of the test will change perioperative management. Although this patient has an elevated risk for a MACE perioperatively, his functional capacity exceeds 4 METs; therefore, he does not require preoperative cardiac stress testing with dobutamine or exercise.

KEY POINT

- Preoperative electrocardiography is reasonable for patients with known atherosclerotic cardiovascular disease, including coronary artery disease, arrhythmia, peripheral artery disease, cerebrovascular disease, or significant structural heart disease, who are undergoing moderate- to high-risk surgeries; cardiac stress testing should generally be reserved for patients at elevated risk for major adverse cardiac event with a functional capacity less than 4 metabolic equivalents, but only if the results of the test will change perioperative management.

Bibliography

Fleisher LA, Fleischmann KE, Auerbach AD, Barnason SA, Beckman JA, Bozkurt B, et al; American College of Cardiology. 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2014;64:e77-137. [PMID: 25091544]

Item 35 Answer: D

Educational Objective: Diagnose ulnar nerve entrapment.

This patient has symptoms consistent with ulnar neuropathy (fourth and fifth finger numbness and, more rarely, interosseous muscle weakness), making ulnar nerve entrapment the most likely diagnosis. Ulnar nerve entrapment, also known as cubital tunnel syndrome, is caused by impingement of the ulnar nerve at the elbow by bone spurs, fibrous tissue, ganglion cysts, or ulnar nerve subluxation. Elbow pain typically worsens with flexion. The diagnosis is usually made clinically and does not require imaging. Initial treatment consists of activity modification, splinting the elbow at night to prevent prolonged elbow flexion, and use of an elbow pad during the day to avoid direct trauma. Surgery is an option when conservative measures fail in the setting of significant or progressive symptoms.

Carpal tunnel syndrome is associated with wrist pain and symptoms of median nerve dysfunction, namely numbness in the first three fingers and pain that radiates into the forearm and hand. Pain frequently worsens at night and with repetitive actions. Findings on physical examination may include weakened thumb abduction; thenar muscle atrophy suggests severe disease. These symptoms and findings are not present in this patient.

Medial epicondylitis is an important differential diagnosis in a patient presenting with medial elbow pain. Patients with this condition usually have pain and tenderness over the medial epicondyle and ventral forearm, which worsens with resisted wrist flexion rather than elbow flexion. Medial epicondylitis is not usually associated with hand symptoms.

Olecranon bursitis is associated with swelling and, depending on the cause, significant tenderness of the posterior elbow over the olecranon bursa. This patient has not had signs of elbow swelling, and olecranon bursitis does not cause neuropathic symptoms.

KEY POINT

- Ulnar nerve entrapment, also known as cubital tunnel syndrome, is caused by impingement of the ulnar nerve at the elbow by bone spurs, fibrous tissue, ganglion cysts, or ulnar nerve subluxation; characteristics include pain at the elbow that worsens with flexion, paresthesias and numbness of the fourth and fifth fingers, and weakness of the interosseous muscles.

Bibliography

Hobson-Webb LD, Juel VC. Common entrapment neuropathies. Continuum (Minneap Minn). 2017;23:487-511. [PMID: 28375915] doi:10.1212/CON.0000000000000452

Item 36 Answer: D

Educational Objective: Evaluate a patient with syncope.

The most appropriate diagnostic tests to perform next are orthostatic blood pressure measurement and electrocardiography

H CONT.

The American Heart Association (AHA), the American College of Cardiology (ACC), and the Heart Rhythm Society (HRS) jointly conclude that the history and physical examination are the most important diagnostic tools in determining the underlying cause of a syncopal event. The history should focus on eliciting prodromal or postepisode symptoms, comorbid medical or psychiatric conditions, the psychosocial context of the event, and bystander information. The patient's prescription and over-the-counter medications should also be thoroughly reviewed. The physical examination should include an in-depth cardiovascular evaluation, including orthostatic (postural) blood pressure measurements, as well as a basic neurologic examination to evaluate for focal defects. Orthostatic blood pressure assessment has consistently been shown to be the most valuable diagnostic tool in the evaluation of syncope. The AHA/ACC/HRS guideline for the evaluation and management of patients with syncope additionally recommends that resting 12-lead electrocardiography (ECG) be performed in all patients with syncope to identify an underlying arrhythmia, myocardial ischemia, or QT prolongation. Further diagnostic testing should be methodically selected on the basis of the clinical circumstances.

The diagnostic yield of 24- to 48-hour electrocardiographic monitoring is low (1%-2%), unless there are frequent episodes over a short period. More prolonged rhythm monitoring with an external loop event recorder improves yield if the patient has clinical or ECG features of arrhythmia-related syncope. Clinical evidence does not support routine echocardiography in patients with syncope. Unexpected findings on echocardiogram to explain syncope are uncommon.

Laboratory testing, such as B-type natriuretic peptide and cardiac enzyme measurement, has considerably low diagnostic yield and is not recommended in the routine evaluation of patients with syncope. Rather, further diagnostic testing should be based on the findings on the history, physical examination, and ECG.

The AHA/ACC/HRS syncope guideline does not recommend MRI and CT of the head in the routine evaluation of patients with syncope in the absence of head injury or focal neurologic findings that support further evaluation. Similarly, carotid artery imaging is not recommended in the routine evaluation of patients with syncope in the absence of focal neurologic findings.

KEY POINT

- In patients with syncope, the physical examination should include an in-depth cardiovascular evaluation, including orthostatic (postural) blood pressure measurements, as well as a basic neurologic examination to evaluate for focal defects; electrocardiography is the only diagnostic study that is routinely recommended in patients with syncope.

Bibliography

Shen WK, Sheldon RS, Benditt DG, Cohen MI, Forman DE, Goldberger ZD, et al. 2017 ACC/AHA/HRS guideline for the evaluation and management of patients with syncope: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol. 2017;70:620-663. doi: 10.1016/j.jacc.2017.03.002. [PMID: 28286222]

Item 37 Answer: C

Educational Objective: Identify appropriate contraceptive care for a smoker.

The most appropriate contraceptive option for this patient is a progesterone-containing intrauterine device (IUD). Hormonal contraception options include oral contraceptive pills, a transdermal patch, a vaginal ring, and long-acting reversible contraceptives. Long-acting reversible contraceptives are progestin-only forms of contraception that include depot medroxyprogesterone acetate injections, subcutaneous implants, and progestin-containing IUDs. These preparations are less reliant on user adherence than oral contraceptive pills, are highly effective, and may be ideal for this patient who has proven difficulty with adhering to a daily pill routine. Return of fertility may be delayed with these methods, with a median time to conception of 10 months after cessation of use. As with other progestin-only methods, irregular bleeding and amenorrhea are prevalent, and weight gain is a common side effect. The levonorgestrel IUD is available in two dosage formulations: one that releases 14 µg/d and is effective for 3 years and one that releases 20 µg/d and is effective for 5 years. The levonorgestrel-containing IUD releases a low dose of progestin, which causes endometrial atrophy and generally leads to decreased or absent menstrual flow. The progesterone-containing IUD may be ideal for this patient who is bothered by heavy menstrual flow, and it will simultaneously eliminate the need for daily adherence to a pill.

Oral contraceptive pills are the most common form of contraception. These include combination estrogen-progestin pills and progestin-only pills ("mini-pill"). Combination preparations differ based on the strength of estrogen and the type of progestin component. All preparations are therapeutically equivalent in preventing pregnancy. Contraindications to estrogen-containing preparations (including oral contraceptives and estrogen-progestin vaginal rings) include breast cancer, liver disease, migraine with aura, uncontrolled hypertension, and venous thromboembolism. They are also contraindicated in women older than age 35 years who smoke more than 15 cigarettes per day, such as this patient, because of an increased risk for venous thromboembolism. When estrogen-containing products are contraindicated, a progesterone-only contraceptive could safely be used. In this patient, a progestin-only pill is less preferable to a progesterone-containing IUD because a pill would require daily adherence.

KEY POINT

- Estrogen-containing hormonal contraceptives are contraindicated in women older than 35 years who smoke more than 15 cigarettes a day because of an increased risk for venous thromboembolism.

Answers and Critiques

Bibliography

Tracy EE. Contraception: menarche to menopause. Obstet Gynecol Clin North Am. 2017;44:143-158. [PMID: 28499527] doi:10.1016/j.ogc.2017.02.001

Item 38 Answer: B

Educational Objective: Treat obesity with liraglutide in a patient with type 2 diabetes mellitus.

Liraglutide is the most appropriate next step in treatment. Weight-loss medications are recommended when a trial of comprehensive lifestyle modification, including reduced dietary intake, exercise, and behavioral therapy, fails to achieve a 5% to 10% reduction in weight at 3 to 6 months. This patient has appropriately adhered to dietary caloric restriction, with regular self-monitoring of calorie intake and weight, and is now exercising for more than 150 minutes per week. Her BMI is greater than 27, and she has obesity-related comorbid conditions (type 2 diabetes mellitus and uncontrolled hypertension). Liraglutide has been shown to increase satiety and aid in achieving more than 5% weight loss after 52 weeks of therapy, and it may help the patient feel less hungry.

Bariatric surgery is recommended for patients with BMI of 40 or greater, and for patients with BMI of 35 or greater who have obesity-related comorbidities and who have tried all other weight loss therapies without achieving significant weight loss or improvements in comorbid conditions.

There is no evidence that low-carbohydrate diets are more effective for reducing weight than low-fat diets. This patient is adherent to her chosen diet but has difficulty reducing her caloric intake to achieve continued weight loss. Clinicians should prescribe a diet with which the patient will adhere (that is, a diet that is palatable and affordable) and that maintains negative energy balance in order to achieve weight loss.

Very-low-calorie diets are recommended when rapid weight loss is medically indicated. This patient does not require rapid weight loss, and neither the risk nor the expense of frequent visits and laboratory monitoring are justified in this case.

KEY POINT

- Weight-loss medications are recommended when a trial of comprehensive lifestyle modification, including reduced dietary intake, exercise, and behavioral therapy, fails to achieve a 5% to 10% reduction in weight after 3 to 6 months.

Bibliography

Jensen MD, Ryan DH, Apovian CM, Ard JD, Comuzzie AG, Donato KA, et al; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society. Circulation. 2014;129:S102-38. [PMID: 24222017] doi:10.1161/01.cir.0000437739.71477.ee

Answers and Critiques

Item 39 Answer: A

H

Educational Objective: Identify appropriate timing for palliative medicine referral in a patient with advanced cancer.

The most appropriate time for palliative medicine referral is now. Palliative medicine (or palliative care) focuses on reducing pain, nonpain symptoms, and psychosocial stress associated with advanced disease. This patient has been diagnosed with incurable lung cancer and would benefit from concurrent specialty palliative medicine in conjunction with initiation of disease-directed therapy. Studies have consistently shown improvements in various quality-of-life metrics when palliative medicine is integrated early in the course of incurable cancer, and such integration is consistent with recommendations from the American Society of Clinical Oncology.

Although referral to palliative care historically occurred at the end of life, an emerging consensus of research indicates that early initiation during a serious or life-threatening illness is associated with substantial advantages. Evidence shows that early palliative medicine referral improves mood and decreases rates of depressive symptoms; anxiety is not heightened by palliative medicine referral. Palliative medicine teams are positioned to work with oncologists and primary care physicians in treating the complex symptoms of serious illness, and an integrated approach is recommended.

Hospice is a specialized form of palliative medicine that can provide a team-based care platform in the patient's preferred setting (for example, home, skilled nursing facility, or residential hospice house). Hospice should be considered for patients with an advanced illness who are no longer candidates for further disease-directed therapy, or whose goals (such as quality of life) are not likely to be met with further disease-directed therapies. Despite significant quality-of-life benefits for patients and their caregivers, hospice referrals often happen late in a patient's illness trajectory, leading to short hospice lengths of stay.

KEY POINT

- Palliative medicine, with its focus on reducing pain, nonpain symptoms, and psychosocial stress associated with advanced disease, improves quality of life for patients and their caregivers; early initiation of palliative medicine during a life-threatening illness has substantial advantages.

Bibliography

Ferrell BR, Temel JS, Temin S, Alesi ER, Balboni TA, Basch EM, et al. Integration of palliative care into standard oncology care: American Society of Clinical Oncology Clinical Practice Guideline Update. J Clin Oncol. 2017;35:96-112. [PMID: 28034065]

Item 40 Answer: B

Educational Objective: Prevent atherosclerotic cardiovascular disease with low-dose aspirin therapy.

The most appropriate measure to reduce this patient's atherosclerotic cardiovascular disease (ASCVD) risk is low-dose

aspirin. The U.S. Preventive Services Task Force (USPSTF) recommends low-dose aspirin for the primary prevention of ASCVD and colorectal cancer in adults aged 50 to 59 years with a 10-year ASCVD risk of 10% or higher who do not have an increased risk for bleeding, have a life expectancy of at least 10 years, and are willing to take low-dose aspirin daily for at least 10 years. In those aged 60 to 69 years with a 10-year ASCVD risk of 10% or higher, the benefits of aspirin use for primary prevention are smaller but still outweigh the risk for bleeding, and the decision to initiate low-dose aspirin in this population should be individualized. In contrast to the USPSTF recommendations, the American Diabetes Association recommends consideration of low-dose aspirin therapy as a primary prevention strategy in patients with type 1 or type 2 diabetes mellitus who are at increased cardiovascular risk. This group of patients includes most men and women with diabetes aged 50 years or older who have at least one additional major risk factor (family history of premature ASCVD, hypertension, dyslipidemia, smoking, or albuminuria) and are not at increased risk for bleeding. Aspirin therapy for the primary prevention of ASCVD is likely underused (approximately 40% of eligible candidates). Among patients told by a physician to take aspirin, 80% adhere to the recommendation.

For patients with ASCVD and documented aspirin allergy, the ADA recommends clopidogrel as an alternative preventive measure. This patient does not have a documented aspirin allergy, and therapy in this patient will be initiated for primary, not secondary, prevention; therefore, clopidogrel is not recommended for this patient.

The most commonly recommended dose of aspirin for primary prevention of cardiovascular events is 75 mg to 100 mg. Primary prevention trials have shown that lower doses are likely as effective as higher doses; however, observational trials and a meta-analysis have demonstrated an increased risk for bleeding with regular-dose aspirin compared with low-dose aspirin.

KEY POINT

- Low-dose aspirin for the primary prevention of atherosclerotic cardiovascular disease (ASCVD) and colorectal cancer is recommended for adults aged 50 to 59 years with a 10-year ASCVD risk of 10% or higher who do not have an increased risk for bleeding.

Bibliography

Bibbins-Domingo K; U.S. Preventive Services Task Force. Aspirin use for the primary prevention of cardiovascular disease and colorectal cancer: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2016;164:836-45. [PMID: 27064677] doi: 10.7326/M16-0577

Item 41 Answer: E

Educational Objective: **Evaluate a patient with symptoms of chronic insomnia with a sleep diary.**

The most appropriate next step in management of this patient with symptoms of chronic insomnia is to obtain a 2-week sleep diary. Symptoms of insomnia vary and may include poor sleep quality, frustration with sleep quantity, difficulty initiating sleep, or an inability to return to sleep after awakening. In patients with symptoms of insomnia, a thorough history, physical examination, and medication review may point to potentially reversible causes, such as sleep apnea or restless legs syndrome. In the absence of specific historical features that are consistent with a primary sleep disorder, the initial evaluation of insomnia additionally involves obtaining a sleep diary to identify adverse environmental factors, inappropriate exposure to electronic screens (computer, phone, tablet, television) before bedtime, and sleep patterns. If the sleep diary reveals red flags for a primary sleep disorder or another condition that may interfere with sleep, further diagnostic testing would be indicated. In this patient with daytime somnolence, fatigue, and difficulty with sleep initiation, a sleep log may facilitate collection of an accurate sleep history.

Polysomnography is indicated in patients for whom there is a strong suspicion of a primary sleep disorder based on the initial history and physical examination. Polysomnography typically involves overnight, laboratory-based testing that is monitored by a sleep technician. Similarly, multiple sleep latency testing is a labor-intensive evaluation designed to identify diagnoses of narcolepsy and idiopathic hypersomnia. Neither study is indicated in the initial evaluation of this patient, whose primary problem appears to be initiating sleep.

Overnight pulse oximetry has a high rate of false-positive and false-negative results and has not been validated as a screening tool for obstructive sleep apnea. Normal-appearing results on overnight pulse oximetry may allow for avoidance of further testing in patients with a low pretest probability. However, there is no clinical suspicion for obstructive sleep apnea in this patient, and it would not be indicated in her initial evaluation.

Low serum ferritin levels are strongly correlated with restless legs syndrome, which is characterized by discomforting sensations in the legs at rest or when falling asleep, an urge to move the legs, and immediate relief after moving the legs or walking. However, no features in the history suggest restless legs syndrome as a cause of this patient's chronic insomnia.

KEY POINT

- The initial evaluation of chronic insomnia involves obtaining a sleep diary to identify adverse environmental factors, inappropriate exposure to electronic screens before bedtime, and sleep patterns.

Bibliography

Masters PA. In the clinic. Insomnia. Ann Intern Med. 2014;161:ITC1-15; quiz ITC16. [PMID: 25285559] doi: 10.7326/0003-4819-161-7-201410070-01004

Item 42 Answer: C

Educational Objective: **Manage online physician-patient communication.**

The most appropriate management is to request that the patient establish care through the office. Professional

assessments should be performed within the context of an existing physician-patient relationship. In general, relationships should be established on the basis of an in-person professional encounter. Telemedicine, or the use of electronic communication and technologies to provide health care to patients at a distance, may increase access to care, improve outcomes, enhance physician-patient collaboration, and reduce costs; however, the American College of Physicians holds the position that a valid patient-physician relationship must be established for professionally responsible telemedicine services to occur. In this situation, the physician should reply to the patient and ask him to contact the office for an appointment to establish care or provide a second opinion, if that is what the patient desires. Once a physician-patient relationship is established, online communication should ideally occur through a secure portal that meets the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA).

Providing specific medical advice, such as suggesting celiac disease testing, without a thorough and proper medical evaluation would be inappropriate.

A request for the patient's records and provision of advice based on review of those records should not be made until a physician-patient relationship is established. Additionally, in digital environments, the sharing of patient information must always be held to a higher level of security than standard residential Internet connections. Encrypted or virtual proxy network connections in hospital-based information technology systems should be used for all patient information exchange and review to ensure a secure digital environment.

If a member of the public contacts a physician electronically in his or her professional role, the physician should politely respond and direct the patient to seek care through suitable channels by appropriately responding to the email or other online query.

KEY POINT

- Telemedicine, or the use of electronic communication and technologies to provide health care to patients at a distance, may increase access to care, improve outcomes, enhance physician-patient collaboration, and reduce costs; however, a valid patient-physician relationship must be established for professionally responsible telemedicine services to occur.

Bibliography

Farnan JM, Snyder Sulmasy L, Worster BK, Chaudhry HJ, Rhyne JA, Arora VM; American College of Physicians Ethics, Professionalism and Human Rights Committee. Online medical professionalism: patient and public relationships: policy statement from the American College of Physicians and the Federation of State Medical Boards. Ann Intern Med. 2013;158:620-7. [PMID: 23579867] doi:10.7326/0003-4819-158-8-201304160-00100

Item 43 Answer: C

Educational Objective: Diagnose optic neuritis.

This patient with acute vision loss and eye pain unassociated with trauma has signs and symptoms suggestive of optic neuritis, including pain with eye movement, loss of color vision out of proportion to the vision loss, and an afferent pupillary defect. Two thirds of optic neuritis cases occur in women. The average age of onset is between 20 and 40 years, and it is often associated with multiple sclerosis. Most of these patients have a normal optic disc on funduscopy, but one third may have a swollen disc or papillitis. An urgent evaluation by an ophthalmologist is required; treatment usually involves high-dose intravenous glucocorticoids.

Corneal abrasion can cause sudden onset of pain and foreign body sensation. It is classically seen in patients who sleep without taking out their contact lenses and then awaken with eye pain and photophobia. If the abrasion is in the central area of the visual axis, visual acuity may be diminished. Corneal abrasion cannot explain the loss of color discrimination and the afferent pupillary defect in this patient.

Herpes simplex keratitis typically presents with acute onset of pain, blurry vision, and watery discharge. The absence of discharge and ciliary flush in this case make keratitis unlikely. Ciliary flush is characterized by erythema that is most marked at the limbus, which is the junction of the sclera and cornea. Keratitis would not be associated with loss of color discrimination or an afferent pupillary defect.

Orbital cellulitis often presents with eye pain as well as eyelid swelling and erythema, although some cases present without erythema. In the case of inflammation of the extraocular muscles and fatty tissue in the orbit, the patient may experience pain with eye movement. When the condition is severe, visual acuity may be impaired. Orbital cellulitis, however, is more likely to be associated with fever and chemosis, which are not present in this patient, and it would not explain the patient's other findings related to optic nerve damage.

KEY POINT

- The hallmarks of optic neuritis are acute vision loss, eye pain with movement, color perception change, and afferent pupillary defect; results of a funduscopic examination may be normal.

Bibliography

Balcer LJ. Clinical practice. Optic neuritis. N Engl J Med. 2006;354:1273-80. [PMID: 16554529]

Item 44 Answer: A

Educational Objective: Recognize threats to validity with a cross-sectional study.

The most likely threat to the validity of this cross-sectional study is confounding. Cross-sectional studies evaluate the relationship between exposures and health outcomes in a population of interest. These studies are characterized by the measurement of factors and outcomes at a single point in time. The validity of cross-sectional studies is particularly susceptible to recall bias and confounding. Recall bias is a systematic error that is introduced into a study by differences

in the accuracy of the recollections of study participants; participants who have unpleasant experiences may recall past events differently than those who do not have similar experiences. Because cross-sectional studies are observational and not experimental, there is also no opportunity to randomly distribute factors that might influence the relationship being studied. Although statistical techniques can be used to control for known potential confounders, unknown confounders remain a threat to the validity of the conclusions. As such, cross-sectional studies are best suited to identifying potentially significant associations that can be more rigorously tested in experimental studies. Finally, because there is no way to verify that the purported cause (statin therapy) preceded the effect (memory loss), cross-sectional studies cannot prove cause-and-effect relationships.

Selection bias occurs when the study participants do not accurately reflect the population being studied, usually because the choice to participate is influenced by the clinical question. Selection bias can compromise the validity of observational study designs; however, in this study, the random sampling according to zip code of residence minimizes the possibility of selection bias.

Although self-reported data are less robust than measured data, well-validated survey designs may use self-reported data to determine the presence or absence of conditions, risk factors, or behaviors in a population.

The conventional level of statistical significance is a *P* value less than or equal to 0.05, and an odds ratio of 1 implies the absence of a significant relationship. In this case, the confidence interval for the odds ratio does not include the value 1, which supports the statistical significance of the findings.

KEY POINT

- The validity of cross-sectional studies is particularly susceptible to recall bias and confounding.

Bibliography

Grimes DA, Schulz KF. Bias and causal associations in observational research. Lancet. 2002;359:248-52. [PMID: 11812579]

H

Item 45 Answer: D

Educational Objective: Manage postoperative urinary retention with urinary catheterization.

Bladder decompression with urinary catheterization is the most appropriate management of this patient who has developed postoperative urinary retention (POUR). POUR is a common complication in the postoperative setting and is characterized by the inability to spontaneously and adequately empty the bladder. Risk factors include type of surgery (incontinence and anorectal surgery, hernia repair, joint arthroplasty), longer surgery, use of regional anesthesia, administration of greater than 750 mL of intraoperative fluids, use of certain postoperative medications (opioids, anticholinergic agents), older age, constipation, pelvic organ prolapse, neurologic disease, history of urinary retention, and history of pelvic surgery. POUR is a urologic emergency. Symptoms of suprapubic pain and the finding of a palpable bladder are insensitive indicators of POUR. Patients may also present with frequent urination of small volumes and overflow incontinence. Reversible causes of POUR, such as medication use, should be addressed. Whenever possible, offending medications, including opioids, anticholinergics, antihistamines, antipsychotics, and calcium-blocking drugs, should be discontinued. Early removal of indwelling urinary catheters and voiding trials are recommended. Retrograde voiding trials are preferred to spontaneous voiding trials because they are more predictive of the need for continued catheterization. A retrograde voiding trial involves infusion of sterile saline, followed by the attempt to void. For patients in whom a voiding trial is unsuccessful, intermittent urinary catheterization should be considered in place of indwelling bladder catheterization. Results of a recent randomized controlled trial in patients undergoing total hip arthroplasty and total knee arthroplasty demonstrated that a catheterization threshold of 800 mL significantly reduced the need for postoperative urinary catheterization and did not increase urologic complications.

Placement of a suprapubic catheter would require another surgical procedure and is reserved for situations in which urethral catheterization is not possible or in cases of pelvic trauma.

Suprapubic application of hot packs or warm wet gauze may stimulate spontaneous voiding but lacks proof from well-designed clinical trials. Some experts recommend consideration of this technique in patients for a limited time when residual bladder volume is 200 mL to 400 mL. Greater residual volume should be treated with bladder catheterization.

There is no role for tamsulosin in the treatment of POUR in women. Randomized studies in men have demonstrated that α_2 blockade for the treatment of acute urinary retention is associated with a reduced need for bladder catheterization. α_2 Blockers should be continued in men with benign prostatic hyperplasia.

KEY POINT

- Patients with postoperative urinary retention and residual bladder volume of 800 mL or more should be treated with bladder decompression and urinary catheterization.

Bibliography

Bjerregaard LS, Hornum U, Troldborg C, Bogoe S, Bagi P, Kehlet H. Postoperative urinary catheterization thresholds of 500 versus 800 ml after fast track total hip and knee arthroplasty: a randomized, open-label, controlled trial. Anesthesiology. 2016;124(6):1256-64. [PMID: 27054365] doi: 10.1097/ALN.0000000000001112

Item 46 Answer: D

Educational Objective: Determine adequacy of previous cervical cancer screening in an older woman.

The most appropriate screening strategy is to obtain the results of the patient's last cervical cancer screening

examination. The U.S. Preventive Services Task Force recommends against cervical cancer screening in women older than age 65 years who have had adequate prior screening and are not otherwise at high risk for cervical cancer. Adequate screening is commonly defined as three consecutive negative cytology (Pap smear) results or two consecutive negative cytology plus human papillomavirus (HPV) test results within the last 10 years, with the most recent test occurring within 5 years. Data suggest that cervical cancer screening rates decline with increasing patient age; however, a Kaiser Permanente registry study found that 13% of 65-year-old women have not been adequately screened, with higher rates in patients without a primary physician or other health care provider. Other populations that are less likely to have received adequate screening include women with limited access to care, women from racial or ethnic minority groups, and women from countries where screening is not available. The study also documented that most cases of invasive cervical cancer in women older than age 65 years occurred among those who had not met criteria for stopping screening. The decision to stop screening at age 65 years should only be made after confirming that the patient has received adequate prior screening. In patients who do not meet the criteria for adequate prior screening, screening may be clinically indicated after age 65 years.

Cervical cytology, high-risk HPV testing, or co-testing with cervical cytology and high-risk HPV testing may all be reasonable methods to screen for cervical cancer in this patient, but reviewing the adequacy of previous screening remains the first step in management.

KEY POINT

- The decision to discontinue cervical cancer screening at age 65 years should be made only after confirming that the patient has received adequate prior screening.

Bibliography

Dinkelspiel H, Fetterman B, Poitras N, Kinney W, Cox JT, Lorey T, Castle PE. Screening history preceding a diagnosis of cervical cancer in women age 65 and older. Gynecol Oncol. 2012;126:203-6. [PMID: 22561038] doi:10.1016/j.ygyno.2012.04.037

Item 47 Answer: B

Educational Objective: Treat chronic pain with structured physical therapy.

The most appropriate next step in treatment is physical therapy. This patient has a long-standing history of chronic pain that is most consistent with a diagnosis of fibromyalgia. All patients with chronic pain should be referred to a structured physical therapy program for evaluation and treatment. Physical therapy teaches patients safe, self-guided exercises to improve functional status, and there is a clear evidence base to support its use in all patients with chronic pain. Guided/progressive physical therapy programs are associated with a reduction in pain and, perhaps most importantly, improvement in function. No evidence suggests that a specific type of physical therapy is superior to another, and programs should be tailored to patient ability and adherence.

Clinicians should avoid prescribing opioids and benzodiazepines concurrently whenever possible. Epidemiologic studies indicate that concomitant use of benzodiazepines, such as lorazepam, and opioids may place patients at increased risk for fatal overdose. In three studies of opioid overdose deaths, there was evidence of concurrent benzodiazepine use in 31% to 61% of persons.

Trials of transcutaneous electrical nerve stimulation (TENS) for the treatment of fibromyalgia have yielded inconclusive results. Positive trials of TENS are frequently contaminated with concurrent use of an exercise program and massage. On the basis of inconclusive evidence, TENS cannot be recommended as the next treatment modality for this patient.

Opioid rotation would not be an ideal next step in this patient with a long history of chronic pain, particularly in the setting of previous unsuccessful opioid trials. Despite high opioid prescribing rates, no evidence supports the use of long-term opioid therapy in patients with chronic noncancer pain. In one study, patients receiving long-term opioids for chronic pain had more pain, poorer quality of life, and poorer function than a population of patients with chronic pain who were not taking opioids. Given the lack of evidence to support chronic opioid therapy, the continued use of opioids for chronic pain should be justified at every follow-up visit by documenting the patient's sustained functional improvement due to effective opioid therapy. In this patient with pain that has failed to improve with opioid therapy, oxycodone should be carefully withdrawn, and nonpharmacologic therapy should be instituted.

KEY POINT

- In patients with chronic noncancer pain, physical therapy reduces pain and improves function.

Bibliography

Hooten M, Thorson D, Bianco J, Bonte B, Clavel A Jr, Hora J. Institute for Clinical Systems Improvement. Pain: assessment, non-opioid treatment approaches and opioid management. Available at www.icsi.org/guidelines_more/catalog_guidelines_and_more/catalog_guidelines/catalog_neurological_guidelines/pain/. Updated August 2017. Accessed February 27, 2018.

Item 48 Answer: D

Educational Objective: Test for cognitive impairment in a symptomatic older woman.

This patient would most benefit from evaluation with the Mini-Cog test or another validated screening test for cognitive function. Cognitive impairment is a progressive decline that impairs function in at least two areas: attention, executive function, language, memory, or visual-spatial function. Patients with signs and symptoms of cognitive impairment, such as this patient who reports difficulty with both memory and executive function, should undergo evaluation. A variety of validated tools are available to

assess cognitive function. Among the free tools, the Montreal Cognitive Assessment and Mini-Cog test have been validated in primary care populations; these instruments screen for impairments in executive function. Self-administered instruments, such as the Self-Administered Gerocognitive Examination and Test Your Memory examination, have been validated in memory clinic populations to detect mild cognitive impairment and early dementia. Although the Mini-Mental State Examination has been the most extensively studied screening instrument, it is now proprietary, with a cost per use.

Although numerous factors have been studied, and some have been associated with a higher risk for progression to dementia (such as baseline functional impairment, abnormal results of fluorodeoxyglucose-PET brain imaging, and the apolipoprotein E [*APOE* ε4] genotype), no reliable clinical markers can predict the clinical likelihood that an individual patient with mild cognitive impairment will develop dementia. More importantly, these tests do not establish the diagnosis of cognitive impairment.

In clinical practice, a careful history and results of a standard mental examination are often sufficient to diagnose cognitive impairment, and extensive formal cognitive testing is not routinely required. Occasionally, a formal battery of neuropsychologic testing beyond the standard mental examination is needed to distinguish particularly mild cases of cognitive impairment from normal aging.

KEY POINT

- Cognitive impairment is a progressive decline that impairs function in at least two areas, including attention, executive function, language, memory, and visual-spatial function; it is best measured with assessment examinations, such as the Mini-Cog and the Mini-Mental State Examination, rather than laboratory testing or imaging.

Bibliography

Lin JS, O'Connor E, Rossom RC, Perdue LA, Eckstrom E. Screening for cognitive impairment in older adults: a systematic review for the U.S. Preventive Services Task Force. Ann Intern Med. 2013;159:601-12. [PMID: 24145578]

Item 49 Answer: C

Educational Objective: Diagnose cervical sprain.

This patient most likely has a cervical sprain (nonspecific or axial neck pain), which is the most common cause of neck pain. The pain associated with cervical sprain is usually an aching sensation that is isolated to the neck, but it can radiate to the posterior head or shoulders. The pain does not typically radiate into the arms. Cervical sprain symptoms can be precipitated by an unaccustomed activity or overuse. Physical examination of the neck usually shows decreased range of motion, tenderness to palpation, and reproduction of the pain with flexion or extension. The condition is also notable for the absence of abnormal neurologic findings.

Cervical myelopathy (compression of the cervical spinal cord) can also cause neck pain. Common clinical manifestations include progressive worsening of symptoms, difficulty with fine object manipulation and manual dexterity, and gait abnormalities. This patient's symptoms are not consistent with cervical myelopathy.

Cervical radiculopathy is caused by disk herniation or bony degeneration causing compression of adjacent nerve roots; it is characterized by neck pain associated with radiating arm pain and paresthesias that follow a dermatomal distribution. On examination, affected patients frequently have reproduction of their pain with the Spurling test (examiner bends the patient's head to the affected side while extending the neck and applying a downward pressure on the top of the head). Symptoms can be improved by holding the patient's hand on the affected side above the patient's head (shoulder abduction test). This patient's presentation is not consistent with cervical radiculopathy.

Whiplash-associated neck pain is a poorly understood entity that refers to cervical sprain that develops in the setting of trauma, such as a car accident, which produces an abrupt flexion/extension movement of the cervical spine. Typical symptoms include persistent severe pain, spasm, loss of range of motion in the neck, and occipital headache. Because this patient's neck pain did not result from direct abrupt flexion/extension trauma, it would be incorrect to classify it as whiplash-associated neck pain.

KEY POINT

- Pain associated with cervical sprain is usually an aching sensation that is isolated to the neck but can radiate to the posterior head or shoulders; physical examination usually shows decreased range of motion, tenderness to palpation, and reproduction of the pain with flexion or extension, but no neurologic findings.

Bibliography

Cohen SP. Epidemiology, diagnosis, and treatment of neck pain. Mayo Clin Proc. 2015;90:284-99. [PMID: 25659245] doi:10.1016/j.mayocp.2014.09.008

Item 50 Answer: C

Educational Objective: Treat trichomoniasis in a sexual partner.

The most appropriate additional management is to treat the patient's sexual partner for trichomoniasis. Trichomoniasis, which is caused by *Trichomonas vaginalis*, is the most common nonviral sexually transmitted infection (STI) worldwide. Unlike other STIs that predominate in adolescents and younger adults, rates of trichomoniasis are evenly distributed among women of all age groups. It is caused by motile flagellated protozoa that infect the urogenital tract, causing inflammatory vaginitis and urethritis. Treatment with a single 2-g dose of metronidazole is associated with a high rate of cure and should be offered to all symptomatic women, including pregnant women. Because of the high

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rate of reinfection among women treated for trichomoniasis (17% within 3 months in one study), retesting for *T. vaginalis* is recommended by the Centers for Disease Control and Prevention (CDC) for all sexually active women within 3 months after initial treatment, regardless of whether they believe their sexual partners were treated. Testing by nucleic acid amplification can be conducted as soon as 2 weeks after treatment. It is important that sexual partners also be treated, even if they are asymptomatic; documentation of infection is not required before treatment in any partners. Data are insufficient to support retesting men after treatment for trichomoniasis. *T. vaginalis* infection is associated with a two- to threefold increased risk for HIV acquisition. Therefore, the CDC recommends that testing for other STIs, including HIV, be performed in persons infected with *T. vaginalis*.

Pap testing is not needed for management of trichomoniasis because the infection is not associated with cervical malignancy.

Because of the high rate of partner infection with *T. vaginalis* and its association with other STIs, it would be inappropriate to not provide further testing or intervention after a primary *T. vaginalis* diagnosis.

KEY POINT

- Following diagnosis and treatment of a woman with *Trichomonas vaginalis* infection, the sexual partner should be treated and both individuals should be screened for other sexually transmitted infections; retesting of women for *T. vaginalis* infection within 3 months of treatment is also recommended.

Bibliography

Mills BB. Vaginitis: beyond the basics. Obstet Gynecol Clin North Am. 2017;44:159-177. [PMID: 28499528] doi:10.1016/j.ogc.2017.02.010

Item 51 Answer: C

Educational Objective: Diagnose a patient with a medically unexplained symptom.

This patient most likely has a medically unexplained symptom. Such symptoms cannot be attributed to a specific medical cause after a thorough medical evaluation. Symptoms that are common in these patients include fatigue, headache, abdominal pain, musculoskeletal pain (back pain, myalgia, and arthralgia), dizziness, paresthesia, generalized weakness, transient edema, insomnia, dyspnea, chest pain, chronic facial pain, chronic pelvic pain, and chemical sensitivities. Symptoms can range from a minor nuisance to functional impairment. In this case, the patient's symptom does not appear to have a pathologic basis, and she is not excessively focused on or functionally limited by her symptom. As such, this patient would most appropriately be diagnosed with a medically unexplained symptom.

Conversion disorder involves at least one symptom of neurologic dysfunction (abnormal sensation or motor function) that is unexplained by a medical condition and not consistent with examination findings. Conversion disorder represents not fabrication of symptoms but rather unexplained symptoms that do not have a pathophysiologic basis. These symptoms, which are functionally limiting, occur during times of substantial physical, emotional, or psychological stress.

Illness anxiety disorder (formerly named hypochondriasis) is characterized by excessive concern about health and preoccupation with health-related activities (for example, measuring pulse). In patients with illness anxiety disorder, no or only mild somatic symptoms are present.

Somatic symptom disorder is characterized by one or more somatic symptoms present for at least 6 months, causing significant distress or interference with life and associated with excessive thoughts, behaviors, and feelings related to the symptoms. The diagnosis of somatic symptom disorder has replaced the previous diagnosis of somatization disorder.

KEY POINT

- Medically unexplained symptoms are diagnosed according to the presence of symptoms that cannot be attributed to a specific medical cause after a thorough medical evaluation.

Bibliography

Haller H, Cramer H, Lauche R, Dobos G. Somatoform disorders and medically unexplained symptoms in primary care. Dtsch Arztebl Int. 2015;112:279-87. [PMID: 25939319] doi: 10.3238/arztebl.2015.0279

Item 52 Answer: D

Educational Objective: Treat drug-induced lower extremity edema.

The most appropriate next step in the management of this patient is to discontinue pregabalin and initiate duloxetine. In most patients with lower extremity edema, a detailed history and physical examination will suggest the cause. The most common causes of lower extremity edema include venous obstruction or insufficiency, heart failure (including right-sided heart failure secondary to pulmonary disease), cirrhosis, and nephrotic syndrome and hypoalbuminemia of other etiologies. Certain drugs and classes of drugs are frequent causes of edema. Direct vasodilators (minoxidil, hydralazine, calcium channel blockers, α blockers) may produce edema by several mechanisms, including arteriolar dilatation (increases intracapillary pressure) and activation of the renin-angiotensin-aldosterone system (sodium retention). The thiazolidinediones, such as pioglitazone and rosiglitazone, stimulate sodium reabsorption by the sodium channels in the cortical collecting tubule cells. NSAIDs increase renal sodium reabsorption by inhibition of renal vasodilatory prostaglandins. Pregabalin is a calcium channel blocker and likely produces edema by the same mechanism as other calcium channel blockers; it is associated with peripheral edema in up to 17% of cases. In drug-induced edema, removal of the offending agent is the treatment of choice. This patient would benefit from switching

pregabalin to a different fibromyalgia drug that is not associated with peripheral edema, such as duloxetine.

This patient's lower extremity edema is associated with the vasodilatory effects of pregabalin and not volume overload (no jugular venous distension, S_3, pulmonary crackles). In this situation, the use of diuretics can lead to volume depletion, electrolyte disorders, and kidney dysfunction. Discontinuing the drug responsible for the edema is a better strategy.

Duplex Doppler ultrasonography is a useful tool in the evaluation of deep venous thrombosis (DVT). However, DVT typically produces unilateral edema. Additionally, this patient has no risk factors for DVT (prolonged immobilization, cancer, previous DVT) and lacks supporting findings, such as calf swelling, tenderness, and superficial venous dilation.

Although compression stockings may help reduce edema, removal of the offending agent will likely resolve this patient's edema and obviate the need for compression stockings. Furthermore, compression stockings have poor adherence rates because of high cost, discomfort, and the difficulty that patients experience in donning and removing the stockings.

KEY POINT

- In patients with drug-induced edema, removal of the offending agent is the treatment of choice.

Bibliography

Ratchford EV, Evans NS. Approach to lower extremity edema. Curr Treat Options Cardiovasc Med. 2017;19:16. [PMID: 28290004] doi: 10.1007/s11936-017-0518-6

Item 53 Answer: C

Educational Objective: Diagnose major depressive disorder.

This patient meets the diagnostic criteria for major depressive disorder. The DSM-5 requires at least five of the following symptoms (at least one of which must be depressed mood or anhedonia) to be present almost all of the time during the same 2-week period: depressed mood, anhedonia, insomnia or hypersomnia, significant change in weight or appetite, fatigue or decreased energy, psychomotor agitation or retardation, difficulty concentrating, feelings of worthlessness or excessive guilt, and recurrent thoughts of death or suicidal ideation. Symptoms of major depressive disorder cause work-related and social impairment and cannot be attributed to a medical condition, drug, or substance use. A tool for identifying and assessing the severity of depression is the PHQ-9 (www.integration.samhsa.gov/images/res/PHQ%20-%20Questions.pdf). The items of the PHQ-9 correlate with the DSM-5 criteria. Each item is scored from 0 (not bothered by the symptom) to 3 (bothered by the symptom every day); the maximum score is 27. A score of 5 to 9 indicates mild depression, 10 to 14 moderate depression, 15 to 19 moderately severe depression, and 20 or more severe depression.

Patients with bipolar disorder often present with major depressive disorder, and it is important for clinicians to inquire about any history of periods of elevated mood, increased energy, and decreased need for sleep. Without a history of such episodes, bipolar disorder cannot be diagnosed.

Generalized anxiety disorder (GAD) and other anxiety disorders can often be comorbid with major depressive disorder. Patients with GAD often experience sweats, dyspnea, palpitations, difficulty swallowing, nausea, chest and abdominal pain, loose stools, muscle tension, insomnia, fatigue, tachycardia, and tremor. Diagnosis should be considered in patients with multiple unexplained physical symptoms. This patient does not exhibit the excessive anxiety and restlessness typical of a patient with GAD.

Persistent depressive disorder, previously known as dysthymic disorder or dysthymia, is characterized by depressed mood most of the time for at least 2 years and with at least two of the following symptoms while depressed: appetite change (increased or decreased), fatigue or low energy, decreased self-esteem, insomnia or hypersomnia, poor concentration, and feelings of hopelessness. The symptoms are less severe than in major depressive disorder. This patient has more severe symptoms that have lasted only 6 months, with no history of depression.

KEY POINT

- Major depressive disorder is diagnosed by the presence of at least five cardinal symptoms, at least one of which is depressed mood or anhedonia, during the same 2-week period; a tool for identifying and assessing the severity of depression is the PHQ-9.

Bibliography

McCarron RM, Vanderlip ER, Rado J. Depression. Ann Intern Med. 2016;165:ITC49-ITC64. [PMID: 27699401] doi:10.7326/AITC201610040

Item 54 Answer: D

Educational Objective: Diagnose systemic exertion intolerance disease.

The most likely diagnosis is systemic exertion intolerance disease (SEID). Fatigue can be classified as fatigue secondary to another cause, secondary to multiple factors (termed chronic multifactorial fatigue), or a primary condition. In the past, the latter condition was termed chronic fatigue syndrome, myalgic encephalitis, or neurasthenia. In 2015, the Institute of Medicine recommended using the term systemic exertion intolerance disease over the other terms. The diagnosis of SEID requires the presence of (1) substantial reduction or impairment in the ability to engage in preillness levels of occupational, educational, social, or personal activities for at least 6 months, accompanied by profound fatigue that is not relieved by rest; (2) postexertional malaise (worsening of symptoms after physical, cognitive, or emotional effort); and (3) unrefreshing sleep. In addition to the three major criteria, the patient must also demonstrate cognitive

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impairment or orthostatic intolerance (symptoms such as lightheadedness, dizziness, fatigue, cognitive deficits, and visual difficulties that worsen when a person stands upright and improve when the person lies back down). This patient meets the validated diagnostic criteria for SEID.

Chronic multifactorial fatigue is a clinical condition defined as chronic fatigue symptoms of at least 6 months' duration in the setting of multiple fatiguing factors (medical and/or psychosocial). This patient's benign history and unrevealing evaluation argue against chronic multifactorial fatigue.

Mood disturbances are highly comorbid in patients with SEID (approximately 70% of patients), and all patients with SEID should be screened for depression and anxiety. This patient was screened appropriately and does not have findings consistent with an underlying mood disorder.

Post-Lyme disease syndrome has been reported in approximately 10% of patients after treatment of erythema migrans. Although the condition is often erroneously called chronic Lyme disease, studies have found no microbiologic evidence of chronic or latent infection after appropriate treatment. Symptoms include fatigue, arthralgia, myalgia, and impairment of memory or cognition that can last for years after treatment of the acute infection. Clinical trials have shown no benefit of prolonged antibiotic treatment for post-Lyme disease syndrome. This patient has unrefreshing sleep, postexertional malaise, and orthostatic intolerance, which are more consistent with SEID.

KEY POINT

- The diagnosis of systemic exertion intolerance disease requires the presence of fatigue of at least 6 months' duration with substantial reduction in preillness activities, postexertional malaise, unrefreshing sleep, and either cognitive impairment or orthostatic intolerance.

Bibliography

Committee on the Diagnostic Criteria for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome, Board on the Health of Select Populations, Institute of Medicine. Beyond Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Redefining an Illness. Washington, DC: National Academies Press; 2015. [PMID: 25695122]

Item 55 Answer: B

Educational Objective: Diagnose epididymitis by physical examination.

This patient is most likely to have pain relief with testicular elevation (Prehn sign). His history and examination findings (erythema and swelling of the hemiscrotum; fever; tenderness to palpation near the epididymis; and lack of worsening symptoms, nausea, vomiting, and abdominal pain) suggest a diagnosis of epididymitis. Prehn sign, which is alleviation of pain with elevation of the testicle or scrotum, can clinically support this diagnosis. Although this finding can suggest a diagnosis of epididymitis, it does not rule out other possibilities, such as testicular torsion; however, testicular torsion is less likely given this patient's presentation.

An absent cremasteric reflex suggests testicular torsion. A patient with testicular torsion would have acutely worsening and severe hemiscrotal pain, hemiscrotum elevation, abdominal pain, nausea, and vomiting. These findings are not present in this patient, and the test result would likely be negative.

Varicoceles are caused by dilation of the testicular vein and pampiniform plexus. They are common, occurring in 15% of men. Scrotal examination reveals a left-sided (90%) scrotal mass with a "bag of worms" consistency that increases with standing and decreases while supine. This patient's findings are not consistent with varicocele, and examining the patient in both standing and supine positions is unlikely to support this diagnosis.

A transillumination study, which is performed to identify a hydrocele, is not likely to have a positive result in this patient with findings that suggest epididymitis. A hydrocele manifests over a longer time frame, initially causing no symptoms and then causing a dull aching scrotal discomfort. Examination can reveal a smooth though tense scrotal mass, which transilluminates when a light source is applied adjacently.

KEY POINT

- A positive Prehn sign (relief of pain with scrotal elevation) suggests a diagnosis of epididymitis, although it does not rule out other possibilities, such as testicular torsion.

Bibliography

Crawford P, Crop JA. Evaluation of scrotal masses. Am Fam Physician. 2014;89:723-7. [PMID: 24784335]

Item 56 Answer: D

Educational Objective: Treat chronic low back pain with an NSAID.

The most appropriate pharmacologic option for this patient is an NSAID, such as ibuprofen. For patients with chronic low back pain, clinicians and patients should initially select nonpharmacologic treatment with acupuncture, cognitive behavioral therapy, electromyography biofeedback, exercise, mindfulness-based stress reduction (moderate-quality evidence), low-level laser therapy, motor control exercise, multidisciplinary rehabilitation, progressive relaxation, operant therapy or spinal manipulation, tai chi, or yoga. According to a 2017 clinical practice guideline from the American College of Physicians (ACP), pharmacologic therapy can be considered in patients with chronic low back pain that has not responded to nonpharmacologic therapy. The ACP recommends NSAIDs as first-line therapy, administered in the lowest effective dosage.

There is little evidence that acetaminophen is effective in reducing pain or improving functional status in patients with acute or chronic low back pain. As such, acetaminophen should not be recommended to this patient.

The FDA recently approved duloxetine for treating chronic low back pain on the basis of evidence from

randomized controlled trials that showed a small improvement in both pain and function with its use. However, the ACP guideline deems both duloxetine and tramadol as second-line pharmacologic options (weak recommendation, moderate quality evidence), reserved for use only after first-line options have been exhausted.

In a randomized controlled trial, opioids, such as hydrocodone, were not more effective than nonopioid therapy in treating chronic low back pain. Opioids should be used only in the treatment of chronic pain when the benefits outweigh the risks (such as abuse potential) and when a clear discussion of risks and benefits has occurred with the patient. This patient is unlikely to benefit from hydrocodone therapy.

Moderate-quality evidence showed that tramadol resulted in moderate short-term pain relief in patients with chronic low back pain and a small improvement in function compared with placebo. Of note, tramadol is a weak opioid agonist that also blocks reuptake of serotonin and norepinephrine; like other opioids, it is associated with the risk for abuse. Its use is relegated to patients who achieve inadequate relief with nonpharmacologic therapy and NSAIDs, and only after a frank discussion of the harms and benefits.

KEY POINT

- For patients with chronic low back pain, clinicians and patients should initially select nonpharmacologic treatment; NSAIDs can be considered in patients who have had an inadequate response to nonpharmacologic therapy.

Bibliography

Qaseem A, Wilt TJ, McLean RM, Forciea MA; Clinical Guidelines Committee of the American College of Physicians. Noninvasive treatments for acute, subacute, and chronic low back pain: a clinical practice guideline from the American College of Physicians. Ann Intern Med. 2017;166:514-530. [PMID: 28192789] doi:10.7326/M16-2367

Item 57 Answer: D

Educational Objective: Evaluate recurrent epistaxis.

The most appropriate management is nasal endoscopy. Ninety percent of episodes of epistaxis occur in the anterior nasal septum in the Kiesselbach area. Anterior bleeding can be managed with compression for at least 15 minutes. Posterior epistaxis (behind the posterior middle turbinate, requiring a nasopharyngoscope for visualization) may be more difficult to manage and is more common in older patients. Common causes of epistaxis include topical intranasal medications (such as glucocorticoids or antihistamines), dehumidification, and self-induced digital trauma. Among patients with epistaxis serious enough to require hospitalization, almost half have a causal systemic condition, such as anticoagulation, hemophilia, hematologic malignancy, neoplasm, and acquired coagulopathies from kidney or liver disease. Recurrent unilateral epistaxis may represent a neoplasm; hence, this patient should be referred for nasal endoscopy.

Low-dose aspirin may be associated with a slight increase in the risk for epistaxis, although data have not been conclusive and do not support routine discontinuation in otherwise healthy patients with epistaxis. Notably, other NSAIDs have not been associated with epistaxis. Even if aspirin were stopped, this patient requires further assessment given the presence of unilateral bleeding.

This patient has no symptoms of anemia or history of excessive blood loss. Although epistaxis may be associated with coagulopathies, this patient is not taking an anticoagulant and is otherwise at low risk for an acquired coagulopathy that manifests only as epistaxis. Therefore, coagulation studies are not warranted.

In 80% of patients with epistaxis, results of laboratory evaluation are normal; therefore, routine laboratory testing is not required. A complete blood count, prothrombin time, and activated partial thromboplastin time might be considered in patients with symptoms or signs of a bleeding disorder and those with severe or recurrent epistaxis.

KEY POINT

- Recurrent unilateral epistaxis may be a sign of neoplasm and warrants referral for nasal endoscopy.

Bibliography

Morgan DJ, Kellerman R. Epistaxis: evaluation and treatment. Prim Care. 2014;41:63-73. [PMID: 24439881] doi:10.1016/j.pop.2013.10.007

Item 58 Answer: D

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Educational Objective: Identify the Plan-Do-Study-Act cycle as an effective quality improvement method.

The most likely intervention to improve hand hygiene in this hospital is to use a Plan-Do-Study-Act (PDSA) cycle. A PDSA cycle is a four-step process involving a rapid cycle of change in which baseline data are collected, an intervention is planned and then implemented on a small scale, the results are analyzed, and an action plan is made. Additional PDSA cycles are completed until the desired results are achieved. In this case, a PDSA cycle could be used to study hand hygiene procedures and implement interventions to increase rates of hand hygiene, with the overall goal of reducing the incidence of hospital-acquired infections.

Spaghetti diagrams are used to visually display flow through a system. The flows are drawn as lines on a map and look similar to spaghetti noodles. As an example, a spaghetti diagram may be used to follow a medication order through a hospital unit from order generation to administration of the medication. The diagram can help highlight inefficiencies or redundancies in a system. Although useful in identifying areas ripe for increased efficiency, a spaghetti diagram will have no impact on improving hand hygiene rates.

The Lean model aims to maximize value and minimize waste by closely examining a system's processes and eliminating non-value-added activities within the system. Value stream mapping can be used to graphically display the steps of a process and the time required for each step, thereby

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highlighting process inefficiencies or areas of waste and allowing for their improvement. The Lean model could be used to determine inefficiencies in hospital processes (such as waiting times); however, it would not help improve hand hygiene rates.

Reiterating the importance of hand hygiene in an email to the entire staff may be a part of a planned intervention to improve hand hygiene, although it alone is unlikely to provide sustained results.

KEY POINT

- A Plan-Do-Study-Act cycle is a four-step process involving a rapid cycle of change in which baseline data are collected, an intervention is planned and then implemented on a small scale, the results are analyzed, and an action plan is made.

Bibliography

Morelli MS. Using the Plan, Do, Study, Act Model to implement a quality improvement program in your practice. Am J Gastroenterol. 2016;111:1220-2. [PMID: 27527744]

Item 59 Answer: D

Educational Objective: **Identify medications associated with increased risk for side effects in an older patient.**

Quetiapine is the medication with greatest potential for adverse effects in this older patient taking multiple prescription medications. Although treatment of comorbid conditions often requires multiple medications, evidence shows that half of older adults take one or more medications that are not medically necessary (that is, not indicated, not effective, or therapeutically duplicative). Frequent review of patient medications to verify their necessity and proper dosing is an essential aspect of optimal geriatric care. Notably, certain medications carry a particularly high risk for geriatric patients. In an effort to improve the care of older adults by reducing the use of potentially inappropriate medications, the American Geriatrics Society (AGS) has compiled a list of high-risk drugs that must be carefully considered in terms of risk-to-benefit ratio in the elderly (available at http://geriatricscareonline.org/ProductAbstract/american-geriatrics-society-updated-beers-criteria-for-potentially-inappropriate-medication-use-in-older-adults/CL001). All antipsychotic medications, both first- and second-generation, have significant adverse effects, including anticholinergic effects, extrapyramidal symptoms, and sedation, and older patients are particularly susceptible to these negative effects. For this reason, the AGS 2015 Beers Criteria for Potentially Inappropriate Medication Use in Older Adults recommends avoidance of quetiapine and all antipsychotic medications.

Acetaminophen is relatively safe for older patients if not used at maximal doses for extended periods. Side effects from acetaminophen are far less likely and less severe than other commonly used systemic analgesics, including opioids and NSAIDs.

Amlodipine is not listed as a medication to avoid in the AGS 2015 Beers Criteria. Although the drug could potentially cause excessive blood pressure reduction, this patient's blood pressure is under acceptable control and without orthostatic changes.

Lisinopril can potentially cause electrolyte abnormalities, orthostatic hypotension, and kidney insufficiency. However, this patient has no evidence of these problems, and lisinopril is not included in the Beers Criteria as a potentially inappropriate medication.

KEY POINT

- Frequent review of patient medications to verify their necessity and proper dosing is an essential aspect of optimal geriatric care.

Bibliography

The American Geriatrics Society 2015 Beers Criteria Update Expert Panel. American Geriatrics Society 2015 updated Beers criteria for potentially inappropriate medication use in older adults. J Am Geriatr Soc. 2015;63:2227-46. [PMID: 26446832] doi:10.1111/jgs.13702

Item 60 Answer: B

Educational Objective: **Diagnose opioid-induced hyperalgesia.**

The most likely diagnosis is opioid-induced hyperalgesia. Opioid-induced hyperalgesia is thought to result from repeated exposure to systemic opioids. In patients with this pain syndrome, the character of their pain may change during the course of opioid therapy, pain may worsen with increased opioid dosages, and pain may decrease when opioid dosages are reduced. In this case, the patient has chronic pain as a sequela of her cancer diagnosis and treatment, and she has required significant dosage escalation in the absence of progressive disease. She also has evidence of cognitive slowing, hyperreflexia, and myoclonus as a result of the neuroexcitatory effects of long-term opioid use; these signs are concerning for opioid-induced toxicity. Appropriate management of opioid-induced hyperalgesia includes opioid dosage reduction in a monitored setting with close follow-up.

Malingering is characterized by the development of symptoms that lack a pathologic basis. The key feature is faking or exaggerating symptoms for an obvious external benefit, such as money, drugs, or escaping criminal prosecution. Malingering should be suspected in patients with inconsistencies in the history and physical examination; nonadherence to recommended diagnostic testing or treatments; known or suspected personality disorder; and legal difficulties. There is no indication of these traits to suggest malingering as the cause of this patient's symptoms.

Opioid withdrawal is unlikely in this patient given her constant symptoms and escalation in the dosages of hydromorphone and transdermal fentanyl.

Pseudoaddiction is a phenomenon in which patients exhibit behaviors concerning for substance use disorder or

addiction that are driven by inadequate pain control in the setting of a documented progressive disease. Although this patient has a sequela of cancer therapy, her clinical status is unchanged, and there is no evidence of progressive disease on physical examination or CT scan.

KEY POINT

- In patients with opioid-induced hyperalgesia, the character of their pain may change during the course of opioid therapy, pain may worsen with increased opioid dosages, and pain may decrease when opioid dosages are reduced.

Bibliography

Yi P, Pryzbylkowski P. Opioid induced hyperalgesia. Pain Med. 2015;16 Suppl 1:S32-6. [PMID: 26461074] doi:10.1111/pme.12914

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Item 61 Answer: D

Educational Objective: **Manage dual antiplatelet therapy in a patient with recent coronary stent placement who is undergoing urgent noncardiac surgery.**

The most appropriate management of this patient's antiplatelet therapy is to withhold clopidogrel 5 to 7 days before surgery and continue aspirin. According to the 2016 American College of Cardiology/American Heart Association focused update on the duration of dual antiplatelet therapy (DAPT), perioperative management is based on surgical bleeding risk balanced with the risk for stent thrombosis. The risk for stent thrombosis is contingent on both the indication for coronary stent placement (stable ischemic heart disease [SIHD] or acute coronary syndrome [ACS]) and the amount of time that has passed from the time of stent placement.

For patients who have a stent placed for SIHD, DAPT (aspirin plus a $P2Y_{12}$ inhibitor) should be continued for at least 30 days after bare metal stent placement and a minimum of 6 months after drug-eluting stent placement. DAPT is recommended for 1 year in patients with ACS, regardless of medical management or cardiac stent placement, with the understanding that discontinuation may be reasonable if high bleeding risk is identified or the patient has overt bleeding on DAPT. However, in the perioperative setting, and especially if the risk of surgical delay exceeds the risk for stent thrombosis, discontinuation of the $P2Y_{12}$ inhibitor can be considered after a minimum of 30 days in the case of bare metal stent placement or 3 months after drug-eluting stent placement. It is optimal to continue DAPT for 6 months after drug-eluting stent placement, especially in the case of ACS, if the risk for surgical delay does not exceed the risk for stent thrombosis. Aspirin should be continued, if at all possible, along with restarting of DAPT as soon as bleeding risk has sufficiently diminished.

If surgery must be performed within those periods after percutaneous coronary intervention, DAPT should be maintained perioperatively unless the risk for major bleeding exceeds the risk for stent thrombosis. Communication with the surgical team and the patient regarding risks and benefits of withholding DAPT within these time frames is advised.

KEY POINT

- In patients taking dual antiplatelet therapy, if the risk of surgical delay exceeds the risk for stent thrombosis, discontinuation of the $P2Y_{12}$ inhibitor can be considered after a minimum of 30 days in the case of bare metal stent placement or 3 months after drug-eluting stent placement.

Bibliography

Levine GN, Bates ER, Bittl JA, Brindis RG, Fihn SD, Fleisher LA, et al. 2016 ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2016;68:1082-115. [PMID: 27036918]

Item 62 Answer: A

Educational Objective: **Engage a patient in shared decision making for prostate cancer screening.**

The most appropriate action is to first engage the patient in a discussion of the benefits and harms of prostate cancer screening. No organization recommends prostate-specific antigen (PSA) testing for prostate cancer screening without a discussion of the benefits and harms and a patient's clear expressed preference for screening. Clinicians should inform men about the limited potential benefits and substantial harms of screening for prostate cancer. Screening offers a small potential benefit of reducing the chance of dying of prostate cancer. However, many men will experience potential harms of screening, including false-positive results that require additional testing and possible prostate biopsy; overdiagnosis and overtreatment; and treatment complications, such as incontinence and impotence. All organizations recommend individualized decision making about screening for prostate cancer so that each man has an opportunity to incorporate his values and preferences into his decision. On the basis of the available evidence, it is not possible to make a definitive recommendation for or against prostate cancer screening in men with a family history of prostate cancer. Although screening may offer additional potential benefits for these men compared with the general population, screening also has the potential to increase exposure to potential harms, especially among men with relatives whose cancer was overdiagnosed.

Although some expert groups recommend performing a digital rectal examination in conjunction with PSA testing for prostate cancer screening, digital rectal examination alone is not recommended because this test has suboptimal sensitivity and very low positive predictive value.

The U.S. Preventive Services Task Force recommends that clinicians should not screen men who do not express a preference for screening and recommends against

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PSA-based screening for prostate cancer in men aged 70 years and older.

KEY POINT

- The decision to pursue prostate cancer screening should be individualized so that each man has an opportunity to understand the potential benefits and harms of screening and to incorporate his values and preferences into his decision.

Bibliography

Grossman DC, Curry SJ, Owens DK, Bibbins-Domingo K, Caughey AB, Davidson KW, et al; US Preventive Services Task Force. Screening for prostate cancer: US Preventive Services Task Force recommendation statement. JAMA. 2018;319:1901-1913. [PMID: 29801017] doi:10.1001/jama.2018.3710

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Item 63 Answer: E

Educational Objective: Manage audible oropharyngeal secretions in a patient at the end of life.

This patient has audible posterior oropharyngeal secretions, which are most appropriately managed with family education and reassurance. Although several studies suggest that respiratory distress is not typically associated with these secretions, caregivers are often concerned by what is commonly referred to as the "death rattle." The first steps in management include caregiver education and anticipatory guidance. Additionally, repositioning often allows secretions to drain without pharmacologic intervention. Mouth hygiene with a sponge swab may also be helpful.

Current literature does not support the routine use of antimuscarinic drugs in the treatment of death rattle. A 2014 literature review acknowledged that death rattle leads to distress in both relatives and professional caregivers; however, its impact on patients is unclear, and medical therapy is unproven. Studies involving atropine, glycopyrronium, scopolamine, hyoscine butylbromide, and/or octreotide were reviewed, and only one study used a placebo group. There is currently no evidence that the use of any antimuscarinic drug is superior to no treatment. In addition, the use of anticholinergic agents in patients who are awake can lead to undesirable symptoms, such as dry mouth and urinary retention.

Suctioning by catheter should be avoided in managing end-of-life secretions unless the secretions are causing the patient obvious respiratory distress or cough. Suction catheters can cause local trauma.

KEY POINT

- Audible posterior oropharyngeal secretions ("death rattle") are common at the end of life and are best managed with family education and reassurance.

Bibliography

Lokker ME, van Zuylen L, van der Rijt CC, van der Heide A. Prevalence, impact, and treatment of death rattle: a systematic review. J Pain Symptom Manage. 2014;47:105-22. [PMID: 23790419] doi:10.1016/j.jpainsymman.2013.03.011

Item 64 Answer: D

Educational Objective: Vaccinate an adult smoker against pneumococcal disease.

This patient should be administered the 23-valent pneumococcal polysaccharide vaccine (PPSV23). Pneumococcal vaccination is recommended in all adults aged 65 years and older and adults aged 19 to 64 years with certain high-risk conditions. Two pneumococcal vaccines are available: PPSV23 and a 13-valent conjugate vaccine (PCV13). The Advisory Committee on Immunization Practices recommends administering PPSV23 alone to select immunocompetent patients aged 19 to 64 years, including those with chronic heart, liver, or lung disease; diabetes mellitus; cochlear implants; cerebrospinal fluid leak; alcoholism; or cigarette smoking. Because this patient is a current smoker, he should be given PPSV23.

In adults aged 19 to 64 years with immunocompromise, cochlear implants, or a history of cerebrospinal fluid leaks, PCV13 should be administered in addition to PPSV23. In these patients, a single dose of PCV13 should be given first, followed by a single dose of PPSV23 at least 8 weeks later. Additionally, all adults aged 65 years and older who have not previously been vaccinated should receive PCV13, followed by a dose of PPSV23 1 year later. For immunocompetent adults aged 65 years and older who previously received one or more doses of PPSV23, a single dose of PCV13 should be given at least 1 year after the most recent PPSV23 dose. This patient does not meet the criteria for PCV13 administration.

All adults aged 50 years and older, including those with a previous episode of zoster, should receive the recombinant (inactivated) zoster vaccine to reduce the incidence of zoster and postherpetic neuralgia. The recombinant zoster vaccine is recommended in preference to the live attenuated zoster vaccine, and adults who have been previously vaccinated with the live attenuated zoster vaccine should be revaccinated with the recombinant zoster vaccine after a period of at least 8 weeks. This patient should receive the recombinant zoster vaccine in 2 years.

In persons who previously received the tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap) vaccine, revaccination with a tetanus and diphtheria toxoids (Td) booster is recommended every 10 years. Additionally, for pregnant women, one dose of the Tdap vaccine should be administered during each pregnancy between 27 weeks' and 36 weeks' gestation, regardless of when the last dose of Td or Tdap was given. This patient last received the Tdap vaccine 9 years ago and should receive a Td booster in 1 year.

Given the patient's history of cigarette smoking, offering no vaccinations at this time would not be the best strategy.

KEY POINT

- The 23-valent pneumococcal polysaccharide vaccine should be administered to select immunocompetent patients aged 19 to 64 years, including those with chronic heart, liver, or lung disease; diabetes mellitus; cochlear implants; cerebrospinal fluid leak; alcoholism; or cigarette smoking.

Bibliography

Kim DK, Riley LE, Hunter P; Advisory Committee on Immunization Practices. Recommended immunization schedule for adults aged 19 years or older, United States, 2018. Ann Intern Med. 2018;168:210-220. [PMID: 29404596] doi:10.7326/M17-3439

Item 65 Answer: B

Educational Objective: Diagnose binge eating disorder.

This patient most likely has binge eating disorder (BED), which is characterized by impulsive overeating and feeling loss of control around food. The diagnosis of this disorder requires at least three of the following characteristics occurring at least once weekly for 3 months: abnormally rapid consumption, consuming large amounts of food when not hungry, eating alone due to embarrassment, eating until uncomfortably full, and feelings of guilt related to overconsumption. BED is more common than both anorexia and bulimia nervosa and is often accompanied by other psychiatric problems. The primary treatment is cognitive behavioral therapy.

Bulimia nervosa and the binging subtype of anorexia nervosa both include episodes of binge eating like BED. The key in differentiating BED from these diseases is the lack of compensatory behaviors (such as induced vomiting and laxative abuse) to avoid weight gain. The major difference between bulimia nervosa and the binging subtype of anorexia nervosa is that patients with anorexia nervosa have a low BMI (usually <18).

Many people have episodes of overeating in which they may eat until uncomfortable or feel guilty about their eating. However, simple overeating does not meet the diagnostic criteria for BED and is not accompanied by the feelings of loss of control over food consumption.

KEY POINT

- The diagnosis of binge eating disorder requires at least three of the following characteristics occurring at least once weekly for 3 months: abnormally rapid consumption, consuming large amounts of food when not hungry, eating alone due to embarrassment, eating until uncomfortably full, and feelings of guilt related to overconsumption.

Bibliography

Attia E. In the clinic. Eating disorders. Ann Intern Med. 2012;156:ITC4-1-ITC4-15, quiz ITC4-16. [PMID: 22473445] doi:10.7326/0003-4819-156-7-201204030-01004

Item 66 Answer: B

Educational Objective: Manage cyclic mastalgia.

The most appropriate next step in this patient's management is the use of a well-fitting bra. Breast pain is common among women and is categorized primarily as cyclic or noncyclic in relation to the menstrual cycle. This patient has cyclic mastalgia, which is bilateral and diffuse and worsens in the days before menses and then abates. Cyclic mastalgia is often related to hormonal changes that occur with ovulation. Because most symptoms of cyclic mastalgia are self-limited, management usually requires only education, reassurance, and appropriate breast support.

There is no evidence from controlled studies that avoidance of caffeine in the diet or beverages relieves breast pain. Similarly, no evidence supports the use of vitamin E and evening primrose oil in reducing pain.

Cyclic mastalgia with no abnormal clinical findings, such as a breast mass or skin changes, does not warrant diagnostic imaging. Hence, ultrasonography and mammography are unnecessary in this patient.

Danazol is approved by the FDA for management of mastalgia, but because of limiting androgenic side effects, it is recommended only for management of persistent severe cyclic breast pain unrelieved by conservative management. If education, reassurance, and appropriate breast support do not sufficiently control symptoms, acetaminophen or an oral or topical NSAID may be useful and can be recommended before consideration of danazol therapy.

KEY POINT

- Cyclic mastalgia is often related to hormonal changes that occur with ovulation, resulting in diffuse premenstrual breast pain that resolves with the menstrual cycle; the most appropriate management is education, reassurance, and appropriate breast support.

Bibliography

Iddon J, Dixon JM. Mastalgia. BMJ. 2013;347:f3288. [PMID: 24336097] doi:10.1136/bmj.f3288

Item 67 Answer: D

H

Educational Objective: Diagnose central vertigo on the basis of Dix-Hallpike maneuver results.

The most likely diagnosis is vertebrobasilar ischemia. In patients with vertigo, it is crucial to differentiate central from peripheral causes, especially in patients with acute vertigo concerning for vertebrobasilar ischemia and other central causes. The Dix-Hallpike maneuver is an effective bedside test for this purpose. In this test, the examiner stands at the patient's side and rotates the patient's head 45 degrees; the examiner then moves the patient, whose eyes are open, from the seated to the supine ear-down position. The patient's neck is extended slightly so that the chin is pointed upward, and the patient is observed for nystagmus. During the test, the latency, duration, fatigability, and direction of nystagmus are noted. The maneuver is repeated with the patient's head turned in the opposite direction. Findings that indicate central vertigo are nystagmus with an immediate onset (no latency), longer duration (>1 minute), no fatigability, and vertical or horizontal directionality without a torsional component. With central vertigo, the direction of nystagmus may vary depending on the direction of the patient's gaze. Potentially life-threatening conditions associated with

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central vertigo include ischemia, infarction, or hemorrhage of the cerebellum or brainstem. Patients at high risk include those with hypertension, diabetes mellitus, hyperlipidemia, or advanced age. Vertebrobasilar stroke is usually, but not always, accompanied by dysarthria, dysphagia, diplopia, weakness, or numbness. Cerebellar infarct may present with gait or truncal ataxia or with vertigo alone. In a patient presenting with suspicion for a central cause of vertigo, brain MRI and magnetic resonance angiography of the posterior cerebral circulation are the preferred diagnostic studies.

Dix-Hallpike maneuver results that suggest peripheral vertigo include nystagmus that is delayed in onset (presence of latency), is of short duration (<1 minute), exhibits fatigability (habituation), and is primarily unidirectional (usually up-beating and torsional [rotary phenomenon]). The presence of severe symptoms also indicates peripheral vertigo. The most common cause of peripheral vertigo (and all types of vertigo) is benign paroxysmal positional vertigo. Vestibular neuronitis (or labyrinthitis, if hearing is affected), another cause of peripheral vertigo, may follow a viral syndrome that has affected the vestibular portion of cranial nerve VIII. Less common causes of peripheral vertigo are Meniere disease (triad of vertigo, hearing loss, and tinnitus), perilymphatic fistula (vertigo and hearing loss with history of straining or trauma), and acoustic neuroma (tinnitus and associated unilateral sensorineural hearing loss).

An additional bedside test that can be performed to help differentiate central from peripheral causes of vertigo is the HINTS (Head Impulse, Nystagmus, and Test of Skew) examination. Findings concerning for a central cause of vertigo are the absence of catch-up saccades on the head impulse test, bidirectional nystagmus on the nystagmus assessment, and the presence of vertical skew on the test of skew.

KEY POINT

- In patients with central vertigo, the Dix-Hallpike maneuver produces nystagmus with an immediate onset (no latency), longer duration (>1 minute), no fatigability, and vertical or horizontal directionality without a torsional component.

Bibliography

Kim JS, Zee DS. Clinical practice. Benign paroxysmal positional vertigo. N Engl J Med. 2014;370:1138-47. [PMID: 24645946] doi: 10.1056/NEJMcp1309481

Item 68 Answer: B

Educational Objective: Evaluate prepatellar bursitis.

This patient has prepatellar bursitis, and the first step in management should be fluid aspiration. Prepatellar bursitis is caused by inflammation of the prepatellar bursa that overlies the patella. Patients present with anterior knee pain and swelling. Physical examination reveals a palpable fluid collection with preserved active and passive range of motion of the knee. The most common cause of chronic prepatellar bursitis is repetitive trauma, as is likely the case in this patient, who must frequently kneel in his job as a carpet installer. Other causes include gout and infection. Most cases of acute prepatellar bursitis are infectious (typically related to skin bacteria), although trauma and gout are other potential causes. Regardless of the duration of the swelling, all patients with prepatellar bursitis should undergo fluid aspiration. Gram stain and culture of the bursal fluid should be obtained and analyzed for leukocyte count and for the presence of crystals to evaluate for the possibility of an underlying infectious cause and gout.

Prepatellar bursitis due to repetitive trauma from kneeling is managed with activity modification (avoidance of kneeling), in addition to the use of oral NSAIDs such as ibuprofen. It would be inappropriate to recommend activity modification or NSAIDs before first analyzing bursal fluid to rule out infection or gout.

Plain radiography is not usually required for the diagnosis of prepatellar bursitis. It may show soft-tissue swelling on lateral views but rarely aids in establishing the correct diagnosis. Plain radiographs should be obtained when knee osteoarthritis is suspected or there is concern for fracture, neither of which applies to this patient.

Prepatellar bursitis caused by gout is diagnosed by bursal fluid analysis and detecting monosodium urate crystals with polarized microscopy. A high serum urate level supports the potential for gout; however, most patients with hyperuricemia do not have gout, and the serum urate level may be low during some acute attacks. Therefore, it would be inappropriate to obtain a serum uric acid level in this patient.

KEY POINT

- Prepatellar bursitis can be caused by repetitive trauma, infection, or gout; fluid aspiration and subsequent analysis should be performed in all patients.

Bibliography

Hong E, Kraft MC. Evaluating anterior knee pain. Med Clin North Am. 2014;98:697-717, xi. [PMID: 24994047] doi:10.1016/j.mcna.2014.03.001

Item 69 Answer: A

H

Educational Objective: Prevent a pressure injury in a patient with limited mobility.

An advanced static mattress is the most appropriate intervention to prevent pressure injuries (also known as pressure ulcers) in this patient. Pressure injuries are common in hospitals and long-term care settings. They can result in decreased quality of life, with associated depression, impaired mobility, and social isolation. The Centers for Medicare & Medicaid Services has selected the development of pressure ulcers as a sentinel health event (unexpected and preventable occurrence that results in serious patient injury) for health care facilities. Prevention of pressure injuries starts with identifying patients at risk. There are many standardized risk assessment tools, but evidence of whether these

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are superior to clinical judgment is inconclusive. Risk factors include advanced age, cognitive impairment, reduced mobility, sensory impairment, and comorbid conditions that affect skin integrity (such as low body weight, incontinence, edema, poor microcirculation, and hypoalbuminemia). Pressure redistribution is the most important factor in preventing pressure injuries through the use of pressure-reducing equipment and proper patient positioning. In 2015, the American College of Physicians (ACP) published a clinical practice guideline for risk assessment and prevention of pressure ulcers. The guideline recommends regular, structured risk assessment of patients and the use of an advanced static mattress or advanced static overlay for patients who are at increased risk. An advanced static mattress is made of specialized sheepskin, foam, or gel and is immobile when a patient lies on it, whereas an advanced static overlay is a pad composed of foam or gel that is secured to the top of a regular mattress.

The ACP guideline recommends against the use of alternating air mattresses because of lack of data showing a clear advantage as well as cost considerations.

There are limited data concerning the preventive effectiveness of frequent patient repositioning, dietary supplements (such as zinc, creams, or dressings), and silicone foam dressings as isolated interventions.

KEY POINT

- An advanced static mattress or mattress overlay made of specialized sheepskin, foam, or gel provides the best protection against the development of pressure injuries in hospitalized patients.

Bibliography

Qaseem A, Mir TP, Starkey M, Denberg TD; Clinical Guidelines Committee of the American College of Physicians. Risk assessment and prevention of pressure ulcers: a clinical practice guideline from the American College of Physicians. Ann Intern Med. 2015;162:359-69. [PMID: 25732278] doi:10.7326/M14-1567

Item 70 Answer: A

Educational Objective: Screen for HIV infection in a high-risk patient.

The most appropriate interval for HIV screening in this high-risk patient is at least annually. The U.S. Preventive Services Task Force (USPSTF) recommends HIV screening for patients aged 15 to 65 years in all health care settings. The currently recommended method for initial testing is combination HIV antibody immunoassay/p24 antigen testing. An "opt-out" approach is preferred; patients are notified that testing will be performed but can decline. Special consent for testing is not required. HIV testing provides a "teachable moment" to conduct HIV/sexually transmitted infection (STI) prevention counseling and offer pre-exposure prophylaxis for high-risk patients. However, prevention counseling should not be a required activity because it can be perceived as a barrier to screening.

The USPSTF suggests that a reasonable approach is one-time screening of adolescent and adult patients and repeated screening of high-risk persons, persons engaged in risky behaviors, and those who reside in or receive medical care in high-prevalence settings for HIV infection. Persons at high risk (as opposed to very high risk) include those who have acquired or requested testing for other STIs. High-prevalence settings include STI clinics, correctional facilities, homeless shelters, tuberculosis clinics, clinics serving men who have sex with men (MSM), and adolescent health clinics with a high prevalence of STIs. The USPSTF suggests rescreening persons at increased risk every 3 to 5 years. In the absence of reliable data, the USPSTF suggests screening very high-risk individuals (MSM and injection drug users) for new HIV infection at least annually. Risk categories may change, and the USPSTF notes that rescreening may not be necessary for persons who have not been at increased risk since they were last tested. Women screened during a previous pregnancy should be rescreened in subsequent pregnancies.

In 2015, the Centers for Disease Control and Prevention recommended that providers should offer HIV screening at least annually to all sexually active MSM. Clinicians can also consider the potential benefits of more frequent HIV screening (such as every 3 or 6 months) for some asymptomatic sexually active MSM based on their individual risk factors, local HIV epidemiology, and local policies. The CDC also recommends yearly testing for syphilis, gonorrhea, and chlamydia in MSM; in contrast, the USPSTF has found insufficient evidence to recommend screening for these diseases in men.

KEY POINT

- Sexually active gay, bisexual, and other men who have sex with men and injection drug users should be screened for HIV infection at least annually.

Bibliography

DiNenno EA, Prejean J, Irwin K, Delaney KP, Bowles K, Martin T, et al. Recommendations for HIV screening of gay, bisexual, and other men who have sex with men - United States, 2017. MMWR Morb Mortal Wkly Rep. 2017;66:830-832. [PMID: 28796758]

Item 71 Answer: D

Educational Objective: Reduce cardiovascular risk with statin therapy in a patient without known atherosclerotic cardiovascular disease.

The most appropriate therapy for primary prevention of atherosclerotic cardiovascular disease (ASCVD) in this patient is simvastatin. All patients at increased cardiovascular risk should be counseled regarding therapeutic lifestyle changes, including dietary modification, regular physical activity, weight loss, and smoking cessation. In addition to therapeutic lifestyle changes, the American College of Cardiology (ACC)/American Heart Association (AHA) cholesterol treatment guideline recommends adding moderate- or high-intensity statin therapy for primary prevention of ASCVD in adults aged 40 to 75 years without known ASCVD or diabetes mellitus if ASCVD risk is 7.5% or higher, taking into account patient preferences, adverse effects, and expected ASCVD

risk reduction. The U.S. Preventive Services Task Force (USPSTF) recommends low- to moderate-intensity statin therapy in asymptomatic adults aged 40 to 75 years without ASCVD who have at least one ASCVD risk factor (dyslipidemia, diabetes, hypertension, or smoking) and a calculated 10-year ASCVD event risk of 10% or higher. This patient with a 10-year risk for ASCVD of 11.1% meets the criteria of both the ACC/AHA and USPSTF guidelines, and both guidelines support initiation of moderate-intensity statin therapy.

In the absence of familial hypercholesterolemia, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, such as alirocumab and evolocumab, are not indicated in the primary prevention of ASCVD. Cost, treatment burden (injections), and minimal long-term safety data argue against their use in primary prevention.

Nonstatin drugs should be considered alone or in combination with statins in patients who do not achieve adequate LDL cholesterol reduction with statin therapy, especially in high-risk patients (those with clinical ASCVD, baseline LDL cholesterol level >190 mg/dL [4.92 mmol/L], or diabetes). This patient does not have an indication for ezetimibe therapy alone or in combination with a statin.

In patients with a fasting triglyceride level of 500 mg/dL (5.65 mmol/L) or higher, triglyceride-lowering drug therapy is useful to prevent pancreatitis. Fibrates, such as gemfibrozil, result in an average reduction in triglyceride levels of 30% to 50%, but this patient does not have an indication for fibrate therapy.

KEY POINT

- In patients aged 40 to 75 years with no atherosclerotic cardiovascular disease (ASCVD) or diabetes mellitus and a 10-year ASCVD risk of 7.5% or higher, the American College of Cardiology/American Heart Association recommend moderate- or high-intensity statin therapy for primary prevention of ASCVD.

Bibliography

Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, et al; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014;129:S1-45. [PMID: 24222016] doi:10.1161/01.cir.0000437738.63853.7a

H Item 72 Answer: A

Educational Objective: Disclose a medical error to an affected patient.

The most appropriate management is to explain to the patient that an error was committed and the steps that will be taken to reduce the chance of recurrence. This case involves the most common type of medical error, one related to inappropriate medication dosing. Current standards recommend full disclosure of serious unanticipated outcomes, and several states mandate such disclosures. Disclosure of errors is necessary to respect the patient's autonomy, promote trust through honesty, and promote justice through appropriate compensation. Error disclosure should include an explanation of the course of events and how the error occurred, an apology by the physician, a description of how the effects of the error will be minimized or rectified, and steps the physician or system will take to reduce recurrences. In this case, the physician should inform his or her colleague of the error, and they should work within the practice to explore factors that caused the error and determine ways to reduce errors in the future.

The pharmacy may have played a role in commission of the error; however, it would be inappropriate to deflect blame to another source. Communication with the pharmacy regarding the correct dosage would be important in rectifying the situation.

The National Practitioner Data Bank is a federal repository of reports regarding serious professional or safety concerns, including medical malpractice payments or serious actions taken against physicians (such as suspension of licensure or clinical privileges). The error in this case should be disclosed and investigated; however, it would not be appropriate to report to the National Practitioner Data Bank.

Although addressing this patient's symptom without disclosing that an error occurred is an attractive option, disclosure respects the patient's autonomy by providing her with information necessary to make an informed decision about her care. Furthermore, the disclosure may enhance physician-patient communication and trust. Data from health systems that implement medical error disclosure policies suggest that disclosure decreases malpractice lawsuits and litigation costs.

KEY POINT

- Error disclosure should include an explanation of the course of events and how the error occurred, an apology by the physician, a description of how the effects of the error will be minimized or rectified, and steps the physician or system will take to reduce recurrences.

Bibliography

Snyder L; American College of Physicians Ethics, Professionalism, and Human Rights Committee. American College of Physicians ethics manual: sixth edition. Ann Intern Med. 2012;156:73-104. [PMID: 22213573] doi:10.7326/0003-4819-156-1-201201031-00001

Item 73 Answer: C

Educational Objective: Evaluate a patient with probable overflow incontinence.

Obtaining a postvoid residual urine volume is the most appropriate next step in the management of this patient. This patient likely has neurogenic bladder with overflow incontinence, characterized by constant urine leaking and dribbling and a palpable bladder. Overflow incontinence is more commonly found in men with prostatic hyperplasia and bladder outlet obstruction. However, this patient has long-standing diabetes mellitus and evidence of autonomic

neuropathy (resting tachycardia, dry feet, distended bladder) on physical examination. Postvoid residual bladder volume measurement with ultrasonography can confirm the presence of large volumes of urine in the bladder, supporting the clinical diagnosis.

Botulinum toxin injection is used in the treatment of urgency urinary incontinence that persists despite behavioral and pharmacologic therapies. A systematic review concluded that botulinum toxin injection was superior to placebo in reducing incontinence in patients with urgency incontinence unresponsive to more conservative measures. Symptoms are typically reduced for 3 to 6 months, and then reinjection is required. Such injections can worsen overflow incontinence and would be contraindicated in this patient.

Oxybutynin is an anticholinergic agent used in the treatment of urgency incontinence. Anticholinergic drugs (oxybutynin, darifenacin, fesoterodine, solifenacin, tolterodine, trospium) block the muscarinic cholinergic receptors and decrease bladder contractility. The use of oxybutynin would worsen overflow incontinence due to neurogenic bladder and would be contraindicated in this patient.

Urodynamic testing is not recommended in the initial evaluation of urinary incontinence. Urodynamic testing consists of measuring bladder pressure during bladder filling, urine flow rate, and pressure-flow correlations and testing for sphincter deficiency. Urodynamic studies are required only for complex cases in which neurologic disease is suspected or surgical intervention is being considered.

KEY POINT

- A postvoid residual urine volume, determined by ultrasonography, can confirm a suspected case of overflow urinary incontinence.

Bibliography

Kadow BT, Tyagi P, Chermansky CJ. Neurogenic causes of detrusor underactivity. Curr Bladder Dysfunct Rep. 2015;10:325-331. [PMID: 26715948]

Item 74 Answer: B

Educational Objective: Treat chronic pelvic pain syndrome.

A trial of pregabalin is the most appropriate treatment for this patient with chronic pelvic pain syndrome (CPPS). CPPS is characterized by chronic pelvic pain and intermittent voiding symptoms without evidence of infection. Subtypes of this condition include inflammatory and noninflammatory forms. Treatment involves a multimodal approach; options include pharmacologic therapies (antibiotics, anti-inflammatory agents, α-blocking agents, 5α-reductase inhibitors, and neuromodulating agents) and nonpharmacologic strategies (biofeedback, cognitive behavioral therapy, and physical therapy). There is limited and conflicting evidence for thermal ablation therapies and direct surgical interventions. Despite these options, treatment can be challenging, with minimal rates of improvement. This patient has already attempted numerous medication regimens without symptomatic improvement. At this time, it would be most prudent to proceed with a neuromodulatory approach, with medications such as pregabalin, gabapentin, or nortriptyline. Nonpharmacologic options could also be recommended at this juncture.

No evidence supports the use of lidocaine-hydrocortisone suppositories in the treatment of CPPS.

This patient has already attempted numerous trials of antibiotics, anti-inflammatory agents, and α-blocking agents without any appreciable symptomatic improvement. Furthermore, the laboratory results do not reflect any evidence for an underlying active infection, systemic inflammation, or urinary retention. Consequently, a trial of tamsulosin or trimethoprim-sulfamethoxazole would not be appropriate.

KEY POINT

- Treatment of chronic pelvic pain syndrome demands a multimodal approach, with options including both pharmacologic and nonpharmacologic strategies; among the pharmacologic options are neuromodulatory agents, such as pregabalin, gabapentin, and nortriptyline.

Bibliography

Bharucha AE, Lee TH. Anorectal and pelvic pain. Mayo Clin Proc. 2016; 91:1471-1486. [PMID: 27712641] doi:10.1016/j.mayocp.2016.08.011

Item 75 Answer: A

Educational Objective: Treat somatic symptom disorder.

Cognitive behavioral therapy (CBT) is the most appropriate next step in management. This patient meets the diagnostic criteria for somatic symptom disorder: one or more somatic symptoms causing distress or interference with daily life; excessive thoughts, feelings, and behaviors related to the somatic symptoms; and persistence of somatic symptoms for at least 6 months. Furthermore, after thorough investigation, her symptoms have no identifiable organic source. In addition to acknowledging the patient's symptoms and establishing rapport through frequent scheduled follow-up visits, CBT is the best next step in management. Several studies have shown that CBT is superior to usual care, and the benefits are maintained after completion of therapy.

Familial Mediterranean fever (FMF) is the classic autoinflammatory disease associated with mutation of the *MEFV1* gene, which codes for pyrin (a regulator of interleukin-1β production). Attacks last 1 to 3 days and are characterized by polyserositis, arthritis, erysipeloid rash around the ankles, and elevation of acute phase reactants. Most cases (90%) present before age 20 years, and a family history of similar symptoms is common. This patient's age of onset, chronic symptoms, and negative evaluation results, including acute phase reactant measurement, argue strongly against the diagnosis of FMF and the need to analyze the *MEFV* gene.

Pregabalin is an FDA-approved treatment for fibromyalgia and other conditions associated with neuropathic pain, such as diabetic peripheral neuropathy and postherpetic neuralgia. However, this patient does not have the fatigue and widespread musculoskeletal symptoms typical of fibromyalgia. Pregabalin has no role in the treatment of somatic symptom disorder.

Whole-body PET is not indicated in a patient without clinical evidence of malignancy. Furthermore, advanced diagnostic testing is not recommended in patients with somatic symptom disorder to provide technological reassurance. In addition to being cost ineffective, such testing may lead to false-positive results, triggering further unnecessary testing and patient stress.

KEY POINT

- Treatment of somatic symptom disorder focuses on acknowledging the patient's symptoms, building a therapeutic relationship with the patient through frequent scheduled visits, implementing cognitive behavioral therapy, and avoiding further testing.

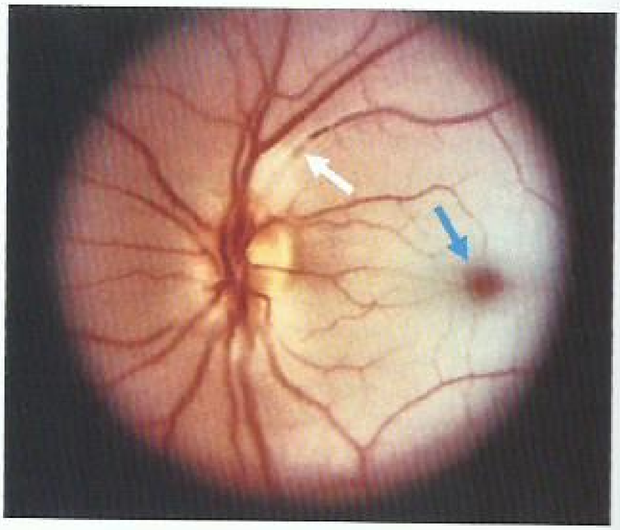
Bibliography

Schröder A, Rehfeld E, Ornbøl E, Sharpe M, Licht RW, Fink P. Cognitive-behavioural group treatment for a range of functional somatic syndromes: randomised trial. Br J Psychiatry. 2012;200:499-507. [PMID: 22539780] doi:10.1192/bjp.bp.111.098681

Item 76 Answer: B

Educational Objective: **Diagnose central retinal artery occlusion.**

The most likely diagnosis for this patient's painless visual loss is central retinal artery occlusion (CRAO). This patient has several risk factors for this condition, including advanced age; male sex; and associated cardiovascular risk factors, such as hypertension and hyperlipidemia. Examination reveals an afferent pupillary defect and cherry red fovea (*blue arrow*) that is accentuated by a pale retinal background. Interruption of the venous blood columns may be recognized with the appearance of "boxcarring" rows of corpuscles separated by clear intervals seen in the vein just superior to the optic disc (*white arrow*). The most likely cause in this case is carotid atherosclerosis, but CRAO may also be caused by cardiogenic emboli; carotid artery dissection; hematologic conditions, such as sickle cell disease; or hypercoagulable states. The occlusion may be preceded by transient visual loss or a stuttering course. Retinal examination may demonstrate emboli. In an older patient who lacks emboli on examination, erythrocyte sedimentation rate and C-reactive protein level should be obtained to rule out giant cell arteritis, which is a rare but important cause of CRAO. Prognosis is based on visual acuity at presentation. Ischemia that lasts 4 hours or longer tends to result in irreversible vision loss. Treatment may include measures to lower intraocular pressure. Emergent ophthalmology consultation is required.



Acute angle-closure glaucoma typically presents with severe eye pain and visual loss. It may involve headache, nausea, and vomiting. Ophthalmoscopic examination reveals a mid-dilated (4-6 mm), nonreactive pupil and intraocular pressure greater than 50 mm Hg. This patient's clinical picture is not consistent with acute angle-closure glaucoma.

Idiopathic intracranial hypertension (previously known as pseudotumor cerebri) may present with diplopia, headache, and, most often, bilateral visual symptoms. These may include transient visual obscurations, which can be brief and triggered by body position change or the Valsalva maneuver. Papilledema is almost always present on examination.

Retinal detachment most commonly presents with photopsias (flashes of light); patients may also report seeing cobwebs and large floaters. Painless complete visual loss is possible, but retinal detachment is more often associated with progressive vision compromise that may involve partial visual fields. A horseshoe-shaped retinal tear may be observed on funduscopic examination.

KEY POINT

- Central retinal artery occlusion presents as acute, profound, and painless loss of monocular vision associated with an afferent pupillary defect and cherry red fovea.

Bibliography

Georgalas I, Pagoulatos D, Koutsandrea C, Pavlidis M. Sudden unilateral painless loss of vision. BMJ. 2014;349:g4117. [PMID: 24986885] doi:10.1136/bmj.g4117

Item 77 Answer: B

Educational Objective: **Treat dyspnea refractory to medical therapy in a patient with heart failure and COPD.**

The most appropriate treatment is oral hydromorphone. This patient has severe chronic dyspnea that is refractory to maximal therapy for his underlying heart failure and COPD. Oral

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opioids, dosed appropriately, have been found to be both safe and efficacious in the treatment of dyspnea. Treatment efficacy is thought to be related to modulation of shared neural structures that are involved in the pathogenesis of both pain and dyspnea, as there are numerous μ-opioid receptors throughout the respiratory centers in the central nervous system. No evidence suggests that one opioid is superior to another in the treatment of dyspnea, and agent selection should be based on individual patient considerations, such as avoidance of morphine products in patients with reduced kidney function.

Furosemide would be a reasonable selection in a patient with volume overload as the driver of dyspnea; however, this patient has no evidence to suggest this cause (such as an elevated central venous pressure, an S_3, crackles, or peripheral edema).

Benzodiazepines, such as lorazepam, are effective for short-term control of anxiety symptoms. However, this patient's anxiety is a result of his shortness of breath, and as such, treatment should focus on relieving the dyspnea, not on treating the associated anxiety. For this reason, benzodiazepines should be considered only when adjunctive therapy is indicated.

Although systemic opioids have shown clear benefit in treating refractory dyspnea, inhaled opioids, such as nebulized morphine, have not shown significant efficacy in several placebo-controlled trials.

KEY POINT

- In patients with severe refractory dyspnea, appropriately dosed oral opioids are first-line therapy for symptomatic relief.

Bibliography

Kamal AH, Maguire JM, Wheeler JL, Currow DC, Abernethy AP. Dyspnea review for the palliative care professional: treatment goals and therapeutic options. J Palliat Med. 2012;15:106-14. [PMID: 22268406] doi:10.1089/jpm.2011.0110

Item 78 Answer: D

Educational Objective: Avoid aspirin therapy for primary prevention of atherosclerotic cardiovascular disease in a patient at high risk for bleeding.

No further intervention is the most appropriate management of this patient. Although he has a 10-year risk for atherosclerotic cardiovascular disease (ASCVD) of 14.6%, he is at high risk for bleeding with the addition of aspirin therapy. The U.S. Preventive Services Task Force recommends low-dose aspirin for the primary prevention of ASCVD and colorectal cancer in adults aged 50 to 59 years with a 10-year ASCVD risk of 10% or higher who do not have an increased risk for bleeding, have a life expectancy of at least 10 years, and are willing to take low-dose aspirin daily for at least 10 years. Patients aged 60 to 69 years may also benefit from aspirin; however, the net benefit is smaller because of the increased risk for bleeding in this population. In addition to increasing age, male sex and use of anticoagulants or NSAIDs increase the risk for bleeding. Many patients with cardiovascular disease who are eligible for secondary prevention with aspirin therapy also require long-term oral anticoagulant therapy for atrial fibrillation. In these patients, the addition of aspirin to anticoagulant therapy provides some additional protection against cardiovascular events, but the risk for major bleeding is significantly increased. Therefore, aspirin is not generally recommended in these patients. Although this patient's risk for ASCVD is higher than 10%, he is already receiving anticoagulant therapy with rivaroxaban; therefore, the potential benefits of aspirin therapy for primary prevention of ASCVD are likely outweighed by the increased risk for bleeding.

High doses of fish oil increase bleeding time in vitro by suppressing platelet-activating factor, but this mechanism has not been associated with higher rates of clinical bleeding, even when the supplement is combined with aspirin or warfarin. However, a 2018 systematic review concluded that omega-3 fatty acid supplementation does not reduce heart disease, stroke, or death; therefore, fish oil supplementation cannot be recommended.

Switching rivaroxaban to low-dose aspirin is not recommended because this patient is at high risk for atrial fibrillation–related stroke. For this patient, anticoagulant therapy is significantly superior to aspirin in reducing his risk for stroke.

KEY POINT

- In the primary and secondary prevention of cardiovascular events, the addition of aspirin to long-term anticoagulation is associated with significantly increased bleeding events and is not routinely recommended.

Bibliography

Whitlock EP, Burda BU, Williams SB, Guirguis-Blake JM, Evans CV. Bleeding risks with aspirin use for primary prevention in adults: a systematic review for the U.S. Preventive Services Task Force. Ann Intern Med. 2016;164(12):826-35. [PMID: 27064261] doi: 10.7326/M15-2112

Item 79 Answer: C

Educational Objective: Diagnose high ankle sprain.

The most likely diagnosis is a high ankle sprain. High ankle sprains result from excessive dorsiflexion or eversion that causes injury to the tibiofibular syndesmotic ligaments connecting the distal tibia and fibula. Pain can be elicited by compressing the leg at mid-calf (squeeze test), by having the patient cross the legs with the lateral malleolus of the injured leg resting on the other knee (crossed-leg test), or by dorsiflexing and externally rotating the foot with the knee flexed (dorsiflexion-external rotation test). The most common mechanism of injury involves an externally rotated force applied to a dorsiflexed ankle, as is the case with this patient. Patients with high ankle sprains report the acute onset of pain proximal to the ankle. Pain is often accompanied by swelling and ecchymosis. Treatment is similar to

that used for other ankle sprains and includes cryotherapy (ice or cold water), mobilization, and analgesics for pain control, but recovery is usually delayed.

Achilles tendon rupture most commonly results from sudden, forceful plantar flexion, such as occurs with jumping and sprinting. Patients report sudden onset of heel pain and often hear a popping sound at the time of the injury. On examination, patients have weak or absent plantar flexion. Absent plantar flexion with calf squeezing (Thompson test) also suggests the diagnosis. This patient's clinical presentation is not consistent with Achilles tendon rupture.

The Ottawa ankle and foot rules are useful in excluding ankle fractures, with an extremely high sensitivity (>95%). According to these validated rules, radiography should be obtained when a patient is unable to walk four steps both immediately after the injury and during evaluation, and when focal tenderness is present at the posterior aspect of the malleolus, the navicular bone, or the fifth metatarsal base. If these criteria are not met, obtaining radiography is not necessary because the probability of an ankle fracture is exceedingly low, as in this patient.

Lateral ankle sprains typically result from inversion injuries to the lateral ankle ligaments (the anterior and posterior talofibular ligaments and the calcaneofibular ligament). Physical examination reveals ecchymosis, lateral ankle tenderness, and swelling, which was not the case with this patient. This patient's symptoms and findings were located above the ankle.

KEY POINT

- Patients with high ankle sprains report the acute onset of pain proximal to the ankle, accompanied by swelling and ecchymosis.

Bibliography

Vopat ML, Vopat BG, Lubberts B, DiGiovanni CW. Current trends in the diagnosis and management of syndesmotic injury. Curr Rev Musculoskelet Med. 2017;10:94-103. [PMID: 28101828] doi:10.1007/s12178-017-9389-4

Item 80 Answer: A

Educational Objective: **Treat vulvovaginal candidiasis.**

The most appropriate treatment for this patient with symptoms of vulvovaginal candidiasis is intravaginal clotrimazole. Vulvovaginitis describes infectious and noninfectious conditions that cause vulvovaginal symptoms, including abnormal vaginal discharge, vulvar itching, burning, irritation, and malodor. When discharge is associated with abnormal findings, the differential diagnoses most commonly include bacterial vaginosis, trichomoniasis, and vulvovaginal candidiasis. Vaginal irritation also may be caused by dermatologic conditions or allergic reactions, cervical infections, or genitourinary syndrome of menopause. A woman may have more than one type of infection at a time. The diagnosis of vulvovaginal candidiasis is suggested by the presence of vaginal discharge and vulvar pruritus, pain, irritation, and redness. Signs include vulvar edema; fissures; excoriations; and thick, white, curdy vaginal discharge. The diagnosis can be made when a saline or 10% potassium hydroxide wet mount of vaginal discharge shows hyphae, pseudohyphae, or yeast. Because the sensitivity of microscopy is low, empiric treatment of vulvovaginal candidiasis can be considered if symptoms are accompanied by characteristic findings. Several therapeutically equivalent topical and oral drugs are available; among the topically applied drugs, imidazoles (fluconazole, miconazole, clotrimazole) are the most effective. Evidence suggests that topical and oral agents have similar efficacy and that treatment preference should be based on cost, convenience, and patient preference.

Intravaginal nystatin, a topical antifungal drug, lacks good supporting evidence for the treatment of vulvovaginal candidiasis and currently is not recommended.

Oral metronidazole is used to treat bacterial vaginosis, the most common cause of vaginal discharge, as well as to treat trichomoniasis. Accepted clinical criteria for diagnosing bacterial vaginosis include the presence of three of four characteristics: vaginal pH greater than 4.5, amine ("fishy") odor on the application of 10% potassium hydroxide to vaginal secretions (whiff test), the presence of a thin homogeneous vaginal discharge, and the finding of at least 20% clue cells on a microscopic saline wet mount examination. Although the presentation of trichomoniasis varies, many women develop a copious, malodorous, pale yellow or gray frothy discharge with vulvar itching, burning, and postcoital bleeding. Point-of-care vaginal swab rapid immunoassays and nucleic acid amplification tests for detection of *Trichomoniasis vaginalis* have replaced microscopy or culture as the gold standard for diagnosis. This patient does not have findings of bacterial vaginosis or trichomoniasis; hence, metronidazole is not indicated.

Oral voriconazole should not be used to treat vulvovaginal candidiasis because no data support its use. Case reports suggest that it is ineffective, and there is the added potential for toxicity.

KEY POINT

- Topical antifungal imidazole therapy, such as intravaginal clotrimazole, is an effective treatment for uncomplicated vulvovaginal candidiasis, which is usually caused by *Candida albicans*.

Bibliography

Mills BB. Vaginitis: beyond the basics. Obstet Gynecol Clin North Am. 2017;44:159-177. [PMID: 28499528] doi:10.1016/j.ogc.2017.02.010

Item 81 Answer: A

Educational Objective: **Implement appropriate monitoring strategies before and during opioid therapy in a patient with chronic pain.**

Baseline urine drug screening is recommended before starting opioid therapy in this patient. Many guidelines, including the Centers for Disease Control and Prevention

(CDC) Guideline for Prescribing Opioids for Chronic Pain, recommend initial and ongoing urine drug screening. Urine drug screening is used to test for adherence to current therapy, identify potential opioid diversion (by assessing whether the expected metabolite is present within an appropriate time frame), and evaluate for the presence of other controlled prescription and nonprescription drugs. Urine drug screening should be performed before opioids are prescribed for chronic pain and at least yearly during therapy. More frequent screening may be necessary in the setting of therapy changes or the presence of red flags (lost prescriptions, early refill requests, multiple concurrent opioid providers or "doctor shopping," consistently missed appointments, or erratic follow-up).

The CDC guideline and other opioid prescribing guidelines recommend that opioid therapy be considered only if expected benefits for both pain and function are anticipated to outweigh the risks. If opioids are used, they should be combined with nonpharmacologic and nonopioid pharmacologic therapies as appropriate. Discontinuing this patient's current nonpharmacologic and pharmacologic therapies is not indicated.

Chronic pain is often associated with comorbid psychological issues. Patients who meet the criteria for diagnosis of a psychological comorbidity, such as depression or anxiety, should be treated accordingly. However, routine referral for a psychiatric evaluation is not mandatory and is based on the presence and severity of comorbid mental health disorders.

KEY POINT

- In patients in whom opioid therapy is being considered for the treatment of chronic pain, urine drug screening should be performed before opioid prescription and at least yearly during therapy to evaluate for adherence to therapy and to identify the presence of other controlled drugs.

Bibliography

Dowell D, Haegerich TM, Chou R. CDC guideline for prescribing opioids for chronic pain – United States, 2016. JAMA. 2016;315:1624-45. [PMID: 26977696]

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Item 82 Answer: C

Educational Objective: **Evaluate preoperative cardiac risk using transthoracic echocardiography in a patient with moderate aortic stenosis.**

In addition to electrocardiography, the most appropriate preoperative testing for this patient is transthoracic echocardiography (TTE). The patient was diagnosed with moderate aortic stenosis several years ago and has occasional dizziness with physical exertion, a potential symptom of severe aortic stenosis. Preoperative TTE should not be ordered routinely but is recommended in certain cases. Indications for preoperative echocardiography include dyspnea of unknown origin, heart failure with change in clinical status, and known left ventricular dysfunction in the absence of an assessment in the previous 12 months. Relevant to this patient, TTE is indicated in patients with known or suspected moderate or greater degrees of valvular stenosis or regurgitation if TTE has not been performed within 1 year or in those whose clinical status has changed or who have referable symptoms. It is reasonable to perform elevated-risk elective noncardiac surgery in patients with severe asymptomatic aortic stenosis, with appropriate intraoperative and postoperative hemodynamic monitoring. For patients who are candidates for valvular intervention because of symptoms or severity of disease, valvular intervention before elective noncardiac surgery is effective at reducing risk.

In a systematic review, a preoperative B-type natriuretic peptide (BNP) level greater than 92 pg/mL (92 ng/L) predicted the composite outcome of death or nonfatal myocardial infarction at 30 days, at 180 days, and beyond. Despite the improvement in predicting poor surgical outcomes, it is unclear what role BNP measurement should play in perioperative cardiovascular care; this test is currently not recommended by American College of Cardiology/American Heart Association guidelines. The Canadian Cardiovascular Society guidelines on perioperative cardiac risk assessment and management for patients who undergo noncardiac surgery strongly recommend that a BNP level be obtained to enhance perioperative cardiac risk estimation in patients with a Revised Cardiac Risk Index score of 1 or more, patients aged 65 years and older, and patients aged 45 to 64 years who have significant cardiovascular disease.

This patient is scheduled to undergo surgery (total knee arthroplasty) and has good functional capacity (able to swim for 30 minutes), and she does not have coronary artery disease or its equivalents (chronic kidney disease, cerebrovascular disease, heart failure, or diabetes mellitus). This patient's risk for major ischemic events is low; therefore, dobutamine stress echocardiography is not indicated.

KEY POINT

- Transthoracic echocardiography to evaluate preoperative cardiac risk is appropriate for patients with moderate to severe valvular stenosis or regurgitation in the absence of an assessment in the previous year or for those whose clinical status has changed or who have referable symptoms.

Bibliography

Fleisher LA, Fleischmann KE, Auerbach AD, Barnason SA, Beckman JA, Bozkurt B, et al; American College of Cardiology. 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines. J Am Coll Cardiol. 2014;64:e77-137. [PMID: 25091544]

Item 83 Answer: D

Educational Objective: **Evaluate serum lipid levels in an obese patient.**

This patient with obesity should undergo serum lipid screening. The American Heart Association, American College of Cardiology, and The Obesity Society guideline for the management of overweight and obesity recommends measurement of height and weight; calculation of BMI; measurement of waist

circumference; and measurement of cardiovascular disease risk factors, including blood pressure, fasting blood glucose (or hemoglobin A_{1c}), and serum lipid levels. Obesity is associated with insulin resistance and dyslipidemia characterized by elevations of total cholesterol, LDL cholesterol, VLDL cholesterol, and triglycerides and a reduction in HDL cholesterol. The history should address symptoms of obesity-related comorbid conditions, but no additional screening is recommended in the absence of suggestive symptoms or findings.

Exercise stress testing is recommended for patients with symptoms of cardiac ischemia. Overweight and obese patients are at increased risk for cardiovascular disease and should be questioned about symptoms and referred for testing if symptoms are present. Routine screening of asymptomatic patients is not recommended.

Hepatic ultrasonography is not necessary for this patient. The risk for nonalcoholic steatohepatitis is increased in overweight and obese patients. A presumptive diagnosis can be made in a patient with mild abnormalities in aminotransferase levels, risk factors for nonalcoholic fatty liver disease (such as diabetes mellitus, obesity, and hyperlipidemia), and ultrasonographic features consistent with hepatic steatosis. The recommended treatment of nonalcoholic steatohepatitis is weight loss, but no screening for this condition is recommended.

Risk for obstructive sleep apnea is increased among overweight and obese patients, particularly those with neck circumference greater than 38 cm (15 in) in women and greater than 43 cm (17 in) in men. The patient should be referred for overnight polysomnography only if symptoms of the disorder are present. He does not report nonrestorative sleep or daytime hypersomnolence, which would suggest obstructive sleep apnea.

The prevalence of an endocrine cause of obesity is very low. Thyroid function testing should be reserved for patients with symptoms and findings indicating thyroid disease.

KEY POINT

- Management guidelines for overweight and obese patients recommend measurement of height and weight; calculation of BMI; measurement of waist circumference; and measurement of cardiovascular disease risk factors, including blood pressure, fasting blood glucose (or hemoglobin A_{1c}), and serum lipid levels.

Bibliography

Jensen MD, Ryan DH, Apovian CM, Ard JD, Comuzzie AG, Donato KA, et al; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society. Circulation. 2014;129:S102-38. [PMID: 24222017] doi:10.1161/01.cir.0000437739.71477.ee

Item 84 Answer: D

Educational Objective: Treat unexplained chronic cough.

Multimodal speech therapy is an appropriate treatment for this patient with unexplained chronic cough (UCC). UCC is defined as cough persisting for more than 8 weeks with no identifiable cause despite comprehensive evaluation. The evidence supporting the diagnosis and management of UCC is limited and generally weak. The American College of Chest Physicians (ACCP) expert panel recommends multimodal speech therapy consisting of two to four sessions of education, cough suppression techniques, breathing exercises, and counseling. This intervention helps reduce cough frequency and severity and improve cough-related quality of life. The ACCP also recommends a therapeutic trial of the neuromodulator gabapentin as long as the potential side effects and the risk-benefit profile are discussed with patients before use of the medication and the risk-benefit profile is reassessed at 6 months before continuation of the drug. Neuromodulators may diminish neural sensitization, which is a key driver of unexplained cough.

Levels of neutrophils are frequently increased in patients with chronic cough. Macrolide antibiotics are effective in the treatment of exacerbations of COPD and bronchiectasis, possibly because of their anti-inflammatory and antineutrophil effects that are independent of antimicrobial effects. However, trials with macrolide antibiotics, such as azithromycin and erythromycin, have not demonstrated benefit in patients with UCC.

Inhaled ipratropium bromide was found to be beneficial in patients with chronic cough after an upper respiratory tract infection. The ACCP does not recommend ipratropium for the treatment of UCC because the findings related to ipratropium were from an older study with a small sample size and limited reporting of methods, and the results have not been replicated.

Like gabapentin, morphine was found to be effective in reducing cough severity and frequency, but the ACCP expert panel has declined to recommend morphine as an intervention for chronic cough. The danger of overdose and addiction potential of morphine have been well described.

KEY POINT

- Recommended treatments for unexplained chronic cough include multimodality speech pathology therapy and neuromodulators, such as gabapentin.

Bibliography

Gibson P, Wang G, McGarvey L, Vertigan AE, Altman KW, Birring SS; CHEST Expert Cough Panel. Treatment of unexplained chronic cough: CHEST guideline and expert panel report. Chest. 2016;149:27-44. [PMID: 26426314] doi:10.1378/chest.15-1496

Item 85 Answer: B

Educational Objective: Manage sexual side effects in a patient taking a selective serotonin reuptake inhibitor for major depressive disorder.

The most appropriate next step in management is to discontinue sertraline and initiate bupropion, which has a lower rate of sexual side effects. Cognitive behavioral therapy (CBT) or a second-generation antidepressant is an appropriate first

choice for the treatment of major depressive disorder. Side effects, comorbid conditions, and cost are important considerations in the selection of therapy for a patient with depression. The most widely prescribed antidepressant drugs are selective serotonin reuptake inhibitors (SSRIs). SSRIs have excellent safety profiles compared with tricyclic antidepressants, but adverse sexual side effects (such as reduced libido, anorgasmia, or delayed orgasm) are common. Bupropion is an appropriate substitute agent for patients experiencing sexual side effects with an SSRI because it is an effective treatment with a low rate of sexual side effects. Bupropion can also be added to SSRI therapy to reduce SSRI-induced sexual side effects, but it is important to note that bupropion is contraindicated in patients with seizure disorders. Substituting CBT for antidepressant therapy in a patient experiencing sexual side effects of an SSRI is also an acceptable alternative.

The addition of CBT to antidepressant therapy is a reasonable approach for depression that does not respond to first-line therapy. This patient's depression is responsive to treatment, and the addition of CBT without stopping sertraline will not affect the patient's sexual side effects.

In patients who develop sexual side effects with one SSRI, there is substantial risk for similar problems with all SSRIs. This patient experienced anorgasmia with sertraline, and paroxetine has the highest rate of sexual side effects of all SSRIs, making it a poor choice for this patient.

Electroconvulsive therapy is appropriate for the management of treatment-resistant depression. This patient's depression is responding to first-line therapy; therefore, electroconvulsive therapy would not be the best treatment choice.

KEY POINT

- Selective serotonin reuptake inhibitors are generally well tolerated among patients with major depressive disorder, but sexual side effects (such as anorgasmia, delayed orgasm, and reduced libido) are common; for these patients, bupropion is an appropriate alternative, as is cognitive behavioral therapy.

Bibliography

Lorenz T, Rullo J, Faubion S. Antidepressant-induced female sexual dysfunction. Mayo Clin Proc. 2016;91:1280-6. [PMID: 27594188] doi:10.1016/j.mayocp.2016.04.033

Item 86 Answer: C

Educational Objective: Treat medically unexplained symptoms.

The most appropriate management strategy in this patient with medically unexplained symptoms (MUS) is to recommend cognitive behavioral therapy (CBT). The foundation of management of patients with MUS is an open, honest, and effective therapeutic relationship. Patients should be treated respectfully and cared for in a nonjudgmental manner. It is important to not only expect but to accept the patient's feelings of frustration; acknowledging these feelings early in the patient's management course can help to build and strengthen the therapeutic alliance. Management of MUS requires a patient-focused, holistic, and multimodal approach. The goals of management are functional restoration, decreased symptom focus, and acquisition of coping mechanisms rather than abatement of symptoms. Office visits should be scheduled at regular intervals, allowing for additional discussion, educational opportunities, and longitudinal reassessment. It should be made clear to patients that the treatment of MUS will not likely be curative and that symptoms may persist. Interventions that may benefit patients with MUS include CBT, physical therapy, occupational therapy, individual or group psychotherapy, social support, biofeedback, graded exercise therapy, stress management activities, and training in coping mechanisms. A systematic review of 29 randomized controlled trials comparing CBT with various control treatments found that CBT was an effective treatment for somatization or symptom syndromes and that physical symptoms were more responsive to treatment than were psychological symptoms. At least one randomized controlled trial found that CBT improves outcomes and decreases clinic visits in patients with several unexplained symptoms. A systematic review of four randomized controlled trials of psychodynamic therapy in patients with chronic pain found that the treatment reduced pain, improved function, and decreased the use of health services.

Anti-Hu paraneoplastic syndrome can cause temporal lobe, brainstem, and cerebellar dysfunction and may also involve the dorsal roots and autonomic nervous system. This syndrome is most commonly associated with small cell lung cancer. The long duration and nature of this patient's symptoms make this an unlikely diagnosis, and antibody measurement is not indicated.

Anti-*N*-methyl-D-aspartate receptor (anti-NMDAR) antibody encephalitis has emerged as an increasingly common cause of encephalitis. The diagnosis is suggested by the presence of choreoathetosis, psychiatric symptoms, seizures, and autonomic instability and is confirmed by detection of anti-NMDAR antibodies in the serum. This patient has no symptoms compatible with this syndrome, and testing is not indicated.

Given the likely diagnosis of MUS, the patient's ongoing symptoms, and numerous available treatment strategies, providing no further treatment is not appropriate.

KEY POINT

- Patients with medically unexplained symptoms may benefit from cognitive behavioral therapy, physical therapy, occupational therapy, individual or group psychotherapy, social support, biofeedback, graded exercise therapy, stress management activities, and training in coping mechanisms.

Bibliography

Evens A, Vendetta L, Krebs K, Herath P. Medically unexplained neurologic symptoms: a primer for physicians who make the initial encounter. Am J Med. 2015;128:1059-64. [PMID: 25910791]

Item 87 Answer: E

Educational Objective: Evaluate a patient with nonspecific low back pain.

No additional diagnostic testing is needed in this patient with acute, nonspecific low back pain. He lacks any concerning features, such as bowel or bladder dysfunction, constitutional symptoms, leg weakness, or saddle anesthesia. Indications to perform immediate imaging include severe and/or progressive neurologic deficits on examination or suspected serious underlying pathology, neither of which are present in this patient.

According to a joint clinical practice guideline released by the American College of Physicians and the American Pain Society, clinicians should not routinely perform diagnostic testing, such as CT, erythrocyte sedimentation rate measurement, MRI, or plain radiography, in patients with nonspecific low back pain. Even in patients with acute radiculopathy or spinal stenosis, routine imaging or testing has not been shown to improve outcomes. Most patients with acute low back pain recover quickly, regardless of the therapeutic intervention used. Whenever possible, maintaining daily activities should be encouraged. Nonpharmacologic treatment with acupuncture, massage, superficial heat, or spinal manipulation is preferred. If pharmacologic treatment is desired for acute low back pain, clinicians and patients should select NSAIDs or skeletal muscle relaxants.

KEY POINT

- Diagnostic studies should not be routinely obtained in patients with nonspecific low back pain; such testing should be reserved for patients with severe or progressive neurologic deficits and patients for whom a serious underlying condition is suspected.

Bibliography

Chou R. In the clinic. Low back pain. Ann Intern Med. 2014;160:ITC6-1. [PMID: 25009837]

Item 88 Answer: D

Educational Objective: Manage a patient with a family history suggestive of an inherited disorder with genetic counseling.

This patient with a family history concerning for familial adenomatous polyposis (FAP) should be referred for genetic counseling. FAP is most commonly inherited in an autosomal-dominant pattern and is caused by a mutation in the adenomatous polyposis coli (*APC*) gene, which functions as a tumor suppressor gene. Nearly 100% of patients with the autosomal-dominant *APC* gene mutation develop colon cancer, with most developing cancer before age 40 years. Because this patient has a strong family history of colon cancer and his brother was recently diagnosed as a carrier of the genetic mutation for FAP, genetic testing is warranted if the patient desires it, and he should undergo genetic counseling first to help guide his decision on whether to pursue genetic testing. Components of genetic counseling include assessment of the patient's risk for the condition of interest and education on the condition, risks and benefits of testing, alternative options to testing, and implications of testing for the patient and family members. Genetic counseling should be performed by individuals with appropriate training. Clinicians can use a searchable database provided by the American College of Medical Genetics to locate a genetic counselor in their area.

Aspirin and NSAIDs have been touted as a means to reduce the appearance and growth of polyps in patients with FAP. In particular, sulindac has been shown to cause regression of colorectal adenomas in FAP; however, the response is incomplete, and the degree of protection is uncertain. Chemoprevention is not a recommended strategy for patients at risk for or diagnosed with FAP.

Classic FAP results in the development of hundreds to thousands of colorectal adenomas that often manifest by the second decade of life. Gastric fundic gland polyposis and duodenal adenomas are also present in most patients. Gastric cancer is rare, but duodenal and periampullary cancers are the second leading cause of cancer death in this group. Papillary carcinoma of the thyroid is increasingly recognized as accompanying FAP. If this patient is diagnosed as a carrier of the FAP mutation, screening for colon, duodenal and periampullary, and thyroid cancers should be initiated now.

All patients in whom genetic testing is being considered should first be referred for genetic counseling.

KEY POINT

- All patients for whom genetic testing is being considered should undergo genetic counseling.

Bibliography

Hampel H, Bennett RL, Buchanan A, Pearlman R, Wiesner GL; Guideline Development Group, American College of Medical Genetics and Genomics Professional Practice and Guidelines Committee and National Society of Genetic Counselors Practice Guidelines Committee. A practice guideline from the American College of Medical Genetics and Genomics and the National Society of Genetic Counselors: referral indications for cancer predisposition assessment. Genet Med. 2015;17:70-87. [PMID: 25394175] doi:10.1038/gim.2014.147

Item 89 Answer: C

Educational Objective: Evaluate decision-making capacity.

The most appropriate management is to discharge this patient home with home care services. Patients should be presumed legally competent to make medical decisions unless found otherwise by judicial determination. However, in the clinical setting, physicians must frequently determine a patient's decision-making capacity by assessing the patient's ability to understand the relevant information, appreciate the medical consequences of the situation, consider various treatment options, and communicate a choice. Decision-making capacity should be evaluated for each decision to be made, and frequent reassessment is necessary to confirm prior determinations of capacity. Patients with depression or mild

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dementia may retain decision-making capacity; however, in such circumstances, the capacity assessment should be performed more cautiously, particularly when a decision may result in serious consequences. Validated tools, such as the Aid to Capacity Evaluation (www.aafp.org/afp/2001/0715/afp20010715p299-f2.pdf), may be useful for capacity assessment in the clinical setting. In this situation, the assessment reveals that the patient demonstrates sufficient capacity to make decisions; thus, he should be discharged home with appropriate services to ensure his safety. This patient's choice is also consistent with his previously expressed wishes, which lends validity to his decision.

Cognitive evaluations, such as the Mini-Mental State Examination, do not assess capacity; rather, they are used to detect cognitive impairment.

This competent and autonomous patient is able to make his own choices; therefore, the patient's daughter should not be asked to make a decision on his behalf.

Formal assessments of competence require judicial determination, although a competency hearing is not usually required for clinical decision making. In this case, a court order for the patient to be discharged to a rehabilitation facility is not required because he demonstrates decision-making capacity.

A psychiatric consultation is unnecessary to determine a patient's decision-making capacity; any physician can perform this assessment. However, some hospitals may suggest a psychiatric evaluation in high-stakes situations, such as when a patient requests to leave against medical advice.

KEY POINT

- In the clinical setting, physicians must determine a patient's decision-making capacity by assessing the patient's ability to understand the relevant information, appreciate the medical consequences of the situation, consider various treatment options, and communicate a choice.

Bibliography

Porrino P, Falcone Y, Agosta L, Isaia G, Zanocchi M, Mastrapasqua A, et al. Informed consent in older medical inpatients: assessment of decision-making capacity. J Am Geriatr Soc. 2015;63:2423-4. [PMID: 26603072]

Item 90 Answer: D

Educational Objective: Treat tobacco dependence with pharmacologic therapy in a patient with a recent cardiovascular event.

The most effective treatment is varenicline. Although bupropion and nicotine replacement therapy (NRT) monotherapy are effective for tobacco cessation, varenicline has been shown to be more effective. Some studies, including a large meta-analysis, have raised concerns of an increased risk for cardiovascular events in patients taking varenicline compared with those taking placebo. However, a recent double-blind, randomized, placebo- and active-controlled trial of varenicline, bupropion, and nicotine replacement therapy showed no evidence that the use of smoking cessation pharmacotherapies increased the risk of serious cardiovascular adverse events during or after treatment. FDA drug labeling information does not list recent cardiovascular events as a contraindication to varenicline therapy. The FDA recently removed the black box warning related to serious mental health adverse reactions with varenicline use after the risk for mental health effects was found to be lower than previously reported. Varenicline should be used with caution in patients with kidney failure.

Bupropion, a norepinephrine and dopamine reuptake inhibitor with nicotinic receptor activity, effectively increases smoking cessation rates. Bupropion should not be used in patients with a history of seizure disorders, stroke, brain tumor, brain surgery, or head trauma. Blood pressure should be monitored carefully, as severity of hypertension may increase with bupropion treatment. In direct comparison trials, bupropion was less effective in achieving smoking cessation than was varenicline.

Electronic cigarettes hold promise as a harm reduction tool that may help patients quit smoking; however, the evidence regarding their efficacy, risks, and benefits is still emerging. Therefore, current FDA-approved, evidence-based agents for tobacco cessation, such as varenicline, would be more appropriate in this patient.

Effectiveness of NRT is similar to that of bupropion for smoking cessation. Options for NRT include patch, gum, lozenges, oral inhaler, and nasal spray. Concomitant use of more than one form of NRT enhances efficacy. NRT should be used with caution in patients with unstable cardiac disease, life-threatening arrhythmias, or a recent cardiac event. In these patients, the decision to initiate NRT should involve a cardiologist. Patients should also be discouraged from smoking during use of NRT. In this patient with recent non–ST-elevation myocardial infarction, NRT would not be the most appropriate smoking cessation therapy.

KEY POINT

- Varenicline is an effective therapy for smoking cessation and should be considered in smokers with a recent cardiac event.

Bibliography

Patel MS, Steinberg MB. In the clinic. Smoking cessation. Ann Intern Med. 2016;164:ITC33-ITC48. [PMID: 26926702]

Item 91 Answer: A

Educational Objective: Screen for abdominal aortic aneurysm in a man with a history of smoking.

The most appropriate screening test to perform in this former smoker is abdominal duplex ultrasonography to screen for abdominal aortic aneurysm (AAA). The most important risk factors for AAA are advancing age, male sex (6:1 male-to-female incidence ratio), and smoking. The U.S. Preventive Services Task Force (USPSTF) recommends one-time

abdominal ultrasonography to screen for AAA in all men aged 65 to 75 years who have ever smoked. Ever smokers are usually defined as those who have smoked more than 100 cigarettes in their lifetime. The USPSTF recommends that clinicians selectively offer screening for AAA in men aged 65 to 75 years who have never smoked, based on the patient's medical history, family history, other risk factors, and preferences. A recently published meta-analysis concluded that screening significantly reduces AAA-related mortality. Abdominal duplex ultrasonography is the preferred screening modality, with a sensitivity of 94% to 100% and specificity of 98% to 100% for detecting AAA.

Chest radiography and sputum cytologic evaluation have not shown adequate sensitivity or specificity as screening tests for lung cancer and are not recommended.

Although the USPSTF concludes that there is insufficient evidence to recommend routine screening for osteoporosis in men, the National Osteoporosis Foundation recommends osteoporosis screening in men aged 70 years or older. Screening may also be considered in men at high risk for osteoporosis (men with low body weight, recent weight loss, physical inactivity, use of oral glucocorticoids, previous fragility fracture, alcohol use, or androgen deprivation via pharmacologic agents or orchiectomy). The American College of Physicians recommends periodic individualized assessment of risk factors for osteoporosis in older men.

The USPSTF and the American College of Chest Physicians (ACCP) recommend lung cancer screening with annual low-dose CT in persons aged 55 to 80 years (or aged 55 to 77 years, according to the ACCP) with a 30-pack-year smoking history, including former smokers who have quit in the last 15 years. Screening should be discontinued once a person has not smoked for 15 years or develops a health problem that substantially limits life expectancy or the willingness to have curative lung surgery. This patient has a 10-pack-year smoking history and quit almost 30 years ago; therefore, he does not meet the criteria for lung cancer screening.

KEY POINT

- All men aged 65 to 75 years who have ever smoked should undergo one-time abdominal ultrasonography to screen for abdominal aortic aneurysm.

Bibliography

Takagi H, Ando T, Umemoto T; ALICE (All-Literature Investigation of Cardiovascular Evidence) Group. Abdominal aortic aneurysm screening reduces all-cause mortality. Angiology. 2017:3319717693107. [PMID: 28193091] doi:10.1177/0003319717693107

H

Item 92 Answer: D

Educational Objective: Prevent medication errors with medication reconciliation.

Medication reconciliation would have most likely prevented this medication error. Medication reconciliation is the process of creating an accurate, comprehensive list of the patient's prescription and nonprescription medications (including the dose, frequency, and route of administration) and comparing the list to medication orders (at admission, transfer, or discharge) to resolve inconsistencies. Completion of medication reconciliation decreases adverse drug events, and although the effect on hospital readmissions, morbidity, and mortality is less clear, medication reconciliation should occur at all care transitions to prevent medication errors. In this case, tamoxifen was withheld upon admission but should have been restarted at the time of the patient's discharge from the hospital. Medication reconciliation at the time of discharge would have prevented this error, which resulted in a lapse in the patient's breast cancer treatment.

Computerized physician order entry (CPOE) systems are designed to improve the medication ordering process and prevent medication errors and medication adverse events. Some CPOE systems are integrated with decision support systems. CPOE has resulted in many practice improvements, including standardization of care, improved legibility of orders, and implementation of medication alerts (such as allergy and drug interaction alerts). However, CPOE cannot replace medication reconciliation and would not have prevented this medication error at a transition of care.

Manually transcribing physician medication orders into a paper-based medication administration record, even if originated by using the CPOE process, can lead to medication administration errors and adverse events. However, using a system that features a direct electronic interface between CPOE and the electronic medication administration record can eliminate transcription errors and errors in reading and interpreting hand-written, paper-based medication administration records. Such a system does not replace medication reconciliation and would not have prevented this medication error at the time of discharge.

Improved medication labeling, including the use of "tall man" lettering (for example, **DOBU**Tamine versus **DOP**amine), helps minimize confusion surrounding look-alike and sound-alike medications, thereby reducing medication errors. However, improved medication labeling would not have prevented this medication error resulting from a transition of care.

KEY POINT

- Medication reconciliation should occur at all transitions of care to prevent medication errors.

Bibliography

Mueller SK, Sponsler KC, Kripalani S, Schnipper JL. Hospital-based medication reconciliation practices: a systematic review. Arch Intern Med. 2012;172:1057-69. [PMID: 22733210]

Item 93 Answer: A

Educational Objective: Diagnose frailty.

Frailty is a multifactorial geriatric syndrome that may predict a patient's response to certain treatments as well as morbidity and mortality in light of chronic illness. This

patient demonstrates unintentional weight loss, low energy and activity levels, slow walking speed, and weakness, all of which are associated with frailty. Indices such as the Frailty Index, the FRAIL (Fatigue, Resistance, Ambulation, Illness, and Loss of weight) scale, and the Osteoporotic Fractures Frailty Scale have been validated for use in primary care. The Frailty Index has been in use for a longer time than other indices; however, its length and complexity limit its usefulness in routine care. The FRAIL scale consists of five self-reported measures and is easy to administer and score in an office setting.

Pharmacologic cardiac stress testing is recommended for patients who cannot exercise and are experiencing symptoms suggestive of cardiac ischemia. There is no established role for pharmacologic stress testing as a predictor of response to cancer treatment.

Lung function during exertion using the 6-minute walk test is helpful to assess disability and prognosis in chronic lung conditions. Simple pulse oximetry and oxygen desaturation studies performed at rest and with exertion assess the need for oxygen supplementation. During a 6-minute walk test, oxygen saturation, heart rate, dyspnea and fatigue levels, and distance walked in 6 minutes are recorded. The 6-minute walk test has no established role in predicting response to cancer chemotherapy in frail older adults.

The Timed Up and Go test is used to identify patients at risk for falls. The individual components of the test (rising from the chair, gait, walking speed, balance maintenance while turning, and sitting) offer insight into the various mechanics of mobility and can guide a more focused evaluation and intervention. Results of the Timed Up and Go test do not predict response to cancer treatment.

KEY POINT

- Frailty is a quantifiable geriatric syndrome that may predict a patient's response to medical treatment.

Bibliography

Puts MT, Santos B, Hardt J, Monette J, Girre V, Atenafu EG, et al. An update on a systematic review of the use of geriatric assessment for older adults in oncology. Ann Oncol. 2014;25:307-15. [PMID: 24256847] doi:10.1093/annonc/mdt386

Item 94 Answer: C

Educational Objective: Treat attention-deficit/hyperactivity disorder.

In addition to cognitive behavioral therapy, methylphenidate is the best initial treatment for this patient with attention-deficit/hyperactivity disorder (ADHD). ADHD is characterized by persistent inattention and/or hyperactivity-impulsivity that disrupts functioning or development in at least two areas of a patient's life (such as work, home, or peer relationships). Some symptoms must be present since age 12 years; however, many patients are not formally diagnosed until adulthood, and up to 60% of children with ADHD continue to have symptoms as an adult. Although symptoms of hyperactivity and impulsivity often lessen over time, adults with ADHD may be easily distracted, disorganized, and restless. Many adults have comorbid psychiatric problems, such as anxiety, depression, sleep disorders, and substance use. Cognitive behavioral therapy alone or in combination with pharmacotherapy is effective for improving executive functioning in patients with ADHD. Stimulants, such as methylphenidate, are first-line pharmacologic therapy for ADHD. However, these drugs should not be prescribed to patients with recent substance use or at high risk for serious adverse effects (arrhythmia, hypertension). Atomoxetine, bupropion, and tricyclic antidepressants can be used when stimulants are contraindicated.

Benzodiazepines, such as clonazepam, can be used for short-term treatment of severe, acute anxiety disorders. Their use is limited by the potential for abuse, and they are not indicated for the treatment of ADHD.

Escitalopram and other selective serotonin reuptake inhibitors are highly effective for the treatment of various mood and anxiety disorders. However, they have no established role in the treatment of ADHD unless there is a comorbid disorder responsive to this class of drugs.

Ropinirole is an effective therapy for restless legs syndrome. This patient is experiencing restlessness but does not report restless legs or sleep disturbance; therefore, ropinirole would not be indicated.

KEY POINT

- Stimulants, such as methylphenidate, are first-line pharmacologic therapy for attention-deficit/hyperactivity disorder; when stimulants are contraindicated, atomoxetine, bupropion, and tricyclic antidepressants can be used.

Bibliography

Volkow ND, Swanson JM. Clinical practice: adult attention deficit-hyperactivity disorder. N Engl J Med. 2013;369:1935-44. [PMID: 24224626] doi:10.1056/NEJMcp1212625

Item 95 Answer: A

Educational Objective: Diagnose iliotibial band syndrome.

The most likely diagnosis is iliotibial band syndrome (ITBS). ITBS is a common cause of lateral knee pain in runners and can also occur in patients with significant leg length difference, an excessively pronated foot, genu varum, or gluteal muscle weakness. Patients with ITBS have pain that is poorly localized to the lateral knee and distal thigh. Initially, the pain is present only after prolonged activity (such as running) that involves repeated knee flexion and extension. As the condition progresses, the pain occurs earlier in the course of activity and may eventually be present at rest. On examination, there is often tenderness to palpation 2 to 3 cm proximal to the lateral femoral condyle. Patients also frequently have weakness with hip abduction. Reproduction of the pain with knee extension from 90 degrees to 30 degrees with the examiner's thumb

exerting pressure on the lateral femoral epicondyle (Noble test) supports the diagnosis of ITBS. Initial treatment consists of activity modification, ice application, and NSAIDs to reduce inflammation. Once inflammation subsides, stretching and then strengthening exercises are indicated.

This patient lacks history of trauma, joint instability, lateral joint line tenderness, or increased laxity with varus force. Lack of these features argues against the presence of a lateral collateral ligament tear.

The lack of prior trauma and absence of catching, grinding, and locking all argue against a meniscal tear, as does the absence of an effusion on examination.

Meralgia paresthetica is due to entrapment of the lateral femoral cutaneous nerve and causes paresthesias on the anterolateral thigh. Risk factors include diabetes mellitus, obesity, pregnancy, and tight clothing or belts around the waist. This patient's findings are not consistent with meralgia paresthetica.

KEY POINT

- Patients with iliotibial band syndrome report diffuse, poorly localized lateral knee and distal thigh pain; there is often tenderness to palpation 2 to 3 cm proximal to the lateral femoral condyle.

Bibliography

Baker RL, Fredericson M. Iliotibial band syndrome in runners: biomechanical implications and exercise interventions. Phys Med Rehabil Clin N Am. 2016;27:53-77. [PMID: 26616177] doi:10.1016/j.pmr.2015.08.001

Item 96 Answer: B

Educational Objective: Evaluate noncyclic mastalgia.

The most appropriate initial management of this patient is breast ultrasonography. Breast pain (mastalgia) is common and may be cyclic or noncyclic. Many younger women experience cyclic breast discomfort with the onset of menses. The discomfort is typically bilateral, lasts for several days, and varies in intensity. Noncyclic breast pain is more likely to be unilateral and may be caused by trauma, cysts, duct ectasia, mastitis, ligamentous stretching secondary to large breasts, or a breast mass. A thorough history with attention to type of pain, location, and relationship to menses and a careful physical examination are essential to rule out palpable masses or anatomic causes. All women should be up to date with screening mammography. Women with a palpable breast mass should be referred for diagnostic imaging. Women with noncyclic breast pain and no evidence of a breast mass should undergo targeted breast ultrasonography because approximately 1% of such patients may have breast cancer at the site of pain.

Despite common perception, there is no evidence that avoiding caffeine will relieve breast hypersensitivity or pain.

Danazol is approved by the FDA for management of mastalgia but is recommended only for management of persistent severe cyclic breast pain unrelieved by conservative management. Because this patient has noncyclic breast pain and danazol is associated with the side effects of acne, hirsutism, weight gain, and irregular vaginal bleeding, danazol is not a therapeutic option for this patient.

The addition of mammography to ultrasonography does not appear to improve diagnostic accuracy in young women with mammographically dense breasts.

Reassurance, coupled with the regular use of a fitted support bra, would be appropriate management for a patient with cyclic mastalgia and a normal physical examination. This patient has focal noncyclic mastalgia necessitating diagnostic imaging as the first step in management.

KEY POINT

- Patients with noncyclic mastalgia with focal breast pain but no palpable mass should undergo targeted breast ultrasonography because approximately 1% of such patients may have breast cancer at the site of pain.

Bibliography

Iddon J, Dixon JM. Mastalgia. BMJ. 2013;347:f3288. [PMID: 24336097] doi:10.1136/bmj.f3288

Item 97 Answer: D

Educational Objective: Estimate posttest probability using likelihood ratios.

This patient's posttest probability of ischemic coronary artery disease is approximately 95%. His pretest probability of ischemic coronary artery disease is estimated to be 50% based on clinical variables (including the nature of the chest pain, age, and sex). Likelihood ratios (LRs) are a statistical indicator of how much the result of a diagnostic test will increase or decrease the pretest probability of a disease in a specific patient. LRs may be determined from the sensitivity and specificity of a diagnostic test, and separate LRs are calculated for use when a test result is positive (LR+) or when a test result is negative (LR−). This patient has a positive result on a treadmill stress echocardiographic study, and the LR for a positive result on this test is approximately 10. Although very specific posttest probabilities may be calculated or estimated by using a nomogram, a clinical rule of thumb is that LR+ values of 2, 5, and 10 correspond to an increase in disease probability of 15%, 30%, and 45%, respectively. With a pretest probability of 50%, a positive result on treadmill stress echocardiography would increase the likelihood of disease by approximately 45%, leading to a posttest probability in the range of 95%; this information would be very useful clinically in making further treatment decisions.

If the stress test result had been negative, LR− values of 0.5, 0.2, and 0.1 correspond to a decrease in disease probability of 15%, 30%, and 45%, respectively. Tests with LRs between 0.5 and 2 do not alter the pretest probability significantly if they are positive or negative. Evaluating the LRs of a particular test may help in selecting an appropriate study to obtain useful clinical information in the diagnostic process.

KEY POINT

- Likelihood ratios (LRs) are a statistical indicator of how much the result of a diagnostic test will increase or decrease the pretest probability of a disease in a specific patient; a clinical rule of thumb is that positive LRs of 2, 5, and 10 correspond to an increase in disease probability of 15%, 30%, and 45%, respectively.

Bibliography

Kent P, Hancock MJ. Interpretation of dichotomous outcomes: sensitivity, specificity, likelihood ratios, and pre-test and post-test probability. J Physiother. 2016;62:231-3. [PMID: 27637768] doi:10.1016/j.jphys.2016.08.008

H

Item 98 Answer: E

Educational Objective: Prevent postoperative venous thromboembolism in a patient at high risk for venous thromboembolism.

Mechanical prophylaxis with intermittent pneumatic compression (IPC) and pharmacologic prophylaxis with low-molecular-weight heparin (LMWH) are appropriate for prevention of postoperative venous thromboembolism (VTE) in this patient undergoing nonorthopedic surgery. The American College of Chest Physicians (ACCP) antithrombotic guideline provides VTE prophylaxis recommendations for both orthopedic and nonorthopedic surgery populations. The ACCP guideline recommends using the Caprini score (https://venousdisease.com/dvt-risk-assessment-online/) to estimate risk for postoperative thrombosis in those undergoing general surgery, gastrointestinal surgery, urologic surgery, gynecologic surgery, bariatric surgery, vascular surgery, and plastic/reconstructive surgery (but not other types of surgeries). It includes weighted patient and surgery-related risk factors for VTE. A score of 0 defines very low risk for VTE (estimated VTE risk in the absence of prophylaxis, <0.5%); scores of 1 to 2 define low risk (VTE risk, 1.5%); scores of 3 to 4 define moderate risk (VTE risk, 3%); and scores of 5 or more define high risk (VTE risk, 6%). For patients at high risk for VTE, pharmacologic prophylaxis with LMWH or low-dose unfractionated heparin and the addition of mechanical prophylaxis are recommended. This patient has a high perioperative risk for VTE, with a Caprini score of 6 (1 point for history of inflammatory bowel disease, 2 points for major surgery >45 minutes, and 3 points for personal history of VTE). Therefore, IPC and LMWH are appropriate.

Evidence on clinical outcomes from randomized controlled trials evaluating graduated compression stockings is sparse. Available evidence shows no statistically significant difference in risk for mortality, symptomatic deep venous thrombosis, or pulmonary embolism. However, risk for lower extremity skin damage significantly increases among patients treated with compression stockings.

The addition of LMWH to graduated compression stockings is believed not to provide additional benefit to LMWH alone. In this patient, the recommended prophylaxis of IPC and heparin is most appropriate.

KEY POINT

- For patients undergoing nonorthopedic surgery who are at high risk for postoperative venous thromboembolism as defined by the Caprini score, pharmacologic prophylaxis with low-molecular-weight heparin or low-dose unfractionated heparin and the addition of mechanical prophylaxis are recommended.

Bibliography

Gould MK, Garcia DA, Wren SM, Karanicolas PJ, Arcelus JI, Heit JA, et al. Prevention of VTE in nonorthopedic surgical patients: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2012;141:e227S-e277S. [PMID: 22315263]

Item 99 Answer: C

H

Educational Objective: Treat radiation-induced nausea and vomiting in a patient with cancer.

The most appropriate treatment of this patient's nausea and vomiting in the setting of chemoradiation therapy is ondansetron. Nausea and vomiting are common complications of radiotherapy. Gastrointestinal mucosal injury and subsequent serotonin release are likely the driving mechanisms of this patient's nausea, and treatment targeting the neurotransmitter suspected of causing the nausea is a 5-hydroxytryptamine-3 ($5\text{-}HT_3$) antagonist, such as ondansetron. Dexamethasone may be added as an additional antiemetic therapy.

Haloperidol is a potent dopamine antagonist with robust antiemetic properties. Its numerous forms (intravenous, oral, sublingual concentrate) make it a versatile partner and commonly used medication to treat nausea in multiple settings, including hospice. However, given that the cause of this patient's nausea is suspected to be $5\text{-}HT_3$ release in the setting of radiotherapy, ondansetron would be a preferred agent.

Olanzapine is a potent antiemetic with a diverse neurotransmitter profile, targeting dopamine, $5\text{-}HT_3$, histaminic, and muscarinic receptors. It is effective in reducing chemotherapy-induced nausea and vomiting, but its efficacy in treating radiation-induced nausea has not yet been studied. However, olanzapine would be a reasonable choice for nausea refractory to other agents given its ability to affect multiple receptors implicated in nausea and vomiting.

Synthetic oral cannabinoids are not recommended as initial antiemetic therapy for any cancer-related condition. Experts recommend their use be limited to breakthrough symptoms caused by chemotherapy. Guidelines from the National Comprehensive Cancer Network, American Society of Clinical Oncology, and Multinational Association of Supportive Care in Cancer do not recommend the use of medical marijuana for the treatment of cancer-related nausea and vomiting.

KEY POINT

- A 5-hydroxytryptamine-3 ($5\text{-}HT_3$) antagonist, such as ondansetron, is the preferred initial agent for radiation-induced nausea and vomiting.

Bibliography

Berger MJ, Ettinger DS, Aston J, Barbour S, Bergsbaken J, Bierman PJ, et al. NCCN guidelines insights: antiemesis, version 2.2017. J Natl Compr Canc Netw. 2017;15:883-893. [PMID: 28687576] doi:10.6004/jnccn.2017.0117

Item 100 Answer: C

Educational Objective: Treat viral pharyngitis with symptom control.

The most appropriate management of this patient with pharyngitis is symptom control that might include an analgesic agent (such as an NSAID or acetaminophen), lozenges or topical sprays, and increased environmental humidity. Pharyngitis most commonly has viral causes; only 5% to 15% of pharyngitis cases are caused by bacteria, most often group A *Streptococcus pyogenes* (GAS). Clinicians must use clinical features to determine whether the patient meets the threshold for using a streptococcal rapid antigen detection test or throat culture. Several features are more predictive of a viral syndrome, and patients who present with a sore throat with accompanying features, such as conjunctivitis, cough, hoarseness, nasal congestion, and rhinorrhea, should not be tested for GAS pharyngitis. Additionally, the High Value Task Force of the American College of Physicians recommends that patients who meet fewer than three Centor criteria (fever by history, tonsillar exudates, tender anterior cervical lymphadenopathy, and absence of cough) need not be tested for GAS pharyngitis; these patients should be treated conservatively with symptom control.

Antibiotic treatment of pharyngitis is reserved for patients with a positive result on a rapid antigen detection test or throat culture; amoxicillin and penicillin are first-line therapy. In this case, the patient has features suggesting a viral cause, including cough and rhinorrhea. She also has only two Centor criteria: fever and tonsillar exudates. Therefore, she should not be treated with amoxicillin or other antibiotics or tested for GAS through rapid antigen detection testing or throat culture. She should be advised that her sore throat may last as long as 1 week.

Patients with severe pharyngitis should be assessed for more serious complications, including peritonsillar abscesses, epiglottitis, and Lemierre syndrome (thrombophlebitis of the internal jugular vein). *Fusobacterium necrophorum* has emerged as a cause of endemic pharyngitis in adolescents and young adults and is associated with Lemierre syndrome. Further study is needed to determine how to best distinguish *F. necrophorum* from other bacteria as the cause of pharyngitis.

KEY POINT

- Hallmark signs of viral pharyngitis include conjunctivitis, cough, nasal congestion, and rhinorrhea; viral pharyngitis should be treated symptomatically.

Bibliography

Harris AM, Hicks LA, Qaseem A; High Value Care Task Force of the American College of Physicians and for the Centers for Disease Control and Prevention. Appropriate antibiotic use for acute respiratory tract infection in adults: advice for high-value care from the American College of Physicians and the Centers for Disease Control and Prevention. Ann Intern Med. 2016;164:425-34. [PMID: 26785402] doi:10.7326/M15-1840

Item 101 Answer: B

Educational Objective: Diagnose neurally mediated syncope.

The most likely diagnosis is neurally mediated syncope. Neurally mediated syncope (also known as neurocardiogenic or reflex syncope) is the most common form of syncope and is seen primarily in younger adults. The underlying syncopal mechanism, termed the neurocardiogenic or vasodepressor reflex, is a response of vasodilation, bradycardia, and systemic hypotension, which leads to transient hypoperfusion of the brain. Neurally mediated syncope includes vasovagal syncope, which may be provoked by noxious stimuli, fear, stress, or heat overexposure; situational syncope, which is triggered by cough, micturition, defecation, or deglutition; and carotid sinus hypersensitivity, which is sometimes experienced during head rotation, shaving, or use of a tight-fitting neck collar. Prodromal symptoms, including nausea and diaphoresis, are classically present before the syncopal event, and fatigue and generalized weakness are typically present afterward.

Hypoglycemia in patients without diabetes mellitus is rare; therefore, evaluation for pathologic hypoglycemia should occur only in the presence of the Whipple triad: symptomatic hypoglycemia, documented plasma glucose level of 55 mg/dL (3.1 mmol/L) or lower, and prompt symptomatic relief with correction of hypoglycemia. This patient's quick recovery from the syncopal episode without any intervention is not compatible with hypoglycemia-induced syncope.

Orthostatic syncope is classically associated with rapid onset of syncope after positional changes. Prodromal symptoms (such as lightheadedness) are often present. Orthostatic syncope is most commonly caused by hypovolemia, medications, and alcohol intoxication. Less commonly, primary autonomic failure (Parkinson disease, multiple system atrophy, multiple sclerosis) or secondary autonomic failure (diabetes, amyloidosis, connective tissue disease, spinal cord injury) can lead to orthostatic syncope. The diagnosis is confirmed by a sustained reduction of 20 mm Hg or more in systolic blood pressure (or ≥10-mm Hg drop in diastolic blood pressure) within 3 minutes of assuming upright posture, which is not present in this patient.

Postural orthostatic tachycardia syndrome is characterized by (1) frequent symptoms that occur with standing (such as lightheadedness, palpitations, generalized weakness, blurred vision, and fatigue), (2) an increase in heart rate of more than 30/min during a positional change from supine to standing, and (3) the absence of orthostatic hypotension. The standing heart rate is often higher than 120/min. This patient's findings are not compatible with postural orthostatic tachycardia syndrome.

KEY POINT

- Neurally mediated syncope is the most common form of syncope and is seen primarily in younger adults; prodromal symptoms (nausea, diaphoresis) are classically present before the syncopal event, and fatigue and generalized weakness are typically present afterward.

Bibliography

Runser LA, Gauer RL, Houser A. Syncope: evaluation and differential diagnosis. Am Fam Physician. 2017;95:303-312. [PMID: 28290647]

Item 102 Answer: C

Educational Objective: Treat a man with urgency urinary incontinence.

This patient reports symptoms consistent with urgency urinary incontinence, which can be best addressed with behavioral training and the use of anticholinergic agents or mirabegron. Urgency incontinence is characterized by loss of urine accompanied by a sense of urgency. The treatment of urinary incontinence generally progresses in a stepwise manner. Lifestyle changes and behavioral therapy should be initiated first, followed by pharmacologic therapy and devices, and finally surgery if all other therapies have failed. The patient is already appropriately using behavioral therapy in the form of bladder training and scheduled voiding. The addition of pharmacologic therapy is now appropriate. Anticholinergic drugs (darifenacin, fesoterodine, oxybutynin, solifenacin, tolterodine, trospium) reduce involuntary bladder contractions by blocking the muscarinic cholinergic receptors. Anticholinergic medications are appropriate for both men and women with urgency urinary incontinence, but caution should be exercised when initiating them in men with benign prostatic hyperplasia due to risk for urinary retention. The β-agonist mirabegron, another pharmacologic option for treatment of urgency urinary incontinence, enhances the inhibitory adrenergic signals to the detrusor muscle. Clinicians should base the choice of pharmacologic agents on tolerability, adverse effect profile, ease of use, and cost of medication.

Dutasteride is a 5α-reductase inhibitor used to treat benign prostatic hyperplasia. In this patient who is already being treated with tamsulosin and in whom postvoid residual bladder volume suggests that bladder outlet obstruction has been adequately addressed, there is no additional benefit from adding another therapy for benign prostatic hyperplasia; this therapy will not address the urgency and incontinence problems.

Intermittent self catheterization might be a useful strategy for a patient with overflow incontinence due to bladder outlet obstruction. However, that is not the case, as demonstrated by this patient's bladder ultrasound, which shows a postvoid residual urine volume of only 30 mL.

Sacral nerve root stimulation is an acceptable treatment for urgency urinary incontinence in patients in whom behavioral and pharmacologic therapies fail. Placement of a sacral nerve root stimulator typically involves conscious sedation and may require general anesthesia.

KEY POINT

- Male patients with urgency urinary incontinence who have not achieved satisfactory relief of symptoms with behavioral therapy may benefit from the use of anticholinergic agents or mirabegron.

Bibliography

Gormley EA, Lightner DJ, Burgio KL, Chai TC, Clemens JQ, Culkin DJ, et al; American Urological Association. Diagnosis and treatment of overactive bladder (non-neurogenic) in adults: AUA/SUFU guideline. J Urol. 2012;188:2455-63. [PMID: 23098785] doi:10.1016/j.juro.2012.09.079

Item 103 Answer: A

Educational Objective: Screen for cervical cancer in a woman vaccinated against human papillomavirus infection.

This patient should be screened for cervical cancer with cytology (Pap testing) alone. Nearly all cases of cervical cancer are precipitated by persistent human papillomavirus (HPV) infection, and HPV (most commonly subtypes 16 and 18 [high-risk HPV]) is detected in most patients with cervical cancer. Immunization against HPV is thought to protect against 70% to 90% of cervical cancers depending on the type of vaccine received. However, in patients who have received the HPV vaccine series, routine cervical cancer screening is still strongly recommended. Recipients of the vaccine series may have been infected with HPV prior to immunization. Furthermore, HPV vaccination is not effective in clearing HPV infection and does not protect against all HPV types. The U.S. Preventive Services Task Force (USPSTF) has concluded that the benefits of screening for cervical cancer in women aged 21 to 29 years every 3 years with cytology alone substantially outweigh the harms.

HPV testing is not indicated in women younger than 30 years because of the higher prevalence of transient HPV in this age group. Therefore, this patient should receive Pap testing alone and not dual testing with cytology and HPV detection, or high-risk HPV testing.

In the 2018 recommendation statement, the USPSTF concluded that in women aged 30 to 65 years, the benefits of screening every 3 years with cytology alone or every 5 years with high-risk HPV testing alone outweigh the harms. Decision analysis modeling suggests that screening every 5 years with high-risk HPV testing alone in women aged 30 to 65 years results in a slightly lower mortality rate than with screening every 3 years with cytology alone but much higher rates of follow-up testing and colposcopy. Four HPV screening tests are approved by the FDA for HPV screening. The tests screen for up to 14 HPV types, but only one test specifically identifies the presence of high-risk HPV types (16 and 18); the other tests report a positive result if any HPV type is present. According to the American Society for Colposcopy and Cervical Pathology and the Society of Gynecologic Oncology, high-risk HPV testing alone can be

considered as a primary cervical cancer screening modality in women aged 25 years and older; however, the American College of Obstetricians and Gynecologists has affirmed that cytology alone or cytology plus HPV testing are still specifically recommended in current guidelines from most major societies.

KEY POINT

- Routine cervical cancer screening with cytology alone is indicated in women aged 21 to 29 years, including those vaccinated against human papillomavirus.

Bibliography

Koliopoulos G, Nyaga VN, Santesso N, Bryant A, Martin-Hirsch PP, Mustafa RA, Schünemann H, Paraskevaidis E, Arbyn M. Cytology versus HPV testing for cervical cancer screening in the general population. Cochrane Database Syst Rev. 2017;8:CD008587. doi: 10.1002/14651858.CD008587.pub2. [PMID:28796882]

Item 104 Answer: B

Educational Objective: **Treat symptomatic left-sided varicocele.**

This patient's history and physical examination findings support a clinical diagnosis of symptomatic varicocele, and the appropriate treatment is analgesic therapy (ibuprofen) and scrotal support. Varicoceles are common, occurring in 15% of men. Notably, they are believed to be a leading cause of infertility; 40% of men who are infertile have varicoceles. They are the result of dilation of the pampiniform plexus of spermatic veins and can have a presentation ranging from no symptoms to dull aching scrotal fullness. Examination reveals a left-sided (90%) soft scrotal mass with a "bag of worms" consistency that increases with standing and decreases while supine. Ultrasonography is used for confirmation. Management is usually conservative, including analgesic agents; scrotal support should be pursued in all patients and is considered first-line therapy. Unilateral right-sided varicoceles are uncommon and may be associated with a significant underlying abnormality, such as inferior vena cava obstruction due to tumor or thrombosis because the right gonadal vein directly empties into the inferior vena cava. Many experts recommend advanced imaging with CT for patients with right-sided varicoceles.

Treatment with ceftriaxone plus doxycycline is recommended for infectious epididymitis. The chronic nature of this patient's symptoms, lack of fever, and a scrotal mass that increases with standing do not support a diagnosis of infectious epididymitis.

Surgical consultation for possible ligation or embolization of the gonadal vein would be appropriate in certain patients with symptomatic varicocele. Ligation or embolization of the gonadal vein prevents retrograde flow of blood to the pampiniform in the scrotum. Surgery may be considered in cases of testicular atrophy or infertility, or in cases refractory to first-line therapies. However, surgical repair may increase sperm counts without improving fertility. In this case, the patient has no evidence of testicular atrophy, and he has not previously received treatment. Although a semen analysis would be reasonable to obtain, conservative therapies should still be offered at this time.

Topical lidocaine can provide local analgesia; however, its use in cases of varicocele has not been thoroughly investigated. Rather, a systemic analgesic agent with anti-inflammatory properties would be preferable.

KEY POINT

- In adult patients, first-line therapy for symptomatic left-sided varicocele that is not associated with testicular atrophy or infertility is analgesic agents and scrotal support.

Bibliography

Baigorri BF, Dixon RG. Varicocele: a review. Semin Intervent Radiol. 2016;33:170-6. [PMID: 27582603] doi:10.1055/s-0036-1586147

Item 105 Answer: C

Educational Objective: **Treat carpal tunnel syndrome.**

The most appropriate management is splinting of the wrist. This patient has symptoms strongly suggestive of carpal tunnel syndrome (CTS). CTS is caused by median nerve compression at the wrist; it presents with wrist pain that may radiate to the fingers or forearm and is often worse at night and with repetitive motion. Risk factors include female sex, pregnancy, connective tissue disorders, diabetes mellitus, hypothyroidism, and obesity. Examination findings are often minimal early in the disease but may include hypalgesia of the median nerve distribution (thumb and first three fingers) and weakened thumb abduction. Thenar muscle atrophy suggests severe disease. For patients with mild to moderate symptoms, initial therapy consists of avoiding repetitive hand and wrist motions; for persistent or more severe symptoms, neutral-position wrist splinting can be helpful. Splinting appears to be more effective when used full time rather than only at night.

CTS can be diagnosed on the basis of history and clinical examination findings. Electromyography is not necessary unless a patient's clinical presentation is atypical, other conditions (such as polyneuropathy, plexopathy, and radiculopathy) need to be excluded, or surgical intervention is being considered.

Local glucocorticoid injection can improve symptoms over the short term (up to 10 weeks). Although generally safe, injection therapy has known harms, including worsening of median nerve compression, accidental injection into nerves or vessels, and flexor tendon rupture. For these reasons, many experts recommend glucocorticoid injection as second-line therapy for CTS.

Surgical decompression of the median nerve is reserved for patients with symptoms that do not respond to conservative therapy or with evidence of severe neuropathy (such as weakened thumb abduction, thenar muscle atrophy, and an

abnormal nerve conduction study). Electrodiagnostic studies are typically performed before surgery to confirm the presence of moderate to severe median nerve injury and to provide prognostic information.

KEY POINT

- Initial therapy for carpal tunnel syndrome consists of avoiding repetitive hand and wrist motions and neutral-position wrist splinting.

Bibliography

Hobson-Webb LD, Juel VC. Common entrapment neuropathies. Continuum (Minneap Minn). 2017;23:487-511. [PMID: 28375915] doi:10.1212/CON.0000000000000452

Item 106 Answer: B

Educational Objective: Diagnose scleritis in a patient with rheumatoid arthritis.

The most likely diagnosis in this patient with rheumatoid arthritis (RA) is scleritis. RA is one of the most common diseases associated with scleritis. Typical features include eye pain, pain with gentle palpation of the globe, and photophobia. The deep scleral vessels are involved and may lead to scleromalacia, which is characterized by thinning of the sclera and is seen as a dark area in the white sclera. Scleromalacia may lead to perforation of the sclera, called scleromalacia perforans. Scleritis can be vision-threatening and lead to blindness; it is therefore important to urgently refer the patient to an ophthalmologist for care.

Episcleritis is an abrupt inflammation of the superficial vessels of the episclera, a thin membrane that lies just beneath the conjunctiva. The cause is often unclear; rarely, it is associated with systemic rheumatologic disease. Patients with episcleritis frequently present without pain or decreased visual acuity. On examination, the inflammation appears localized. White sclera can be seen between superficial dilated blood vessels. Episcleritis typically resolves spontaneously. The presence of severe pain, diffuse redness, and decreased visual acuity make episcleritis an unlikely diagnosis.

Subconjunctival hemorrhage is a common disorder and typically benign in origin. It is caused by painless bleeding into the superficial portion of the eye. Examination reveals a blotchy redness (from extravascular blood) that is typically confined to one area of the conjunctiva. Subconjunctival hemorrhage is painless and not associated with loss of vision. Most cases resolve within several weeks without intervention. The patient's findings are not compatible with subconjunctival hemorrhage.

Viral conjunctivitis also causes a red eye. Typically, the underlying vessels are visible, a watery discharge may be seen, and the eyelids are matted in the morning. The eye may feel irritated, but there is no pain or loss of visual acuity. In general, conjunctivitis is a diagnosis of exclusion. The presence of pain and decreased visual acuity exclude viral conjunctivitis in this patient.

KEY POINT

- Rheumatoid arthritis is one of the most common diseases associated with scleritis, which can be vision threatening and lead to thinning of the sclera and perforation.

Bibliography

Artifoni M, Rothschild PR, Brézin A, Guillevin L, Puéchal X. Ocular inflammatory diseases associated with rheumatoid arthritis. Nat Rev Rheumatol. 2014;10:108-16. [PMID: 24323074] doi:10.1038/nrrheum.2013.185

Item 107 Answer: C

H

Educational Objective: Select appropriate preoperative testing in a patient with chronic kidney disease.

This patient should undergo preoperative assessment of serum creatinine and electrolyte levels. Preoperative testing should be ordered selectively according to the patient's symptoms, medical history, medications, and physical examination findings. Serum creatinine and electrolyte levels should be measured preoperatively in patients with kidney disease and those who are taking medications that may affect kidney function or predispose them to electrolyte abnormalities, such as this patient, who has chronic kidney disease and is taking an ACE inhibitor (lisinopril) and diuretic (hydrochlorothiazide). In patients with chronic kidney disease undergoing surgery, electrolyte abnormalities should be corrected, and volume status should be optimized.

Serum aminotransferases (alanine aminotransferase and aspartate aminotransferase) should not be routinely ordered in the absence of known liver disease, symptoms suggestive of underlying liver disease, physical examination findings suspicious for liver disease, or history of abnormal liver chemistry results.

Coagulation testing is reserved for patients with a history of abnormal bleeding, those taking anticoagulants, and patients with medical conditions that predispose to coagulopathy (such as liver disease or hemophilia). For the patient with a history suggesting a bleeding disorder, preoperative prothrombin time, activated partial thromboplastin time, and platelet count measurements are indicated.

Routine preoperative laboratory panels are not recommended because they expose patients to unnecessary testing, risk for incidental findings that are lost to follow-up evaluation, and increased anxiety. However, given this patient's comorbidities and medication use, forgoing preoperative testing would be inappropriate.

KEY POINT

- Preoperative measurement of serum electrolyte and creatinine levels is recommended in patients with kidney disease and those who are taking medications that may affect kidney function or predispose them to electrolyte abnormalities.

Bibliography

Apfelbaum JL, Connis RT, Nickinovich DG, Pasternak LR, Arens JF, Caplan RA, et al; Committee on Standards and Practice Parameters. Practice advisory for preanesthesia evaluation: an updated report by the American Society of Anesthesiologists Task Force on Preanesthesia Evaluation. Anesthesiology. 2012;116:522-38. [PMID: 22273990] doi:10.1097/ALN.0b013e31823c1067

Item 108 Answer: B

Educational Objective: Avoid NSAID therapy in a patient who has undergone bariatric surgery.

Ibuprofen should be discontinued in this patient. This patient likely has patellofemoral pain syndrome, which is characterized by anterior knee pain that is usually gradual in onset and worsens with running, prolonged sitting, and climbing stairs. Applying direct pressure to the patella with the knee extended may reproduce the pain. Treatment generally includes activity modification and physical therapy. NSAIDs, acetaminophen, bracing, and patellar taping all have limited efficacy. Additionally, the use of NSAIDs in patients who have undergone bariatric surgery is associated with increased risk for internal bleeding; bleeding risk is increased at the sites of anastomoses and staple or suture lines in the early postoperative period, with increased risk of marginal or gastric ulceration in the later postoperative period. Therefore, ibuprofen and other NSAIDs should be avoided after bariatric surgery.

This patient with known risk factors for atherosclerotic cardiovascular disease meets the criteria for moderate- to high-intensity statin therapy and should continue atorvastatin. There is no association between statin therapy and adverse events after bariatric surgery.

Patients who have undergone bariatric surgery may experience a decline in blood pressure such that antihypertensive agents need to be reduced or discontinued. Close monitoring of blood pressure in the postoperative period is recommended. This patient's blood pressure is appropriate on the current dose of lisinopril and this drug does not need to be discontinued.

Similarly, patients who have undergone bariatric surgery may experience reduced need for medications for type 2 diabetes mellitus. Close monitoring for the development of hypoglycemia in the postoperative period is recommended. Hypoglycemia is unlikely with metformin therapy alone and does not need to be discontinued.

KEY POINT

- The use of NSAIDs in patients who have undergone bariatric surgery is associated with increased risk for internal bleeding; therefore, ibuprofen and other NSAIDs should be avoided after bariatric surgery because their use is associated with increased risk for internal bleeding.

Bibliography

Marcotte E, Chand B. Management and prevention of surgical and nutritional complications after bariatric surgery. Surg Clin North Am. 2016;96:843-56. [PMID: 27473805] doi:10.1016/j.suc.2016.03.006

Item 109 Answer: B

Educational Objective: Diagnose borderline personality disorder.

This patient demonstrates a behavioral pattern consistent with borderline personality disorder. A personality disorder is characterized by persistent patterns of inner experiences and behaviors that digress substantially from the expectations of the affected person's culture. These disorders are entrenched, rigid, and stable over time and lead to substantial impairment and distress. Onset is usually during adolescence or early adulthood. Persons with personality disorders usually do not recognize their interactions with others as abnormal. In borderline personality disorder, patients have chaotic interpersonal relationships, emotional lability, and impulsive and self-destructive behaviors (such as suicide attempts). Patients have exaggerated responses to social stressors and often perceive people as "all good" or "all bad." Comorbid psychiatric illness is common in patients with borderline personality disorder. The initial management focuses on establishing rapport and boundaries with the patient, which can improve the patient's acceptance of psychiatry referral. Psychotherapy can be effective at improving coping mechanisms. No pharmacologic therapies are approved for treating personality disorders directly, but medications can be prescribed for specific symptoms (such as mood stabilizers for impulsivity).

Bipolar disorder is characterized by manic episodes (in which patients have decreased need for sleep, greater distractibility, and increased energy) and major depressive episodes. Although patients with bipolar disorder may engage in self-destructive behavior, it is not related to interpersonal discord.

Patients with generalized anxiety disorder have excessive anxiety and worry about multiple aspects of their lives. This leads to insomnia, irritability, and fatigue. Patients with generalized anxiety disorder do not typically have impulsivity, relationship instability, or the tendency to idealize and devalue individuals as do patients with borderline personality disorder.

Histrionic personality disorder is characterized by excessive need for approval and attention-seeking behaviors. Patients with this disorder are emotionally vulnerable, and their behaviors focus on obtaining approval from others. Patients with histrionic personality disorders are uncomfortable if not the center of attention and typically use physical appearance to draw attention to self. Interaction with others may be inappropriately sexually seductive or provocative. Histrionic personality disorder is not accompanied by the same degree of emotional lability and risk for suicidality as borderline personality disorder, as exhibited in this patient.

KEY POINT

- Patients with borderline personality disorder have chaotic interpersonal relationships, emotional lability, impulsive and self-destructive behaviors, and exaggerated responses to social stressors; comorbidity with other psychiatric illnesses is high.

Bibliography

Gunderson JG. Clinical practice. Borderline personality disorder. N Engl J Med. 2011;364:2037-42. [PMID: 21612472] doi:10.1056/NEJMcp1007358

Item 110 Answer: A

Educational Objective: Treat systemic exertion intolerance disease with cognitive behavioral therapy.

The most appropriate treatment for this patient with systemic exertion intolerance disease (SEID) is cognitive behavioral therapy. According to the Institute of Medicine (now the National Academy of Medicine), SEID is diagnosed by the presence of fatigue of at least 6 months' duration with substantial reduction in preillness activities, postexertional malaise, unrefreshing sleep, and either cognitive impairment or orthostatic intolerance (symptoms such as lightheadedness, dizziness, fatigue, cognitive deficits, and visual difficulties that worsen with upright posture and improve with recumbency). Patients with SEID benefit most from a structured, well defined, multimodal approach that includes regularly scheduled office visits, which allow for discussion, educational opportunities, and longitudinal reassessment. There is evidence that cognitive behavioral therapy and graded exercise therapy may decrease fatigue and improve function, and these therapies should be offered to patients. Additionally, all patients should receive instruction on effective sleep hygiene. Other modalities that may be of benefit include physical therapy, occupational therapy, biofeedback therapy, massage therapy, acupuncture, yoga, tai chi, and stress management activities. Considering this patient's depression (which is likely a consequence of her chronic symptoms), cognitive behavioral therapy is an ideal treatment.

Although methylphenidate, prednisone, opioids, anti-inflammatory agents, and antimicrobial agents are commonly requested in clinical practice for the treatment of chronic fatigue symptoms, there is no consistent evidence that these agents improve symptoms or prognosis in patients with SEID. Given the lack of benefit, risk for abuse, addictive potential, and array of adverse effects, these options are not recommended.

Mirtazapine (an α_2 agonist) and sertraline (a selective serotonin reuptake inhibitor) are used to treat depression. In general, selective antidepressant therapy may be useful in treating associated depression; however, it is not a direct treatment for SEID. Mirtazapine and sertraline might improve this patient's symptoms of depression, but it will not address the other symptoms associated with SEID.

KEY POINT

- The treatment of systemic exertion intolerance disease involves a structured, multimodal, nonpharmacologic approach that includes regularly scheduled office visits, cognitive behavioral therapy, graded exercise therapy, and sleep hygiene education.

Bibliography

Janse A, Nikolaus S, Wiborg JF, Heins M, van der Meer JWM, Bleijenberg G, Tummers M, Twisk J, Knoop H. Long-term follow-up after cognitive behaviour therapy for chronic fatigue syndrome. J Psychosom Res. 2017;97:45-51. [PMID: 28606498] doi:10.1016/j.jpsychores.2017.03.016

Item 111 Answer: D

Educational Objective: Manage hormonal contraception prescribing by first excluding pregnancy.

Pregnancy testing is the next step in this patient's management. Strategies to reduce unintended pregnancy require assessing pregnancy risk, counseling patients regarding contraceptive options, and ensuring correct and consistent use of contraceptives. Most women can start most contraceptive methods at any time. Available contraceptive methods include hormonal contraception; long-acting reversible preparations, including intrauterine devices; barrier contraceptives; and sterilization. Other than a thorough history and blood pressure and BMI measurements, few examinations or tests, if any, are needed before starting a contraceptive method. A pregnancy test should be obtained if more than 7 days have elapsed since the start of the last menses.

Hormonal contraceptive options include oral contraceptive pills (combination estrogen-progesterone or progesterone only pills), long-acting reversible contraceptives, transdermal patches, and vaginal rings. Contraindications to combination products include breast cancer, liver disease, migraine with aura, uncontrolled hypertension, and venous thromboembolism. Estrogen-containing preparations are contraindicated in women older than 35 years who smoke more than 15 cigarettes a day. A family history of breast cancer is not a contraindication for hormonal contraception.

In healthy women of reproductive age, a breast examination, pelvic examination, or mammography are not needed before beginning hormonal contraception. Breast cancer and cervical cancer screenings should be performed according to established guidelines. In 2016, the U.S. Preventive Services Task Force (USPSTF) reaffirmed its recommendation for biennial screening mammography in all women aged 50 to 74 years. The USPSTF recommends individualized screening decisions for women aged 40 to 49 years based on patient context and values regarding specific benefits and harms. The patient has no indications for mammography at this time.

According to the USPSTF, cervical cancer screening in women aged 21 to 65 years may be accomplished with cytology (Pap test) every 3 years. This patient's last Pap smear was normal 2 years ago, and she does not need to undergo repeat Pap testing for another 12 months.

KEY POINT

- Before initiating hormonal contraception, a negative pregnancy test result must be documented if 7 days have passed since the onset of the last menstrual period.

Bibliography

Curtis KM, Jatlaoui TC, Tepper NK, Zapata LB, Horton LG, Jamieson DJ, Whiteman MK. U.S. Selected practice recommendations for contraceptive use, 2016. MMWR Recomm Rep. 2016;65:1-66. [PMID: 27467319] doi:10.15585/mmwr.rr6504a1

Item 112 Answer: C

Educational Objective: Treat a patient with acute low back pain with nonpharmacologic modalities.

The most appropriate initial treatment of this patient's low back pain is nonpharmacologic therapy. According to a 2017 clinical practice guideline issued by the American College of Physicians, clinicians should choose nonpharmacologic treatments as first-line therapy for acute low back pain. Options include superficial heat, acupuncture, massage, and spinal manipulation. The quality of evidence supporting individual nonpharmacologic measures is moderate or low. Recommendations for their use are based on the fact that most patients with acute low back pain will improve over time (most within 4 weeks), regardless of the treatment chosen. Harms of nonpharmacologic interventions were seldom and minor. Superficial heat was associated with increased risk for skin flushing, and massage and spinal manipulation were associated with muscle soreness.

Recent evidence, including a Cochrane review, has demonstrated that acetaminophen is not effective in treating acute low back pain. As such, it would be inappropriate to recommend its use in this patient.

The FDA has approved the use of duloxetine in chronic back pain (pain lasting >12 weeks), as studies have demonstrated its effectiveness. However, no evidence supports its use for acute low back pain.

Guidelines recommend that opioids should be the last treatment option considered for chronic back pain and should be considered only in patients in whom other therapies have failed, as these drugs are associated with substantial harms. Harms of short-term opioid therapy include increased constipation, dizziness, dry mouth, nausea, somnolence, and vomiting. Studies assessing opioids for the treatment of chronic low back pain did not address the risk for addiction, abuse, or overdose, although observational studies have shown a dose-dependent relationship between opioid use for chronic pain and serious harms. A 2018 randomized trial demonstrated that treatment with opioids was not superior to treatment with nonopioid medications for improving pain-related function for chronic back pain. In addition, pain intensity was significantly improved in the nonopioid group. There are no studies of opioids for the treatment of acute back pain, but given their questionable effect and substantial harms as well as the self-limited nature of acute nonspecific back pain, opioids should likely be avoided entirely.

KEY POINT

- First-line treatment of acute low back pain is nonpharmacologic therapy, including acupuncture, massage, spinal manipulation, and superficial heat; most patients will improve over time, regardless of the treatment chosen.

Bibliography

Qaseem A, Wilt TJ, McLean RM, Forciea MA; Clinical Guidelines Committee of the American College of Physicians. Noninvasive treatments for acute, subacute, and chronic low back pain: a clinical practice guideline from the American College of Physicians. Ann Intern Med. 2017;166:514-530. [PMID: 28192789] doi:10.7326/M16-2367

Item 113 Answer: C

Educational Objective: Prevent atherosclerotic cardiovascular disease in a patient with type 2 diabetes mellitus with statin therapy.

The most appropriate treatment for primary prevention of atherosclerotic cardiovascular disease (ASCVD) in this patient is moderate- or high-intensity atorvastatin. Intensity of statin therapy is defined by the expected decrease in LDL cholesterol levels; high-intensity statin therapy should decrease LDL cholesterol levels by at least 50% from baseline levels, whereas moderate-intensity statin therapy should decrease LDL cholesterol levels by 30% to 50%. High-intensity statin regimens recommended by the 2013 American College of Cardiology (ACC)/American Heart Association (AHA) cholesterol treatment guideline include atorvastatin, 40 mg/d to 80 mg/d, and rosuvastatin, 20 mg/d to 40 mg/d. For primary prevention of ASCVD in patients with diabetes mellitus, the decision to initiate high-intensity statin therapy or moderate-intensity statin therapy is based on the patient's estimated 10-year ASCVD risk. According to the ACC/AHA guideline, patients with diabetes with an estimated 10-year ASCVD risk of 7.5% or higher should receive high-intensity statin therapy, whereas those with an estimated 10-year ASCVD risk less than 7.5% should receive moderate-intensity statin therapy. In contrast to the ACC/AHA recommendations, the U.S. Preventive Services Task Force recommends initiating low- to moderate-intensity statin therapy in adults aged 40 to 75 years without a history of ASCVD who have one or more ASCVD risk factors (dyslipidemia, diabetes, hypertension, or smoking) and a calculated 10-year ASCVD event risk of 10% or higher.

Nonstatin drugs are not considered first-line therapy for the prevention of ASCVD in patients with or without diabetes. Fibrates, such as fenofibrate, would be first-line therapy for hypertriglyceridemia (typically, when the triglyceride level is >500 mg/dL [5.65 mmol/L]) for prevention of triglyceride-induced acute pancreatitis.

A 2017 systematic review concluded that among randomized controlled trials and observational studies, evidence of variable strength showed no association between increased fish oil intake and lower cardiovascular disease event risk. Expert opinion recommends that the use of fish oil supplementation be restricted to patients with refractory hypertriglyceridemia.

All patients should receive education on therapeutic lifestyle changes, including regular exercise, weight loss, and dietary changes. However, lifestyle modifications alone are not considered adequate for cardiovascular risk reduction in many patient groups, including patients with diabetes.

KEY POINT

- Patients with diabetes mellitus are at significantly increased lifetime risk for cardiovascular events and should receive statin therapy for primary prevention.

Bibliography

Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, et al; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014;129:S1-45. [PMID: 24222016] doi:10.1161/01.cir.0000437738.63853.7a

Item 114 Answer: A

Educational Objective: Treat insomnia with cognitive behavioral therapy.

The most appropriate next step in management would be to pursue targeted cognitive behavioral therapy for this patient. The American College of Physicians recommends cognitive behavioral therapy for insomnia (CBT-I) as first-line therapy for insomnia. CBT-I combines components of sleep hygiene with cognitive therapeutic interventions (to understand and identify appropriate sleep expectations) and behavioral interventions (such as relaxation techniques). Elements of sleep hygiene include avoiding strenuous exercise, large meals, caffeine, alcohol, and nicotine close to bedtime; establishing a relaxing prebedtime routine; keeping the room dark and quiet; avoiding reading, television, and use of electronic devices while in bed; and keeping a stable bedtime and arising time. CBT-I may be delivered in various formats, such as individual or group therapy, web-based modules, or written materials. It provides significant value over pharmacologic-driven approaches and carries little risk for adverse effects.

Although diphenhydramine and melatonin are popular over-the-counter remedies for insomnia, there is insufficient evidence to recommend their use before a trial of CBT-I. Additionally, sedating antihistamines (such as diphenhydramine) are associated with anticholinergic side effects and carry-over daytime sleepiness.

Some antidepressants, such as mirtazapine, are sedating and may improve sleep. Doxepin, in low doses, is the only antidepressant approved for the treatment of insomnia. Most expert opinion recommends against using antidepressants for treating insomnia in patients without depression; however, doxepin, trazodone, and mirtazapine can be useful if a sedating antidepressant is indicated.

Benzodiazepines (flurazepam, triazolam, temazepam) are effective for short-term insomnia treatment. However, their use is limited by tolerance; side effects of daytime somnolence, falls, cognitive impairment, and anterograde amnesia; and the potential for dependence. Rebound insomnia may occur upon discontinuation, especially if discontinuation is abrupt. The selective nature and shorter half-life of nonbenzodiazepines (zolpidem, zaleplon, eszopiclone) lead to fewer side effects (including rebound insomnia), making these drugs better initial choices if pharmacotherapy is warranted. However, sedation, disorientation, and agitation may still occur; rare side effects include sleep driving, sleep walking, and sleep eating. In this patient, CBT-I should be tried before pharmacologic therapy with zolpidem is considered.

KEY POINT

- Cognitive behavioral therapy for insomnia, which combines components of sleep hygiene with cognitive therapy and behavioral interventions, is first-line therapy for insomnia.

Bibliography

Qaseem A, Kansagara D, Forciea MA, Cooke M, Denberg TD; Clinical Guidelines Committee of the American College of Physicians. Management of chronic insomnia disorder in adults: a clinical practice guideline from the American College of Physicians. Ann Intern Med. 2016;165:125-33. [PMID: 27136449] doi: 10.7326/M15-2175

Item 115 Answer: C

Educational Objective: Effectively manage termination of a physician-patient relationship.

The most appropriate management is to send the patient a formal, written warning informing him that the patient-physician relationship may be terminated unless he is able to meaningfully participate in the plan of care. Physician-patient relationships are formed on the basis of mutual agreement. Rarely, the relationship fails to reach mutual goals and becomes unproductive. In some cases, the patient may not adhere to recommended therapies or may demonstrate inappropriate behavior with the physician or staff members, and it may be appropriate for the physician to terminate the relationship. After reasonable attempts to resolve differences have failed, the patient should be notified in writing that the relationship has been terminated and that care should be obtained from a different provider, usually with a several-week time frame for the patient to continue receiving urgent care. Terminations should occur only if the patient is medically stable and when alternative care is available. If a patient threatens a physician or staff member, the termination may be immediate.

Although a psychiatrist might provide interventions to help this patient better adhere to care recommendations, such a referral is unnecessary in making a decision to terminate an ineffective physician-patient relationship.

This patient has not demonstrated signs of an unstable mental health condition that warrants intervention by a crisis team.

Patient abandonment is unethical and may be a cause for legal action. In this case, the patient has not yet received a formal warning that his failure to adhere to treatment goals may result in his termination from the practice. Therefore, he should not be released from the practice immediately.

KEY POINT

- If the physician-patient relationship becomes irreparably compromised because of lack of trust, lack of mutual goals, or failure to maintain an effective working relationship despite efforts to resolve differences, the relationship can be terminated.

Bibliography

Snyder L; American College of Physicians Ethics, Professionalism, and Human Rights Committee. American College of Physicians ethics manual: sixth edition. Ann Intern Med. 2012;156:73-104. [PMID: 22213573] doi: 10.7326/0003-4819-156-1-201201031-00001

Item 116 Answer: C

Educational Objective: Treat neurogenic thoracic outlet syndrome.

Physical therapy aimed at shoulder girdle muscle strengthening and improving posture would be the best therapeutic option for this patient with thoracic outlet syndrome (TOS). TOS is caused by compression of the brachial plexus, subclavian artery, or subclavian vein as these structures pass through the thoracic outlet. There are three main clinical subtypes of TOS, defined by the primary structure involved (nerve, artery, vein). Neurogenic TOS is the most common subtype and is caused by compression of the brachial plexus nerve roots as they exit the triangle formed by the first rib and the scalenus anticus and medius muscles. Symptoms include paresthesias and pain that typically worsen with activities that involve continued use of the arm or hand, especially those that include elevation of the arm. This patient's presentation is most consistent with neurogenic TOS. In most patients, there are no abnormal neurologic findings. Electrodiagnostic studies frequently fail to reveal any abnormalities. Although imaging studies are often obtained, they are not required to make the diagnosis; they may, however, reveal the presence of a structural abnormality, such as an anomalous cervical rib. First-line therapy for neurogenic TOS includes improving posture and strengthening shoulder girdle muscles.

Although neurogenic TOS is caused by intermittent compression of the brachial plexus within the thoracic outlet, the role of gabapentin in managing this condition has not been well studied. Gabapentin is not considered to be first-line therapy.

Observational studies have supported the use of interscalene injection of anesthetic agents, glucocorticoids, or botulinum toxin type A in patients with neurogenic TOS. However, in a randomized, double-blind clinical trial, patients treated with botulinum toxin did not show improvement in function, pain, or paresthesias compared with patients treated with placebo.

Surgical decompression is not considered to be first-line therapy for neurogenic TOS, especially in patients who lack neurologic abnormalities. The procedure is reserved for patients who do not respond to conservative measures or for those with progressive or disabling neurologic symptoms.

KEY POINT

- Symptoms of neurogenic thoracic outlet syndrome include paresthesias and pain that typically worsen with activities that involve continued use of the arm or hand, especially those that include elevation of the arm; first-line therapy includes improving posture and strengthening the shoulder girdle muscles.

Bibliography

Buller LT, Jose J, Baraga M, Lesniak B. Thoracic outlet syndrome: current concepts, imaging features, and therapeutic strategies. Am J Orthop (Belle Mead NJ). 2015;44:376-82. [PMID: 26251937]

Item 117 Answer: D

Educational Objective: Diagnose sudden sensorineural hearing loss.

The most likely diagnosis for this patient's acute, unilateral hearing loss is sudden sensorineural hearing loss (SSHL). The right-sided hearing loss and the finding of lateralization to the left ear on Weber testing support the diagnosis. Approximately 90% of cases of SSHL are idiopathic; however, viral infection, drug reactions, acoustic neuroma, multiple sclerosis, head injury, vascular issues, systemic immune-mediated conditions, and Meniere disease can all be causes. SSHL most commonly presents as unilateral tinnitus and ear fullness; vertigo occurs less often. Because this patient lacks other features to explain the acute hearing loss, she should undergo urgent referral to an otolaryngologist for audiometry, clinical assessment, and MRI to exclude tumors, multiple sclerosis, or vascular causes. Treatment involves oral glucocorticoids, although strong evidence of efficacy is lacking.

Meniere disease, which is associated with endolymphatic hydrops (excess fluid in the endolymphatic spaces), can cause unilateral sensorineural hearing loss, but its presentation is characterized by episodic vertigo (lasting between 20 minutes and 24 hours) and tinnitus, which is often low pitched. The hearing loss may be described as fluctuating, and early in the disease it often involves low frequencies. Meniere disease may also present with a sensation of ear fullness.

Otosclerosis involves bony overgrowth on the footplate of the stapes, leading to a lack of functioning of the ossicles. This middle ear process typically causes gradual, painless, bilateral conductive hearing loss, not sensorineural hearing loss, as seen in this patient. Otosclerosis occurs more often in women, and there is often a family history of the condition.

Ototoxicity also can result in sensorineural hearing loss; it may be caused by a variety of medications, including antibiotics (particularly aminoglycosides), chemotherapeutic agents, loop diuretics, and aspirin or other NSAIDs. Often occurring gradually and bilaterally, ototoxicity may be reversible or permanent, depending on the agent involved. This patient is not taking and has not been exposed to drugs known to be ototoxic.

KEY POINT

- All patients with sudden sensorineural hearing loss should undergo audiometric evaluation, and most patients will require MRI.

Bibliography

Chin CJ, Dorman K. Sudden sensorineural hearing loss. CMAJ. 2017;189:E437-E438. [PMID: 28385715] doi:10.1503/cmaj.161191

Item 118 Answer: A

Educational Objective: Treat a pressure injury with a hydrocolloid dressing.

This patient's pressure injury would be best managed with hydrocolloid or foam dressings, which have been found to be superior to standard gauze dressings in reducing ulcer size in low-quality studies. Pressure injuries (also known as pressure ulcers) are characterized by localized injury to the skin or soft tissue as a result of pressure and shear forces. They may be classified by use of a staging system, with each stage distinguished by the amount of tissue loss. In 2015, the American College of Physicians (ACP) published a clinical practice guideline for the treatment of pressure ulcers. The ACP recommends that clinicians use hydrocolloid or foam dressings in patients with pressure ulcers to reduce wound size. Hydrocolloid dressings consist of a mixture of adhesive absorbent polymers and a gelling agent, with a film covering to make them water and gas permeable. The dressing interacts with the wound fluid to form a gel. Hydrocolloids may promote wound healing by enhancing fibrinolytic activity and growth of granulation tissue and inhibiting bacterial overgrowth through their physical barrier properties. Hydrocolloids are convenient to use because they require infrequent dressing changes and are easy to apply. Foam dressings are sheets of foam polymers and are used primarily for heavily exudative wounds. Other treatment options include managing the conditions that caused the pressure injury, wound protection, surgical debridement and repair, and vacuum-assisted closure. There is moderate-quality evidence that air-fluidized beds reduce the size of pressure injuries compared with other support surfaces. The ACP also recommends protein or amino acid supplements (low-quality evidence) and electrical stimulation (moderate-quality evidence) as adjunctive therapy to accelerate wound healing.

There is insufficient evidence to recommend for or against platelet-derived growth factor dressings in the treatment of pressure injuries, and no studies have explored the benefits of vitamin- or mineral-infused dressings (such as a zinc-infused dressing). In addition, insufficient evidence was found to recommend for or against hydrotherapy, hyperbaric oxygen therapy, or maggot therapy.

KEY POINT

- Hydrocolloid or foam dressings are superior to standard gauze dressings in the treatment of pressure injuries; protein supplements and the use of electrical stimulation to accelerate wound healing are also recommended treatment strategies.

Bibliography

Qaseem A, Humphrey LL, Forciea MA, Starkey M, Denberg TD; Clinical Guidelines Committee of the American College of Physicians. Treatment of pressure ulcers: a clinical practice guideline from the American College of Physicians. Ann Intern Med. 2015;162:370-9. [PMID: 25732279] doi:10.7326/M14-1568

Item 119 Answer: C

Educational Objective: Treat obsessive-compulsive disorder with cognitive behavioral therapy.

The preferred initial treatment for this patient with obsessive-compulsive disorder (OCD) is cognitive behavioral therapy (CBT). OCD is an anxiety disorder in which patients experience obsessions (recurrent, intrusive thoughts, images, or impulses causing distress) and compulsions (repetitive behaviors done to alleviate obsession-related anxiety). Loss of time and disrupted social interactions from these thoughts and behaviors cause significant functional impairment. CBT is first-line treatment because it is more effective than pharmacotherapy alone. However, a combination of CBT and selective serotonin reuptake inhibitor (SSRI) therapy is useful for patients with severe symptoms or inadequate response to CBT. Although evidence is strongest for adjunctive therapy with SSRIs, more recent data support the adjunctive use of neuroleptics, deep brain stimulation, and neurosurgical ablation for treatment-resistant OCD.

Buspirone is beneficial in the treatment of generalized anxiety disorder without comorbid anxiety or mood disorders but has no demonstrated benefit in patients with OCD.

Benzodiazepines, such as clonazepam, are used for short-term treatment of debilitating symptoms from severe generalized anxiety disorder and panic disorder, but they are not effective in the treatment of OCD.

Risperidone is an antipsychotic medication that can be used in the treatment of schizophrenia or other psychiatric conditions with psychotic features. Patients with OCD have obsessions and compulsions but do not have hallucinations, delusions, or disorganized thoughts that would warrant antipsychotic therapy.

KEY POINT

- Obsessive-compulsive disorder should be treated with cognitive behavioral therapy (CBT); a combination of CBT and selective serotonin reuptake inhibitor therapy is useful for patients with severe symptoms or inadequate response to CBT.

Bibliography

Hirschtritt ME, Bloch MH, Mathews CA. Obsessive-compulsive disorder: advances in diagnosis and treatment. JAMA. 2017;317:1358-1367. [PMID: 28384832] doi:10.1001/jama.2017.2200

Item 120 Answer: C

Educational Objective: Treat a patient with acute epididymitis.

The most appropriate treatment is ceftriaxone and levofloxacin. This patient's history and physical examination findings (fever, erythema, and swelling of the hemiscrotum; tenderness to palpation near the epididymis; and urinary symptoms) are concerning for a diagnosis of acute epididymitis. Prehn sign, which is alleviation of pain with elevation of the testicle or scrotum, can clinically support this diagnosis. Infectious

epididymitis has a bimodal distribution: men younger than 35 years and older than 55 years. In younger patients, sexually transmitted infections (chlamydia and gonorrhea) are the most likely cause. In older patients and those who practice insertive anal intercourse, *Escherichia coli*, Enterobacteriaceae, and *Pseudomonas* species should be considered. In older men and persons who practice insertive anal intercourse, infectious epididymitis should be treated with ceftriaxone and a fluoroquinolone, such as levofloxacin.

Empiric treatment with ceftriaxone alone would provide adequate coverage for *Chlamydia trachomatis* infection but would be inadequate therapy. This older patient, who has risk factors for gram-negative infection, should be treated with ceftriaxone and a fluoroquinolone.

In younger patients (age <35 years), the most common infectious etiologies of acute epididymitis include *C. trachomatis* and *Neisseria gonorrhoeae*. In these men, and in the absence of risk factors for gram-negative infection (anal intercourse, urologic instrumentation), empirically treating with ceftriaxone and doxycycline (or azithromycin, if the patient is intolerant to doxycycline) would be appropriate.

Epididymitis can also have noninfectious causes (for example, trauma, autoimmune disease, or vasculitis). Treatment includes scrotal support, ice, and NSAIDs. Analgesic agents and scrotal support are supportive measures that can be offered to all patients presenting with acute epididymitis. However, the most appropriate treatment for this patient with risk factors for bacterial epididymitis and no history of trauma or findings supporting autoimmune disease or vasculitis would be initiation of an antimicrobial regimen rather than supportive therapies alone.

KEY POINT

- In older men and persons who practice insertive anal intercourse, infectious epididymitis should be treated with ceftriaxone and a fluoroquinolone, such as levofloxacin.

Bibliography

McConaghy JR, Panchal B. Epididymitis: an overview. Am Fam Physician. 2016;94:723-726. [PMID: 27929243]

Item 121 Answer: C

Educational Objective: Evaluate a breast mass in a woman aged 30 years and older.

This patient's breast mass should be evaluated with both diagnostic mammography and ultrasonography. Any dominant mass in the breast warrants diagnostic imaging to determine the nature of the mass and the appropriate management. A clinical examination alone cannot differentiate between a cyst and a solid mass. In a woman aged 30 years or older, diagnostic mammography is recommended for evaluation of a palpable mass, to assess for a spiculated density or associated pleomorphic calcifications that may indicate malignancy. Diagnostic mammography may also include magnification views of the focal area of concern. In addition, targeted ultrasonography is needed to determine whether the mass is cystic or solid; however, ultrasonography is unnecessary in cases in which mammography shows a clearly benign correlate or a normal, fatty area of breast tissue in the location of the palpable finding. This diagnostic evaluation can help determine a benign finding from an indeterminate or suspicious finding requiring needle biopsy. For women aged 40 years or older, mammography, followed in most cases by ultrasonography, is recommended. For women aged 30 to 39 years old, ultrasonography or mammography may be performed first at the discretion of the radiologist or referring clinician.

Breast MRI and other advanced imaging have little to no role in the routine diagnostic evaluation of palpable breast abnormalities. Breast MRI is not an appropriate imaging technique for evaluation of palpable symptoms because it provides little added information to careful evaluation with mammography and ultrasonography.

Definitive diagnosis of a breast mass is obtained by tissue sampling using fine-needle aspiration, core-needle biopsy with or without stereotactic or ultrasound guidance, or excisional biopsy. Fine-needle aspiration is generally reserved for ultrasound-confirmed cystic lesions. Core-needle biopsy is the test of choice for most solid lesions, as it provides more tissue for histology and tissue markers. Excisional biopsy is used when core-needle biopsy findings are nondiagnostic or when biopsy and imaging studies do not concur. Further management of abnormal pathologic findings requires consultation with a breast surgeon and oncologist. Needle aspiration, core-needle biopsy, and excision are all premature until the imaging evaluation is completed.

Ultrasonography is often preferred in women younger than age 30 years because the increased density of breast tissue in younger women limits the usefulness of mammography. Ultrasonography may also be a better choice for pregnant patients in order to avoid radiation exposure.

KEY POINT

- For evaluation of palpable breast abnormalities in women aged 40 years or older, mammography, followed in most cases by ultrasonography, is recommended.

Bibliography

Lehman CD, Lee AY, Lee CI. Imaging management of palpable breast abnormalities. AJR Am J Roentgenol. 2014;203:1142-53. [PMID: [illegible]] doi:10.2214/AJR.14.12725

Item 122 Answer: C

Educational Objective: Identify medications to avoid during pregnancy.

This patient should discontinue the ACE inhibitor lisinopril. Medication adjustments are an important component of preconception counseling in women who are planning pregnancy. All antihypertensive medications cross the placenta. Some antihypertensive medications are absolutely

contraindicated during pregnancy, including ACE inhibitors, angiotensin receptor blockers (ARBs), and, likely, renin inhibitors. Women taking ACE inhibitors or ARBs should be counseled about the associated teratogenicity throughout all trimesters, and these medications should be stopped if pregnancy is anticipated or possible. Blood pressure goals with medical therapy in patients with chronic hypertension during pregnancy are 120 to 160/80 to 105 mm Hg. However, treatment of hypertension during pregnancy is controversial. If blood pressure control is not adequate after stopping lisinopril, methyldopa and labetalol have been used safely. Calcium channel blockers (such as long-acting nifedipine) can also be used during pregnancy. Diuretics may induce oligohydramnios if initiated during pregnancy but generally can be continued if the patient was taking a diuretic preconception. Spironolactone and eplerenone should be avoided because their safety has never been proven.

Although acetaminophen is generally considered safe during pregnancy, caution is needed with the use of NSAIDs due to their effect on organogenesis during pregnancy.

A goal for preconception wellness is the absence of uncontrolled depression. Evidence shows that women who are depressed during pregnancy have worse birth outcomes. Selective serotonin reuptake inhibitors, including citalopram, fluvoxamine, and sertraline, are pregnancy category C agents that can be continued during pregnancy. An alternative to antidepressant therapy is psychotherapy, specifically cognitive behavioral therapy, which is equally as efficacious as pharmacologic therapy. In this patient who is already taking an antidepressant, it would be more important to continue therapy than to discontinue treatment.

Optimal glycemic control with a goal hemoglobin A_{1c} value of less than 6.5% is recommended for women with diabetes mellitus who are contemplating pregnancy. Metformin is a diabetes medication deemed safe during pregnancy, as it is FDA category B. Category B denotes that animal reproduction studies have not demonstrated a fetal risk, and no controlled studies in pregnant women have shown adverse effects.

KEY POINT

- Antihypertensive medications absolutely contraindicated during pregnancy include ACE inhibitors, angiotensin receptor blockers, and, likely, renin inhibitors.

Bibliography

Frayne DJ, Verbiest S, Chelmow D, Clarke H, Dunlop A, Hosmer J, et al. Health care system measures to advance preconception wellness: consensus recommendations of the Clinical Workgroup of the National Preconception Health and Health Care Initiative. Obstet Gynecol. 2016;127:863-72. [PMID: 27054935] doi:10.1097/AOG.0000000000001379

Item 123 Answer: D

Educational Objective: Manage perioperative anticoagulation in a patient receiving warfarin.

The most appropriate management of this patient's preoperative anticoagulation is to withhold warfarin without bridging anticoagulation. Anticoagulant therapy increases the risk for perioperative hemorrhage and should be discontinued in most patients before surgery. Bridging anticoagulation is the administration of therapeutic doses of short-acting parenteral therapy, usually heparin, when anticoagulant therapy is being withheld during the perioperative period in patients with elevated thrombotic risk. This patient is undergoing a procedure associated with elevated bleeding risk, and she has no history of stroke, transient ischemic attack (TIA), or intracardiac thrombus. Therefore, the risks of bridging anticoagulation outweigh the thrombotic risk, and the warfarin should be withheld without bridging anticoagulation.

There is no role for aspirin in bridging anticoagulation. In patients with normal kidney function who require bridging anticoagulation, low-molecular-weight heparin is the agent of choice.

The American College of Chest Physicians (ACCP) and the American College of Cardiology (ACC)/American Heart Association (AHA) have made recommendations regarding bridging anticoagulation in patients with atrial fibrillation. Most recently in 2017, the ACC published an expert consensus decision pathway for periprocedural management of anticoagulation in patients with nonvalvular atrial fibrillation. The ACCP recommends bridging anticoagulation in patients with a $CHADS_2$ score of 3 or higher or with a history of stroke or transient ischemic attack (TIA). However, according to the ACCP guideline, bridging anticoagulation is not indicated if bleeding risk is elevated in patients with a $CHADS_2$ score of 3 or 4 and no history of stroke or TIA. The 2017 ACC decision pathway suggests forgoing bridging anticoagulation in patients with CHA_2DS_2-VASc scores of 5 and 6 or lower without a history of stroke, TIA, or systemic embolism. Because this patient has a $CHADS_2$ score of 2 and a CHA_2DS_2-VASc score of 4, bridging anticoagulation is not necessary.

KEY POINT

- In patients taking warfarin, bridging anticoagulation may be deferred if thrombotic risk is low.

Bibliography

Doherty JU, Gluckman TJ, Hucker WJ, Januzzi JL Jr, Ortel TL, Saxonhouse SJ, et al. 2017 ACC expert consensus decision pathway for periprocedural management of anticoagulation in patients with nonvalvular atrial fibrillation: a report of the American College of Cardiology Clinical Expert Consensus Document Task Force. J Am Coll Cardiol. 2017;69:871-898. [PMID: 28081965]

Item 124 Answer: C

***Educational Objective:* Screen for genital and extragenital gonorrhea and chlamydia in a man who has sex with men.**

The most appropriate screening strategy in this patient is nucleic acid amplification testing (NAAT) of urine, rectal, and pharyngeal specimens for *Neisseria gonorrhoeae* and *Chlamydia trachomatis*. Multiple studies have demonstrated an increased prevalence of genital and extragenital

chlamydial and gonorrheal infections in men who have sex with men (MSM). In one study, prevalence rates of *N. gonorrhoeae* in MSM were 6.9% (rectal), 6% (urethral), and 9.2% (pharyngeal); for *C. trachomatis*, prevalence rates in MSM were 7.9% (rectal), 5.2% (urethral), and 1.4% (pharyngeal). Most infections are asymptomatic. The Centers for Disease Control and Prevention (CDC) recommends at least annual gonorrhea screening with NAAT of urethral, pharyngeal, and rectal specimens and at least annual screening for chlamydia with NAAT of urethral and rectal specimens. The CDC notes that commercially available NAATs have not been cleared by the FDA for some of these indications; however, these tests can be used by laboratories that have met all regulatory requirements for an off-label procedure. The CDC also recommends screening for syphilis and HIV at least annually in MSM. In contrast to the CDC, the U.S. Preventive Services Task Force has found insufficient evidence to recommend screening for chlamydia and gonorrhea in men.

Human papillomavirus (HPV)-associated conditions (such as anogenital warts and anal squamous intraepithelial lesions) are common among MSM. However, data are insufficient to recommend routine anal cancer screening with anal cytology in MSM. The quadrivalent HPV vaccine is recommended for MSM through age 26 years.

Sexual transmission of hepatitis C infection can occur in MSM with HIV infection. The CDC recommends that screening should be performed at least yearly for hepatitis C in this population. Hepatitis C screening is also indicated in all past and current injection drug users. Because the patient does not use drugs and his HIV status is unknown, screening for hepatitis C is not indicated at this time.

All MSM should also be tested for hepatitis A and B. Vaccination against hepatitis A and B is recommended for all MSM in whom previous infection or vaccination cannot be documented.

KEY POINT

- The Centers for Disease Control and Prevention recommends that men who have sex with men should be screened at least annually for genital and extragenital chlamydial and gonorrheal infections, syphilis, and HIV infection.

Bibliography

Wilkin T. Clinical practice. Primary care for men who have sex with men. N Engl J Med. 2015;373:854-62. [PMID: 26308686] doi:10.1056/NEJMcp1401303

Item 125 Answer: C

Educational Objective: Treat recurrent major depressive disorder.

Long-term continuation of fluoxetine at the current dosage is appropriate for this patient with recurrent depression. Guidelines from the American Psychiatric Association (APA) recommend long-term maintenance therapy for patients with three or more episodes of major depressive disorder, persistent depressive disorder, or residual depressive symptoms. The same antidepressant and dosage that were effective in the treatment of acute depression should be continued for long-term maintenance.

Fluoxetine therapy for 8 months should be sufficient for the treatment of the patient's major depressive disorder, but the medication should not be tapered. Because he has had two other episodes of depression, he should be maintained on antidepressant therapy to prevent recurrence.

Switching to another antidepressant medication (such as bupropion) for long-term maintenance is not indicated unless the patient develops intolerable adverse effects from the initial medication.

Discontinuing fluoxetine is not recommended, even if the patient were not a candidate for long-term therapy. APA guidelines recommend continuing treatment for at least 4 to 9 months after resolution of major depressive disorder, followed by gradual tapering of the antidepressant dosage. Antidepressant drugs should not be stopped abruptly because of the risk for discontinuation syndrome, which is most frequently seen in patients who abruptly stop selective serotonin reuptake inhibitors. The most common discontinuation symptoms include dizziness, fatigue, headache, and nausea. Other symptoms include agitation, anxiety, dysphoria, and irritability. Onset of the syndrome is within 1 to 4 days of abruptly stopping antidepressant therapy or after a rapid taper. Although fluoxetine has the lowest incidence of discontinuation syndrome, therapy should be tapered rather than abruptly stopped.

KEY POINT

- The American Psychiatric Association recommends long-term maintenance therapy for patients with three or more episodes of major depressive disorder, persistent depressive disorder, or residual depressive symptoms; the antidepressant dosage that was effective in acute treatment should be continued for long-term maintenance.

Bibliography

American Psychiatric Association. Practice Guideline for the Treatment of Patients With Major Depressive Disorder. 3rd edition. Arlington, VA: American Psychiatric Association; 2010. Available at https://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/mdd.pdf. Accessed July 25, 2018.

Item 126 Answer: C

Educational Objective: Evaluate a patient with medically unexplained symptoms.

The most appropriate management of this patient with medically unexplained symptoms (MUS) is to avoid testing and obtain previous medical records. The most common symptoms in patients presenting with MUS are chest pain, fatigue, dizziness, headache, swelling, back pain, shortness of breath, insomnia, abdominal pain, and numbness. Frequently, patients have seen many primary care and subspecialty physicians over the course of many years and

have undergone extensive laboratory testing, imaging studies, and procedures. Because patients with MUS present on a continuum of physical and mental health, a comprehensive, holistic approach is essential. Each presenting symptom merits a relevant history and physical examination. In most cases, prior records should be reviewed before repeating or extending the evaluation unless the patient's condition has changed substantially. Physicians must possess excellent patient-centered communication skills and listen carefully to the patient, validating concerns and responding to emotions. Additionally, the initial assessment should include specific questions to elicit the patient's concerns, underlying psychological status, and the degree of distress and disability attributable to the symptoms. Long-term management of the patient with MUS is challenging. A therapeutic alliance and a mutually respectful physician patient relationship are key features in the successful management of the patient with MUS. In keeping with a patient-centered approach, the patient should be engaged fully in the plan, focusing on physical, psychological, and social aspects of health. The physician and patient should work together to create and maintain an atmosphere of mutual trust.

Physicians often find it difficult to limit further testing, prescribing, or referral because they fear missing an elusive diagnosis. The evidence that more testing helps reassure patients with MUS or improves outcomes is limited. Additional testing, such as a comprehensive metabolic profile, C-reactive protein level, rheumatoid factor, and antinuclear antibody titer, should not occur without an initial thorough investigation of the results of previous evaluations and determining whether symptoms have changed.

Familial Mediterranean fever (FMF) is the classic autoinflammatory disease, characterized by discrete attacks of pain lasting up to 72 hours associated with serosal inflammation (joints, chest, abdomen), rash, and abnormalities on *MEFV1* genetic testing. This patient's presentation does not match that of FMF. More importantly, additional testing should be avoided until after a review of previous medical records.

It is possible that the patient may ultimately benefit from a psychiatric consultation. However, before that occurs, the physician should review the patient's medical records; evaluate the current status of his symptoms; elicit his concerns, psychological status, and degree of distress and disability attributable to the symptoms; and establish a trusting relationship with the patient.

KEY POINT

- In patients with medically unexplained symptoms, clinicians must approach each symptom in a focused manner and diligently review any previous diagnostic evaluations.

Bibliography

Evens A, Vendetta L, Krebs K, et al. Medically unexplained neurologic symptoms: a primer for physicians who make the initial encounter. Am J Med. 2015;128:1059-64. [PMID: 25910791]

Item 127 Answer: E

Educational Objective: Treat a patient with cervical radiculopathy with neck exercises.

The most appropriate management of this patient with symptoms consistent with cervical radiculopathy is neck exercises. Stretching and strengthening exercises provide intermediate term relief of symptoms and should be part of a multimodal approach. Other nonpharmacologic options include acupuncture, early mobilization, and spinal manipulation. Cervical traction appears to be of limited benefit. Patients should also be informed that most patients with neck pain have resolution or near-resolution of symptoms within 2 to 3 months of onset by using conservative measures.

The use of a cervical collar in patients with neck pain should be avoided because it can lead to neck muscle atrophy, especially when used for longer than 1 to 2 weeks. Shorter-term use appears to be no more effective for symptom relief than sham interventions.

This patient lacks any "red flag" findings that would warrant imaging, whether in the form of plain radiography or MRI. Features that would prompt imaging include constitutional symptoms; personal history of or concern for malignancy; progressive neurologic symptoms; or myelopathic findings, such as difficulty writing, gait disturbance, hypertonia, hyperflexia, or problems with fine manipulation.

Electrodiagnostic testing is most helpful to diagnose peripheral nerve entrapment syndromes or peripheral neuropathy as the cause of arm symptoms. Both of these conditions should be considered when arm symptoms are more prominent than neck symptoms. Electrodiagnostic testing can also identify cervical radiculopathy as the cause of neck pain but only when motor axonal injury is present; cervical radicular pain can exist in the absence of axonal injury. Therefore, the best course of action for this patient is conservative treatment without diagnostic testing.

NSAIDs are considered first line pharmacologic therapy for acute neck pain, including acute cervical radiculopathy. Cyclobenzaprine, when used at doses greater than 15 mg/d, has been shown to be effective for treating acute neck pain when muscle spasm is present, although it should be used with caution in older patients. Gabapentin, a neuromodulator, can be used to treat chronic radicular pain; however, it does not have a role in the management of acute radicular symptoms.

KEY POINT

- Cervical radiculopathy, caused by nerve root compression, usually resolves within 2 to 3 months by using conservative measures; stretching and strengthening exercises of the neck muscles provide the best intermediate-term relief.

Bibliography

Iyer S, Kim HJ. Cervical radiculopathy. Curr Rev Musculoskelet Med. 2016;9:272-80. [PMID: 27250042] doi:10.1007/s12178-016-9349-4

Item 128 Answer: A

Educational Objective: Prevent human papillomavirus infection with appropriate immunization.

This healthy 25-year-old woman should be offered the human papillomavirus (HPV) vaccine. HPV vaccination prevents persistent HPV infection, which can lead to cervical, anogenital, and nasopharyngeal cancers. HPV genotypes 16 and 18 are responsible for causing most cases of cervical cancer and many cases of vulvar, vaginal, anal, penile, and oropharyngeal cancers. HPV genotypes 6 and 11 cause most cases of genital warts. The HPV vaccine series is recommended for all females aged 11 or 12 years or between the ages of 13 and 26 years if not given previously. In males, the series should be administered at age 11 or 12 years, between the ages of 13 and 21 years if not previously administered, or through age 26 years for immunocompromised men (including those with HIV infection) or men who have sex with men. Three different HPV vaccines are licensed for use in females (bivalent, quadrivalent, and nine-valent), and two HPV vaccines are licensed for use in males (quadrivalent and nine-valent). All vaccines target genotypes 16 and 18, and the quadrivalent vaccine also targets genotypes 6 and 11. The nine-valent vaccine protects against five additional genotypes that cause cervical cancer, resulting in the potential prevention of 90% of cervical, vulvar, vaginal, and anal cancers. If administered after age 15 years, a three-dose series is recommended, whereas a two-dose series is recommended in younger individuals.

Vaccination against meningococcal serogroups A, C, W135, and Y with the quadrivalent meningococcal conjugate vaccine is recommended in all persons by age 18 years. Revaccination with a single dose of the quadrivalent meningococcal conjugate vaccine is indicated in adult patients who are considered to be at increased risk, including those with asplenia (functional or anatomic), those with persistent complement deficiencies, first-year college students living in a dormitory, travelers to endemic areas, microbiologists exposed to *Neisseria meningitidis*, military recruits, persons at increased risk during an outbreak, and persons infected with HIV. Revaccination is indicated every 5 years in those who remain at increased risk. This patient does not have any indications for quadrivalent meningococcal conjugate revaccination.

Adults aged 19 years and older who did not receive the tetanus, diphtheria, and acellular pertussis (Tdap) vaccine during adolescence should receive a dose of the Tdap vaccine, followed by tetanus and diphtheria toxoids (Td) boosters every 10 years. Because this patient received a Tdap vaccine 7 years ago, she should receive a Td booster in 3 years.

Pneumococcal vaccination is recommended in all adults aged 65 years and older and adults aged 19 to 64 years with certain high-risk conditions. This young patient does not smoke or have any immunocompromising or chronic medical conditions; therefore, the 23-valent pneumococcal polysaccharide vaccine is not indicated.

KEY POINT

- Vaccination against human papillomavirus is recommended for all females aged 11 or 12 years or between the ages of 13 and 26 years if not previously vaccinated and for all males aged 11 or 12 years, between the ages of 13 and 21 years if not previously vaccinated, or through age 26 years for immunocompromised men and men who have sex with men.

Bibliography

Petrosky E, Bocchini JA Jr, Hariri S, Chesson H, Curtis CR, Saraiya M, et al; Centers for Disease Control and Prevention (CDC). Use of 9-valent human papillomavirus (HPV) vaccine: updated HPV vaccination recommendations of the advisory committee on immunization practices. MMWR Morb Mortal Wkly Rep. 2015;64:300-4. [PMID: 25811679]

Item 129 Answer: B

Educational Objective: Treat vasomotor symptoms of menopause.

The most appropriate management is hormone replacement therapy with estrogen and progesterone. The hallmark symptoms of menopause vary greatly in duration, frequency, and severity, but they may include vasomotor symptoms (hot flushes, night sweats) and urogenital symptoms (dyspareunia, vaginal dryness). Symptoms generally resolve spontaneously within a few years, and treatment should be based on symptom severity. Hormone therapy is effective treatment for relief of vasomotor symptoms of menopause, and for women who are younger than 60 years and are within 10 years of menopause onset, the low absolute risk of adverse events supports the option to prescribe hormone therapy for women with moderate to severe vasomotor or urogenital symptoms who are at low risk for breast cancer, coronary heart disease, stroke, and thromboembolic disease. The clinician should prescribe the lowest effective dosage, titrating up if needed, for the shortest period of time needed to control symptoms. Use of hormone therapy in menopause should be reassessed every year; treatment duration is based on the continued presence of vasomotor symptoms. Estrogen-progesterone therapy taken for more than 5 years is associated with increased risk for breast cancer and requires that women receive individualized breast cancer risk evaluation. For this patient with an intact uterus and no contraindications, combination estrogen-progesterone therapy is the best choice.

Long-term unopposed endometrial estrogen exposure increases the risk for endometrial hyperplasia or malignancy, and for women who experience menopausal symptoms and have an intact uterus, estrogen should be combined with progestin to avoid unopposed estrogen-related endometrial proliferation. For women who have had a hysterectomy, estrogen alone would be the preferred hormone therapy but would be inappropriate for this patient.

Ospemifene is an estrogen agonist/antagonist that is used in postmenopausal women to reduce the severity of

moderate to severe dyspareunia associated with genitourinary symptoms of menopause; however, it is not indicated for vasomotor symptom management.

Vaginal estrogen therapy is effective for managing genitourinary syndrome of menopause, although vaginal estrogen alone will not be adequate therapy for vasomotor symptoms of menopause, as experienced by this patient.

KEY POINT

- Hormone therapy is an option for women with moderate to severe vasomotor symptoms of menopause who are younger than 60 years and within 10 years of menopause onset, provided they are at low risk for breast cancer, coronary heart disease, stroke, and thromboembolic disease.

Bibliography

The NAMS 2017 Hormone Therapy Position Statement Advisory Panel. The 2017 hormone therapy position statement of The North American Menopause Society. Menopause. 2017;24:728-753. [PMID: 28650869] doi:10.1097/GME.0000000000000921

Item 130 Answer: B

Educational Objective: Diagnose labyrinthitis.

The most likely diagnosis in this patient with vertigo is labyrinthitis. Patients with vertigo often describe a spinning or whirling sensation, which is frequently associated with concomitant nausea, vomiting, and sudden-onset fatigue. Once vertigo is suspected, the next important step is to distinguish central from peripheral causes. The Dix-Hallpike maneuver can help with this task but could not be performed in this patient. The identification of central vertigo is important because it can be associated with ischemia, infarction, or hemorrhage of the cerebellum or brainstem and may be life threatening. More than 80% of patients with central vertigo have focal neurologic signs, and many have experienced recurrent symptoms over days to weeks. In this patient's case, he has no risk factors for stroke (hypertension, diabetes mellitus), no focal signs, and a preceding upper respiratory tract infection, making central vertigo unlikely. Common causes of peripheral vertigo include benign paroxysmal positional vertigo (BPPV), vestibular neuronitis, labyrinthitis, and Meniere disease. Labyrinthitis is caused by postviral inflammation of both branches of the vestibulocochlear nerve (cranial nerve VIII), resulting in sudden-onset, severe, persistent vertigo and hearing loss. This patient has signs and symptoms consistent with labyrinthitis preceded by an acute viral infection, making it the most likely diagnosis.

BPPV is the most common cause of peripheral vertigo. It is characterized by sudden-onset, recurrent, and brief (usually <1 minute) vertiginous symptoms, which are provoked and worsened with positional changes of the head. Although prolonged head positioning can trigger BPPV, BPPV is not associated with auditory changes, as seen in this patient.

Meniere disease presents with recurrent, spontaneous, and brief episodes of vertigo, tinnitus, and hearing loss. Nystagmus may be present. Symptoms resolve completely between episodes. In patients with Meniere disease, episodes of vertigo typically last hours, whereas this patient has experienced unremitting symptoms for the past 2 days.

Vestibular neuronitis is a peripheral vestibular condition caused by inflammation of the vestibular branch of the vestibulocochlear nerve, leading to vertiginous symptoms and nystagmus. It is most often preceded by a viral infection. Symptoms are sustained, ranging from days to weeks; however, auditory symptoms are not present, which is the key distinction between vestibular neuronitis and labyrinthitis.

KEY POINT

- Labyrinthitis is characterized by sudden-onset, severe, persistent peripheral vertigo accompanied by hearing loss; it is most often preceded by a viral infection affecting both branches of the vestibulocochlear nerve (cranial nerve VIII).

Bibliography

Kim JS, Zee DS. Clinical practice. Benign paroxysmal positional vertigo. N Engl J Med. 2014;370:1138-47. [PMID: 24645946] doi: 10.1056/NEJMcp1309481

Item 131 Answer: D

Educational Objective: Treat cough due to acute rhinosinusitis.

This patient with acute cough due to acute rhinosinusitis should be treated with an intranasal glucocorticoid, such as fluticasone. Most upper respiratory tract infections (URIs) are caused by viral infections and resolve spontaneously within a few days. Patients without clear evidence of bacterial infection should be treated symptomatically. A meta-analysis of patients with acute rhinosinusitis found that use of intranasal glucocorticoids increased the rate of symptom response compared with placebo; there was a dose-response curve, with higher doses offering greater relief. Analgesics, such as NSAIDs and acetaminophen, may relieve pain. Only limited evidence supports saline irrigation in the relief of nasal symptoms; careful attention should be paid to the use of sterile or bottled water. Instructions for nasal saline irrigation are available online (www.fda.gov/ForConsumers/ConsumerUpdates/ucm316375.htm). First-generation antihistamines may help dry nasal secretions; however, evidence supporting their efficacy is lacking, and sedation is a common side effect. Decongestants are of possible benefit in patients with evidence of eustachian tube dysfunction but should be used with caution in elderly patients and those with cardiovascular disease, hypertension, angle-closure glaucoma, or bladder neck obstruction. Antitussive agents are generally ineffective.

Empiric treatment of URI symptoms with antibiotics (such as amoxicillin) is ineffective, increases bacterial antibiotic resistance, and may cause multiple adverse effects, including *Clostridium difficile* colitis. Antibiotics should be reserved for patients with symptoms lasting more than 10 days, worsening symptoms after initially improving viral illness, or severe symptoms or signs of high fever (>39 °C [102.2 °F]) with purulent nasal discharge or facial pain for at least 3 consecutive days.

A systematic review concluded that centrally acting (codeine, dextromethorphan) or peripherally acting (moguisteine) antitussive therapy results in little improvement in acute cough and is not recommended.

Inhaled albuterol is indicated for patients with evidence of wheezing, which this patient does not have. For patients who develop postinfectious airway hyperreactivity with a subacute or chronic cough, albuterol and other asthma therapies are beneficial.

KEY POINT

- Acute rhinosinusitis may be treated symptomatically with analgesics and intranasal glucocorticoids; antibiotics are not recommended without clearly established bacterial infection.

Bibliography

Harris AM, Hicks LA, Qaseem A; High Value Care Task Force of the American College of Physicians and for the Centers for Disease Control and Prevention. Appropriate antibiotic use for acute respiratory tract infection in adults: advice for high-value care from the American College of Physicians and the Centers for Disease Control and Prevention. Ann Intern Med. 2016;164:425-34. [PMID: 26785402] doi:10.7326/M15-1840

H

Item 132 Answer: C

Educational Objective: Treat pain in a patient with advanced serious illness and chronic kidney disease with hydromorphone.

The most appropriate treatment of this patient's pain is hydromorphone. This patient's back pain is caused by progressive myeloma, and she requires rapid treatment of her pain with oral opioids initially. Given the concern for worsening back pain in the setting of malignancy, she requires an urgent MRI of her spine to rule out impending malignant spinal cord compression, and aggressive pain treatment while pursuing a diagnostic strategy is critical. Hydromorphone is a potent opioid agonist that is thought to be safer in patients with severe kidney impairment, such as this patient on hemodialysis.

A transdermal fentanyl patch is an effective analgesic for opioid-tolerant patients. It does not have clinically relevant active metabolites that would accumulate in the setting of end-stage kidney disease; however, it should be used only in opioid-tolerant patients. This patient is opioid naïve, and she should not be started on a long-acting agent until her total daily opioid needs are identified and an appropriate equianalgesic dose of fentanyl is calculated.

Gabapentin binds to the $\alpha_2\delta$ subunit of voltage-gated calcium channels; it can be an effective nonopioid adjuvant in the treatment of various pain types, including neuropathic pain. Titration of gabapentin can be prolonged to avoid adverse effects; therefore, it would not be helpful in this patient in need of more rapid analgesia.

Morphine is a prototypical opioid agonist, but its active metabolites accumulate in the setting of kidney failure and increase the risk for adverse neuroexcitatory effects with aggressive titration. Morphine, codeine, and meperidine are all contraindicated in patients with kidney failure (glomerular filtration rate <30 mL/min/1.73 m²).

Tramadol is a weak opioid agonist whose analgesic activity is influenced by its inhibition of serotonin and norepinephrine reuptake. It is a poor analgesic in the setting of cancer-related pain and should not be used in patients with kidney failure due to accumulation of active metabolites. In addition, tramadol has the potential for significant drug interactions.

KEY POINT

- Hydromorphone is the preferred opioid to treat cancer-related pain in patients with chronic kidney disease.

Bibliography

Swetz KM, Kamal AH. Palliative care. Ann Intern Med. 2018;168:ITC33-ITC48. [PMID: 29507970] doi:10.7326/AITC201803060

Item 133 Answer: A

H

Educational Objective: Evaluate for coronary artery disease preoperatively in a patient with elevated cardiac risk and poor functional capacity.

Dobutamine stress echocardiography is indicated in this patient undergoing elective noncardiac surgery with an elevated cardiac risk, poor functional capacity, symptoms, and electrocardiographic findings concerning for possible silent ischemia. In patients undergoing noncardiac surgery, risk calculators, including the Revised Cardiac Risk Index (RCRI) and American College of Surgeons National Surgical Quality Improvement Program myocardial infarction and cardiac arrest calculator, can be used to determine the risk for a perioperative major adverse cardiac event (MACE). Asymptomatic patients at low risk (<1% risk for perioperative MACE) may proceed to surgery without preoperative cardiac stress testing, whereas patients with elevated risk (>1% risk for perioperative MACE) should undergo assessment of functional capacity. Metabolic equivalents (METs) are used to represent the patient's functional capacity based on the intensity of activity able to be performed. If the patient's functional capacity exceeds 4 METs, the patient may proceed to surgery without further testing. Cardiac stress testing should be considered in patients at elevated risk for MACE with a functional capacity of less than 4 METs or if functional capacity cannot be determined, but only if the results of stress testing will change perioperative manage-

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ment. In this case, the patient's RCRI score is 4 (pathologic Q waves on electrocardiogram, stroke, insulin-dependent diabetes mellitus, and preoperative creatinine >2.0 mg/dL [176.8 µmol/L]) corresponding to a MACE (cardiac death, nonfatal myocardial infarction, and nonfatal cardiac arrest) risk of greater than 5.4%, and stress testing is indicated. Because of the elective nature of his scheduled surgery, he would be able to proceed with preoperative coronary angiography if indicated based on the results of stress testing.

This patient's exercise capacity is limited by fatigue, dyspnea, and hip pain; therefore, exercise electrocardiography would most likely be nondiagnostic.

Echocardiography to evaluate left ventricular function should not be routinely performed preoperatively. However, it is recommended in certain clinical scenarios, such as in the presence of dyspnea of unknown origin, heart failure with worsening dyspnea or overall change in clinical status, known left ventricular dysfunction without assessment in the last year, and known or suspected moderate to severe valvular stenosis or regurgitation without echocardiographic assessment in the last year or with a change in clinical status. In this patient, transthoracic echocardiography would not provide the necessary evaluation for myocardial ischemia.

KEY POINT

- Preoperative cardiac stress testing should be considered in patients at elevated risk for a major adverse cardiac event or if functional capacity cannot be determined, but only if the results of stress testing will change perioperative management.

Bibliography

Fleisher LA, Fleischmann KE, Auerbach AD, Barnason SA, Beckman JA, Bozkurt B, et al; American College of Cardiology. 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines. J Am Coll Cardiol. 2014;64:e77-137. [PMID: 25091544] doi:10.1016/j.jacc.2014.07.944

Item 134 Answer: B

Educational Objective: Manage impairment in a physician colleague.

The most appropriate management is to directly approach the colleague with the concerns of impairment and guide her through a plan to determine whether impairment exists and, if so, how to manage it. Impairment may be caused by medical or psychiatric illness or the use of psychoactive substances; however, the presence of these conditions does not necessarily signify impairment. According to the American College of Physicians *Ethics Manual*, every physician is responsible for protecting patients from an impaired colleague and for assisting an impaired colleague by identifying appropriate sources of help. These responsibilities should not be hampered by personal relationships, shame, or fear of harming a colleague. This physician's colleague, who may be demonstrating signs of cognitive impairment, would benefit from assistance.

When signs of physician impairment are present, it is preferable to intervene before patient harm occurs, if possible. Therefore, continuing to monitor the colleague is not the best option.

Although the physician may be tempted to offer to perform the colleague's medical evaluation, several risks are associated with caring for patients with whom a previous relationship exists, including impaired objectivity, insufficient history taking (for example, sexual history), incomplete examination, and incomplete or biased assessment. The colleague should undergo a confidential and complete medical assessment with another physician to search for reversible causes of impairment.

There is a clear ethical responsibility to report a physician who appears to be impaired to an appropriate authority, which may include a chief of staff, chief of service, or, if the impairment is serious, a state medical board. The legal requirements and thresholds for reporting impaired physicians vary. Most state medical societies or medical boards have physician health programs for physicians with potentially impairing illnesses that can be accessed through a voluntary or mandatory track; these physician health programs provide confidential assessment and treatment, with the goal of restoration of function. At this point, there is no objective evidence of impairment, and a confidential evaluation would be the most appropriate first step.

KEY POINT

- Every physician is responsible for protecting patients from an impaired colleague and for assisting an impaired colleague by identifying appropriate sources of help.

Bibliography

Snyder L; American College of Physicians Ethics, Professionalism, and Human Rights Committee. American College of Physicians ethics manual: sixth edition. Ann Intern Med. 2012;156:73-104. [PMID: 22213573] doi:10.7326/0003-4819-156-1-201201031-00001

Item 135 Answer: B

Educational Objective: Treat erectile dysfunction in a patient with multiple comorbid conditions.

The most appropriate treatment for this patient's erectile dysfunction (ED) is psychotherapy. The patient has a history of depression, which can predispose to intermittent ED. Given that the patient is still able to achieve an erection 50% of the time and experiences nocturnal penile tumescence, a diagnosis of ED secondary to his other medical comorbidities or medication usage is far less likely. On the basis of these findings, he likely has situational or mood-related ED. In situations such as this one, it can be beneficial to proceed with therapies such as cognitive behavioral therapy, biofeedback therapy, and sensory awareness exercises.

Alprostadil is considered second-line therapy, as it requires routine intracavernous injections, transurethral injections, or transurethral suppositories. For many patients, this option is poorly tolerated. In patients with depression and intermittent ED, alprostadil would not be recommended before trying psychotherapy, which is much better tolerated.

Sildenafil and other oral phosphodiesterase-5 inhibitors are considered first-line medical therapy for ED. However, sildenafil is contraindicated in patients taking nitrate therapy, such as this one.

Testosterone supplementation is recommended only in patients with ED and confirmed symptomatic androgen deficiency. This patient has a normal total testosterone level and has no alterations in secondary sexual characteristics, which make the diagnosis of clinically relevant androgen deficiency unlikely. Furthermore, testosterone therapy should be avoided in patients with untreated obstructive sleep apnea.

KEY POINT

- Erectile dysfunction in a patient who experiences nocturnal penile tumescence is most likely situational or mood related; cognitive behavioral therapy, biofeedback, or sensory awareness exercises with a psychotherapist are first-line therapies.

Bibliography

Mobley DF, Khera M, Baum N. Recent advances in the treatment of erectile dysfunction. Postgrad Med J. 2017;93:679-685. [PMID: 28751439] doi:10.1136/postgradmedj-2016-134073

Item 136 Answer: C

Educational Objective: Diagnose Morton neuroma.

This patient's symptoms are most likely due to a Morton neuroma, a condition that causes compression of the interdigital nerve. Common symptoms include paresthesias and the sensation of walking on a pebble. On examination, there are usually no obvious abnormalities, but some patients may have tenderness to direct palpation of the involved interspace. The cause is thought to be use of constricting footwear, such as high-heeled shoes. First-line therapy consists of wearing nonconstricting footwear and local padding. In patients who do not respond to these measures, a local glucocorticoid injection can be offered. For recalcitrant cases, sclerosing alcohol injections, radiofrequency ablation, and surgery (neurectomy) have been used with some success.

Bunion (hallux) deformity refers to lateral deviation of the great toe with medial bone deformity. This condition typically causes pain at the site of the deformity due to footwear pressure. The location of this patient's pain and lack of visible deformity on examination make bunion deformity an incorrect diagnosis.

Hammertoe deformity is also associated with constricting footwear; it refers to a proximal interphalangeal joint flexion deformity with dorsal interphalangeal joint extension and extended or neutral position of the metatarsophalangeal joint. This patient's normal foot appearance makes this diagnosis incorrect.

Plantar fasciitis typically causes pain localized to the medial inferior heel at the insertion of the plantar fascia in the medial calcaneal tubercle. Pain is usually present at activity initiation following prolonged rest and improves with further walking (for example, the first few steps in the morning after arising from bed). As the condition progresses, pain may be present with both activity and rest. The location and description of this patient's pain are not consistent with plantar fasciitis.

KEY POINT

- Hallmarks of a Morton neuroma are pain between the metatarsal heads, the sensation of walking on a pebble, and no obvious abnormalities of the foot upon clinical examination or palpation.

Bibliography

Ferkel E, Davis WH, Ellington JK. Entrapment neuropathies of the foot and ankle. Clin Sports Med. 2015;34:791-801. [PMID: 26409596] doi:10.1016/j.csm.2015.06.002

Item 137 Answer: D

H

Educational Objective: Identify an appropriate quality improvement model to reduce postoperative wound infection.

The most appropriate tool to assist in reducing postoperative wound sepsis at this institution is the Model for Improvement. The Model for Improvement focuses on achieving specific and measurable results in a specified population. This model relies on identifying a goal to be accomplished with a change, determining how the results of a change will be measured, and deciding on the changes that will bring about an improvement. These changes are tested and implemented using the Plan-Do-Study-Act (PDSA) cycle. PDSA cycles are rapid tests of improvement, and additional PDSA cycles are completed until the desired results are achieved. A medical center, for example, may set the specific goal of decreasing central line–associated bloodstream infections and use the PDSA cycle to rapidly implement and assess the impact of changes, such as using a central line bundle.

A clinical audit involves measuring current practices against desirable outcomes, which are usually guideline based. Feedback is often provided at the individual level. The audit can identify deviations from desired care (for example, surgical infection rate) but does not establish a goal, an intervention, or a metric to gauge the success of the intervention for the purposes of systematically improving care.

A control chart is a commonly used quality improvement tool. Control charts graphically display variation in a process over time and can help determine whether variation is related to a predictable or unpredictable cause. Control charts can additionally be used to determine whether an

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intervention has had a positive change. This tool could be useful in measuring change but does not involve goal setting or selecting and implementing an intervention, which are required elements in quality improvement models.

The Lean model focuses on closely examining a system's processes and eliminating non-value-added activities, or waste, within that system. By using a tool called value stream mapping that graphically displays the steps of a process (and the time required for each step) from beginning to end, inefficient areas (waste) in a process can be identified and addressed. The Lean model would not be particularly helpful in identifying causes of surgical site infection, selecting and implementing an intervention, and measuring the outcome.

KEY POINT

- The Model for Improvement relies on identifying a goal to be accomplished with a change, determining how the results of a change will be measured, and deciding on the changes that will bring about an improvement.

Bibliography

Lau CY. Quality improvement tools and processes. Neurosurg Clin N Am. 2015;26:177-87, viii. [PMID: 25771273] doi: 10.1016/j.nec.2014.11.016

Item 138 Answer: C

Educational Objective: Treat functional incontinence in a cognitively impaired patient.

The most appropriate management is prompted voiding every 2 to 3 hours. There are four main classifications of urinary incontinence: urgency incontinence, stress incontinence, mixed incontinence, and overflow incontinence. Functional incontinence, which occurs in patients who cannot reach and use the toilet in a timely manner, may occur in patients with significant cognitive or mobility impairments. Classifying the type(s) of incontinence helps guide management. This patient demonstrates functional incontinence, in which decreased cognitive function limits her ability to recognize early signs of the need to void, and impaired mobility limits her ability to get to the bathroom when she does recognize the need. Providing assistance and scheduled toileting through prompting are effective for patients who have impaired cognition or mobility.

Oxybutynin is appropriate therapy for urgency incontinence, but only after behavioral therapy has been implemented and found to be inadequate to control symptoms. Additionally, in this elderly woman, anticholinergic therapy would be associated with increased risk for confusion.

This patient does not report stress incontinence, which occurs with increased intra-abdominal pressure (coughing, laughing, sneezing). Stress incontinence is best treated with pelvic muscle floor training. In addition, the ability of a cognitively impaired patient to comprehend the instructions for pelvic floor muscle training and to remember to perform the maneuvers is likely to be limited.

Sling cystourethropexy is used to treat stress urinary incontinence when behavioral therapy (pelvic floor muscle training) has failed. Carefully balancing surgical risk against potential for benefit would have to be considered. This patient does not have stress urinary incontinence, and surgery is not indicated.

KEY POINT

- Functional incontinence, which occurs in patients who cannot reach and use the toilet in a timely manner, is treated with prompted voiding.

Bibliography

Griebling TL. Urinary incontinence in the elderly. Clin Geriatr Med. 2009;25:445-57. [PMID: 19765492] doi:10.1016/j.cger.2009.06.004

Item 139 Answer: C

Educational Objective: Treat posttraumatic stress disorder.

This patient with posttraumatic stress disorder (PTSD) would benefit most from psychotherapy provided by a specialist with experience in treating the disorder. PTSD is a disorder triggered by the experience of a traumatic event. The experience can be personal, through a loved one, or by repeated exposure to details or footage of such an event. Patients have intrusive memories of the event, such as nightmares and flashbacks, and avoid situations that remind them of the event. PTSD also causes functional impairment, hypervigilance, irritability, and sleep disturbance. In addition to psychotherapy, antidepressants are useful adjunctive therapies.

Clonazepam and other benzodiazepines are not effective in the treatment of PTSD and have significant potential for adverse effects given the high rates of concomitant substance use and suicidality in this condition.

Because of the high prevalence of hyperarousal symptoms associated with PTSD, β-blocker therapy with propranolol would seem to be a reasonable therapeutic option. However, evidence suggests that β-blocker therapy is ineffective in patients with PTSD.

Anticonvulsant medications with mood-stabilizing properties, such as topiramate, have been studied as potential therapies to improve symptoms of impulsive behavior, hyperarousal, and flashbacks in patients with PTSD. However, studies have been small and largely negative, and this class of drugs is not considered first-line therapy for PTSD.

KEY POINT

- Treatment of posttraumatic stress disorder requires psychotherapy from a specialist with experience in treating the disorder; antidepressants are useful adjunctive therapies.

Bibliography

Shalev A, Liberzon I, Marmar C. Post-traumatic stress disorder. N Engl J Med. 2017;376:2459-2469. [PMID: 28636846] doi:10.1056/NEJMra1612499

H

Item 140 Answer: A

Educational Objective: Diagnose acute angle-closure glaucoma.

In this patient with an acute onset of headache and visual changes with nausea and vomiting, the most likely diagnosis is acute angle-closure glaucoma (AACG). Risk factors for AACG include age older than 60 years, family history, and female sex. Several medications may precipitate an attack or worsen the condition, including anticholinergics; antihistamines; diuretics; and antidepressants, including selective serotonin reuptake inhibitors. Characteristic features include the description of halos around lights, as well as a mid-dilated, nonreactive pupil. An acute attack may be precipitated by dilation of the pupil, which may cause the iris to adhere to the lens, blocking the draining of aqueous humor; the blockage results in increased intraocular pressure. Other situations that can precipitate attacks include excitement, stress, or watching television in a dark room. AACG is an ophthalmologic emergency. Prompt intervention may prevent vision loss.

Bacterial endophthalmitis is inflammation of the aqueous and vitreous humors. It is typically associated with ocular surgery, especially cataract surgery. Patients usually have a subacute history of decreasing vision and eye pain, often mild in intensity. Visual acuity is decreased, and a hypopyon (layering of white blood cells in the anterior chamber) is typically present. Treatment includes intravitreal antibiotics.

Central retinal vein occlusion, which is often caused by a thrombus in the retinal vein, presents as painless onset of blurry vision or vision loss. It is not usually associated with redness or pupillary changes; however, if it is severe, patients may have a relative afferent pupillary defect.

Scleritis can present with severe eye pain that radiates to the periorbital region and watery discharge. Pain may occur with eye movement due to inflammation of the extraocular muscles. The sclera appears violaceous with notable edema. Severe local tenderness can be elicited by exerting pressure on the overlying closed eyelid. In approximately half of scleritis cases, an associated systemic rheumatic or inflammatory disorder is present. The local tenderness to touch and the violaceous and edematous sclera differentiate scleritis from AACG.

KEY POINT

- Characteristic features of acute angle-closure glaucoma include the sudden onset of headache, nausea, vomiting, and vision changes; the appearance of halos around lights; and the presence of a mid-dilated, nonreactive pupil.

Bibliography

Tarff A, Behrens A. Ocular emergencies: red eye. Med Clin North Am. 2017;101:615-639. [PMID: 28372717] doi:10.1016/j.mcna.2016.12.013

Item 141 Answer: B

Educational Objective: Manage a request for genetic testing by first taking a family history.

The most appropriate management of this patient is to obtain a three-generation family history. Obtaining a family history is an inexpensive and important risk assessment tool that allows clinicians to identify persons at increased risk for developing certain conditions. Up to 40% of genetic risk factors that would otherwise be missed can be detected with a family history. Features that suggest the presence of a genetically inherited condition include earlier age of onset than expected for a common disease; two or more relatives with the same disorder, especially if the disorder is uncommon or known to be caused by a single gene mutation; and the presence of a disease in the less often-afflicted gender, such as breast cancer in a man. Obtaining a comprehensive family history in this patient will help determine her risk for developing Huntington disease, a neurodegenerative condition most commonly inherited in an autosomal-dominant pattern. Huntington disease has a very high penetrance, meaning that nearly all persons with a mutation in the *huntingtin* protein gene will ultimately develop the disease.

Although persons affected with Huntington disease have various abnormalities on MRI, including cortical atrophy and ventriculomegaly, obtaining MRI in this patient would not be helpful given the absence of symptoms and neurologic deficits on physical examination.

Genetic testing should be reserved for patients at increased risk for developing a disease who have received appropriate genetic counseling. Genetic testing raises many ethical questions, as the results affect not only the patient but also other members of the family. Testing can also lead to possible discrimination. The Genetic Information Nondiscrimination Act of 2008 protects against genetic discrimination in regard to both health insurance and employment but does not protect against discrimination involving disability, life, or long-term care insurance.

Genetic counseling is indicated in all patients for whom genetic testing is being considered. The basic components of genetic counseling are education on the condition being tested, including the natural history, possible treatments, and preventive measures; the risks and benefits of genetic testing; alternatives to testing, including the option to forgo testing; and the implications for the patient and family members. A referral for genetic counseling would be indicated if this patient's family history is positive for family members with Huntington disease. Genetic counseling for this disease is unnecessary in the absence of an affected family member.

KEY POINT

- The three-generation family history is an inexpensive and important risk assessment tool that allows clinicians to identify persons at increased risk for developing certain conditions.

Bibliography

Pyeritz RE. The family history: the first genetic test, and still useful after all those years? Genet Med. 2012;14:3-9. [PMID: 22237427] doi:10.1038/gim.0b013e3182310bcf

Item 142 Answer: C

Educational Objective: Treat abnormal uterine bleeding with a levonorgestrel-containing intrauterine device.

The most appropriate management of abnormal uterine bleeding in this patient is a levonorgestrel-containing intrauterine device (IUD). Abnormal uterine bleeding can generally be categorized into ovulatory and anovulatory patterns. Ovulatory abnormal uterine bleeding (menorrhagia) occurs at normal regular intervals but is excessive in volume or duration. Women with ovulatory bleeding have estrogen-mediated endometrial proliferation, produce progesterone, slough the endometrium regularly following progesterone withdrawal, and have a minimal risk for uterine cancer. Anovulatory cycles are characterized by unpredictable bleeding of variable flow and duration caused by the absence of normal cyclic hormonal flux. Without cyclic progesterone, the estrogen-mediated endometrium proliferates excessively, resulting in endometrial instability, erratic bleeding, and an increased risk for uterine cancer. For this perimenopausal patient who is anemic secondary to excessive menstrual blood loss and has contraindications to combination oral contraceptive use (previous deep venous thrombosis and current smoking), using a progestin-containing IUD would likely result in amenorrhea and prevent future blood loss. Managing anovulatory cycles involves the use of progestin to maintain endometrial stability to reduce the risk for endometrial cancer, which a levonorgestrel-containing IUD would do.

An estrogen-progestin oral contraceptive protects against unplanned pregnancy and regulates the menstrual cycle to prevent bleeding between cycles. However, this patient has contraindications to combination hormone therapy, leaving a progestin-containing IUD as the most appropriate choice.

Endometrial ablation or hysterectomy may be considered for patients who do not respond to medical treatment or in whom anatomic causes are identified as the cause of the bleeding. These interventions are not indicated for this patient at this time.

Treatment of anovulatory bleeding is directed toward restoring hormonal balance and stabilizing the endometrium. A progestin such as medroxyprogesterone acetate may be used to promote withdrawal bleeding for women who wish to become pregnant. However, this patient has not expressed a desire to become pregnant, and such treatment is unlikely to prevent future abnormal bleeding in a patient with continued anovulatory cycles.

KEY POINT

- For women with anovulatory abnormal uterine bleeding and contraindications to combination oral contraceptive use, a progestin-containing intrauterine device will likely reduce blood loss and maintain the stability of the endometrium, thereby reducing the risk for uterine cancer.

Bibliography

Bacon JL. Abnormal uterine bleeding: current classification and clinical management. Obstet Gynecol Clin North Am. 2017;44:179-193. [PMID: 28499529] doi:10.1016/j.ogc.2017.02.012

Item 143 Answer: D

Educational Objective: Treat persistent postural-perceptual dizziness.

The most appropriate treatment in addition to vestibular and balance rehabilitation therapy (VBRT) is sertraline. Dizziness that remains nonspecific despite a thorough history, examination, and evaluation is referred to as persistent postural-perceptual dizziness (PPPD; formerly known as chronic subjective dizziness). PPPD is described as persistent, nonvertiginous dizziness or imbalance that worsens with personal motion, upright positioning, and movement of objects in the surrounding environment. Symptoms must be present on most days for at least 3 months. PPPD is most often preceded by another vestibular process (benign paroxysmal positional vertigo, vestibular neuronitis, vestibular migraine, stroke), trauma (concussion, traumatic brain injury), infection, or certain psychiatric conditions (anxiety, panic disorder, major depression). Approximately 75% of patients with PPPD have concomitant anxiety or depressive symptoms. The treatments of choice are VBRT and medical therapy, including selective serotonin reuptake inhibitors (SSRIs) or serotonin-norepinephrine reuptake inhibitors (SNRIs). VBRT focuses on balance training, core stabilization, and desensitization exercises; it is often performed by physical and occupational therapists. SSRIs and SNRIs take 8 to 12 weeks to produce a clinical response; if effective, treatment for at least 1 year is recommended. A positive response to these medications does not depend on the presence of psychiatric symptoms. In this patient with a history of concussion, a cause of dizziness has not been identified after thorough evaluation, and he should be treated with VBRT and an SSRI (such as sertraline) or SNRI.

Treatment response with other classes of antidepressants has been disappointing, and amitriptyline has not been found to be effective in the treatment of PPPD.

The canalith repositioning maneuver (Epley maneuver) is used to treat benign paroxysmal positional vertigo (BPPV). Patients with BPPV have brief episodes of vertigo (10-30 seconds) precipitated by abrupt head movement. This patient's symptoms are not compatible with BPPV, and the canalith repositioning maneuver is not indicated.

Lorazepam and other benzodiazepines have been used in the treatment of acute vertigo. This patient does not have vertigo, which is characterized by a spinning, swaying, or tilting sensation that is often accompanied by nausea and vomiting. In addition, long-term treatment with lorazepam can lead to dependence and may suppress vestibular feedback and central compensation mechanisms, resulting in worsening of PPPD symptoms.

KEY POINT

- The treatments of choice for persistent postural-perceptual dizziness are vestibular and balance rehabilitation therapy and medical therapy with selective serotonin reuptake inhibitors or serotonin-norepinephrine reuptake inhibitors.

Bibliography

Popkirov S, Staab JP, Stone J. Persistent postural perceptual dizziness (PPPD): a common, characteristic and treatable cause of chronic dizziness. Pract Neurol. 2018;18:5-13. [PMID: 29208729] doi: 10.1136/practneurol-2017-001809

H

Item 144 Answer: C

Educational Objective: Identify the appropriate level of postdischarge care.

The most appropriate discharge plan for this patient is rehabilitation at a long-term acute care hospital (LTACH). The patient requires continued mechanical ventilation but otherwise no longer requires hospitalization. LTACHs provide longer-term, higher-intensity medical treatment, such as complex wound care, mechanical ventilation weaning, and treatment with intravenous medications. Patients can also receive physical rehabilitation at such facilities.

Acute rehabilitation in a specialized rehabilitation facility is an appropriate choice for patients who require short-term rehabilitation (typically <4 weeks). To ensure reimbursement of services, such facilities require that a patient be able to participate in therapy at least 3 hours per day, 5 days per week. This patient clearly does not meet these criteria.

In-home rehabilitation services are useful for patients who may safely return home but still require physical or occupational therapy to continue optimizing return to their previous level of functioning. In-home rehabilitation services would not be a safe option for this patient who still requires mechanical ventilation and has significant physical deconditioning.

Subacute rehabilitation at a skilled nursing facility is a good option for patients who are not physically ready to return to their previous living situation but cannot tolerate at least 3 hours of therapy per day, 5 days per week. Skilled nursing facilities have physician directors but do not have the physician or staff resources to provide the complex medical care this patient requires.

KEY POINT

- Long-term acute care hospitals provide longer-term, higher-intensity medical treatment, such as complex wound care, mechanical ventilation weaning, and treatment with intravenous medications; such facilities also provide physical rehabilitation services.

Bibliography

Kane RL. Finding the right level of posthospital care: "We didn't realize there was any other option for him." JAMA. 2011;305:284-93. [PMID: 21245184] doi:10.1001/jama.2010.2015

Item 145 Answer: A

Educational Objective: Recognize the types of bias that affect screening tests.

Lead-time bias is most likely to threaten the validity of the authors' conclusions. Lead-time bias occurs when survival time (time from diagnosis to death) appears to be lengthened because the screened patient is diagnosed earlier during the preclinical phase but does not live longer in actuality. To guard against this bias, disease-specific mortality rates rather than survival time should be used as an outcome derived from randomized clinical trials.

Screening is also more likely to detect indolent disease, which has a long latent period, than aggressive disease, which has a short latent period and is most often detected with onset of symptoms. This causes length-time bias, in which a screen-detected cohort will have overrepresentation of indolent disease, whereas a symptom-detected cohort will have overrepresentation of aggressive disease. Consequently, the screen-detected cohort falsely appears to have a better prognosis. Length-time bias is unlikely in studies of ovarian cancer because ovarian cancer is an aggressive disease with a poor survival rate. The cancer has spread beyond the ovary at the time of detection in 75% of patients. This may be the result of rapid progression from unifocal disease to diffuse disease or to multiple foci of cancer within the abdomen, as carcinomatosis has been shown to develop after the removal of normal ovaries in high-risk patients.

Recall bias occurs when patients with a disease of interest are more likely to recall past exposures compared with controls. Recall bias primarily affects observational retrospective study designs. In this case, the screening protocol was a prospective observation study, and those being screened are not being asked to recall exposures; therefore, recall bias would not affect the study authors' conclusions.

Selection bias occurs when the study participants do not accurately reflect the population being studied, usually because the choice to participate is influenced by the clinical question. A national study of randomly selected women with a high participation rate would not be expected to be influenced by selection bias.

KEY POINT

- Lead-time bias occurs when early detection of a disease with a screening test leads to an increase in measured survival but not overall survival time.

Bibliography

Berry DA. Failure of researchers, reviewers, editors, and the media to understand flaws in cancer screening studies: application to an article in Cancer. Cancer. 2014;120:2784-91. [PMID: 24925345] doi: 10.1002/cncr.28795

Item 146 Answer: D

Educational Objective: Treat a patient with alcohol use disorder with naltrexone.

The most appropriate treatment is naltrexone. Recent developments in the pharmacologic treatment of alcohol

use disorder focus on modifying the reinforcing effects of alcohol use. Physicians underprescribe medications to treat alcohol use disorder and prevent relapse, despite their demonstrated efficacy. This patient, with hypertension and stage 3 chronic kidney disease, would likely benefit most from naltrexone. Available in both oral and long-acting injectable forms, naltrexone has been associated with a substantial decrease in 30-day readmission and emergency department visits when prescribed to patients with alcohol dependence at the time of hospital discharge. Multiple systematic reviews and meta-analyses of clinical trials have found naltrexone to reduce alcohol consumption compared with placebo. Naltrexone carries a risk for hepatotoxicity, for which the patient should be monitored; however, hepatotoxicity is rare with the dosages used for alcohol use disorder. Because naltrexone is an opioid receptor antagonist, opioids are contraindicated while the patient is taking naltrexone. Caution should also be used in patients with depression, due to an increased risk for suicidal ideation.

Acamprosate is FDA approved for the maintenance of abstinence in alcohol use disorder. This medication likely works through the *N*-methyl-D-aspartate receptor to modulate γ-aminobutyric acid and glutamate levels. In patients with moderate kidney disease, dosage should be adjusted; acamprosate is contraindicated in cases of severe kidney disease (estimated glomerular filtration rate <30 mL/min/1.73 m²). Recently, conflicting evidence regarding its effectiveness has been published, with some studies finding that acamprosate is no more effective than placebo. Although methodological differences may explain these discrepant results, many experts now recommend naltrexone as preferred therapy in patients without contraindications. Additionally, the thrice-daily dosage regimen can hinder adherence to acamprosate.

Although chlordiazepoxide can be used to treat alcohol withdrawal, it is not indicated for relapse prevention because of its addiction potential and ineffectiveness.

Disulfiram inhibits acetaldehyde dehydrogenase, causing buildup of aldehyde after alcohol consumption; the associated flushing, nausea, and vomiting act as a deterrent to further alcohol use. Unlike naltrexone and acamprosate, disulfiram does not directly diminish the motivation to drink, but it is an aversion therapy causing an unpleasant physiologic reaction when alcohol is consumed. Disulfiram is now considered second-line therapy.

KEY POINT

- Naltrexone, which is available in both oral and long-acting injectable forms, is associated with a substantial decrease in 30-day readmission and emergency department visits when prescribed to patients with alcohol dependence at the time of hospital discharge.

Bibliography

Akbar M, Egli M, Cho YE, Song BJ, Noronha A. Medications for alcohol use disorders: an overview. Pharmacol Ther. 2017. [PMID: 29191394] doi:10.1016/j.pharmthera.2017.11.007

Item 147 Answer: C

H

Educational Objective: **Effectively elicit goals, preferences, and values in a patient with terminal illnesses.**

The most appropriate initial strategy to develop goals of care is to ask the patient what he understands about his illnesses. This patient has multisystem organ dysfunction, recurrent hospitalizations, and a poor prognosis. He is at high risk for readmission and dying within the next 12 months, and assessing his understanding of his current illnesses is the first step in starting a conversation about the patient's goals, preferences, and values, after which the clinical care team can make recommendations on how best to meet those goals.

Discussions regarding hospice should occur only after the clinician has assessed the patient's understanding of the prognosis and after the patient's goals, hopes, and worries have been established.

Asking questions regarding resuscitation preferences is often important during a hospitalization, but a meaningful conversation regarding resuscitation preferences must be grounded in a patient's prognostic awareness, as well as their hopes and worries.

The patient's prognosis must be shared before a conversation regarding care preferences can occur. Before sharing the prognosis, however, evaluating the patient's understanding of his illnesses will allow for appropriate and efficient information sharing.

KEY POINT

- For seriously ill patients, understanding of their health and prognosis must be assessed before a conversation regarding care preferences and pathways can occur.

Bibliography

Bernacki RE, Block SD; American College of Physicians High Value Care Task Force. Communication about serious illness care goals: a review and synthesis of best practices. JAMA Intern Med. 2014;174:1994-2003. [PMID: 25330167] doi:10.1001/jamainternmed.2014.5271

Item 148 Answer: A

Educational Objective: **Evaluate liver function before initiating statin therapy.**

The most appropriate diagnostic testing to perform before initiating high-intensity statin therapy in this patient is alanine aminotransferase level measurement. This patient with clinical atherosclerotic cardiovascular disease (defined as acute coronary syndrome, or a history of myocardial infarction, stable or unstable angina, coronary or other arterial revascularization, stroke/transient ischemic attack, or peripheral artery disease attributable to atherosclerosis) meets the criteria for high-intensity statin therapy for secondary prevention of cardiovascular events. In patients in whom statin therapy is being considered, an initial fasting lipid panel (including total cholesterol, triglycerides, HDL

cholesterol, and calculated LDL cholesterol levels) is recommended. A lipid panel should also be obtained 4 to 12 weeks after initiation of therapy to determine treatment adherence and response. Because statin therapy may infrequently cause liver dysfunction, the 2013 American College of Cardiology/American Heart Association cholesterol treatment guideline recommends measuring the alanine aminotransferase level at baseline before initiating statin therapy. Further hepatic monitoring is unnecessary if the baseline alanine aminotransferase level is normal, unless the patient develops symptoms suggestive of liver dysfunction.

In patients who are at risk for adverse muscle events because of personal history of a muscle disease, current muscle symptoms, or concomitant drug therapy that might increase the risk for myopathy, it is reasonable to obtain a creatine kinase level before beginning statin therapy. Routine baseline measurement of creatine kinase, however, is not recommended.

During statin therapy, routine measurement of liver aminotransferases and creatine kinase is not recommended. However, if the patient develops symptoms of hepatotoxicity (such as jaundice, fatigue, weight loss, or abdominal pain), liver aminotransferases should be measured. Likewise, if a patient develops muscle symptoms (such as pain, weakness, generalized fatigue, or tenderness), creatine kinase level measurement is indicated.

KEY POINT

- In patients in whom statin therapy is being considered, an alanine aminotransferase level should be obtained at baseline to evaluate for liver dysfunction; further hepatic monitoring is unnecessary if the baseline level is normal.

Bibliography

Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, et al; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014;129:S1-45. [PMID: 24222016] doi:10.1161/01.cir.0000437738.63853.7a

Item 149 Answer: B

Educational Objective: Screen for diabetes mellitus in a patient with risk factors.

Screening for diabetes mellitus should occur at this visit. The U.S. Preventive Services Task Force (USPSTF) recommends routine screening for abnormal blood glucose and diabetes in asymptomatic adults aged 40 to 70 years who are overweight or obese. Clinicians should offer or refer patients with an abnormal blood glucose level to intensive behavioral counseling interventions to promote a healthful diet and physical activity. In contrast to the USPSTF, the American Diabetes Association (ADA) recommends that screening be performed in obese or overweight patients of any age with one or more additional risk factors for diabetes. Risk factors include a first-degree relative with diabetes; high-risk race or ethnicity (African American, Latino, Native American, Asian American, Pacific Islander); history of cardiovascular disease; hypertension; HDL cholesterol level less than 35 mg/dL (0.91 mmol/L) and/or triglyceride level greater than 250 mg/dL (2.82 mmol/L); polycystic ovary syndrome; physical inactivity; and other conditions associated with insulin resistance (such as acanthosis nigricans and severe obesity). In patients with normal results, the ADA recommends repeat screening at 3-year intervals. This 40-year-old obese patient meets the screening criteria of both the USPSTF and the ADA and should be screened for diabetes now.

In the absence of risk factors for diabetes, the ADA recommends that all patients be screened for diabetes at age 45 years. The USPSTF recommends screening only in asymptomatic adults aged 40 to 70 years who are overweight or obese. This patient, who has risk factors for diabetes (age 40 years, sedentary lifestyle, obesity), should be screened now, not at age 45 years or upon development of an additional diabetes risk factor.

KEY POINT

- Screening for diabetes mellitus is recommended for patients who are overweight or obese and have other risk factors for diabetes.

Bibliography

Selph S, Dana T, Blazina I, Bougatsos C, Patel H, Chou R. Screening for type 2 diabetes mellitus: a systematic review for the U.S. Preventive Services Task Force. Ann Intern Med. 2015;162:765-76. [PMID: 25867111] doi:10.7326/M14-2221

Item 150 Answer: D

Educational Objective: Diagnose schizophrenia.

This patient's clinical presentation is most consistent with schizophrenia. This heterogeneous disorder is characterized by a combination of positive symptoms (delusions, disorganized thought, hallucinations) and negative symptoms (decreased activity, flattened affect). Typical age of onset is early adulthood. Diagnosis also requires at least one area of functional impairment (occupation, social interactions, or self-care) and duration of at least 6 months (including 1 month of active symptoms).

Bipolar disorder is characterized by major depressive episodes and periods of mania or hypomania. During manic episodes, patients experience increased energy and risk-taking behaviors, as well as inflated self-worth. Patients with major depressive disorder have depressed mood and/or anhedonia, plus other symptoms of depression, including difficulty concentrating, fatigue, feelings of worthlessness, psychomotor agitation or retardation, sleep disturbance, thoughts of suicide, and weight or appetite changes. Although patients may have major depressive disorder or bipolar disorder with psychotic features, this patient does not meet the criteria for either depression (depressed mode and/or anhedonia) or mania (abnormally expansive, euphoric, or irritable mood).

In paranoid personality disorder, patients are distrustful of others, including loved ones, and misperceive social interactions as personal attacks. However, disorganized thoughts, hallucinations, and negative symptoms are not present in patients with paranoid personality disorder.

KEY POINT

- Schizophrenia is a heterogeneous disorder characterized by at least two of the following symptoms: delusions, hallucinations, disorganized speech, disorganized or catatonic behavior, and negative symptoms; the typical age of onset is early adulthood.

Bibliography

Owen MJ, Sawa A, Mortensen PB. Schizophrenia. Lancet. 2016;388:86-97. [PMID: 26777917] doi:10.1016/S0140-6736(15)01121-6

Item 151 Answer: D

Educational Objective: Diagnose bacterial vaginosis.

Bacterial vaginosis can be diagnosed in this patient with detection of at least 20% clue cells on saline microscopy. Bacterial vaginosis is the most common cause of vaginal discharge and results from an imbalance in the normal vaginal bacterial flora—loss of the normal hydrogen producing lactobacilli in the vagina and subsequent overgrowth of *Gardnerella vaginalis*, *Mycoplasma* species, and other anaerobes. Clinical diagnosis is made when three of the following features are present: vaginal pH greater than 4.5, thin and homogenous vaginal discharge, positive result on a whiff test (application of 10% potassium hydroxide to vaginal secretions resulting in a fishy odor), and clue cells comprising at least 20% of all squamous cells on saline microscopy. Clue cells are vaginal epithelial cells with ill-defined cell borders on microscopy as a result of adherent coccobacilli. The patient has vaginal pH greater than 4.5 and a homogenous thin discharge but a negative whiff test result. A saline wet mount that demonstrates at least 20% clue cells on microscopy will establish the diagnosis of bacterial vaginosis. Treatment is metronidazole or clindamycin.

Because bacterial vaginosis represents changes in the vaginal flora, vaginal culture has no role in diagnosis. Although cultures for *G. vaginalis* will be positive in almost all women with bacterial vaginosis, cultures lack specificity—the organism is found in over 50% of healthy asymptomatic women. Therefore, culture is not a reasonable test to confirm the diagnosis of bacterial vaginosis and would also be costly and inefficient compared with an office-based diagnosis.

The nucleic acid amplification test (NAAT) is a highly sensitive test for diagnosis of trichomoniasis and other sexually transmitted infections, such as chlamydia and gonorrhea. Although NAAT can detect *G. vaginalis*, it is time consuming, expensive, and unnecessary, and simple office-based diagnosis is preferred in straightforward cases such as this one. When office microscopy is not available, NAAT is a reasonable test to perform.

Vulvovaginal candidiasis is typically characterized by vaginal itching, irritation, and discharge and may be associated with dysuria and dyspareunia. Examination reveals vulvar edema and excoriation, with thick, white, curdy vaginal discharge. The diagnosis can be made when a saline or 10% potassium hydroxide wet mount of vaginal discharge shows yeast, hyphae, or pseudohyphae. This patient's clinical presentation is not consistent with vaginal candidiasis; a 10% potassium hydroxide wet mount is unnecessary and will not establish the most likely diagnosis.

KEY POINT

- Clinical diagnosis of bacterial vaginosis requires three of the following four features: vaginal pH greater than 4.5, thin and homogenous vaginal discharge, positive whiff test result, and clue cells comprising at least 20% of all squamous cells on saline microscopy; culture is not a reasonable test to confirm the diagnosis of bacterial vaginosis and would also be costly and inefficient compared with an office-based diagnosis.

Bibliography

Mills BB. Vaginitis: beyond the basics. Obstet Gynecol Clin North Am. 2017;44:159-177. [PMID: 28499528] doi:10.1016/j.ogc.2017.02.010

Item 152 Answer: C

Educational Objective: Treat benign prostatic hyperplasia and erectile dysfunction with tadalafil.

The most appropriate treatment for this patient with benign prostatic hyperplasia and erectile dysfunction is tadalafil. This patient has lower urinary tract symptoms (LUTS) due to benign prostatic hyperplasia (BPH), with both obstructive symptoms (decreased stream, incomplete emptying, hesitancy) and irritative symptoms (nocturia, frequency, urgency). Diagnosing BPH can be challenging because of the many causes of LUTS; furthermore, there is poor correlation between prostate size on examination and urinary symptoms. Nonetheless, a careful history and examination can usually render the diagnosis. Men older than 50 years are likely to have BPH as a cause of LUTS, whereas men younger than 40 years are likely to have other causes of LUTS. Furthermore, the patient has a history of untreated erectile dysfunction; in cases of BPH and erectile dysfunction, a trial of tadalafil, a phosphodiesterase-5 inhibitor, is recommended. In this setting, tadalafil has been shown to be clinically and symptomatically effective and is the only FDA-approved option to treat the symptoms of both conditions.

Finasteride and other 5α-reductase inhibitors are considered second-line medical therapy for BPH. The American Urological Association recommends the addition of 5α-reductase inhibitors in cases of BPH refractory to α-blocker monotherapy, not as a first-line monotherapy choice. Furthermore, this medication class has been known to lead to erectile and ejaculatory dysfunction.

Oxybutynin and other anticholinergic agents are effective in treating irritative LUTS of BPH. However, given their mechanism of action, anticholinergic agents can lead to worsening obstructive symptoms and could also lead to worsening erectile dysfunction.

Tamsulosin and other α-blocking agents are first-line medical therapy for symptomatic BPH. However, α-blockers have numerous side effects, including hypotension, orthostasis, and sexual dysfunction. Tamsulosin could worsen this patient's erectile dysfunction and thus would not be the most appropriate treatment choice.

KEY POINT

- For patients with concomitant benign prostatic hyperplasia and erectile dysfunction, a trial of tadalafil (a phosphodiesterase-5 inhibitor) has been shown to be effective and is the only FDA-approved option to treat both conditions.

Bibliography

Albisinni S, Biaou I, Marcelis Q, Aoun F, De Nunzio C, Roumeguère T. New medical treatments for lower urinary tract symptoms due to benign prostatic hyperplasia and future perspectives. BMC Urol. 2016;16:58. [PMID: 27629059] doi:10.1186/s12894-016-0176-0

H

Item 153 Answer: D

Educational Objective: Manage long-term medications in the perioperative setting.

This patient should continue all medications the morning of surgery. In general, many medications are well tolerated throughout the perioperative period. The 2014 American College of Cardiology/American Heart Association guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery includes recommendations for the management of statins, β-blockers, and antiplatelet agents.

Statins should be continued in patients who have been taking statins long term. In patients undergoing vascular surgery, initiation of statins is reasonable, and perioperative statin initiation can also be considered in patients who would otherwise qualify for statin therapy based on current guideline-directed medical therapy.

Likewise, β-blockers should be continued in patients who have been taking β-blockers long term, especially those with coronary artery disease. Preoperative initiation of β-blockers may be indicated for some patients undergoing nonurgent surgery, including those with intermediate- or high-risk myocardial ischemia on preoperative stress testing, those with three or more Revised Cardiac Risk Index risk factors (diabetes mellitus, heart failure, coronary artery disease, chronic kidney disease, cerebrovascular disease), or those who otherwise have a compelling indication for β blockade. However, β-blockers should never be started on the day of surgery, but rather with enough time preoperatively to assess safety and tolerability.

There are very few data available regarding the benefits versus risks of continuing calcium channel blockers such as amlodipine. There are no known interactions with anesthetic agents, and continuing calcium channel blockers is not associated with hemodynamic instability. Most experts, in the absence of data, recommend continuing this class of medication for patients already taking them.

In general, patients with coronary stents should be continued on aspirin throughout the perioperative period unless the bleeding risk is prohibitively high, as is the case with many neurosurgical procedures. It is important to discuss perioperative management of aspirin and $P2Y_{12}$ inhibitors with the surgical team to reach a consensus recommendation.

KEY POINT

- In patients undergoing noncardiac surgery, β-blockers and statins should be continued in those who have been taking the drugs long term, and aspirin generally should be continued in patients with coronary stents unless the bleeding risk is prohibitively high.

Bibliography

Fleisher LA, Fleischmann KE, Auerbach AD, Barnason SA, Beckman JA, Bozkurt B, et al; American College of Cardiology; 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines. J Am Coll Cardiol. 2014;64:e77-137. [PMID: 25091544]

Item 154 Answer: D

Educational Objective: Avoid adjunctive breast cancer screening in a low-risk patient with dense breast tissue.

This patient should not undergo adjunctive screening. Breast density is an increasingly recognized risk factor for breast cancer. It is categorized by the Breast Imaging Reporting and Data System (BI-RADS) as (a) almost entirely fatty, (b) scattered areas of fibroglandular tissue, (c) heterogeneously dense, or (d) extremely dense. Women with dense breasts should be informed that high breast density is common (present in up to 50% of women) and increases breast cancer risk but not breast cancer–related mortality. Dense breasts also decrease the sensitivity of mammography. However, women with high breast density without additional risk factors may experience more harms than benefits from supplemental breast imaging. Although supplemental screening with ultrasonography or MRI may increase the cancer detection rate, the impact on important clinical outcomes is unknown. Up to 90% of positive results on supplemental ultrasonography and 66% to 97% of positive results on supplemental MRI are false-positive findings, which may result in additional testing or invasive procedures. Despite this, nearly a quarter of state legislatures mandate that patients be notified of breast density findings, and some specifically recommend adjunctive screening with ultrasonography.

Women with dense breasts and other risk factors that impart a lifetime risk for breast cancer of 20% to 25% or higher, as calculated by models largely dependent on family history, should also undergo breast MRI in addition to screening mammography. The use of supplemental breast MRI in women who have less than a 20% lifetime risk for breast cancer is not currently supported by guidelines.

Digital breast tomosynthesis creates a three-dimensional image of the breast. Clinical studies suggest that tomosynthesis may have a sensitivity equal to or exceeding

the sensitivity of digital mammography in the detection of breast cancer in women with dense breasts and that tomosynthesis may decrease the recall rate from screening mammography. Despite these promising findings that may improve screening accuracy, there are no randomized trials or long-term follow-up data.

Most major breast cancer screening guidelines promote biennial screening from age 50 to 75 years. No guideline recommends biannual digital mammography for patients whose only risk factor is high breast density.

KEY POINT

- High breast density alone does not necessitate adjunctive breast imaging other than routine screening mammography.

Bibliography

Melnikow J, Fenton JJ, Whitlock EP, Miglioretti DL, Weyrich MS, Thompson JH, et al. Supplemental screening for breast cancer in women with dense breasts: a systematic review for the U.S. Preventive Services Task Force. Ann Intern Med. 2016;164:268-78. [PMID: 26757021] doi:10.7326/M15-1789

Item 155 Answer: B

Educational Objective: **Treat chronic noncancer pain with medical cannabis.**

A trial of oral medical cannabis oil would be a reasonable treatment in the management of this patient's chronic pain. Medical cannabis, although classified as a scheduled agent by the U.S. Drug Enforcement Administration on a federal level, has been approved by many states as a treatment for chronic pain. Current data on the effectiveness of medical cannabis for chronic pain are characterized by significant heterogeneity in both patient populations and cannabis preparations, although recent systematic reviews have demonstrated that cannabis has some efficacy in the treatment of chronic noncancer pain. Only two cannabinoid drugs (dronabinol and nabilone) are licensed for sale in the United States, and both drugs are available only in oral form. The pharmacokinetics of oral cannabis differ greatly from those of smoked cannabis, which has varying implications. Oral cannabis is slow in onset of action but produces more pronounced, and often unfavorable, psychoactive effects that last much longer than those experienced with smoking. On the other hand, smoked cannabis is quickly absorbed into the blood, and effects are immediate. However, examining the effects of smoked marijuana can be difficult because the absorption and efficacy of cannabis on symptom relief depend on subject familiarity with smoking and inhaling. This patient with end-stage kidney disease has a complex chronic pain syndrome that is unresponsive to multiple trials of nonpharmacologic and nonopioid analgesic therapies. If she resides in a state in which medical cannabis is available, oral medical cannabis oil would be a reasonable treatment option.

Oral immediate-release morphine sulfate should be avoided in this patient with end-stage kidney disease who is receiving dialysis because it could cause opioid-induced neurotoxicity with repeated use.

Oral methadone is a potent opioid agonist and *N*-methyl-D-aspartate receptor antagonist. Its complex pharmacokinetics and variable half-life restrict its general use, and it should not be prescribed by clinicians who lack experience in its management.

Topical lidocaine does not penetrate into the deep myofascial tissues and would not be an effective agent for this patient with pelvic pain.

KEY POINT

- Medical cannabis has demonstrated some efficacy in the treatment of chronic noncancer pain.

Bibliography

Whiting PF, Wolff RF, Deshpande S, Di Nisio M, Duffy S, Hernandez AV, et al. Cannabinoids for medical use: a systematic review and meta-analysis. JAMA. 2015;313:2456-73. [PMID: 26103030] doi: 10.1001/jama.2015.6358

Item 156 Answer: E

Educational Objective: **Treat a patient with a popliteal cyst.**

The most appropriate management is no treatment. This patient has a popliteal (Baker) cyst. Popliteal cysts are synovial fluid-containing extensions of the knee joint space and generally occur as a result of inflammatory arthritis, osteoarthritis, or trauma of the knee. Swelling is seen in the popliteal fossa on physical examination. The cyst is usually asymptomatic but may become painful as it enlarges or ruptures, which may cause significant pain and swelling of the calf, mimicking thrombophlebitis. The knee should be examined for signs of meniscal pathology, effusion, or mechanical signs that indicate an intra-articular irritant causing excessive joint fluid. Treatment is usually directed at the underlying cause of the cyst (such as repair of a torn meniscus). Given this patient's lack of symptoms, no treatment is required.

In this asymptomatic patient, fluid aspiration is not necessary; it should be performed solely for symptom relief, which is unnecessary in this patient. Although the procedure is considered extremely safe, it does carry a small risk for infection.

When arthritis-related popliteal cysts cause symptoms, joint aspiration of the fluid with a subsequent glucocorticoid injection can often relieve the symptoms. Given that this patient lacks symptoms, the procedure is not indicated.

Ibuprofen or another NSAID can be offered to patients with popliteal cysts to treat pain from the underlying cause of the cyst (such as trauma or osteoarthritis), but these analgesics are not considered first-line therapy for the cysts themselves. In patients with asymptomatic popliteal cysts, NSAIDs have no role.

Plain radiographs can be obtained in patients with trauma when there is concern for fracture or to confirm the diagnosis of osteoarthritis. There is no role for plain radiography in patients with an asymptomatic popliteal cyst.

KEY POINT

- Asymptomatic popliteal cysts do not require treatment; in symptomatic cases, treatment is usually directed at the underlying cause.

Bibliography

Herman AM, Marzo JM. Popliteal cysts: a current review. Orthopedics. 2014;37:e678-84. [PMID: 25102502] doi:10.3928/01477447-20140728-52

Item 157 Answer: D

Educational Objective: Exclude a diagnosis of a female sexual disorder in a postmenopausal woman.

This patient does not currently meet the diagnostic criteria for any sexual disorder. Female sexual dysfunction describes sexual difficulties that are persistent, personally distressing to the patient, and not explained by a nonsexual mental disorder. The patient reports that she is only occasionally distressed by these symptoms. Intervention may still be appropriate for patients reporting significant distress, such as sexual health education and/or referral to a sex therapist.

Female orgasmic disorder is the persistent or recurrent absence, delay, or diminished intensity of orgasm following a normal excitement phase with at least 75% of sexual encounters. The patient does not describe symptoms compatible with this disorder.

Genitopelvic pain/penetration disorder is diagnosed when there is persistent or recurrent difficulty in vaginal penetration during intercourse, marked vulvovaginal or pelvic pain during penetration, fear of pain or anxiety about pain in anticipation of or during penetration, or tightening or tensing of pelvic floor muscles during attempted penetration. For this diagnosis, symptoms must occur more than 75% of the time for at least 6 months and cause clinically significant distress. These symptoms are not present in this patient.

Female sexual interest/arousal disorder includes hypoactive sexual desire or arousal dysfunction that is present for a minimum of 6 months and causes significant distress. It is diagnosed if the patient reports at least three of the following symptoms: lack of sexual interest, lack of sexual thoughts or fantasies, decreased initiation of sexual activity or decreased responsiveness to the partner's initiation attempts, reduced excitement or pleasure during sexual activity, reduced response to sexual cues, or decreased genital or nongenital sensations during sexual activity. This patient reports only occasional distress that has been present for 3 months.

KEY POINT

- The diagnosis of a female sexual disorder requires both significant distress and the persistence of symptoms not explained by a nonsexual mental disorder.

Bibliography

Faubion SS, Rullo JE. Sexual dysfunction in women: a practical approach. Am Fam Physician. 2015;92:281-8. [PMID: 26280233]

Item 158 Answer: B

H

Educational Objective: Evaluate a patient with suspected central vertigo with MRI.

The most appropriate diagnostic test to perform next in this patient with risk factors for stroke is MRI of the brain. Patients with central vertigo secondary to vertebrobasilar stroke (posterior circulation ischemic or hemorrhagic events) frequently display concomitant neurologic findings in addition to vertigo. However, roughly 20% of patients with vertebrobasilar stroke present with isolated vertigo, and studies have shown that up to one third of cases of vertebrobasilar stroke that manifest as isolated vertigo are misclassified as peripheral vertigo, leading to considerable morbidity and mortality. In patients with findings concerning for centrally mediated vertigo (nystagmus, dysphagia, dysarthria, diplopia, ataxia, postural instability, hemiparesis, or mental status changes), or in patients with acute sustained vertigo and risk factors for vertebrobasilar stroke (advanced age, hypertension, hyperlipidemia, diabetes mellitus, peripheral vascular disease, atrial fibrillation), urgent evaluation with MRI is strongly recommended. MRI can detect infarction in the posterior fossa on the first day and is typically performed with magnetic resonance angiography (MRA). MRA is both sensitive and specific in the identification of stenosis or occlusion of the posterior cerebral circulation.

CT can provide an effective and expedited evaluation of hemorrhagic stroke, although hemorrhagic vertebrobasilar stroke accounts for a very small minority of cases of centrally mediated vertigo. MRI is far more sensitive for the early detection of ischemic stroke in these patients.

Vestibular laboratory testing using electronystagmography and videonystagmography can be helpful in distinguishing between peripheral and central vertigo. Electronystagmography and videonystagmography use electrodes and video cameras, respectively, to record eye movements. These techniques record and quantify both spontaneous and induced nystagmus. Vestibular laboratory testing should not take precedence over urgent brain imaging for a potentially life threatening condition, such as a cerebellar stroke.

Imaging studies are generally unnecessary in the diagnosis of peripheral vertigo. However, because this patient is at high risk for posterior circulation stroke (cardiovascular disease risk factors; acute, sustained vertigo; gait ataxia), further evaluation is urgently required.

KEY POINT

- In patients with findings concerning for centrally mediated vertigo or patients with acute sustained vertigo and risk factors for vertebrobasilar stroke, urgent evaluation with MRI and posterior circulation magnetic resonance angiography are strongly recommended.

Bibliography

Venhovens J, Meulstee J, Verhagen WI. Acute vestibular syndrome: a critical review and diagnostic algorithm concerning the clinical differentiation of peripheral versus central aetiologies in the emergency department. J Neurol. 2016;263:2151-2157. [PMID: 26984607]

Item 159 Answer: B

Educational Objective: Treat an obese patient with comprehensive behavioral therapy.

The initial recommendation to achieve weight loss is lifestyle modification, which includes reducing calorie intake by at least 500 kcal/day, physical activity exceeding 150 minutes weekly, and comprehensive behavioral therapy. High-intensity behavioral therapy programs (≥14 sessions of at least 6 months' duration) delivered by a trained interventionist and including regular self-monitoring of weight and calorie intake are associated with successful weight loss. Although face-to-face interventions most reliably result in weight loss, success has also been demonstrated with phone- or electronic-based interventions. Comprehensive programs lasting 1 year or longer and with at least monthly contact are associated with more successful maintenance of lifestyle change, and they are usually a reimbursable service.

Bariatric surgery for obesity is reserved for when a trial of comprehensive lifestyle intervention does not succeed. Additionally, surgical therapy is recommended only for patients with a BMI of 40 or greater, or with a BMI of 35 or greater and obesity-related comorbid conditions; this patient does not meet these criteria.

This patient is already exercising at the recommended level of at least 150 minutes of moderate to vigorous physical activity per week. Although increasing her physical activity may reduce the caloric restriction required to achieve weight loss, the impact of exercise is thought to be less important in initial weight loss than that of calorie restriction.

This patient admits that she has difficulty adhering to a diet plan; there is no reason to suspect that her adherence to a different plan (whether low-carbohydrate, Mediterranean, or another diet) would improve without the behavioral intervention components of regular calorie tracking and weight monitoring.

Combination low-dose phentermine (a sympathomimetic drug) and low-dose topiramate (an antiepileptic drug) has demonstrated efficacy in reducing weight, possibly by suppressing appetite, altering taste, and increasing metabolism. As with bariatric surgery, pharmacologic therapy is recommended only if a trial of lifestyle intervention is not successful. This patient has not yet truly engaged in a program of behavioral intervention.

KEY POINT

- Weight loss is best achieved with a high-intensity behavioral therapy program (≥14 sessions of ≥6 months' duration) delivered by a trained interventionist and including regular self-monitoring of weight and calorie intake.

Bibliography

Jensen MD, Ryan DH, Apovian CM, Ard JD, Comuzzie AG, Donato KA, et al; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society. Circulation. 2014;129:S102 38. [PMID: 24222017] doi:10.1161/01.cir.0000437739.71477.ee

Item 160 Answer: C

H

Educational Objective: Manage surrogate decision making in a patient without an advance directive.

The most appropriate basis for the decision regarding the patient's management is the patient's previously expressed wishes, otherwise known as substituted judgment. The strongest evidence of a patient's preferences derives from a living will, in which a patient can outline specific preferences for treatment decisions (for example, use of dialysis or mechanical ventilation). A patient could also formally designate a health care proxy through a durable power of attorney. Unfortunately, few patients have completed an advance directive, and when one is not available, it is important to be familiar with the local state laws regarding surrogate decision making. Many states have a health consent statute that designates the order in which family members are selected to provide surrogate decisions. The patient's spouse usually takes precedence over parents or adult children.

Decisions based on the patient's best interests should be reserved for situations in which there are no previously expressed oral or written statements of preferences or values from the patient. Family members and physicians may have divergent opinions of what is in the patient's best interests, which may not correlate with what the patient would want for himself.

Although this patient's medical condition is a crucial consideration, proper management of complex cases such as this one depend upon knowledge of the values and ethical principles at play. These decisions should be made in accord with local legal standards; risk management should not be the driving factor. Practicing according to ethical standards of care should reduce legal risk.

KEY POINT

- When decisions are made on behalf of a patient who lacks decision-making capacity, they should be based on previously expressed oral or written statements of preferences or values, also known as substituted judgment.

Bibliography

Snyder L; American College of Physicians Ethics, Professionalism, and Human Rights Committee. American College of Physicians ethics manual: sixth edition. Ann Intern Med. 2012;156:73-104. [PMID: 22213573] doi:10.7326/0003-4819-156-1-201201031-00001

Item 161 Answer: B

H

Educational Objective: Treat opioid-induced constipation in a patient with serious illness.

The most appropriate treatment of this patient's constipation is methylnaltrexone. This patient presents with significant constipation refractory to enema therapy, osmotic laxatives (lactulose), and stimulants (bisacodyl, senna). There are several causes of this patient's constipation, but special attention must be paid to his opioid use for dyspnea palliation. Methylnaltrexone is a peripherally acting μ-opioid receptor

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antagonist, which is rapid acting and effective in the treatment of opioid-induced constipation. By reversing μ-opioid receptor activation in the gut, methylnaltrexone can cause laxation in less than 60 minutes and does not reverse analgesic or antidyspneic effects of systemically administered opioids. It is contraindicated in patients with bowel obstruction.

When constipation symptoms do not respond to osmotic and stimulant laxative therapy, the chloride channel activator lubiprostone can be considered. Two randomized clinical trials in patients with opioid-induced constipation have demonstrated that patients receiving lubiprostone had significant improvement in spontaneous bowel movements, abdominal discomfort, and constipation severity. Lubiprostone is FDA approved for the treatment of opioid-induced constipation; however, it can cause shortness of breath and is likely a poor choice for a patient taking opioids to palliate dyspnea.

Polyethylene glycol is an osmotic laxative that increases the water content of stools to improve bowel motility. This patient is already taking an osmotic laxative (lactulose), and the addition of polyethylene glycol is unlikely to have any effect in the setting of opioid-induced bowel dysmotility refractory to stimulants and enema therapy.

Sodium phosphate enemas are contraindicated in older adult patients and in patients with kidney failure or heart failure because of the risks for dangerous electrolyte shifts and renal toxicity.

KEY POINT

- If maximal medical therapy has failed to achieve laxation in patients taking opioids, peripheral opioid antagonists, such as methylnaltrexone, can be considered; methylnaltrexone does not reverse the analgesic or antidyspneic effects of systemically administered opioids.

Bibliography

Streicher JM, Bilsky EJ. Peripherally acting μ-opioid receptor antagonists for the treatment of opioid-related side effects: mechanism of action and clinical implications. J Pharm Pract. 2017:897190017732263. [PMID: 28946783] doi:10.1177/0897190017732263

Item 162 Answer: B

Educational Objective: Diagnose autism spectrum disorder.

This patient demonstrates behaviors most consistent with autism spectrum disorder. This is a heterogeneous group of disorders that share two diagnostic features: (1) repetitive, nonpurposeful behaviors and (2) deficiencies in communication and social interaction. Although the disorder may not be diagnosed until adulthood, the abnormal behaviors begin in childhood. The exact prevalence is debated, but it is estimated to affect 0.5% to 1% of the U.S. population. Early intervention with behavioral and educational interventions improves long-term functioning, but most patients require lifelong assistance.

Antisocial personality disorder is characterized by lack of empathy for others and engaging in socially unacceptable activities (such as stealing or cheating) without remorse. Patients with this personality disorder do not engage in repetitive behaviors and do not have communication difficulties.

Obsessive-compulsive disorder is characterized by obsessions (persistent and intrusive thoughts, images, or impulses that are associated with distress) and compulsions (repetitive behaviors [such as counting, hand washing, and inspecting] that are performed to decrease anxiety caused by the obsession) that result in marked distress, wasted time, or impaired social function. Although patients with obsessive-compulsive disorder may engage in repetitive behaviors such as those exhibited by this patient, they do not have difficulties with communication or social interaction.

Social anxiety disorder is characterized by severe, persistent anxiety or fear of social or performance situations (public speaking, meeting unfamiliar people) lasting 6 months or longer. In these situations, affected patients experience anxiety and physical symptoms, such as palpitations, dyspnea, and flushing. Patients recognize their anxiety is excessive but nonetheless avoid trigger situations (or endure them with extreme anxiety), resulting in impairments at home, work, and other settings. This patient's repetitive behaviors and difficulty with social interactions are not consistent with social anxiety disorder.

KEY POINT

- Autism spectrum disorder is a heterogeneous group of disorders that share two diagnostic features: (1) repetitive, nonpurposeful behaviors and (2) deficiencies in communication and social interaction.

Bibliography

Nicolaidis C, Kripke CC, Raymaker D. Primary care for adults on the autism spectrum. Med Clin North Am. 2014;98:1169-91. [PMID: 2513[illegible]] doi:10.1016/j.mcna.2014.06.011

Item 163 Answer: D

Educational Objective: Treat hyperlipidemia in a patient at low risk for atherosclerotic cardiovascular disease.

This patient with hyperlipidemia and low risk for atherosclerotic cardiovascular disease (ASCVD) should be counseled regarding therapeutic lifestyle changes and followed to monitor progress. Key components of therapeutic lifestyle changes include dietary modification, regular physical activity, weight loss, smoking cessation (if applicable), and addressing risk factors associated with the metabolic syndrome. Patients should be encouraged to adhere to a dietary pattern that focuses on consumption of fruits, vegetables, fiber, and monounsaturated fats and minimizes intake of saturated and *trans* fats, simple carbohydrates, and red meats. Replacing saturated fats with polyunsaturated fats has been shown to reduce LDL cholesterol levels and cardiovascular

mortality. Recommended diets include the American Heart Association (AHA) diet and the DASH (Dietary Approaches to Stop Hypertension) diet. The AHA/American College of Cardiology (ACC) lifestyle management guideline additionally recommends that patients engage in 40 minutes of moderate to vigorous activity 3 to 4 days per week to lower LDL and non-HDL cholesterol levels.

According to the ACC/AHA cholesterol treatment guideline, the two groups for which a strong body of evidence supports statin initiation for the primary prevention of ASCVD are patients with an LDL cholesterol level of 190 mg/dL (4.92 mmol/L) or higher and patients aged 40 to 75 years with a 10-year ASCVD risk of 7.5% or higher. In this patient with an ASCVD risk of 3.4% and LDL cholesterol level less than 190 mg/dL (4.92 mmol/L), statin therapy would not be appropriate.

The U.S. Preventive Services Task Force recommends low- to moderate-intensity statin therapy in asymptomatic adults aged 40 to 75 years without ASCVD who have at least one ASCVD risk factor (dyslipidemia, diabetes mellitus, hypertension, or smoking) and a calculated 10-year ASCVD event risk of 10% or higher. Although this patient has hyperlipidemia, his 10-year ASCVD event risk is 3.4%, and neither low- nor moderate-intensity statin therapy is indicated.

KEY POINT

- Therapeutic lifestyle changes, including dietary modification, regular physical activity, weight loss, and smoking cessation, are the initial treatment for hyperlipidemia.

Bibliography

Eckel RH, Jakicic JM, Ard JD, de Jesus JM, Houston Miller N, Hubbard VS, et al; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2013 AHA/ACC guideline on lifestyle management to reduce cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014;129:S76-99. [PMID: 24222015] doi:10.1161/01.cir.0000437740.48606.d1

Item 164 Answer: A

Educational Objective: Treat a patient with greater trochanteric pain syndrome (trochanteric bursitis).

This patient's clinical presentation is consistent with greater trochanteric pain syndrome (GTPS; formerly trochanteric bursitis), and first-line therapy is pain relief with acetaminophen or an oral NSAID, such as ibuprofen. Patients with GTPS typically have pain localized to the greater trochanter that may radiate down the lateral leg to the knee. The pain is often exacerbated by lying on the affected side and climbing stairs. Pain onset is usually insidious. GTPS can be differentiated from hip joint pain in that GTPS does not usually radiate to the groin or limit hip range of motion. Diagnosis is made by history and by eliciting pain with palpation over the greater trochanter or reproduction of the pain when the patient takes a step up. Use of pain-relieving agents should accompany activity modification, such as avoiding or minimizing painful activities. Physical therapy to strengthen the muscles of the hip may help with reducing friction and therefore pain.

Glucocorticoid injections (frequently combined with a local anesthetic) are reserved for patients with GTPS with persistent symptoms and for those who do not respond to acetaminophen or an oral NSAID. Because this patient has not yet received any therapy, it would be most appropriate to start with an oral agent such as ibuprofen instead of progressing directly to glucocorticoid injection.

Most patients respond to acetaminophen, NSAIDs, or glucocorticoid injections. Opioid pain medications are typically unnecessary, have a significant risk profile, and do not have a role in the management of GTPS. Therefore, hydrocodone/acetaminophen would not be an appropriate management option.

GTPS is diagnosed clinically based on a consistent clinical presentation. Plain radiographs are typically normal in patients suspected of having GTPS. The role of imaging studies is to evaluate for alternative diagnoses when the diagnosis of GTPS is unclear. In this patient, plain radiography is unnecessary.

KEY POINT

- Patients with greater trochanteric pain syndrome (trochanteric bursitis) typically have pain localized to the greater trochanter, which may radiate down the lateral leg to the knee, and pain to palpation over the greater trochanter; treatment includes avoiding painful activities, acetaminophen or NSAIDs, and muscle strengthening.

Bibliography

Redmond JM, Chen AW, Domb BG. Greater trochanteric pain syndrome. J Am Acad Orthop Surg. 2016;24:231-40. [PMID: 26990713] doi:10.5435/JAAOS-D-14-00406

Item 165 Answer: B

Educational Objective: Diagnose genitourinary syndrome of menopause.

The most likely diagnosis is genitourinary syndrome of menopause (vaginal atrophy). The clinical history and physical examination are most helpful for diagnosing genitourinary syndrome of menopause. Approximately 10% to 40% of menopausal women experience symptoms related to vaginal atrophy, including vulvar itching, vaginal dryness, and dyspareunia. On physical examination, pale and shiny vaginal walls, decreased rugae, and petechiae are characteristic findings. In contrast to menopausal vasomotor symptoms, which may last for a few years and resolve spontaneously, genitourinary syndrome of menopause is frequently progressive and often requires treatment. Mild to moderate symptoms can be treated with vaginal moisturizers and lubricants, but more severe symptoms, as experienced by this patient, are best treated with vaginal estrogen.

Like genitourinary syndrome of menopause, acute allergic contact dermatitis presents with intense pruritus, often

worse at night, as well as burning and stinging. Defining characteristics on physical examination include a discrete, well demarcated area of erythema and edema. Fissures may be present along the labial folds. Excoriations are common and may become secondarily infected. The course of acute contact dermatitis progresses over days, not months as experienced by this patient. The most commonly implicated culprits are fragrances, medications, and preservatives in medications, such as glucocorticoids. Diagnosis is typically made on clinical grounds; biopsy is rarely necessary. Treatment generally consists of allergen avoidance and soaking in warm water (bathtub or sitz bath), followed by application of an emollient, such as petrolatum or a low-potency glucocorticoid.

Lichen planus is an inflammatory condition that can affect the skin, nails, or mucosa. Clinical presentation includes white lines and patches (Wickham striae) or painful erythema and erosions (erosive variant). Therapies are glucocorticoids (systemic and topical) and immunosuppressive agents in severe disease.

Lichen sclerosus is an inflammatory condition that often presents as white, atrophic patches on the genital and perianal skin. It differs from lichen planus in its clinical presentation of white patches that circumferentially involve the vaginal introitus and perianal area ("figure 8" appearance). Prepubertal girls and postmenopausal women are at highest risk. Biopsy establishes the diagnosis and can differentiate it from other inflammatory disorders. Treatment is with potent topical glucocorticoids.

KEY POINT

- Genitourinary syndrome of menopause is a clinical diagnosis characterized by vulvar itching, vaginal dryness, and dyspareunia; pelvic examination findings include pale, shiny vaginal walls; decreased rugae; and petechiae.

Bibliography

Faubion SS, Sood R, Kapoor E. Genitourinary syndrome of menopause: management strategies for the clinician. Mayo Clin Proc. 2017;92:1842-1849. [PMID: 29202940] doi:10.1016/j.mayocp.2017.08.019

Item 166 Answer: C

Educational Objective: Screen a patient for opioid-related risk.

The recommended next step in management before prescribing opioid therapy is to perform an opioid risk assessment. Opioid therapy may be reasonably prescribed to this patient with pain that has not responded to nonpharmacologic and nonopioid therapies as part of a multimodal treatment plan, which may also include cognitive behavioral therapy and/or physical therapy. The Centers for Disease Control and Prevention Guideline for Prescribing Opioids for Chronic Pain recommends that before starting and periodically during continuation of opioid therapy, clinicians should evaluate risk factors for opioid-related harms. Clinicians should incorporate into the management plan strategies to mitigate risk, including considering offering naloxone when factors that increase risk for opioid overdose (such as history of overdose, history of substance use disorder, higher opioid dosages [≥50 morphine milligram equivalents per day], or concurrent benzodiazepine use) are present. Other recommended risk-mitigation strategies include reviewing the patient's history of controlled substance use with state prescription monitoring program data and urine drug testing before initiation of therapy and at least annually thereafter.

The Current Opioid Misuse Measure is a brief self-report survey of current aberrant drug-related behavior. It is intended for use in patients currently receiving long-term opioid therapy who may be misusing opioid medications. Its value in improving outcomes related to misuse or overuse of opioids is unknown, and it would not be the next management step in this patient who has yet to be prescribed opioid therapy.

Coprescription of naloxone is recommended in patients at high risk for opioid overdose, such as those receiving daily doses of 50 mg of oral morphine equivalents or more. In this patient, opioid risk assessment would further delineate the patient's risk and may prompt consideration of naloxone, but until the risk assessment is completed, prescribing naloxone is premature.

In patients with no apparent mental health diagnoses, psychiatry referral is not routinely needed before prescribing long-term opioid therapy. Psychiatry referral may be appropriate for patients with a comorbid psychiatric diagnosis and, in those circumstances, could be part of a multimodal treatment plan. However, it is not the next recommended step in the management of this patient's opioid therapy.

KEY POINT

- In patients with chronic pain, risk assessment should be performed before initiating or continuing opioid therapy.

Bibliography

Dowell D, Haegerich TM, Chou R. CDC guideline for prescribing opioids for chronic pain - United States, 2016. JAMA. 2016;315:1624-45. [PMID: 26977696] doi:10.1001/jama.2016.1464

Item 167 Answer: B

H

Educational Objective: Manage perioperative anticoagulation in a patient receiving non–vitamin K antagonist oral anticoagulant therapy.

Apixaban should be discontinued 3 days before surgery because there is a moderate to high bleeding risk with partial colectomy. Perioperative management of non–vitamin K antagonist oral anticoagulant (NOAC) therapy, such as with the factor Xa inhibitors (apixaban, edoxaban, rivaroxaban), is based on the patient's creatinine clearance and bleeding risk. When it is necessary to discontinue anticoagulation for surgery, NOACs can generally be stopped 2 to 3 days preoperatively because of their short half-lives. The shorter period is considered for patients undergoing procedures with low bleeding risk, and the longer period is considered for patients

H CONT.

undergoing procedures with moderate or high bleeding risk. This applies to patients with normal kidney function or mild to moderate kidney disease (creatinine clearance ≥30 mL/min). For patients with creatinine clearance less than 30 mL/min, there are no data to guide recommendations; clinicians are advised to obtain an anti-Xa level or discontinue anticoagulation at least 72 hours before surgery. In patients taking the direct thrombin inhibitor dabigatran with creatinine clearance greater than 80 mL/min, dabigatran can be discontinued 2 to 3 days before surgery, with the longer period considered for moderate to high bleeding risk; for creatinine clearance less than 80 mL/min, dabigatran should be withheld at least 3 days preoperatively. The lower the creatinine clearance, the longer it must be withheld preoperatively.

For procedures with low bleeding risk, withholding apixaban 2 days preoperatively is usually sufficient; however, withholding apixaban only 1 day before surgery is insufficient for all procedures. Discontinuing apixaban 5 or 7 days before surgery would expose this patient to a small but increased thrombotic risk during that time frame.

In patients taking NOACs, bridging anticoagulation is unnecessary because of the rapid onset and short half-life associated with these drugs. Postoperative timing of NOAC reinstitution depends on the bleeding risk associated with the surgery, as NOACs reach therapeutic levels in 1 to 3 hours, at which point the patient is presumed to be fully anticoagulated. NOACs may be resumed once adequate hemostasis is ensured, usually 24 to 72 hours after surgery. Close collaboration with the surgeon is advised.

KEY POINT

- When it is necessary to discontinue anticoagulant therapy for surgery, non–vitamin K antagonist oral anticoagulants can be stopped 2 to 3 days preoperatively because of their short half-lives.

Bibliography

Doherty JU, Gluckman TJ, Hucker WJ, Januzzi JL Jr, Ortel TL, Saxonhouse SJ, et al. 2017 ACC expert consensus decision pathway for periprocedural management of anticoagulation in patients with nonvalvular atrial fibrillation: a report of the American College of Cardiology Clinical Expert Consensus Document Task Force. J Am Coll Cardiol. 2017;69:871-898. [PMID: 28081965] doi:10.1016/j.jacc.2016.11.024

Item 168 Answer: B

Educational Objective: Treat major depressive disorder with cognitive behavioral therapy.

Cognitive behavioral therapy (CBT) is the most appropriate initial therapy for this patient with major depressive disorder. Most patients with mild or moderate depression (PHQ-9 score <15) are treated in the primary care setting. Referral to a psychiatrist is indicated for patients with severe depression, failure of initial therapy, complex psychiatric comorbidities, and high suicide risk. In a 2016 clinical practice guideline, the American College of Physicians recommends that clinicians treat patients with major depressive disorder with CBT or second-generation antidepressants (selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, serotonin modulators, or atypical antidepressants) after discussing adverse effect profiles, accessibility, cost, and preferences with the patient. On the basis of moderate-quality evidence, CBT and second-generation antidepressants were equally effective treatments for major depressive disorder, with similar rates of discontinuation. For this patient who is opposed to the use of psychotropic medications, CBT is the best initial treatment.

Amitriptyline and other tricyclic antidepressants can be used to treat major depressive disorder, but these agents are second-line therapy because of the higher rate of associated side effects.

Paroxetine is a second-generation antidepressant that is a reasonable choice for initial management of major depressive disorder. However, there is a particularly high incidence of side effects with paroxetine use. This patient is wary of psychotropic medications, and if one were to be tried, a different second-generation antidepressant with a lower incidence of side effects would be preferred to improve patient adherence.

Quetiapine is FDA approved for use in combination with an antidepressant for the treatment of depression that does not respond to initial therapy. First-line treatment has not yet been attempted in this patient, and quetiapine is not appropriate as monotherapy for major depressive disorder.

KEY POINT

- Cognitive behavioral therapy and second-generation antidepressants have proved equally effective for treatment of major depressive disorder, with similar rates of discontinuation; treatment selection should be made after discussion of adverse effect profiles, accessibility, cost, and preferences with the patient.

Bibliography

Qaseem A, Barry MJ, Kansagara D; Clinical Guidelines Committee of the American College of Physicians. Nonpharmacologic versus pharmacologic treatment of adult patients with major depressive disorder: a clinical practice guideline from the American College of Physicians. Ann Intern Med. 2016;164:350-9. [PMID: 26857948] doi:10.7326/M15-2570

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◯ Dermatology	16
◯ Gastroenterology and Hepatology	22
◯ Hematology and Oncology	33
◯ Neurology	22
◯ Rheumatology	22
◯ Endocrinology and Metabolism	19
◯ General Internal Medicine	36
◯ Infectious Disease	25
◯ Nephrology	25
◯ Pulmonary and Critical Care Medicine	25

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CREDITS OR POINTS CLAIMED ON SECTION
1 hour = 1 credit or 1 point

Enter the number of credits earned on the test to the nearest quarter hour. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

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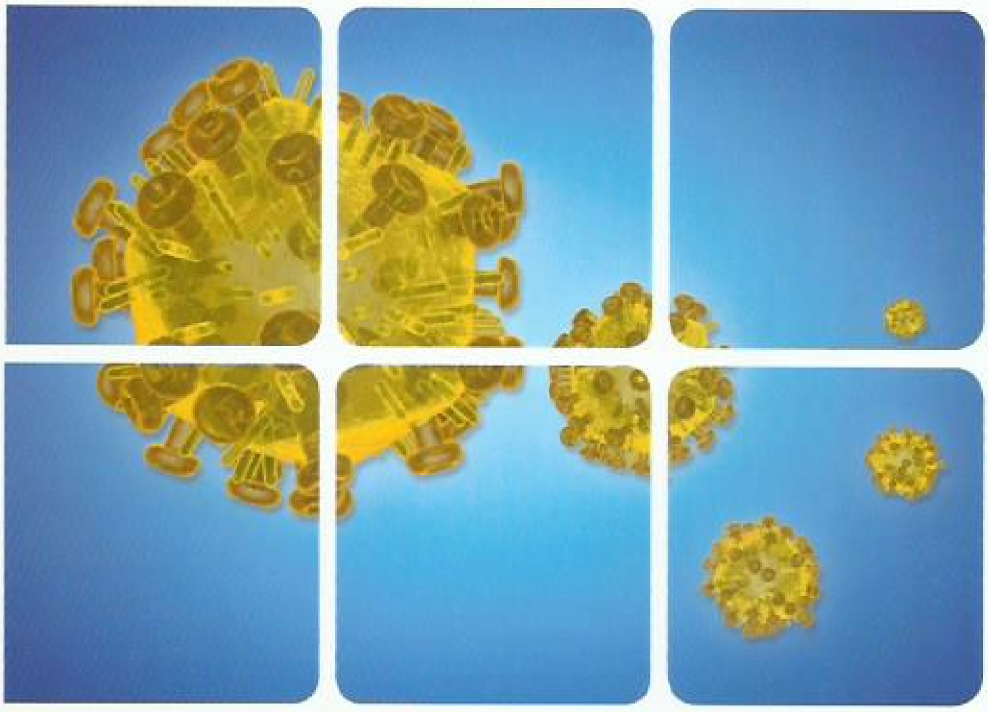

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Infectious Disease

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Welcome to the Infectious Disease Section of MKSAP 18!

In these pages, you will find updated information on central nervous system infections, skin and soft tissue infections, community-acquired pneumonia, tick-borne diseases, urinary tract infections, *Mycobacterium tuberculosis* and nontuberculous mycobacterial infections, sexually transmitted infections, bioterrorism, travel medicine, infectious gastrointestinal syndromes, transplant-associated infections, HIV and AIDS, health care–associated infections, and other clinical challenges. All of these topics are uniquely focused on the needs of generalists and subspecialists *outside* of infectious disease.

The core content of MKSAP 18 has been developed as in previous editions—all essential information that is newly researched and written in 11 topic areas of internal medicine—created by dozens of leading generalists and subspecialists and guided by certification and recertification requirements, emerging knowledge in the field, and user feedback. MKSAP 18 also contains 1200 all-new peer-reviewed, psychometrically validated, multiple-choice questions (MCQs) for self-assessment and study, including 108 in Infectious Disease. MKSAP 18 continues to include *High Value Care* (HVC) recommendations, based on the concept of balancing clinical benefit with costs and harms, with associated MCQs illustrating these principles and HVC Key Points called out in the text. Internists practicing in the hospital setting can easily find comprehensive *Hospitalist*-focused content and MCQs, specially designated in blue and with the H symbol.

If you purchased MKSAP 18 Complete, you also have access to MKSAP 18 Digital, with additional tools allowing you to customize your learning experience. MKSAP Digital includes regular text updates with new, practice-changing information, 200 new self-assessment questions, and enhanced custom-quiz options. MKSAP Complete also includes more than 1200 electronic, adaptive learning–enhanced flashcards for quick review of important concepts, as well as an updated and enhanced version of Virtual Dx, MKSAP's image-based self-assessment tool. As before, MKSAP 18 Digital is optimized for use on your mobile devices, with iOS- and Android-based apps allowing you to sync between your apps and online account and submit for CME credits and MOC points online.

Please visit us at the MKSAP Resource Site (mksap.acponline.org) to find out how we can help you study, earn CME credit and MOC points, and stay up to date.

On behalf of the many internists who have offered their time and expertise to create the content for MKSAP 18 and the editorial staff who work to bring this material to you in the best possible way, we are honored that you have chosen to use MKSAP 18 and appreciate any feedback about the program you may have. Please feel free to send any comments to mksap_editors@acponline.org.

Sincerely,

Patrick C. Alguire, MD, FACP
Editor-in-Chief
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The learning objectives of MKSAP 18 are to:

- Close gaps between actual care in your practice and preferred standards of care, based on best evidence
- Diagnose disease states that are less common and sometimes overlooked and confusing
- Improve management of comorbid conditions that can complicate patient care
- Determine when to refer patients for surgery or care by subspecialists
- Pass the ABIM Certification Examination
- Pass the ABIM Maintenance of Certification Examination

Target Audience

- General internists and primary care physicians
- Subspecialists who need to remain up to date in internal medicine
- Residents preparing for the certifying examination in internal medicine
- Physicians preparing for maintenance of certification in internal medicine (recertification)

ABIM Maintenance of Certification

Check the MKSAP Resource Site (mksap.acponline.org) for the latest information on how MKSAP tests can be used to apply to the American Board of Internal Medicine (ABIM) for Maintenance of Certification (MOC) points following completion of the CME activity.

Successful completion of the CME activity, which includes participation in the evaluation component, enables the participant to earn up to 275 medical knowledge MOC points in the ABIM's MOC program. It is the CME activity provider's responsibility to submit participant completion information to ACCME for the purpose of granting MOC credit.

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Errata

Errata for MKSAP 18 will be available through the MKSAP Resource Site at mksap.acponline.org as new information becomes known to the editors.

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Infectious Disease High Value Care Recommendations

The American College of Physicians, in collaboration with multiple other organizations, is engaged in a worldwide initiative to promote the practice of High Value Care (HVC). The goals of the HVC initiative are to improve health care outcomes by providing care of proven benefit and reducing costs by avoiding unnecessary and even harmful interventions. The initiative comprises several programs that integrate the important concept of health care value (balancing clinical benefit with costs and harms) for a given intervention into a broad range of educational materials to address the needs of trainees, practicing physicians, and patients.

HVC content has been integrated into MKSAP 18 in several important ways. MKSAP 18 includes HVC-identified key points in the text, HVC-focused multiple choice questions, and, for subscribers to MKSAP Digital, an HVC custom quiz. From the text and questions, we have generated the following list of HVC recommendations that meet the definition below of high value care and bring us closer to our goal of improving patient outcomes while conserving finite resources.

High Value Care Recommendation: A recommendation to choose diagnostic and management strategies for patients in specific clinical situations that balance clinical benefit with cost and harms with the goal of improving patient outcomes.

Below are the High Value Care Recommendations for the Infectious Disease section of MKSAP 18.

- Blood cultures are not routinely indicated in patients with erysipelas and cellulitis.
- Primary treatment for abscesses, furuncles, and carbuncles is incision and drainage; mild infections do not require antibiotic therapy.
- Uninfected diabetic foot wounds should not be cultured or treated with antibiotics.
- Diagnostic studies to identify a causative organism are not routinely indicated in outpatients with community-acquired pneumonia.
- Patients with erythema migrans and a compatible exposure history do not require confirmatory laboratory testing for Lyme disease and should receive oral antibiotic therapy.
- No treatment is indicated for asymptomatic bacteriuria in otherwise healthy, nonpregnant patients (see Item 100).
- Urine culture is not recommended in women with uncomplicated cystitis.
- Indications for screening for and possibly treating asymptomatic bacteriuria include pregnancy and before an invasive urologic procedure (see Item 12).
- Follow-up urine cultures for acute pyelonephritis are only indicated in pregnant women.
- Acute, uncomplicated pyelonephritis can usually be managed with oral outpatient antimicrobial therapy (see Item 14).
- *Candida* isolated from the respiratory tract and urinary tract usually represents colonization; treatment is not indicated unless clinical infection is suspected.
- Test of cure is not recommended for *Chlamydia trachomatis* infection except in pregnancy.
- Test of cure in patients with *Neisseria gonorrhoeae* infection is recommended only when pharyngeal gonorrhea is treated with an alternate antibiotic regimen.
- The specificity of plain radiographs can confirm the diagnosis of osteomyelitis in most patients.
- Fluid replacement is the mainstay of treatment for travelers' diarrhea.
- Most healthy patients with watery diarrhea of less than 3 days' duration can be treated with supportive care and no antibiotic therapy or microscopic assessment.
- Most uncomplicated *Salmonella* infections in adults younger than 50 years resolve within 1 week and require only supportive care.
- Enterotoxigenic *Escherichia coli* infection is usually a self-limiting illness that resolves without treatment after approximately 4 days.
- Hand hygiene is the foundation of infection prevention.
- Catheter-associated asymptomatic bacteriuria generally does not require treatment.
- Antimicrobial- or antiseptic-coated catheters have not shown benefit for short-term or long-term bladder catheterization.
- Central venous catheters should be assessed daily for continued necessity and removed promptly when they are no longer needed (see Item 41).

Infectious Disease

Central Nervous System Infections

Meningitis

A positive Gram stain result for bacteria or yeast is seen in only 5% of patients with community-acquired meningitis. Meningitis with a negative Gram stain result is a diagnostic and management challenge because the differential diagnosis includes urgent treatable causes, such as bacterial or fungal meningitis. Bacterial cultures of cerebrospinal fluid (CSF) or blood are needed for antimicrobial sensitivity studies in suspected bacterial meningitis, but results are insufficiently timely to differentiate bacterial from viral meningitis. In situations of clinical uncertainty, rapid diagnostic techniques such as polymerase chain reaction (PCR) for common viruses and arboviral serologies can reduce use of clinically unhelpful cranial imaging, hospitalization, and antimicrobial therapy.

Viral Meningitis

Enteroviruses are the most common cause of viral meningitis, usually presenting between May and November in the Western Hemisphere, with symptoms including headache, fever, nuchal rigidity, photophobia, nausea, vomiting, myalgias, pharyngitis, maculopapular rash, and cough. Lymphocytic pleocytosis of the CSF with a normal glucose level and mildly elevated protein level is typical (**Table 1**). The diagnosis is confirmed by enterovirus PCR. Treatment is supportive with a benign clinical course.

Herpesviruses can cause meningitis year round and include herpes simplex virus (HSV) types 1 and 2, varicella-zoster virus (VZV), cytomegalovirus, Epstein-Barr virus, and human herpesvirus 6. Of the herpesviruses, HSV-2 is the most common cause of viral meningitis that can sometimes recur (recurrent benign lymphocytic meningitis, also called Mollaret meningitis). The CSF findings resemble enteroviral meningitis. Outcomes for HSV-2 meningitis are generally favorable without the need for acyclovir therapy.

VZV can cause encephalitis, aseptic meningitis, myelitis, and a vasculitis presenting as a stroke. Vesicular lesions are a clue to the diagnosis but may be absent (zoster sine herpete). VZV encephalitis and vasculitis may present with a hemorrhagic CSF. VZV may be present in the CSF without meningitis or encephalitis, and patients with primary varicella or zoster do not require lumbar puncture unless they have clinical signs of central nervous system (CNS) involvement. Immunocompromised and older adult patients are at higher risk of VZV meningitis and encephalitis. The diagnosis is confirmed by VZV PCR of the CSF, and therapy is parenteral acyclovir.

TABLE 1. Typical CSF Findings in Patients with Viral and Bacterial Meningitis

CSF Parameter	Viral Meningitis[a]	Bacterial Meningitis
Opening pressure	≤250 mm H_2O	200-500[b] mm H_2O
Leukocyte count	50-1000/µL (50-1000 × 10^6/L)	1000-5000/µL (1000-5000 × 10^6/L)[c]
Leukocyte predominance	Lymphocytes[d]	Neutrophils
Glucose level	>45 mg/dL (2.5 mmol/L)[e]	<40 mg/dL (2.2 mmol/L)[f]
Protein level	<200 mg/dL (2000 mg/L)	100-500 mg/dL (1000-5000 mg/L)
Gram stain	Negative	Positive in 60%-90%[g]
Culture	Negative	Positive in 70%-85%[h]

CSF = cerebrospinal fluid.

[a]Primarily nonpolio enteroviruses (echoviruses and coxsackieviruses) and West Nile virus between June and October; herpes simplex type 2 year round.

[b]Values exceeding 600 mm H_2O suggest the presence of cerebral edema, intracranial suppurative foci, or communicating hydrocephalus.

[c]Range may be <100/µL (100 × 10^6/L) to >10,000/µL (10,000 × 10^6/L).

[d]Neutrophil predominance occurs in 25% of viral meningitis cases, usually early in infection and more likely in young children with enteroviral infection.

[e]A mild hypoglycorrhachia (30-45 mg/dL [1.7-2.5 mmol/L]) can be seen in viral infections such as herpes simplex virus and West Nile virus.

[f]The CSF-to-plasma glucose ratio is ≤0.40 in most patients.

[g]The likelihood of a positive Gram stain correlates with the number of bacteria in the CSF.

[h]The yield of positive results is significantly reduced by previous administration of antimicrobial therapy.

H CONT.

Mosquito-borne viruses such as West Nile virus (WNV), St. Louis encephalitis, and California encephalitis can cause meningitis or encephalitis between June and October in the Western Hemisphere. Neuroinvasive WNV may present with acute flaccid paralysis, which may lead to persistent weakness or death. The CSF formula resembles enteroviral meningitis. The diagnosis is made by serum or CSF serology (WNV IgM); WNV PCR of the CSF is insensitive. Treatment is supportive.

Acute HIV infection can present as aseptic meningitis associated with a mononucleosis-like syndrome with fever, rash, and myalgias.

Less common viral causes include mumps, lymphocytic choriomeningitis virus, parainfluenza, adenoviruses, influenza A and B, measles, rubella, poliovirus, rotavirus, and parvovirus B19. H

KEY POINTS

- Enteroviruses are the most common cause of viral meningitis, usually presenting with symptoms of headache, fever, nuchal rigidity, photophobia, nausea, vomiting, myalgias, pharyngitis, maculopapular rash, and cough between May and November.
- Herpesviruses can cause meningitis year round; herpes simplex virus 2 is the most common cause and can recur.
- Neuroinvasive West Nile virus may present with acute flaccid paralysis, which may lead to persistent weakness or death.

H

Bacterial Meningitis

Bacterial meningitis usually presents with acute meningeal signs (fever, nuchal rigidity) and altered mental status. Since the introduction of conjugate vaccines, *Haemophilus influenzae* and *Neisseria meningitides* meningitis incidence has decreased, making *Streptococcus pneumoniae* the most common cause of community-acquired bacterial meningitis. *N. meningitides* serogroup B accounts for 40% of infections in the United States because the quadrivalent conjugate vaccine (ACYW-135) does not include serogroup B. Two FDA-approved vaccines that target serogroup B are available in the United States. *Streptococcus agalactiae* is now the third most common cause of bacterial meningitis in adults. *Listeria monocytogenes* is an uncommon cause of meningitis in adults; however, the risk increases in older adults and those with altered cell-mediated immunity.

Bacterial endocarditis caused by *S. pneumoniae* and *Staphylococcus aureus* can present as purulent meningitis. Clinical clues include a history of valvular disease, a new regurgitant murmur, embolic phenomena, or other stigmata of endocarditis. Injection drug use and hemodialysis are risk factors for *S. aureus*, and alcoholism is a risk factor for *S. pneumoniae* endocarditis. Patients may also present with stroke symptoms secondary to embolic infarction.

Lyme disease, caused by *Borrelia burgdorferi*, can present with a lymphocytic meningitis approximately 2 to 10 weeks after development of erythema migrans. Common clinical features include headache, photophobia, nausea, history of erythema migrans, tick bite in an endemic area, and facial paralysis, which can be unilateral or bilateral. Because the CSF formula resembles enteroviral meningitis, the "rule of 7s" was derived and validated to accurately classify a patient at low risk of having Lyme disease (headache duration <7 days, <70% CSF mononuclear cells, and absence of a seventh facial nerve palsy).

Treponema pallidum meningitis can occur in the secondary or tertiary phase of syphilis. Headache and meningismus are common, and the CSF usually shows a lymphocytic pleocytosis with an elevated protein level. In tertiary syphilis, neurosyphilis can be asymptomatic or symptomatic. Symptomatic neurosyphilis can present with primarily meningovascular (stroke presentation) or parenchymatous (tabes dorsalis, general paresis) features.

Leptospiral meningitis develops in the immune or second phase of the illness and is classically associated with uveitis, rash, conjunctival suffusion, lymphadenopathy, and hepatosplenomegaly. The CSF formula resembles enteroviral meningitis, and the diagnosis is established by CSF or urine culture or by serology.

Evaluation

All patients with suspected meningitis should undergo lumbar puncture. CSF findings characteristic of bacterial meningitis are provided in Table 1. A negative CSF Gram stain result is more common in patients with previous antibiotic therapy or in patients with *L. monocytogenes* or gram-negative bacilli (sensitivity <50%) infections. CSF latex agglutination tests for detecting bacterial antigens are no longer recommended because of low sensitivity (70%) and specificity, although they may play a role in patients with previous antibiotic therapy or culture-negative meningitis. Multiplex PCR assay for detection of *S. pneumoniae*, *N. meningitidis*, *H. influenzae*, and *L. monocytogenes* has high sensitivity (100%) and specificity (98%) and is increasingly available. If a head CT is indicated before lumbar puncture (focal neurologic findings, altered mental status, papilledema, new seizure, history of CNS disease, or immunocompromise), imaging should not delay empiric antibiotic therapy, which should be started after promptly obtaining blood cultures. See **Figure 1** for management of suspected bacterial meningitis.

Management

Intravenous antibiotic therapy should be started as soon as possible. If the CSF Gram stain result is negative, initial empiric antibiotic selection is based on age, local epidemiologic patterns of pneumococcal resistance, and the necessity for ampicillin coverage for *L. monocytogenes* (**Table 2**). Despite antibiotic therapy, mortality for bacterial meningitis remains approximately 25%. Adjunctive dexamethasone (10 mg every 6 hours for 4 days)

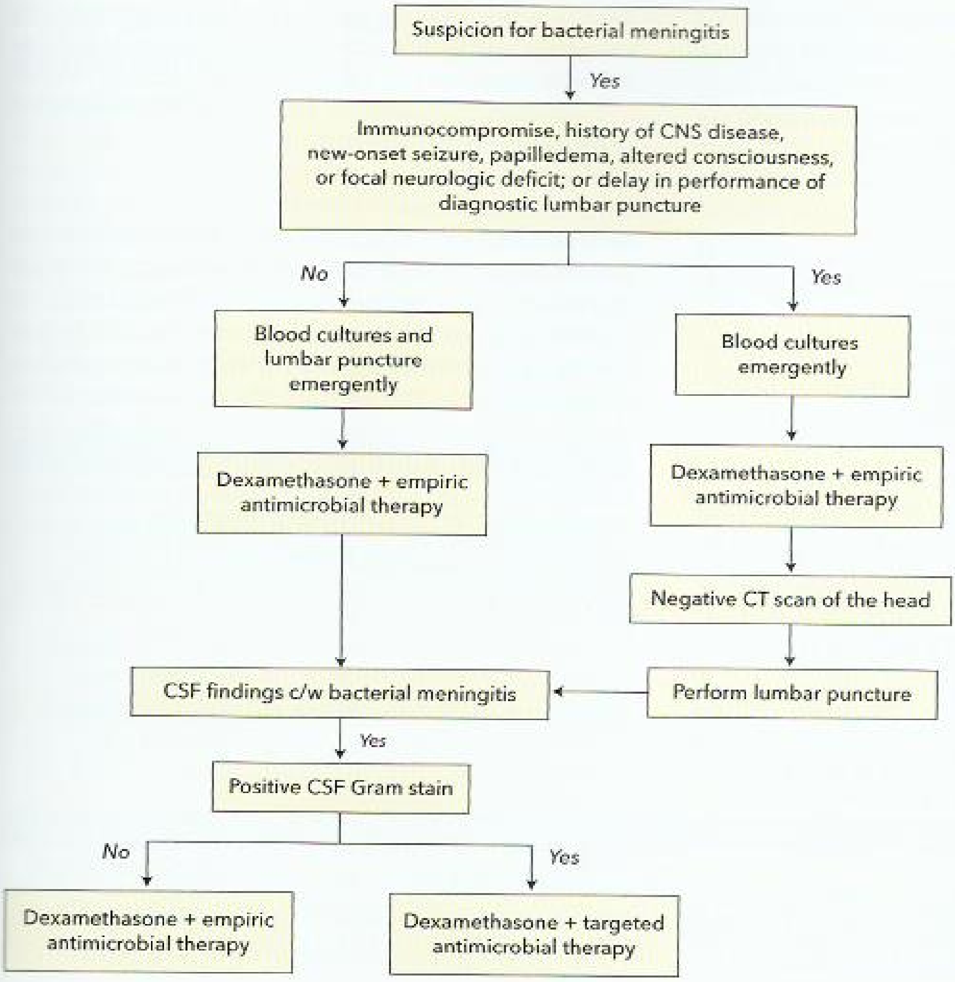

FIGURE 1. Management algorithm for adults suspected of having bacterial meningitis. CNS = central nervous system; c/w = consistent with; CSF = cerebrospinal fluid.

Adapted with permission from Tunkel AR, Hartman BJ, Kaplan SL, Kaufman BA, Roos KL, Scheld WM, et al. Practice guidelines for the management of bacterial meningitis. Clin Infect Dis. 2004;39:1267-84. [PMID: 15494903] Copyright 2004 Oxford University Press.

TABLE 2. Antibiotic Management of Bacterial Meningitis

Clinical Characteristics	Empiric Antibiotic Regimen
Immunocompetent host age <50 y with community-acquired bacterial meningitis	IV ceftriaxone *or* cefotaxime plus IV vancomycin
Patient age >50 y or those with altered cell-mediated immunity	IV ampicillin (*Listeria* coverage) plus IV ceftriaxone *or* cefotaxime plus IV vancomycin
Allergies to β-lactams	IV moxifloxacin instead of cephalosporin IV trimethoprim-sulfamethoxazole instead of ampicillin
Hospital-acquired bacterial meningitis	IV vancomycin plus either IV ceftazidime, cefepime, or meropenem
Neurosurgical procedures	IV vancomycin plus either IV ceftazidime, cefepime, or meropenem

IV = intravenous.

reduces morbidity and mortality in adults with pneumococcal meningitis and reduces the risk of neurologic sequelae in bacterial meningitis in developed countries; it should be given concomitantly with the first dose of antibiotic therapy. H

H CONT.

KEY POINTS

- For diagnosis of bacterial meningitis, the cerebrospinal fluid Gram stain result is positive in 60% to 90% of infections; latex agglutination testing for bacterial antigens is not recommended because of low sensitivity and specificity.
- Intravenous antibiotic therapy and dexamethasone should be started as soon as possible when bacterial meningitis is suspected; selection of initial empiric antibiotics is based on age, local epidemiologic patterns of pneumococcal resistance, and the necessity for ampicillin coverage for *Listeria monocytogenes*.
- Adjunctive dexamethasone reduces morbidity and mortality in adults with pneumococcal meningitis and reduces the risk of neurologic sequelae in bacterial meningitis in developed countries.

Subacute and Chronic Meningitis

Subacute and chronic meningitis are defined by symptom duration between 5 and 30 days and more than 30 days, respectively. The most common infectious causes are *Mycobacterium tuberculosis* and fungi.

Tuberculous Meningitis

Mycobacterial tuberculosis meningitis classically presents as basilar meningitis with cranial neuropathies (particularly of cranial nerve VI), mental status changes, and the syndrome of inappropriate secretion of antidiuretic hormone. A history of tuberculosis exposure, an abnormal chest radiograph, a positive tuberculin skin test result, and a positive interferon-γ release assay result are suggestive but can be absent. CSF examination shows a lymphocytic pleocytosis (leukocyte count of 100-500/µL [100-500 × 10^6/L]), elevated protein level, and hypoglycorrhachia. CSF acid-fast bacilli smear is insensitive, and culture results are positive in only 38% to 88% of patients. Culture sensitivity increases when lumbar punctures are performed serially for at least 3 days. Nucleic acid amplification testing should be performed when possible, especially when the acid-fast bacilli stain result is negative and suspicion is high, because it might increase diagnostic yield. Antituberculous therapy should be administered for 1 year, and adjunctive glucocorticoids should be given initially because of their association with improved outcomes.

Fungal Meningitis

Fungal pathogens, including *Cryptococcus neoformans*, *Coccidioides immitis*, *Histoplasma capsulatum*, and endemic mycoses, are a significant cause of subacute or chronic meningitis syndromes. Fungal meningitis is discussed in the Fungal Infections chapter.

Neurobrucellosis

Neurobrucellosis occurs in 4% to 11% of patients with brucellosis, which is endemic to countries in the Mediterranean, Middle East, and Central America. It may present with meningitis, meningoencephalitis, cranial neuropathies, myelopathy, radiculopathy, or stroke or as a brain abscess. The diagnosis is made by a positive culture or serologic test result for brucellosis in the CSF or blood. Treatment consists of combination antimicrobial therapy (such as ceftriaxone, rifampin, and doxycycline) for at least 6 months.

Parasitic Meningitis

Acute primary amebic meningoencephalitis caused by *Naegleria*, *Balamuthia*, and *Acanthamoeba* species is a fatal infection that clinically resembles bacterial meningitis. Freshwater exposure is a key historical clue. Examination of a fresh CSF sample can reveal motile trophozoites, but the Centers for Disease Control and Prevention should perform confirmatory testing by PCR. Treatment should include miltefosine.

Helminth infections causing eosinophilic meningitis include *Angiostrongylus cantonensis*, *Baylisascaris procyonis*, *Taenia solium* (neurocysticercosis), *Schistosoma* species (schistosomiasis), and *Gnathostoma*. Neurocysticercosis is endemic in Mexico, South America, and Asia. It most commonly presents with seizures or hydrocephalus, and CT scan of the head shows multiple cysts or calcified lesions.

Noninfectious Causes

Medications such as NSAIDS, antibiotics, and intravenous immune globulin can occasionally cause aseptic meningitis. Meningeal involvement of leukemia, lymphoma, and metastatic carcinoma can also present as aseptic meningitis, with the CSF cytology showing atypical or immature cells and severe hypoglycorrhachia (<10 mg/dL [0.6 mmol/L]). Systemic lupus erythematosus, Behçet disease (recurrent oral and genital ulcers with iridocyclitis), Vogt-Koyanagi-Harada syndrome (uveomeningoencephalitis), and neurosarcoidosis can all present with aseptic meningitis. Finally, chemical meningitis can be seen after intrathecal injections, neurosurgical procedures, or spinal anesthesia.

KEY POINTS

- Tuberculous meningitis classically presents as basilar meningitis with cranial neuropathies, mental status changes, and the syndrome of inappropriate secretion of antidiuretic hormone; it should be treated with antituberculous therapy for 1 year along with initial adjunctive glucocorticoids.
- Freshwater exposure is a key historical clue in suspected acute primary amebic meningoencephalitis.
- Medications such as NSAIDS, antibiotics, and intravenous immune globulin can occasionally cause aseptic meningitis.

Health Care-Associated Meningitis and Ventriculitis

Health care-associated meningitis and ventriculitis, or nosocomial meningitis, can occur after head trauma or a neurosurgical procedure (craniotomy, lumbar puncture) or secondary to a device infection (for example, CSF shunt or drain, intrathecal pump, deep brain stimulator). Normal or abnormal CSF cell count, glucose level, and protein level do not reliably confirm or rule out infection in these patients. *Staphylococcus* species and enteric gram-negative bacteria are the most common causes, but up to 50% of infections can have negative culture results. The use of β-D-glucan and galactomannan CSF assays may aid in the diagnosis of health care-related fungal ventriculitis and meningitis. Empiric antimicrobial therapy is outlined in Table 2 and should be accompanied by device removal if present.

KEY POINT

- *Staphylococcus* species and enteric gram-negative bacteria are the most common causes of health care-associated meningitis and ventriculitis, but up to 50% of infections can have negative culture results.

Focal Central Nervous System Infections

Brain Abscesses

Brain abscesses can occur in immunocompetent or immunosuppressed persons and are most commonly seen in men. Predisposing conditions in immunocompetent patients can be seen in **Table 3**. Brain abscesses are most commonly caused by anaerobes, aerobic and microaerophilic streptococci, and Enterobacteriaceae. Initial empiric therapy is guided by the likely predisposing condition and is outlined in **Table 4**. Aspiration of the brain abscess for culture is preferred for definitive diagnosis; surgical or stereotactic drainage should be performed if the abscess is large (>2.5 cm). Antibiotic therapy should be given for 4 to 8 weeks with follow-up cranial imaging to ensure resolution of the infection.

TABLE 3. Predisposing Conditions for Brain Abscess

Condition	Incidence
Contiguous foci of infection such as sinusitis (frontal lobe) and otitis media (temporal lobe or cerebellum)	~50%
Hematogenous, sometimes with multiple abscesses (odontogenic resulting from viridans streptococci, endocarditis, injection drug use)	25%
Cryptogenic (most likely odontogenic)	15%
Neurosurgery or penetrating head trauma	10%

Immunosuppressed patients (those with HIV or AIDS, patients undergoing solid organ or bone marrow transplantation) are at risk for development of brain abscesses from several opportunistic infections. See HIV/AIDS and Infections in Transplant Recipients for further discussion.

KEY POINT

- Brain abscesses in immunocompetent patients are treated empirically based on the likely predisposing factor with surgical or stereotactic drainage of abscesses greater than 2.5 cm.

Cranial Abscess

Cranial epidural and subdural abscesses can arise from underlying osteomyelitis complicating paranasal sinusitis (Pott puffy tumor) or otitis media or after neurosurgical procedures or head trauma. Rarely, they may arise as a complication of bacterial meningitis. Cranial epidural abscesses are usually slow growing, presenting with subacute to chronic symptoms of headache, localized bone pain, and focal neurologic signs. In contrast, subdural empyema is a rapidly progressive infection

TABLE 4. Predisposing Conditions, Causative Agents, and Empiric Antimicrobial Therapy in Patients with Bacterial Brain Abscess

Predisposing Condition	Usual Causative Agents	Empiric Antimicrobial Therapy
Otitis media or mastoiditis	Streptococci (aerobic or anaerobic), *Bacteroides* species, *Prevotella* species, Enterobacteriaceae	Metronidazole plus a third-generation cephalosporin[a]
Sinusitis	Streptococci, *Bacteroides* species, Enterobacteriaceae, *Staphylococcus aureus*, *Haemophilus* species	Metronidazole plus a third-generation cephalosporin[a,b]
Dental sepsis	Mixed *Fusobacterium*, *Prevotella*, and *Bacteroides* species; streptococci	Penicillin plus metronidazole
Penetrating trauma or after neurosurgery	*S. aureus*, streptococci, Enterobacteriaceae, *Clostridium* species	Vancomycin plus a third-generation cephalosporin[a,c]
Lung abscess, empyema, bronchiectasis	*Fusobacterium*, *Actinomyces*, *Bacteroides*, and *Prevotella* species; streptococci; *Nocardia* species	Penicillin plus metronidazole plus a sulfonamide[d]
Endocarditis	*S. aureus*, streptococci	Vancomycin plus gentamicin
Hematogenous spread from pelvic, intra-abdominal, or gynecologic infections	Enteric gram-negative bacteria, anaerobic bacteria	Metronidazole plus a third-generation cephalosporin[a,b,c]
Immunocompromised patients HIV-infected patients	*Listeria* species, fungal organisms (*Cryptococcus neoformans*), or parasitic or protozoal organisms (*Toxoplasma gondii*); *Aspergillus*, *Coccidioides*, and *Nocardia* species	Metronidazole plus a third-generation cephalosporin[a,b,c,d,e]; antifungal or antiparasitic agent

[a]Cefotaxime or ceftriaxone; the fourth-generation cephalosporin cefepime may also be used.

[b]Add vancomycin if infection caused by methicillin-resistant *Staphylococcus aureus* is suspected. Vancomycin can then be transitioned to antistaphylococcal β-lactam (oxacillin-nafcillin)-penicillin if methicillin-sensitive *S. aureus* is confirmed.

[c]Use ceftazidime or cefepime if infection caused by *Pseudomonas aeruginosa* is suspected. Meropenem can also be used for antipseudomonal coverage.

[d]Use trimethoprim-sulfamethoxazole if infection caused by *Nocardia* species is suspected.

[e]Use ampicillin if infection caused by Listeria species is suspected.

NOTE: If predisposing condition is unknown, empiric treatment should include vancomycin plus metronidazole and a third-generation cephalosporin.

with high mortality that represents a neurosurgical emergency. The CSF formula in both parameningeal infections shows neutrophilic pleocytosis and a very high protein level, frequently with negative Gram stain and culture results. Pathogen identification is best achieved by culture of the abscess obtained during surgical drainage.

KEY POINT

- In cranial epidural and subdural abscess, pathogen identification is best achieved by culture of the abscess obtained during surgical drainage.

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Spinal Epidural Abscess

Spinal epidural abscess most commonly results from hematogenous dissemination, with *S. aureus* accounting for approximately 50% of infections; streptococcus and gram-negative bacilli such as *Escherichia coli* are also implicated. Predisposing factors for bacteremia include endocarditis, injection drug use, long-term intravenous catheters (hemodialysis catheters, central lines), and urinary tract infection. Spinal epidural abscess can also occur after neurosurgical procedures (spinal fusion, epidural catheter placement) or paraspinal injection. Patients usually develop localized pain at the site of infection that later radiates down the spine. MRI is the imaging modality of choice to identify location and extent of the abscess. All patients should undergo a baseline laboratory evaluation, including erythrocyte sedimentation rate and C-reactive protein. Blood cultures should be obtained before starting antibiotics. Although the duration of antibiotic therapy lacks robust supporting data and must be determined on a case-by-case basis, at least 6 weeks of effective antimicrobial therapy is reasonable. Surgical drainage is indicated in patients with neurologic symptoms or signs (lower extremity weakness, numbness, bladder and bowel dysfunction). Follow-up MRI is not indicated unless the patient has persistent elevation of inflammatory markers, lack of clinical response, or new neurologic symptoms or signs. Tuberculosis (Pott disease) and brucellosis should be considered in patients with negative culture results and appropriate travel history and risk factors. H

KEY POINT

- MRI is the imaging modality of choice to identify location and extent of a spinal epidural abscess, and blood cultures should be obtained before starting antibiotic therapy.

Encephalitis

Encephalitis is inflammation of the brain parenchyma. Possible encephalitis is defined by the presence of one major (altered consciousness for more than 24 hours) and two minor (fever, new onset seizure, new onset focal neurologic findings, CSF pleocytosis, and abnormal MRI or electroencephalographic findings) criteria from the International Encephalitis Consortium; probable or confirmed encephalitis requires one major and at least three minor criteria. The causative agent is unknown in 37% to 70% of infections, depending on whether viral PCR is used and autoimmune causes are investigated. The most common known causes are viral (herpes simplex virus types 1 and 6, varicella-zoster virus, and West Nile virus) and autoimmune diseases.

Viral Encephalitis

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Herpes Simplex Encephalitis

HSV-1 is the most common cause of sporadic encephalitis in the United States, requiring prompt identification and treatment with intravenous acyclovir. Factors associated with an adverse outcome include older age, abnormal Glasgow coma scale, and delay in starting antiviral therapy. HSV-1 encephalitis presents with fever, seizures, altered mental status, and focal neurologic deficits with unilateral temporal lobe edema, hemorrhage, or enhancement on imaging. Bilateral temporal lobe findings in the insula or cingulate are less commonly seen. The CSF formula usually shows lymphocytic pleocytosis, an elevated protein level, and a normal glucose level. The diagnosis is confirmed by HSV PCR of the CSF (98% sensitivity, 94% specificity). However, false-negative results have been reported; if HSV is suspected, a repeat PCR should be obtained within 1 week while continuing acyclovir therapy. Therapy duration for HSV encephalitis should be 14 to 21 days. Electroencephalography can be helpful in identifying the degree of cerebral dysfunction and specific area of the brain involved and in detecting subclinical seizure activity.

Human herpesvirus 6 can cause severe encephalitis in transplant recipients. Cytomegalovirus can cause encephalitis with periventricular enhancement on imaging in immunosuppressed patients (those with AIDS or after transplantation). Diagnosis is by PCR of the CSF for cytomegalovirus, and treatment is parenteral ganciclovir. Cytomegalovirus and Epstein-Barr virus can cause meningoencephalitis in young, immunocompetent patients presenting with infectious mononucleosis syndromes.

Varicella-Zoster Virus Encephalitis

Varicella-zoster virus (VZV) is a commonly underdiagnosed, treatable cause of encephalitis in adults. VZV can present with vasculopathy with a stroke, encephalitis, meningitis, radiculopathy, or myelitis. Patients can present without a vesicular rash, so a PCR of the CSF or a serum-to-CSF anti-VZV IgG should be ordered in all patients with encephalitis. Treatment with intravenous acyclovir for 10 to 14 days is recommended.

Arboviruses

Arboviral CNS infections in the United States are most commonly seen in summer or fall and include West Nile (WNV), Eastern and Western equine encephalitis, St. Louis encephalitis, Powassan, and La Crosse viruses. WNV is the most common cause of epidemic viral encephalitis in the United States. WNV can cause meningitis, encephalitis, acute flaccid paralysis (similar to poliomyelitis), neuropathy, and retinopathy.

H CONT Older patients and those who have undergone transplantation or are immunosuppressed have a higher risk of death. WNV affects the thalamus and the basal ganglia; patients present with facial or arm tremors, parkinsonism, and myoclonus. Hypodense lesions or enhancements may be seen in the thalamus, basal ganglia, and midbrain on MRI of the brain. Diagnosis is confirmed by a positive WNV IgM in the CSF or serum; treatment is supportive.

HIV encephalitis is the cause of HIV-associated dementia in later stages of the untreated illness; it can also present as CD8 encephalitis, consisting of perivascular inflammation resulting from infiltration of $CD8^+$ lymphocytes, which may occur as part of an immune reconstitution syndrome, in some cases associated with viral escape (low levels of detectable HIV RNA in CSF). H

KEY POINTS

- Herpes simplex virus 1 is the most common cause of sporadic encephalitis in the United States, presenting with fever, seizures, altered mental status, and focal neurologic deficits; prompt identification and treatment with intravenous acyclovir improves outcomes.
- Varicella-zoster virus (VZV) is a treatable form of encephalitis and may present without vesicular rash, so polymerase chain reaction of the cerebrospinal fluid (CSF) or a serum-to-CSF anti-VZV IgG should be ordered in all patients with encephalitis.
- West Nile virus is the most common cause of epidemic viral encephalitis in the United States.

Autoimmune Encephalitis

Autoimmune neurologic diseases can manifest as encephalitis, cerebellitis, dystonia, status epilepticus, cranial neuropathies, and myoclonus. Anti-*N*-methyl-D-aspartate receptor encephalitis is most common; it was initially described as a paraneoplastic syndrome affecting young women with ovarian teratomas, but it can be associated with other tumors (sex cord stromal tumors, small cell lung cancer) or occur without a tumor. Young women (<35 years) often present after viral-like illness with behavioral changes, headaches, and fever followed by altered mental status, seizures, abnormal movements, and autonomic instability. Treatment includes intravenous glucocorticoids, intravenous immune globulin, tumor removal (if present), and, in some cases, plasmapheresis and rituximab.

Prion Diseases of the Central Nervous System

Prions cause rare but relentlessly progressive and rapidly fatal neurodegenerative diseases characterized by dementia and ataxia. The cause of disease is an abnormally folded prion protein. In humans, prion diseases occur by three mechanisms: sporadic (spontaneous), familial (genetic), and acquired (infectious or transmissible). In patients of any age presenting with otherwise unexplained rapidly progressive dementia and ataxia, diagnosis of a prion disease should be considered (**Table 5**); the infectious forms are now rare (**Table 6**). Prion diseases have no known therapy.

Sporadic Creutzfeldt-Jakob Disease

Spontaneous (sporadic) disease is the most common form of Creutzfeldt-Jakob disease (CJD), with an incidence of 1 per million worldwide. No environmental risk factors are known. Clinical manifestations include rapidly progressive dementia, usually over 4 to 6 months. Ataxia, myoclonus, and pyramidal and extrapyramidal signs may be observed. Loss of vision is not uncommon, and patients become comatose before dying.

TABLE 5. Criteria for Diagnosis of Probable Prion Disease[a,b]

University of California, San Francisco Criteria (2007)[b]
Rapid cognitive decline
Two of the following signs or symptoms:
Myoclonus
Pyramidal/extrapyramidal dysfunction
Visual dysfunction
Cerebellar dysfunction
Akinetic mutism
Focal cortical signs (for example, neglect, aphasia, acalculia, apraxia)
Typical EEG and/or MRI
Other investigations should not suggest an alternative diagnosis
European MRI-CJD Consortium Criteria (2009)[b]
Progressive dementia
One of the following signs or symptoms:
Myoclonus
Pyramidal/extrapyramidal symptoms
Visual/cerebellar dysfunction
Akinetic mutism
AND
Either
Typical EEG
Elevated CSF protein 14-3-3 (with total disease duration <2 years)
OR
Typical MRI
Routine investigations should not suggest an alternative diagnosis

CJD = Creutzfeldt-Jakob disease; CSF = cerebrospinal fluid; EEG = electroencephalography.

[a]Definitive diagnosis requires neuropathologic confirmation.

[b]Fulfilling one criterion in all categories signifies a probable diagnosis.

TABLE 6. Human Transmissible Spongiform Encephalopathies	
Disease Classification	**Presentation**
Acquired	
Idiopathic only (not environmental)	Sporadic fatal familial insomnia
	Sporadic CJD
Idiopathic/transmissible	Variant CJD (from BSE)
	Kuru
Inherited	Familial CJD
	GSS
	Fatal familial insomnia

BSE = bovine spongiform encephalopathy; CJD = Creutzfeldt-Jakob disease; GSS = Gerstmann-Sträussler-Scheinker syndrome.

The diagnosis can be made by clinical history and MRI; a cerebrospinal fluid analysis positive for either total Tau or 14-3-3 protein may also be useful.

Transmissible Prion Diseases

Variant CJD (vCJD) is the human form of bovine spongiform encephalopathy. It generally affects younger persons (age 15-50 years), frequently presenting with rapidly progressive neuropsychiatric manifestations (depression, withdrawal) and peripheral neuropathy, followed by cerebellar ataxia, involuntary movements, and cognitive decline over a 12-month period. Because vCJD can be transmitted through blood products and tissue, it is a serious public health concern worldwide. Probable vCJD is diagnosed by typical MRI findings ("hockey stick sign" in the posterior thalamus) and tonsil biopsy to detect scrapie-associated prion protein in a patient with a compatible clinical presentation (see Table 5).

Iatrogenic CJD is exceedingly rare, but transmission has been documented with contaminated cadaveric pituitary-derived human growth hormone and gonadotropin, dura mater, stereotactic electroencephalography needles, neurosurgical instruments, corneal transplants, medical instruments, implanted electroencephalography electrodes, and blood transfusions.

Familial Prion Disease

Many mutations have been associated with the prion protein gene. All are autosomally dominant. These include the gradually progressive Gerstmann-Sträussler-Scheinker syndrome and the rapidly progressive fatal familial insomnia.

KEY POINTS

- Prion disease should be included in the differential diagnosis of a patient of any age presenting with otherwise unexplained rapidly progressive dementia and ataxia.
- Spontaneous Creutzfeldt-Jakob disease is the most common form of prion disease and has no known risk factors.

Skin and Soft Tissue Infections

Introduction

Skin infections usually result from epidermal compromise that allows skin colonizers such as *Staphylococcus aureus* and *Streptococcus pyogenes* to become pathogenic. Predisposing conditions include vascular disease, immunodeficiency, neuropathy, previous cellulitis, obesity, skin trauma, tinea pedis, and lymphedema. Infections can be characterized by anatomic involvement and presence or absence of pus. Nonpurulent spreading skin infections include erysipelas, cellulitis, and necrotizing soft tissue infection; purulent skin infections refer to abscesses (**Figure 2**), furuncles, and carbuncles. Purulent skin infections are generally caused by staphylococci, including methicillin-resistant *Staphylococcus aureus* (MRSA); nonpurulent skin infections are usually caused by β-hemolytic streptococci. **Table 7** includes other skin pathogens and their associated risk factors for less common causes of skin infection. Complications of infections include systemic inflammatory response (as in severe cellulitis) or systemic toxin release (as in toxic shock syndrome).

Erysipelas and Cellulitis

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Erysipelas refers to infection of the epidermis, upper dermis, and superficial lymphatics. Usually involving the face or lower extremities, this infection is brightly erythematous with distinct elevated borders and associated fever, lymphangitis, and regional lymphadenopathy (see MKSAP 18 Dermatology). Cellulitis refers to infection involving the deeper dermis and subcutaneous fat tissue. Inflammatory signs of infection are similar to erysipelas, but the area of involvement is less well demarcated.

Although the diagnosis of erysipelas or cellulitis is usually established clinically, approximately one third of patients are

FIGURE 2. A cutaneous abscess draining purulent material is shown; it is caused by methicillin-resistant *Staphylococcus aureus* bacteria.

Image credit to the Centers for Disease Control and Prevention/Bruno Coignard, MD; Jeff Hageman, MHS.

TABLE 7. Skin Pathogens and Associated Risk Factors

Pathogen	Risk Factor	Comment
Aeromonas hydrophila	Contact with freshwater lakes, streams, rivers (including brackish water) Contact with leeches	Cellulitis nonspecific in clinical appearance; minor trauma to skin usually leads to inoculation of organism
Vibrio vulnificus, Vibrio parahaemolyticus	Contact with salt water or brackish water Contact with drippings from raw seafood Consumption of undercooked shellfish (particularly oysters) Liver cirrhosis or chronic liver disease	Cellulitis through direct inoculation into skin Ingestion leads to bacteremia with secondary skin infection Hallmark is hemorrhagic bullae in area of cellulitis lesion(s)
Erysipelothrix rhusiopathiae	Contact with saltwater marine life (can also infect freshwater fish)	Cellulitis usually involves the hand or arm, especially in those handling fish, shellfish, or, occasionally, poultry or meat contaminated with bacterium Causes erysipeloid disease
Pasteurella multocida	Contact primarily with cats and dogs	Cellulitis occurs as a result of cat scratch or bite
Capnocytophaga canimorsus	Contact primarily with dogs	Cellulitis and sepsis are present, particularly in patients with hyposplenism
Bacillus anthracis	Contact with infected animals or animal products. May be the result of bioterrorism	Edematous pruritic lesion with central eschar; spore-forming organism
Francisella tularensis	Contact with or bite from infected animal (particularly cats); arthropod bites (particularly ticks)	Ulceroglandular syndrome characterized by ulcerative lesion with central eschar and localized tender lymphadenopathy; constitutional symptoms often present
Burkholderia mallei	Contact with tissues or bodily fluids of infected mules or horses	Pustules with suppurative localized lymph nodes or ulcerative nodules at site of inoculation
Clostridium perfringens	Surgery or other significant trauma	Necrotizing infection, often referred to as clostridial myonecrosis or gas gangrene
Mycobacterium marinum	Contact with fresh water or salt water, including fish tanks and swimming pools	Lesion is often trauma associated and often involves the upper extremity; papular lesions become ulcerative at site of inoculation; ascending lymphatic spread can be seen ("sporotrichoid" appearance); systemic toxicity usually absent
Mycobacterium fortuitum	Exposure to freshwater footbaths/pedicures at nail salons, particularly after razor shaving; surgery	Furuncle(s); postoperative wound infection

H CONT

misdiagnosed. Clinical mimics include contact or stasis dermatitis, lymphedema, erythema nodosum, deep venous thrombosis, thrombophlebitis, lipodermatosclerosis, erythromelalgia, trauma-related inflammation, and hypersensitivity reactions (see MKSAP 18 Dermatology). Blood culture results are positive in approximately 5% of patients with erysipelas and cellulitis and are not routinely indicated; however, cultures should be performed for those who are immunocompromised, exhibit severe sepsis, or have unusual precipitating circumstances, including immersion injury or animal bites. Culture of skin tissue aspirate or biopsy should also be considered for these patients. Radiographic imaging is not helpful for the diagnosis of erysipelas or cellulitis but may be helpful when a deeper necrotizing infection is suspected.

For immunocompetent patients with cellulitis or erysipelas who have no systemic signs or symptoms (mild infection), empiric oral therapy directed against streptococci is recommended as outlined in **Table 8** (see MKSAP 18 Dermatology). Treatment duration for uncomplicated infection can be as short as 5 days but should be extended as necessary until the infection improves. In patients with systemic signs (moderate infection), intravenous treatment is recommended (see Table 8). Treating predisposing factors (such as tinea pedis, edema, and primary skin disorders) may decrease the risk for recurrent infection. Prophylactic antibiotics such as penicillin or erythromycin can be considered in patients with more than three episodes of cellulitis annually.

Patients who are immunocompromised, who have systemic inflammatory response syndrome and hypotension, or who have evidence of deeper necrotizing infection such as bullae and desquamation (severe infection) should receive urgent surgical evaluation for debridement. Initial empiric

TABLE 8. Treatment of Skin Infections

Infection	Treatment
Erysipelas or cellulitis	Mild: Oral penicillin, amoxicillin, cephalexin, dicloxacillin, clindamycin
	Moderate: Intravenous penicillin, ceftriaxone, cefazolin, clindamycin
	Severe: Surgical assessment for possible necrotizing component and empiric intravenous vancomycin plus piperacillin-tazobactam, imipenem, or meropenem
Necrotizing fasciitis	Polymicrobial infection: Surgical assessment/debridement and combination therapy such as vancomycin plus piperacillin-tazobactam or imipenem or meropenem
	Streptococcus pyogenes or *Clostridium perfringens*: Surgical assessment/debridement and penicillin plus clindamycin
	Aeromonas hydrophila: Surgical assessment/debridement and ciprofloxacin plus doxycycline
	Vibrio vulnificus: Surgical assessment/debridement and ceftazidime, ceftriaxone, or cefotaxime plus doxycycline
Furuncle, carbuncle, or abscess	Mild: Incision and drainage
	Moderate: Incision and drainage plus empiric trimethoprim-sulfamethoxazole or doxycycline pending culture and susceptibilities
	Severe: Incision and drainage plus empiric vancomycin, daptomycin, linezolid, telavancin, or ceftaroline pending culture and susceptibilities

H CONT.

broad spectrum antibiotic therapy should be started (see Table 8); then treatment may be adjusted based on culture and sensitivity results from lesion-associated specimens. H

KEY POINTS

HVC
- Blood cultures are positive in approximately 5% of patients with erysipelas and cellulitis and are not routinely indicated; however, cultures should be performed for those who are immunocompromised, exhibit severe sepsis, or have unusual precipitating circumstances, including immersion injury or animal bites.
- Patients with evidence of deeper necrotizing infection such as bullae and desquamation (severe infection) should receive urgent surgical evaluation for debridement and empiric broad-spectrum antibiotic therapy.

Necrotizing Fasciitis

Necrotizing soft tissue infections, which involve subdermal compartments including fascia and possibly muscle, are uncommon but potentially life threatening. In necrotizing fasciitis (NF), infection usually spreads along the superficial fascia. These infections may be monomicrobial or polymicrobial, consisting of a mixture of aerobic and anaerobic bacteria, and are often associated with the production of toxins. In monomicrobial infection, the classically associated pathogen is *Streptococcus pyogenes*; other potential organisms include *Staphylococcus aureus*, *Streptococcus agalactiae*, *Aeromonas hydrophila*, *Vibrio vulnificus*, and *Clostridium perfringens*.

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NF characteristically occurs in the setting of previous skin trauma or infection and most commonly affects the extremities. Risk factors include diabetes mellitus, injection drug use, malignancy, immunosuppression, and liver disease. Patients with liver disease are at particular risk for infection with *V. vulnificus* (**Figure 3**). Patients with diabetes are at risk for NF of the perineum, a polymicrobial infection known as Fournier gangrene that usually results from antecedent genitourinary, traumatic, or anorectal infection.

The initial presentation of NF resembles cellulitis before potentially rapid progression with edema, severe pain, hemorrhagic bullous lesions, skin necrosis, and local crepitus. Systemic toxicity manifests with fever, hypotension, tachycardia, mental status changes, and tachypnea. A hallmark of infection is "woody" induration appreciated by palpation of involved subcutaneous tissues. Necrosis of local nerves may result in anesthesia.

Laboratory study results are individually nonspecific. The Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC) score is derived from six variables that, when added together, are associated with an increased likelihood of necrotizing skin

FIGURE 3. Bullous cellulitis characteristic of *Vibrio vulnificus* infection is shown in a patient with cirrhosis; cutaneous necrosis is also evident, most likely associated with disseminated intravascular coagulation.

infection: C-reactive protein level (>15 mg/dL [150 mg/L]), total leukocyte count (>15,000-25,000/µL [15-25 × 10^9/L]), hemoglobin level (<11-13.5 g/dL [110-135 g/L]), sodium level (<135 mEq/L [135 mmol/L]), creatinine level (>1.6 mg/dL [141 µmol/L]), and glucose level (>180 mg/dL [10 mmol/L]). This tool was developed to improve diagnostic accuracy; the reported positive and negative predictive values are 92% and 96%, respectively. However, use of the score has not been prospectively validated in all clinical settings, so operative debridement should be pursued in patients with a high index of clinical suspicion for NF.

Plain radiographs and CT scans may demonstrate gas in soft tissues, but MRI with contrast is more sensitive and can help delineate anatomic involvement. Surgical exploration can confirm the diagnosis of NF. Blood culture(s) obtained before surgery and antibiotic administration or deep intraoperative specimen culture can establish the microbiologic cause.

In confirmed cases of NF, repeated surgical debridement is typically required. Pending culture results, empiric antibiotic treatment includes broad spectrum coverage for aerobic and anaerobic organisms (including MRSA) and consists of vancomycin, daptomycin, or linezolid plus piperacillin-tazobactam, a carbapenem, ceftriaxone plus metronidazole, or a fluoroquinolone plus metronidazole. Some experts also recommend adding empiric clindamycin because of its suppression of toxin production by staphylococci and streptococci. See Table 8 for treatment of NF caused by *S. pyogenes*, *V. vulnificus*, *A. hydrophila*, or clostridial species. Antimicrobial discontinuation can be considered when the patient is afebrile and clinically stable, and surgical debridement is no longer required.

KEY POINTS

- Necrotizing fasciitis initially resembles cellulitis before rapid progression of subdermal infection manifesting with clinical signs of edema, "woody" induration, severe pain, hemorrhagic bullous lesions, skin necrosis, local crepitus, fever, hypotension, tachycardia, mental status changes, and tachypnea; necrosis of local nerves may result in anesthesia.
- In patients with suspected necrotizing fasciitis, MRI with contrast is more sensitive than plain radiography or CT and can help delineate anatomic involvement.

Purulent Skin Infections

Abscesses are erythematous, nodular, localized collections of pus within the dermis and subcutaneous fat. Furuncles (boils) are hair follicle–associated abscesses that extend into the dermis and subcutaneous tissue. These inflammatory nodules are typically seen on the face, neck, and axilla. Infection that extends subcutaneously to involve several furuncles is known as a carbuncle. This coalescence of abscesses can result in systemic signs of infection.

Primary treatment for abscesses, furuncles, and carbuncles is incision and drainage. Gram stain and culture should be obtained from the purulent drainage when antibiotic administration is planned. Mild lesions without systemic symptoms do not require antibiotic therapy after drainage. For patients with moderate infections who have systemic signs of infection, empiric treatment is recommended (see Table 8). Empiric treatment with parenteral therapy is also recommended in immunocompromised patients, patients with hypotension and systemic inflammatory response syndrome (severe infection), or patients in whom incision and drainage plus oral antibiotics fail. Treatment is adjusted based on sensitivities from culture of the purulent drainage.

If MRSA is the cause of multiple recurrences of purulent skin infection, decolonization with topical intranasal mupirocin and chlorhexidine washes should be considered. Other diagnoses such as hidradenitis suppurativa, pilonidal cysts, or a foreign body should be considered when no microbial cause is identified.

Newer antibiotics for skin and soft tissue infections caused by *Streptococcus* and *Staphylococcus* species (including MRSA) include tedizolid, oritavancin, and dalbavancin. Use of these antibiotics is recommended in consultation with infectious disease specialists.

KEY POINTS

- Primary treatment for abscesses, furuncles, and carbuncles is incision and drainage; mild infections (without systemic symptoms) do not require antibiotic therapy. HVC
- For moderate and severe purulent infections associated with systemic symptoms, Gram stain and culture should be performed on the purulent drainage followed by empiric oral antibiotic treatment for moderate infections and empiric intravenous antibiotics for severe infections.

Animal Bites

Bites from cats and dogs represent approximately 1% of emergency department visits in the United States; most wounds (about 80%) will not become infected. Cat bites are more likely to become infected because of deeper puncture wounds created by cats' sharp, slender teeth. The microbiology of infection depends on the microbiota of the animal's mouth and of the patient's skin. Mixed aerobes and anaerobes, including staphylococci, streptococci, *Bacteroides* species, *Porphyromonas* species, *Fusobacterium* species, and *Pasteurella* species, typically compose the bacteria in bite wounds. *Capnocytophaga canimorsus* is a common constituent of canine microbiota and can cause severe infections in patients with asplenia.

Wound management includes irrigation with sterile normal saline. Irrigation also allows for characterization of wound extent and dimensions; signs of inflammation and infection, including edema, erythema, pain, necrosis, lymphangitis, and

pus; and local neurovascular involvement. Surgical evaluation for possible debridement and removal of foreign bodies is particularly important with hand bites. Culture of deep intraoperative tissue and antibiotic susceptibilities of isolated organisms allows for pathogen-directed therapy. Radiographs may demonstrate fracture, other bony involvement, or foreign bodies. Assessment for tetanus and rabies prophylaxis is essential. With the exception of facial wounds, primary wound closure is not generally pursued.

The decision to begin early antibiotic prophylaxis in the absence of clinical signs of infection is based on the severity of the wound and the immune status of the patient. Because of its activity against pathogens associated with animal bite wounds, a 3- to 5-day course of amoxicillin-clavulanate is recommended for patients who are immunosuppressed, including patients with cirrhosis and asplenia. Pre-emptive antibiotic therapy is also recommended for wounds with associated edema or lymphatic or venous insufficiency; crush injury; wounds involving a joint or bone; deep puncture wounds; or moderate to severe injuries, especially involving the face, genitalia, or hand. If a patient is allergic to penicillin, a combination of trimethoprim-sulfamethoxazole, or a fluoroquinolone, or doxycycline plus clindamycin or metronidazole can be used.

For clinically infected bite wounds, antibiotics are recommended after tissue wound cultures (and blood cultures, if systemic signs of infection are present) are obtained. For outpatient management of mildly infected wounds, oral antibiotics are recommended. The duration of antibiotic therapy is usually less than 2 weeks unless bone or joint involvement dictates a more prolonged course. Intravenous therapy is indicated for severe infections with systemic involvement, including sepsis; severe injuries, particularly those associated with tendon, nerve, vascular, or crush injuries; and hand infections. Intravenous antibiotic options include β-lactam or β-lactamase inhibitors (ampicillin-sulbactam, piperacillin-tazobactam), carbapenems (imipenem, meropenem, ertapenem), or ceftriaxone or a fluoroquinolone plus clindamycin or metronidazole. Empiric MRSA coverage may be included in patients with risk factors for MRSA infection (MRSA nasal colonization, recent hospitalization, recent antibiotic use, previous MRSA infection). Surgical consultation is usually obtained.

KEY POINTS

- Bite wound management includes irrigation with sterile normal saline; with the exception of facial wounds, primary closure is not generally pursued.
- Assessment for tetanus and rabies prophylaxis is essential in patients with animal bite wounds.
- Pre-emptive amoxicillin-clavulanate is recommended for patients who are immunosuppressed; wounds with associated edema or lymphatic or venous insufficiency; crush injury; wounds involving a joint or bone; deep puncture wounds; or moderate to severe injuries, especially involving the face, genitalia, or hand.

Human Bites

Intentional biting of others, self-inflicted wounds such as those occurring from fingernail biting, and clenched-fist injuries after a punch to another person's mouth are the most common causes of human bite wounds. These wounds are at risk for infection with human skin and mouth organisms. These organisms comprise aerobic organisms, including staphylococci, streptococci, and *Eikenella corrodens*, and anaerobic organisms, including *Peptostreptococcus*, *Fusobacterium*, and *Prevotella* species. Short-course prophylactic antibiotic therapy with amoxicillin-clavulanate is recommended for all human bites. The management of infected wounds is similar to that for animal bites, including empiric MRSA coverage in patients at increased risk for MRSA infection. Hand involvement warrants surgical evaluation. In addition to assessment for tetanus prophylaxis, evaluation for potential exposure to hepatitis B and C viruses, HIV, and other bodily fluid-transmitted pathogens is warranted.

KEY POINTS

- Short-course prophylactic antibiotic therapy with amoxicillin-clavulanate is recommended for all human bites.
- In addition to assessment for tetanus prophylaxis, evaluation of human bites for potential exposure to hepatitis B and C viruses, HIV, and other bodily fluid-transmitted pathogens is warranted.

Diabetic Foot Infections

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Diabetic foot infections typically result after trauma in persons with vasculopathy, neuropathy, suboptimal glucose control, and immunologic deficits. Additional risk factors for infection include presence of an ulcer for greater than 1 month, recurrent ulcers, lower extremity amputation, kidney function impairment, walking barefoot, and a positive probe-to-bone test in the wound. Infection is diagnosed when pus or two or more inflammatory signs (warmth, induration, erythema, pain, and tenderness) are present.

Following debridement of overlying callous or necrotic tissue as necessary, infections should be classified according to severity and extent. Mild infections involve only skin and subcutaneous tissue with erythema confined to 2 cm beyond the ulcer. Moderate infections extend deeper than subcutaneous tissue (for example, abscess, fasciitis, and osteomyelitis), or the erythema is more extensive. Severe infections are associated with systemic signs such as fever, tachycardia, tachypnea, leukocytosis, and hypotension or metabolic complications such as acidosis, worsening kidney function, and hyperglycemia. The affected foot or limb should also be assessed for arterial ischemia, venous insufficiency, neuropathy, and biomechanical abnormalities such as Charcot arthropathy or hammer toe. Evidence of critical ischemia can be considered a proxy for severe infection.

Uninfected wounds should not be cultured or treated with antibiotics. Mild infections are typically caused by aerobic

staphylococci (non-MRSA) and streptococci and can be empirically treated with a short course (7-14 days) of oral antibiotics, such as cephalexin, clindamycin, amoxicillin-clavulanate, or dicloxacillin. For mild infections with pus or MRSA risk factors (previous MRSA infection or colonization within the last year or high local prevalence), wound cultures should be obtained by curettage or biopsy of deep tissue before initiating antibiotics. Doxycycline or trimethoprim-sulfamethoxazole can also be used with a β-lactam antibiotic. For moderate and severe infections, polymicrobial coverage of staphylococci (including MRSA), streptococci, aerobic gram-negative bacilli, and anaerobes is recommended. Following deep tissue culture, initial antibiotic regimens include β-lactam or β-lactamase inhibitors, carbapenems, or metronidazole plus a fluoroquinolone or third-generation cephalosporin in addition to an anti-MRSA agent (vancomycin, daptomycin, linezolid). Antibiotic choices are guided by culture results. Moderate to severe infections are usually treated with a longer course of antibiotics (2-4 weeks); if osteomyelitis is present, approximately 6 weeks of antibiotic therapy is administered after surgical debridement.

A positive probe-to-bone test in a diabetic foot wound is associated with increased risk for osteomyelitis. Surgical consultation is often pursued to evaluate the need for debridement, resection, amputation, or revascularization. Plain imaging is recommended for all patients with new foot infections to assess for soft tissue gas, foreign body, and bony involvement; additional imaging with ultrasonography (for abscess) or MRI (for bone involvement) is recommended when clinically indicated. CT with intravenous contrast or a labeled leukocyte scan combined with a radionuclide bone scan can be considered when MRI is not possible. Wound care, glycemic control, and off-loading areas of biomechanical stress are essential.

KEY POINTS

- Diabetic foot infection is diagnosed when pus or two or more inflammatory signs (warmth, induration, erythema, pain, and tenderness) are present.
- HVC Uninfected diabetic foot wounds should not be cultured or treated with antibiotics.
- Deep-tissue culture (curettage or biopsy) is indicated before antibiotic therapy for moderate or severe infections and complicated mild infections (presence of pus or MRSA risk factors).
- Plain imaging is recommended for all patients with new diabetic foot infections; additional imaging with ultrasonography or MRI is recommended when abscess or bone involvement is suspected.

Toxic Shock Syndrome

S. aureus- and *S. pyogenes*-associated exotoxins result in cytokine production that can result in toxic shock syndrome (TSS) (**Table 9** and **Table 10**). Staphylococcal TSS is associated with tampon use, nasal packings, surgical wounds, skin ulcers,

TABLE 9. Diagnostic Criteria for Staphylococcal Toxic Shock Syndrome[a]

Fever >38.9 °C (102.0 °F)
Systolic blood pressure <90 mm Hg
Diffuse macular rash with subsequent desquamation, especially on palms and soles
Involvement of three or more of the following organ systems:
Gastrointestinal (nausea, vomiting, diarrhea)
Muscular (severe myalgia or fivefold or greater increase in serum creatine kinase level)
Mucous membrane (hyperemia of the vagina, conjunctivae, or pharynx)
Kidney (blood urea nitrogen or serum creatinine level at least twice the upper limit of normal)
Liver (bilirubin, aspartate aminotransferase, or alanine aminotransferase concentration twice the upper limit of normal)
Blood (platelet count <100,000/µL [100×10^9/L])
Central nervous system (disorientation without focal neurologic signs)
Negative results on serologic testing for Rocky Mountain spotted fever, leptospirosis, and measles; negative cerebrospinal fluid cultures for organisms other than *Staphylococcus aureus*

[a]Diagnosis is considered confirmed when fever, hypotension, and rash with involvement of three or more organ systems listed and negative serologic and cerebrospinal fluid results listed are all present.

Adapted with permission from Moreillon P, Que YA, Glauser MP. *Staphylococcus aureus*. In: Mandell GL, Dolin R, Bennett JE, eds. Principles and practice of infectious disease. 6th ed. Philadelphia, PA: Churchill Livingstone; 2005:2331. Copyright 2005, Elsevier.

TABLE 10. Diagnostic Criteria for Streptococcal Toxic Shock Syndrome[a]

Definite case
Isolation of GABHS from a sterile site (blood, cerebrospinal fluid, operative wound)
Probable case
Isolation of GABHS from a nonsterile site (throat, vagina, skin lesion)
Hypotension (systolic pressure ≤90 mm Hg)
The presence of ≥2 of the following findings:
Kidney (acute kidney injury or failure)
Liver (elevated aminotransferase concentrations)
Skin (erythematous macular rash, soft tissue necrosis)
Blood (coagulopathy, including thrombocytopenia and disseminated intravascular coagulation)
Pulmonary (acute respiratory distress syndrome)

GABHS = group A β-hemolytic streptococci.

[a]A definite case is defined by the isolation of GABHS from a sterile site; hypotension with systolic blood pressure ≤90 mm Hg; plus the presence of two or more of the clinical findings listed.

H CONT.

burns, catheters, and injection drug use. Streptococcal TSS is associated with skin and soft tissue infection, particularly NF. Bacteremia and mortality rates are higher with streptococcal than staphylococcal TSS. Source control typically requires surgical debridement. Antibiotics for streptococcal TSS consist of penicillin plus clindamycin, the latter added to eradicate the high inoculum of bacteria present and to suppress toxin production. If methicillin-susceptible *S. aureus* is the cause, nafcillin and clindamycin are recommended; for MRSA, vancomycin plus clindamycin or linezolid monotherapy is preferred. More studies are needed to establish the exact role of intravenous immune globulin in this setting, and it is not recommended in the most recent guidelines by the Infectious Diseases Society of America. H

KEY POINTS

- Source control for toxic shock syndrome typically requires surgical debridement.
- Streptococcal toxic shock syndrome is treated with penicillin and clindamycin.
- Infection with methicillin-susceptible *Staphylococcus aureus* is treated with nafcillin and clindamycin; linezolid monotherapy or vancomycin plus clindamycin is preferred for infection with methicillin-resistant *S. aureus*.

Community-Acquired Pneumonia

H Epidemiology

Community-acquired pneumonia (CAP) is a leading cause of infection and hospitalization in the United States, associated with more than $10 billion annually in health care expenditures. The spectrum of illness due to CAP ranges from mild disease, with approximately 50% of patients managed in the ambulatory setting, to fatal infections. Rates of hospitalization increase with advanced age; the incidence of hospitalization for CAP among adults 80 years or older is 25 times higher than in adults younger than 50 years.

The definition of CAP has recently expanded to include some patients previously categorized as having health care–associated pneumonia (HCAP). This change was made because the microbiology and treatment of patients with CAP in long-term care facilities or who were hospitalized in the preceding 3 months do not differ substantially from that of community-dwelling patients with similar comorbidities. Practically, elimination of the HCAP classification simplifies treatment and has antibiotic stewardship implications, leading to a decrease in the use of unnecessarily broad antibiotics. Differentiating CAP from true hospital-acquired pneumonia (HAP) remains clinically meaningful (see Health Care–Associated Infections for HAP discussion).

Microbiology

CAP is usually caused by infection with a viral or bacterial pathogen; fungal or mycobacterial infections occur much less frequently. The probability of infection with a specific organism varies based on age, comorbidities, seasonality, and geography. Epidemiologic risk factors or conditions associated with specific pathogens are listed in **Table 11**. Because causative organisms have variable virulence, severity of illness, which influences site of care, is used to guide empiric antibiotic therapy (**Table 12**).

Streptococcus pneumoniae, previously considered the leading cause of CAP, accounts for only 5% to 15% of hospitalized cases in recent studies. This decrease in incidence at least partially results from the success of vaccination strategies. Conversely, rates of CAP caused by *Staphylococcus aureus* and Enterobacteriaceae are rising, even among patients without identifiable health care exposure. The CDC-EPIC trial, a recent multicenter study that performed prospective microbiologic and molecular testing on patients hospitalized with CAP, more frequently identified a single or multiple viruses rather than a bacterial pathogen in CAP infections requiring hospitalization (**Figure 4**). *S. pneumoniae* was the most common bacterial cause, although rhinovirus (9%) and influenza virus (6%) were higher in incidence. The significance of viral detection in CAP is unclear; an antecedent mild respiratory viral infection may increase the risk for a secondary bacterial infection. This phenomenon is well documented for postinfluenza CAP caused by *S. aureus*, *S. pneumoniae*, and *Streptococcus pyogenes*. Despite extensive laboratory investigation, no causative organism was identified in 62% of patients in the CDC-EPIC trial.

Atypical pneumonia refers to CAP caused by organisms not cultivatable on standard bacterial media, including viruses and fastidious bacteria such as *Legionella* species, *Mycoplasma*

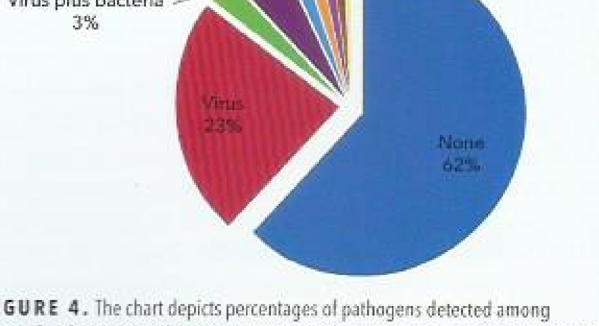

FIGURE 4. The chart depicts percentages of pathogens detected among hospitalized patients with community-acquired pneumonia in the CDC-EPIC Study.

Data from Jain S, Self WH, Wunderink RG, et al. Community-acquired pneumonia requiring hospitalization among U.S. adults. N Engl J Med. 2015;373:415-27.

TABLE 11. Risk Factors for Pathogens Causing Community-Acquired Pneumonia

Risk Factor	Common Pathogens
Heavy alcohol use	*Streptococcus pneumoniae*, oral flora (aspiration), *Klebsiella pneumoniae*
COPD	*Haemophilus influenzae*, *S. pneumoniae*, *Moraxella catarrhalis*, *Legionella pneumophila*, *Pseudomonas aeruginosa*
Structural lung disease (bronchiectasis, cystic fibrosis)	*P. aeruginosa*, *Burkholderia cepacia*, *Stenotrophomonas maltophilia*, *Staphylococcus aureus*
Aspiration (seizures, neurologic impairment, loss of consciousness)	Oral anaerobes, Enterobacteriaceae
Age >65 years	Influenza virus, *S. pneumoniae*, rhinovirus
Post-viral illness	*S. aureus*, *Streptococcus pyogenes*, *S. pneumoniae*
Animal exposure	
Birds	*Chlamydophila psittaci*, *Histoplasma capsulatum*, *Cryptococcus neoformans*
Dogs	*Bordetella bronchiseptica*
Cats	*Pasteurella multocida*
Farm animals or domesticated pregnant animals	*Coxiella burnetii*, *Brucella* species
Horses	*Rhodococcus equi*
Rodent droppings	Hantavirus
Rabbits	*Francisella tularensis*
Hot tub exposure	*Legionella pneumoniae*, atypical mycobacteria (causing a hypersensitivity pneumonitis)
Geographic	
Eastern United States	*Histoplasma capsulatum*, *Blastomyces dermatitidis*
Southwest United States	Coccidioides
Southeast Asia	*Burkholderia pseudomallei*, SARS, avian influenza
Middle East	MERS
Late fall, winter, early spring (Western hemisphere)	Influenza virus, parainfluenza virus, rhinovirus

MERS = Middle East respiratory syndrome; SARS = severe acute respiratory syndrome.

pneumoniae, and *Chlamydophila pneumoniae*. Respiratory viruses account for nearly all viral pneumonia infections, but less common pathogens include varicella-zoster virus or Hantavirus. *Legionella pneumophila* is a recognized cause of CAP requiring hospitalization or ICU admission. Legionellosis is associated with water exposure, including hot tubs and air conditioning units; however, infection may occur without an obvious source. A history of travel has been reported in approximately 10% of *Legionella* cases reported to the CDC.

CAP caused by anaerobic bacteria is uncommon, is primarily seen with aspiration, and is caused by microaerophilic oropharyngeal flora. Risk factors for aspiration pneumonia include decreased consciousness (alcohol or illicit substance use, seizures, stroke), poor dentition, gastroesophageal reflux, and vomiting. Zoonotic causes of CAP include *Coxiella burnetii* and *Francisella tularensis*. Mycobacterial or fungal causes of CAP should be considered in patients with immunocompromising conditions, epidemiologic risk factors for infection (such as incarceration, certain hobbies or occupations, and pertinent regional or foreign travel), or subacute presentations and in those who do not respond to conventional antibacterial treatment. H

KEY POINTS

- The definition of community-acquired pneumonia (CAP) has recently expanded to include some patients previously categorized as having health care–associated pneumonia because the microbiology and treatment of patients with CAP in long-term care facilities or who were hospitalized in the preceding 3 months do not differ substantially from that of community-dwelling patients with similar comorbidities.
- *Streptococcus pneumoniae* accounts for only 5% to 15% of community-acquired pneumonia (CAP) infections requiring hospitalization, whereas rates of CAP caused by *Staphylococcus aureus* and Enterobacteriaceae are rising, even among patients without identifiable health care exposure.
- The significance of viral detection in community-acquired pneumonia is unclear; however, an antecedent mild respiratory viral infection may increase the risk for a secondary bacterial infection.

TABLE 12. IDSA/ATS Recommendations for Empiric Antibiotics in Community-Acquired Pneumonia

Site of Treatment	Patient or Epidemiologic Considerations	Most Common Organisms	Regimens(s)
Outpatient	Healthy patient without antibiotics in preceding 3 months	*Streptococcus pneumoniae* *Mycoplasma* *Chlamydophila* Respiratory viruses	Macrolide OR Doxycycline
	Healthy patient from region with >25% macrolide resistance among *S. pneumoniae*	Same as above	Respiratory quinolone OR β-lactam plus a macrolide
	Comorbidities[a] or antibiotic use in preceding 3 months	Same as inpatient, non-ICU	Respiratory quinolone OR β-lactam plus a macrolide
Inpatient, non-ICU		*S. pneumoniae* *Mycoplasma* *Chlamydophila* *Haemophilus influenzae* *Legionella* Oral anaerobes Respiratory viruses	β-lactam plus a macrolide OR Respiratory quinolone
ICU treatment		*S. pneumoniae* *Staphylococcus aureus* *H. influenzae* *Legionella* Gram-negative bacilli	Parenteral β-lactam plus either azithromycin or a respiratory quinolone OR If penicillin allergic, a respiratory quinolone plus aztreonam
Any	Risk factor for *Pseudomonas* (see text)		Antipseudomonal β-lactam plus an antipseudomonal quinolone OR If penicillin allergic, a respiratory quinolone plus aztreonam
Any	Risk factor for CA-MRSA (see text)		Standard therapy PLUS vancomycin OR linezolid

CA-MRSA = community-acquired methicillin-resistant *Staphylococcus aureus*.

[a]Comorbidities include chronic heart, lung, liver, or kidney disease; diabetes mellitus; alcoholism; asplenia; malignancies; and immunosuppression.

Adapted with permission from Mandell LA, Wunderink RG, Anzueto A, Bartlett JG, Campbell GD, Dean NC, Dowell SF, File TM Jr, Musher DM, Niederman MS, Torres A, Whitney CG; Infectious Diseases Society of America; American Thoracic Society. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis. 2007 Mar 1;44 Suppl 2:S27-72. [PMID: 17278083]

H Diagnostic Evaluation

CAP should be suspected and chest imaging performed in any patient presenting with fever associated with cough, dyspnea, or chest pain. Symptoms may be subtle or absent in older adults or immunosuppressed patients, and clinicians should maintain a low threshold for pursuing radiographic studies in these populations. Posteroanterior and lateral chest radiography is recommended. In addition to confirming the diagnosis, radiographic patterns may provide clues to particular pathogens (**Table 13**) and guide clinical decisions regarding appropriate site of care. When plain radiographs are normal but suspicion for CAP remains high, chest radiography may be repeated after 24 hours; for patients at high risk (febrile neutropenia, risk for anthrax, or acute respiratory distress syndrome requiring intervention) with normal radiographs, chest CT should be pursued.

Routine laboratory studies are indicated to ascertain the severity of infection, determine the optimal site of care, and ensure appropriate antimicrobial dosing. HIV testing should

TABLE 13. Radiographic Patterns Associated with Specific Causes of Community-Acquired Pneumonia

Radiographic Appearance	Common Pathogens
Lobar pneumonia	*Streptococcus pneumoniae*
Right lower lobe pneumonia	Oral anaerobes (aspiration)
Lung abscess/ cavitary lesion	Oral anaerobes, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Nocardia*, *Actinomyces*, *Rhodococcus*, mycobacteria, endemic fungi
Interstitial infiltrate	Atypical pathogens (*Legionella*, *Mycoplasma*, *Chlamydophila*), viruses
Pleural effusion/ empyema	Oral anaerobes, anginosus-constellatus group streptococci, *S. aureus*, *S. pneumoniae*

be performed if indicated; a positive result expands the spectrum of potentially causative organisms. Procalcitonin level, if available as a point-of-care test, is insufficiently sensitive or specific to independently diagnosis CAP or a microbiologic cause but may support a diagnosis along with other clinical findings. Rapid testing for influenza virus may assist in identifying patients who would benefit from oseltamivir and who require droplet precautions at hospital admission, but a positive test result does not exclude a concomitant bacterial pathogen.

Diagnostic studies to identify a causative organism are not routinely indicated in outpatients with CAP but should be considered in non-ICU hospitalized patients when this information would change therapy or allow treatment de-escalation. All patients with CAP who require admission to the ICU should undergo diagnostic evaluation in an attempt to confirm a microbial cause. Interpretation of sputum Gram stain and culture is hampered by the presence of oropharyngeal colonization, and growth may reflect nonpathogenic organisms. A good-quality sputum culture obtained before antibiotic initiation is suggestive or diagnostic in up to 80% of cases of pneumococcal pneumonia; sensitivity decreases after antibiotic therapy. Sputum Gram stain and culture are appropriate for patients admitted to the ICU, patients who did not respond to outpatient antibiotic therapy, patients with cavitary lung lesions, and patients with underlying structural lung disease. In these cases, consideration for mycobacterial or fungal causes may be necessary.

Blood culture results are positive in 20% to 25% of patients with pneumococcal pneumonia; fewer culture results are positive in patients with other bacterial causes. Pneumococcal urinary antigen testing is more than 70% sensitive, and results are not affected by antibiotic administration. *Legionella* urinary antigen test results are positive in most patients with *L. pneumophila* serotype 1 infection. However, the test does not detect other strains, and results can remain positive for prolonged periods after infection. Rapid antigen testing for influenza virus on nasal swabs offers the advantage of point-of-care diagnosis but is less sensitive than polymerase chain reaction–based techniques. Respiratory viral panel results using nucleic acid amplification are positive in up to 40% of patients hospitalized with CAP; however, a positive result may reflect viral coinfection or antecedent predisposing infection rather than current clinical illness. Although these panels are less helpful in guiding decisions about discontinuing antibiotic therapy, a positive respiratory viral panel might have significant infection control implications among patients admitted to the hospital.

Additional testing is indicated only in select patients based on epidemiologic risk factors (see Table 11), clinical findings, or radiographic patterns (see Table 13). Fungal and acid-fast bacilli stains of sputum or fungal antigen testing can be performed. Serology for *Coxiella burnetii*, *Francisella tularensis*, *Legionella*, *Mycoplasma*, and *Chlamydophila*, using acute and convalescent sera, can document seroconversion or a fourfold increase in titers.

Patients with pleural effusions of unknown cause or those thicker than 1 cm should undergo thoracentesis to exclude concomitant empyema requiring drainage (see MKSAP 18 Pulmonary and Critical Care Medicine). Bronchoscopy with transbronchial biopsy should be considered in patients with an unrevealing noninvasive evaluation who do not respond to empiric therapy. H

KEY POINTS

- Diagnostic studies to identify a causative organism are not routinely indicated in outpatients with community-acquired pneumonia (CAP) but should be considered in non-ICU hospitalized patients when this information would change management; diagnostic studies should be performed in all patients admitted to the ICU with CAP. HVC
- For patients with pneumococcal pneumonia, a good-quality sputum culture obtained before antibiotic initiation is suggestive or diagnostic in up to 80% of cases; blood culture results are positive in 20% to 25% of cases; pneumococcal urinary antigen testing is more than 70% sensitive, and results are not affected by antibiotic administration.
- *Legionella* urinary antigen test results are positive in most patients with *L. pneumophila* serotype 1 infection, but it does not detect other strains, and results can remain positive for prolonged periods after infection.

Management

Site of Care

H

Ambulatory management is adequate for many patients with CAP. Multiple clinical prediction models are available to identify patients who would most benefit from hospital or ICU admission (**Table 14**), but complexity and lack of consensus limit their use. Although prediction rules may aid in

TABLE 14. Community-Acquired Pneumonia Clinical Decision Support Scoring Systems for Site of Care

Variable	PSI[a]	CURB-65[b]	IDSA/ATS Criteria[c]
Age	>50 years	≥65 years	
Comorbidities	Malignancy		
	Congestive heart failure		
	Cerebrovascular disease		
	Kidney disease		
	Liver disease		
Vital signs	Heart rate ≥125/min		
	Respiration rate ≥30/min	Respiration rate ≥30/min	Respiration rate ≥30/min
	Temperature <35 °C (95 °F) or ≥40 °C (104 °F)		Temperature <36 °C (96.8 °F)
	SBP <90 mm Hg	SBP <90 mm Hg or DBP ≤60 mm Hg	Hypotension requiring aggressive fluid resuscitation
Physical examination	Altered mentation	Confusion	Confusion or disorientation
Laboratory findings		BUN >20 mg/dL (7.1 mmol/L)	BUN ≥20 mg/dL (≥7.1 mmol/L)
			Leukocyte count <4000/µL (4×10^9/L)
			Platelet count <100,000/µL (100×10^9/L)
			Po_2/Fio_2 ratio ≤250
Radiographic findings			Multilobar infiltrate

ATS = American Thoracic Society; BUN = blood urea nitrogen; CURB = Confusion, Urea, Respiration rate, Blood pressure; DBP = diastolic blood pressure; IDSA = Infectious Diseases Society of America; PSI = Pneumonia Severity Index; SBP = systolic blood pressure.

[a]PSI Step 1 Screen: If no factors are present, patient is assigned risk class I and can likely be managed as an outpatient. Patients with at least one risk factor are stratified by a more complex Step 2 scale (not shown) into risk class II-V.

[b]CURB-65 Score: Each variable present is assigned one point. Patients with a cumulative score of 0-1 are usually appropriate for outpatient treatment.

[c]IDSA/ATS ICU admission scale: Patients with a major criterion (either need for mechanical ventilation or septic shock requiring vasopressors) or ≥3 of the minor criteria are best managed in the ICU.

H CONT.

site-of-care decisions, scores should not supersede clinical judgment.

The Pneumonia Severity Index (PSI) is a validated predictor of all-cause mortality at 30 days. The initial assessment determines the presence of 11 variables associated with adverse outcomes (see Table 14). Patients with no risk factors (severity risk class I) can typically be managed as outpatients. Those with at least one risk factor are stratified using a second scoring system into a risk classification between II and V based on a more complex point system that includes residence in a nursing home, abnormal laboratory test results, and radiographic findings.

The CURB-65 (Confusion, blood Urea nitrogen [BUN], Respiratory rate, Blood pressure, and age ≥65 years) score is a simplified, albeit slightly less predictive, tool for identifying patients at low risk. Thirty-day mortality among patients with a CURB-65 score of 0 or 1 was less than 3%, so ambulatory treatment is appropriate for most patients with scores less than 2. The modified CRB-65 omits BUN measurement and supports ambulatory clinical assessment; patients with a score of 1 or more warrant consideration for hospitalization.

Consensus guidelines by the Infectious Diseases Society of America and American Thoracic Society (IDSA/ATS) provide criteria to identify patients best managed in the ICU. The need for mechanical ventilation or vasopressor support to maintain blood pressure was considered a major criterion and mandated ICU admission. Minor criteria are listed in Table 14; the presence of three or more criteria suggests a higher mortality rate and necessitates ICU admission. H

KEY POINT

- A clinical prediction model (the Pneumonia Severity Index, CURB-65 or CRB-65, or Infectious Diseases Society of America/American Thoracic Society criteria) can be used to identify patients with community-acquired pneumonia who may require hospital or ICU admission.

Antimicrobial Therapy

IDSA/ATS guidelines for CAP treatment balance the need to effectively treat infection, often in the absence of an identified pathogen, with the competing imperative for judicious antibiotic use. Treatment recommendations are stratified by site of

care (see Table 12). Since publication of these guidelines, studies have documented the changing microbiology of CAP in the United States and questioned the importance of empiric treatment for atypical bacteria. Updated CAP guidelines, which are scheduled to be published in 2018, are anticipated to address these issues.

Ambulatory empiric therapy for CAP is directed against *S. pneumoniae*, *Haemophilus influenzae*, and atypical bacteria, even though a significant proportion of patients with CAP infected with viral pathogens do not benefit from antibiotic therapy. In otherwise healthy patients, regimens include monotherapy with doxycycline or a macrolide (either azithromycin or clarithromycin). If local *S. pneumoniae* macrolide resistance is greater than 25%, a β-lactam plus a macrolide or a respiratory quinolone could be used instead. Respiratory quinolones include levofloxacin and moxifloxacin, which are active against *S. pneumoniae*; ciprofloxacin is not a respiratory quinolone because its activity against streptococcal species is limited.

For patients with significant comorbidities treated as outpatients, a respiratory quinolone or a β-lactam plus a macrolide is recommended. Options for oral β-lactams include high-dose amoxicillin; a second-generation cephalosporin is an alternative for patients allergic to penicillin. The risk of infection with drug-resistant *S. pneumoniae* is increased with antibiotic use in the preceding 3 months; these patients should be treated similarly to outpatients with comorbidities using an agent from a different class. Macrolides and quinolones may rarely induce fatal arrhythmias, and care should be used when these antibiotics are prescribed in conjunction with other medications that prolong the QTc interval. When macrolides and quinolones are contraindicated, doxycycline can be substituted for a macrolide and given in conjunction with a β-lactam.

H

Patients with more severe infections requiring hospitalization may be infected with a broader spectrum of bacterial pathogens, reflecting host susceptibility and organism virulence. Patients with CAP who warrant non-ICU hospital admission are most commonly infected with the organisms shown in Figure 1. Recommended empiric regimens include a parenteral β-lactam agent (a third-generation cephalosporin or ampicillin-sulbactam) plus a macrolide or a respiratory fluoroquinolone. Use of ampicillin-sulbactam or other penicillin-based antibiotics offers the advantage of increased anaerobic spectrum and should be considered when aspiration pneumonia is a concern. For patients allergic to β-lactams or those treated with a component of this regimen in the preceding 3 months, monotherapy with a respiratory quinolone is appropriate.

An area of controversy is whether empiric therapy for atypical bacterial infection confers an outcome advantage among hospitalized patients with CAP who do not require ICU care. The CAP-START study, a randomized controlled trial published in 2015, evaluated the two currently recommended regimens (a β-lactam plus a macrolide or a respiratory quinolone) compared with β-lactam monotherapy in this population and found no significant difference in outcomes among the three groups. This result was not replicated in a second randomized trial or in several observational studies that found excess mortality associated with β-lactam monotherapy compared with standard therapy. Furthermore, several studies have shown a survival benefit for patients with bacteremic CAP caused by *S. pneumoniae* treated with combination β-lactam plus macrolide therapy; whether this benefit reflects a direct antimicrobial effect or the anti-inflammatory properties of azithromycin is uncertain.

The microbiology among patients with CAP requiring ICU care is shown in Table 12. In this population, monotherapy with a respiratory quinolone is contraindicated. Suggested regimens include coadministration of a parenteral β-lactam active against *S. pneumoniae* and a second agent active against *Legionella* species (either azithromycin or a quinolone). For patients with a history of immediate hypersensitivity reaction to β-lactam antibiotics, aztreonam, which is purely active against gram-negative bacteria, is an acceptable alternative if given with a respiratory quinolone to treat *S. pneumoniae* and atypical organisms.

Methicillin-resistant *S. aureus* (MRSA) is not adequately treated by the previously discussed empiric regimens, yet is increasingly recognized as causing CAP, particularly in critically ill patients. CAP caused by MRSA is associated with preceding influenza infection and injection drug use, although it may present in patients without any identifiable risk factors. Empiric therapy for MRSA should be considered in patients with one of these risk factors, a suspicious Gram stain (gram-positive cocci in clusters), conventional therapy failure, pleural-based lung nodules (suggesting septic pulmonary emboli), or cavitary lung lesions. Optimal treatment for MRSA CAP has not been defined, but options include vancomycin, linezolid, and ceftaroline. Notably, daptomycin binds to surfactant, resulting in negligible alveolar levels, and is therefore not effective in pulmonary infections.

Pseudomonas aeruginosa, a significant cause of HAP, can also cause CAP and is not adequately treated by standard empiric regimens. *Pseudomonas* should be considered in immunocompromised patients and in patients with underlying structural lung disease (bronchiectasis or cystic fibrosis) or medical conditions requiring repeated courses of antibiotics. When clinical concern for *Pseudomonas* is present, initial empiric therapy with two active agents is indicated. Options include an antipseudomonal β-lactam (piperacillin-tazobactam, cefepime, or meropenem) in conjunction with either a quinolone (levofloxacin or ciprofloxacin) or an aminoglycoside. If an aminoglycoside is chosen, a macrolide should be added for empiric coverage of atypical bacteria. Moxifloxacin, a respiratory quinolone with activity against *S. pneumoniae*, is relatively ineffective against *Pseudomonas* and should not be used for treatment when *Pseudomonas* is a concern. Inclusion of a quinolone in the empiric regimen is relatively contraindicated in patients who did not respond to previous courses of this drug.

Controversy exists over optimal management of hospitalized patients with CAP and a positive rapid viral test result.

H CONT.

Although respiratory viruses may cause severe CAP, a viral cause does not exclude a bacterial coinfection. *S. aureus*, *S. pneumoniae*, and *Streptococcus pyogenes* have all been associated with postinfluenza necrotizing CAP. Therefore, many authorities recommend continuing antibiotics for CAP even when a viral pathogen is identified.

For patients with uncomplicated CAP who demonstrate rapid defervescence and clinical improvement over the first 3 days, a 5-day course of therapy is adequate for cure. Exceptions include patients with cavitary disease or lung abscess, empyema, concomitant bacteremia, extrapulmonary infection, or ongoing instability, defined as persistent fever, abnormal vital signs, or hypoxia. Many authorities also recommend prolonged duration of antibiotics (at least 14 days) for CAP caused by *S. aureus* or Enterobacteriaceae; fungal or mycobacterial lung infections may require a more prolonged course of treatment. H

KEY POINTS

- Ambulatory empiric therapy for community-acquired pneumonia in otherwise healthy patients includes monotherapy with doxycycline or a macrolide (either azithromycin or clarithromycin); if local *Streptococcus pneumoniae* macrolide resistance is greater than 25%, a β-lactam plus a macrolide or a respiratory quinolone could be used instead.
- Recommended empiric regimens for hospitalized non-ICU patients include a parenteral β-lactam agent (a third-generation cephalosporin or ampicillin-sulbactam) plus a macrolide; for patients allergic to β-lactams or those treated with a component of this regimen in the preceding 3 months, monotherapy with a respiratory quinolone is appropriate.

(Continued)

KEY POINTS *(continued)*

- Treatment regimens for patients with community-acquired pneumonia requiring ICU care include coadministration of a parenteral β-lactam active against *Streptococcus pneumoniae* and a second agent active against *Legionella* species.

Complications

H

CAP has a mortality rate of 10% to 12% among hospitalized patients. Survivors may experience significant morbidity, including prolonged hospitalization, protracted convalescence, and high rates of hospital readmission. Related complications include localized lung inflammation, secondary spread of infection, and toxicity related to treatment (**Table 15**).

Lack of response to antimicrobials raises consideration of a resistant or atypical organism, loculated infection (such as empyema), or an infection mimic (tumor, vasculitis, pulmonary embolism). Patients with significant pleural fluid collections should undergo diagnostic thoracentesis; chest tube drainage is indicated for empyema.

Severe CAP is often associated with a vigorous immune response resulting in acute respiratory distress syndrome. A recent meta-analysis found that for patients hospitalized for CAP, glucocorticoid administration was associated with significantly reduced mortality, reduced mechanical ventilation needs, and shorter hospital stay. Whether this glucocorticoid benefit extends to all hospitalized patients with CAP or is restricted to a subset at highest risk for acute respiratory distress syndrome has not been established; therefore, adjunctive glucocorticoids should not be routinely administered to all patients with severe CAP. H

TABLE 15. Complications of Community-Acquired Pneumonia

Organ System	Syndrome	Comments
Pulmonary	Nonresolving pneumonia	Consider resistant infections, noninfectious causes
	Lung abscess	Prolonged course of antimicrobial treatment
	Empyema	Chest tube drainage of infected pleural fluid
	ARDS	Lung protective ventilation strategy indicated; glucocorticoids may decrease this complication
Neurologic	Delirium	May reflect hypoxemia, hypercarbia, or ICU stay
Hematologic	Leukopenia	May be related to sepsis, medication effect
	Thrombocytopenia	May be related to sepsis, medication effect
Cardiac	Acute coronary syndrome	Seen in 5%-10% of hospitalized patients
	Cardiac arrhythmias	Most commonly atrial fibrillation
Kidney	Acute kidney injury	May be related to hypoperfusion or medication effect
Endocrine	Adrenal insufficiency	Waterhouse-Friderichsen syndrome (acute adrenal necrosis), occurring in the setting of overwhelming bacterial infection/septic shock

ARDS = acute respiratory distress syndrome.

KEY POINTS

- Lack of response to antimicrobials in patients with community-acquired pneumonia raises consideration of a resistant or atypical organism, loculated infection, an infection mimic, or empyema.
- Patients hospitalized with community-acquired pneumonia experience significant morbidity and are at high risk for readmission.

Follow-up

For patients who do not require hospitalization, additional evaluation is only necessary in those who do not respond to empiric therapy within 3 days (of a standard 5-day course) or who develop new symptoms.

In contrast, readmission rates among hospitalized patients approach 20%. This population should have close outpatient follow-up to ensure clinical stability after therapy completion. Radiographic clearance often lags behind clinical response, so repeat imaging should be deferred at initial follow-up unless clinical improvement is slow or new symptoms have developed. Postobstructive pneumonia may be the presenting symptom of bronchial carcinoma, and repeat chest radiography in 2 to 3 months is recommended in patients at high risk (age >50 years or those with a significant smoking history) to document resolution.

KEY POINT

HVC • For patients who do not require hospitalization for community-acquired pneumonia, additional evaluation is only necessary in those who do not respond to empiric therapy within 3 days (of a 5-day course) or who develop new symptoms.

Tick-Borne Diseases

Lyme Disease

Lyme disease is the most common vector-borne infection in the United States. More than 30,000 new infections are reported annually, which likely represent only 10% of actual infections. More than 95% of infections in the United States occur in the northeastern, mid-Atlantic, and upper Midwest regions (**Figure 5**). These areas are endemic for the vector, *Ixodes scapularis* (the black-legged deer tick). The causative spirochete, *Borrelia burgdorferi*, is transmitted intradermally when a tick ingests a blood meal. In Europe, *Borrelia garinii* and *Borellia afzelii* cause Lyme disease, with *Ixodes ricinus* as the tick vector.

After a tick bite by *I. scapularis*, administration of a single dose (200 mg) of doxycycline may decrease the risk of subsequent Lyme disease development but should be considered only if (1) the tick is reliably identified as a black-legged deer tick; (2) attachment lasts 36 hours or longer; (3) antibiotics can be started less than 72 hours after tick removal; (4) prevalence of *B. burgdorferi* infection of ticks in the region exceeds 20%; and (5) doxycycline treatment is not contraindicated. Except for these selected situations, observation is recommended, with treatment given if suggestive symptoms occur.

FIGURE 5. Lyme disease cases reported during 2016. Each dot represents the county of residence (not necessarily acquisition) for a confirmed case.

Reprinted with permision from "Reported Cases of Lyme Disease—United States 2016" (Washington, D.C.: Department of Health and Human Services, 2016). https://www.cdc.gov/lyme/resources/reportedcasesoflyme disease_2016.pdf.

The clinical manifestations, diagnostic testing, and treatment of Lyme disease vary according to the stage of infection (**Table 16**).

Early Localized Disease

Early localized disease presents within 4 weeks of infection. Most infected persons (70% to 80%) develop erythema migrans (EM), an annular skin lesion that often presents with central clearing (**Figure 6**). Systemic symptoms are variably present.

EM lesions are typically painless, nonpruritic, and circumferentially enlarging. Atypical presentations of EM, with confluent erythroderma, ulceration, or vesiculation, may confound the diagnosis. Local cutaneous reactions due to hypersensitivity to tick saliva may resemble EM but tend to occur earlier, are pruritic, and do not enlarge significantly after onset.

A patient with EM and a compatible exposure history does not require confirmatory laboratory testing. In fact, antibody testing in early localized disease is insensitive because seroconversion may be delayed for several weeks after onset of an EM lesion. Treatment is with an oral agent. Doxycycline offers the advantage of treating incubating *Anaplasma phagocytophilum*, which also is spread by black-legged ticks and can coinfect patients with Lyme disease.

Early Disseminated Disease

In the absence of treatment, hematogenous dissemination occurs in up to 60% of patients. Symptoms of early disseminated disease present weeks to months after infection. The most common manifestation is a flu-like illness characterized by fevers, arthralgia, myalgia, and lymphadenopathy and often

TABLE 16. Clinical Manifestations, Diagnostic Testing, and Treatment of Lyme Disease by Stage of Infection

Lyme Stage	Onset after Infection	Clinical Findings	Laboratory Confirmation	Treatment[a]
Early localized	≤4 wk	EM at site of tick attachment, fever, lymphadenopathy, myalgia	Not needed if EM present	Doxycycline, 100 mg PO BID × 10-21 d (first-line therapy) *or* Amoxicillin, 500 mg PO TID × 14-21 d *or* Cefuroxime axetil, 500 mg PO BID × 14-21 d
Early disseminated	2 wk-6 mo	Multiple sites of EM, flu-like syndrome, heart block, myocarditis, facial nerve palsy, meningitis, radiculitis	Not needed if EM is present; otherwise, two-tier serologic testing CSF testing for intrathecal antibody production if CNS involvement is a concern	1. First-degree block with PR interval ≥300 msec, second- or third-degree AV nodal block, myocarditis: IV penicillin or IV ceftriaxone × 28 d 2. First-degree AV block with PR interval <300 msec: oral treatment same as for early localized disease × 14-28 d 3. Meningitis: IV penicillin or IV ceftriaxone × 28 d 4. Other manifestations (including facial palsy): oral treatment the same as for early localized disease × 14-28 d
Late disseminated	≥6 mo	Recurrent large joint arthritis; neurologic symptoms (peripheral neuropathy, encephalopathy), or dermatologic symptoms (acrodermatitis chronica atrophicans)	Two-tier serologic testing	Initial rheumatologic treatment: same as for early localized but × 30 d Recurrent arthritis after initial treatment: IV ceftriaxone Neurologic disease: IV ceftriaxone × 28 d

AV = atrioventricular; BID = twice daily; CSF = cerebrospinal fluid; CNS = central nervous system; EM = erythema migrans; IV = intravenous; PO = by mouth; TID = three times daily.

[a]Doses are for adults with normal kidney function.

FIGURE 6. Erythema migrans lesion at site of tick attachment.

Figure courtesy of Dr. Karen Bloch.

associated with multiple concurrent EM lesions at sites distant from the original tick attachment.

Infection of cardiac tissue results in injury to the conduction system and atrioventricular (AV) nodal block. Progression to complete heart block can occur rapidly despite antibiotic treatment, so hospitalization is indicated for close monitoring of patients with severe cardiac involvement: symptomatic patients with dizziness, syncope, or dyspnea; asymptomatic patients with first-degree AV block and a PR interval of 300 milliseconds or greater; and patients with a higher degree AV block. Permanent pacemaker placement is not necessary because the heart block is reversible.

Infection of neurologic tissue occurs in approximately 15% of untreated patients. Aseptic meningitis, facial palsy (unilateral or bilateral), and radiculopathy may be present in isolation or associated with skin, musculoskeletal, or cardiac findings. Lumbar puncture is indicated when central nervous system infection (such as neuroborreliosis) is suspected; cerebrospinal fluid lymphocytic pleocytosis supports the diagnosis (see Central Nervous System Infection).

When EM lesions are present, laboratory confirmation is unnecessary. In the absence of diagnostic skin findings, serologic diagnosis should be pursued through a two-tiered approach (**Figure 7**); the initial enzyme-linked immunosorbent assay (ELISA) is highly sensitive but lacks specificity and must be confirmed by a Western blot test. The C6 ELISA test detects antibody against a highly conserved bacterial epitope and may be more sensitive than traditional whole cell sonicate ELISA, especially for the

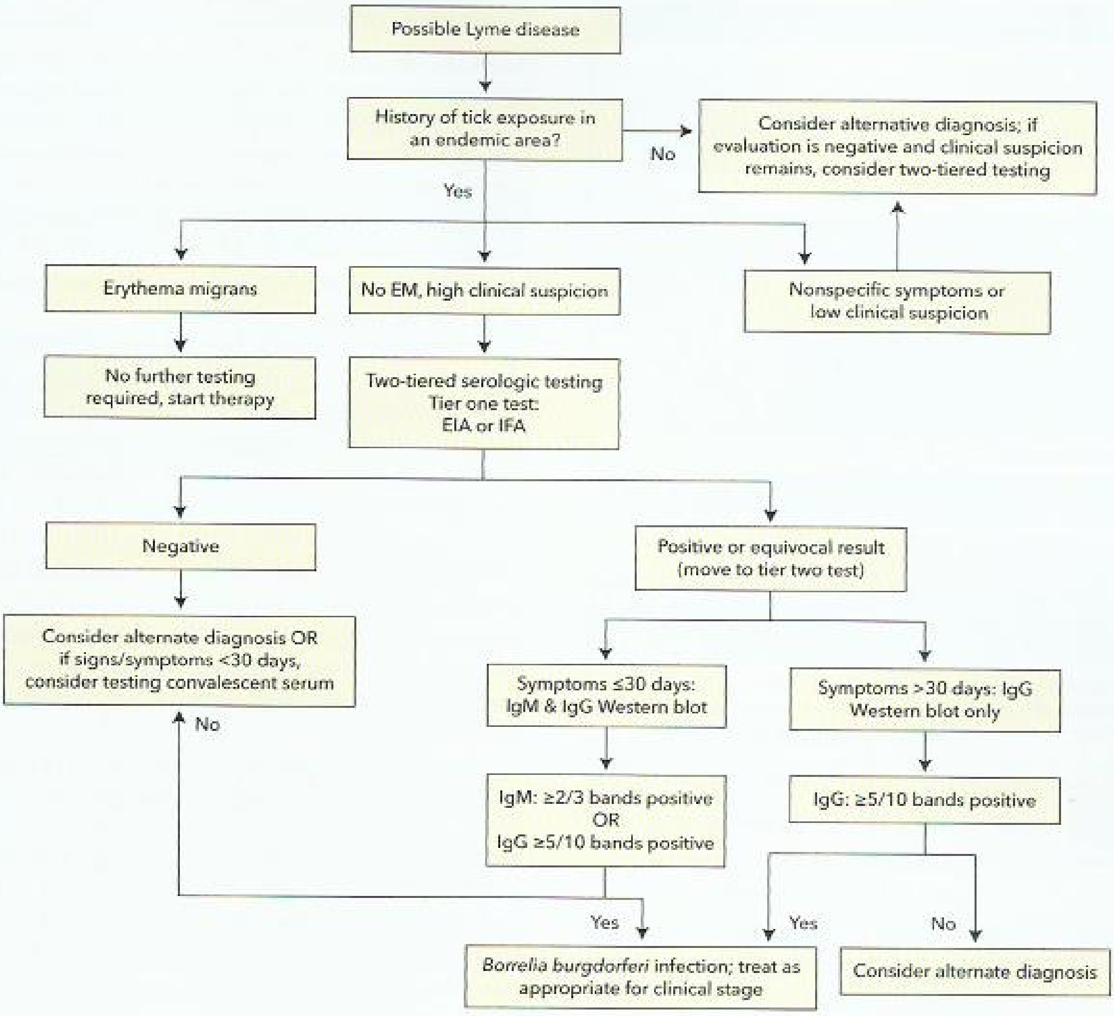

FIGURE 7. Serologic testing for Lyme disease. EIA = enzyme-linked immunosorbent assay; EM = erythema migrans; IFA = immunofluorescent antibody assay.

Adapted with permission from Moore A, Nelson C, Molins C, Mead P, Schriefer M. Current guidelines, common clinical pitfalls, and future directions for laboratory diagnosis of Lyme disease, United States. Emerg Infect Dis. 2016;22:1169. [PMID: 27314832] doi:10.3201/eid2207.151694

European strains *B. garinii* and *B. afzelii*, but, because of insufficient specificity, confirmatory Western blot testing is still required.

IgM antibody is detectable before IgG antibody in early infection; however, IgG antibody should be detectable after 30 days of symptoms. Because isolated IgM positivity is likely to be a false positive after the first month of symptoms, testing for IgM is not recommended after this time period. Antibodies may remain for years despite treatment; therefore, serial titers are not useful.

Late Disseminated Disease

Approximately 60% of untreated patients with Lyme disease develop a monoarticular or oligoarticular inflammatory arthritis as a late complication. The knee and other large joints are disproportionally affected. Even without antibiotic treatment, inflammation typically resolves over weeks to months but can have a relapsing remitting pattern. In approximately 10% of untreated patients, arthritis persists (see MKSAP 18 Rheumatology). Late neurologic or skin findings (acrodermatitis chronica atrophicans and borrelial lymphocytoma) are rare in the United States but more frequent in European infections. Diagnosis is made with the two-tier serologic test. Treatment requires prolonged oral antibiotics; parenteral therapy is used when oral therapy is unsuccessful (see Table 16).

Post-Lyme Disease Syndrome

Post-Lyme disease syndrome has been reported in approximately 10% of patients after treatment of EM (**Table 17**). Although often erroneously called "chronic Lyme disease," studies have found no microbiologic evidence of chronic or latent infection after appropriate treatment. Symptoms include fatigue, arthralgia, myalgia, and impairment of memory or cognition that can last for years after treatment of the acute infection. Clinical trials have shown no benefit of prolonged antibiotic treatment for post-Lyme disease syndrome.

TABLE 17. Definition of Post-Lyme Disease Syndrome
Inclusion Criteria
Diagnosis of Lyme disease based on CDC case criteria (EM or positive serologic finding)
Resolution or stabilization of the objective manifestations of Lyme disease after standard treatment
Onset of at least one of the following within 6 months of Lyme disease diagnosis, with persistence for at least 6 months after antibiotic treatment, that is of sufficient severity to result in decreased level of functioning:
1. Fatigue
2. Widespread musculoskeletal pain
3. Cognitive impairment
Exclusion Criteria
An untreated tick-borne coinfection (such as babesiosis)
Ongoing symptoms attributable to Lyme disease (such as antibiotic-refractory Lyme arthritis)
Symptoms of fatigue or musculoskeletal pains or a diagnosis of fibromyalgia or chronic fatigue syndrome predating the onset of Lyme disease
An alternative diagnosis accounting for the symptoms

CDC = Centers for Disease Control and Prevention; EM = erythema migrans.

Source: Wormser GP, Dattwyler RJ, Shapiro ED, Halperin JJ, Steere AC, Klempner MS, et al. The clinical assessment, treatment, and prevention of Lyme disease, human granulocytic anaplasmosis, and babesiosis: clinical practice guidelines by the Infectious Diseases Society of America. Clin Infect Dis. 2006;43:1089-134. [PMID: 17029130]

Evaluation for coinfection with another tick-borne pathogen or for a noninfectious cause is indicated; when no alternative diagnosis is found, treatment is symptomatic.

KEY POINTS

- The causative spirochete of Lyme disease may be transmitted when an infected *Ixodes scapularis* tick attaches for at least 36 hours.
- HVC Early localized Lyme disease usually presents within 4 weeks of infection and is characterized by erythema migrans (EM) at the site of tick attachment; patients with EM and a compatible exposure history do not require confirmatory laboratory testing and should receive oral antibiotic therapy.
- Early disseminated Lyme disease can affect the cardiovascular and neurologic systems; the diagnosis should be confirmed through an enzyme-linked immunosorbent assay followed by confirmatory Western blot testing, with presumptive treatment depending on disease severity.
- Post-Lyme disease syndrome (fatigue, arthralgia, myalgia, and impairment of memory or cognition) can last for years, even after treatment of the acute infection; there is no role for prolonged antibiotics for this condition.

Babesiosis

Babesiosis is caused by the intraerythrocytic protozoan *Babesia microti*, which is spread by the black-legged deer tick. Because of the common vector, babesiosis occurs in areas of Lyme endemicity (see Figure 5), most frequently during summer months. In Europe, babesiosis is caused by several different *Babesia* species and is spread by the *I. ricinus* tick. Transfusion of infected blood products and rare congenital transmission also allows for year-round infection, which may occur outside endemic regions.

Clinical findings range from asymptomatic presentations (approximately 20%) to fatal disease (10%). Risk factors for severe disease include age older than 50 years, immunocompromise, or asplenia. Symptoms begin within 1 month after tick bite and within 6 months after transfusion of infected blood products. Symptoms are nonspecific and include fever (89%), fatigue (82%), chills (67%), headache (47%), myalgia (43%), and cough (28%). Physical examination may reveal jaundice, hepatomegaly, and splenomegaly, which rarely progresses to splenic rupture. The hallmark of babesiosis is hemolysis, with anemia almost invariably present. With severe disease, thrombocytopenia, elevated liver enzyme levels, and acute kidney injury are possible.

Babesiosis is diagnosed by visualization of the causative organism on thin blood smears, manifesting as intraerythrocytic ring forms similar to those seen in malaria or as tetrads resembling a Maltese cross (**Figure 8**). With low-level parasitemia, multiple smears may need to be examined, and the sensitivity of microscopy is low. Therefore, polymerase chain reaction or serology should be pursued if smear findings are negative but clinical suspicion of babesiosis is high.

Treatment depends on disease severity (**Table 18**). After treatment, patients should be monitored closely for relapse; if relapse occurs, prolonged therapy extending more than 2 weeks after clearance of parasitemia is necessary for cure.

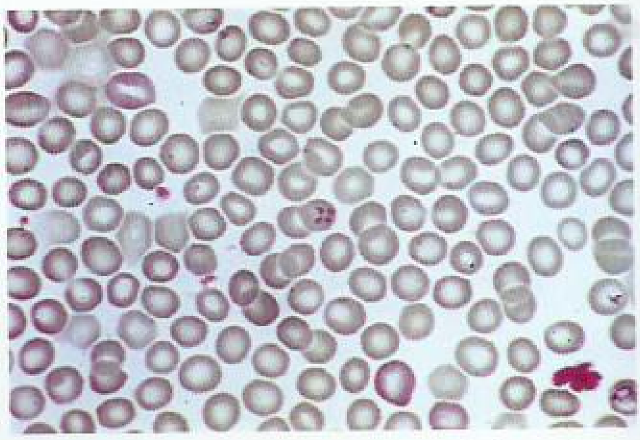

FIGURE 8. Peripheral blood smear showing babesiosis. The diagnosis of babesiosis is typically established by evaluation of a peripheral blood smear showing intraerythrocytic parasites. Occasionally, merozoites are arranged in tetrads, resembling a Maltese cross.

TABLE 18. Treatment for Babesiosis

Severity	Regimen
Asymptomatic, ≤3 months of parasitemia	Monitor for clearance; no treatment indicated
Asymptomatic, >3 months of parasitemia	Atovaquone plus azithromycin
Mild to moderate disease	Atovaquone plus azithromycin
Severe disease requiring ICU admission	Clindamycin plus quinine
Severe disease with >10% parasitemia, hemoglobin level <10 g/dL (100 g/L), ARDS, liver failure or kidney failure	Clindamycin plus quinine *and* Exchange transfusion

ARDS = acute respiratory distress syndrome.

KEY POINTS

- Babesiosis, an infection caused by an intraerythrocytic protozoan, presents with clinical findings ranging from asymptomatic infection to fatal disease; symptoms are usually nonspecific, but hemolytic anemia is a hallmark of disease.
- Diagnosis of babesiosis is by visualization of the organism on blood smear, serology, or polymerase chain reaction.
- Treatment of babesiosis depends on disease severity; atovaquone plus azithromycin are most appropriate for mild disease, whereas clindamycin plus quinine remains the regimen of choice for severe disease.

Southern Tick-Associated Rash Illness

Southern tick-associated rash illness (STARI) presents with EM lesions identical to those seen in Lyme disease but without clinical progression or complications. STARI is associated with *Amblyomma americanum*, also known as the Lone Star tick, and occurs in the southeastern, south central, and eastern United States. No infectious cause has been confirmed. Therefore, diagnosis is based on clinical and geographic features. Because STARI and early-stage Lyme disease may be clinically indistinguishable, treatment with doxycycline is recommended.

KEY POINT

- Southern tick-associated rash illness may be clinically indistinguishable from early-stage Lyme disease, and thus treatment with doxycycline is recommended.

Human Monocytic Ehrlichiosis and Granulocytic Anaplasmosis

Human monocytic ehrlichiosis (HME) and human granulocytic anaplasmosis (HGA) are clinically similar illnesses spread by different tick vectors and caused by distinct bacterial pathogens. HME is caused by *Ehrlichia chaffeensis*, which is transmitted by the Lone Star tick, and occurs most commonly in the southeastern and south central United States. HGA is caused by *Anaplasma phagocytophilum*, which is transmitted by *Ixodes* ticks, and occurs in areas of Lyme endemicity (see Figure 5).

These syndromes typically begin with a nonspecific febrile illness 1 to 2 weeks after a tick bite (**Table 19**). Rash is uncommon in contrast to Rocky Mountain spotted fever. Laboratory study abnormalities, including leukopenia, thrombocytopenia, and increased serum aminotransferase levels, are nonspecific.

The organisms causing HME and HGA replicate inside leukocytes and cause hallmark basophilic inclusion bodies called morulae (**Figure 9**). Serologic findings often are negative in acute illness; testing of a convalescent specimen 2 to 4 weeks after onset of symptoms is usually confirmatory. Polymerase chain reaction of whole blood at the time of acute illness may be diagnostic, particularly if performed before therapy. Doxycycline is the recommended treatment for both HME and HGA. Because delay in treatment is associated with increased mortality, empiric therapy should be started even in the absence of confirmatory testing.

KEY POINTS

- Human monocytic ehrlichiosis and human granulocytic anaplasmosis cause a nonspecific febrile illness beginning 1 to 2 weeks after a tick bite.
- Acute serologic findings are often negative in both human monocytic ehrlichiosis and human granulocytic anaplasmosis; polymerase chain reaction of whole blood at the time of acute illness may be diagnostic.
- Doxycycline is recommended for both human monocytic ehrlichiosis and human granulocytic anaplasmosis; empiric therapy should be started without awaiting results of confirmatory testing.

Rocky Mountain Spotted Fever

Rocky Mountain spotted fever (RMSF) is caused by *Rickettsia rickettsii* and transmitted by multiple tick vectors. It has been reported throughout the continental United States but occurs most frequently in the "RMSF belt" extending from North Carolina to Oklahoma.

Clinically, RMSF presents with nonspecific symptoms similar to those of HME and HGA (Table 19) but can progress to aseptic meningoencephalitis. The hallmark feature is a macular eruption around the ankles or wrists, with central spread and progression to petechiae or purpura (**Figure 10**). Lesions are found on the palms and soles in as many as 50% of patients; the face is generally spared. Purpura fulminans may occur and result in loss of digits or limbs. Although skin findings are ultimately noted in greater than 90% of patients with RMSF, the earliest macular rash occurs a median of 3 days after onset

TABLE 19. Comparison of Epidemiologic and Clinical Features of Human Monocytic Ehrlichiosis, Human Granulocytic Anaplasmosis, and Rocky Mountain Spotted Fever

Feature	HME	HGA	RMSF
Vector	Lone Star tick	Black-legged deer tick	American dog tick, brown dog tick, Rocky Mountain wood tick
Geography	Southeastern, mid-Atlantic, and south-central United States	Northeastern and upper Midwest United States	Throughout the United States[a]
Coinfection	Not reported; potential for coinfection with STARI or Heartland virus because of common vector	Lyme disease, babesiosis, Powassan virus, *Borrelia miyamotoi*	None
Incubation period	5-14 days	5-14 days	3-12 days
Presenting signs and symptoms	Fever, headache, myalgias, nausea, vomiting, diarrhea, conjunctival injection	Fever, headache, myalgias, chills	Fever, headache, chills, mylagia, nausea, abdominal pain, photophobia, aseptic meningitis
Cutaneous signs	Nonspecific rash in <30% of adults, with median onset 5 days after fever	Rash rare (<10%)	Maculopapular eruption in >90% of patients, progressing to petechia with involvement of palms and soles, edema; onset, median of 3 days after fever
Laboratory study abnormalities	Leukopenia, thrombocytopenia, increased serum aminotransferase levels, mild anemia	Leukopenia, thrombocytopenia, increased serum aminotransferase levels, mild anemia	Thrombocytopenia, increased serum aminotransferase levels, normal or slightly increased leukocyte count, hyponatremia
Diagnosis	Morulae in monocytes (<30%), acute and convalescent serologies, whole-blood PCR	Morulae in neutrophils (~50%), acute and convalescent serologies, whole-blood PCR	Acute and convalescent serologies, biopsy of skin with immunohistochemical analysis
Treatment	Doxycycline	Doxycycline	Doxycycline
Fatality	3%	<1%	5%-10%

HGA = human granulocytic anaplasmosis; HME = human monocytic ehrlichiosis; PCR = polymerase chain reaction; RMSF = Rocky Mountain spotted fever; STARI = Southern tick-associated rash illness.

[a]Two thirds of all patients with RMSF are infected in Arkansas, Missouri, North Carolina, Oklahoma, and Tennessee.

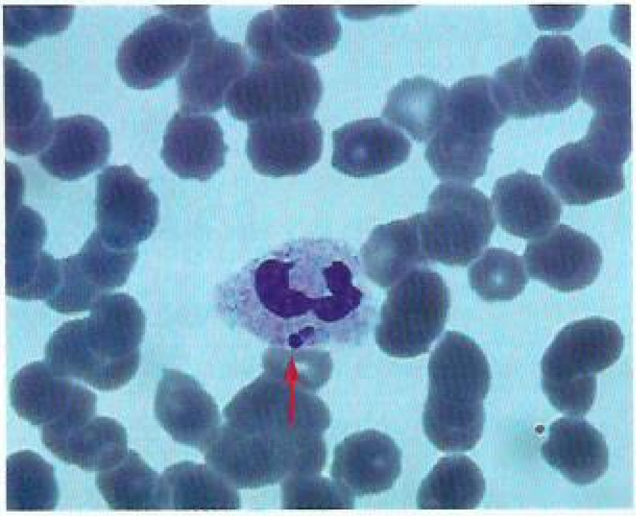

FIGURE 9. Morulae (*arrow*) appearing as basophilic inclusion bodies in leukocytes of a patient with ehrlichiosis.

FIGURE 10. Petechial and purpuric skin eruption in a patient with late-stage Rocky Mountain spotted fever.

Reprinted with permission from Biggs HM, Behravesh CB, Bradley KK, Dahlgren FS, Drexler NA, Dumler JS, et al. Diagnosis and management of tickborne rickettsial diseases: Rocky Mountain spotted fever and other spotted fever group rickettsioses, ehrlichioses, and anaplasmosis - United States. MMWR Recomm Rep. 2016;65:1-44. [PMID: 27172113] doi:10.15585/mmwr.rr6502a1

of fever and thus may not be found at the first clinical presentation.

Immunohistochemical analysis of skin biopsy samples may be diagnostic. As with HME and HGA, acute serology is not sensitive, although testing convalescent serum may provide a retrospective diagnosis. Doxycycline should be given empirically when RMSF is clinically suspected because treatment delay is associated with more severe disease and increased mortality.

KEY POINTS

- Rocky Mountain spotted fever (RMSF) presents similarly to both human monocytic ehrlichiosis and human granulocytic anaplasmosis; the major differentiating feature of RMSF is the presence of a rash, but the rash may not appear until 3 days after onset of fever.
- Doxycycline should be given empirically when Rocky Mountain spotted fever is clinically suspected.

Urinary Tract Infections

Epidemiology and Microbiology

Community-acquired urinary tract infections (UTIs) account for approximately 8 million ambulatory visits and 1 million hospitalizations each year in the United States, making them one of the most common infections for which an antibiotic is prescribed in clinical practice. Another 1 million nosocomial UTIs are diagnosed annually, primarily indwelling urinary catheter-associated UTIs, accounting for an estimated 40% of all health care-associated infections (see Health Care-Associated Infections). Approximately half of all women experience a UTI by age 30 years; sexual activity is a major risk factor. Approximately 5% of otherwise healthy women who experience a UTI are at greater risk of developing future infections. Other UTI risk factors include structural and functional abnormalities, use of spermicidal agents and diaphragms, pregnancy, diabetes mellitus, obesity, urethral catheterization (or other urinary tract instrumentation), immunosuppression, and genetic factors.

UTIs are classified based on anatomic location as lower (cystitis), upper (pyelonephritis, perinephric abscess), or prostatitis. The term *uncomplicated* UTI refers to infections in nonpregnant women without structural or neurologic abnormalities or comorbidities. UTIs in men, pregnant women, and persons with foreign bodies (for example, indwelling catheters, calculi), kidney disease, immunocompromise, obstruction, urinary retention from neurologic disorders, health care-associated infections, or recent antibiotic use are considered to be *complicated*. Advanced age in the presence of other major comorbidities or with significant frailty may be considered a complicating factor in UTI, although age alone does not define a complicated versus uncomplicated infection. Designating an infection as complicated influences the choice and duration of antimicrobial therapy and extent of investigation. Nevertheless, the potential for uncomplicated UTIs to evolve into clinically severe disease should not be underestimated, nor should the urgency or seriousness of complicated UTIs be overstated.

Most infections occur by the ascending route. In 95% of these cases, UTIs are caused by a single bacterial species, mainly gram-negative aerobic bacilli originating from the bowel. Uropathogenic *Escherichia coli* accounts for 75% to 95% of UTIs in women. Less common urinary pathogens include other members of the Enterobacteriaceae family, streptococci (in particular *Streptococcus agalactiae*), enterococci, and staphylococci (most often *Staphylococcus saprophyticus*). UTIs occurring in hospitals and long-term care facilities frequently involve a more varied group of organisms (such as *Enterobacter*, *Providencia*, *Morganella*, *Citrobacter*, *Serratia*, and *Pseudomonas*). Isolation of *Staphylococcus aureus* from the urine may be related to instrumentation but should suggest the possibility of a hematogenous infection from a source outside the urinary tract.

KEY POINTS

- The term *uncomplicated* urinary tract infection refers to infections in nonpregnant women without structural or neurologic abnormalities or comorbidities.
- Designating an infection as complicated influences the choice and duration of antimicrobial therapy and extent of investigation.
- Urinary tract infections in men, pregnant women, and persons with foreign bodies, kidney disease, immunocompromise, obstruction, urinary retention from neurologic disorders, health care–associated infections, or recent antibiotic use are considered to be *complicated*.

Diagnosis

In persons with symptoms of UTI, diagnosis in the outpatient setting is based on a combination of clinical features, determining if the presumed infectious process is in the lower or upper urinary tract, and the findings of significant pyuria (≥10 leukocytes/µL) and bacteriuria (bacteria in the urine). Pyuria can be detected by urine dipstick, which relies on the presence of leukocyte esterase. Although the sensitivity and specificity of dipstick testing are high (about 75% and 85%, respectively), pyuria may result from urinary tract disorders other than infection. The presence of leukocyte casts supports a diagnosis of pyelonephritis. Microscopic or gross hematuria may be present with a UTI but may also be encountered with nephrolithiasis and tumors. A positive nitrite test result signifies the presence of gram-negative bacteria capable of converting nitrates into nitrites but is negative in UTI caused by nonconverting organisms (*Enterococcus*, *Staphylococcus*, or *Streptococcus* species).

Quantitative cultures of a midstream, clean-void urine sample are the most accurate way to demonstrate bacteriuria in patients with suspected UTI. Because the microbiology is predictable and treatment courses are short, culture is not recommended in women with uncomplicated cystitis. Urine cultures are indicated in pyelonephritis, complicated cystitis, and recurrent UTIs; additionally, they are recommended in patients with histories of multiple antibiotic allergies and in those in whom the presence of a resistant organism is suspected (such as recent antibiotic treatment, health care-associated infection, previous multidrug-resistant UTI). The growth of 10^5 colony-forming units (CFU)/mL of urine is considered significant bacteriuria; however, lower CFU counts support a diagnosis in those with UTI symptoms.

H CONT.

In most adults, imaging studies are not required for diagnosis or treatment of UTIs. Imaging may be indicated when the diagnosis is unclear, when a structural abnormality or complication is suspected, or in patients with severe illness, immunocompromise, or lack of response to appropriate therapy. Ultrasonography can detect obstruction, whereas noncontrast helical CT is recommended for visualizing kidney stones. Although less sensitive than CT, kidney ultrasonography is less expensive, requires less radiation exposure, and can be used in pregnant women or if CT is unavailable. Contrast-enhanced CT (CT urography) is recommended when intrarenal or perinephric abscess is suspected. H

KEY POINTS

- Quantitative cultures of a midstream, clean-void urine sample are the most accurate way to demonstrate bacteriuria in patients with suspected urinary tract infection.
- HVC Urine culture is not recommended in women with uncomplicated cystitis but is indicated in pyelonephritis, complicated cystitis, recurrent urinary tract infections, patients with multiple antibiotic allergies, and in patients in whom a resistant organism is suspected.

Management

H

Asymptomatic Bacteriuria

Asymptomatic bacteriuria is defined as the presence of at least 10^5 CFU/mL of a uropathogen from two consecutive voided urine specimens in women or one specimen in men, or more than 10^2 CFU/mL of one bacterial species from a catheterized urine specimen in women or men, in all cases without local or systemic signs or symptoms of active infection. The prevalence of asymptomatic bacteriuria is as low as 1% to 5% in healthy premenopausal women (2%-10% in pregnant women) and nearly 100% in patients with long-term indwelling urinary catheters.

The presence of pyuria accompanying asymptomatic bacteriuria is not an indication for antimicrobial treatment. Although bacteriuria increases the risk of symptomatic UTI, treatment of asymptomatic bacteriuria neither decreases the frequency of symptomatic infections nor improves other outcomes. Inappropriate treatment of asymptomatic bacteriuria is a major driver of antimicrobial resistance, particularly in health care facilities. Treatment of asymptomatic bacteriuria is, however, indicated in pregnant women and in patients scheduled to undergo an invasive procedure involving the urinary tract. H

KEY POINTS

- HVC Inappropriate treatment of asymptomatic bacteriuria is a major driver of antimicrobial resistance, particularly in health care facilities.
- Treatment of asymptomatic bacteriuria is indicated in pregnant women and in patients scheduled to undergo an invasive procedure involving the urinary tract.

Cystitis

Recommended first-line antibiotic regimens for uncomplicated cystitis (urinary frequency and urgency, dysuria, and suprapubic discomfort) should consider the increased rate of antimicrobial resistance of *E. coli*, the efficacy and advantages of short-course therapies, and the potential adverse effects (of the ecology and on patients). Preferred agents include nitrofurantoin (5 days), trimethoprim-sulfamethoxazole (3 days), and fosfomycin (1 dose, but expensive and less efficacious).

In geographic areas where trimethoprim-sulfamethoxazole resistance exceeds 20%, an alternative agent should be selected. The FDA recently indicated that fluoroquinolones should be reserved for other serious bacterial infections; however, fluoroquinolones (3 days) and β-lactam agents (including amoxicillin-clavulanate, cefdinir, cefaclor, and cefpodoxime-proxetil, each 3-7 days) are considered acceptable alternative second-line therapies. β-Lactams are not preferred if other recommended agents are available because they are less effective in eradicating infection. During pregnancy, the safest antibiotics are amoxicillin-clavulanate, cephalosporins, and nitrofurantoin. Tetracyclines and fluoroquinolones are contraindicated, and trimethoprim-sulfamethoxazole can only be used safely during the second trimester. Extended-spectrum β-lactamase-producing strains of Enterobacteriaceae causing cystitis have increased in frequency, especially in patients with recent antimicrobial or health care-facility exposure. Because of the greater risk of resistant and polymicrobial infections, urine culture and susceptibility testing are indicated in all patients with complicated cystitis. Fluoroquinolones are the preferred choice pending results, although fosfomycin and nitrofurantoin are reasonable options. The recommended treatment duration is 7 to 10 days rather than a 3-day, short-course regimen but is much less well defined. Other than in pregnant women, test of cure is not indicated in those reporting resolution of symptoms. H

KEY POINT

- Preferred agents for uncomplicated cystitis include nitrofurantoin (5 days), trimethoprim-sulfamethoxazole (3 days), and fosfomycin (1 day, but least preferred); fluoroquinolones should not be used as first-line therapy in cystitis.

H

Acute Pyelonephritis

Lower urinary tract symptoms (frequency, urgency, and dysuria) often precede the onset of fever, chills, flank pain, and at times nausea and vomiting, which characterize acute pyelonephritis. Infection can usually be managed in the outpatient setting with oral antibiotics. Hospitalization is advised for patients with hemodynamic instability, obstructive disease, pregnancy, complicating comorbidities, known pathogen resistance requiring parenteral antibiotic therapy, inability to tolerate oral medications, or lack of reliable home supervision and clinical follow-up.

Every patient requires a urine culture with susceptibility testing obtained before initiation of empiric therapy. Fluoroquinolones (ciprofloxacin for 7 days or levofloxacin for 5 days for uncomplicated infections, 10-14 days in complicated infections) are the only oral agents recommended for empiric outpatient treatment, but an initial dose of a long-acting parenteral antibiotic (such as ceftriaxone, 1 g, or a once-daily aminoglycoside) should replace fluoroquinolones when local resistance rates exceed 10%. When a fluoroquinolone is contraindicated, trimethoprim-sulfamethoxazole twice daily for 14 days may be used after the pathogen is proven to be susceptible; trimethoprim-sulfamethoxazole should be avoided as initial empiric therapy because of the high level of *E. coli* resistance to this antibiotic in the community.

Depending on the risk of antimicrobial resistance and on recent antibiotic use, inpatient parenteral antimicrobial options include a fluoroquinolone, extended-spectrum cephalosporins (ceftriaxone or cefepime) or penicillins (piperacillin-tazobactam), or a carbapenem (meropenem, imipenem, or ertapenem). Again, fluoroquinolones are avoided for empiric therapy in severely ill patients with complicated pyelonephritis because of the increasing potential for resistance in *E. coli* and other aerobic gram-negative bacilli.

Therapy can be completed with active oral agents when an adequate clinical response has been observed. Patients with bacteremia do not require longer courses of treatment and may be converted to appropriate oral therapy when clinically stable.

Imaging studies are only necessary in patients with prolonged fever (>72 hours) or persistent bacteremia, in which complications such as obstruction or perinephric and intrarenal abscesses must be excluded. Routine follow-up urine cultures are only indicated in pregnant women.

KEY POINTS

- Every patient with acute pyelonephritis requires a urine culture with susceptibility testing obtained before initiation of empiric therapy; follow-up urine cultures are only indicated in pregnant women.
- It is prudent to avoid choosing a fluoroquinolone in severely ill patients with complicated pyelonephritis because of the increasing potential for resistance in *Escherichia coli* as well as other aerobic gram-negative bacilli.

Recurrent Urinary Tract Infections in Women

An estimated 25% to 30% of patients experience a second episode of infection within 6 months of their first UTI. *Relapsed* infections are those that recur within 2 weeks of completing antimicrobial therapy (5%-10% of cases) with the same organism (determined by repeat culture). Relapse suggests infection with a resistant strain of bacteria, incomplete treatment of an infection of the upper urinary tract, or a structural abnormality, including renal calculi. *Reinfection*, the most common type of recurrent UTI, is generally caused by a bacterial strain separate from the original infection and presents more than 2 weeks after cessation of treatment for the previous infection. Symptomatic relapsed infection requires a urine culture. Assuming the organism is sensitive, patients are treated for infection of the upper urinary tract for 7 to 10 days with the same antibiotic as prescribed for the previous infection or, if bacterial resistance is discovered, an alternative agent. Likewise, the same first-line antimicrobial agent can be given for reinfections, although an alternative antibiotic should be used if the recurrence occurs within 6 months, particularly if the original agent was trimethoprim-sulfamethoxazole, because of the increased chance of resistance.

Strategies to prevent infection recurrence include avoidance of spermicide contraceptives, urination soon after intercourse, topical vaginal estrogens, ascorbic acid (vitamin C), and methenamine salts. Cranberry products have not been proven effective in controlled trials. Prophylactic daily antimicrobial agents have been found to reduce the risk of recurrences by nearly 95%; they are an option in women who have had three or more UTIs in the previous 12 months, or two or more in the previous 6 months, and have received no benefit from other prevention efforts. Prophylactic therapy should be considered in pregnant patients who have required treatment for cystitis or asymptomatic bacteriuria to prevent recurrence during pregnancy. Antibiotic complications and potential emergence of resistance must be considered. Approximately 50% of patients revert to previous recurrence patterns within 6 months of prophylaxis discontinuation. Recommended prophylactic antibiotics include nitrofurantoin, trimethoprim-sulfamethoxazole, trimethoprim, cephalexin, or fosfomycin. Fluoroquinolones are very effective but not recommended. Other options include postcoital antimicrobial prophylaxis and self-diagnosis with self-treatment.

KEY POINTS

- Reinfection is generally caused by a bacterial strain separate from the original infection and presents more than 2 weeks after cessation of treatment for the previous infection.
- Prophylactic daily antimicrobial therapy is an option in women who have had three or more urinary tract infections in the previous 12 months or two or more in the previous 6 months; other options include postcoital antimicrobial prophylaxis and self-diagnosis with self-treatment.

Acute Bacterial Prostatitis

Benign prostatic hyperplasia resulting in urinary obstruction and altered urine flow is the most common reason for the increased incidence of UTIs in men older than 60 years. Other risk factors include unprotected sexual intercourse, chronic indwelling urinary catheters, and transrectal prostate biopsy. Approximately 5% of men develop chronic prostatitis after acute infection.

H CONT.

Presenting symptoms include sudden onset of fever, pelvic or perineal pain, urinary frequency and dysuria, and increasing obstructive symptoms. Acute bacterial prostatitis frequently presents as a severe systemic infection and is the most common cause of bacteremia in older men. Cautious digital rectal examination of the prostate reveals a boggy and tender gland. Urinalysis and culture are required to confirm the diagnosis. Although pyuria may be present for reasons other than infection, its absence strongly indicates no infection. Prostate-specific antigen test results may be elevated because of inflammation of the gland and should be avoided in the setting of presumed infection.

Hospitalized patients and those with severe infection require blood cultures. Gram-negative uropathogens account for about 80% of infections, two thirds of which are *E. coli*; *Proteus*, *Enterobacter*, *Serratia*, *Klebsiella*, and sometimes *Pseudomonas* and enterococcal species compose most of the other pathogens. In men 35 years or younger, sexually transmitted infections, including *Neisseria gonorrhoeae* and *Chlamydia trachomatis*, must be considered.

Fluoroquinolone antibiotics (ciprofloxacin, levofloxacin) are the preferred oral agents for treating acute bacterial prostatitis but should not be used if recent genitourinary instrumentation was performed, especially transrectal prostate biopsies, because most *E. coli* strains are now resistant to fluoroquinolones. Treatment duration is typically 4 weeks. Hospitalized patients should initially receive a broad-spectrum parenteral antibiotic, such as an extended-spectrum penicillin or cephalosporin, with the possible addition of an aminoglycoside. Imaging studies are not recommended unless a prostatic abscess is suspected clinically. H

KEY POINTS

- Gram-negative uropathogens account for about 80% of acute prostatitis infections; in men 35 years or younger, sexually transmitted infections, including *Neisseria gonorrhoeae* and *Chlamydia trachomatis*, must be considered.
- Fluoroquinolone antibiotics are the preferred oral agents for treating acute bacterial prostatitis but should not be used if recent genitourinary instrumentation was performed because most *E. coli* strains are now resistant to fluoroquinolones.

Mycobacterium tuberculosis Infection

Epidemiology

Tuberculosis is one of the oldest and most prevalent infectious diseases in the world. It remains one of the most common causes of death from an infectious disease worldwide. Although rates of *Mycobacterium tuberculosis* infection remain relatively low in North America, approximately one third of the world's population is infected with the bacteria. As of 2015, approximately 10 million new cases are reported each year throughout the world, and approximately 2 million deaths are documented each year, including 360,000 in persons infected with HIV. More than 60% of infections are reported from Southeast Asia, India, China, Micronesia, Russia, and sub-Saharan Africa. Multidrug-resistant tuberculosis (MDR-TB) accounts for 3.3% of new infections and 20% of relapsed infections. Extremely drug-resistant tuberculosis now accounts for approximately 10% of all MDR-TB infections worldwide. In 2015, 9557 tuberculosis infections were reported in the United States (3.0 per 100,000 persons). Most infections in the United States occur in foreign-born persons; however, other persons at high risk include those with alcoholism, urban poor, homeless persons, injection drug users, prison inmates, persons living in shelters, HIV-positive persons, and older adults.

Despite great strides worldwide in controlling *M. tuberculosis*, it remains a major global health concern. The burden of disease throughout the world and rapid travel from country to country ensures a steady stream of active tuberculosis cases in the United States.

KEY POINTS

- Most *Mycobacterium tuberculosis* infections in the United States occur in foreign-born persons; however, other persons at high risk include those with alcoholism, urban poor, homeless persons, injection drug users, prison inmates, persons living in shelters, HIV-positive persons, and older adults.
- Multidrug-resistant tuberculosis (MDR-TB) accounts for 3.3% of new infections and 20% of relapsed infections; extremely drug-resistant tuberculosis now accounts for approximately 10% of all MDR-TB infections worldwide.

Pathophysiology

Humans are the only known reservoir for *M. tuberculosis*, which is most commonly transmitted from person to person by aerosolized droplets. Although the droplets dry rapidly, the smallest droplets may remain suspended in the air for several hours. Persons who have visible acid-fast bacilli (AFB) on microscopy are the most likely to transmit infection. The most contagious patients are those with cavitary or laryngeal tuberculosis and those whose sputum contains a high bacterial load. After deposition in the respiratory tract, tubercular bacilli are ingested by alveolar macrophages that initiate an immunologic cascade eventually resulting in the development of classic caseating granulomas.

Most persons (>90%) who become infected with *M. tuberculosis* remain asymptomatic and develop latent tuberculosis. The risk of developing disease after infection depends primarily on endogenous factors such as the person's innate immune system, nonimmunologic defenses (alveolar macrophages, phagosome formation, phagocytosis), and the

function of cell mediated immunity. Specific risk factors for developing active tuberculosis among infected persons are shown in **Table 20**. The risk for developing active infection is approximately 5% in the first 2 years after infection and then 5% for the remainder of their life, assuming no cause of immunosuppression is present (see Table 20).

KEY POINTS

- Most persons who become infected with *Mycobacterium tuberculosis* remain asymptomatic and develop latent tuberculosis.
- Risk factors for developing active tuberculosis include immunosuppression, tumor necrosis factor-α inhibitors, injection drug use, silicosis, chronic kidney disease, diabetes mellitus, recent infection, and malnutrition.

Clinical Manifestations

Tuberculosis is classified as pulmonary, extrapulmonary, or both; the two main forms are primary and secondary tuberculosis. Primary tuberculosis occurs soon after the initial infection, most frequently in children and immunosuppressed persons. Often, the lesions heal spontaneously. Secondary or reactivation tuberculosis results from endogenous reactivation of a latent infection. Most cases of active tuberculosis are caused by reactivation of latent tuberculosis in the setting of immunosuppression. Seventy-five percent of secondary infections are pulmonary, except in those infected with HIV, in whom two thirds of patients have pulmonary and extrapulmonary infection.

H Frequent manifestations include fever, weight loss, productive cough (occasionally blood tinged), anorexia, malaise, and pleuritic chest pain. Patients may have a normal lung examination or have crackles, rhonchi, or dullness to percussion. Hemoptysis occurs in 10% to 20% of patients with positive AFB smear results. In immunosuppressed patients, the infection may also disseminate into the bloodstream, producing miliary (disseminated) tuberculosis, which can result in a systemic inflammatory response syndrome, septic shock, and ultimately death if not diagnosed and treated early. Additionally, patients with disseminated infection may present with atypical clinical manifestations and chest radiographs. Extrapulmonary disease may be the result of hematogenous dissemination, can be seen in up to 30% of patients with active tuberculosis, and may involve almost any organ or organ system, including the pleura, lymph nodes, central nervous system, skeletal system, pericardium, larynx, peritoneum, and genitourinary system. H

TABLE 20. Risk Factors for Acquiring *Mycobacterium tuberculosis*

Recent infection (<1 year)
Pulmonary fibrotic lesions
Malnutrition
Comorbidities
HIV infection
Silicosis
Chronic kidney disease
Diabetes mellitus
Injection drug use
Immunosuppressive therapy
Jejunoileal bypass
Solid organ transplantation
Tumor necrosis factor-α inhibitors
Head and neck cancer

KEY POINTS

- Clinical manifestations of tuberculosis include fever, weight loss, productive cough (occasionally blood tinged), anorexia, malaise, and pleuritic chest pain.
- In immunosuppressed patients, tuberculosis infection may disseminate to the bloodstream, which can result in a systemic inflammatory response syndrome, septic shock, and ultimately death if not treated early.

Diagnosis

The key to the diagnosis of tuberculosis is a high index of suspicion in patients at high risk.

Diagnosis of Latent Tuberculosis Infection

The goal of diagnosing latent tuberculosis infection (LTBI) is to identify and treat persons at increased risk for reactivation tuberculosis. Testing methods include interferon-γ release assay (IGRA) performed on a blood sample or tuberculin skin testing (TST). LTBI is diagnosed when an asymptomatic patient has a positive TST result or an IGRA with no clinical or radiographic manifestations of active tuberculosis.

The Centers for Disease Control and Prevention (CDC) recommends performing an IGRA rather than a TST in persons 5 years or older who are likely to have *M. tuberculosis* infection, have a low or intermediate risk of disease progression, have a history of bacillus Calmette-Guérin (BCG) vaccination, or are unlikely to return to have their TST result interpreted. IGRAs are in vitro assays that measure T-cell release of interferon-γ in response to stimulation with highly tuberculosis-specific antigens ESAT-6 and CFP-10 (QuantiFERON-TB Gold In-Tube and T-SPOT.TB test). IGRAs are more specific than TST because they have less cross-reactivity resulting from BCG vaccination and sensitization by nontuberculous mycobacteria. Although not used to diagnose active tuberculosis, IGRAs appear to be at least as sensitive as the TST in patients with active tuberculosis.

TST has become the alternative diagnostic test if IGRA is not feasible or available. The purified protein derivative is

injected intradermally and interpreted after 48 to 72 hours by measuring the transverse diameter of induration, not erythema. A positive result indicates delayed-type hypersensitivity response. The criteria for a positive TST result are based on the patient's risk factors for tuberculosis (**Table 21**). A false-negative TST result may occur in patients with recent tuberculosis infection, overwhelming active tuberculosis infection, recent viral infections, or severe immunocompromise (AIDS) and in those younger than 6 years. Patients with remote exposure to *M. tuberculosis* may initially have a negative TST result that can become positive several weeks later after a second TST, known as the "booster effect." The second test is recommended in health care workers 7 to 21 days after initial testing and should be performed on the opposite forearm; it is not required if IGRA is used. IGRAs are recommended in nearly all clinical settings in which TST is recommended; one exception is children younger than 5 years, for whom experts recommend both tests to increase specificity.

KEY POINTS

HVC
- The Centers for Disease Control and Prevention recommends performing an interferon-γ release assay instead of tuberculin skin testing in persons 5 years or older who are likely to have *Mycobacterium tuberculosis* infection, have a low or intermediate risk of disease progression, have a history of bacillus Calmette-Guérin vaccination, or are unlikely to return to have their tuberculin skin test interpreted.
- Latent tuberculosis infection is diagnosed when an asymptomatic patient has a positive tuberculin skin test or interferon-γ release assay result with no clinical or radiographic manifestations of active tuberculosis.

H Diagnosis of Active Tuberculosis Infection

The CDC recommends AFB smear microscopy in all patients suspected of having active pulmonary tuberculosis. In vitro fluorescence microscopy of sputum is the preferred methodology. Testing three specimens is highly recommended because false-negative results from a single specimen are not uncommon. However, false-positive results are also not uncommon, thus a positive smear result requires mycobacterial culture confirmation. At least 3 mL of sputum should be submitted, although 5 to 10 mL is preferred. Serial specimens must be obtained at least 8 hours apart, and one must be an early morning specimen. Sputum induction is preferable to bronchoscopy as the sample methodology because of its greater sensitivity in patients who are unable to expectorate sputum.

The gold standard for diagnosis of active *M. tuberculosis* infection remains the mycobacterial culture. Whether AFB staining results are positive or negative, liquid and solid cultures should be performed for every specimen obtained. Liquid culture allows for faster growth and more rapid identification of organisms (2-4 weeks).

When a sputum smear result is positive for AFB, nucleic acid amplification testing (NAAT) is highly recommended to verify the organism. The positive predictive value of a NAAT on a smear-positive sputum sample is 95%. In patients with an intermediate to high level of suspicion for active disease who have a negative smear, the NAAT result will be positive in 65% of cases. If available, a NAAT assay that also detects for rifampin resistance is recommended for timely detection of rifampin resistance. Although the NAAT assays are quick and sensitive, mycobacterial cultures are still recommended for performance of in vitro susceptibilities to all antimicrobial agents. It is important to note that a negative NAAT result cannot be used to exclude pulmonary tuberculosis; NAAT can rapidly confirm the presence of *M. tuberculosis* in 50% to 80% of AFB smear-negative, culture-positive specimens. Moreover, NAAT can facilitate earlier decision making regarding whether to initiate tuberculosis therapy.

If signs of extrapulmonary infection are present, samples from those areas should be obtained and sent for AFB stain, mycobacterial culture, and histopathology. Histopathology may be beneficial by demonstrating caseating granulomas, which are suggestive for but not exclusive to or diagnostic of tuberculosis. In disseminated tuberculosis, blood cultures for mycobacteria using isolator methodology are helpful. H

TABLE 21. Interpretation of Tuberculin Skin Test Results

Criteria for Tuberculin Positivity by Risk Group		
≥5 mm Induration	**≥10 mm Induration**	**≥15 mm Induration**
HIV-positive persons	Recent (<5 years) arrivals from high-prevalence countries	All others with no risk factors for TB
Recent contacts of persons with active TB	Injection drug users	
Persons with fibrotic changes on chest radiograph consistent with old TB	Residents or employees of high-risk congregate settings: prisons and jails, nursing homes and other long-term facilities for the elderly, hospitals and other health care facilities, residential facilities for patients with AIDS, homeless shelters	
Patients with organ transplants and other immunosuppressive conditions (receiving the equivalent of ≥15 mg/d of prednisone for >4 weeks)	Mycobacteriology laboratory personnel; persons with clinical conditions that put them at high risk for active disease (silicosis, diabetes mellitus, severe kidney disease, certain types of cancer, some intestinal conditions); children aged <4 years or exposed to adults in high-risk categories	

TB = tuberculosis infection.

KEY POINTS

- The gold standard for the diagnosis of active *Mycobacterium tuberculosis* infection remains the mycobacterial culture; when a sputum smear result is positive for acid-fast bacilli, nucleic acid amplification testing is highly recommended to verify the organism.
- If signs of extrapulmonary tuberculosis infection are present, samples from those areas should be obtained and sent for acid-fast bacilli staining, mycobacterial culture, and histopathology.

H Radiographic Procedures

The classic radiographic finding in pulmonary tuberculosis is that of upper lobe disease with air space disease and cavities. However, any radiographic pattern can be seen, from a "normal chest radiograph" or a solitary pulmonary nodule to diffuse alveolar infiltrates with acute respiratory distress syndrome. H

Management

The primary goals of therapy include preventing additional morbidity, preventing mortality, and disrupting transmission of *M. tuberculosis* by eradicating the infection. When suitable antimicrobial therapy is administered and taken appropriately, clinical trials demonstrate clinical and microbiologic cure rates of approximately 95%. Therapy depends on several factors, including the classification of infection (latent versus active), pulmonary versus extrapulmonary infection, and patient adherence.

Treatment of Latent Tuberculosis

Patients who have a positive IGRA or a positive TST result should be evaluated for active disease with a full medical history, physical examination, and chest radiography. If no sign of active infection is present, all patients should be offered treatment for LTBI. CDC guidelines recommend four different treatment regimens (**Table 22**). Pyridoxine is recommended in

TABLE 22. Treatment Regimens for Latent Tuberculosis Infection

Drugs[a]	Duration	Dose[b]	Frequency	Total Doses
Isoniazid	9 months	5 mg/kg Maximum dose: 300 mg	Daily	270
		15 mg/kg Maximum dose: 900 mg	Twice weekly[c]	76
	6 months	5 mg/kg Maximum dose: 300 mg	Daily	180
		15 mg/kg Maximum dose: 900 mg	Twice weekly[c]	52
Isoniazid and rifapentine	3 months	Isoniazid[d]: 15 mg/kg rounded up to the nearest 50 or 100 mg; 900 mg maximum Rifapentine[d]: 10.0-14.0 kg: 300 mg 14.1-25.0 kg: 450 mg 25.1-32.0 kg: 600 mg 32.1-49.9 kg: 750 mg ≥50.0 kg: 900 mg maximum	Once weekly[e]	12
Rifampin	4 months	10 mg/kg Maximum dose: 600 mg	Daily	120

[a]Isoniazid is the preferred regimen, with therapy for 9 months preferable in patients with HIV and therapy for 6 months for patients without HIV and pulmonary lesions. CDC recommendations include isoniazid plus rifapentine in adults, in children aged 2-17 years, and in persons with HIV/AIDS taking antiretroviral therapy that does not interact with rifapentine. Rifampin is an option if other regimens cannot be used.

[b]Doses listed are for adults.

[c]Therapy may be either directly observed therapy (DOT) or self administered therapy (SAT) in patients ≥2 years of age.

[d]Isoniazid is formulated in 100-mg and 300-mg tablets. Rifapentine is formulated in 150-mg tablets in blister packs that should be kept sealed until use.

[e]May be provided by DOT or SAT. Factors that should be considered when choosing between DOT and SAT include local practice, patient attributes and preferences, and risk of progression to severe disease. Use of concomitant latent tuberculosis infection treatment and antiretroviral agents should be guided by clinicians experienced in the management of both conditions.

Recommendations from the Centers for Disease Control and Prevention. Latent tuberculosis infection: a guide for primary health care providers. Treatment of latent TB infection. Table 2. Choosing the most effective LTBI treatment regimen. www.cdc.gov/tb/publications/ltbi/treatment.htm#2. Accessed October 15, 2017; and Borisov AS, Bamrah Morris S, Njie GJ, Winston CA, Burton D, Goldberg S, et al. Update of recommendations for use of once-weekly isoniazid-rifapentine regimen to treat latent mycobacterium tuberculosis infection. MMWR Morb Mortal Wkly Rep. 2018;67:723-726. [PMID: 29953429] doi:10.15585/mmwr.mm6725a5

patients who will receive isoniazid and are at risk for peripheral neuropathy (diabetes mellitus, chronic kidney disease, malnutrition, HIV, and alcoholism). Baseline and monthly monitoring of liver chemistry tests are not routinely required unless patients are at risk for hepatotoxicity (HIV infection, chronic hepatitis B or C, alcohol abuse, pregnancy, concurrent hepatotoxic drugs, or underlying liver disease).

In pregnant women with LTBI, a 6- to 9-month regimen of isoniazid plus pyridoxine may be offered; however, some experts prefer to defer therapy until after delivery, unless the patient is at high risk of developing active infection owing to immunocompromise, including HIV infection.

KEY POINTS

- Patients with a positive interferon γ release assay or tuberculin skin test result should be evaluated for active disease; if no sign of active infection is present, patients should be offered treatment for latent tuberculosis infection.
- Recommended treatment regimens for latent tuberculosis infection are isoniazid (daily or twice weekly) for 9 or 6 months, isoniazid plus rifapentine weekly for 3 months, or rifampin daily for 4 months.

Treatment of Active Tuberculosis

When active tuberculosis is verified, in vitro susceptibility testing of the initial isolate should be done for the first-line agents (isoniazid, rifampin, pyrazinamide, and ethambutol). This becomes increasingly important because of the advent of multidrug-resistant and extensively drug-resistant tuberculosis. If rifampin resistance has been detected during NAAT assessment, in vitro susceptibilities to first-line and second-line agents should be performed (**Table 23**).

The American Thoracic Society/CDC guidelines published in 2016 recommend 6 to 9 months of treatment in patients with drug-susceptible active tuberculosis. A four-drug regimen is given daily for 2 months, followed by a continuation phase of isoniazid plus rifampin daily, usually for 4 months (**Table 24**).

Directly observed therapy, generally through the local health department, is recommended for the treatment of active tuberculosis. Sputum specimens should be evaluated at 1- and 2-month intervals to assess for efficacy. In addition, clinical assessment and laboratory testing (complete blood count, liver chemistry testing, hepatitis serology) should be performed before initiating therapy.

It is essential to advise the patient of the possible adverse effect profiles of the various medications (see Table 23). In several studies, approximately 15% to 25% of patients receiving the four-drug regimen experienced some type of adverse effect. Most adverse effects are mild, and therapy may be continued; up to 15% are severe enough that therapy must be discontinued temporarily. If a hypersensitivity reaction is observed, then all four drugs should be discontinued and rechallenged sequentially to determine the cause.

KEY POINTS

- Directly observed therapy is recommended for the treatment of active tuberculosis.
- American Thoracic Society/Centers for Disease Control and Prevention guidelines recommend 6 to 9 months of treatment in patients with drug-susceptible active tuberculosis; a four-drug regimen is given daily for 2 months, followed by a continuation phase of isoniazid plus rifampin daily, usually for 4 months.

Drug-Resistant Tuberculosis

M. tuberculosis resistance to individual drugs arises by spontaneous point mutations. Depending on the resistance, the regimen must be altered. In isoniazid-resistant tuberculosis, the regimen of isoniazid, rifampin, and ethambutol can be safely administered for 6 months, although some experts would add a fluoroquinolone. In those with isoniazid- and rifampin-resistant tuberculosis (MDR TB), experts agree that a five-drug regimen depending on the susceptibility of the isolate should be provided for 4 months, followed by a four-drug regimen for an additional 12 to 18 months (see Table 23). Consultation with an expert in the event of MDR TB is required.

Tuberculosis in patients with HIV infection may be complicated by immune reconstitution inflammatory syndrome. Although the general recommendations for treatment are the same, antiretroviral therapy should be initiated within 2 weeks for patients with a CD4 cell count less than 50/µL and by 8 to 12 weeks for those with CD4 cell counts of 50/µL or more. An exception is HIV-positive patients with tuberculous meningitis, in whom antiretroviral therapy should not be initiated during the first 8 weeks of tuberculosis therapy regardless of the CD4 cell count to avoid increased morbidity because of immune reconstitution inflammatory syndrome.

KEY POINTS

- In patients with multidrug-resistant tuberculosis, experts agree that a five-drug regimen should be provided for 4 months, followed by a four-drug regimen for an additional 12 to 18 months.
- Tuberculosis in patients with HIV infection may be complicated by immune reconstitution inflammatory syndrome, and antiretroviral therapy initiation should be delayed to prevent this occurrence.

Tumor Necrosis Factor Antagonist and Tuberculosis

Patients being treated with a tumor necrosis factor inhibitor (such as infliximab, etanercept, adalimumab, or certolizumab) have been reported to have an increased risk of reactivation to active infection or death from disseminated disease. It is recommended that these patients be evaluated for active or latent tuberculosis by performing chest radiography and simultaneous TST or IGRA. All patients should receive treatment for LTBI if identified, although LTBI treatment does not completely

TABLE 23. Antituberculous Drugs

Agent	Adverse Effects	Notes
First-Line Medications		
Isoniazid	Rash; liver enzyme elevation; hepatitis; peripheral neuropathy; lupus-like syndrome	Hepatitis risk increases with age and alcohol consumption. Pyridoxine may prevent peripheral neuropathy. Adjust for kidney injury.
Pyrazinamide	Hepatitis; rash; GI upset; hyperuricemia	May make glucose control more difficult in patients with diabetes. Adjust for kidney injury.
Rifampin	Hepatitis; rash; GI upset	Contraindicated or should be used with caution when administered with protease inhibitors and nonnucleoside reverse transcriptase inhibitors. Do not administer to patients also taking saquinavir/ritonavir. Colors body fluids orange.
Rifabutin	Rash; hepatitis; thrombocytopenia; severe arthralgia; uveitis; leukopenia	Dose adjustment required if taken with protease inhibitors or nonnucleoside reverse transcriptase inhibitors. Monitor for decreased antiretroviral activity and for rifabutin toxicity.
Rifapentine	Similar to rifampin	Contraindicated in patients who are HIV positive (unacceptable rate of failure/relapse).
Ethambutol	Optic neuritis; rash	Baseline and periodic tests of visual acuity and color vision. Patients are advised to call immediately if visual acuity or color vision changes. Adjust for kidney injury.
Second-Line Medications[a]		
Streptomycin	Auditory, vestibular, and kidney toxicity	Avoid or reduce dose in adults >59 years. Monitor hearing and kidney function test results. Adjust for kidney injury.
Cycloserine	Psychosis; convulsions; depression; headaches; rash; drug interactions	Pyridoxine may decrease CNS adverse effects. Measure drug serum levels.
Capreomycin	Kidney, vestibular, and auditory toxicity	Monitor hearing and kidney function test results. Adjust for kidney injury.
Ethionamide	GI upset; hepatotoxicity; hypersensitivity	May cause hypothyroidism.
Kanamycin and amikacin	Auditory, vestibular, and kidney toxicity	Not approved by the FDA for TB treatment. Monitor vestibular, hearing, and kidney function.
Levofloxacin, moxifloxacin	GI upset; dizziness; hypersensitivity; drug interactions	Not approved by the FDA for TB treatment. Should not be used in children.
Para-aminosalicylic acid	GI upset; hypersensitivity; hepatotoxicity	May cause hypothyroidism, especially if used with ethionamide. Measure liver enzyme levels.
Bedaquiline	Nausea, joint pain, headache, elevated aminotransferase levels, hemoptysis, prolonged QT interval	FDA-approved oral agent for MDR pulmonary TB treatment indicated for combination therapy when other alternatives are not available. Novel mechanism of action inhibits mycobacterial adenosine triphosphate synthase. Should be given as directly observed therapy.

CNS = central nervous system; GI = gastrointestinal; MDR = multidrug resistant; TB = tuberculosis.

[a]Use these drugs in consultation with a clinician experienced in the management of drug-resistant TB.

eliminate risk for active mycobacterial infection in this population.

KEY POINT

- All patients diagnosed with latent tuberculosis who are being treated with a tumor necrosis factor inhibitor should receive treatment to reduce risk of reactivation and death from disseminated disease.

Prevention

From the public health perspective, the best way to prevent tuberculosis is to diagnose, isolate, and treat infection rapidly until patients are considered noncontagious and the disease is cured. In the hospital, this means having a high index of suspicion for *M. tuberculosis* in high-risk groups and initiating immediate airborne isolation in negative pressure rooms (airborne infection isolation rooms) until the diagnosis can be excluded.

Recent CDC guidelines recommend criteria to determine that a patient is no longer contagious and a possible public health threat. These include appropriate antimicrobial therapy for at least 2 weeks, clinical improvement of signs and symptoms, and three negative sputum smears collected at least 8 hours apart, with one being an early morning specimen. Patients with negative smear results are less contagious, although they may still have tuberculosis.

TABLE 24. Preferred Treatment Regimens for Active Tuberculosis

Treatment Phase	Regimen	Comments
Initial	Daily INH, RIF, PZA, and EMB[a] for 56 doses (8 wk) *or*	Alternative regimens available at https://www.cdc.gov/tb/topic/treatment/tbdisease.htm
	DOT 5 d/wk for 90 doses (18 wk)	DOT should be used when medications are administered less than 7 d/wk
		Pyridoxine 25-50 mg/d is given to all patients at risk for neuropathy[b]; 100 mg/d for patients with peripheral neuropathy
Continuation	INH and RIF 7 d/wk for 126 doses (18 wk) or	Based on expert opinion, patients with cavitation on the initial chest radiograph and positive cultures at completion of 2 months of therapy should receive a 7-month (31-wk) continuation phase
	DOT 5 d/wk for 90 doses (18 wk)	

DOT = directly observed therapy; EMB = ethambutol; INH = isoniazid; PZA = pyrazinamide; RIF = rifampin.

[a]EMB can be discontinued if drug susceptibility studies demonstrate susceptibility to first line drugs.

[b]Pregnant women; breastfeeding infants; persons with HIV; patients with diabetes, alcoholism, malnutrition, or chronic kidney disease; patients of advanced age.

Recommendations from the Centers for Disease Control and Prevention. Tuberculosis. Treatment for TB disease. Table 1. Basic TB disease treatment regimens. Available at www.cdc.gov/tb/topic/treatment/tbdisease.htm. Accessed August 27, 2014.

The BCG vaccination is a live-attenuated vaccine derived from an attenuated strain of *Mycobacterium bovis*. It has been in use for more than 90 years throughout the world, although it is not routinely used in the United States. It is recommended for use at birth in countries with high rates of *M. tuberculosis*. In several international studies, the BCG vaccine has been shown to be effective in preventing severe infection, including meningitis in children. However, the efficacy in adults has not been established. CDC guidelines do not recommend the vaccine in the United States; however, the World Health Organization still recommends its use in high-prevalence areas.

KEY POINT

- Guidelines for determining a patient with tuberculosis is no longer contagious include appropriate antimicrobial therapy for at least 2 weeks, clinical improvement in signs and symptoms, and three negative sputum smears collected at least 8 hours apart.

TABLE 25. Classification of Common Nontuberculous Mycobacteria

Slow-growing Mycobacteria
M. kansasii
M. marinum
M. gordonae
M. scrofulaceum
M. avium complex
M. ulcerans
M. xenopi
Rapidly Growing Mycobacteria
M. abscessus
M. chelonae
M. fortuitum

Nontuberculous Mycobacterial Infections

Nontuberculous mycobacteria (NTM) comprise species other than *Mycobacterium tuberculosis* complex and *Mycobacterium leprae*. NTM are often divided into slow and rapid growers (**Table 25**). These organisms are found in surface water, soil, domestic and wild animals, milk, and food products. Additionally, they can be colonizers, particularly in the airways of persons with chronic lung disease. They can cause a spectrum of infections (**Table 26**).

Risk factors for NTM infections include immunocompromise, chronic lung disease, and postoperative status. Health care–associated *Mycobacterium chimaera* infections have been documented worldwide in association with heater-cooler units used during cardiac surgery.

NTM diagnosis is difficult because a positive culture result from a nonsterile site (such as the lung) without other evidence of disease may reflect colonization rather than infection. However, when recovered from a normally sterile site, active infection is very likely. Because antibiotic susceptibility of species vary, it is important to identify organisms to species level. American Thoracic Society (ATS) guidelines recommend fulfillment of clinical, radiologic, and microbiologic criteria to diagnose an NTM pulmonary infection. Most NTM infections require treatment with two to four antimicrobials; ATS guidelines should be used to guide therapy.

TABLE 26. Diseases Caused by Nontuberculous Mycobacteria

Clinical Disease	More Common	Less Common	Infection Risks
Pulmonary	MAC *M. kansasii* *M. abscessus*	*M. fortuitum* *M. xenopi* *M. malmoense* *M. szulgai* *M. simiae* *M. asiaticum*	Older persons with or without underlying lung disease; cystic fibrosis
Lymphadenitis	MAC	*M. abscessus* *M. fortuitum* *M. scrofulaceum* *M. malmoense*	Children
Skin and soft tissue	*M. marinum* *M. ulcerans* *M. abscessus*	MAC *M. kansasii*	Direct inoculation
Catheter-related bloodstream infections	Rapidly growing mycobacteria	MAC *M. kansasii*	Long-term catheterization
Disseminated	MAC *M. kansasii* (in persons with AIDS and CD4 cell count <100/µL)	Rapidly growing mycobacteria	Immunocompromise, especially persons with AIDS or those taking tumor necrosis factor-α inhibitors

MAC = *Mycobacterium avium* complex.

KEY POINTS

- Risk factors for nontuberculous mycobacteria infections include immunocompromise, chronic lung disease, and postoperative status; additionally, health care–associated *Mycobacterium chimaera* infections have been documented in association with heater-cooler units used during cardiac surgery.
- Because antibiotic susceptibility of nontuberculous mycobacteria species varies, it is important to identify organisms to species level.

Mycobacterium avium Complex Infection

Mycobacterium avium complex is the most common cause of chronic lung infection worldwide. Cavitary lung disease is seen classically in white, middle-aged, or older adult men, especially those with underlying lung disease, such as COPD, cystic fibrosis, or interstitial lung disease. Disseminated infection is seen predominantly in patients with HIV with CD4 cell counts less than 50/µL. The clinical presentation often consists of fever, night sweats, weight loss, and gastrointestinal symptoms.

Mycobacterium kansasii

M. kansasii infection mimics pulmonary tuberculosis with cavitary lung disease. Predisposing conditions include underlying lung disease, alcoholism, cancer, and immunocompromised status.

Rapidly Growing Mycobacteria

Rapidly growing NTM have been implicated in NTM outbreaks. The most common rapidly growing mycobacterial species include *M. abscessus*, *M. chelonae*, and *M. fortuitum*. Of these, *M. abscessus* is most frequently identified and one of the most difficult to treat. These mycobacteria are associated with chronic, nonhealing ulcers unresponsive to appropriate empiric antibiotic therapy for typical skin and soft tissue infections.

KEY POINTS

- *Mycobacterium avium* complex is the most common cause of chronic lung infection worldwide, causing cavitary lung disease.
- *Mycobacterium abscessus*, *Mycobacterium chelonae*, and *Mycobacterium fortuitum* can produce lung disease, adenitis, skin and soft tissue infections, surgical site infections, and prosthetic device infections.

Fungal Infections

The incidence of fungal infection is increasing because of the increased recognition of these infections and an increase in

the population at risk worldwide. According to a recent analysis by the Prospective Antifungal Therapy Alliance, the most commonly encountered infections in North America were caused by *Candida* species (73%) followed by *Aspergillus* species (14.8%), other yeast (such as *Cryptococcus* species; 6.2%), and mucormycetes (including *Rhizopus* species and *Mucor* species; 1.7%).

Systemic Candidiasis

Candida species are the fourth most commonly isolated organisms in bloodstream infections and are associated with a mortality rate of 30% to 40%. Risk factors for systemic candidiasis are listed in **Table 27**.

Manifestations of candidiasis depend on the organ involved. Candidemia can present as an isolated fever or septic shock. Signs and symptoms of focal infection depend on the site involved (abscess or peritonitis in the peritoneum, empyema in the pleural cavity, or pyelonephritis in the kidneys). Other forms of invasive infection include meningitis, osteomyelitis, septic arthritis, and endocarditis. Although often found in the respiratory tract, *Candida* species rarely cause infections there and are likely the result of colonization. The presence of yeast in the urinary tract (for example, because of the presence of an indwelling catheter) may represent colonization (most commonly) or true infection.

Diagnosis of invasive candidiasis is challenging because only 40% to 60% of patients with infection have positive blood culture results, and cultures can take days to demonstrate growth. Recognizing risk factors (see Table 27) for candidiasis is thus essential to avoid delays in initiating antifungal therapy and resultant increased mortality. The T2 magnetic resonance assay of whole blood provides rapid (within hours) diagnosis of culture-negative invasive candidal infections and can be performed on blood samples even after initiation of antifungal therapy. The β-D-glucan assay also can be used to diagnose invasive candidiasis in patients with negative blood culture results. These assays should be obtained when a patient at high risk (see Table 27) receiving antimicrobial agents is not responding to therapy.

When the *Candida* genus is identified from a sterile site (blood or tissue), specific species identification is necessary. Although more than 160 species of *Candida* are known, fewer than 15 produce disease in humans. Additionally, several species (such as *C. glabrata* and *C. krusei*) have intrinsic resistance to antifungal agents, especially the azoles, and their proper identification guides therapy.

Treatment of candidemia and invasive candidiasis should include an echinocandin (caspofungin, micafungin, or anidulafungin) and removal of intravascular devices (if possible). However, because of poor penetration of echinocandins into the central nervous system (CNS) and the eye, patients with these infections should be treated with an azole or amphotericin B. Additional treatment of candidal endophthalmitis varies depending on the extent of disease (chorioretinitis with or without macular involvement, vitreous involvement). All patients initially given amphotericin B or an echinocandin may be de-escalated to an oral azole (fluconazole or voriconazole) if the *Candida* species is susceptible and the gastrointestinal tract is functional. Duration of antifungal therapy for candidemia should be 14 days from the first negative blood culture result in patients with uncomplicated candidemia or 14 to 42 days in patients with invasive candidal infections.

TABLE 27. Risk Factors for Systemic Candidiasis
Central venous catheters
Broad-spectrum antimicrobial agents
Neutropenia
ICU stay for more than 3 days
Total parenteral nutrition
General surgery (especially of the gastrointestinal tract)
Burns
Trauma
Mechanical ventilation for more than 3 days
Transplantation (bone marrow/solid organ)
Hemodialysis-associated catheters
Severe acute pancreatitis

KEY POINTS

- *Candida* species are the fourth most commonly isolated organisms in bloodstream infections and are associated with a 30% to 40% mortality rate.
- Because only 40% to 60% of patients with invasive candidal infection have positive blood culture results, recognizing risk factors of candidiasis is essential to avoid delays in initiating effective antifungal therapy.
- The T2 magnetic resonance assay of whole blood may provide a rapid diagnosis of culture-negative invasive candidal infections.
- *Candida* species isolated from the respiratory tract and from the urinary tract usually represent colonization; treatment is not indicated unless clinical infection is suspected. HVC
- Treatment of candidemia and invasive candidiasis should include an echinocandin (caspofungin, micafungin, or anidulafungin) and removal of intravascular devices (if possible); central nervous system and ocular infections require amphotericin B or an azole.

Aspergillosis and Aspergilloma

Aspergillus is ubiquitous in the environment. The most common species are *A. fumigatus*, *A. flavus*, *A. niger*, and the amphotericin-resistant *A. terreus*. *Aspergillus* produces disease after inhalation of airborne spores (90%) and only

occasionally by traumatic skin inoculation. Of all the fungi, *Aspergillus* is notable for the diverse settings in which it can occur and the various clinical manifestations it can produce.

Invasive pulmonary aspergillosis, the most serious form of *Aspergillus* infection, most often occurs in immunosuppressed patients who are neutropenic or are hematopoietic stem cell transplant recipients (**Table 28**). This type of aspergillosis usually begins in the respiratory tract and then enters the circulatory system (angioinvasion). This is followed by the formation of a fungus-septic emboli complex with subsequent hematogenous dissemination. The most common manifestation of angioinvasive disease is pulmonary aspergillosis (60%), but sinusitis, brain abscess, endocarditis, disseminated infection, and osteomyelitis also may occur. Timely diagnosis of invasive aspergillosis is essential to decrease morbidity and mortality, but symptoms and signs are nonspecific (**Table 29**), and blood culture results are generally negative. Therefore, bronchoscopy, bronchoalveolar lavage, and, if possible, tissue biopsy are often necessary to establish a definitive diagnosis. Early CT of the chest in patients with suspected invasive pulmonary aspergillosis—with typical findings suggestive of septic emboli (nodules, often with a "halo sign") (**Figure 11**), thromboembolic pulmonary infarction (wedge shaped peripheral densities), or necrosis with cavitation and a crescent sign—and the serum galactomannan assay can be useful in establishing a presumptive diagnosis of invasive infection, especially in neutropenic patients and hematopoietic stem cell transplant recipients, in whom the assay has a sensitivity of approximately 80%. First-line treatment of invasive aspergillosis is with a triazole (voriconazole, posaconazole, or isavuconazole); amphotericin B deoxycholate or liposomal amphotericin B can be used for amphotericin-sensitive *Aspergillus* species if triazoles are not available. When possible, reversal of immunosuppression improves treatment response.

TABLE 28. Risk Factors for Invasive Aspergillosis

Major	Minor
Neutropenia	COPD treated with glucocorticoids
Graft-versus-host disease	Cirrhosis
Cytomegalovirus infection/reactivation	Burns
Hematopoietic stem cell transplantation	Solid organ malignancies
Solid organ transplantation	Immunosuppressants
Systemic glucocorticoids (>1 mg/kg/d) or inhaled steroids	Cyclosporine
Hematologic malignancies	Methotrexate
	Azathioprine
	Cyclophosphamide
	Advanced HIV with CD4 cell count <50/µL (50 × 10⁶/L)
	Injection drug use (rare)
	Gram-negative bacterial pneumonia

TABLE 29. Clinical Features of Invasive Aspergillosis

Fever[a]
Pulmonary findings
Pleuritic chest pain, pleural rub
Dry cough
Dyspnea
Hemoptysis: usually minor but occasionally catastrophic
Chest radiograph: potentially normal in early disease; infiltrates, infarction, nodules, and cavitation in late disease
Focal neurologic deficits
Multiorgan dysfunction
Hemorrhagic skin lesions

[a]Frequently the only feature present.

Other forms of *Aspergillus* infection occur in different clinical settings. Chronic necrotizing aspergillosis is a semi-invasive indolent form of infection that does not disseminate and occurs in patients who have lesser degrees of immunosuppression (such as those who take chronic glucocorticoids or those who have intrinsic immune defects) or chronic pulmonary disease. Treatment is similar to that for invasive pulmonary aspergillosis.

H Allergic bronchopulmonary aspergillosis results from a hypersensitivity overreaction to *Aspergillus* species colonizing the respiratory tract; this disorder is seen primarily in patients with cystic fibrosis and occasionally in those with asthma (see MKSAP 18 Pulmonary and Critical Care Medicine for more information). Because allergic bronchopulmonary aspergillosis represents a hypersensitivity response, systemic glucocorticoids are the mainstay of treatment (sometimes supplemented by antifungal therapy with an azole). H

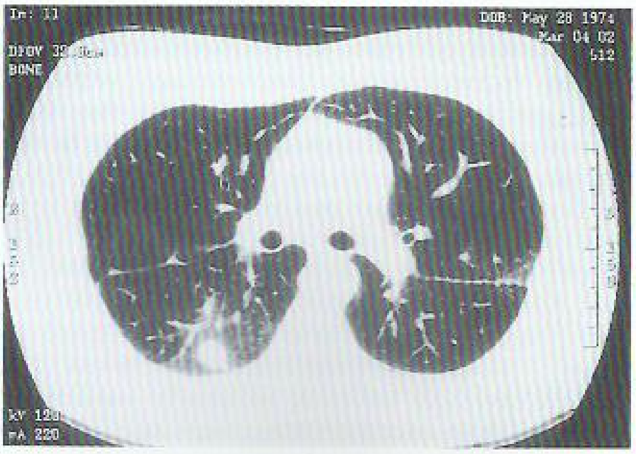

FIGURE 11. CT scan showing typical findings suggestive of septic emboli. Note the nodule with a "halo sign," which is a surrounding area of low attenuation that reflects hemorrhage into the tissues surrounding the fungus.

Pulmonary aspergillomas (fungus balls consisting of hyphae, mucus, and cellular debris) may form in patients with pre-existing cavities, such as old tuberculosis cavities and in bullae of patients with COPD; the presence of significant hemoptysis is a potential complication. In the absence of associated symptoms or hemoptysis, pulmonary aspergillomas may not require therapy; however, in the setting of significant bleeding, surgical resection or embolization may be necessary. Antifungal therapy is typically not effective against pulmonary aspergillomas, and its role in aspergilloma treatment is unclear.

KEY POINTS

- *Aspergillus* species produce disease after inhalation of airborne spores (90% of affected patients).
- *Aspergillus* infection can manifest in various ways, including invasive pulmonary aspergillosis, chronic necrotizing pulmonary aspergillosis, allergic bronchopulmonary aspergillosis, and aspergillomas.
- Tissue biopsy is frequently necessary to establish a definitive diagnosis of invasive aspergillosis; however, early chest CT and the serum galactomannan assay can be useful in establishing a presumptive diagnosis in patients at high risk of infection.
- First-line treatment of invasive or chronic pulmonary *Aspergillus* infection is with a triazole, such as voriconazole, posaconazole, or isavuconazole; liposomal amphotericin B can be used as an alternative in sensitive species and if triazoles are not available.

Cryptococcosis

Cryptococcus is an encapsulated yeast that is ubiquitous in the environment. Although cryptococcal infection can occur in healthy persons, most infected patients have advanced immune suppression, such as AIDS, neutropenia, or organ transplantation. *C. neoformans* is the most commonly identified species, but *C. gattii* is seen with increased frequency in the Pacific Northwest region of North America and has been associated with severe and recalcitrant infection. Pathogenesis of cryptococcosis involves inhalation of spores into the respiratory tract, followed by dissemination into susceptible tissues, especially the CNS.

H Cryptococcal infection most commonly manifests in the CNS, and cryptococcosis is the most common cause of fungal meningitis worldwide. Clinical manifestations are listed in **Table 30**, and indicators of a poor prognosis in cryptococcal meningitis are provided in **Table 31**. Because patients with cryptococcosis-related increased intracranial pressure (ICP) may develop sudden blindness, deafness, or coma, initial opening pressure should be documented during lumbar puncture. Cerebrospinal fluid analysis is essential to diagnose CNS involvement; classic findings include an increased leukocyte count (mainly lymphocytes), an increased protein level, a low to normal glucose level, and the presence of cryptococcal antigen. Serum cryptococcal antigen also is positive in greater than 95% of infected patients; occasionally, blood culture results are positive and thus indicate disseminated disease. H

TABLE 30. Clinical Features of Cryptococcosis

Signs and Symptoms of Meningeal Infection (% Affected)
Fever (60%-90%)
Headache (80%-90%)
Nausea/vomiting (~50%)
Meningism (30%)
Altered mental status (20%-30%)
Extrameningeal Infection Sites
Lung
Bone marrow
Skin
Prostate (cryptic source)

TABLE 31. Indicators of Poor Prognosis in Cryptococcal Meningitis

Altered mental state
Visual abnormalities
CSF leukocyte count less than 20/µL (20×10^6/L)
CSF cryptococcal antigen assay greater than 1:10,000
No previous antiretroviral therapy in those with HIV infection

CSF = cerebrospinal fluid.

Many symptoms of increased ICP may be improved by cerebrospinal fluid removal through daily lumbar puncture or insertion of a shunt. Aggressive reduction of ICP reduces early morbidity and mortality. Amphotericin B plus flucytosine is the treatment of choice and is effective in more than 90% of patients. HIV-infected patients require maintenance antifungal therapy until they have maintained their CD4 cell counts above 100/µL (100×10^6/L) for a minimum of 3 months and have a suppressed viral load.

KEY POINTS

- In patients with suspected cryptococcal infection, cerebrospinal fluid (CSF) analysis is necessary, as is documentation of the CSF opening pressure; CSF and serum cryptococcal antigen are both highly sensitive for identifying infection.
- Amphotericin B plus flucytosine is effective in more than 90% of patients; for those with elevated intracranial pressure (ICP), cerebrospinal fluid removal through daily lumbar puncture or insertion of a shunt can reduce ICP and thus early morbidity and mortality.

Histoplasmosis

Histoplasma capsulatum is responsible for one of the most common endemic mycoses in the world. Acquired by inhalation of airborne conidia, this organism primarily produces asymptomatic pulmonary infection. It is distributed along the Mississippi River Valley (Ohio, Missouri, Indiana, Mississippi) in the United States, in Central and South America, in the Caribbean, and in regions of Africa, Australia, and India.

Histoplasmosis most commonly presents with acute respiratory symptoms. Other presentations, in declining order of frequency, include asymptomatic infection, disseminated infection, chronic pulmonary symptoms, rheumatologic symptoms, pericarditis, and sclerosing mediastinitis.

The *Histoplasma* urinary antigen assay has a sensitivity and specificity of greater than 85% in acute and disseminated infection but less than 50% in chronic infection. Identification of the fungus by tissue culture can be a lengthy process but is indicated for clinically suspected cases in which the urinary antigen assay result is negative.

Asymptomatic and mild pulmonary histoplasmosis typically resolves without treatment. Antifungal therapy is recommended for more severe or disseminated disease. Itraconazole is the agent of choice; duration of therapy is 6 to 12 weeks for acute infection and as long as 12 months for chronic cavitary pulmonary infection. For severe lung disease and disseminated infection, liposomal amphotericin B should be used initially, followed by de-escalation to oral itraconazole for an additional 12 weeks.

KEY POINTS

- *Histoplasma* urinary antigen assay has a sensitivity and specificity of greater than 85% in acute and disseminated infection but less than 50% in chronic infection.
- Itraconazole is the antifungal agent of choice for most patients with histoplasmosis; liposomal amphotericin B should be used initially for those with severe lung disease and disseminated infection.

Coccidioidomycosis

Coccidioides is a dimorphic fungus that exists as a mold in the environment. There are two species: *C. immitis* refers to isolates from California, and *C. posadasii* refers to isolates from all other endemic areas, including Arizona, New Mexico, western Texas, northern Mexico, and parts of Central and South America. In endemic areas, the annual risk of infection is approximately 3% for most persons, although the risk of infection (and dissemination) is greater in those who are pregnant, younger than 5 years or older than 50 years, or of African, Filipino (and possibly other Asian), and Native American ancestry.

Infection is usually acquired by inhalation of aerosolized arthroconidia. Once inhaled, the fungus begins its dimorphic change in the lungs and becomes a yeast cell. Several clinical syndromes are seen in coccidioidomycosis and may manifest as acute or chronic pulmonary infection, as cutaneous infection (~40%), as meningitis (~33%), or as musculoskeletal infection.

Diagnosis is straightforward in endemic areas and usually is based on clinical manifestations and confirmatory testing by a mycologic culture of affected tissue, histopathologic evaluation of tissue, serology for *Coccidioides* antibodies, or urinary antigen testing.

Fluconazole is the first-line treatment for symptomatic infection. In patients with meningitis, fluconazole is continued for life. In patients who do not respond to azoles, intrathecal amphotericin B may be an alternative.

KEY POINTS

- The diagnosis of coccidioidomycosis should be suspected clinically in endemic areas and may be confirmed by a mycologic culture of affected tissues, histopathologic evaluation of tissue, serology for *Coccidioides* antibodies, or urinary antigen testing.
- Fluconazole is first-line treatment for symptomatic coccidioidomycosis infection.

Blastomycosis

Blastomyces dermatitidis is a dimorphic, round, budding yeast; daughter cells form a bud with a broad base. Blastomycosis affects immunocompetent hosts. In the United States, blastomycosis is found primarily along the Mississippi and Ohio River valleys but can be found as far north as Wisconsin and Minnesota and as far south as Florida. As with most dimorphic yeast, infection occurs by inhalation of conidia and manifests initially as a primary pulmonary infection (acute or chronic pneumonia). Occasionally, a chest radiograph shows a spiculated nodular appearance that may be mistaken for lung cancer. Rarely, dissemination occurs and produces extrapulmonary disease (osteomyelitis, genitourinary infection, or CNS infection).

Diagnosis of blastomycosis can be made by direct fungal stain of clinical specimens (sputum, tissue, or purulent material) and confirmed by culture or serology for *Blastomyces* antibodies. Urinary antigen testing is also available. The preferred treatment for mild to moderate infection is itraconazole for 6 to 12 months. Liposomal amphotericin B is recommended for CNS, severe pulmonary, and disseminated infections.

KEY POINTS

- Blastomycosis occurs by inhalation of *Blastomyces dermatitidis* conidia and manifests initially as a primary pulmonary infection; diagnosis is made by direct fungal stain of clinical specimens and confirmed by culture, urinary antigen testing, or serology for *Blastomyces* antibodies.
- The preferred treatment for mild to moderate infection is itraconazole, with liposomal amphotericin B used for central nervous system and disseminated infection.

Sporotrichosis

Sporothrix schenckii is a dimorphic fungus found most often in soil, living plants, or plant debris. Although found worldwide, most reported infections are from North and South America and Japan. Infection can occur after direct contact with plants, such as roses and sphagnum moss. Direct inoculation of the organism into the skin or subcutaneous tissue manifests as fixed, "plaque-like" cutaneous sporotrichosis or as lymphocutaneous sporotrichosis presenting as papular lesions along lymphatic channels proximal to the inoculation site. Extracutaneous infection (osteoarticular, pulmonary, ocular, or disseminated) can occur in immunocompromised hosts.

Diagnosis requires culture of the organism from affected tissues. Treatment is with itraconazole and should extend for 2 to 4 weeks after lesions have resolved.

KEY POINTS

- Sporotrichosis is an infection of cutaneous and lymphocutaneous tissues and usually is caused by direct contact with plants; extracutaneous infection can occur in immunocompromised hosts.
- Itraconazole is the preferred treatment for cutaneous and lymphocutaneous sporotrichosis.

Mucormycosis

Mucormycosis (formerly zygomycosis) is the third most frequent cause of invasive fungal infections in immunocompromised hosts but is rarely seen in immunocompetent hosts. Particularly at risk are patients with neutropenia, diabetes mellitus, and acidosis. The most common mucormycetes are *Rhizopus arrhizus* and *Mucor* species. These fungi are commonly found in the environment on decaying organic debris, including fruit, bread, and soil.

Infection is acute and rapidly fatal, even with early diagnosis and treatment. Major blood vessels are invaded, with ensuing ischemia, necrosis, and infarction of adjacent tissues. Mucormycosis has five major clinical forms: (1) rhinocerebral; (2) pulmonary; (3) abdominal, pelvic, gastric, gastrointestinal; (4) primary cutaneous; and (5) disseminated.

Because laboratory studies are nonspecific, diagnosis relies on a high index of suspicion in a host with appropriate risk factors and evidence of tissue invasion, including the characteristic appearance of broad, nonseptate hyphae with acute-angle branches. Serologic tests and blood cultures offer no diagnostic benefit.

Treatment requires reversal of any predisposing condition, extensive surgical removal of affected tissue, and early antifungal therapy. Initial treatment is high-dose liposomal amphotericin B, with later de-escalation to posaconazole or isavuconazole. If amphotericin B is not tolerated, initial therapy with one of the azoles is warranted. Mortality rates remain as high as 60% to 80%, even with therapy.

KEY POINTS

- Mucormycosis is acute and rapidly fatal, even with early diagnosis and treatment.
- Because laboratory studies are nonspecific, diagnosis relies on a high index of suspicion; serologic tests and blood cultures offer no diagnostic benefit.
- Treatment requires reversal of any predisposing condition, extensive surgical removal of affected tissue, and initial antifungal therapy with high-dose liposomal amphotericin B.

Sexually Transmitted Infections

Introduction

Sexually transmitted infections (STIs) occur most commonly in adolescents, young adults, and men who have sex with men (MSM), but STIs affect all demographics. Most infections are asymptomatic, so it is imperative that a detailed sexual history, including sexual practices, be obtained to understand individual risk. STI risk factors include a new partner, more than one current partner, a partner with an STI, or a partner who has concurrent partners. Particularly high-risk populations include persons attending STI clinics and MSM.

Unrecognized or inadequately treated upper genitourinary tract infection is a preventable cause of infertility in women. Evidence-based guidelines for the evaluation and management of STIs are available from the World Health Organization and the Centers for Disease Control and Prevention (CDC); the CDC guidelines are recommended for use in the United States. Any patient diagnosed with an STI should be evaluated for other STIs, including HIV, and receive risk reduction counseling.

Chlamydia trachomatis Infection

Chlamydia trachomatis is the most commonly reported bacterial STI in the United States, and incidence has increased steadily over the past two decades. Screening of all sexually active women younger than 25 years is recommended. Women aged 25 years and older should be screened if they have STI risk factors. The U.S. Preventive Services Task Force (USPSTF) concluded that evidence is insufficient to support routine screening in men; the CDC recommends screening men in settings or populations with high prevalence or burden of disease (MSM, STI clinics).

Nucleic acid amplification testing (NAAT) is preferred for screening and diagnosis. First-catch urine (for men and women) and endocervical (for women) or urethral (for men) swabs can be used. NAAT of urine samples for *C. trachomatis* and *Neisseria gonorrhoeae* has been shown to have a

sensitivity and specificity nearly identical to tests obtained from urethral and endocervical samples. In addition to cervicitis and urethritis, chlamydia may cause oropharyngeal and rectal infection, and these sites should be evaluated based on history of sexual practices. Although commercially available, NAAT may not be FDA cleared for testing extragenital sites; laboratories can provide this testing if they have confirmed internal criteria for validity of test results.

Treatment of clinical syndromes caused by *C. trachomatis* is outlined in **Table 32**. Test of cure is not recommended.

TABLE 32. Treatment of *Chlamydia trachomatis* and *Neisseria gonorrhoeae* Infections and Their Complications

Clinical Syndrome	Preferred Regimen	Alternate Regimen
Cervicitis and urethritis (empiric therapy)	Ceftriaxone, 250 mg IM single dose, plus azithromycin, 1 g PO single dose (preferred), *or* doxycycline[a], 100 mg PO twice daily for 7 d (only if azithromycin cannot be used)	Cefixime, 400 mg PO single dose, plus azithromycin, 1 g PO single dose (preferred), or doxycycline, 100 mg PO twice daily for 7 d
Chlamydia cervicitis, urethritis, or proctitis	Azithromycin, 1 g PO single dose, *or* doxycycline, 100 mg PO twice daily for 7 d (21 d if *C. trachomatis* LGV serovars suspected or confirmed)	Erythromycin base, 500 mg PO four times daily, *or* erythromycin ethylsuccinate, 800 mg PO four times daily, *or* levofloxacin, 500 mg PO daily, *or* ofloxacin, 300 mg PO twice daily for 7 d
Gonococcal cervicitis, urethritis, or proctitis and pharyngeal infection[b]	Ceftriaxone, 250 mg IM single dose, plus azithromycin, 1 g PO single dose (preferred), *or* doxycycline, 100 mg PO twice daily for 7 d (only if azithromycin cannot be used)	Cefixime[c], 400 mg PO single dose, plus azithromycin, 1 g PO single dose (preferred), *or* doxycycline, 100 mg PO twice daily for 7 d Test of cure 2 weeks after treatment for pharyngeal gonorrhea treated with an alternate regimen
Disseminated gonococcal infection[d]	Ceftriaxone, 1 g IM or IV every 24 h, plus azithromycin, 1 g PO single dose	Cefotaxime, 1 g IV every 8 h, *or* ceftizoxime[e], 1 g IV every 8 h, plus azithromycin, 1 g PO single dose
Pelvic inflammatory disease		
Parenteral therapy[f]	Cefotetan, 2 g IV every 12 h, *or* cefoxitin, 2 g IV every 6 h, plus doxycycline, 100 mg IV or PO every 12 h OR Clindamycin, 900 mg IV every 8 h, plus gentamicin, 2 mg/kg IV loading dose followed by 1.5 mg/kg IV every 8 hours or a single daily dose of 3-5 mg/kg/d	Ampicillin-sulbactam, 3 g IV every 6 h, plus doxycycline, 100 mg IV or PO every 12 h
Oral/IM therapy	Ceftriaxone, 250 mg IM single dose, plus doxycycline, 100 mg PO twice daily for 14 d, with or without metronidazole, 500 mg PO twice daily for 14 d, *or* cefoxitin, 2 g IM single dose, with probenecid, 1 g PO, plus doxycycline, 100 mg PO every 12 h for 14 d, with or without metronidazole, 500 mg PO twice daily for 14 d	
Epididymitis	Ceftriaxone, 250 mg IM single dose, plus doxycycline, 100 mg PO twice daily for 10 d if infection most likely due to chlamydia/gonorrhea Ceftriaxone, 250 mg IM single dose, plus levofloxacin, 500 mg PO once daily, or ofloxacin, 300 mg PO twice daily for 10 d if infection might be caused by chlamydia/gonorrhea and enteric organisms (insertive anal intercourse) Levofloxacin, 500 mg PO once daily, or ofloxacin, 300 mg PO twice daily, for 10 d if infection most likely caused by enteric organisms	

IM = intramuscularly; IV = intravenously; LGV = lymphogranuloma venereum; PO = orally.

[a]Doxycyline should be avoided or used with caution in pregnant patients.

[b]Treatment for possible chlamydial infection is recommended for all patients diagnosed with gonorrhea. Currently recommended treatment regimens for gonorrhea provide this coverage.

[c]Cefixime should be used only if ceftriaxone is unavailable because oral cephalosporin resistance to *N. gonorrhoeae* has been increasingly reported.

[d]For arthritis dermatitis syndrome, parenteral therapy should be used until 24 to 48 hours after substantial clinical improvement and then switched to an oral therapy based on susceptibility results for a total of 7 to 10 days of treatment. Parenteral therapy is required for the entire course of treatment for meningitis (10 to 14 days) and endocarditis (at least 28 days).

[e]Not available in the United States.

[f]Patients can be switched to oral therapy within 24 to 48 hours of clinical improvement using doxycycline, 100 mg PO twice daily, with or without metronidazole, 500 mg PO twice daily, to complete a total of 14 days of therapy.

except in pregnancy. Because of the high risk of repeat infection, men and women should be retested after 3 months or the next time they are seen for medical care.

KEY POINTS

- First-catch urine (or genital swab) nucleic acid amplification testing is the preferred screening and diagnostic method for *Chlamydia trachomatis* infection.
- HVC Test of cure is not recommended in patients with *Chlamydia trachomatis* infection except in pregnancy; however, patients should be retested for possible repeat infection after 3 months or at their next medical visit.

Neisseria gonorrhoeae Infection

The incidence of *N. gonorrhoeae* infection has been increasing since 2013, with rates of infection increasing more rapidly among men than women. Persons aged 20 to 24 years are at highest risk. In addition to cervicitis, urethritis, pharyngitis, and rectal infection, disseminated gonococcal infection (presenting as arthritis-dermatitis syndrome) can occur (see MKSAP 18 Rheumatology). Infection can be asymptomatic, especially in women, so screening is recommended for women younger than 25 years and those 25 years and older with STI risk factors. The USPSTF does not recommend screening for men; the CDC recommends screening men at high risk, as for *C. trachomatis*.

H For screening and diagnosis, NAAT is preferred. Men and women can be screened using a first-catch urine sample; endocervical and urethral swabs may also be used. NAAT availability for samples from extragenital sites is limited, and physicians should determine what testing is available from their preferred laboratory. In patients with disseminated gonococcal infection (arthritis-dermatitis, endocarditis, or meningitis), all *N. gonorrhoeae* isolates should be tested for antimicrobial susceptibility. Patients with suspected disseminated gonococcal infection should have cultures performed on blood, joint fluid (if arthritis is present), purulent skin lesions (if present), and cerebrospinal fluid (if meningitis is suspected); however, culture yield is not high, so NAAT from all potential sites of exposure (genital, pharyngeal, rectal) should be obtained.

Treatment of *N. gonorrhoeae* is outlined in Table 32. Because of the increasing prevalence of antimicrobial resistance among *N. gonorrhoeae* isolates in the United States, cephalosporins are the only antimicrobial class recommended. Previously, the rationale for combination therapy was to treat concomitant *C. trachomatis* infection; the current rationale is based on increased efficacy of combination therapy. In the United States, *N. gonorrhoeae* isolates are more likely to be susceptible to azithromycin than doxycycline, and azithromycin can be given as a single dose. Doxycycline should only be used in the setting of macrolide allergy. In patients with an allergy precluding use of cephalosporins, oral gemifloxacin or parenteral gentamicin plus oral azithromycin is an option; however, the dose of azithromycin is higher, which is associated with a high incidence of gastrointestinal intolerance. H

Test of cure is only recommended 2 weeks after therapy when pharyngeal gonorrhea is treated with an alternate antibiotic regimen. Patients with infections caused by *N. gonorrhoeae* who do not respond to treatment should have repeat testing with NAAT and culture so that susceptibility data can be obtained; consultation with an expert in the management of these infections should be sought.

KEY POINTS

- Screening for *Neisseria gonorrhoeae* infection is recommended for women younger than 25 years and those 25 years and older with risk factors (new partner, more than one partner, a partner with an STI, or a partner who has concurrent partners).
- First-catch urine (or genital swab) sample nucleic acid amplification testing is the preferred screening and diagnostic method for *Neisseria gonorrhoeae* infection.
- Parenteral ceftriaxone with oral azithromycin is the preferred regimen for the treatment of *Neisseria gonorrhoeae* infection.
- Test of cure in patients with *Neisseria gonorrhoeae* infection is recommended 2 weeks after therapy only when pharyngeal gonorrhea is treated with an alternate antibiotic regimen. HVC

Clinical Syndromes

Cervicitis

Women with cervicitis may present with vaginal discharge and intermenstrual bleeding, but many are asymptomatic. The major diagnostic criteria are (1) visualization of mucopurulent discharge from the cervical os or on a swab obtained from the endocervical canal and (2) eliciting bleeding by passing a swab into the cervical os; cervicitis should be considered in women with either of these findings. *N. gonorrhoeae* and *C. trachomatis* are the most commonly isolated pathogens; however, many cases are enigmatic. The role of *Mycoplasma genitalium* is still unclear; herpes simplex virus is occasionally implicated. Noninfectious causes (for example, chemical irritation from douching) should be sought. Patients should be tested for *N. gonorrhoeae* and *C. trachomatis* with NAAT; evaluation for bacterial vaginosis and trichomoniasis should also be performed (see MKSAP 18 General Internal Medicine).

Pelvic Inflammatory Disease

Unrecognized pelvic inflammatory disease (PID) may result in long-term sequelae, including infertility, chronic pelvic pain, and ectopic pregnancy. Symptoms include lower abdominal pain, vaginal discharge, intermenstrual bleeding or bleeding after intercourse, and dyspareunia. Some women have fever and other signs of systemic toxicity, but this is uncommon.

The diagnostic accuracy of clinical examination is poor; however, because of the potential consequences of untreated infection, clinical findings with a high sensitivity for PID should be used. The presence of uterine tenderness, adnexal tenderness, or cervical motion tenderness is sufficient to make a clinical diagnosis of PID, especially if accompanied by mucopurulent cervical discharge.

PID is believed to be polymicrobial; however, testing only for *N. gonorrhoeae* and *C. trachomatis* is indicated. Most women can be managed in the ambulatory setting with oral antibiotics (see Table 32). Indications for hospitalization include inability to exclude a surgical emergency such as appendicitis, pregnancy, severe systemic toxicity, tubo-ovarian abscess, inability to tolerate oral antibiotics, and failure of initial outpatient management.

Urethritis

H Men with urethritis present with dysuria, urethral pruritus, and discharge. Mucopurulent discharge may be the only symptom and is clinically diagnostic. *N. gonorrhoeae*, *C. trachomatis*, and *M. genitalium* are common causes of urethritis; *Trichomonas* may also be causative. The role of other *Mycoplasma* and *Ureaplasma* species is uncertain at present. A first-catch urine sample should be tested for *N. gonorrhoeae* and *C. trachomatis* by NAAT for diagnosis and for public reporting purposes; FDA-approved tests for *M. genitalium* are not yet available. Microscopic examination of a urethral sample that reveals more than 2 leukocytes per high-powered field has a high positive predictive value for infectious urethritis, but the negative predictive value is poor. A positive leukocyte esterase test result or a microscopic examination with 10 or more leukocytes on a first-void urine specimen is also diagnostic for infectious urethritis. This testing is not required if mucoid, mucopurulent, or purulent urethral discharge is demonstrated on examination. H

Epididymitis

Men with epididymitis present with unilateral pain and swelling in the epididymis; the testes may also be inflamed (epididymo-orchitis). Testicular torsion must be excluded in men with symptoms of sudden onset. *N. gonorrhoeae* and *C. trachomatis* are likely causes in younger, sexually active men. Older men and men who practice insertive anal intercourse may be infected with enteric gram-negative organisms such as *Escherichia coli*. NAAT for STI pathogens should be performed on first-catch urine, and a urine culture should be obtained. See MKSAP 18 General Internal Medicine for further information.

Anorectal Infections

Patients who present with anorectal pain, rectal discharge, or tenesmus should be questioned regarding sexual practices. In addition to receptive anal intercourse, infection may occur in women as a result of autoinoculation from vaginal discharge. Causes include *C. trachomatis*, *N. gonorrhoeae*, syphilis, and herpes simplex virus (HSV). Infections caused by the lymphogranuloma venereum (LGV) serovars (L1, L2, or L3) of *C. trachomatis* had previously been rarely described in the United States, but they are increasingly reported as a cause of proctitis and proctocolitis, mainly among MSM.

Diagnostic evaluation should include NAAT for *C. trachomatis*, *N. gonorrhoeae*, and HSV as well as serologic testing for syphilis (dark-field examination should be performed if available). Additional molecular testing is required to identify LGV serovars of *C. trachomatis*, but it is not widely available commercially; LGV serovars of *C. trachomatis* will be detected by currently available NAATs.

KEY POINTS

- *Chlamydia trachomatis* and *Neisseria gonorrhoeae* are the primary causative organisms in cervicitis, pelvic inflammatory disease, urethritis, epididymitis, and anorectal infections, although other organisms may also be implicated.
- The two major diagnostic criteria of cervicitis are visualization of mucopurulent discharge from the cervical os or on a swab obtained from the endocervical canal or eliciting bleeding by passing a swab into the cervical os.
- The presence of uterine tenderness, adnexal tenderness, or cervical motion tenderness is sufficient to make a clinical diagnosis of pelvic inflammatory disease, especially if accompanied by mucopurulent cervical discharge.
- *Neisseria gonorrhoeae* and *Chlamydia trachomatis* are likely causes of epididymitis in younger, sexually active men; older men and men who practice insertive anal intercourse may be infected with enteric gram-negative organisms such as *Escherichia coli*.

Treatment

Treatment of the clinical syndromes discussed previously is outlined in Table 32. Symptomatic patients evaluated in urgent care centers or emergency departments and others who may not be able to return for follow-up should be treated empirically based on clinical syndrome. Diagnostic testing should still be obtained because STIs are reportable and test results will be informative if the infection fails to respond to empiric therapy.

Patients should abstain from sexual contact for 7 days after completion of therapy and until all sexual partners have been treated. Sexual partners in the previous 60 days, or the most recent partner if greater than 60 days, should be referred for evaluation and treatment. Although independent evaluation and testing of sexual partners is preferred, most states have provisions for providing empiric antibiotic therapy prescriptions to the patient for their partners (expedited partner therapy, or EPT).

KEY POINTS

- Diagnostic testing should be performed even if empiric therapy will be provided to patients unlikely to return for follow up care, because *Neisseria gonorrhoeae* and *Chlamydia trachomatis* infections are reportable, and because test results will be informative if the infection fails to respond to therapy.
- Most states have provisions for providing empiric antibiotic therapy prescriptions for sexual partners (expedited partner therapy, or EPT).

Genital Ulcers

Herpes Simplex Virus

The epidemiology of HSV genital ulcer disease is changing; in some populations, such as young heterosexual women and MSM, HSV-1 is now a more common cause of symptomatic primary infection than HSV-2. Although the clinical manifestations of primary infection by HSV-1 and HSV-2 are indistinguishable, HSV-1 is less likely than HSV-2 to cause symptomatic recurrent ulcers and subclinical shedding. Differentiation between the two viral subtypes is important in counseling patients regarding the natural history of their infection.

H Primary infection presents as multiple painful lesions that begin as erythematous papules, progress to vesicles, then ulcerate, crust, and eventually heal within 2 to 3 weeks (**Figure 12**). Primary infection is often accompanied by significant systemic symptoms. Tender inguinal lymphadenopathy may be present.

Although the clinical manifestations of primary infection are quite characteristic, the viral cause and HSV subtype should be confirmed. NAAT, such as polymerase chain reaction, for HSV-1 and HSV-2 is preferred; other methodologies are far less sensitive. Testing is performed by obtaining a swab from the ulcer base; if only vesicles are present, a vesicle must be unroofed to obtain cells from the ulcer base. The swab must be placed in viral transport medium, so the appropriate sample collection kit must be used. Type-specific serologic testing is not advised for the diagnosis of symptomatic ulcer disease because patients can be seropositive for HSV-1 or HSV-2 yet have genital ulcers from another cause. Potential roles for serologic testing include testing a sexual partner when evaluating the potential benefits of long-term suppressive therapy because a partner who is already infected would not be at risk for transmission. The CDC recommends considering HSV serologic testing in persons who present for STI evaluation, MSM, and persons with HIV infection. Serologic screening in the general population is not recommended.

FIGURE 12. Penile lesions seen in herpes simplex virus (HSV) type 2. Patients with genital HSV infection initially have painful lesions that begin as vesicles and progress to ulcers on an erythematous base.

Antiviral therapy for primary infection has been shown to decrease time to resolution of symptoms, lesion healing, and viral shedding. Antiviral regimens appropriate for treatment of primary infection are outlined in **Table 33**.

Recurrent genital HSV infections are less severe, and symptom duration, time to lesion healing, and duration of viral shedding are reduced. Many patients will experience prodromal itching, burning, or tingling before ulcers appear. Atypical presentations such as fissures and excoriations may occur. Recurrent infection can be managed with either episodic self-start therapy (initiated within 24 hours of symptoms) or long-term suppressive therapy (see Table 33). Long-term suppressive therapy should be considered for persons with frequent recurrences and should be discussed with all patients because this strategy has been shown to decrease the risk of transmission to sexual partners. Laboratory monitoring is not required for patients undergoing long-term suppressive therapy; however, the continued need for therapy should be reviewed annually. Length of time since last recurrence and potential benefits of continued suppression in preventing

TABLE 33. Treatment of Herpes Simplex Virus Genital Infections

Clinical Syndrome	Recommended Regimen[a]
Primary infection[b]	Acyclovir, 400 mg three times daily, *or* acyclovir, 200 mg five times daily, *or* famciclovir, 250 mg three times daily, *or* valacyclovir, 1 g twice daily; all regimens for 7-10 days
Recurrent infection	Acyclovir, 400 mg three times daily for 5 days, *or* acyclovir, 800 mg twice daily for 5 days, *or* acyclovir, 800 mg three times daily for 2 days, *or* famciclovir, 125 mg twice daily for 5 days, *or* famciclovir, 1 g twice daily for 1 day, *or* famciclovir, 500 mg once followed by 250 mg twice daily for 2 days, *or* valacyclovir, 500 mg twice daily for 3 days, *or* valacyclovir, 1 g once daily for 5 days
Suppressive therapy	Acyclovir, 400 mg twice daily, *or* famciclovir, 250 mg twice daily, *or* valacyclovir, 500 mg daily[c], *or* valacyclovir, 1 g daily

[a]All regimens are given orally; topical preparations are not recommended for treatment of genital herpes simplex virus.

[b]Therapy can be extended if healing is incomplete after 10 days of treatment.

[c]The 500-mg dose of valacyclovir may be less effective than the 1-g dose in patients who have very frequent recurrences (≥10 episodes per year).

transmission to sexual partners are factors that can inform the decision to stop suppressive therapy.

Patients should be counseled regarding the natural history of infection and informed that asymptomatic viral shedding is the most common source of HSV transmission to sexual partners. Condoms and abstinence from sexual activity when lesions are present can reduce the risk of transmission. Suppressive therapy to reduce risk of transmission should be discussed. Men and women should be counseled about the risks of neonatal HSV infection. Women should be advised to inform their obstetric provider and pediatrician of HSV infection in themselves or their sexual partner if they become pregnant.

KEY POINTS

- Viral cause and herpes simplex virus subtype in primary infection should be confirmed by nucleic acid amplification testing, such as polymerase chain reaction, using a swab obtained from the ulcer base.
- The Centers for Disease Control and Prevention recommend considering herpes simplex virus serologic testing in persons who present for sexually transmitted infection evaluation, men who have sex with men, and persons with HIV infection; screening in the general population is not recommended.
- Long-term suppressive therapy of recurrent herpes simplex virus infection may be preferred over self-start episodic therapy because of decreased risk of transmission to sexual partners.

Syphilis

The incidence of primary and secondary syphilis has been increasing in the United States since 2000. The USPSTF recommends screening nonpregnant adolescents and adults at high risk of infection. Persons at risk include MSM and commercial sex workers and those with HIV infection, multiple sex partners, and previous syphilis. In 2015, the CDC issued a clinical advisory regarding the increasing incidence of ocular syphilis.

Primary syphilis presents as a painless genital ulcer (chancre) with a raised regular border that demonstrates firm induration on palpation (**Figure 13**). Several chancres may be present and may occur in the oral cavity. Regional lymphadenopathy may be present. The diagnosis of primary syphilis can be made on the basis of dark-field examination of material from a suspect lesion. Serologic test results may be negative in early primary infection. Even in the absence of treatment, lesions heal spontaneously in 3 to 6 weeks.

The most common manifestation of secondary syphilis is rash. Various morphologies are described; involvement of the palms and soles is characteristic. In intertriginous areas, papules may coalesce to form condyloma lata (plaque-like lesions). Mucous patches (superficial erosions on mucosal surfaces) may occur in the oral cavity and moist genital regions and are

FIGURE 13. The primary ulcerative lesion (chancre) in patients with syphilis develops approximately 3 weeks after infection occurs, has a clean appearance with heaped-up borders, and is indurated and usually painless. It is often unrecognized.

highly infectious. Prominent systemic symptoms and generalized lymphadenopathy are common. Uveitis and neurosyphilis (meningitis) can occur. Secondary syphilis manifestations can also resolve without treatment, followed by latent infection (a positive serologic test result without clinical manifestations). If latent infection is of less than 12 months' duration, it is termed early latent; if greater than 12 months' duration, it is late latent. Practically, these determinations can be made only if past serology results are available. Otherwise, patients are considered to have syphilis of unknown duration.

Tertiary syphilis is rarely seen in the United States, although neurologic disease still occurs. Spinal fluid examination should be sought in any patient with unexplained neurologic symptoms and serologic evidence of syphilis as well as in those who do not demonstrate an appropriate serologic response to syphilis treatment.

Diagnosis of secondary and tertiary syphilis relies on serologic testing. Many laboratories use the "reverse" serologic testing strategy, starting with an automated enzyme immunoassay followed by a nonspecific test (rapid plasma reagin or Venereal Disease Research Lab test). Patients with a positive enzyme immunoassay result but negative rapid plasma reagin or Venereal Disease Research Lab test result should have a second specific treponemal antibody test to confirm the result. Those with a confirmed positive result and no history of syphilis treatment should be offered treatment for syphilis of unknown duration.

H CONT. Syphilis treatment is outlined in **Table 34**. Sexual partners of those with primary, secondary, or early latent syphilis exposed in the preceding 90 days should be treated regardless of serologic results. H

KEY POINTS

- Primary syphilis presents as a painless genital ulcer (chancre) with a raised regular border that demonstrates firm induration on palpation; lesions heal spontaneously in 3 to 6 weeks even without treatment.
- The most common manifestation of secondary syphilis is rash, with characteristic involvement of the palms and soles; in intertriginous areas, papules may coalesce to form condyloma lata (plaque-like lesions), and mucous patches (superficial erosions on mucosal surfaces) may occur in the oral cavity and moist genital regions and are highly infectious.
- Diagnosis of secondary and tertiary syphilis relies on serologic testing; patients with a positive enzyme immunoassay result and positive rapid plasma reagin or Venereal Disease Research Lab test result and no history of syphilis treatment should be offered treatment for syphilis of unknown duration.

Chancroid and Lymphogranuloma Venereum

With the exception of proctitis or proctocolitis caused by the LGV serovars of *C. trachomatis*, these two STIs are rarely seen in the United States. The clinical presentation and evaluation are outlined in **Table 35**, and treatment is outlined in **Table 36**.

Genital Warts

Genital warts have a variety of appearances, including papular or pedunculated lesions (**Figure 14**). Larger, verrucous, exophytic lesions can occur. Most are asymptomatic; however, large lesions may cause irritation or pain depending on their location. Nononcogenic types of human papillomavirus (HPV) are responsible for most lesions. Oncogenic subtypes less commonly cause genital warts. HPV infection can be diagnosed based on the presence of lesions with a consistent morphologic appearance. Specific testing for HPV is not recommended for diagnosis.

Warts will often resolve without therapy, but treatment is indicated for symptomatic warts or if the cosmetic appearance of the warts is causing psychological distress. Patients should be counseled that successful treatment may not eliminate the risk of transmission. Therapy includes patient-applied

TABLE 34. Treatment of Syphilis

Stage	Recommended Regimen[a]	Alternate Regimen for Penicillin-Allergic Patients
Primary and secondary	Benzathine penicillin G, 2.4 million units IM single dose	Doxycycline, 100 mg PO twice daily, *or* tetracycline, 500 mg PO four times daily, for 14 days
Early latent	Benzathine penicillin G, 2.4 million units IM single dose	Doxycycline, 100 mg PO twice daily, *or* tetracycline, 500 mg PO four times daily, for 14 days
Late latent or syphilis of unknown duration	Benzathine penicillin G, 2.4 million units IM at 1-week intervals for 3 doses	Doxycycline, 100 mg PO twice daily, *or* tetracycline, 500 mg PO four times daily, for 28 days
Neurosyphilis	Aqueous crystalline penicillin G, 18-24 million units daily given as 3-4 million units IV every 4 hours or by continuous infusion for 10-14 days, *or* procaine penicillin, 2.4 million units IM daily, plus probenecid, 500 mg PO four times daily, both for 10-14 days	Ceftriaxone, 2 g IM or IV daily for 10-14 days[b]

IM = intramuscularly; IV = intravenously; PO = orally.

[a]Penicillin is the only effective antimicrobial agent for treatment of syphilis at any stage in pregnancy; therefore, pregnant penicillin-allergic patients should be desensitized and treated with the appropriate penicillin regimen as outlined above.

[b]Limited data are available to support the use of this alternate regimen, and the possibility of cross-reaction in penicillin-allergic patients must be considered. In patients who cannot take ceftriaxone, penicillin desensitization is recommended.

TABLE 35. Clinical Presentation and Diagnosis of Chancroid and Lymphogranuloma Venereum

Clinical Entity	Causative Agent	Presentation	Diagnosis
Chancroid	*Haemophilus ducreyi*	Painful genital ulcer; tender inguinal lymph nodes, which often suppurate	Culture is difficult; consider diagnosis if painful ulcer with tender and suppurative regional lymphadenopathy, no evidence of syphilis by dark-field examination or serology, and negative HSV PCR or HSV culture
LGV	L1, L2, and L3 serovars of *Chlamydia trachomatis*	Painless genital papule or ulcer with unilateral tender inguinal lymphadenopathy	NAAT for *C. trachomatis*; does not distinguish the serovars, so diagnosis is made based on clinical and epidemiologic findings

HSV = herpes simplex virus; LGV = lymphogranuloma venereum; NAAT = nucleic acid amplification test; PCR = polymerase chain reaction.

TABLE 36. Treatment of Chancroid and Lymphogranuloma Venereum

Clinical Entity	Recommended Regimen
Chancroid	Azithromycin, 1 g PO single dose, *or* ceftriaxone, 250 mg IM single dose, *or* ciprofloxacin, 500 mg PO twice daily for 3 days, *or* erythromycin base, 500 mg PO three times daily for 7 days
Lymphogranuloma venereum	Doxycycline[a], 100 mg PO twice daily for 21 days (preferred), *or* erythromycin base, 500 mg PO four times daily for 21 days (alternate)

IM = intramuscularly; PO = orally.

[a]Doxycyline should be avoided or used with caution in pregnant patients.

FIGURE 14. Genital warts caused by human papillomavirus infection are typically flesh colored and exophytic; pedunculated lesions often occur.

or physician-administered modalities. Patient-applied therapies include imiquimod, podofilox, and sinecatechins; provider-administered therapies include trichloroacetic acid or bichloroacetic acid, cryotherapy with liquid nitrogen or cryoprobe, or surgical removal. The modality chosen depends on size, number, and location of warts; patient preference; and provider experience. No evidence indicates superiority of any of the modalities recommended. Ulcerated or pigmented warts and those that fail to respond to or worsen after therapy should be biopsied to exclude a cancerous lesion.

KEY POINT

- Nononcogenic types of human papillomavirus are responsible for most genital warts, which often resolve without therapy.

Osteomyelitis

Osteomyelitis occurs as a result of hematogenous dissemination or contiguous spread of bacteria. Hematogenous osteomyelitis in adults most commonly affects vertebral bodies, although involvement of other sites has been described, particularly in persons who inject drugs. Contiguous spread osteomyelitis may arise from direct contamination (fracture, joint replacement, orthopedic implant), wounds (pressure sores, diabetic foot ulcers), or adjacent soft tissue infection. Population-based studies suggest that the incidence of osteomyelitis among adults is increasing in the United States, most likely because of the increasing prevalence of diabetes mellitus. Osteomyelitis can be difficult to diagnose, can cause indolent infections that persist for prolonged periods, and requires long-term antibiotic treatment; thus, the economic impact of this infection is substantial.

Clinical Manifestations

Osteomyelitis frequently presents as subacute or chronic pain over the affected region of bone. If osteomyelitis has resulted from direct contamination of a wound, the wound may fail to heal or may reopen after healing. Spontaneously opening wounds accompanied by drainage (sinus tracts) are a late manifestation of infection. Underlying osteomyelitis should be considered when chronic wounds, such as pressure ulcers, do not respond to appropriate therapy. Fever and other systemic manifestations of infection are not common but are more likely in patients with acute hematogenously disseminated infection. Clinical findings in patients with diabetes-associated foot ulcer osteomyelitis and vertebral osteomyelitis are discussed separately. H

KEY POINTS

- Osteomyelitis frequently presents as subacute to chronic pain over the affected region of bone; fever and other systemic manifestations of infection are uncommon.
- Underlying osteomyelitis should be considered when chronic wounds, such as pressure ulcers, do not respond to appropriate therapy.

Diagnosis

Laboratory and Imaging Studies

Laboratory studies are nondiagnostic for osteomyelitis. Elevated inflammatory markers, such as erythrocyte sedimentation rate or C-reactive protein level, increase the pretest probability of infection and can be useful in monitoring therapeutic response; normal inflammatory markers alone are insufficient to exclude the diagnosis. Except in acute hematogenous osteomyelitis, leukocytosis is uncommon; in chronic osteomyelitis, anemia may be present. Blood culture results are rarely positive, except in patients with hematogenous osteomyelitis (such as vertebral osteomyelitis). Blood cultures should be obtained when hematogenous osteomyelitis is suspected or in patients with systemic manifestations of sepsis.

Plain radiography is not adequately sensitive to exclude a diagnosis of osteomyelitis, but it is recommended during

H CONT. initial evaluation because of the relatively low cost. The specificity of plain radiography is sufficient to confirm the diagnosis in most patients. If a plain radiograph is not diagnostic, MRI, with and without intravenous contrast, is preferred. If MRI cannot be obtained because of specific contraindications, CT with intravenous contrast is an alternative. Nuclear medicine studies are less sensitive and specific for osteomyelitis but can be used when neither CT with contrast nor MRI are possible after review with the consulting radiologist. H

KEY POINTS

- Laboratory studies are nondiagnostic for osteomyelitis; blood culture results are rarely positive, except in patients with hematogenous osteomyelitis.
- HVC The specificity of plain radiographs is sufficient to confirm the diagnosis in most patients; if plain radiographs do not positively identify osteomyelitis, MRI, with and without intravenous contrast, is the preferred imaging modality.

H Bone Biopsy

Obtaining biopsy material for culture and pathologic examination is essential to the evaluation of suspected osteomyelitis. Confirming the presence of a pathogen maximizes the chance that the chosen antibiotic therapy will be successful. Specimens may be obtained at surgery or by image-guided biopsy. A bone biopsy is generally not required in persons with positive blood culture results. A possible exception is injection drug users because they have frequent bacteremias, and the organism in the blood culture may not represent the pathogen in the bone. In culture-negative disease, additional testing of biopsy material with nucleic acid amplification techniques, such as broad-range 16S ribosomal RNA gene amplification, may yield the causative organism, although these techniques will not provide information regarding antimicrobial susceptibilities. H

KEY POINT

- Obtaining biopsy material for culture and pathologic examination is essential to the evaluation of suspected osteomyelitis.

H Treatment

Antibiotic therapy for osteomyelitis should be based on results of susceptibility testing from bone or blood culture isolates and knowledge of antibiotic levels achievable in bone for the selected agent. Unless systemic signs of sepsis or concomitant soft tissue infection or bacteremia are present, empiric antibiotics should be withheld until a bone biopsy is obtained. Surgical debridement is indicated if bone necrosis is extensive. Orthopedic hardware should be removed, if possible, to increase the chance of therapeutic success. Parenteral antimicrobial agents are usually chosen initially, but highly bioavailable oral agents with good bone penetration, such as fluoroquinolones, may be considered. Rifampin should be used in combination with another antistaphylococcal agent to manage *Staphylococcus aureus* infections in the setting of orthopedic hardware if the hardware cannot be removed. Little evidence is available to guide recommendations on duration of therapy; 4 to 6 weeks of antibiotics is considered sufficient for acute infections, whereas longer courses may be required for chronic infections. In some circumstances, especially when hardware cannot be removed, indefinite suppressive therapy may be required. Patients should be informed about the risk of relapse and told that relapse can occur many years after therapy completion. H

KEY POINTS

- Unless systemic signs of sepsis or concomitant soft tissue infection or bacteremia are present, empiric antibiotics should be withheld in suspected osteomyelitis until a bone biopsy is obtained.
- Surgical debridement is indicated for osteomyelitis if bone necrosis is extensive.
- Generally, 4 to 6 weeks of antibiotic therapy is sufficient for acute osteomyelitis; longer courses are required for chronic infections.

H Evaluation and Management of Osteomyelitis in Diabetic Foot Ulcers

The incidence of diabetic foot infection is increasing with the increasing prevalence of diabetes mellitus both in the United States and worldwide (see MKSAP 18 Dermatology). These infections are the most frequent diabetes-related complication necessitating hospitalization, cause significant morbidity (especially limb amputation), and are associated with increased mortality. Nonhealing ulcers become colonized with bacteria, after which infection may develop with contiguous spread to bone.

A diagnosis of osteomyelitis should be considered when a diabetic foot ulcer is deep (presence of exposed bone), large (>2 cm in diameter), or chronic (nonhealing after 6 weeks of standard care). Up to two thirds of affected patients do not have leukocytosis or elevated inflammatory markers. A probe-to-bone test (sterile probe inserted into the ulcer base to evaluate for contact with a hard or gritty surface representing bone or joint capsule) should be performed. In a clinically infected ulcer (presence of pus), the positive predictive value of the probe-to-bone test is high; in a noninfected ulcer, the negative predictive value is high. Imaging options are as described for other causes of osteomyelitis. All patients with a new diabetic foot infection should have plain radiography to assess for bony abnormalities, soft tissue gas, and foreign bodies.

Bone samples for histologic confirmation of diagnosis and for culture can be obtained during bone debridement; if debridement is not required, a bone biopsy should be

obtained. *S. aureus* and streptococcal species account for most osteomyelitis complicating diabetic foot ulcers; gram-negative organisms are found in as many as 25% of infections. Anaerobes are much less common. Infections may be polymicrobial.

Although deep sinus-tract tissue cultures can be obtained, the correlation with bone biopsy samples is variable, and bone biopsy remains the recommended modality for microbiologic diagnosis. Recent evidence shows that patients treated with antibiotics chosen on the basis of bone culture results have a better outcome than those treated without these results. If infected but viable bone is present, a 4- to 6-week course of parenteral or oral antibiotic therapy is recommended, as it is for other forms of osteomyelitis. Prolonged oral therapy is indicated if there is residual necrotic bone.

Indications for amputation include persistent sepsis, inability to tolerate antibiotic therapy, progressive bone destruction despite appropriate therapy, or bone destruction that compromises the mechanical integrity of the foot. The patient may also choose amputation over prolonged antibiotic therapy. Hyperbaric oxygen therapy, growth factors, and topical negative-pressure therapy have insufficient evidence of benefit to recommend their use. However, limb salvage may be possible far more often than previously thought when treatment is directed by a dedicated multidisciplinary team consisting of a foot surgeon, a vascular surgeon, an internist, an infectious diseases specialist, nurses, and a physical therapist. H

KEY POINTS

- Osteomyelitis should be considered when a diabetic foot ulcer is deep (presence of exposed bone), large (>2 cm in diameter), or chronic (nonhealing after 6 weeks of standard care).
- Bone samples for diagnosis and guidance of antimicrobial therapy should be obtained in patients with osteomyelitis during bone debridement or by bone biopsy.
- If infected but viable bone is present in patients with diabetes mellitus–associated osteomyelitis, a 4- to 6-week course of antibiotic therapy is recommended; prolonged oral therapy is indicated for patients with residual necrotic bone.

Evaluation and Management of Vertebral Osteomyelitis

Except when resulting from surgical instrumentation, vertebral osteomyelitis is almost exclusively secondary to hematogenous dissemination. Risk factors for vertebral osteomyelitis include older age, immunocompromise, indwelling catheters, hemodialysis, and injection drug use. Infection occurs in the intervertebral disk space and then spreads to the adjacent vertebral bodies (spondylodiskitis). The lumbar spine is most frequently involved, followed by the thoracic and then the cervical spine. Most infections are due to *S. aureus*, but *S. lugdunensis* is increasingly implicated. Persistent bacteremia with other coagulase-negative staphylococci in patients treated with hemodialysis and those with intravascular devices may obviate the need for biopsy. Enterobacteriaceae, *Pseudomonas aeruginosa* (especially in persons who inject drugs), and *Candida* species also may cause vertebral osteomyelitis.

New-onset back or neck pain or progressive worsening of chronic pain that is unresponsive to conservative management should raise concern for vertebral osteomyelitis, especially when accompanied by elevated levels of inflammatory markers, neurologic findings, or unexplained fever. Neurologic findings can include sensory loss, weakness, or radiculopathy and are reported in up to one third of patients. Point tenderness is present in as few as one third of patients. Delay in diagnosis is common; in a third of patients, pain is initially attributed to degenerative disease.

As with other forms of osteomyelitis, MRI is the preferred imaging modality. Blood cultures should be performed in all patients. Testing for *Mycobacterium tuberculosis* infection (with tuberculin skin testing or an interferon-γ release assay), fungal blood cultures, and serologic tests for *Brucella* species are appropriate for patients at risk for these pathogens (see *Mycobacterium tuberculosis* Infection, Fungal Infections, and Travel Medicine). A positive *Brucella* serologic result in the correct epidemiologic setting is considered diagnostic, and biopsy is not needed. Otherwise, image-guided biopsy has a diagnostic yield of approximately 60% and should be used in patients with negative blood culture results. A second biopsy should be obtained if the first is not diagnostic. Nucleic acid amplification techniques can increase biopsy yield; specimens should also be sent for pathologic examination. Open biopsy or percutaneous endoscopic diskectomy and drainage may be considered if the microbiologic diagnosis remains elusive after a second image-guided biopsy attempt.

Patients with neurologic compromise or evidence of spinal instability should undergo evaluation for immediate surgical intervention. Patients with complications, such as severe sepsis, progressive neurologic deficit, spinal instability, or epidural abscess, should receive empiric antibiotic therapy. Otherwise, initiation of antibiotic therapy for uncomplicated vertebral osteomyelitis is based on culture results. Parenteral therapy is generally recommended, especially for *S. aureus*. However, oral agents with high bioavailability and good bone penetration (such as fluoroquinolones) may be used, especially for Enterobacteriaceae. The duration of antibiotic therapy for vertebral osteomyelitis is typically 6 weeks. Patients should be followed clinically for improvement in symptoms, and inflammatory markers can be monitored. Repeat imaging, especially MRI, should be reserved for patients who do not respond clinically; worsening of imaging findings in patients with a satisfactory clinical response is well described. H

KEY POINTS

- New-onset back or neck pain or progressive worsening of chronic pain that is unresponsive to conservative management should raise concern for vertebral osteomyelitis, especially when accompanied by elevated inflammatory markers, neurologic findings, or unexplained fever.
- The diagnostic evaluation of vertebral osteomyelitis should include blood cultures for all patients; testing for *Mycobacterium tuberculosis* infection, fungal blood cultures, and serologic tests for *Brucella* species are appropriate for patients at risk for these pathogens.
- Parenteral antibiotic therapy chosen on the basis of culture results is recommended for uncomplicated vertebral osteomyelitis, although oral agents with high bioavailability and good bone penetration also can be used; duration of treatment is 6 weeks.

Fever of Unknown Origin

Introduction

The classic definition of fever of unknown origin (FUO) has changed over time (including removing the requirement for in-hospital evaluation), and three categories have been added: health care–associated, neutropenic, and HIV-associated (**Table 37**). Diagnostic advances have revealed a spectrum of diseases causing FUO, with origins more rapidly identifiable for many cases.

Causes

The differential diagnosis of FUO includes more than 200 diseases, although most adult cases are attributed to one of several dozen causes. Common causes of FUO include infections, neoplasm or malignancy, rheumatologic or inflammatory disorders, and miscellaneous causes (see Table 37).

Evaluation

Many FUO occurrences are atypical presentations of common diseases. A careful history and physical examination should be performed and repeated intermittently during the period of evaluation. The history should include procedures, surgeries, presence of foreign bodies or implants, immunosuppression, travel, animal and other exposures (including hobbies), dietary habits, and medications (including over-the-counter medications). The degree and pattern of fever is not specific and not diagnostic in most instances.

TABLE 37. Categories and Common Causes of Fever of Unknown Origin

Category	Definition	Common Causes
Classic	Temperature >38.3 °C (100.9 °F) for at least 3 weeks with at least 1 week of in-hospital investigation[a] or Temperature >38.3 °C (100.9 °F) for at least 3 weeks that remains undiagnosed after 2 visits in the ambulatory setting[b] or 3 days in the hospital	Infection (endocarditis, tuberculosis [extrapulmonary/disseminated], abscess, endemic mycoses), neoplasm (leukemia, lymphoma, renal cell carcinoma, hepatocellular carcinoma), connective tissue disease (adult-onset Still disease, polymyalgia rheumatica, vasculitis, systemic lupus erythematosus, giant cell arteritis), endocrine disorder (hyperthyroidism, subacute thyroiditis), genetic (familial Mediterranean fever), or miscellaneous (drug fever, factitious fever)
Health care–associated	Temperature >38.3 °C (100.9 °F) in patients hospitalized ≥3 days (without fever or evidence of potential infection at the time of admission) and negative evaluation for at least 3 days	Drug fever, septic thrombophlebitis, deep venous thrombosis/pulmonary embolism, sinusitis in the setting of a nasogastric tube, chronic sinusitis without a nasogastric tube, postoperative abscess, *Clostridium difficile* infection, device- or procedure-related endocarditis
Neutropenic	Temperature >38.3 °C (100.9 °F) and neutrophil count <500/µL (0.5×10^9/L) for >3 days and negative evaluation after 48 hours	Bacteremia, opportunistic fungal infections (aspergillosis, candidiasis; more common than bacteremia after 7 days), drug fever, deep venous thrombosis/pulmonary embolism, underlying malignancy, allograft rejection in transplant; undocumented in 40%-60% of cases
HIV-associated	Temperature >38.3 °C (100.9 °F) for >3 weeks (outpatients) or >3 days (inpatients) in patients with confirmed HIV infection	Primary HIV infection, opportunistic infections (cytomegalovirus, cryptococcosis, tuberculosis, atypical mycobacteria, toxoplasmosis, *Pneumocystis jirovecii* pneumonia), lymphoma, immune reconstitution inflammatory syndrome

[a]Original definition of fever of unknown origin.

[b]Ambulatory setting is the preferred venue for evaluation and treatment.

Initial testing for the evaluation of classic FUO includes complete blood count with differential, electrolyte levels, kidney and liver function tests (hepatitis serology if results are abnormal), lactate dehydrogenase level, urinalysis or microscopy and urine culture, erythrocyte sedimentation rate, C-reactive protein, antinuclear antibodies, rheumatoid factor, HIV testing, cytomegalovirus polymerase chain reaction testing, blood cultures (three sets, each set obtained at least several hours apart), tuberculosis testing, and chest radiography (or chest CT). Q fever serology should be considered if risk factors exist, and mycobacterial blood cultures should be obtained in HIV-positive patients with CD4 cell counts of 50/µL or less.

If initial tests do not suggest a cause, abdominal or pelvic CT may be considered to evaluate for intra-abdominal abscess or lymphoproliferative disorders. Liver, lymph node, and temporal artery biopsies have a diagnostic yield of about 35%, particularly when performed when infection is unlikely. Posterior cervical, supraclavicular, infraclavicular, epitrochlear, hilar, mediastinal, and mesenteric lymph node biopsies are more likely to provide a diagnosis than that of other lymph nodes. Bone marrow biopsy can be helpful when leukopenia or thrombocytopenia is present.

A definitive diagnosis is lacking in up to half of patients after extensive evaluation. FUO lasting more than 1 year is unlikely to be caused by infection or malignancy. Undiagnosed FUO is generally associated with a benign long-term course, particularly when fever is not associated with weight loss or other signs of underlying serious disease.

KEY POINTS

- The classic definition of fever of unknown origin no longer requires inpatient evaluation and has been expanded to include health care–associated, neutropenic, and HIV-associated designations.
- In patients with fever of unknown origin, a careful history and physical examination should be performed, including past procedures or surgeries, presence of foreign bodies or implants, immunosuppression, travel, animal or other exposures, dietary habits, and medications.
- A definitive diagnosis is lacking in up to half of patients with fever of unknown origin after extensive evaluation, but duration of more than 1 year is unlikely to be caused by infection or malignancy.

Primary Immunodeficiencies

Introduction

Primary immunodeficiency disorders often present during childhood, but milder heritable forms may not manifest until adulthood. Primary immunodeficiency should be considered when patients present with frequent infections or infections with unusual organisms. The specific microbiology is often a clue to which arm of the immune system is affected (**Table 38**).

TABLE 38. Properties of Selected Primary Immunodeficiency Disorders

	Common Infections and Pathogens	Diagnostic Testing	Treatment
Selective IgA deficiency	Sinopulmonary infections: *Streptococcus pneumoniae* *Haemophilus influenzae* Diarrhea/malabsorption: *Giardia lamblia*	Undetectable (severe deficiency) or low (partial deficiency) IgA level with normal IgG and IgM levels	Vaccination against *S. pneumoniae* Prophylactic antibiotics are controversial
Common variable immunodeficiency	Sinopulmonary infections: *S. pneumoniae* *H. influenzae* *Mycoplasma pneumoniae* Respiratory viruses Diarrhea: Norovirus *Campylobacter* *G. lamblia* Urethritis: *Mycoplasma* *Ureaplasma*	IgG level and either IgA or IgM ≤2 standard deviations below the mean PLUS impaired humoral response to vaccination	Immune globulin replacement therapy Immunization with inactivated vaccines Prophylactic antibiotics are controversial
Complement deficiency	Early components (C2-C4): Similar to CVID Late components (C5-C9): Recurrent infections with *Neisseria gonorrhoeae* or *Neisseria meningitidis*	Decreased level of total hemolytic complement (CH_{50})	Same as CVID for C2-C4 complement deficiency Quadrivalent meningococcal conjugate and serogroup B meningococcal vaccines for C5-C9 complement deficiency

CVID = common variable immunodeficiency.

Diagnosis of primary immunodeficiency allows directed therapy, targeted immunization, and optimized empiric treatment of secondary infections.

Selective IgA Deficiency

Although most patients with selective IgA deficiency (SIgAD) remain asymptomatic, it is the most common primary antibody deficiency. IgA provides mucosal immunity; therefore, patients with SIgAD are susceptible to infections of the respiratory tract and, less frequently, gastrointestinal tract. Sinopulmonary infections are the most common presenting manifestation, particularly with encapsulated bacteria (see Table 38). Anaphylaxis to blood products may occur because of the presence of anti-IgA antibodies. Testing for anti-IgA antibodies should be considered in patients with severe SIgAD or history of reaction to blood products or intravenous immune globulin infusion.

KEY POINT

- Patients with selective IgA deficiency may be asymptomatic, present with sinopulmonary or gastrointestinal tract infections, or experience anaphylaxis to blood products.

Common Variable Immunodeficiency

Common variable immunodeficiency (CVID) is a heterogenous syndrome associated with decreased quantitative immunoglobulin levels and impaired humoral response to antigens. Impaired humoral response can be tested by measuring specific antibody production before and after immunization with tetanus and pneumococcal polysaccharide vaccines. Diagnosis is usually delayed until adolescence or adulthood, although a history of recurrent infection throughout childhood may often be elicited.

CVID increases risk of infections of the upper and lower respiratory tracts caused by encapsulated bacteria, *Mycoplasma* species, and respiratory viruses. Gastrointestinal infections typically present with acute diarrhea caused by common enteropathogenic viruses or bacteria. Chronic diarrhea with malabsorption suggests giardiasis or chronic norovirus infection, an increasingly recognized pathogen in this population. Additionally, patients with CVID are at increased risk of autoimmune disease, inflammatory bowel disease, granulomatous disease (noncaseating granulomas in the lymphoid or solid organs), bronchiectasis, and malignancy.

Pooled immune globulin replacement therapy for CVID is performed through intravenous infusions or subcutaneous injections. Passive replacement is associated with lower rates of infections and hospitalizations. Immunization is only partially effective because of impaired vaccination response; live vaccines should be avoided. The role of prophylactic antibiotics is controversial because they can predispose patients to infection with more resistant organisms.

KEY POINTS

- Patients with common variable immunodeficiency can experience recurrent infections and are at increased risk of noninfectious complications, including autoimmune disease, inflammatory bowel disease, granulomatous disease, bronchiectasis, and malignancy.
- Live vaccines should be avoided in persons with common variable immunodeficiency.

Abnormalities in the Complement System

Infections and other antigenic stimuli trigger an inflammatory reaction through the classical, alternative, or lectin pathway of the complement cascade system. The result is formation of the membrane attack complex, which adheres to pathogens to facilitate immune detection and destruction.

Complement deficiencies can be divided into deficiencies in early or activating components (C2, C3, C4) and late or terminal components (C5-C9). Early component deficiency, especially C4, is associated with increased rates of systemic lupus erythematosus and increased risk of infection with encapsulated organisms. Patients with early complement deficiency present similarly to patients with CVID, with recurrent sinopulmonary infections. Terminal complement protein defects lead to an inability to form the membrane attack complex and typically present with recurrent infections of *Neisseria* species, particularly meningococcal meningitis. *N. meningitidis* infection in this population tends to be less severe than in immunocompetent persons, perhaps owing to uncommon serogroups. A personal or family history of recurrent *Neisseria* infections is an indication to test the total hemolytic complement (CH_{50}) level because any defect in the classical complement pathway will result in a low total level.

KEY POINTS

- Early component complement deficiency is associated with an increased rate of systemic lupus erythematosus and risk of infection with encapsulated organisms; terminal complement defects can result in recurrent *Neisseria* infections.
- Any defect in the classical complement pathway will result in low total hemolytic complement (CH_{50}) level.

Bioterrorism

Introduction

Unusually severe illness, rapid increase in disease incidence, atypical clinical presentation, and uncommon

geographic, temporal, or demographic clustering of disease outbreaks suggest a bioterrorism attack. Bioterrorism agents are classified (**Table 39**) according to ease of dissemination, mortality rate, potential for public panic and social disruption, and need for special action for public health preparedness.

Anthrax

Anthrax infection is caused by *Bacillus anthracis* spores (**Figure 15** panel A and Figure 15 panel B). Spores may be spread by aerosolization or in the mail, with infection following inhalation; any case of inhalation anthrax must be considered potential bioterrorism. Infection may also occur by cutaneous contact, with a characteristic black eschar forming (Figure 15 panel C), or by ingestion. Person-to-person transmission does not occur.

The clinical presentation of inhalational anthrax includes malaise, myalgia, fever, cough, dyspnea, and substernal chest discomfort. Meningitis occurs in up to 50% of persons. Rapid clinical deterioration leads to shock and death. Diagnosis is made by culture or polymerase chain reaction (PCR) of blood, tissues, or fluid samples. Radiographic imaging reveals a widened mediastinum (Figure 15 panel D).

Treatment is outlined in **Table 40**. Toxin-neutralizing human monoclonal antibodies and anthrax immune globulin are approved for treatment and prevention of inhalation anthrax in conjunction with antibiotics. Postexposure prophylaxis consists of a fluoroquinolone or doxycycline in conjunction with vaccination.

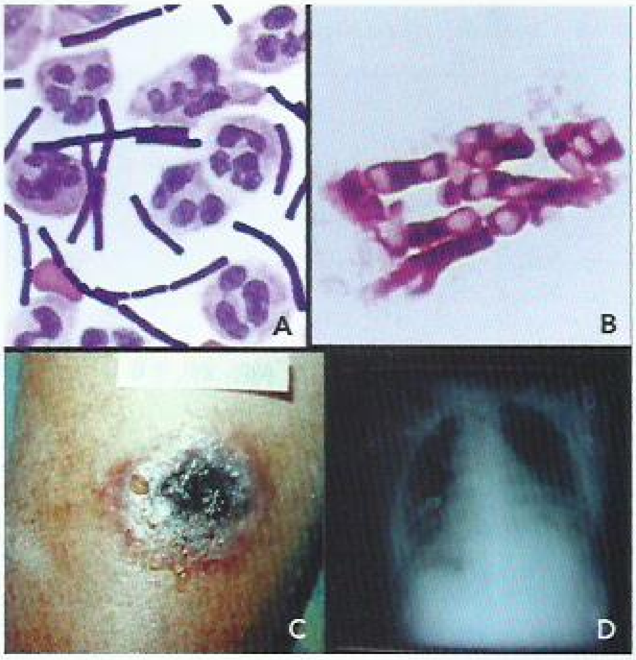

FIGURE 15. *A*, "box-car"-shaped, gram-positive *Bacillus anthracis* bacilli in the cerebrospinal fluid of the index case of inhalational anthrax resulting from bioterrorism in the United States; *B*, terminal and subterminal spores of *B. anthracis*; *C*, black eschar lesion of cutaneous anthrax; *D*, chest radiograph of a patient with anthrax showing a widened mediastinum caused by hemorrhagic lymphadenopathy.

KEY POINTS

- Any case of inhalation anthrax should be considered potential bioterrorism.
- Patients with inhalational anthrax infection present with malaise, myalgia, fever, cough, dyspnea, and substernal chest discomfort; radiographic imaging reveals a widened mediastinum.

TABLE 39. Potential Agents of Bioterrorism

Class A[a]	Class B[b]	Class C[c]
Anthrax	Q fever	Emerging infectious diseases
Botulism	Brucellosis	Nipah virus
Plague	Glanders	Hantavirus
Smallpox	Melioidosis	
Tularemia	Viral encephalitis	
Viral hemorrhagic fever	Typhus fever	
	Ricin toxin	
	Staphylococcal enterotoxin B	
	Psittacosis	
	Foodborne illness	
	Waterborne illness	

[a]Greatest potential for use in an attack, easy dissemination, high mortality, and profound public health implications.

[b]Less easily spread, fewer illnesses and deaths, fewer public health preparation measures required.

[c]Potential to be engineered for future mass dissemination and significant mortality.

Smallpox (Variola)

Routine smallpox vaccination ceased in 1980, after the World Health Organization declared the disease eradicated, leaving much of the world's population without immunity. Following inhalation, multiplication in regional lymph nodes results in viremia.

Secondary viremia occurs 1 week later, accompanied by fever, systemic symptoms, and rash, beginning with lesions on the oral mucosa and face and then the arms, legs, hands and feet, and to a lesser extent the trunk. Lesions evolve synchronously (same stage of maturation on any one area of the body) from macules to papules to vesicles to pustules before eventually crusting (**Figure 16**). Patients remain contagious until all scabs and crusts are shed. Mortality ranges from 15% to 50%.

Treatment is listed in Table 40. The oral antiviral agent tecovirimat was approved in 2018 for the treatment of smallpox in the event of a potential outbreak. Vaccination within

TABLE 40. Class A Bioterrorism Agents

Disease—Agent	Incubation Period	Clinical Features	Treatment	Prophylaxis
Anthrax—*Bacillus anthracis*	1-60 days	Inhalational: febrile respiratory distress Cutaneous: necrotic eschar Gastrointestinal: distention, peritonitis	Ciprofloxacin, levofloxacin, moxifloxacin, or doxycycline plus one or two additional agents[a] for 60 days Consider raxibacumab, obiltoxaximab, or intravenous anthrax immune globulin	Ciprofloxacin, levofloxacin, moxifloxacin, or doxycycline Amoxicillin if penicillin-sensitive strain
Smallpox virus—variola virus	7-17 days	Fever followed by pustular cutaneous rash (face, followed by upper extremities, lower extremities, and trunk)	Tecovirimat	Vaccine if exposure occurred in the previous 7 days
Plague—*Yersinia pestis*	1-6 days	Fulminant pneumonia and sepsis	Streptomycin or gentamicin for 7 to 10 days Alternatives: doxycycline or levofloxacin if aminoglycosides contraindicated	Doxycycline or levofloxacin for 7 days
Botulism—*Clostridium botulinum*	2 hours to 8 days	Cranial nerve palsies and descending flaccid paralysis	Antitoxin and supportive care	Antibotulinum antitoxin (equine serum heptavalent botulism toxin)
Tularemia—*Francisella tularensis*	3-5 days	Fever, respiratory distress, and sepsis	Streptomycin or gentamicin (severe disease) for 7 to 14 days Doxycycline or ciprofloxacin (nonsevere disease) for 14 days	Doxycycline or ciprofloxacin
Viral hemorrhagic fevers—Ebola and Marburg viruses	Variable	Hemorrhage and multiorgan failure	Supportive care	None available

[a]Penicillin, ampicillin, imipenem, meropenem, clindamycin, linezolid, rifampin, vancomycin, or clarithromycin.

FIGURE 16. Diffuse synchronous skin lesions of smallpox.

7 days of potential exposure is effective in preventing or lessening disease severity and should be provided to close contacts. Intravenous vaccinia immune globulin is indicated in certain vaccinia-related complications or when vaccination is contraindicated.

KEY POINT

- Smallpox viremia results in fever and systemic symptoms, followed by lesions on the oral mucosa, then the face, and then the arms, legs, hands and feet, and to a lesser extent the trunk.

Plague

Primary pneumonic plague occurs after *Yersinia pestis* (**Figure 17**) exposure through infectious aerosols and person-to-person transmission through respiratory droplets, which are likely scenarios for bioterrorism. Patients with suspected pneumonic plague require droplet precautions.

Bubonic plague is characterized by lymphadenopathy (buboes), fever, rigors, and headache. Chest radiographs are nonspecific. Gram stain and cultures of sputum and blood (performed using the highest level biosafety procedures) are often diagnostic.

Untreated, pneumonic plague is uniformly fatal. Treatment is outlined in Table 40. Asymptomatic persons exposed to aerosolized *Y. pestis* and close contacts of infected patients within the previous 7 days warrant postexposure

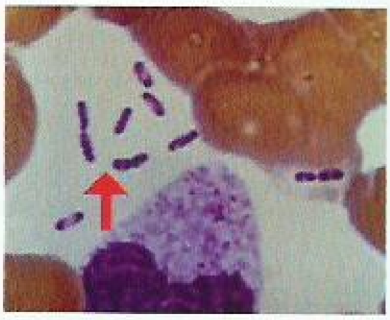

FIGURE 17. This Wright-Giemsa stain shows *Yersinia pestis*, a gram-negative coccobacillus with a "safety-pin" appearance (bipolar staining pattern).

prophylaxis. The available vaccine is ineffective at protecting against pneumonic plague. A live attenuated vaccine with protection from respiratory challenge is under investigation.

KEY POINTS

- Primary pneumonic plague occurs after *Yersinia pestis* exposure through infectious aerosols and person-to-person transmission through respiratory droplets, which are likely scenarios for bioterrorism.
- Asymptomatic persons exposed to aerosolized *Yersinia pestis* and close contacts of infected patients within the previous 7 days warrant postexposure prophylaxis with levofloxacin or doxycycline.

Botulism

Botulism may spread in a bioterrorism attack through inhalation or ingestion of botulinum neurotoxin after deliberate aerosol release or purposeful food contamination. Patients present with symmetric, descending flaccid paralysis with prominent bulbar signs (the "4 Ds": diplopia, dysarthria, dysphonia, and dysphagia), which may progress to respiratory failure. Patients remain afebrile and mental status remains normal, but nausea, abdominal pain, and dry mouth often accompany the paralysis. Autonomic dysfunction may also occur.

Diagnosis depends on identifying the toxin from serum, vomitus, stool, gastric contents, or foods. Organism isolation is rare. Treatment is supportive (see Table 40). Antitoxin should be obtained from the Centers for Disease Control and Prevention and administered promptly but will not reverse existent paralysis. Antibiotics are not useful.

KEY POINT

- Botulism treatment includes supportive care and early administration of antitoxin, although this will not reverse existent paralysis.

Tularemia

Francisella tularensis transmission to humans occurs by vectors, direct animal contact, and inhalation; person-to-person spread does not occur. Abrupt onset of fever and respiratory symptoms follow inhalation of even a small inoculum of organisms. Chest radiographs demonstrate infiltrates, hilar lymphadenopathy, and pleural effusions.

Rapid diagnosis relies on serologic, immunohistochemical, and PCR testing; culture of tissues and fluids is low yield and potentially dangerous to laboratory personnel. Treatment is noted in Table 40. Death occurs in less than 4% of treated patients, with mortality rates reaching 30% in untreated pneumonic or typhoidal tularemia. No vaccine is available.

KEY POINT

- Patients with tularemia experience abrupt onset of fever and respiratory symptoms, and chest radiographs demonstrate infiltrates, hilar lymphadenopathy, and pleural effusions.

Viral Hemorrhagic Fever

The Ebola and Marburg viruses are the most likely to be used as biologic weapons. In endemic areas, spread to humans occurs by vectors, contact with bodily fluids, or fomites. Aerosolization is a likely mode of terrorist dissemination. Symptoms of fever, headache, myalgia, abdominal pain, diarrhea, and unexplained bleeding and bruising appear 2 to 21 days after exposure. Disease progression results in maculopapular rash, hemorrhagic diathesis, shock, and multiorgan failure. Mortality rates can reach 90%. Persons are contagious only after symptom onset, but virus may spread by sexual contact in semen for weeks to months after recovery.

Depending on the stage of infection, diagnosis may be confirmed by virus detection in blood or other bodily fluids and tissues, antigen and antibody assays, and PCR. Exposed persons are monitored during the 21-day incubation period, with prompt isolation if symptoms develop. Treatment is supportive (see Table 40). Vaccine and antiviral medications are under development.

KEY POINT

- Symptoms of viral hemorrhagic fever include fever, headache, myalgia, abdominal pain, diarrhea, and unexplained bleeding and bruising, appearing 2 to 21 days after exposure; disease progression results in maculopapular rash, hemorrhagic diathesis, shock, and multiorgan failure.

Travel Medicine

Introduction

Pretravel consultation should occur no less than 4 to 6 weeks before departure. Regularly updated information by country is available on the Centers for Disease Control and Prevention (CDC) and World Health Organization (WHO) websites (http://www.cdc.gov/travel and http://www.who.int/ith).

Travel-related illnesses (mostly febrile, diarrheal, respiratory, and cutaneous infections) are reported in 20% to 60% of returning travelers; many of these are vaccine preventable. Required and recommended pretravel immunizations are listed in **Table 41**. Potentially severe travel-associated infections are listed in **Table 42**, the most significant of which are reviewed here.

Malaria

Malaria is transmitted to humans by the female *Anopheles* mosquito. It is the most common cause of febrile illness in returning travelers, particularly from sub-Saharan Africa and large parts of Asia. Preventive measures include limiting outdoor exposure between dusk and dawn, using insecticide-impregnated bed nets and insect repellents containing 20% N-diethyl-3-methylbensamide (DEET), and using antimalarial chemoprophylaxis.

Incubation periods vary by species and range from 1 week to 3 months in semi-immune persons or those taking inadequate prophylaxis. Symptoms include fever (characteristically paroxysms in 48- or 72-hour cycles), headache, myalgia, and gastrointestinal symptoms. More severe disease occurs with hyperparasitemia (5%-10% parasitized erythrocytes) leading to adherence in small blood vessels causing infarcts, capillary leakage, and multiorgan system dysfunction. Serious disease primarily occurs with *Plasmodium falciparum*; manifestations include mental status alterations, seizures, hepatic failure, disseminated intravascular coagulation, brisk intravascular hemolysis, metabolic acidosis, kidney disease, hemoglobinuria, and hypoglycemia. Subsequently, patients may develop anemia, thrombocytopenia, splenomegaly, and elevated aminotransferase levels. See **Table 43** for specific features of the five *Plasmodium* species.

TABLE 41. Immunizations for Travel[a]

Recommended According to Destination, Itinerary, and Purpose of Travel
Hepatitis A[b]: 1 month before travel, booster at 6-18 months
Hepatitis B[b]: 0, 1 month, 6 months; accelerated schedule: 0, 1 week, 3 weeks, and 12 months (combination vaccine with hepatitis A available)
Typhoid[c]: Live-attenuated oral vaccine (Ty21a); 0, 2 days, 4 days, 6 days; capsular Vi polysaccharide intramuscular vaccine; 1 dose (preferred for immunocompromised persons)
Cholera: Live oral, 10 days before travel; killed oral, whole-cell-B subunit; 0, 1 week (available outside the United States)
Rabies: Inactivated; 0, 7 days, 21-28 days
Japanese encephalitis: Inactivated; 0, 28 days
Tick-borne encephalitis: Inactivated; 0, 1-3 months, 9-12 months (not available in the United States)
Required for Certain Destinations
Yellow fever: Live attenuated; 1 dose
Meningococcal: Quadrivalent conjugate (MenACWY) or polysaccharide (MPSV4); 1 dose; travel to Saudi Arabia during the Hajj
Meningococcal B (MenB); 2 or 3 doses; high-risk groups

[a]All patients being evaluated for travel should receive or be up to date with all scheduled immunizations, including influenza, pneumococcal, tetanus-diphtheria-pertussis, polio, varicella, and zoster vaccines. See MKSAP 18 General Internal Medicine for routine adult immunization recommendations.

[b]If not received as part of routine scheduled immunizations. If the vaccine series was completed as part of scheduled immunization, repeat immunization is not required.

[c]Oral vaccine should not be administered within 24 hours of the antimalarial drug mefloquine because of the potential to decrease the vaccine's immunogenicity; patients must not take any antibiotic for at least 72 hours before receiving the vaccine.

Data from the Centers for Disease Control and Prevention. CDC Yellow Book 2018: Health Information for International Travel. New York: Oxford University Press; 2017. Available online at https://wwwnc.cdc.gov/travel/yellowbook/2018/.

Diagnosis is made by identification of malarial parasites on the peripheral blood smear. Morphologic features help determine the specific species. Rapid tests that detect malaria antigens are available but may lack sensitivity and specificity. Polymerase chain reaction (PCR) and serologic assays exist, although each has limitations.

It is critical to identify *P. falciparum* and *P. knowlesi* because of their potential for severe infection. The onset of malarial symptoms shortly after returning from travel to endemic zones, such as Africa, and recognition of a high level of parasitemia and distinctive morphologic characteristics (**Figure 18**) should raise suspicion for *P. falciparum* infection. *P. knowlesi* is an emerging human pathogen found in South and Southeast Asia; high levels of parasitemia may occur, and examination of the peripheral blood smear reveals all stages of the parasite.

Malarial chemoprophylaxis and treatment depend on possible drug resistance and individual contraindications to specific medications (**Table 44** on page 61 and **Table 45** on page 62). Additional detailed information about malaria is provided in the CDC Yellow Book (https://wwwnc.cdc.gov/travel/yellowbook/2018/infectious-diseases-related-to-travel/malaria) or by calling the CDC malaria hotline (855-856-4713).

KEY POINTS

- Malaria is the most common cause of febrile illness in returning travelers; symptoms include fever, headache, myalgia, and gastrointestinal symptoms.
- The onset of malarial symptoms shortly after returning from travel to endemic zones, such as Africa, and recognition of a high level of parasitemia and distinctive morphologic characteristics should raise suspicion for *Plasmodium falciparum* infection.

Typhoid (Enteric) Fever

Salmonella typhi and *Salmonella paratyphi* (A, B, and C) cause prolonged febrile and often serious infection (typhoid fever). Infection is acquired by consuming food or water contaminated by organisms shed in the stool of infected humans.

TABLE 42. Travel-Associated Infections

Condition	Clinical Clues
Febrile Illnesses	
Malaria	Paroxysmal fever (every 48 or 72 hours, depending on the species and may be continuous with *Plasmodium falciparum*), intraerythrocytic parasites, thrombocytopenia
Dengue fever	Acute onset of fever with chills, biphasic fever pattern ("saddleback"), frontal headache, lumbosacral pain, extensor surface petechiae
Chikungunya fever	Fever (abrupt onset up to 40 °C [104 °F] with rigors with recrudescent episodes), rash, and small joint polyarthritis
Zika virus	Mosquito exposure in endemic areas; nonspecific symptoms of fever, rash, joint pain, and/or conjunctivitis (asymptomatic in up to 80% of persons)
Typhoid fever	Prolonged fever, pulse-temperature dissociation, diarrhea or constipation, faint salmon-colored macules on the abdomen and trunk ("rose spots")
Rickettsial infection	Tick or flea exposure, maculopapular or petechial rash, eschar, lymphadenopathy, fever
Coxiella infection (Q fever)	Animal contact, self-limited febrile illness common, atypical pneumonia, elevated aminotransferase levels
Yellow fever	Abrupt fever with periods of remission, bradycardia, jaundice, kidney injury, hemorrhage
Viral hepatitis	High fever initially, then low-grade fever, fatigue and anorexia, hepatomegaly, dark urine, clay-colored stools
Mononucleosis syndrome (cytomegalovirus and Epstein-Barr virus)	Sore throat, fever, cervical lymphadenopathy, splenomegaly, atypical lymphocytes, elevated aminotransferase levels
Brucellosis	Zoonotic exposure, waxing and waning (undulant) fever, arthralgia, hepatosplenomegaly, depression
Leptospirosis	Conjunctival suffusion (erythema without inflammatory exudates), calf and lumbar spine muscle tenderness, aseptic meningitis, jaundice, kidney failure, acute high remittent fever in initial septicemic phase with brief decline before second immune phase
Lyme disease	Flu-like syndrome, target skin lesions (erythema migrans) may be accompanied by fever, arthralgias, bilateral Bell palsy
Histoplasmosis	Nonproductive cough, chest pain, fever
Legionellosis	Pneumonia, diarrhea, dry cough, progressive dyspnea, lymphopenia, thrombocytopenia, elevated aminotransferase and lactate dehydrogenase levels
Novel coronaviruses (severe acute respiratory syndrome [SARS], Middle East respiratory syndrome [MERS-CoV])	Flu-like syndrome prodrome, diarrhea, dry cough with progressive dyspnea, lymphopenia, thrombocytopenia, elevated lactate dehydrogenase levels
Japanese encephalitis	High fever, altered mentation, cranial nerve palsies
Hemorrhagic fever viruses (Ebola, Marburg, and Lassa)	Fever, malaise, myalgia, vomiting, diarrhea, coagulation disorders, and bleeding
Rabies	Paresthesias or pain at wound site, fever, nausea and vomiting, hydrophobia, delirium, agitation
Travelers' Diarrhea	
Bacterial agents: *Escherichia coli*, *Campylobacter* species, *Salmonella* species, *Vibrio* species, *Shigella* species	Abrupt onset, crampy diarrhea, blood in stools
Viral agents: rotavirus, norovirus	Closed setting (such as cruise ship or classroom) acquisition, vomiting, diarrhea, short duration
Protozoa: *Cryptosporidium* species, microsporidia, *Giardia* species, *Entamoeba histolytica*, and *Isospora* species	Gradual onset, progressive and prolonged diarrhea, foul-smelling and greasy stools, mucus or visible blood in stools

Travel to South, East, and Southeast Asia (Indian subcontinent) and portions of sub-Saharan Africa pose the greatest risk of infection. Unlike other nontyphoidal *Salmonella* (see Infectious Gastrointestinal Syndromes), the causative agents of enteric fever are human-only pathogens. Oral and parenteral vaccines (see Table 41) afford temporary protective immunity in 50% to 80% of recipients.

The gradual onset of fever with headache, arthralgia, myalgia, pharyngitis, and anorexia follows a 1- to 2-week incubation period. Abdominal pain and tenderness can be

TABLE 43. Characteristics of *Plasmodium* Species

Characteristics	*P. vivax*	*P. ovale*	*P. malariae*	*P. falciparum*	*P. knowlesi*
Incubation period	10-30 days	10-20 days	15-35 days	8-25 days	Indeterminate
Geographic distribution	Tropical and temperate zones	West Africa and Southeast Asia	Tropical zones	Tropical and temperate zones	South and Southeast Asia
Parasitemia	Low	Low	Very low	High	Can be high
Risk for disease severity	Low risk	Low risk	Very low risk	High risk	High risk
Disease relapse risk	Yes	Yes	Yes	No	No
Chloroquine resistance	Yes	No	Rare	Yes	No

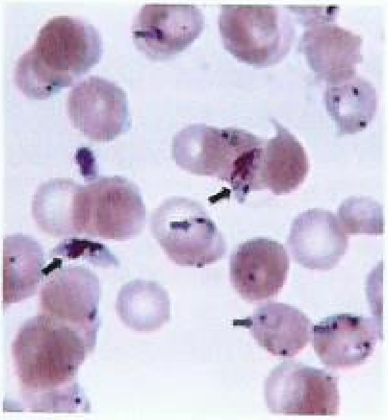

FIGURE 18. Thin, often multiple rings (*blue arrows*) on the inner surface of young and old erythrocytes as well as banana-shaped gametocytes (*black arrows*) are distinctive morphologic characteristics of *Plasmodium falciparum* species.

accompanied by early-onset diarrhea, which may spontaneously resolve or become severe late in disease. One fifth of patients have constipation at diagnosis. In untreated illness, temperature progressively increases and may remain elevated (up to 40 °C [104 °F]) for 4 to 8 weeks. A pulse-temperature dissociation (relative bradycardia) and prostration are common. During the second week of illness, discrete, blanching, 1- to 4-mm salmon-colored macules, known as rose spots (**Figure 19**, on page 63) develop in crops on the chest and abdomen in about 20% of patients. Moderate hepatosplenomegaly, leukopenia, anemia, thrombocytopenia, and elevated aminotransferase levels are common. Secondary bacteremia may cause pyogenic complications such as empyema, muscle abscess, and endovascular infections. Intestinal hemorrhage or perforation may occur 2 to 3 weeks after infection onset. Encephalopathy occurs in more severe cases.

Invasion of the gallbladder by typhoid bacilli may result in a long-term carrier state with shedding of organisms in the stool for more than 1 year. Those with gallstones and chronic biliary disease are at greatest risk.

Diagnosis is made through isolation of *S. typhi* or *S. paratyphi* from blood, stool, urine, or bone marrow; isolation success declines after the first week of illness. Rapid serologic tests are available to distinguish *Salmonella enterica* serotype *typhi* antibodies.

Antibiotic treatment decreases mortality and shortens the duration of fever. The emergence of antibiotic resistance in many geographic areas necessitates that in vitro susceptibility testing be performed on all clinical isolates. Ceftriaxone, fluoroquinolones, and azithromycin are preferred treatments. Dexamethasone has been shown to decrease mortality in severe illness, such as in patients with shock and encephalopathy. A 28-day course of ciprofloxacin is effective in eradicating chronic carriage, although cholecystectomy may be needed in cases of cholelithiasis.

KEY POINTS

- Typhoid fever commonly presents with fever, headache, arthralgia, myalgia, pharyngitis, anorexia, abdominal pain with early-onset diarrhea, pulse-temperature dissociation (relative bradycardia), and prostration.
- Ceftriaxone, fluoroquinolones, and azithromycin are preferred treatments for typhoid fever; dexamethasone decreases mortality in severe disease, such as patients with shock and encephalopathy.

Travelers' Diarrhea

The most common travel-associated infection is diarrhea, defined by the sudden onset of three or more loose or watery stools per day with at least one additional gastrointestinal or systemic clinical sign or symptom (fever, cramps, nausea, abdominal pain, or blood in the stools). Risk factors, including geographic location (greatest in South and Southeast Asia, sub-Saharan Africa, the Middle East, and Latin America), type and duration of travel, and host characteristics, contribute to the 30% to 60% occurrence rate.

Most travelers' diarrhea episodes occur within the first 2 weeks of travel. Episodes are usually self-limited, lasting approximately 4 days; however, life-threatening volume depletion or severe colitis with systemic manifestations can occur. Some travelers develop chronic diarrhea or a postinfective irritable bowel syndrome.

TABLE 44. Antimalarial Chemoprophylaxis Regimens

Drug	Dose	Time of Prophylaxis Initiation (before Travel)	Time of Prophylaxis Discontinuation (after Returning)
For endemic areas with chloroquine-resistant *Plasmodium falciparum*			
Atovaquone/proguanil[a]	250 mg/100 mg once daily	1-2 days	7 days
Mefloquine	250 mg once weekly	1-2 weeks	4 weeks
Doxycycline[a]	100 mg once daily	1-2 days	4 weeks
For endemic areas with chloroquine and mefloquine-resistant *P. falciparum*[b]			
Atovaquone/proguanil	250 mg/100 mg once daily	1-2 days	7 days
Doxycycline	100 mg once daily	1-2 days	4 weeks
For endemic areas with chloroquine-sensitive *P. falciparum*			
Chloroquine	500 mg once weekly	1-2 weeks	4 weeks
Hydroxychloroquine	400 mg once weekly	1-2 weeks	4 weeks
Atovaquone/proguanil	250/100 mg once daily	1-2 days	7 days
Mefloquine	250 mg once weekly	2 weeks	4 weeks
Doxycycline	100 mg once daily	1-2 days	4 weeks
Primaquine	26.3 mg once daily	1-2 days	1 week
For endemic areas with *Plasmodium vivax*			
Primaquine[c]	52.6 mg once daily	1-2 days	1 week
Chloroquine	500 mg once weekly	1-2 days	4 weeks
Hydroxychloroquine	400 mg once weekly	1-2 days	4 weeks
Atovaquone/proguanil	250/100 mg once daily	1-2 days	7 days
Mefloquine	250 mg once weekly	2 weeks	4 weeks
Doxycycline	100 mg once daily	1-2 days	4 weeks
Prophylaxis for relapse due to *P. vivax* or *Plasmodium ovale*			
Primaquine	52.6 mg once daily	As soon as possible	2 weeks

[a]Should not be used in pregnant women.

[b]Borders of Thailand with Cambodia and Myanmar (Burma).

[c]Contraindicated in persons with severe forms of glucose-6-phosphate dehydrogenase deficiency or methemoglobin reductase deficiency; should not be administered to pregnant women.

Recommendations from the Centers for Disease Control and Prevention. CDC Yellow Book 2018: Health Information for International Travel. New York: Oxford University Press; 2017. Available online at https://wwwnc.cdc.gov/travel/yellowbook/2018/infectious-diseases-related-to-travel/malaria.

Enterotoxigenic *Escherichia coli* is the most common causative agent (see Table 42). Younger age, use of gastric acid-reducing medications, abnormal gastrointestinal motility or altered anatomy, O blood type, and other genetic factors increase risk. Immunocompromised travelers may experience more serious and protracted illness with typical pathogens and are more prone to infection with opportunistic infectious agents. Chronic gastrointestinal conditions (such as inflammatory bowel disease) do not increase risk of infection but do predispose travelers to more severe symptoms.

Pretravel advice includes avoiding consumption of tap water (through drinks, ice, or when brushing teeth), undercooked meats, unpasteurized dairy products, and fruits that are not peeled just before eating. Water disinfection can be accomplished by boiling for 3 minutes or by chemical means using chlorine and iodine. Two drops of sodium hypochlorite (bleach) or five drops of tincture of iodine per liter of water are equally effective. Commercial water filters are not as dependable.

Antimicrobial prophylaxis for travelers' diarrhea is effective but is generally not recommended because of the potential for adverse effects. Prophylaxis should be considered in persons with coexisting inflammatory bowel disease, immunocompromised states (including advanced HIV), and comorbidities that would be adversely affected by significant dehydration. Bismuth subsalicylate can be used to prevent diarrhea, but the doses required are inconvenient and can lead to salicylate toxicity. Probiotics have not been proven

TABLE 45. Malaria Treatment Regimens[a]

Drug	Dose and Duration
Non-*falciparum* Species[b]	
Chloroquine phosphate (500 mg)	1000 mg, then 500 mg at 6, 24, and 48 h
Hydroxychloroquine (400 mg)	800 mg, then 400 mg at 6, 24, and 48 h
***Plasmodium falciparum* or Species Not Identified**	
Acquired in chloroquine-sensitive area	
Chloroquine phosphate (500 mg)	Same as for non-*falciparum* species
or	
Hydroxychloroquine (400 mg)	
Acquired in chloroquine-resistant area	
Atovaquone-proguanil (250 mg/100 mg)	4 tabs daily (or 2 tabs twice/d) for 3 d
Artemether-lumefantrine[c] (20 mg/120 mg)	4 tabs at 0, 8, 24, 36, 48, and 60 h
Quinine sulfate (325 mg) plus one of the following:	2 tabs (650 mg) three times/d for 3 or 7 d[d]
Doxycycline (100 mg)	100 mg twice/d for 7 d
Tetracycline (250 mg)	250 mg four times/d for 7 d
Clindamycin (300 mg)	20 mg base/kg/d divided three times/d for 7 d
Mefloquine[e] (250 mg)	3 tabs (750 mg), then 2 tabs (500 mg) in 6-12 h
Acquired in mefloquine-resistant area[f]	
Atovaquone-proguanil	Same as above
or	
Quinine sulfate plus doxycycline or tetracycline or clindamycin	
Relapse prevention (infection *with Plasmodium vivax* or *Plasmodium ovale*)	
Primaquine phosphate[g] (15 mg)	2 tabs daily for 14 d
Treatment in pregnant women	
Chloroquine-sensitive species: Chloroquine phosphate (500 mg)	Same as above
P. vivax and *P. ovale* relapse prevention: Chloroquine phosphate (500 mg)	Once weekly until after delivery
Chloroquine-resistant *P. falciparum*[h]: Quinine sulfate plus clindamycin or mefloquine	Same as above
Treatment of severe disease (acquired in all malarial areas)	
Quinidine gluconate	Initial 10 mg/kg IV over 1-2 h, then 0.02 mg/kg/min continuous IV for at least 24 h until parasitemia ≤1% and oral medications can be tolerated
Artesunate[i] (parenteral)	2.4 mg/kg IV at 0, 12, 24, and 48 h

IV = intravenous.

[a]Patients who develop malaria while receiving prophylaxis should be treated with a different drug regimen.

[b]*P. vivax* acquired in Papua New Guinea or Indonesia should be considered chloroquine resistant.

[c]Artemisin-based combination therapies (ACTs) are the most rapid and effective therapies and active against all malarial species. Artemether-lumefantrine is the only approved ACT in the United States.

[d]Seven-day duration is indicated if infection was acquired in Southeast Asia.

[e]Increased risk of neuropsychiatric reactions; not recommended for *P. falciparum* infection acquired in Southeast Asia because of drug resistance.

[f]Found on the eastern border of Myanmar (Burma) and adjacent parts of China, Laos, and Thailand; western border of Thailand and adjacent parts of Cambodia and Laos; and southern Vietnam.

[g]Confirm absence of glucose-6-phosphate dehydrogenase deficiency in patient. Not indicated in pregnant women.

[h]Atovaquone-proguanil and artemether-lumefantrine are generally not recommended for use in pregnant women. Doxycycline and tetracycline are not indicated in pregnancy.

[i]Available in the United States from the CDC under an investigational new drug protocol; www.CDC.gov/malaria (call 770-448-7100).

FIGURE 19. Rose spots on the chest of a patient with typhoid fever caused by the bacterium *Salmonella typhi*.

Reproduced from the CDC Public Health Image Library.

effective in the prevention of travelers' diarrhea and are not recommended.

Fluid replacement is the mainstay of treatment. Antimicrobials reduce the duration of diarrhea by 1 to 2 days but are recommended only in severe disease (**Table 46**). Self-treatment with a fluoroquinolone, azithromycin (preferred in South and Southeast Asia), or rifaximin is usually sufficient. Bismuth subsalicylate in large doses can be beneficial in decreasing the frequency and duration of diarrhea in milder cases. Antimotility drugs such as loperamide and diphenoxylate should only be given in conjunction with antimicrobial

TABLE 46. Oral Treatment and Prophylaxis for Travelers' Diarrhea

Agent	Regimen
Treatment	
Bismuth subsalicylate	1 oz every 30 min for 8 doses
Norfloxacin	400 mg twice daily for 3 d
Ciprofloxacin	500 mg twice daily for 3 d
Ofloxacin	200 mg twice daily for 3 d
Levofloxacin	500 mg once daily for 3 d
Azithromycin	1000 mg, single dose
Rifaximin	200 mg three times daily for 3 d
Prophylaxis	
Bismuth subsalicylate	Two tablets chewed 4 times daily
Norfloxacin	400 mg daily[a]
Ciprofloxacin	500 mg daily[a]
Rifaximin	200 mg once or twice daily[a]

[a]Chemoprophylaxis is recommended for no more than 2 to 3 weeks (the duration studied in trials and a period short enough to minimize the risk for antimicrobial-associated adverse effects).

Source: Hill DR, Ericsson CD, Pearson RD, Keystone JS, Freedman DO, Kozarsky PE, et al; Infectious Diseases Society of America. The practice of travel medicine: guidelines by the Infectious Diseases Society of America. Clin Infect Dis. 2006;43:1499-539. [PMID: 17109284]

therapy but should not be used in cases of dysentery or bloody diarrhea because of increased risk of colitis and colonic perforation.

KEY POINTS

- Fluid replacement is the mainstay of treatment for travelers' diarrhea; fluoroquinolones, azithromycin (preferred in South and Southeast Asia), and rifaximin reduce the duration of diarrhea by 1 to 2 days but are recommended only in severe disease. **HVC**
- Antimicrobial prophylaxis for travelers' diarrhea is generally not recommended; however, prophylaxis should be considered in persons with coexisting inflammatory bowel disease, immunocompromised states (including advanced HIV), and comorbidities that would be adversely affected by significant dehydration.

Dengue Fever, Chikungunya, and Zika

Arboviruses are spread by arthropod vectors. Mosquitoes spread most travel-related arboviral diseases. Some arboviruses, such as yellow fever, are endemic throughout the tropics, and several countries require proof of vaccination before allowing entry by travelers. Other viruses, such as Japanese encephalitis, have more restricted geographic areas. The dengue fever, chikungunya, and Zika arboviruses are all spread by *Aedes* species mosquitoes and will be discussed here (**Table 47**).

Dengue fever is the most prevalent arthropod-borne viral infection in the world. Endemic areas include Southeast Asia, the South Pacific, South and Central America, and the Caribbean. The incubation period is 4 to 7 days. Patients may be asymptomatic or present with an acute febrile illness associated with frontal headache, retro-orbital pain, myalgia, and arthralgia, with or without minor spontaneous bleeding. Gastrointestinal or respiratory symptoms may predominate. Severe lumbosacral pain is characteristic. As the fever abates, a macular or

TABLE 47. Important Clinical Distinguishing Features of Arbovirus Infection

Clinical Finding	Dengue	Chikungunya	Zika
Fever	+++	+++	++
Myalgia	++	+	+
Arthralgia	+	+++	++
Headache	++	++	+
Conjunctivitis	–	–	++
Rash	+	++	+++
Bleeding	++	–	–
Shock	+	–	–

+++ = always; ++ = common; + = rare; – = almost never

scarlatiniform rash, which spares the palms and soles, may develop and evolve into areas of petechiae on extensor surfaces (**Figure 20**). Fever resolves after 5 to 7 days; however, some patients experience a second febrile period (saddleback pattern). A prolonged period of severe fatigue may follow. In patients with severe infection, life-threatening hemorrhage (dengue hemorrhagic fever) or shock may ensue, with liver failure, encephalopathy, and myocardial damage. This syndrome appears to be related to previous infection of a different serotype and is unlikely in travelers who have not had dengue fever previously. Abnormal laboratory findings include leukopenia, thrombocytopenia, and elevated serum aminotransferase levels.

Diagnosis of dengue fever is based on clinical suspicion in a patient who traveled to an endemic area and presents with fever and other typical signs, symptoms, and abnormal laboratory findings. Diagnosis is confirmed by serology (IgM and IgG) or reverse transcriptase PCR. Therapy is supportive. No licensed dengue vaccine is available in the United States, although clinical trials are ongoing. A live attenuated tetravalent vaccine, CYD-TDV, which is recommended for use only in persons previously infected by dengue virus, is available in several countries outside the United States.

Historically, chikungunya virus was limited to Southeast Asia and Africa but has recently emerged in the Americas, with outbreaks in Central and South America and the Caribbean. No vaccine is available. Symptoms resemble dengue fever, including abrupt onset of fever (≥39.0 °C [102.2 °F]) and severe bilateral and symmetrical polyarthralgia, often involving the hands and feet. A maculopapular rash on the limbs and trunk is common. Rarely, central nervous system, ophthalmologic, hepatic, and kidney manifestations are present. Abnormal laboratory findings include lymphopenia, thrombocytopenia, and elevated aminotransferase levels. Definitive diagnosis relies on serologic assays or detection of viral RNA by reverse transcriptase PCR testing. Disease is generally self-limited, resolving in 7 to 10 days. However, some patients may experience relapsing and chronic rheumatologic symptoms for months or even years. Symptomatic treatment includes NSAIDs and aspirin avoidance (risk of bleeding complications and potential risk of Reye syndrome in children).

FIGURE 20. Petechial rash following application of blood pressure cuff constituting a positive "tourniquet test" that supports the presence of microvascular fragility compatible with dengue fever.

Before the 2015 Zika virus epidemic in Central and South America, human infection occurred chiefly in Africa, Southeast Asia, and the Pacific Islands. More than 5600 infections have been reported in the United States since the epidemic, of which greater than 225 are presumed to be from local transmission (Florida and Texas) and 55 acquired by sexual or laboratory transmission. This flavivirus is closely related to dengue, yellow fever, and Japanese encephalitis viruses. Intrauterine and perinatal maternal-fetal spread and sexual transmission from an infected male partner are other less common modes of transmission. An estimated 18% of those infected demonstrate clinical symptoms, which are similar to dengue and chikungunya virus infections, with the additional finding of conjunctivitis in most Zika infections. Most patients recover uneventfully after a mild illness lasting about 1 week, but some develop Guillain-Barré syndrome. Of most concern are risks to fetal development in pregnant women infected with Zika, including microcephaly, other severe brain and eye defects, and impaired growth and fetal loss. Women who are pregnant must be advised against travel to areas where Zika virus is known to be present. Likewise, women and men who are planning to conceive in the near future should consider avoiding nonessential travel to areas with risk of Zika infection; it is recommended couples wait to conceive until at least 3 months (for men) or 8 weeks (for women) after the last possible Zika virus exposure or from the onset of symptoms or diagnosis. Those not planning to conceive should use condoms for all forms of sexual activity together with their chosen birth control method or abstain from sex if Zika virus transmission is a concern. All pregnant women should be assessed for possible Zika exposure, and those who return from areas with outbreaks should be screened for evidence of infection. Reverse transcriptase PCR testing on serum and urine is used for diagnostic evaluation during the initial 2 weeks after illness onset. Thereafter, IgM antibody detection is used. Virus-specific plaque reduction neutralization tests can discriminate between Zika virus and cross-reacting antibodies against related flaviviruses. Because the epidemiology of Zika infection in the United States is still evolving, women who are pregnant and those who are planning to conceive should consult the CDC website for the most updated information when considering travel. No specific medications are available for treating Zika virus. Active vaccine development is ongoing.

KEY POINTS

- Dengue fever typically presents with acute febrile illness, frontal headache, retro-orbital pain, myalgia, and arthralgia, with or without minor spontaneous bleeding; gastrointestinal or respiratory symptoms may predominate, and severe lumbosacral pain is characteristic.

(Continued)

KEY POINTS *(continued)*

- Symptoms of chikungunya resemble dengue fever, including abrupt onset of fever (≥39.0 °C [102.2 °F]) and severe bilateral and symmetrical polyarthralgia, often involving the hands and feet; a maculopapular rash on the limbs and trunk is common.
- Of most concern in Zika virus infection is the risk to fetal development in infected pregnant women, including microcephaly, other severe brain and eye defects, impaired growth, and fetal loss.

Hepatitis Virus Infections

Hepatitis A virus (HAV) infection is acquired through ingestion of food and water contaminated with fecal waste from another infected human in geographic areas with poor sanitation practices. Travel to Central and South America, Mexico, South Asia, and Africa poses the greatest risk of infection (for further information, see MKSAP 18 Gastroenterology and Hepatology).

Hepatitis A vaccination is recommended for persons traveling to developing countries who are not already immune (see Table 41). Protective antibody titers develop within 2 to 4 weeks in almost 100% of healthy recipients. A booster dose is given 6 to 12 months after the initial injection and provides protection for at least 10 years. Serum immune globulin is indicated for persons aged 12 months or younger and for those who decline vaccination or are allergic to its components. It has also been recommended for immunocompromised persons (who are less responsive to hepatitis A vaccine) and patients with chronic liver disease. Concurrent administration of hepatitis A vaccine and immune globulin is no longer recommended for those planning to depart within 2 weeks.

The risk for travel-associated acquisition of hepatitis B virus (HBV) is low. Previously unvaccinated persons traveling as health care workers, seeking medical care, or likely to engage in sexual activity with local residents in countries where HBV is prevalent warrant pretravel vaccination. Persons with insufficient time before travel to receive the standard three-dose/6-month vaccination series can complete an accelerated vaccination schedule (0, 7, and 21-30 days); these persons require a booster dose at 12 months to ensure long-term protection. A combined hepatitis A/B vaccine is also available for this rapid three-dose schedule.

No vaccine prevents hepatitis C virus infection, and immune globulin offers no protection (see MKSAP 18 Gastroenterology and Hepatology).

KEY POINTS

- Protective hepatitis A antibody titers develop within 2 to 4 weeks following vaccination in almost 100% of healthy recipients; concurrent administration of hepatitis A vaccine and immune globulin is no longer recommended for those planning to depart within 2 weeks.

(Continued)

KEY POINTS *(continued)*

- Persons with insufficient time before travel to receive the standard three-dose/6-month hepatitis B vaccination series can complete an accelerated vaccination schedule (0, 7, and 21-30 days), which is also available in a combined hepatitis A/B vaccine; these persons require a booster dose at 12 months to ensure long-term protection.

Rickettsial Infection

Rickettsial infections occur worldwide. They usually belong to the typhus or spotted fever groups and are transmitted by small vectors (fleas, lice, mites, and ticks). Outbreaks have been associated with war and natural disasters and are promoted by suboptimal hygiene conditions and tick infestation. *Rickettsia typhi* is prevalent in tropical and subtropical areas. *Rickettsia prowazeki* is the only rickettsial species transmitted by human body lice and has a worldwide distribution.

Fever is the most common presenting symptom; African tick typhus (*Rickettsia africae*) is second only to malaria as the cause of febrile illness in those who have journeyed to Africa, especially South Africa. Clinical presentation also includes headache, malaise, conjunctivitis, and pharyngitis often accompanied by a maculopapular, vesicular, or petechial rash. Following the bite of an infected tick or mite, an eschar with regional lymphadenopathy develops at the site of inoculation with *R. africae*, *Rickettsia conorii*, and *Orientia tsutsugamushi*. Endothelial damage in the microcirculation leads to increased vascular permeability and is the hallmark of rickettsial infections, with extensive vasculitic-appearing lesions. Severe complications may include shock, meningoencephalitis, and significant damage to the kidneys, lungs, liver, and gastrointestinal tract. Recrudescent attacks designated Brill-Zinsser disease are known to occur months and even years later.

Diagnosis is confirmed by PCR, immunohistochemical analysis of tissue samples, or culture during the acute stage of illness before antibiotics are initiated. Confirmatory serologic assays often do not detect antibodies until the convalescent phase of illness, limiting their utility with acute disease. When clinical suspicion is high, empiric therapy is warranted. The treatment of choice for all rickettsial infections is doxycycline for 7 to 10 days.

KEY POINTS

- Rickettsial infections occur worldwide, with clinical presentation including fever, headache, malaise, conjunctivitis, and pharyngitis often accompanied by a maculopapular, vesicular, or petechial rash.
- The treatment of choice for all rickettsial infections is doxycycline for 7 to 10 days.

Brucellosis

Human brucellosis may follow ingestion of unpasteurized dairy products or undercooked meat, by direct contact with fluids from infected animals through skin wounds or mucous membranes, or by inhalation of contaminated aerosols. *Brucella* is present in animal reservoirs worldwide, but the highest prevalence is found in the Mediterranean countries, Balkans, Persian Gulf, Middle East, and Central and South America. *Brucella melitensis* (from sheep and goats) has the highest pathogenicity and is the leading cause of human brucellosis.

After a variable incubation period, patients develop fever, myalgia, arthralgia, fatigue, headache, and night sweats. Focal infection may occur, commonly affecting the central nervous system and osteoarticular, cardiovascular, and genitourinary systems. Depression is frequent. Hepatosplenomegaly and lymphadenopathy may be apparent on physical examination with granuloma formation in reticuloendothelial tissues and organs. Disease relapse and chronic infection may occur owing to persistent foci of infection or inadequate antibiotic treatment.

Diagnosis relies on isolating the organism from cultures of blood, bone marrow, other body fluids, or tissue. The serum agglutination test is the most widely used available serologic test. An initial elevated titer of 1:160 or greater or demonstration of a fourfold increase from acute to convalescent titers is considered diagnostic. The Rose Bengal slide agglutination test, if available, is a convenient, simple, rapid, and sensitive point-of-care screening test.

The treatment of choice for uncomplicated brucellosis is a combination of doxycycline, rifampin, and streptomycin (or gentamicin), often given for several weeks. Neurobrucellosis requires several months of combined ceftriaxone, doxycycline, and rifampin.

KEY POINT

- The treatment of choice for uncomplicated brucellosis is a combination of doxycycline, rifampin, and streptomycin (or gentamicin), often given for several weeks; neurobrucellosis requires several months of combined ceftriaxone, doxycycline, and rifampin.

Infectious Gastrointestinal Syndromes

Overview

Diarrhea, defined as three or more unformed stools daily or a quantity greater than 250 grams daily, is a major public health concern. Diarrhea lasting less than 14 days is considered acute, 14 to 30 days is persistent, and longer than 30 days is chronic. Acute infectious diarrheal presentations include acute gastroenteritis, with associated fever, nausea, vomiting, flatulence, tenesmus, and crampy abdominal pain. Chronic infectious diarrhea is most likely due to parasites. Not all diarrheal presentations are infectious, such as inflammatory bowel disease, endocrine disorders, celiac disease, irritable bowel syndrome, and medication induced diarrhea.

Patients with mucoid or bloody diarrhea, fever, significant abdominal cramping, or suspected sepsis and those who are immunocompromised or require hospitalization should have diagnostic assessment of their stool to guide antimicrobial use. Additional areas of concern include symptoms that persist for longer than 1 week or outbreak settings where day care participants, institutional residents, health care providers, or food handlers are involved. Increasingly more available, rapid multiplex molecular gastrointestinal assays that identify common bacterial, parasitic, and viral pathogens from a single stool sample are generally more sensitive than historical stool culture and microscopy with special stains. (**Table 48**). Isolates from culture, however, can provide antibiotic susceptibilities and strain-typing information in outbreak situations that are not available from culture-independent diagnostic assays.

Most healthy patients with watery diarrhea of less than 3 days' duration can be treated with supportive care and no antibiotic therapy or diagnostic assessment. When acute diarrhea is debilitating (moderate or severe) and associated with travel, antibiotic therapy with a fluoroquinolone, azithromycin, or rifaximin is recommended. If a patient has dysentery with visible mucus or blood in the stool and a temperature less than 37.8 °C (100 °F), then microbiologic assessment is recommended to guide therapy. When severe debilitating disease is present with temperatures of 38.4 °C (101.1 °F) or greater, microbiologic assessment should be considered, followed by empiric azithromycin treatment (see Table 48). Antimotility agents, such as loperamide, are discouraged in patients with inflammatory diarrhea (fever, abdominal pain, bloody stools) or *Clostridium difficile*-associated infection.

KEY POINTS

- Patients with mucoid or bloody diarrhea, fever, significant abdominal cramping, or suspected sepsis and those who are immunocompromised or require hospitalization should have diagnostic assessment of their stool to guide antimicrobial use; rapid multiplex molecular gastrointestinal assays that identify common bacterial, parasitic, and viral pathogens in stool specimens are generally more sensitive than historical stool culture and microscopy with special stains.
- Most healthy patients with watery diarrhea of less than 3 days' duration can be treated with supportive care and no antibiotic therapy or microscopic assessment; when the illness is debilitating and associated with travel, antibiotic therapy with a fluoroquinolone, azithromycin, or rifaximin is recommended.

TABLE 48. Causative Agents, Clinical Presentation, and Management of Infectious Diarrhea

Agent	Clinical Findings	Diagnosis[a]	Antimicrobial Treatment[b]
Bacterial Agent			
Campylobacter	Fevers, chills, diarrhea (watery or bloody), crampy abdominal pain; postinfection Guillain-Barré syndrome, IBS, or reactive arthritis	Standard stool culture or NAAT	Azithromycin; ciprofloxacin (alternative)
Shigella	Dysentery (fevers, abdominal cramps, tenesmus, bloody/mucous-filled stools); postinfection HUS, reactive arthritis or IBS	Routine stool culture or NAAT; blood cultures (with severe disease)	Fluoroquinolone (ciprofloxacin) or azithromycin or ceftriaxone
Salmonella	Fever, chills, diarrhea (watery or bloody), cramps, myalgia; bacteremia in 10%-25% of patients; postinfection reactive arthritis	Routine stool culture or NAAT; blood cultures (moderate to severe disease); bone marrow and duodenal fluid cultures may also be helpful when enteric fever suspected	Mild: none Underlying disease or severe illness: fluoroquinolone (ciprofloxacin) and/or parenteral third-generation cephalosporin
EHEC/STEC, including *Escherichia coli* O157:H7	Bloody stools in >80% of patients; fever often absent or low grade; may be associated with HUS	Stool culture with specialized media and immunoassay for Shiga toxin or NAAT	None
ETEC (travelers' diarrhea)	Nonbloody, watery stools; constitutional symptoms rare	None—usually a clinical diagnosis	Fluoroquinolone, azithromycin, or rifaximin
Yersinia	Fever, diarrhea, right lower quadrant pain (may mimic appendicitis); pharyngitis; postinfection reactive arthritis and erythema nodosum	Stool culture with specialized media (or culture of other involved sites); NAAT	Trimethoprim-sulfamethoxazole Alternatives: a fluoroquinolone (ciprofloxacin) or a third-generation cephalosporin (such as cefotaxime or ceftriaxone) Severe extraintestinal disease: requires a longer treatment duration, including intravenous agents (such as a third-generation cephalosporin)
Vibrio (not *V. cholerae*)	Bloody stools (>25% of patients), fever, vomiting (>50% of patients)	Stool culture with specialized media (blood culture with suspected invasive disease)	Usually no treatment unless invasive Fluoroquinolone (ciprofloxacin), azithromycin, or doxycycline if treating gastrointestinal illness Doxycycline plus ceftriaxone for invasive infection
Clostridium difficile	Diarrhea, fever, abdominal pain/cramping, colonic distention (including toxic megacolon in severe disease), leukocytosis, sepsis; gross blood uncommon	Stool NAAT alone or stool EIA toxin test as part of stepwise approach, including NAAT plus toxin, or GDH plus toxin, or GDH plus toxin followed by NAAT when results are discordant	Nonsevere: oral vancomycin or oral fidaxomicin; if neither is available, oral metronidazole Severe: oral vancomycin or fidaxomicin Fulminant: oral vancomycin, IV metronidazole, and (possibly) vancomycin enema
Viral			
Norovirus	Watery, noninflammatory diarrhea and fever; vomiting in >50% of patients; short incubation period and high attack rate	NAAT, particularly for outbreak investigations	None
Parasitic			
Giardia	Watery diarrhea, abdominal cramping, nausea, steatorrhea, flatulence, weight loss; fever uncommon; postinfection lactose intolerance	EIA or NAAT preferred; stool microscopy for ova and parasites	Tinidazole, nitazoxanide, or metronidazole
Cryptosporidium	Watery diarrhea; abdominal cramping; malaise; weight loss	Modified acid-fast stain; immunoassays; NAAT	Nitazoxanide Effective antiretroviral therapy in patients with HIV infection
Amebiasis	Dysentery, abdominal pain, fever, weight loss	Stool microscopy for ova and parasites; stool antigen immunoassay; NAAT; serologic antibodies	Tinidazole or metronidazole followed by paromomycin or diloxanide
Cyclospora	Watery diarrhea, bloating, flatulence, weight loss, nausea, anorexia	Modified acid-fast stain; fluorescence microscopy; NAAT	Trimethoprim-sulfamethoxazole

EHEC = enterohemorrhagic *E. coli*; EIA = enzyme immunoassay; ETEC = enterotoxigenic *E. coli*; GDH = glutamate dehydrogenase; HUS = hemolytic uremic syndrome; IBS = irritable bowel syndrome; IV = intravenous; NAAT = nucleic acid amplification test; STEC = Shiga toxin-producing *E. coli*.

[a]Multiplex molecular assays are becoming increasingly available for identification of bacterial, parasitic, and viral gastrointestinal pathogens.

[b]Empiric treatment, with the final choice of the antimicrobial agent to use guided by in vitro susceptibility testing.

Campylobacter Infection

Campylobacter species–associated gastroenteritis is usually foodborne, often secondary to consumption of inadequately cooked poultry. The incubation period is several days, and symptoms typically include diarrhea (visibly bloody in <15% of patients), crampy abdominal pain, and fever. Stool culture can confirm the diagnosis, and blood cultures can identify extraintestinal disease. Diarrhea usually resolves spontaneously without antibiotics. Patients who have severe disease (bloody stools, bacteremia, high fever, or prolonged [>1 week] symptoms) or are immunocompromised should receive antibiotic therapy. When indicated, macrolide therapy is preferred empirically because of increasing fluoroquinolone resistance. Possible post–*Campylobacter* infection complications include irritable bowel syndrome, reactive arthritis, and Guillain-Barré syndrome.

KEY POINT

- *Campylobacter* infection–associated diarrhea usually resolves spontaneously without antibiotic therapy; macrolides are the preferred empiric treatment for those who have severe disease or are immunocompromised.

Shigella Infection

Shigella infection is more commonly spread from person to person than by consumption of contaminated food or water. Fewer than 100 bacteria can cause infection, and the incubation period is approximately 3 days. Patients typically present with crampy abdominal pain, tenesmus, small-volume bloody and/or mucoid diarrhea, high fever, and (possibly) vomiting. More serious complications include bacteremia, seizures, and intestinal obstruction and perforation. Potential postinfectious sequelae include hemolytic uremic syndrome, reactive arthritis, and irritable bowel syndrome. Routine stool culture or molecular testing will establish the diagnosis. Invasive disease in patients with severe infection can also be established with blood cultures. Treatment with antibiotic agents is recommended for those with severe illness (that is, those who require hospitalization, have invasive disease, or have complications of infection) and those who are immunocompromised. Public health officials may also recommend treatment when outbreaks occur. Antibiotic susceptibilities should be obtained to determine treatment because of increasing resistance rates against the quinolones.

KEY POINT

- In patients with *Shigella* infection, treatment with antibiotic agents is recommended for those with severe illness (that is, those who require hospitalization, have invasive disease, or have complications of infection) and those who are immunocompromised.

Salmonella Infection

Salmonella infection can be typhoidal (serotypes Paratyphi or Typhi) or nontyphoidal. The typhoidal types cause enteric fever, a syndrome consisting of fever, abdominal pain, rash, hepatosplenomegaly, and relative bradycardia. This type of infection is uncommon in the United States, with most affected persons traveling to endemic areas and ingesting contaminated water or food. In contrast, nontyphoidal *Salmonella* serotypes are the most common bacterial cause of foodborne illness in the United States.

Nontyphoidal *Salmonella* infection usually results from ingesting fecally contaminated water or food of animal origin, including poultry, beef, eggs, and milk. Contact with infected animals (including pet reptiles, turtles, and snakes; farm animals; amphibians; and rodents) is a much less common mode of transmission. The incubation period is usually less than 3 days, and symptoms typically include crampy abdominal pain, fever, diarrhea (not usually visibly bloody), headache, nausea, and vomiting. Diagnosis can be made by stool culture or molecular testing. Illness is usually self-limited, although bacteremia with extraintestinal infection (involving vascular endothelium, joints, or meninges) may occur; *Salmonella* osteomyelitis also can occur and is classically associated with sickle cell disease. Severe invasive disease is more likely in infants, older adults, patients with cell-mediated immunodeficiency, and patients with hypochlorhydria. Reactive arthritis is a potential postinfection complication.

Most uncomplicated *Salmonella* infections in adults younger than 50 years resolve within 1 week and require only supportive care. Antibiotic agents are typically reserved for patients with more serious illness (including severe diarrhea requiring hospitalization, bacteremia, or high fever or sepsis) and those at high risk for severe complicated invasive disease (including infants, patients 50 years and older, or those with prosthetic materials, significant atherosclerotic disease, or immunocompromising conditions [such as HIV infection]). When empiric treatment is indicated, fluoroquinolones (such as levofloxacin or ciprofloxacin) are most likely to be effective, but azithromycin, trimethoprim-sulfamethoxazole, and amoxicillin also are potentially active agents. A fluoroquinolone, third-generation cephalosporin (such as ceftriaxone), or both are often initiated as empiric therapy for patients with severe disease requiring hospitalization. Local antibiotic susceptibilities of *Salmonella* should dictate choice of empiric therapy.

KEY POINTS

- Nontyphoidal *Salmonella* serotypes are the most common bacterial cause of foodborne illness in the United States; diagnosis is made by stool culture or molecular testing, and the illness is usually self-limited, although bacteremia with extraintestinal infection may occur.

(Continued)

KEY POINTS *(continued)*

HVC
- Most uncomplicated *Salmonella* infections in adults younger than 50 years resolve within 1 week and require only supportive care; when empiric treatment is indicated for those with more severe or invasive disease, fluoroquinolones (such as levofloxacin or ciprofloxacin) are most likely to be effective.

Escherichia coli Infection

Although *Escherichia coli* are normal inhabitants of the intestinal microbiome, some strains become enteropathogenic by using different mechanisms of infection (**Table 49**).

Enterotoxigenic *E. coli* infection (ETEC) is the most common cause of travelers' diarrhea. ETEC results from ingestion of water or food contaminated with stool and has an incubation period of 1 to 3 days. Enterotoxins cause watery diarrhea with associated abdominal cramping, nausea, and low-grade or no fever. Usually self-limiting, the illness resolves after approximately 4 days. Hydration and empiric antibiotic therapy with fluoroquinolones, azithromycin, or rifaximin are recommended in travelers with ETEC when symptoms restrict activities.

Enterohemorrhagic *E. coli* (EHEC) strains, such as -0157:H7 and -0104:H4, produce a Shiga-like toxin that can cause hemorrhagic colitis. EHEC bacteria are found in cow intestines and are transmitted by ingestion of undercooked hamburgers or fecally contaminated food (such as spinach, lettuce, fruit, milk, and flour) and water; fecal-oral transmission through exposure to infected animals at petting zoos is also possible. The incubation period is 3 to 4 days, and patients typically have visibly bloody diarrhea, crampy abdominal pain, and no fever, the latter a distinguishing feature from other causes of bloody diarrhea. Alerting the laboratory about the symptoms is recommended so that appropriate media, antigen testing, and Shiga toxin assays can be performed. Hemolytic uremic syndrome is found in less than 10% of patients infected with EHEC and manifests as microangiopathic hemolytic anemia, thrombocytopenia, and kidney injury. Treatment of EHEC infection is primarily supportive; antibiotics and antimotility agents may increase the risk of developing hemolytic uremic syndrome and do not appear to shorten the duration of infection.

TABLE 49. Diarrheagenic Strains of *Escherichia coli*

Strain	Epidemiology	Clinical Findings
Enteroaggregative *E. coli* (EAEC)	Diarrhea in travelers, young children, and patients with HIV infection	Watery diarrhea, fever typically absent
Enteroinvasive *E. coli* (EIEC)	All ages, primarily in developing countries	Inflammatory diarrhea (dysentery) with fever, abdominal pain
Enteropathogenic *E. coli* (EPEC)	Sporadic, occasionally persistent diarrhea in young children	Nausea, vomiting, malnutrition (when chronic)
Enterotoxigenic *E. coli* (ETEC)	Diarrhea in travelers, foodborne outbreaks	Watery diarrhea, fever typically absent or low grade
Shiga toxin-producing *E. coli* (STEC)	Foodborne outbreaks (associated with beef and other contaminated food), person-to-person, and zoonotic transmission	Bloody stools, progression to hemolytic uremic syndrome, fever typically absent

KEY POINTS

- Enterotoxigenic *Escherichia coli* infection is usually a self-limiting illness that resolves without treatment after approximately 4 days; hydration and empiric antibiotic therapy with fluoroquinolones, azithromycin, or rifaximin are recommended in travelers when symptoms restrict activities. HVC
- Enterohemorrhagic *Escherichia coli* strains produce a Shiga-like toxin that can cause hemorrhagic colitis; treatment is primarily supportive because antibiotics and antimotility agents may increase the risk of developing hemolytic uremic syndrome and do not appear to shorten the duration of infection. HVC

Yersinia Infection

Most diarrheal illness due to *Yersinia* species is caused by *Yersinia enterocolitica*, usually after ingestion of contaminated food, particularly undercooked pork. Patients with iron overload states, including hemochromatosis, are at increased risk for infection (including bacteremia) owing to the siderophilic characteristics of *Yersinia* species. The incubation period is approximately 5 days, and patients typically have fever, abdominal pain, diarrhea (possibly bloody), and (sometimes) nausea and emesis at presentation. The organism has tropism for lymphoid tissue (including tonsillar tissue and mesenteric lymph nodes), which results in pharyngitis or right lower-quadrant pain mimicking appendicitis. Postinfection complications include erythema nodosum and reactive arthritis. The diagnosis is confirmed by molecular testing of stool or by culture of stool, blood, a throat swab, or infected tissue; the testing laboratory should be alerted when *Yersinia enterocolitica* infection is suspected so that optimal media and enrichment conditions are applied. When treatment is indicated, trimethoprim-sulfamethoxazole (first choice) or a fluoroquinolone (such as ciprofloxacin) or a third-generation cephalosporin is recommended.

KEY POINTS

- Most diarrheal illness due to *Yersinia* species is caused by *Yersinia enterocolitica*, usually after ingestion of contaminated food, particularly undercooked pork; the diagnosis is confirmed by molecular testing of stool or by culture of stool, blood, a throat swab, or infected tissue.
- When treatment is indicated, trimethoprim-sulfamethoxazole (first choice) or either a fluoroquinolone (such as ciprofloxacin) or a third-generation cephalosporin is recommended.

Vibrio Infection

In the United States, *Vibrio parahaemolyticus* is the most common *Vibrio* species to cause gastrointestinal illness, usually after consumption of contaminated or undercooked oysters and other shellfish. The incubation period is approximately 1 day; infected patients typically report diarrhea (not commonly bloody), fever, nausea or emesis, and crampy abdominal pain at presentation. *V. parahaemolyticus* can cause septicemia in patients who have liver disease, which may lead to secondary necrotizing skin infections. Severe noninvasive gastrointestinal illness can be treated with doxycycline, although fluoroquinolones and macrolides also can be used. Patients with septicemia require more aggressive combination therapy, typically with doxycycline plus ceftriaxone.

KEY POINTS

- *Vibrio parahaemolyticus* can cause septicemia and necrotizing skin infections in patients who have liver disease.
- Severe noninvasive *Vibrio parahaemolyticus* gastrointestinal illness is treated with doxycycline, although fluoroquinolones and macrolides also can be used.

H *Clostridium difficile* Infection

Clostridium difficile is the leading cause of hospital-acquired infectious diarrhea and results from fecal-oral transmission. The number of these infections reported in the United States has increased significantly since the year 2000, owing in large part to the emergence of a hypervirulent strain. Risk factors for infection include exposure to antibiotic and chemotherapeutic agents, older age, presence of inflammatory bowel disease, gastrointestinal surgery, and (possibly) gastric acid suppression with proton pump inhibitors. Antibiotic stewardship is paramount in reducing incidence of infection, and hand washing with soap and water is the gold standard for infection control; alcohol-based gels do not eliminate spores.

Asymptomatic colonization can occur; for those with pathologic infection, the incubation period can be as long as 6 weeks after perturbation of the intestinal flora with antibiotic agents. Community-acquired infections without previous exposure to health care settings, antibiotic agents, or both have been increasingly reported.

Clostridium difficile produces both an enterotoxin (toxin A) and a cytotoxin (toxin B) that are pathogenic. Symptomatic patients typically have watery diarrhea (rarely bloody), crampy abdominal pain, malaise, and sometimes nausea and fever. Abnormal laboratory study findings are nonspecific but can include leukocytosis, an elevated creatinine level, and hypoalbuminemia. Radiographic imaging, also nonspecific, may demonstrate colonic wall thickening, mucosal edema, fat stranding, and megacolon. Colonoscopy, although not a routine diagnostic modality, may visualize pseudomembranes associated with infection.

Diagnosis is usually established by testing unformed stools from persons not taking laxatives who have unexplained new-onset diarrhea occurring three or more times daily. Although highly specific and rapid, enzyme immunoassay (EIA) testing for presence of toxin A or B lacks sensitivity. EIA testing for presence of glutamate dehydrogenase, an antigenic protein present in all *C. difficile* isolates, is quite sensitive but lacks specificity. Nucleic acid amplification testing (NAAT) for *C. difficile* toxin genes is rapid, highly sensitive, and specific. If NAAT is not used as a stand-alone technique, then combining EIA tests for glutamate dehydrogenase plus toxin (discordant results require polymerase chain reaction testing for resolution) or NAAT plus toxin can be performed.

In all infected patients, the antibiotic agent associated with the infection should be stopped if possible. Treatment is otherwise dictated by severity of disease (**Table 50**). Severe disease is supported clinically by a leukocyte count of 15,000/µL (15×10^9/L) or greater or a serum creatinine level greater than 1.5 mg/dL (133 µmol/L). Oral vancomycin or fidaxomicin for 10 days is recommended. Fulminant disease is defined as severe *C. difficile* infection with associated shock, ileus, toxic megacolon, ICU admission, elevated serum lactate level, hypotension, altered mental status, or organ failure. Higher-dose oral or nasogastric vancomycin, intravenous metronidazole, and (possibly) vancomycin enema (when ileus is present) are recommended. Patients with

TABLE 50. Treatment of *Clostridium difficile* Infection[a]

Severity of Disease	Treatment
Nonsevere	Vancomycin, 125 mg four times daily PO × 10 d *or*
	Fidaxomicin, 200 mg twice daily PO × 10 d
	If neither of these agents is available, metronidazole, 500 mg three times daily PO × 10 d
Severe	Vancomycin, 125 mg four times daily PO × 10 d *or*
	Fidaxomicin, 200 mg twice daily PO × 10 d
Fulminant	Vancomycin, 500 mg four times daily PO *or*
	NGT plus metronidazole, 500 mg every 8 h IV
	When ileus is present, consideration of vancomycin PR

IV = intravenously; NGT = by nasogastric tube; PO = by mouth; PR = per rectum.

[a]Initial presentation.

H fulminant disease warrant surgical evaluation. For nonsevere disease, defined as *C. difficile* infection that is neither severe nor fulminant, oral vancomycin or fidaxomicin for 10 days is recommended. If neither of these agents is available, oral metronidazole for 10 days can be used.

Recurrent infection is reported in as many as 25% of patients, and treatment recommendations are found in **Table 51**. Studies have shown that fecal microbiota transplantation is effective in the management of patients with multiple recurrences. Retesting stool for *C. difficile* after treatment for evidence of cure in patients who have no symptoms is not recommended. H

KEY POINTS

HVC
- *Clostridium difficile* is the leading cause of hospital-acquired infectious diarrhea; antibiotic stewardship is paramount in reducing incidence of infection, and hand washing with soap and water is important to eliminate spores.
- Testing unformed stools usually establishes the diagnosis; nucleic acid amplification testing for *Clostridium difficile* toxin genes is rapid, highly sensitive, and specific; enzyme immunoassay testing for presence of toxin A or B is highly specific and rapid but lacks sensitivity, and enzyme immunoassay testing for presence of glutamate dehydrogenase is quite sensitive but lacks specificity.
- Treatment of an initial *Clostridium difficile* infection is dictated by severity of disease, with nonsevere disease treated with oral vancomycin or fidaxomicin (or with oral metronidazole if neither of these drugs is available), severe disease treated with oral vancomycin or fidaxomicin, and fulminant disease treated with higher dose oral vancomycin, intravenous metronidazole, and (when ileus is present) vancomycin enema.

TABLE 51. Treatment of Recurrent *Clostridium difficile* Infection

First recurrence	Vancomycin, 125 mg four times daily PO × 10 d, if metronidazole used for initial episode *or*
	Prolonged tapered and pulsed vancomycin if standard regimen was used for initial episode (that is, vancomycin, 125 mg four times daily PO × 10 d, then 125 mg twice daily PO × 7 d, then 125 mg every 2 or 3 d PO for 2-8 wk) *or*
	Fidaxomicin, 200 mg twice daily PO × 10 d, if vancomycin was used for the initial episode
Second or subsequent recurrence	Prolonged tapered and pulsed vancomycin PO (see above) *or*
	Vancomycin, 125 mg four times daily PO × 10 d, followed by rifaximin, 400 mg three times daily PO × 20 d *or*
	Fidaxomicin, 200 mg twice daily PO × 10 d *or*
	Fecal microbiota transplantation (after two recurrences treated with appropriate antibiotics)

PO = by mouth.

Viral Gastroenteritis

Viruses are responsible for acute gastroenteritis in most patients. Rotavirus infects young children, and noroviruses, which are estimated to cause more than 50% of foodborne gastroenteritis in the United States, affect all ages. Norovirus outbreaks on cruise ships and in schools and other institutionalized settings are well documented. Transmission from person to person is primarily fecal-oral. Highly contagious infection can develop after ingestion of fewer than 100 viral particles. The incubation period is typically less than 2 days, and infected patients typically have watery diarrhea, nausea, vomiting, and fever at presentation. Infection is usually self-limited and requires supportive care because of the lack of effective antiviral agents. Diagnostic molecular testing is available. Viral shedding persists for as long as 2 weeks after symptom resolution, which contributes to its high infectivity.

KEY POINT

- Noroviruses cause more than 50% of foodborne gastroenteritis in the United States; the incubation period is typically less than 2 days; viral shedding persists as long as 2 weeks after symptom resolution, which contributes to high infectivity.

Parasitic Infection

Parasitic infection should be considered in patients with persistent or chronic diarrhea. Immunosuppressed persons are at increased risk for more chronic and severe infection.

Giardia lamblia Infection

Giardia lamblia is the most common parasitic pathogen in the United States. Cysts from infected animals are excreted in stool into reservoirs of natural fresh water, and subsequent ingestion of contaminated water (or food) can lead to human infection. Secondary spread from person to person via fecal-oral transmission is also possible because cysts may be excreted for many months. Persons at risk for infection include international outdoor travelers, children in day care centers, immunocompromised hosts (particularly those with humoral immunodeficiency), and persons engaged in sexual activity that includes oral-anal contact. The incubation period ranges from 1 to 3 weeks. More than half of infected patients are asymptomatic. Symptomatic patients typically report watery diarrhea that is fatty and foul smelling, flatulence, bloating, nausea, and crampy abdominal pain; fever is uncommon. Symptoms can last for several weeks until spontaneously resolving; chronic infection may develop, particularly in persons with hypogammaglobulinemia. EIA and molecular testing of stool is more sensitive than stool microscopy for confirming the diagnosis. Treatment is recommended for symptomatic patients; metronidazole, tinidazole, or nitazoxanide can be used. Postinfection lactose intolerance is common and may be mistaken for recurrent or resistant *Giardia* infection.

KEY POINTS

- More than half of patients infected with *Giardia lamblia* are asymptomatic; treatment with metronidazole, tinidazole, or nitazoxanide can be used.
- Postinfection lactose intolerance is common and may be mistaken for recurrent or resistant *Giardia* infection.

Cryptosporidium Infection

Cryptosporidium species can infect humans and other mammals. Infection occurs through consumption of fecally contaminated water or food or through close person-to-person or animal-to-person transmission. Municipal water supplies and swimming pools can be a source of infection because the thick-walled oocysts are chlorine resistant and can evade filtration. This parasite is highly infectious; ingestion of fewer than 50 oocysts may result in infection. The incubation period is 7 days. Although some infected patients will be asymptomatic, symptomatic patients typically report watery diarrhea, crampy abdominal pain, nausea, vomiting, malaise, fever, dehydration, and weight loss. Symptoms usually last less than 2 weeks before spontaneously resolving in immunocompetent hosts. Immunocompromised patients, in particular patients with AIDS, can develop serious and prolonged infection. Diagnosis can be established microscopically by visualization of oocysts with modified acid-fast staining, molecular testing, and enzyme or direct fluorescent immunoassay testing. Treatment for immunocompetent patients usually consists of supportive care. When antimicrobial agents are considered for severe or prolonged infection, nitazoxanide is recommended. In HIV-infected patients, antiretroviral therapy is most effective in resolving infection. Nitazoxanide also can be considered when supportive care does not result in symptom resolution.

KEY POINTS

- The diagnosis of *Cryptosporidium* infection can be established microscopically by visualization of oocysts using modified acid-fast staining, polymerase chain reaction testing, and enzyme immunoassay or direct fluorescent antibody testing.
- Treatment of *Cryptosporidium* infection consists of supportive care for most immunocompetent hosts; nitazoxanide is recommended for severe or prolonged infection or if supportive care does not resolve symptoms; antiretroviral therapy is most effective in resolving infection in HIV-infected patients.

Amebiasis

Entamoeba histolytica is the parasitic organism responsible for amebiasis. In the United States, most infections are diagnosed in travelers returning from visits to unsanitary tropical or developing countries, immigrants from these areas, persons in institutionalized settings, or those who practice oral-anal sex. Amebiasis is highly infectious, with ingestion of only a small number of infective cysts in contaminated water or food needed for infection. The incubation period is 2 to 4 weeks. Most infections are asymptomatic, but some patients develop diarrhea with visible blood, mucus, or both and associated abdominal pain, fever, and weight loss. Colonic perforation, peritonitis, and death may complicate more fulminant infections. Risk factors for severe infection in adults include immunodeficiency. Diagnosis can be established microscopically by visualization of cysts or trophozoites, immunoassay testing, molecular testing, and serologic antibody testing, although the latter technique does not distinguish current from remote infection. Treatment is recommended for all infected patients. In symptomatic patients, treatment with metronidazole or tinidazole is recommended initially for parasitic clearance followed by an intraluminal amebicide, such as paromomycin or diloxanide, for cyst clearance. In asymptomatic infections, an intraluminal agent for eradication of cysts is recommended.

KEY POINT

- Treatment is recommended for all patients with amebiasis; for symptomatic patients, treatment with metronidazole or tinidazole is recommended initially for parasitic clearance followed by an intraluminal amebicide for cyst clearance, and for asymptomatic patients, an intraluminal agent for eradication of cysts is recommended.

Cyclospora Infection

Cyclospora infections are typically acquired after consumption of food or water that is fecally contaminated with *Cyclospora* oocysts. In the United States, most of these infections have been traced to imported fresh produce from tropical areas or have occurred in persons who have traveled to areas of endemicity. The incubation period is approximately 1 week. Infected patients typically report watery diarrhea, decreased appetite, weight loss, crampy abdominal pain, bloating, flatulence, nausea, fatigue, and (sometimes) fever. Symptoms can last for several weeks and may be more pronounced in HIV-infected patients. Diagnosis is typically established microscopically by visualization of oocysts with modified acid-fast staining, microscopy with ultraviolet fluorescence, or molecular testing. Trimethoprim-sulfamethoxazole is recommended for treatment of symptomatic infection.

KEY POINT

- *Cyclospora* infection is typically diagnosed microscopically by visualization of oocysts with modified acid-fast staining, microscopy with ultraviolet fluorescence, or molecular testing; trimethoprim-sulfamethoxazole is recommended for treatment of symptomatic infection.

Infections in Transplant Recipients

Introduction

Despite improvements in immunosuppression and antimicrobial therapy, infection remains a significant cause of morbidity and mortality after solid organ transplantation (SOT) and hematopoietic stem cell transplantation (HSCT). Infection is the most common cause of death in the first year after SOT. Additionally, the interaction of the immune system and infection goes both ways; although immune suppression to prevent rejection increases risk of infection, infection also raises the risk of rejection.

The occurrence of SOT and HSCT procedures continues to increase, as do long-term survival rates owing to improved management of rejection and decreased complications. With more patients living longer after transplantation, awareness of principles involved in the recognition and prevention of infection in transplant recipients remains important for physicians who are not transplant specialists.

Antirejection Drugs in Transplant Recipients

Success after transplantation depends on modulating the immune system to prevent organ rejection in SOT and to minimize graft-versus-host disease (GVHD) in allogeneic HSCT. Antirejection regimens involve multiple agents (**Table 52**) with different mechanisms of action, which are chosen to minimize overlapping toxicities. After SOT, an induction and maintenance strategy is applied; immunosuppression is most intensive in the early period after transplantation and often includes lymphocyte depletion therapy. Immunosuppression may require intensification later for episodes of rejection, and this may again increase the risk of infection.

Glucocorticoids have historically been the cornerstone of antirejection therapy, but steroid-sparing or minimizing regimens are increasingly being used to avoid the toxicities of long-term therapy. Tacrolimus, cyclosporine, or sirolimus are the cornerstones, usually with mycophenolate or, less commonly, azathioprine. Drug interactions are common with these agents, and many drugs can affect antirejection medication levels. Monitoring is important to balance adequate immunosuppression with toxicity.

TABLE 52. Immunosuppressive Agents Used in Transplantation

Class	Agents
Glucocorticoids	Prednisone, others
Cytotoxic agents (DNA synthesis inhibitors, antimetabolites)	Mycophenolate mofetil
	Mycophenolate sodium
	Azathioprine
	Methotrexate
	Cyclophosphamide
Calcineurin pathway inhibitors	Cyclosporine
	Tacrolimus
mTOR inhibitors	Sirolimus (rapamycin)
	Everolimus
Lymphocyte-depleting antibodies	
Polyclonal	Antithymocyte globulins
Monoclonal	Muromonab (anti-CD3)
	Basiliximab (anti-IL-2 receptor)
	Daclizumab (anti-IL-2 receptor)
	Rituximab (anti-CD20)
	Alemtuzumab (anti-CD52)

IL-2 = interleukin-2; mTOR = mammalian target of rapamycin.

KEY POINT

- Glucocorticoid-sparing or minimizing regimens (with tacrolimus, cyclosporine, or sirolimus) are increasingly used to avoid the toxicities of long-term steroid therapy.

Posttransplantation Infections

Timeline and Type of Transplant

Infection may occur at any time after transplantation, but periods of highest immunosuppression, usually within the first few months after transplantation, carry the highest likelihood. Risk for infection is also affected by pre-existing conditions (such as diabetes mellitus, cirrhosis, or neutropenia) and by colonization with resistant organisms (such as *Burkholderia* in cystic fibrosis).

The risk of specific infections varies depending on the time frame after transplantation. **Table 53** shows the typical timeline of risk for specific infections after SOT. However, the timeline restarts when treating episodes of rejection, and infection risk in the late period depends on the level of immunosuppression required. Knowledge of the risk timeline and effect of the immunosuppression level can be helpful in recognizing likely infections and in preventing infections through targeted prophylaxis. In the first month after SOT, infections are similar to those seen in other hospitalized postsurgical patients, including a risk of resistant bacteria, and most often involve the lungs, urinary tract, and surgical sites. The middle period usually encompasses the most intensive immunosuppression, with significant risk for viral (such as cytomegalovirus) and fungal (such as *Pneumocystis*) infections owing to defects in cell-mediated immunity. If immunosuppression can be de-escalated during the late period, risk for opportunistic infections decreases overall, but patients remain at risk for certain viral infections and have increased risk for community-acquired bacterial infections.

Additional general considerations include the higher likelihood of infections to disseminate after transplantation and the subtle or atypical presentation of infection because of

TABLE 53. Timeline of Common Infections after Solid Organ Transplantation

Early Period (<1 Month after Transplantation)	Middle Period (1-6 Months after Transplantation)	Late Period (>6 Months after Transplantation)[a]
Staphylococcus aureus infection (including methicillin-resistant)	Cytomegalovirus infection	Epstein-Barr virus (including PTLD) infection
Nosocomial gram-negative bacterial infection	Epstein-Barr virus (including PTLD) infection	Varicella-zoster virus infection
Clostridium difficile colitis	Herpes simplex virus infection	Community-acquired pneumonia
Candida infection	Varicella-zoster virus infection	Urinary tract infections
Aspergillus infection	Polyoma BK virus infection	Polyoma BK virus infection
Surgical site infections	*Pneumocystis jirovecii* infection	Cytomegalovirus infection
Nosocomial pneumonia	*Toxoplasma, Trypanosoma, Strongyloides*	
Catheter-related bacteremia	*Listeria* infection	
Urinary tract infections	*Nocardia* infection	
	Tuberculosis reactivation	
	Fungal infections, including *Cryptococcus*	

PTLD = posttransplant lymphoproliferative disorder.

[a]For opportunistic infections in the late period, risk depends on level of immunosuppression. Infections such as *Pneumocystis* and other fungi, *Listeria*, and *Nocardia* can be seen in the late period in patients with higher immunosuppression.

changed anatomy after transplantation. Immunosuppressive drugs may also contribute to altered presentation because of reduction in fever and other inflammatory responses making the usual signs and symptoms of infection less prominent. Noninfectious complications such as GVHD or malignancy may also be confused with infection. For some infections, the risk strongly depends on donor and recipient characteristics. Standard donor and recipient pretransplantation testing includes serologies for cytomegalovirus; Epstein-Barr virus; varicella-zoster virus; HIV; hepatitis B, C, and E viruses; syphilis; toxoplasmosis; and *Strongyloides*, *Leishmania*, and *Trypanosoma* if from an endemic area and interferon-γ release assay for latent tuberculosis infection.

Risk after HSCT is much greater for allogeneic than autologous transplantation because of the myeloablative conditioning regimen. After allogeneic HSCT, patients undergo a prolonged period of intense neutropenia, putting them at risk for bacterial infections, *Candida* and mold infections, and herpes simplex and other virus reactivation. This is followed by a prolonged period of impaired cell-mediated and humoral immunity because of immunosuppression to reduce GVHD. Development of chronic GVHD can also increase risk for infections caused by immune system effects and breakdowns in mucosal and other barriers. Infections in this later period are similar to those in the later period after SOT. **Figure 21** shows the timeline of risk for specific infection after allogeneic HSCT.

KEY POINTS

- Infection may occur at any time after transplantation but is most likely at periods of highest immunosuppression; the risk for specific organisms varies depending on the time frame after transplantation.
- Infection risk is much greater after allogeneic than autologous hematopoietic stem cell transplantation because of myeloablative conditioning with a prolonged period of neutropenia and immunosuppression given to reduce graft-versus-host disease.

Specific Posttransplantation Infections

Viral Infections

Cytomegalovirus is the most significant viral infection after transplantation, with risk for infection depending on donor and recipient serology. After SOT, the risk for cytomegalovirus is highest (>50%) for donor-positive/recipient-negative, intermediate (15%-20%) for recipient-positive, and lowest for donor-negative/recipient-negative transplantations. Risk is also significantly increased with use of lymphocyte-depleting agents. Comparatively, after allogeneic HSCT, the risk of cytomegalovirus is highest for donor-negative/recipient-positive transplantations. Cytomegalovirus is an immunomodulatory virus, and active cytomegalovirus infection after transplantation is associated with increased rates of rejection and GVHD, as well as increases in other opportunistic infections and posttransplant lymphoproliferative disorder (PTLD). Cytomegalovirus often presents as a nonspecific viral syndrome with fever and cytopenias. Specific organ disease owing to cytomegalovirus includes pneumonitis (more common in HSCT than SOT), encephalitis, hepatitis, and other gastrointestinal sites. Although cytomegalovirus can cause disease anywhere in the gastrointestinal tract, colitis is the most common gastrointestinal disease after SOT, whereas esophagitis is more common after HSCT. Definitive diagnosis of organ disease depends on demonstration of cytomegalovirus in biopsy, although presumptive diagnosis can be made based on cytomegalovirus viremia, demonstrated by quantitative nucleic acid amplification testing, in the appropriate clinical setting.

Epstein-Barr virus is most significant for its relationship to PTLD resulting from B cell proliferation; PTLD should be suspected in any patient in the middle or late period presenting with lymphadenopathy or an extranodal mass, often with fever. Treatment of PTLD involves rituximab and decreasing immunosuppression. Reactivation of herpes simplex virus is especially common after HSCT and can be reduced with acyclovir prophylaxis (if the patient is not already receiving an agent for cytomegalovirus). Patients with chronic hepatitis B

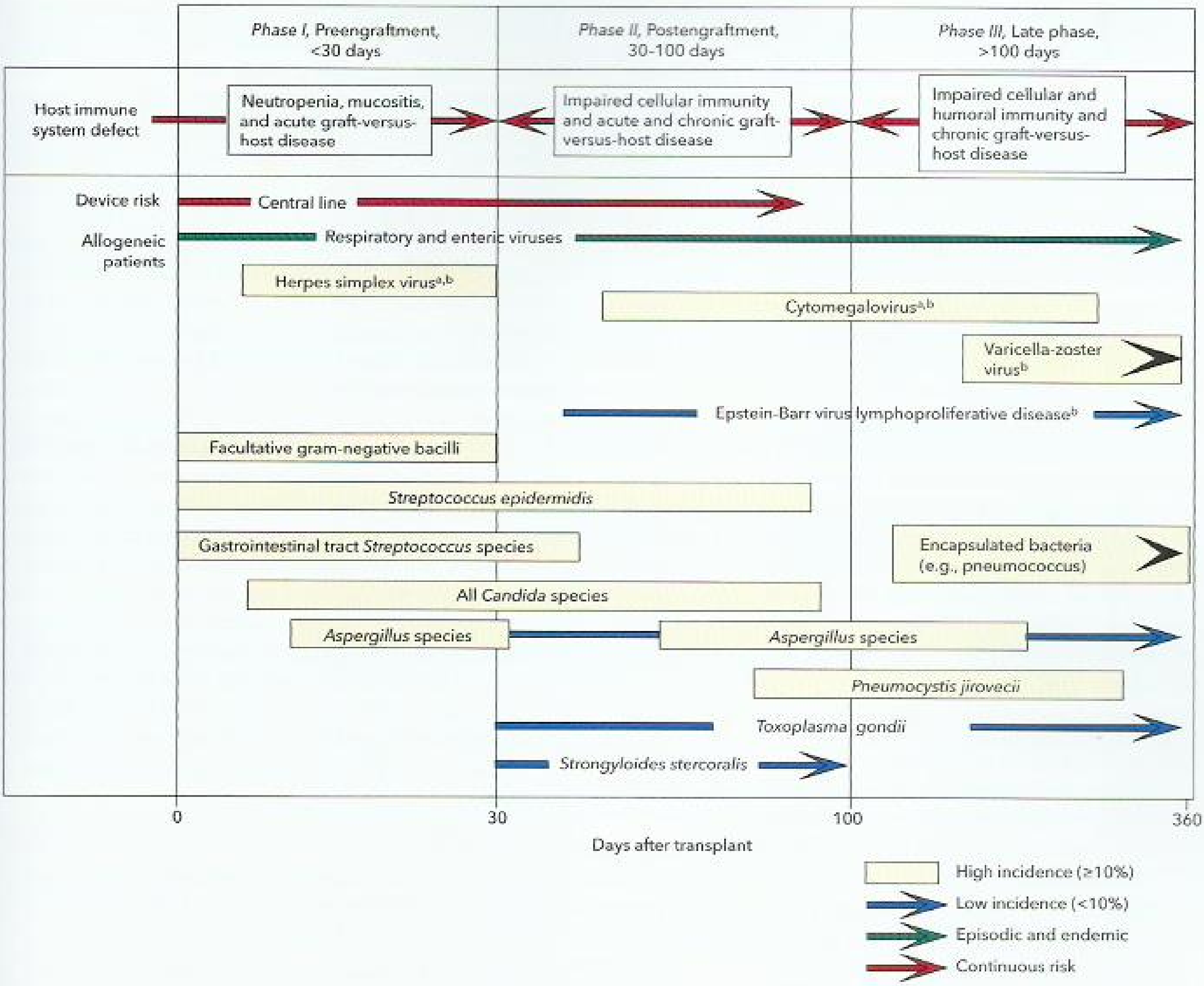

FIGURE 21. Phases of opportunistic infections in allogeneic hematopoietic stem cell transplant recipients.

[a]Without standard prophylaxis.

[b]Primarily among persons who are seropositive before transplantation.

Reprinted with permission from CDC, Infectious Diseases Society of America, and the American Society of Blood and Marrow Transplantation. Guidelines for preventing opportunistic infections among hematopoietic stem cell transplant recipients. Recommendations of CDC, the Infectious Diseases Society of America, and the American Society of Blood and Marrow Transplantation. Cytotherapy. 2001;3(1):41-54. PMID: 12028843

can have flares of disease if not taking suppressive therapy. Polyoma BK virus can cause a nephropathy in the middle or late period after transplantation.

Bacterial Infections

Bacterial infections are common in the early period after SOT and during neutropenia after HSCT. These are often typical nosocomial infections, including resistant organisms such as methicillin-resistant staphylococci, vancomycin-resistant enterococci, and multidrug-resistant gram-negative organisms. *Clostridium difficile* colitis is common, especially with the extensive antibiotic use that accompanies transplantation. *Mycobacterium tuberculosis* can reactivate with the immunosuppression of transplantation and may present with an atypical pattern on chest radiography or with extrapulmonary disease. Related to persistently low antibody levels, encapsulated organisms such as *Streptococcus pneumoniae* remain common even late after HSCT.

Fungal Infections

Fungal infections are most common in the middle period after SOT but may also occur late, especially in the setting of rejection or cytomegalovirus infection. The most common fungal infection without prophylaxis is *Pneumocystis* pneumonia, which is typically a more aggressive pneumonia in patients after transplantation than in those with AIDS. Cryptococcosis usually presents as subacute meningitis with fever, headache, mental status changes, and lymphocytic pleocytosis in

cerebrospinal fluid, although skin and other organ involvement may also occur; cryptococcal antigen testing is key to diagnosis. Histoplasmosis may also occur in geographically endemic areas and is more likely to present with disseminated disease after transplantation. Mucocutaneous candidiasis is common after SOT and HSCT. Invasive *Candida* infections and candidemia can be seen, especially in the neutropenic phase after HSCT, as can aspergillosis and other invasive molds, such as *Mucor*. The risk for invasive fungal infection after HSCT is also increased in later periods by the use of immunosuppressive agents for GVHD. In SOT, pulmonary aspergillosis is most common after lung transplantation.

Protozoa and Helminths

Toxoplasma gondii is a protozoan that can reactivate with immunosuppression after transplantation, usually causing encephalitis with fever, headache, and focal neurologic deficits and with multiple ring-enhancing brain lesions on imaging. *Strongyloides* can cause a hyperinfection syndrome with significant immunosuppression (especially glucocorticoid use), often with secondary pneumonia and gram-negative bacteremia. Reactivation of *Trypanosoma* or *Leishmania* can also occur after transplantation, if the recipient or donor were from an endemic area.

KEY POINTS

- Cytomegalovirus is the most significant viral infection after transplantation and may present as a nonspecific viral syndrome with fever and cytopenias or with specific organ disease, including pneumonitis, encephalitis, esophagitis, and colitis.
- *Clostridium difficile* colitis is common after transplantation, complicating the extensive antibiotic use that accompanies transplantation.
- *Mycobacterium tuberculosis* can reactivate with the immunosuppression of transplantation and may present with an atypical pattern on chest radiography or with extrapulmonary disease.
- *Pneumocystis* pneumonia is the most common fungal infection without prophylaxis; it is typically a more aggressive pneumonia in patients after transplantation than in those with AIDS.

Prevention of Infections in Transplant Recipients

Prevention is preferred over treatment strategies for most common infections after transplantation because most opportunistic infections have devastating effects and the cost and toxicity of prophylaxis and immunization are relatively low. Recommended immunizations for SOT and HSCT are shown in **Table 54**. Most immunizations are safe in patients after transplantation except for live virus vaccines, which should be avoided after transplantation.

Trimethoprim-sulfamethoxazole is one of the most important prophylactic medications after transplantation. Used to prevent *Pneumocystis*, it may also reduce toxoplasmosis and certain bacteria, including *Listeria* and agents causing urinary tract infections. Trimethoprim-sulfamethoxazole is usually given up to 1 year after transplantation and often longer if immunosuppression cannot be adequately reduced.

Antifungal prophylaxis is indicated during the early months after HSCT and may need to be extended in the setting of GVHD. Coverage should include *Candida* and *Aspergillus*, typically with posaconazole or voriconazole.

Strategies to reduce the effects of cytomegalovirus remain important and include primary prophylaxis, usually with valganciclovir, or regular monitoring for active cytomegalovirus replication by quantitative nucleic acid amplification testing and institution of pre-emptive therapy based on results. Monitoring and pre-emptive therapy is more often used after HSCT, partially because of increased concerns for neutropenia as an adverse effect of prophylaxis and because prophylaxis was not found to be superior to pre-emptive therapy in a randomized controlled trial. The potential role of letermovir, a new antiviral agent without the hematologic toxicity of ganciclovir, is being studied for cytomegalovirus prophylaxis. For SOT, prophylaxis with valganciclovir is preferred for patients at high risk (donor-positive/recipient-negative, those receiving lymphocyte-depleting agents, lung transplants) and is usually given for at least 3 to 6 months.

KEY POINTS

- Prophylaxis and immunization are preferred over treating active infections after transplantation; live virus vaccines should not be given after transplantation. HVC
- Monitoring by quantitative nucleic acid amplification testing for active cytomegalovirus replication and institution of pre-emptive therapy based on results is preferred to ganciclovir primary prophylaxis of cytomegalovirus infection after hematopoietic stem cell transplantation.

Health Care-Associated Infections

H

Epidemiology

Health care-associated infections (HCAI) have been linked to indwelling medical devices, prosthetic devices and materials, surgery, invasive procedures, transmission of organisms between patients and health care personnel, and environmental factors. Four percent of hospitalized patients acquire at least one HCAI, costing the U.S. health care system an estimated $28 billion to $45 billion annually. HCAIs include pneumonia and surgical site infections (21.8% each), gastrointestinal infections (17.1%), urinary tract infections (12.9%; 67.7%

TABLE 54. Immunization Recommendations for Adult Recipients of Transplants[a]

Immunization	Recommendations for Solid Organ Transplantation	Recommendations for Hematopoietic Stem Cell Transplantation[b]
Pneumococcal	Before transplantation: PCV13 followed 8 weeks later by PPSV23 After transplantation: PCV13 (if not administered pretransplantation) 2-6 months after transplantation; 1 dose PPSV23 at least 8 weeks after PCV13 and 5 years after any previous PPSV23	3-6 months after transplantation: 3-4 doses of PCV13 12 months after transplantation: 1 dose of PPSV23
Influenza (inactivated only)	Annually	Annually
Tdap	Before transplantation: complete series, including Tdap booster	6 months after transplantation: 3 doses Tdap
MMR	Contraindicated after transplantation	24 months after transplantation: 1-2 doses, only if no GVHD or immune suppression
Inactivated polio	Before transplantation: complete series	6-12 months after transplantation: 3 doses
Haemophilus influenzae type B	No recommendation	6-12 months after transplantation: 3 doses
Meningococcal	Per recommendations for nontransplant patients	6 months after transplantation: both quadrivalent conjugate vaccine and serogroup B vaccine
Hepatitis B	Before transplantation: complete series if not already immune	6-12 months after transplantation: 3 doses if indications for nontransplant patients are met
Hepatitis A	Before transplantation: complete series if not already immune	Per recommendations for nontransplant patients
Varicella-zoster virus		
Live attenuated vaccine	>4 weeks before transplantation: varicella if not immune >4 weeks before transplantation: zoster if same indications as nontransplant patients are met Both contraindicated after transplantation	>4 weeks before transplantation: varicella if not immune 24 months after transplantation: 2 doses varicella if seronegative and only if no GVHD or immunosuppression
Recombinant adjuvanted zoster vaccine	Theoretically safe, but data in severely immunocompromised patients not yet available; no recommendations after transplantation Should be given before transplantation if possible	Theoretically safe, but data in severely immunocompromised patients not yet available; no recommendations after transplantation Should be given before transplantation if possible
Human papillomavirus	Before transplantation: per recommendations for nontransplant patients	Per recommendations for nontransplant patients

GVHD = graft versus host disease; MMR = measles, mumps, and rubella vaccine; PCV13 = 13-valent pneumococcal conjugate vaccine; PPSV23 = 23 valent pneumococcal polysaccharide vaccine; Tdap = tetanus, diphtheria, and acellular pertussis vaccine.

[a]See MKSAP 18 General Internal Medicine for more information on vaccination recommendations and schedules.

[b]For multiple-dose immunizations, the time period between doses is generally 1 2 months.

H CONT.

associated with catheters), and primary bloodstream infection (9.9%; 84% associated with central venous catheters).

Elimination of HCAIs remains important for the U.S. health care system. Sixty five percent to 70% of catheter-associated bloodstream and urinary tract infections and 55% of ventilator-associated pneumonias and surgical site infections are preventable. Progress toward elimination varies by type of infection. Central line associated bloodstream infections decreased by 50% and surgical site infections by 17% between 2008 and 2014; rates of catheter associated urinary tract infections showed little change between 2009 and 2014. H

KEY POINT

- Approximately 65% to 70% of catheter-associated bloodstream and urinary tract infections and 55% of ventilator-associated pneumonias and surgical site infections are preventable.

Prevention

H

Hand hygiene is the foundation of infection prevention, but adherence has been reported as less than 50%. Most facilities have improved in the last decade, with some facilities showing

H CONT.

sustained improvement to 90% adherence. Hand hygiene should be performed at least before and after every patient contact. The World Health Organization's five key hand hygiene moments are commonly used to define hand hygiene opportunities: before touching a patient, before clean or aseptic procedures, after body fluid exposure risk, after touching a patient, and after touching patient surroundings. Hand hygiene should include all surfaces of the hands up to the wrists, between fingers, and the fingertips. Alcohol-based hand rubs are generally preferred to soap and water hand disinfection, except when hands are visibly soiled, when personnel come in direct contact with blood or body fluids, or after contact with a patient with *Clostridium difficile* infection or his or her environment.

Standard precautions should be practiced for every patient to protect health care personnel from exposure to bloodborne pathogens. Blood and all body fluids except sweat are potentially infectious, regardless of the patient's presumed or known infection status. Personal protective equipment (gloves, gown, mask, and eye protection) are barriers protecting health care personnel from exposure to blood and body fluids. Protective equipment should be removed in the following order: 1) gloves, careful not to contaminate hands; 2) goggles/face shields; 3) gown, pull away from neck and shoulders, turn inside out to discard; 4) mask/respirator by grasping bottom then top ties/elastic. This process should be followed by hand hygiene. Transmission-based precautions (airborne, contact, droplet) are performed in addition to standard precautions to prevent transmission of epidemiologically significant organisms (**Table 55**).

Additional preventive measures include careful and judicious device use, safe injection practices (one needle, one syringe, only one time), aseptic technique for invasive procedures and surgery, and a clean environment and patient equipment. HCAI prevention "bundles" comprise three to five evidence-based processes of care that, when performed together, consistently have a greater impact on decreasing HCAIs than individual components performed inconsistently. H

KEY POINT

- Hand hygiene is the foundation of infection prevention; the World Health Organization has identified five key hand hygiene moments (before touching a patient, before clean or aseptic procedure, after body fluid exposure risk, after touching a patient, and after touching patient surroundings). HVC

Catheter-Associated Urinary Tract Infections

H

Catheter-associated urinary tract infections (CAUTIs) are the most common device-associated HCAI, and 17% to 69% may be preventable. Urinary catheters are used in 15% to 25% of hospitalized patients in the United States, compelling efforts to establish appropriateness criteria for catheter use. Adverse outcomes related to CAUTI include pyelonephritis, perinephric abscess, and bacteremia (<5%). *Escherichia coli* is the most common CAUTI pathogen, followed by *Pseudomonas aeruginosa*, *Klebsiella pneumoniae/Klebsiella oxytoca*, *Candida* species, and *Enterococcus* species; antibiotic resistance among these pathogens is increasing.

Duration of catheterization is the primary modifiable risk factor for CAUTI; each day of catheterization increases the risk of CAUTI. Nonadherence to aseptic technique (for example, opening a closed system) and insertion by a less experienced operator also increase the risk. Other risk factors for CAUTI include female sex, age older than 50 years, diabetes mellitus, severe or nonsurgical underlying illness, and serum creatinine level greater than 2.0 mg/dL (176.8 µmol/L). Appropriate indications for indwelling urinary catheters are listed in **Table 56**. Management of urinary incontinence using external catheters is preferred when feasible. Provision of care in the ICU is not itself an indication for a catheter.

Diagnosis

Patients with an indwelling urethral or suprapubic catheter (or catheter removed in the 48 hours before symptom onset) or

TABLE 55. Transmission-Based Precautions[a]

Precaution Type	Indications	Precaution	Examples
Airborne	Organisms transmitted from respiratory tract by small droplet nuclei (≤5 microns) that travel long distances on air currents	Airborne infection isolation room (negative-pressure room); HCP wear fit-tested N95 respirator	Chickenpox (plus contact precautions), tuberculosis, measles
Contact	Organisms transmitted by direct or indirect contact	Single room; gloves and gown for HCP entering room	Multidrug-resistant organisms (such as MRSA, VRE, ESBL-producing gram-negative organisms), *Clostridium difficile*, rotavirus
Droplet	Organisms transmitted from respiratory tract by large droplet nuclei (>5 microns) that travel less than 3 feet on air currents	Single room; HCP wear face or surgical mask when within 3 feet of patient	Influenza, *Bordetella pertussis*, *Neisseria meningitidis* for first 24 hours of therapy, mumps

ESBL = extended-spectrum β-lactamase; HCP = health care personnel; MRSA = methicillin-resistant *Staphylococcus aureus*; VRE = vancomycin-resistant enterococci.

[a]Some organisms and infections require a combination of transmission-based precautions (adenovirus: contact and droplet; disseminated varicella-zoster virus: airborne and contact).

TABLE 56. Appropriate Indications for Use of Indwelling Urinary Catheters
Indication
Management of acute urinary retention without bladder outlet obstruction
Management of acute urinary retention with bladder outlet obstruction not related to infection or trauma
Management of chronic urinary retention with bladder outlet obstruction when ISC is not feasible
Management of stage III or IV or unstageable pressure ulcers that cannot be kept clear of urinary incontinence despite other urinary management strategies (e.g., barrier creams, absorbent pads, prompted toileting, non-indwelling catheters)
Hourly measurement of urine volume required to provide treatment
Daily measurement of urine volume required to provide treatment when it cannot be assessed by other volume (e.g., daily weighing, physical examination) and urine collection (e.g., urinal, bedside commode, bedpan, external catheter, ISC) strategies
Collection of a single 24-hour urine sample needed for diagnostic test that cannot be obtained by other urine collection strategies
Reduction in instances of acute, severe pain with movement when other urine management strategies are difficult
Improvement in comfort when urine collection by catheter addresses patient and family goals in a dying patient
Management of gross hematuria with blood clots in urine
Management of clinical condition for which ISC or external catheter is appropriate but placement is difficult or bladder emptying is inadequate for the patient with non-indwelling strategies

ISC = intermittent straight catheterization.

H CONT

using intermittent catheterization who have signs and symptoms compatible with urinary tract infection (UTI; see Urinary Tract Infections for information), no other identifiable infection source, and $\geq 10^3$ colony-forming units/mL of one or more bacterial species in a urine specimen are diagnosed with a CAUTI. Catheter-associated asymptomatic bacteriuria ($\geq 10^3$ colony-forming units/mL without urinary tract signs or symptoms) is common and generally does not require treatment. H

KEY POINT

- Catheter-associated asymptomatic bacteriuria ($\geq 10^3$ colony-forming units/mL without urinary tract signs or symptoms) is common and generally does not require treatment. HVC

H

Treatment

A urinalysis and urine culture should always be obtained before initiating antimicrobial treatment to determine if antimicrobial resistance is present and to guide definitive therapy. CAUTI management includes removing the urinary catheter (and only replacing if still needed). Removal is strongly recommended for catheters in place for 2 or more weeks because biofilm on the catheter makes it difficult to eradicate bacteriuria or funguria and may lead to antimicrobial resistance. Therapy should always be adjusted to the narrowest coverage spectrum possible based on culture results. Treatment is given for 7 days if symptoms resolve promptly and longer (10-14 days) for patients with delayed response. Candiduria in a patient with a catheter almost always represents colonization and rarely requires treatment. *Candida* CAUTI is considered when significant candiduria persists despite catheter removal or replacement and the patient is symptomatic. CAUTIs caused by *Candida* species requiring treatment should be treated for 14 days. H

KEY POINTS

- Catheter-associated urinary tract infection management includes catheter removal, with replacement only if still necessary. HVC
- Candiduria in a patient with a catheter almost always represents colonization and rarely requires treatment. HVC

H

Prevention

Key prevention strategies include appropriately limiting urinary catheter use (see Table 56) and considering other options associated with lower infection risk (intermittent straight catheterization, external catheters) when urine collection is necessary (**Table 57**). Most studies have not shown definitive benefit of antimicrobial- or antiseptic-coated catheters for short- (<14 days) or long-term catheterization; these catheters are more expensive and, in some cases (such as nitrofurazone-coated catheters), cause more patient discomfort. H

KEY POINT

- Antimicrobial- or antiseptic-coated catheters have not shown benefit for short-term or long-term catheterization, are more expensive, and, in some cases, cause more patient discomfort. HVC

H

Surgical Site Infections

Surgical site infections (SSIs) account for 23% of HCAIs. The overall risk of developing an SSI after surgery is 1.9%. Wound class affects the risk of infection, with clean wounds having less than a 2% risk of infection, clean-contaminated wounds having less than a 10% risk, and contaminated wounds having a 20% risk. Most infections occur within 30 days after surgery or within 90 days after surgery with implants; however, infections can manifest beyond these ranges. Risk factors include patient-related, procedure-related, and postoperative factors (**Table 58**). The patient's skin and gastrointestinal or female genital tracts are major sources of organisms causing infection, depending on the type of surgery. The time during which the surgical site is open represents the period of greatest risk. Common SSI pathogens are *Staphylococcus aureus* (23%), coagulase-negative staphylococci (17%), enterococci (7%), *Escherichia coli* (5%), and

TABLE 57. Prevention of Catheter-Associated Urinary Tract Infection

Period	Preventive Measures
Before catheterization	Avoid catheterization whenever possible
	Insert catheter only for appropriate indications
	Consider alternatives, such as condom catheters and intermittent catheterization
At time of catheter insertion	Ensure that only properly trained persons insert and maintain catheters
	Adhere to hand hygiene practices and standard (or appropriate isolation) precautions according to CDC HICPAC/WHO guidelines
	Use proper aseptic techniques and sterile equipment when inserting the catheter (acute care setting)
After catheter insertion	Promote early catheter removal whenever possible
	Secure the catheter
	Use aseptic technique when handling the catheter, including for sample collection from the designated port (not collecting bag)
	Maintain a closed drainage system
	Avoid unnecessary system disconnections
	Maintain unobstructed urine flow
	Keep the collecting bag below the level of the bladder and off the floor
	Empty the collecting bag regularly, using a separate collecting container for each patient

CDC = Centers for Disease Control and Prevention; HICPAC = Healthcare Infection Control Practices Advisory Committee; WHO = World Health Organization.

TABLE 58. Mitigation of Risk Factors for Surgical Site Infection

Risk Factor	Intervention
Hyperglycemia	Maintain blood glucose level ≤180 mg/dL (10 mmol/L) during first 48 hours after surgery
Immunosuppression	Reduce doses of immunosuppressive agents
Tobacco use	Cease 30 days before surgery
Obesity	Weight loss
Malnutrition	Optimize nutritional status before surgery
S. aureus nasal carriage	For cardiovascular and orthopedic surgeries, test for nasal carriage 1-2 weeks before
	If positive, decolonize using intranasal 2% mupirocin ointment with or without chlorhexidine body wash
Skin preparation	Shower the night before (soap or an antiseptic)
	Use an alcohol-based chlorhexidine scrub at incision site
Hair removal	Do not shave site of incision
	If hair must be removed, it should be clipped as close to time of incision as possible
Hypothermia and hypovolemia	Maintain perioperative normothermia (temperature >36 °C [96.8 °F]) and adequate volume replacement to ensure maximum tissue oxygen delivery
	2 °C (3.6 °F) decrease in body temperature associated with threefold increase in surgical site infection
Incision dressing	Primarily closed incision covered with sterile dressing for 24-48 hours

H CONT.

Pseudomonas aeruginosa (5%). Exogenous sources of organisms (surgical personnel, surgical instruments, environment) are less common causes of SSIs, usually identified when a cluster of infections is present. H

KEY POINT

- Most surgical site infections occur within 30 days after surgery or within 90 days after surgery with implants.

H

Diagnosis

Clinical signs and symptoms vary by site and type of infection as well as by implicated organism (for example, some are more likely to cause purulence). Inflammatory changes at the surgical site (pain or tenderness, warmth, swelling, erythema) and purulent drainage suggest a superficial incisional infection. Deep incisional SSIs have more extensive tenderness expanding outside the area of erythema and more systemic signs, such as fever and leukocytosis. Wound dehiscence suggests a deep incisional SSI unless the wound or drainage is culture negative. Organ and deep-space SSIs are associated with more systemic signs and local symptoms related to a deep abscess or infected fluid collection. In cases of suspected organ or deep-space SSIs, CT is helpful to localize the infection and determine the best approach to drainage of the fluid or abscess for culture and treatment. When an SSI is suspected, drainage, purulent fluid, and infected tissue should be obtained for culture. Deep-tissue or wound cultures are preferable to superficial wound swab cultures that are likely to reflect skin or wound colonization and not necessarily yield the causative pathogen. H

KEY POINT

- Deep tissue, drainage, and purulent fluid should be obtained for culture in surgical site infections; superficial wound swab cultures are likely to reflect skin or wound colonization rather than the causative pathogen.

Treatment

H

SSI treatment requires debridement of necrotic tissue, drainage of abscesses or infected fluid, and specific antimicrobial therapy

for organ or deep-space and deep incisional infections. Repeat debridement or drainage may be required to control and resolve the infection even with appropriate antimicrobial therapy. When an SSI involves an implant, removal of the implant is preferred, followed by a prolonged course of antibiotics (6-8 weeks). Superficial incisional infections can usually be managed with oral antibiotics without tissue debridement. The choice of antimicrobial agent is guided by culture results; duration of treatment varies by anatomic site and by depth of infection.

KEY POINT

- Surgical site infection treatment requires debridement of necrotic tissue, drainage of abscesses or infected fluid, and specific antimicrobial therapy for organ or deep-space and deep incisional infections.

Prevention

Prevention is divided into preoperative, intraoperative, and postoperative measures (see Table 58). Modifiable host factors should be optimized before surgery. If antibiotic prophylaxis is indicated, select the correct agent, dose, and time for administration (60 minutes before incision, 2 hours before incision for vancomycin or fluoroquinolones), and redose during surgery based on surgery duration and antibiotic half-life. Continuing antibiotics postoperatively does not decrease SSI incidence, even in cases of intraoperative spillage of gastrointestinal contents or presence of wound drains.

KEY POINT

- Optimizing modifiable risk factors before surgery (hyperglycemia control, reduction of immunosuppressive agents, cessation of tobacco use, weight loss) can help prevent surgical site infections.

Central Line–Associated Bloodstream Infections

Central line-associated bloodstream infections (CLABSIs), associated with all types of central venous catheters (CVCs), are the most preventable HCAI. In the United States, CVC rates are 55% in ICU patients and 24% in non-ICU patients. Pathogens associated with CLABSIs include coagulase-negative staphylococci (20.5%), *S. aureus* (12.3%), *Enterococcus faecalis* (8.8%), non-albicans *Candida* species (8.1%), *Klebsiella pneumoniae* or *oxytoca* (7.9%), *Enterococcus faecium* (7%), and *Candida albicans* (6.5%). Antimicrobial resistance is a problem for many of these pathogens. CLABSI risk factors include prolonged hospitalization before catheterization, neutropenia, and reduced nurse-to-patient ratio in the ICU. Additional risk factors (modifiable) are shown in **Table 59.**

TABLE 59. Mitigation of Risk Factors for Central Line-Associated Bloodstream Infections

Modifiable (Extrinsic) Risk Factor	Intervention
Prolonged catheterization	Daily review of continued need for CVC
	Discontinue as soon as practical
Multiple CVCs (increases risk 3.4-fold)	Minimize the number of CVCs as much as practical
Multilumen CVC	Use a catheter with the minimum number of lumens needed
Femoral vein catheterization; particularly in obese patients	Use subclavian site when possible
	Use ultrasonographic guidance for internal jugular catheter insertion
	Remove femoral vein CVCs as soon as practical, relocate to another site (e.g., subclavian, internal jugular vein) when possible
Heavy microbial colonization at insertion site and catheter hub	Chlorhexidine skin antisepsis at time of insertion
	Chlorhexidine-impregnated dressing
	Daily chlorhexidine bathing of patients in ICU
	Minimize catheter access
	Hand hygiene before manipulation of IV system; use aseptic technique for all IV access
	Disinfect catheter hub and needleless connectors ("scrub the hub") before accessing
Lack of maximal sterile barriers for insertion and breaks in aseptic technique	Follow CVC insertion bundle
Emergent insertion	When adherence to aseptic technique cannot be ensured, replace CVC as soon as possible (at least within 48 hours) to a new site
Total parenteral nutrition	Consider other options for delivering nutrition when possible

CVC = central venous catheter; IV = intravenous.

Diagnosis

CLABSI is suspected when a patient with a CVC has bacteremia not resulting from infection at another site. Two sets of peripheral blood cultures (20 mL blood/set) should be obtained from different sites before starting antibiotics. Blood cultures drawn directly from CVCs have a higher rate of false-positivity and should be avoided; they may falsely identify a CLABSI and lead to unnecessary antibiotic therapy.

KEY POINT

- A central line-associated bloodstream infection should be suspected when a patient with a central venous catheter has bacteremia not resulting from infection at another site.

Treatment

Infected CVCs should be removed. CVC removal is particularly important for *S. aureus*, *P. aeruginosa*, and *Candida* species infections. The duration of therapy for most cases of uncomplicated non–*S. aureus* CLABSI is 7 to 14 days (**Table 60**). *S. aureus* CLABSI is usually treated for at least 4 weeks; however, shorter-term therapy may be considered in select patients who have immediate catheter removal with resolution of fever and bacteremia within 72 hours of starting appropriate therapy and who have no implanted prosthetic devices, no evidence of endocarditis by echocardiography (preferably transesophageal), no evidence of suppurative thrombophlebitis, no evidence of metastatic infection, and neither diabetes mellitus nor immunosuppression. Bacteremia clearance should be confirmed with follow-up blood cultures. If bacteremia persists after CVC removal and appropriate antimicrobial therapy, evaluation for a deeper source of infection, including endocarditis, should be performed. All patients with candidemia should be evaluated by an ophthalmologist to rule out the presence of candida endophthalmitis within 1 to 2 weeks.

TABLE 60. Management of Central Venous Catheter-Related Bloodstream Infection Based on Pathogen[a]

Organism	Treatment
Uncomplicated[b]	
Coagulase-negative staphylococci	Remove catheter, antimicrobial therapy for 5-7 days If catheter is not removed, systemic antimicrobials and antimicrobial lock treatment[c] for 10-14 days
Staphylococcus aureus (no active malignancy or immunosuppression)	Remove catheter, antimicrobials for ≥14 days (usually 4 weeks)
Enterococcus species	Remove catheter, antimicrobials for 7-14 days
Gram-negative bacilli	Remove catheter, antimicrobials for 7-14 days
Candida species	Remove catheter, antifungal agent for 14 additional days after first negative blood culture
Complicated	
Suppurative thrombophlebitis, endocarditis, osteomyelitis, other site of metastatic or deep-seated infection	Remove catheter, antimicrobials for 4-6 weeks (6-8 weeks for osteomyelitis)

[a]Short-term catheters.

[b]Bloodstream infection and fever resolve in 72 hours, no intravascular hardware, no endocarditis or suppurative thrombophlebitis.

[c]Antimicrobial solution (such as vancomycin) instilled into the lumen of a catheter and removed after a specified period of time.

KEY POINT

- The duration of therapy for most cases of uncomplicated non–*Staphylococcus aureus* central line–associated bloodstream infection is 7 to 14 days, although *S. aureus* infection is usually treated for at least 4 weeks.

Prevention

CVCs should be inserted only by experienced personnel using the insertion bundle of hand hygiene, chlorhexidine skin antisepsis of the insertion site using recommended application methods and contact time, maximal barrier precautions (mask, cap, gown, sterile gloves, large sterile drape covering patient), and optimal catheter site selection (subclavian site preferred, avoid femoral site). See Table 59 for further modifiable factors to prevent CLABSI. Insertion bundles, checklists, and staff education have significantly reduced CLABSIs. If CLABSI rates remain high despite adherence to these strategies, patient chlorhexidine bathing and antimicrobial-impregnated catheters (silver sulfadiazine–chlorhexidine, minocycline-rifampin) may be considered. Routine CVC exchange or replacement or administration of systemic antimicrobial prophylaxis at time of insertion or during CVC use should be avoided.

Staphylococcus aureus Bacteremia

S. aureus is a leading cause of hospital-acquired bacteremia. Endocarditis and vertebral osteomyelitis are two important complications of *S. aureus* bacteremia, although they are less likely when the infection is hospital acquired. The source of bacteremia and possible metastatic infection should be determined, starting with a detailed history and examination. All patients should undergo evaluation for endocarditis with echocardiography, preferably transesophageal. Source control with removal or drainage of any focus of infection is important for treatment success. Blood cultures should be repeated every 2 to 4 days until results are negative to document clearance.

Bacteremia caused by methicillin-sensitive *S. aureus* (MSSA) should be treated with a penicillinase-resistant semisynthetic penicillin (such as oxacillin) or first-generation cephalosporin (such as cefazolin) at maximal doses. Vancomycin should be avoided in patients with MSSA who are not allergic to β-lactam antibiotics. Vancomycin is associated with higher rates of relapse and microbiologic failure in the treatment of MSSA bacteremia.

For methicillin-resistant *S. aureus* (MRSA) bacteremia, vancomycin and daptomycin are the preferred antibiotics. Vancomycin trough concentrations of 15 to 20 µg/mL are recommended; however, these concentrations increase the risk of nephrotoxicity, and kidney function should be closely monitored. Patients with concomitant *S. aureus* pneumonia should not receive daptomycin because it is inactivated by surfactant. The clinical and microbiologic response (clearance of bacteremia) determines whether to continue vancomycin or change to daptomycin when the MRSA isolate has a vancomycin

minimum inhibitory concentration of ≤2 µg/mL. Persistent bacteremia may be the result of slow bactericidal activity of vancomycin, inadequate dosing, poor tissue penetration, or inadequate source control. Higher-dose daptomycin (8-10 mg/kg/d) is sometimes used if bacteremia persists despite adequate source control. Vancomycin should not be used when the isolate has a minimum inhibitory concentration greater than 2 µg/mL; daptomycin is an acceptable alternative if the isolate is susceptible. The median time to clearance of MRSA bacteremia is 7 to 9 days.

Bacteremia that persists beyond 72 hours of starting appropriate antibiotic treatment suggests a complicated *S. aureus* infection and requires additional evaluation and a longer course of antibiotics (4-6 weeks). Management of persistent MSSA and MRSA bacteremia also includes a thorough search for and removal of all foci of infection, including surgical debridement of infected wounds and abscess drainage. A new focus of infection may develop with persistent bacteremia and should always be considered in the evaluation of persistent bacteremia. Combination antimicrobial agents (for example, a β-lactam and aminoglycoside, vancomycin and rifampin) have not been shown to improve outcomes and should not be used. H

KEY POINTS

- Bacteremia caused by methicillin-sensitive *Staphylococcus aureus* (MSSA) should be treated with a penicillinase-resistant semisynthetic penicillin or first-generation cephalosporin at maximal doses; vancomycin should be avoided in patients who are not allergic to β-lactam antibiotics because it is associated with higher rates of relapse and microbiologic failure in the treatment of MSSA bacteremia.
- Vancomycin and daptomycin are the preferred antibiotics for methicillin-resistant *Staphylococcus aureus* bacteremia, although patients with concomitant *S. aureus* pneumonia should not receive daptomycin because it is inactivated by surfactant.

Hospital-Acquired Pneumonia and Ventilator-Associated Pneumonia

Hospital-acquired pneumonia (HAP) is pneumonia developing more than 48 hours after hospitalization. Ventilator-associated pneumonia (VAP) is pneumonia developing 48 hours after endotracheal intubation; it occurs in 10% of patients undergoing ventilation. Half of patients with HAP develop serious complications, including respiratory failure, pleural effusion, septic shock, empyema, and kidney injury. Mechanical ventilation increases the risk of pneumonia 6-fold to 21-fold. HAP and VAP risk factors include age older than 70 years, recent abdominal or thoracic surgery, immunosuppression, and underlying chronic lung disease. Modifiable risk factors are listed in **Table 61**.

TABLE 61. Mitigation of Risk Factors for Ventilator-Associated Pneumonia

Risk Factor	Intervention
Mechanical ventilation	Consider noninvasive, positive-pressure ventilation
Sedation	Minimize
	Intermittent infusions or daily interruption and daily assessment of readiness for extubation
Supine position	Risk highest for patients receiving enteral nutrition
	Elevate head of bed 30°-45°
Oropharyngeal colonization	Daily oral care; oral care with chlorhexidine may be beneficial in some patients
Physical conditioning	Facilitate early mobility (speeds extubation)
Reintubation	Consider noninvasive, positive-pressure ventilation

HAP and VAP are most commonly caused by bacteria, but viral and fungal pathogens should be considered in immunocompromised patients. The main risk factor for MRSA, antibiotic-resistant *Pseudomonas*, or other antibiotic-resistant pathogens is intravenous antibiotic use within the past 90 days. Additional risk factors for multidrug-resistant pathogens associated with VAP are septic shock at the time of VAP, acute respiratory distress syndrome preceding VAP, 5 or more days of hospitalization before VAP, and acute kidney replacement therapy before VAP.

Diagnosis

Diagnosis relies on a combination of clinical, radiographic, and microbiologic findings. A new lung infiltrate on imaging plus clinical findings, including new-onset fever (temperature >38 °C [100.4 °F]), leukocytosis or leukopenia, purulent sputum, and decline in oxygenation, suggest pneumonia. Noninvasive sampling (endotracheal aspiration) with semiquantitative sputum cultures (heavy, moderate, light, and no growth) are suggested for diagnosing VAP. Clinical findings without radiographic support suggest tracheobronchitis, which does not require antibiotic treatment. H

KEY POINT

- The diagnosis of hospital-acquired and ventilator-associated pneumonia are suggested by a new lung infiltrate on imaging plus clinical findings, including new-onset fever, leukocytosis or leukopenia, purulent sputum, and decline in oxygenation.

Treatment

Therapy for suspected HAP should be based on respiratory sample culture results; a specimen from the lower respiratory tract should be obtained before starting antimicrobial therapy. However, inability to obtain a specimen should not delay therapy initiation for VAP, and empiric antimicrobial therapy

H CONT. should be instituted for patients with VAP pending results of noninvasive sampling with semiquantitative cultures and based on local VAP antibiograms, if available.

Empiric VAP regimens should include coverage for *S. aureus*, *P. aeruginosa*, and other gram-negative bacilli. An agent active against MRSA (vancomycin, linezolid) should be included for patients with MRSA risk factors or those in a unit with MRSA prevalence greater than 10% to 20% or unknown. Two antipseudomonal agents of different classes are recommended for empiric regimens only for patients with risk factors for resistance, with structural lung disease (bronchiectasis, cystic fibrosis), or in a unit with greater than 10% resistance to an agent being considered for monotherapy. Similar regimens are recommended for patients with HAP who are treated empirically. Antimicrobial coverage for oral anaerobes may be considered in patients with witnessed aspiration events or recent surgery. Cephalosporins should be avoided as monotherapy in settings where extended-spectrum β-lactamase (ESBL)-producing gram-negative organisms (such as *Klebsiella pneumoniae*) are prevalent; consider a carbapenem instead. VAP caused by gram-negative organisms sensitive only to aminoglycosides or colistin may be treated with a combination of systemic and aerosolized antibiotics.

Microbiologic results should be reviewed at 48 to 72 hours, and all patients should be re-evaluated for clinical improvement. Antimicrobial therapy should be de-escalated (to narrow-spectrum or oral therapy) based on microbiologic results and clinical stabilization or discontinued if the diagnosis of pneumonia is in doubt. Patients who do not improve within 72 hours of appropriate therapy should undergo investigation for infectious complications, an alternate diagnosis, or another site of infection. HAP and VAP should be treated for 7 days or less. H

KEY POINT

- Empiric ventilator-associated pneumonia regimens should include coverage for *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and other gram-negative bacilli; an agent active against methicillin-resistant *S. aureus* (MRSA) should be included for patients with MRSA risk factors or where MRSA prevalence exceeds 10% (or is unknown); similar regimens are recommended for empiric hospital-acquired pneumonia treatment.

H Prevention

Commonly used ventilator bundles include subglottic suctioning, peptic ulcer disease and deep venous thrombosis prophylaxis, and avoiding gastric overdistention. Use of ventilator bundles has been shown to decrease VAP rates by 71%. Additional interventions are listed in Table 61. H

KEY POINT

HVC
- In patients receiving mechanical ventilation, the head of the bed should be elevated 30° to 45°; a supine position, particularly in patients receiving enteral nutrition, increases the risk for developing ventilator-associated pneumonia.

Hospital-Acquired Infections Caused by Multidrug-Resistant Organisms

H

Antimicrobial resistance has been noted in nearly all bacterial pathogens. Multidrug-resistant organisms (MDROs) are most prevalent in health care settings (highest incidence in long-term acute care hospitals) but are also observed in the community. Seven of the 15 MDROs deemed urgent threats are predominantly health care associated. Nearly half of *S. aureus* HCAIs in the United States are methicillin resistant, 30% of enterococci are vancomycin resistant, 18% of Enterobacteriaceae produce ESBL and are resistant to all β-lactam antibiotics, 4% of Enterobacteriaceae are resistant to carbapenems, and 16% of *P. aeruginosa* and about half of *Acinetobacter* species are multidrug resistant. *Clostridium difficile* is not technically an MDRO, but it is a problematic pathogen in health care settings.

MDRO infections are difficult to treat, with mortality rates up to four times higher than infections caused by antibiotic-sensitive strains. Limiting transmission of MDROs in health care settings requires full adherence to hand hygiene protocols, contact precautions, and cleaning and disinfecting of the environment and patient care equipment. More than half of hospitalized patients receive antibiotics, a major risk for acquiring an antibiotic-resistant organism and *C. difficile* infection. Judicious use of antimicrobial agents is increasingly important to combat the rise of MDROs and emergence of untreatable infections. H

KEY POINTS

- Multidrug-resistant organisms (MDROs) are most prevalent in health care settings (highest incidence in long-term acute care hospitals) but are also observed in the community.
- Limiting emergence and transmission of multidrug-resistant organisms in health care settings requires full adherence to hand hygiene protocols, contact precautions, cleaning and disinfecting of the environment and equipment, and judicious use of antimicrobial agents. HVC

HIV/AIDS

HIV is a retrovirus that infects CD4 lymphocytes, among other cell types. Depletion of CD4 T-helper cells results in impairment of cell-mediated immunity and increasing risk for opportunistic infections. This chapter will focus on HIV-1. Infection with HIV-2 primarily occurs in parts of Africa and remains rare in the United States; HIV-2 generally is a less progressive disease with less immunocompromise and lower risk of opportunistic infections. Current testing for HIV infection detects HIV-1 and HIV-2 antibodies (see Screening and Diagnosis).

Epidemiology and Prevention

HIV infection remains a significant global health concern despite being a treatable disease. Many persons living with HIV infection are not aware of their status because they have never been tested; others have been diagnosed but are not receiving care. Those with undiagnosed or untreated infection are responsible for most new infections. Diagnosis and successful treatment are crucial for personal and public health.

HIV transmission occurs through sexual contact or exposure to other body fluids (**Table 62**). Reducing transmission can be accomplished by using barrier methods, such as condoms during sexual contact, and through clean syringe services programs (needle exchange programs) for injection drug users. Universal blood donor testing has all but eliminated infection through blood transfusion in the United States, with current risk estimated to be one in 2 million.

HIV treatment has extraordinary potential to reduce new infections in addition to benefiting the treated person. Successful treatment is associated with significant reductions in HIV transmission. Although reducing viral load to an undetectable level in blood does not prove absence of virus in semen or vaginal fluid, the rate of transmission from a sexual partner with undetectable blood viral load has been demonstrated to be close to zero, at a level the Centers for Disease Control and Prevention (CDC) called "effectively no risk" in a September 2017 statement, leading to the slogan "Undetectable = Untransmissable" ("U=U"). In what is known as the "treatment cascade," steps of medical care necessary to achieve successful viral suppression consist of testing and diagnosing infected persons, linking them to health care for counseling and treatment, keeping them in a treatment program, and ensuring antiretroviral and other treatment adherence. Each step along this continuum of care is a potential obstacle to successful management of HIV on a personal and public health level. Even high-income countries, such as the United States, have poor rates of retention in care and adherence to medication. One study estimated that the undiagnosed and not-in-care groups with HIV infection were responsible for 91.5% of HIV transmissions in the United States in 2009.

In 2014, the Joint United Nations Programme on HIV/AIDS (UNAIDS) launched its "90-90-90" program of ambitious goals for reducing new HIV infection worldwide. These goals include that by 2020, 90% of HIV-infected persons will have been diagnosed, 90% of those diagnosed will be receiving treatment, and 90% of those receiving treatment will have successful viral suppression. Achieving such goals will require considerable resource commitment but, if achieved, will also dramatically reduce transmission and new HIV infections.

Postexposure prophylaxis antiretroviral therapy has been used successfully for many years in uninfected persons to prevent infection after occupational and nonoccupational HIV exposure. Prophylaxis should be started as soon as possible after exposure; it is not recommended if more than 72 hours have passed. A three-drug regimen is given for 4 weeks; the preferred regimen is tenofovir disoproxil fumarate and emtricitabine plus either raltegravir or dolutegravir. HIV testing of the exposed person should be conducted at baseline and at 4 to 6 weeks and 3 months after exposure. **Figure 22** shows an algorithm for evaluation of possible HIV exposure.

Pre-exposure prophylaxis (PrEP) with antiretroviral medication is recommended in select persons at high risk for exposure to HIV to reduce the risk of infection. A two-drug combination of tenofovir disoproxil fumarate and emtricitabine, taken once daily, is FDA approved for HIV PrEP; it has been shown to be effective in reducing infection in heterosexual couples, men who have sex with men, and injection drug users. Effectiveness is greater than 90% in those with proven adherence. Patients should also be counseled on the need to continue barrier precautions, on medication toxicity, and on continued risk for other sexually transmitted infections (STIs). Testing should be performed for HIV, hepatitis B virus (HBV), kidney function, and pregnancy before PrEP initiation; monitoring for HIV, other STIs, and pregnancy every 3 months and performing kidney function assessment every 6 months are also recommended during PrEP therapy. Persons taking PrEP who test positive for HIV should have a third drug (either ritonavir-boosted darunavir or dolutegravir) added to the two-drug PrEP regimen pending results of HIV RNA and viral resistance testing. The evidence is conflicting concerning potentially increased high-risk behavior and incidence of other STIs in PrEP users during therapy. PrEP has also been calculated to have favorable cost effectiveness, well below that for other accepted preventive health measures.

TABLE 62. Risk of HIV-1 Transmission per Single Exposure

Exposure	Risk (%)
Occupational—needlestick	0.23
Occupational—mucous membrane	0.09
Needle-sharing injection drug use	0.63
Receptive anal intercourse	1.4
Receptive vaginal intercourse	0.08
Insertive anal intercourse	0.11
Insertive vaginal intercourse	0.04
Oral sex	0.01

KEY POINTS

- Although reducing viral load to an undetectable level in blood does not equal absence of virus in semen or vaginal fluid, the rate of transmission from a sexual partner with undetectable blood viral load is exceedingly low, with reductions in risk greater than 95%.
- Postexposure prophylaxis with a three-drug regimen (tenofovir disoproxil fumarate and emtricitabine plus either raltegravir or dolutegravir) should be started as soon as possible after HIV exposure; it is not recommended if more than 72 hours have passed.

(Continued)

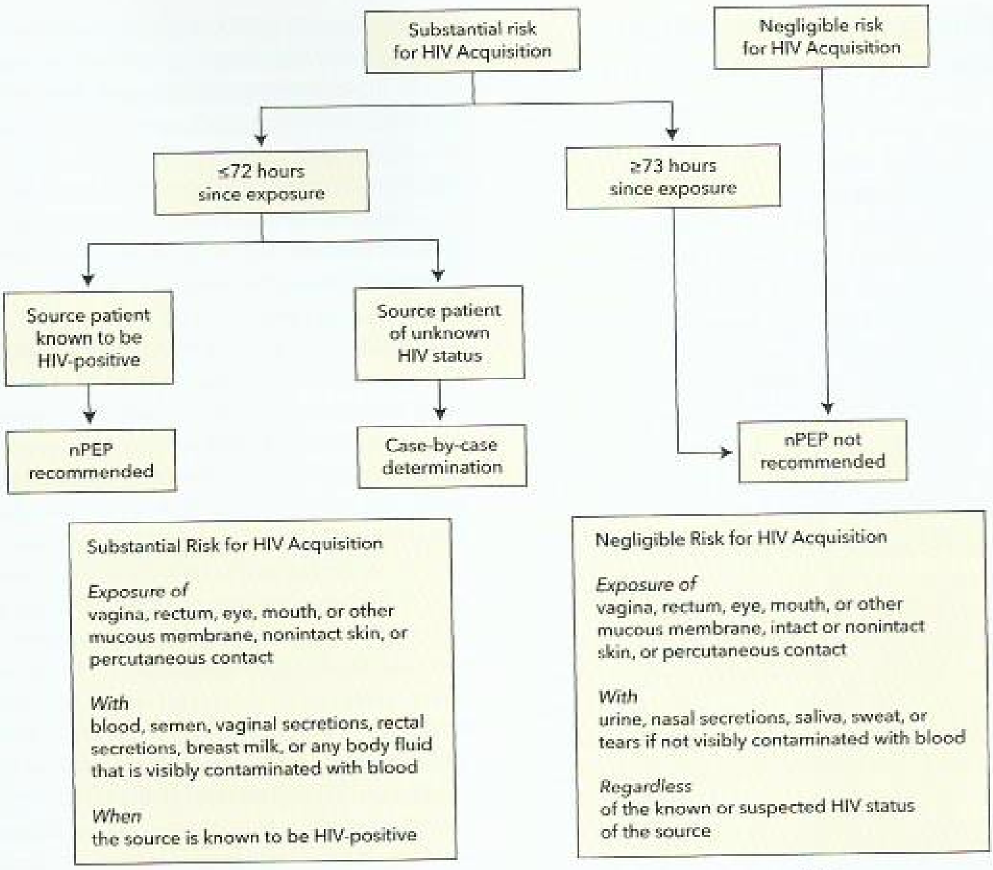

FIGURE 22. Algorithm for evaluation and treatment of possible HIV exposure. nPEP = nonoccupational postexposure prophylaxis.

Centers for Disease Control and Prevention. Updated guidelines for antiretroviral postexposure prophylaxis after sexual, injection drug use, or other nonoccupational exposure to HIV—United States, 2016. Available at https://stacks.cdc.gov/view/cdc/38856. Accessed January 29, 2018.

KEY POINTS *(continued)*

- Pre-exposure prophylaxis with two antiretroviral medications (tenofovir disoproxil fumarate and emtricitabine) is recommended in select persons at high risk for exposure to HIV to reduce the risk of infection.

Pathophysiology and Natural History

Acute Retroviral Syndrome

Most persons with acute HIV infection are symptomatic; however, because symptoms are nonspecific and self-limited, most acute infections are not diagnosed accurately. The frequency of signs and symptoms at presentation is shown in **Table 63**. The differential diagnosis includes Epstein-Barr virus infection, cytomegalovirus infection, and secondary syphilis. During symptomatic acute infection, HIV antibody may not yet be detectable, and diagnosis depends on demonstration of p24 antigen or HIV RNA. Currently recommended HIV testing includes p24 antigen testing as part of the initial evaluation (see Screening and Diagnosis). Persons with acute HIV infection should be immediately linked to care for prompt initiation of treatment.

TABLE 63. Signs and Symptoms of Acute HIV Infection (Acute Retroviral Syndrome)

Sign/Symptom	Frequency (%)
Fever	75
Fatigue	68
Myalgia	49
Rash	48
Headache	45
Pharyngitis	40
Lymphadenopathy	39
Arthralgia	30
Night sweats	28
Diarrhea	27

KEY POINT

- Most persons with acute HIV infection are symptomatic; however, because symptoms are nonspecific and self-limited, most acute infections are not diagnosed accurately.

Chronic HIV Infection and AIDS

Patients with chronic HIV infection may present with opportunistic infections, especially when CD4 counts are less than 200/µL, meeting the definition for AIDS (see Opportunistic Infections). Even before progression to AIDS, patients with HIV infection may present with recurrent or severe episodes of infections that do not qualify as opportunistic, such as bacterial pneumonia, herpes zoster, herpes simplex virus, or vaginal candidiasis. Other symptoms can result from chronic HIV infection itself, including lymphadenopathy, fever, night sweats, fatigue, weight loss, chronic diarrhea, and various oral and skin conditions (see MKSAP 18 Dermatology). HIV should also be considered in patients with unexplained cytopenias or nephropathy.

KEY POINTS

- Before progression to AIDS, patients with chronic HIV infection may present with recurrent or severe episodes of infections that do not qualify as opportunistic, such as bacterial pneumonia, herpes zoster, herpes simplex virus, or vaginal candidiasis.
- Symptoms that can result from chronic HIV infection itself include lymphadenopathy, fever, night sweats, fatigue, weight loss, chronic diarrhea, and various oral and skin conditions.

Screening and Diagnosis

Although any of the presenting symptoms described previously should prompt HIV testing, testing only symptomatic persons neglects numerous persons who are infected. Thus, the CDC, American College of Physicians, Infectious Diseases Society of America, and U.S. Preventive Services Task Force (USPSTF) recommend universal screening for HIV in all adults at least once. The USPSTF suggests those at higher risk (injection drug users and their sexual partners, people who exchange sex for money or drugs, sexual partners of HIV-infected persons, and those with more than one sexual partner since their most recent HIV test) should undergo repeat HIV testing at least annually. In 2017, the CDC reaffirmed its support for this recommendation but noted that clinicians can consider the potential benefits of more frequent HIV screening (for example, every 3 or 6 months) for some asymptomatic sexually active men who have sex with men based on their individual risk factors, local HIV epidemiology, and local policies.

Current (fourth generation) HIV testing uses a combination assay for HIV antibody and HIV p24 antigen, which detects acute infection at least 1 week earlier than older assays. A positive result on the combination assay leads to testing with an HIV-1/HIV-2 antibody differentiation immunoassay, which, if positive, confirms infection. Specimens that test positive on the initial combination assay but negative for HIV antibody are tested for HIV RNA by nucleic acid amplification testing; if positive, acute HIV infection is confirmed (**Figure 23**). Although the initial combination assay has a 99.6% specificity, testing in low prevalence populations (such as general screening) can still result in false positives, so waiting for the results of the confirmatory antibody differentiation immunoassay and nucleic acid amplification testing is important for a definitive diagnosis.

KEY POINTS

- It is recommended that all adults be tested for HIV infection at least once.
- A combination assay for HIV antibody and HIV p24 antigen now detects acute infection at least 1 week earlier than older assays; a positive HIV-1/HIV-2 antibody immunoassay result confirms infection, or a positive HIV RNA nucleic acid amplification test result confirms acute HIV infection.

Initiation of Care

Initial Evaluation and Laboratory Testing

All persons who test positive for HIV should be immediately referred to a health care provider with HIV infection management expertise. Initial evaluation should include complete history (including social and sexual) and examination for signs and symptoms of opportunistic infection or other complications. Patient education and counseling should include information on transmission and prevention. Initial laboratory tests include baseline organ function and evaluation for other infections with higher prevalence in persons with HIV (**Table 64**). A baseline CD4 cell count guides opportunistic infection prophylaxis, and a baseline viral load supports monitoring antiretroviral therapy effectiveness (see Management of HIV Infection).

Immunizations and Prophylaxis for Opportunistic Infections

Numerous immunizations are recommended for all persons with HIV, starting with the 13-valent pneumococcal conjugate and 23-valent pneumococcal polysaccharide vaccines, respectively, at least 8 weeks apart; a 23-valent polysaccharide vaccine booster is also recommended after 5 years. Patients who are not already immune or infected with HBV should receive the hepatitis B vaccine series. Influenza, tetanus diphtheria pertussis, hepatitis A, and human papillomavirus vaccinations are indicated as for the general population. Measles mumps rubella and varicella vaccines can be given as long as the CD4 cell count is greater than 200/µL. Although the recombinant zoster vaccine is considered safe in immunocompromised persons because it does not contain live virus, safety and efficacy data in patients with HIV are not yet available to inform recommendations. The Advisory Committee on Immunization Practices recommends that all persons with HIV infection be vaccinated for meningococcal disease with the quadrivalent meningococcal vaccine, including boosters every 5 years.

Prophylaxis for opportunistic infections depends on the patient's CD4 cell count (**Table 65**). Before beginning

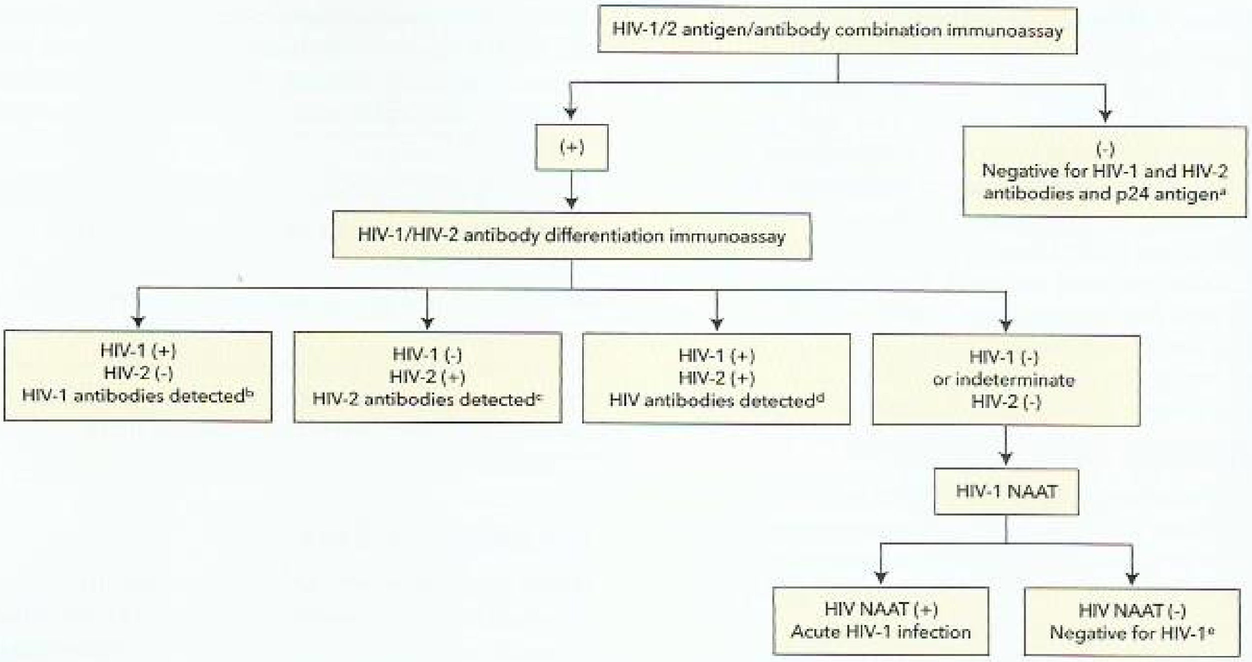

FIGURE 23. CDC-recommended algorithm for laboratory HIV testing. NAAT = nucleic acid amplification test. (+) indicates reactive test result. (−) indicates nonreactive test result.

[a]No evidence of HIV infection.

[b]HIV-1 infection.

[c]HIV-2 infection.

[d]HIV-1 and HIV-2 infection.

[e]HIV-1/2 antigen/antibody combination immunoassay result was a false positive.

Centers for Disease Control and Prevention; Association of Public Health Laboratories. Laboratory testing for the diagnosis of HIV infection: updated recommendations. January 2018. Available at https://stacks.cdc.gov/view/cdc/50872.

TABLE 64. Laboratory Testing as Part of the Evaluation of HIV Infection

Repeat HIV antibody testing if no documentation
Viral resistance testing at baseline and for treatment failure
Quantitative HIV RNA assay (viral load)
T-cell subsets (CD4 cell count)
Complete blood count with differential
Chemistries, including kidney function studies and fasting plasma glucose level
Liver chemistry studies/liver enzyme levels
Fasting serum lipid profile
Urinalysis or quantitative measure of proteinuria
Tuberculin skin test or interferon-γ release assay
Serologic testing for hepatitis A, B, and C virus infection
Serologic testing for syphilis; testing for other sexually transmitted infections
Serologic testing for toxoplasmosis
Cervical Pap test

TABLE 65. Prophylaxis against Opportunistic Infections in HIV/AIDS

Opportunistic Infection	Indication	Preferred Drug
Pneumocystis jirovecii	CD4 cell count <200/μL[a]	TMP-SMX, double-strength or single-strength tablet once daily
Toxoplasmosis	CD4 cell count <100/μL and positive serologic results[a]	TMP-SMX, double-strength tablet once daily
Mycobacterium avium complex	CD4 cell count <50/μL	Azithromycin, 1200 mg once weekly or 600 mg twice weekly; clarithromycin, 500 mg twice daily
Latent tuberculosis	TST >5 mm or positive IGRA results	Isoniazid, 300 mg once daily for 9 months or 900 mg twice weekly, both with pyridoxine, 25 mg once daily

IGRA = interferon-γ release assay; TMP-SMX = trimethoprim-sulfamethoxazole; TST = tuberculin skin test.

[a]Prophylaxis may be discontinued in patients with suppressed viral load and CD4 cell count ≥200/μL for ≥3 months.

prophylaxis, active infection should be ruled out clinically and with any indicated testing to avoid undertreatment and selection for resistance, especially for tuberculosis and disseminated *Mycobacterium avium* complex.

KEY POINTS

- All persons with HIV should receive the 13-valent pneumococcal conjugate and 23-valent polysaccharide vaccines, hepatitis B vaccine series (in those not already infected or immune), and meningococcal vaccine; influenza, tetanus-diphtheria-pertussis, hepatitis A, and human papillomavirus vaccines are indicated as for the general population.
- Active infection should be ruled out before initiation of prophylaxis for opportunistic infections.

Complications of HIV Infection in the Antiretroviral Therapy Era

Metabolic, Kidney, and Liver Disorders

As HIV has become a treatable illness and persons with HIV age, metabolic disorders and specific organ diseases have become increasingly significant. HIV infection itself may be associated with manifestations of accelerated aging, and neurocognitive impairment can be exacerbated by HIV. Age-associated comorbidities and declines in kidney and liver function can also complicate management through drug interactions and increased toxicity.

HIV infection itself and some antiretrovirals affect lipids and can worsen hyperlipidemia; this is especially true for boosted protease inhibitor–based regimens, which can also worsen insulin resistance. Fasting glucose or hemoglobin A_{1c} and lipid levels should be checked at baseline and 3 months after initiating or changing antiretrovirals.

Chronic kidney disease is increasingly common in HIV infection, although, with effective antiretroviral therapy, it is less often attributed to HIV nephropathy. It is recommended that kidney function be assessed at least every 6 months in patients with HIV. Tenofovir, a very commonly used nucleoside analogue, is associated with risk for tubular nephrotoxicity, which usually manifests as proteinuria. Patients using a regimen containing tenofovir should undergo urinalysis or quantitative measurement of urine protein twice per year.

Bone mineral density is reduced in HIV, and tenofovir is also associated with possible worsening of bone density. Dual-energy x-ray absorptiometry scanning is recommended in men older than 50 years, postmenopausal women, patients with a history of fragility fracture, those with chronic glucocorticoid use, and those at high risk for falls. A newer prodrug of tenofovir, tenofovir alafenamide (TAF), achieves high intracellular levels of active drug with much lower dosing and lower systemic levels compared with the older formulation, tenofovir disoproxil fumarate (TDF). Compared with TDF, TAF has equal antiviral efficacy with reduced kidney and bone toxicity and should be used preferentially over TDF in patients with or at risk for bone or kidney disease.

Liver disease is also increased in HIV infection, often because of coinfection with hepatitis B or C virus. All patients with HIV should be screened for hepatitis B and C viruses. Patients should be immunized if they are HBV negative. If coinfected with HIV and HBV, patients should receive treatment with a tenofovir (either TDF or TAF) plus emtricitabine or lamivudine-based regimen, which treats both viruses. Patients coinfected with hepatitis C virus should be given a course of curative direct-acting antiviral treatment, although attention must be paid to drug interactions between the antiviral regimens (see MKSAP 18 Gastroenterology and Hepatology).

KEY POINTS

- Fasting glucose or hemoglobin A_{1c} and lipid levels should be checked at baseline and 3 months after initiating or changing antiretroviral therapy.
- Tenofovir disoproxil fumarate (TDF), a very commonly used nucleoside analogue in HIV therapy, is associated with increased risks of tubular nephrotoxicity and worsening of bone mineral density; tenofovir alafenamide should be used preferentially over TDF in patients with or at risk for bone or kidney disease.

Cardiovascular Disease

Rates of cardiovascular disease, including myocardial infarction and stroke, are higher in persons with HIV infection; this association remains after correction for increased risk factors such as smoking. Some of the increase may result from hyperlipidemia, but evidence indicates that the increase partially results from HIV infection being a chronic inflammatory state. It is clear that patients with untreated HIV infection have a higher risk of cardiovascular events compared with patients taking effective antiretroviral therapy, regardless of any worsening of lipid levels from the antiretroviral therapy. Attention to traditional risk factors such as smoking, lipid levels, and hypertension is crucial in patients with HIV, as is use of statin therapy (with attention to drug interactions between some statins and some antiretrovirals) based on current risk calculations. An international multicenter trial is addressing whether patients with HIV should be treated with statins even with a 10-year risk less than 7.5%.

KEY POINT

- Rates of cardiovascular disease, including myocardial infarction and stroke, are higher in persons with HIV infection; control of cardiovascular risk factors (smoking, lipid levels, and hypertension) is essential, including statin therapy based on clinical risk calculations.

Immune Reconstitution Inflammatory Syndrome

Immune reconstitution inflammatory syndrome (IRIS) is a disorder associated either with worsening of a pre-existing

infectious process (paradoxical IRIS) or with revelation of a previously unrecognized pre-existing infection (unmasking IRIS). It has also been reported with noninfectious complications, such as lymphoma. IRIS usually occurs within a few months of initiating effective antiretroviral therapy in patients with low pretreatment CD4 cell counts (<100/µL). Management of IRIS includes continuing antiretroviral therapy while treating the opportunistic infection. In select patients, NSAIDs or glucocorticoids may be useful in mitigating inflammatory symptoms.

KEY POINT

- Immune reconstitution inflammatory syndrome is caused by an inflammatory response to a pre-existing infectious process; it usually occurs within a few months of initiating effective antiretroviral therapy and presents with a wide variety of infections and noninfectious complications.

Opportunistic Infections

Mucocutaneous *Candida* infections can occur in HIV-infected patients at relatively preserved CD4 cell counts. HIV-infected patients do not usually develop invasive *Candida* infection unless they have other risk factors, such as neutropenia. Oral candidiasis usually presents as thrush, with mucosal whitish plaques, and can be treated topically (for example, with clotrimazole troches) or with a short course of oral fluconazole. Swallowing symptoms suggest esophageal disease, which requires systemic treatment, such as fluconazole, for a longer course; a lack of treatment response is an indication for endoscopy.

Reactivation of latent tuberculosis is also significantly increased in HIV infection, even without a decreased CD4 cell count. Tuberculosis is also more likely to present in extrapulmonary sites or with an atypical chest radiograph. Tuberculosis treatment in HIV must consider interactions of rifamycins with many antiretrovirals.

Infections with other opportunistic organisms usually occur at CD4 cell counts less than 200/µL. *Pneumocystis jirovecii* pneumonia usually presents as a subacute illness with fever, dyspnea, and dry cough in a patient with a CD4 cell count less than 200/µL who is not receiving prophylaxis. Chest radiographs most often show bilateral interstitial infiltrates; cavitation or pleural effusion is unusual and suggests another diagnosis. A normal chest radiograph does not exclude the diagnosis, and chest CT is more sensitive, demonstrating patchy "ground-glass" opacities. Normal lactate dehydrogenase levels and stable exercise oxygen saturation have a high negative predictive value, but elevated lactate dehydrogenase levels and oxygen desaturation with exercise are nonspecific. Diagnosis depends on demonstration of causative organisms and often requires bronchoscopy. The treatment of choice is high dose trimethoprim-sulfamethoxazole; patients who are hypoxic at presentation should be given adjunctive glucocorticoids to prevent the worsening that may accompany initiation of treatment.

Cryptococcus infection usually presents as subacute meningitis with headache, mental status changes, and fever. Because it often involves the basilar area, cranial nerve deficits may also be seen. The diagnosis can be made most swiftly by antigen testing of cerebrospinal fluid and blood. Management includes antifungal therapy and attention to increased intracranial pressure, which is usually responsible for the morbidity and mortality associated with cryptococcal meningitis (see Fungal Infections). H

Toxoplasma gondii infection in AIDS usually presents in patients with CD4 cell counts less than 100/µL. Because it is a reactivation disease, patients are usually serology positive. Clinical presentation includes headache, fever, and focal neurologic deficits. Imaging by CT or MRI (which is more sensitive) reveals multiple ring-enhancing lesions. The differential diagnosis includes primary central nervous system lymphoma, which most often appears as a single lesion on imaging, and progressive multifocal leukoencephalopathy, which is usually nonenhancing. Diagnosis of central nervous system toxoplasmosis is usually presumptive based on presentation, imaging, and response to empiric treatment.

Mycobacterium avium complex infection usually presents as disseminated disease in patients with CD4 cell counts less than 50/µL; symptoms and signs include fever, sweats, weight loss, hepatosplenomegaly, lymphadenopathy, and cytopenias. Blood cultures for acid-fast bacilli will usually grow *Mycobacterium avium* complex, but it may also be found on lymph node or liver biopsy when necessary.

Cytomegalovirus most commonly presents with CD4 cell counts less than 50/µL. Cytomegalovirus retinitis, presenting with vision changes or floaters, is much more likely in AIDS than in other immunocompromised conditions, such as after transplantation. Gastrointestinal cytomegalovirus disease is also common, most often as esophagitis or colitis.

Patients with AIDS are also more likely to develop certain malignancies, especially those related to viruses. Non-Hodgkin lymphoma, especially primary central nervous system lymphoma related to Epstein-Barr virus, is significantly increased compared with age-matched controls. Kaposi sarcoma is caused by human herpes virus type 8 and presents as dark red, brown, or violaceous lesions of the skin or mucous membranes (**Figure 24**); human herpes virus type 8 can also cause primary effusion lymphoma and Castleman disease (giant lymph node hyperplasia). Human papillomavirus-related malignancies are significantly increased in HIV, including cervical and anal cancers, and regular guideline-based screening is important.

KEY POINTS

- *Pneumocystis jirovecii* pneumonia usually presents as a subacute illness with fever, dyspnea, and dry cough; although chest radiographs most often show bilateral interstitial infiltrates, a normal chest radiograph does not exclude the diagnosis.

(Continued)

FIGURE 24. Kaposi sarcoma, presenting as firm purple nodules on the face and purple palatal nodules, is seen in a patient with AIDS.

KEY POINTS ***(continued)***

- Successful management of *Cryptococcus* infection in patients with HIV includes antifungal therapy and attention to increased intracranial pressure, which is usually responsible for the morbidity and mortality associated with cryptococcal meningitis.
- *Toxoplasma gondii* infection in patients with HIV presents as multifocal central nervous system abscesses; MRI is more sensitive than CT in revealing characteristic ring-enhancing lesions.
- *Mycobacterium avium* complex and cytomegalovirus infections usually present in patients with HIV with CD4 cell counts less than 50/µL.
- Patients with AIDS are more likely to develop certain malignancies, including non-Hodgkin lymphoma, Kaposi sarcoma, and human papillomavirus–related malignancies (cervical and anal cancers).

Management of HIV Infection

When to Initiate Treatment

All persons with HIV infection should begin antiretroviral therapy as soon as they are ready, regardless of CD4 cell count. Previous controversy over whether to start antiretroviral treatment in asymptomatic patients with normal CD4 cell counts has been resolved with demonstration of clear clinical benefit in a large prospective, randomized clinical trial.

Antiretroviral Regimens

Antiretroviral agents used in the United States are shown in **Table 66**. Standards for effective antiretroviral regimens include use of three drugs from two different classes, preferably combining two nucleoside reverse transcriptase inhibitors with an integrase strand transfer inhibitor. Preferred regimens also feature a high barrier to resistance, good tolerability and safety, and combination pills with once-daily dosing to facilitate adherence (**Table 67**).

Patients with or at risk for reduced kidney function or osteopenia should not be given TDF. Patients who are prescribed abacavir must first undergo testing to show they are HLA-B*5701 negative to reduce the risk of hypersensitivity. Many antiretrovirals have interactions with other drugs, and potential drug interactions must always be assessed when beginning HIV therapy or beginning any drug for someone already taking antiretroviral therapy. Such assessment is especially necessary when pharmacokinetic boosters (ritonavir or cobicistat) are used specifically to inhibit drug metabolism and raise levels of antiretrovirals.

Viral load levels and CD4 cell counts are monitored to ensure effectiveness and to assess for immune recovery. With optimal therapy, HIV RNA in blood should become and stay undetectable. CD4 cell counts will increase, although cell counts may take time to improve and may not show full recovery, especially in those who are older or who have other factors affecting lymphocytes. Patients taking antiretroviral therapy who are stable with a CD4 cell count of 500/µL or more for more than 2 years can stop T-cell monitoring as long as viral load remains undetectable.

Resistance Testing

Viral resistance testing should be performed at baseline to ensure selection of a fully active regimen and should be repeated if the viral load increases during antiretroviral treatment. The most common reason for breakthrough viremia is poor medication adherence. In general, plasma levels of HIV RNA must be greater than 500 copies/mL to provide enough virus for resistance testing. Viral resistance testing can be genotypic (looking for mutations associated with drug resistance) or phenotypic (assessing whether virus can replicate in the presence of the drug). Genotypic testing is faster and cheaper, but phenotypic testing may be better in the presence of multiple mutations or for drugs such as protease inhibitors in which the correlation of specific mutations and resistance is less straightforward. Resistance testing results are used to guide selection of a new regimen in the event resistant virus develops, but previous resistance testing results as well as previous regimens and responses must also be considered. Resistance testing may not be reliable if performed while the patient is not taking an antiretroviral regimen because resistance may not be detectable without the selective pressure of the antiretrovirals. Once selected for, previous mutations are generally archived in the viral population and may re-emerge even if resistance testing does not demonstrate the mutation. A regimen may also be switched because of adverse effects or to ease adherence or avoid drug interactions. Laboratory monitoring tests should be repeated 1 month after switching regimens to assess effectiveness and toxicity.

TABLE 66. Antiretroviral Agents Used in the United States to Treat HIV Infection

Class	Agent[a]	Adverse Effects
Nucleoside RTIs	Abacavir	Hypersensitivity[b] (exclude HLA-B*5701 before prescribing)
	Emtricitabine	Minimal toxicity; has activity against HBV, and exacerbations have occurred with discontinuation of therapy
	Lamivudine	Minimal toxicity; has HBV activity, but dosing differs for HIV and HBV treatment
	TDF	Nausea, kidney disease, Fanconi syndrome, decreased bone density; has activity against HBV, and exacerbations have occurred with discontinuation of therapy
	TAF	Nausea; less kidney and bone toxicity than TDF
	Zidovudine	Nausea, headache, anemia[b], leukopenia[b], lactic acidosis[b], lipodystrophy, myopathy[b]
Nonnucleoside RTIs	Efavirenz	Neuropsychiatric symptoms (dizziness, somnolence, sleep disturbance, vivid dreams, mood changes), rash, dyslipidemia
	Etravirine	Nausea, rash
	Nevirapine	Hypersensitivity[b], rash, hepatitis[b]
	Rilpivirine	Rash, headache, insomnia; requires food and gastric acid (no concomitant PPI use) for absorption
Protease inhibitors	Atazanavir	Nausea, hyperbilirubinemia, nephrolithiasis, rash; requires food and gastric acid (no concomitant PPI use) for absorption
	Darunavir	Nausea, diarrhea, rash
	Fosamprenavir	Nausea, diarrhea, rash
	Lopinavir	Nausea, diarrhea, hyperlipidemia, insulin resistance
	Saquinavir	Nausea, diarrhea, hyperlipidemia, QT prolongation
	Tipranavir	Nausea, diarrhea, hyperlipidemia, rash, hepatitis[b], intracranial hemorrhage[b]
CCR5 antagonist	Maraviroc	Hypersensitivity, hepatitis[b]
Integrase inhibitors	Dolutegravir	Elevated creatinine level (decrease in tubular secretion, not GFR), insomnia, headache (generally well tolerated)
	Elvitegravir	Nausea, diarrhea (generally well tolerated)
	Raltegravir	Rash, myopathy (generally well tolerated)
	Bictegravir	Elevated creatinine level (decrease in tubular secretion, not GFR), nausea, diarrhea, headache (generally well tolerated)
Pharmacokinetic boosters	Cobicistat	Elevated creatinine level (decrease in tubular creatinine secretion, not GFR), not recommended if CrCl <70 mL/min
	Ritonavir	Nausea, diarrhea, hyperlipidemia, insulin resistance, lipodystrophy, drug interactions[b]

CrCl = creatinine clearance; GFR = glomerular filtration rate; HBV = hepatitis B virus; PPI = proton pump inhibitor; RTIs = reverse transcriptase inhibitors; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate.

[a]Many agents are also available as components of combination medications.

[b]Black box warning. Note all nucleoside analogues have a black box warning about possible lactic acidosis, although it is far more likely with stavudine, didanosine, and zidovudine than the other agents.

TABLE 67. Preferred Regimens for Initial Treatment of HIV Infection[a]

Abacavir/lamivudine/dolutegravir
Tenofovir alafenamide/emtricitabine/dolutegravir
Tenofovir alafenamide/emtricitabine/cobicistat/elvitegravir
Tenofovir alafenamide/emtricitabine/raltegravir
Tenofovir alafenamide/emtricitabine/bictegravir

[a]Endorsed by the 2016 International Antiviral Society–USA Panel guidelines and the 2018 Department of Health and Human Services guidelines.

KEY POINTS

- All persons with HIV infection should begin antiretroviral therapy as soon as they are ready, regardless of CD4 cell count.
- Standards for effective antiretroviral regimens include use of three drugs from two different classes; preferred regimens combine two nucleoside reverse transcriptase inhibitors with an integrase strand transfer inhibitor.
- HIV resistance testing may not be reliable if performed while the patient is not taking an antiretroviral regimen because resistance may not be detectable without the selective pressure of the antiretrovirals.

Management of Pregnant Patients with HIV Infection

The management of pregnant women with HIV does not significantly differ from the management of nonpregnant women. Initiating antiretroviral therapy is recommended as soon as possible in pregnant women with HIV who are not already being treated, and it is especially important that women already receiving HIV treatment who become pregnant continue treatment without interruption. Antiretroviral therapy in pregnancy benefits the woman and significantly reduces the risk of perinatal transmission of HIV to her baby. Previous concerns about teratogenicity of some antiretrovirals, including concerns about neural tube defects with efavirenz, have been allayed by data showing no difference in birth defect rates compared with the general population regardless of when therapy was started. Initial treatment regimen selection in pregnant women does not typically differ from nonpregnant women; however, elvitegravir-cobicistat is not recommended because levels are inadequate in the second and third trimesters, and bictegravir and TAF are not recommended until safety and pharmacokinetic data in pregnancy are available. Dolutegravir is not recommended in the first 8 weeks of pregnancy until more data are available regarding possible increased risk of neural tube defects.

KEY POINTS

- Pregnant women should promptly initiate or continue receiving HIV treatment without interruption; previous concerns about teratogenicity of efavirenz and tenofovir disoproxil fumarate have been allayed by data showing no difference in birth defect rates compared with the general population.
- In pregnant women with HIV, bictegravir and tenofovir alafenamide are not recommended until safety and pharmacokinetic data in pregnancy are available; dolutegravir should be avoided in the first 8 weeks of pregnancy until more safety data are available.

Viral Infections

Influenza Viruses

Overview

Three types of influenza viruses primarily infect humans: A, B, and C. Influenza A viruses are divided into subtypes based on two surface proteins, hemagglutinin (H) and neuraminidase (N). Influenza A viruses can infect animals and humans and produce epidemics and pandemics. Influenza B viruses only affect humans and cause yearly epidemics but not pandemics. Influenza C causes mild illness and does not cause epidemics.

Minor changes in the H and N surface envelope glycoproteins (*antigenic drift*) of influenza A and B viruses cause yearly epidemics, and major changes (*antigenic shift*) in influenza A after genetic recombination from animals cause global pandemics. The last influenza pandemic occurred in 2009 and was caused by H1N1. Emerging subtypes of importance include H7N9, which circulates among poultry in China and can cause severe illness in humans; H5N1, which infects humans through close contact with infected poultry and can spread from person to person; and variants circulating in pigs that can sporadically infect humans.

Clinical Features and Evaluation

H

During the winter, influenza A causes a self-limiting illness with fever, cough, rhinorrhea, myalgia, and headache in most patients; influenza B causes a milder illness. Older adults (>65 years), young children, pregnant women, and patients with chronic medical conditions (especially chronic lung disease) are at higher risk for severe primary influenza, complications such as superimposed bacterial pneumonia caused by *Streptococcus pneumoniae* or *Staphylococcus aureus*, and death (see Community Acquired Pneumonia). Less common but severe complications include asthma or chronic obstructive pulmonary disease exacerbations, myocarditis, encephalitis, rhabdomyolysis, myositis, sepsis, and multiorgan failure. Parotitis caused by influenza was reported during the 2015-2016 influenza season.

During the endemic season, patients can be diagnosed within 20 minutes using either rapid antigen tests or polymerase chain reaction (PCR) testing of nasopharyngeal swabs. Both tests are highly specific, but PCR has a sensitivity of nearly 100%; the rapid antigen tests have a sensitivity between 59% and 93%. Starting antiviral therapy following a negative antigen test result is reasonable if clinical suspicion is high. Serologic assays are not used clinically. Testing should be performed in patients at risk for complications (for example, those older than 65 years, patients with chronic medical conditions, immunocompromised patients, pregnant and postpartum women, those with a BMI of 40 or more, and persons with neuromuscular disease) and in health care workers, if the result will influence clinical management (decisions on initiation of antiviral treatment, impact on other diagnostic testing, antibiotic treatment decisions, and infection control practices). H

KEY POINTS

- Older adults (>65 years), young children, pregnant women, and patients with chronic medical conditions (especially chronic lung disease) are at higher risk for severe primary influenza, superimposed bacterial pneumonia caused by *Streptococcus pneumoniae* or *Staphylococcus aureus*, and death.
- Rapid antigen and polymerase chain reaction (PCR) tests of nasopharyngeal swabs are highly specific for influenza, but PCR has a higher sensitivity and can identify the virus subtype.

Management

H

Antiviral therapy should be started within 48 hours of symptom onset in patients with a positive PCR or rapid antigen test result to speed up recovery and decrease hospitalization rates and complications. Antiviral therapy should also be initiated

as soon as possible in hospitalized patients because some observational studies have shown decreased adverse outcomes. Treatment initiation should not be delayed while waiting for the results of confirmatory testing.

Neuraminidase inhibitors are active against influenza A and B and can be given orally (oseltamivir), intranasally (zanamivir), or, more recently, intravenously (peramivir). Antiviral therapy is recommended for patients with severe disease, including all hospitalized patients, and those at high risk for complications with confirmed or suspected influenza infection. Antiviral therapy should be given for at least 5 days, but in severely ill or immunosuppressed patients, a longer duration should be considered with repeat follow-up testing to document clearance. Immunosuppressed patients are at risk for neuraminidase inhibitor resistance during or after therapy.

Widespread influenza vaccination is the most important preventive intervention; all persons aged 6 months or older without contraindications and all health care personnel should be vaccinated (see MKSAP 18 General Internal Medicine). Oral oseltamivir and inhaled zanamivir are FDA approved for chemoprophylaxis (zanamivir is not approved in patients with chronic lung diseases) to contain outbreaks in institutional settings (such as long-term care facilities) and hospitals in conjunction with droplet precautions and vaccination. Chemoprophylaxis is given for at least 2 weeks, continuing at least 1 week after the last identified infection. Good hand hygiene and face masks can prevent secondary infections in households.

KEY POINTS

- Widespread influenza vaccination is the most important preventive intervention; all persons aged 6 months or older without contraindications and all health care personnel should be vaccinated.
- Antiviral therapy should be started within 48 hours of symptom onset but can be initiated up to 5 days after symptom onset in hospitalized patients; treatment should not be delayed while awaiting testing.

Novel Coronaviruses

Coronaviruses are RNA viruses that cause respiratory and gastrointestinal diseases. Six known types infect humans, with some infecting animals as well. Two novel coronaviruses, severe acute respiratory syndrome-coronavirus (SARS-CoV) and Middle East respiratory syndrome-coronavirus (MERS-CoV), can infect animals and also cause severe disease and epidemics in humans. In 2002, SARS-CoV emerged in China, causing an acute pneumonia epidemic with a mortality rate of approximately 10%. No infections have been reported since 2004. Treatment is supportive. MERS-CoV emerged in 2012 in Saudi Arabia in humans and camels, with most infections occurring in the Arabian Peninsula. MERS-CoV causes pneumonia, diarrhea, and kidney failure with a mortality rate of approximately 40%. Because all types of coronaviruses may spread from human to human, contact and airborne precautions should be implemented for hospitalized patients with suspected infection.

KEY POINT

- Middle East respiratory syndrome-coronavirus infection occurs primarily in the Arabian Peninsula and can cause severe pneumonia with diarrhea, kidney failure, and death.

Human Herpesvirus Infections

Human herpesviruses (HHVs) are a group of eight DNA viruses (**Table 68**). In humans, infection with HHV results in lifelong viral latency with the possibility of reactivation and oncogenesis. HHV can be transmitted by physical or sexual contact during active infection or through asymptomatic shedding of the virus (in saliva, semen, or cervical secretions); other routes include blood transfusion, organ transplantation, or maternofetal transmission. Varicella-zoster virus (VZV) is the only HHV that can be transmitted by the airborne route; it is also the only HHV with a vaccine that produces protective humoral immunity. Antivirals are available for some HHVs, and immunoglobulin therapy is available for cytomegalovirus and VZV.

Herpes Simplex Virus Types 1 and 2

Herpes simplex virus (HSV) type 1 infection is transmitted by oral-oral or oral-genital contact. It typically causes oral ulcers and affects 90% of adults (see MKSAP 18 Dermatology). During stress, severe illness, or immunosuppression, patients may experience recurrence of oral stomatitis or esophagitis. The incidence of primary genital infection by HSV-1 is increasing (see Sexually Transmitted Infections). HSV-1 is the most common cause of viral encephalitis (see Central Nervous System Infections).

HSV-2 is sexually transmitted and typically causes genital and rectal ulcers with or without proctitis. HSV-2 affects approximately one sixth of adults in the United States and can also cause recurrent benign lymphocytic meningitis (Mollaret meningitis), myelitis, sacral radiculopathy, and neonatal infection or death (maternofetal transmission in primary genital infection). HSV-1 and HSV-2 can cause herpetic whitlow (on fingers), herpes gladiatorum (a skin infection typically associated with contact sports), keratoconjunctivitis, retinitis, and erythema multiforme.

HSV-1 and HSV-2 infections can be treated and suppressed with oral nucleoside analogues (acyclovir, valacyclovir, and famciclovir). Topical antiviral agents (trifluridine and vidarabine) are used for herpetic keratitis. Intravenous acyclovir is used for severe mucocutaneous disease, disseminated infections in immunosuppressed persons, esophagitis, and suspected HSV encephalitis.

TABLE 68. Human Herpesviruses and Associated Manifestations

Type	Synonym	Subfamily	Manifestations	Latency Site
HHV-1	Herpes simplex virus 1	α	Primary infection: oral and/or genital herpes (predominantly orofacial: gingivostomatitis, pharyngitis, herpes labialis) Reactivation: Bell palsy, viral encephalitis; other sites, including skin and eye (recurrent herpes labialis)	Nerve ganglion
HHV-2	Herpes simplex virus 2	α	Primary infection: oral and/or genital herpes (predominantly genital); meningitis, sacral radiculopathy, and transverse myelitis	Nerve ganglion
HHV-3	Varicella-zoster virus	α	Varicella (chickenpox), herpes zoster (shingles)	Nerve ganglion
HHV-4	Epstein-Barr virus	γ	Infectious mononucleosis, nasopharyngeal carcinoma; in immunocompromised patients: Burkitt lymphoma, central nervous system lymphoma (in patients with AIDS), posttransplant lymphoproliferative disease, hairy leukoplakia	B cell
HHV-5	CMV	β	CMV mononucleosis; in immunocompromised patients: CMV retinitis, leukopenia and thrombocytopenia, pneumonitis, colitis, esophagitis, or hepatitis	Monocyte, lymphocyte, endothelial cell, epithelial cell
HHV-6 (6A and 6B)	Roseolovirus, herpes lymphotropic virus	β	Mononucleosis-like syndrome, roseola (sixth disease, exanthema subitum) in children; may affect various organ systems in transplant patients	T cell
HHV-7	Roseolovirus	β	Usually asymptomatic; may be associated with pityriasis rosea; roseola (sixth disease, exanthema subitum) in children	T cell
HHV-8	Kaposi sarcoma-associated virus	γ	Kaposi sarcoma, PEL, multicentric Castleman disease	B cell, endothelial cell

CMV = cytomegalovirus; HHV = human herpesvirus; PEL = primary effusion lymphoma.

KEY POINTS

- Herpes simplex virus (HSV) type 1 is the most common cause of viral encephalitis, and the incidence of primary genital infection caused by HSV-1 is increasing.
- Intravenous acyclovir is used for severe mucocutaneous herpes, disseminated infections in immunosuppressed persons, esophagitis, and suspected HSV encephalitis.

Varicella-Zoster Virus

Overview

H

VZV (HHV-3) is transmitted by inhalation and colonization of the respiratory tract, with subsequent viremic dissemination to skin, liver, spleen, and sensory ganglia (varicella, or chickenpox). VZV establishes latency in the ganglia and can later reactivate, causing herpes zoster (shingles), especially in adults older than 60 years or in immunosuppressed patients. Contact and airborne precautions should be used for all hospitalized patients with varicella, for patients with disseminated herpes zoster, and for those with dermatomal zoster who are immunosuppressed.

Clinical Features and Diagnosis

Primary varicella infection (chickenpox) presents with a febrile pruritic vesicular rash affecting the skin and mucocutaneous surfaces (oropharynx, conjunctiva, genitals); the rash commonly begins on the face and trunk, then spreads to the extremities (centrifugal distribution). Lesions may comprise macules, papules, vesicles, and scabs in different stages of development. Skin lesions may become superinfected with *Streptococcus pyogenes* or *Staphylococcus aureus* (impetigo). Most children recover without sequelae, but adults may develop pneumonia, encephalitis, hepatitis, and cerebellar ataxia.

Herpes zoster typically causes a painful vesicular rash that follows a dermatomal distribution that does not cross the midline (see MKSAP 18 Dermatology). Young patients presenting with herpes zoster should be tested for HIV. Immunosuppressed patients can present with multiple dermatomes affected or with disseminated disease. Postherpetic neuralgia, defined as neuropathic pain lasting more than 1 month after resolution of the vesicular rash, is the most significant complication of herpes zoster. Other complications

H CONT include herpes zoster ophthalmicus with visual loss, Ramsay-Hunt syndrome (vesicular rash in external ear associated with ipsilateral peripheral facial palsy and altered taste), pneumonia, hepatitis, and central nervous system complications such as meningitis, encephalitis, myelitis, and stroke caused by vasculitis (see Central Nervous System Infections).

Varicella or herpes zoster can be diagnosed clinically by the typical vesicular rash and confirmed with VZV PCR testing of the base of a vesicular lesion. VZV is underdiagnosed in the absence of a rash (zoster sine herpete); in such cases, cerebrospinal fluid serologic (VZV IgM and IgG) and PCR testing can be used to diagnose the infections. H

Management

H Antiviral therapy (acyclovir, valacyclovir, and famciclovir) speeds recovery and decreases the severity and duration of neuropathic pain if begun within 72 hours of VZV rash onset. Intravenous acyclovir should be used for immunosuppressed or hospitalized patients and those with neurologic involvement. H

Vaccination is the most important preventive strategy (see MKSAP 18 General Internal Medicine). Postexposure prophylaxis should be provided to susceptible persons (VZV IgG negative); postexposure varicella vaccination is appropriate in immunocompetent persons, and varicella-zoster immune globulin should be used in immunocompromised adults and in pregnant women.

KEY POINTS

- The rash of primary varicella infection (chickenpox) commonly begins on the face and trunk, then spreads to the extremities (centrifugal distribution) and may comprise macules, papules, vesicles, and scabs in various stages of development.
- In immunosuppressed patients, herpes zoster (shingles) can affect multiple dermatomes or present with disseminated disease; young patients presenting with herpes zoster should be tested for HIV.
- Postexposure varicella vaccination is appropriate in immunocompetent persons, and varicella-zoster immune globulin should be used in immunocompromised adults and pregnant women.
- Antiviral therapy speeds recovery and decreases the severity and duration of neuropathic pain if begun within 72 hours of VZV rash onset.

Epstein-Barr Virus

Epstein-Barr virus (EBV) (HHV-4) is highly prevalent; serologic studies show evidence of previous EBV infection in almost all adults. It is most commonly transmitted by saliva and is the main cause of infectious mononucleosis in children and adolescents. Patients present with fever, severe fatigue, exudative pharyngitis, cervical and axillary lymphadenopathy, and splenomegaly. Atypical lymphocytosis and aminotransferase level elevations are clues to the diagnosis, which is established by the presence of heterophile antibodies (Monospot test) or IgM to the EBV viral capsid antigen. The Monospot test result may be negative in the first week of illness. Treatment is supportive, with no role for acyclovir; glucocorticoids may be given to patients with autoimmune hemolytic anemia, central nervous system involvement, or tonsillar enlargement with a compromised airway. EBV is associated with the development of T-cell and B-cell lymphomas, Hodgkin and Burkitt lymphoma, nasopharyngeal carcinoma, and posttransplant lymphoproliferative disease in solid organ transplantation.

KEY POINTS

- Epstein-Barr virus infection, the primary cause of infectious mononucleosis, presents with fever, severe fatigue, exudative pharyngitis, cervical and axillary lymphadenopathy, and splenomegaly.
- The diagnosis of Epstein-Barr virus is established by the presence of heterophile antibodies on the Monospot test, although this test result may be negative during the first week of illness.

Human Cytomegalovirus

H Cytomegalovirus (HHV-5) infections are most commonly asymptomatic but may present with a mononucleosis-like syndrome without pharyngitis and with negative heterophile antibody results. Cytomegalovirus may be transmitted through the placenta (congenital cytomegalovirus), breastfeeding, saliva, blood transfusion, or organ transplantation (cytomegalovirus-positive donor to cytomegalovirus-seronegative recipient). Approximately 60% to 90% of adults have latent cytomegalovirus infection with reactivation of disease more common in immunosuppressed persons (those with AIDS, transplant recipients, those receiving glucocorticoid therapy). Cytomegalovirus can cause retinitis, pneumonitis, hepatitis, bone marrow suppression, colitis, esophagitis, and adrenalitis in immunocompromised persons. Immunocompetent patients occasionally also present with colitis.

Because cytomegalovirus can cause a myriad of clinical manifestations, a high index of clinical suspicion is important. Diagnosis is commonly confirmed with molecular tests, such as PCR testing of serum, bronchoalveolar lavage fluid, or cerebrospinal fluid, or by demonstrating typical cytopathic "owl's eye" intracellular inclusions on biopsy specimens (**Figure 25**). Pathologic diagnosis is confirmed by cytomegalovirus immunostains. Serologic assays have limited diagnostic utility because most adults are seropositive; however, they are performed routinely in pretransplant evaluations to assess the risk of cytomegalovirus reactivation after transplantation and to determine appropriate prophylaxis.

Antiviral therapy with intravenous ganciclovir or oral valganciclovir is used in immunocompromised patients or in immunocompetent patients with severe disease. Oral valganciclovir is also used as prophylaxis or pre-emptive therapy (treat if the PCR serum testing result is positive) in transplant

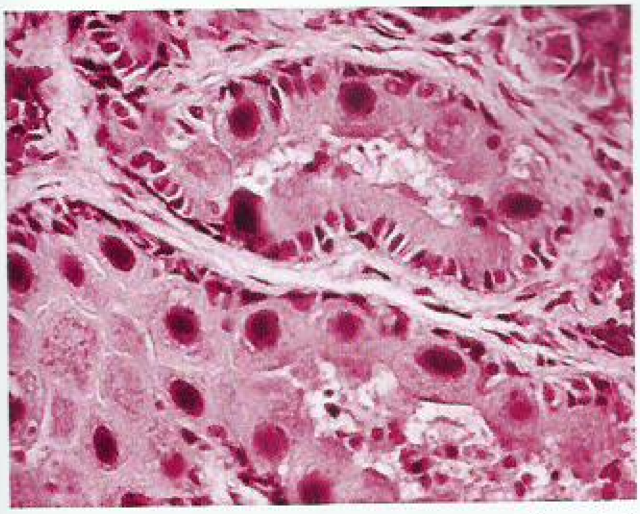

FIGURE 25. Under a magnification of 500X, a photomicrograph of a sample of kidney tissue reveals the presence of what are referred to as cytomegalic inclusion cells. With enlarged, darkly stained nuclei, such cells are also known as owl's-eye inclusion cells and are caused by cytomegalic inclusion disease resulting from cytomegalovirus.

H CONT. recipients. Foscarnet and cidofovir can be used in instances of ganciclovir resistance or intolerance. H

KEY POINTS

- Serologic assays for cytomegalovirus have limited diagnostic utility because most adults are seropositive; however, they are performed routinely in pretransplant evaluations to assess the risk of cytomegalovirus reactivation following transplantation and to determine appropriate prophylaxis.
- Diagnosis of cytomegalovirus is confirmed with molecular tests of infected fluids, by demonstrating typical cytopathic "owl's-eye" intracellular inclusions on biopsy specimens, or by cytomegalovirus immunostaining of pathologic samples.

Stewardship and Emerging Resistance

Introduction

Emergence of antibiotic resistance is potentiated by all antibiotic use. Careful antibiotic use is essential to preserving the armamentarium. Among outpatient visits, 12.6% are associated with antibiotic prescriptions, and 30% of those prescriptions are considered inappropriate. Most prescriptions are for acute respiratory infections (usually caused by viruses) and asymptomatic bacteriuria not requiring antibiotic treatment. One fifth of emergency department visits for adverse drug events are related to antibiotics. Inpatient antibiotic use accounts for 38.5% of all antibiotic use; half of hospitalized patients receive antibiotics, and half of these medications are considered unnecessary or inappropriate. The World Health Organization has named carbapenem-resistant *Acinetobacter baumannii* and *Pseudomonas aeruginosa* and carbapenem-resistant and extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae as priority-one pathogens, for which new antibiotics are critically needed.

Antimicrobial Stewardship and the Value of Infectious Disease Consultation

Antibiotic stewardship refers to coordinated interventions to improve antibiotic use and clinical outcomes by promoting optimal antibiotic regimens. Goals include minimizing adverse events (5% risk per antibiotic per patient), risk of *Clostridium difficile* infection, and emergence of resistance. A key aspect of stewardship is avoiding antibiotic administration when not indicated. Antibiotic selection, dosing, therapy duration, and route of administration are also considered. Furthermore, antimicrobial stewardship programs include simplifying unnecessary combination therapy, avoiding redundant double anaerobic coverage, converting intravenous to oral agents, streamlining de-escalation, and minimizing duration of therapy.

Combination therapy does not prevent the emergence of resistance. However, it may be considered in specific circumstances, such as empiric therapy regimens, to broaden the spectrum of activity or provide coverage for potential antimicrobial-resistant organisms pending culture and susceptibility results. Antibiotic combination therapy may also provide synergistic activity in limited situations, such as enterococcal endocarditis and bacteremia caused by carbapenem-resistant Enterobacteriaceae (CRE).

H Conversion from an intravenous to an oral antimicrobial agent should be considered for ease of administration and to limit intravenous catheter access and use, thereby decreasing the risk of catheter-related bloodstream infection. Factors supporting readiness for conversion include a temperature of 38 °C (100.4 °F) or less, an improving leukocyte count, clinical stability and improvement of signs and symptoms related to infection, a functioning gastrointestinal tract and ability to swallow medications or having a nasogastric tube in place, no diagnostic indication for intravenous therapy (endocarditis, *Staphylococcus aureus* bacteremia), and availability of a suitable oral alternative with good oral bioavailability (fluoroquinolones, oxazolidinones, metronidazole, clindamycin, trimethoprim-sulfamethoxazole, fluconazole, doxycycline, voriconazole). H

Antimicrobial stewardship programs use various interventions to optimize antimicrobial use. Interventions that have been shown to be effective in improving outcomes, decreasing resistance, and decreasing costs include preauthorization and prospective audit with feedback to the

TABLE 69. Newer Antimicrobial Agents

Agent	Class	Mechanism of Action	Route	Adverse Effects	Issues/Limitations	FDA Indications	Relative Cost
Ceftolozane-tazobactam	Antipseudomonal cephalosporin with β-lactamase inhibitor	Inhibits cell wall synthesis by binding to PBP; tazobactam irreversibly inhibits activity of many penicillinases and cephalosporinases	IV, every 8 hours	Similar to other cephalosporins	Reduced efficacy in patients with creatinine clearance ≤50 mL/min	Complicated intra-abdominal infections (combined with metronidazole); complicated urinary tract infections, including pyelonephritis Active against many gram-negative organisms, including some ESBL-producing Enterobacteriaceae and multidrug-resistant *Pseudomonas aeruginosa*, including carbapenem-resistant strains	$$$
Ceftaroline	Cephalosporin	Inhibits cell wall synthesis by high affinity binding to PBPs; high affinity for PBP2a that leads to activity against MRSA	IV, every 12 hours	Similar to other cephalosporins	Limited clinical experience for MRSA outside of skin infections	Community-acquired pneumonia (not caused by MRSA, clinical trial data lacking), ABSSSI caused by susceptible organisms (including MRSA)	$$
Ceftazidime-avibactam	Third-generation cephalosporin with novel β-lactamase inhibitor	Inhibits cell wall synthesis by binding to PBP; avibactam inhibits broader range of β-lactamases than other available β-lactamase inhibitors	IV, every 8 hours	Similar to other cephalosporins	Approved on limited clinical safety and efficacy data Reserve use for patients with limited or no alternative treatment options Decreased efficacy in patients with baseline creatinine clearance between 30-50 mL/min Monitor kidney function daily; adjust dose as needed	Complicated intra-abdominal infections (combined with metronidazole); complicated urinary tract infections, including pyelonephritis Active against many multidrug-resistant gram-negative organisms, ESBL, and carbapenemases Not active against metallo-β-lactamases or gram-negative organisms that overexpress efflux pumps or have porin mutations	$$$$$
Dalbavancin	Lipoglycopeptide	Disrupts cell wall membrane synthesis	IV, once weekly	Nausea, headache, diarrhea, elevation of liver enzyme levels	Rapid IV infusion may cause flushing of the upper body, urticaria, pruritus, rash	ABSSSI caused by susceptible strains of gram-positive organisms (*Staphylococcus aureus* including MRSA, *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus anginosus* group)	$$$$

Delafloxacin	Fluoroquinolone	Acts on DNA gyrase and topoisomerase IV inhibiting DNA replication	IV, oral twice daily	Nausea, headache, diarrhea, aminotransferase elevation	Tendinitis, tendon rupture, peripheral neuropathy, central nervous system effects Avoid coadministration of oral formulation with chelating agents, such as antacids	ABSSSI caused by susceptible gram-positive organisms, including MRSA Has activity against gram-negative organisms, including *P. aeruginosa* Studies ongoing for community-acquired pneumonia and complicated urinary tract infection	$$$
Oritavancin	Lipoglycopeptide	Disrupts cell wall membrane synthesis, disrupts cell membrane integrity	IV, one dose	Headache, nausea, elevation of liver enzyme levels	Interaction with anticoagulation tests to monitor heparin; increases warfarin level by 30%, monitor patients for bleeding	ABSSSI caused by susceptible gram-positive organisms: *S. aureus* (MRSA and MSSA), *S. pyogenes*, *S. agalactiae*, *Streptococcus dysgalactiae*, *S. anginosus* group, and vancomycin-susceptible *Enterococcus faecalis*	$$$
Tedizolid	Oxazolidinone	Disrupts bacterial protein synthesis initiation	IV, oral, once daily for 6 days	Nausea, headache, diarrhea	Patients taking selective serotonin reuptake inhibitors were excluded from clinical trials	ABSSSI caused by susceptible gram-positive organisms (MRSA, MSSA, linezolid-resistant *S. aureus*, *S. pyogenes*, *S. agalactiae*, *S. anginosus* group, *Streptococcus intermedius*, *Streptococcus constellatus*, *E. faecalis*)	$$
Telavancin	Glycopeptide	Disrupts cell wall synthesis and function	IV, once daily	Nephrotoxicity	Interaction with coagulation tests to monitor heparin; may prolong QTc interval; decreased efficacy in pre-existing chronic kidney disease (eGFR <90 mL/min/1.73 m^2)	Complicated skin and soft tissue infections caused by susceptible organisms and *S. aureus* (including MRSA) hospital-acquired pneumonia	$$$

ABSSSI = acute bacterial skin and skin-structure infection; eGFR = estimated glomerular filtration rate; ESBL = extended-spectrum β-lactamase; IV = intravenous; MRSA = methicillin-resistant *Staphylococcus aureus*; MSSA = methicillin-sensitive *Staphylococcus aureus*; PBP = penicillin-binding protein.

prescriber, targeting antibiotics associated with a high risk of *C. difficile* infection (such as clindamycin, broad-spectrum antibiotics, and fluoroquinolones), using dedicated pharmacokinetic monitoring and adjustment programs, increasing the use of oral antimicrobial agents, and reducing antimicrobial therapy to the shortest effective duration.

KEY POINT

- Important components of antimicrobial stewardship programs include avoiding unnecessary antibiotic use, simplifying unnecessary combination therapy, avoiding double anaerobic coverage, converting intravenous to oral agents, streamlining de-escalation, and minimizing duration of therapy.

Newer Antibacterial Drugs

Two newer cephalosporin antibiotics, ceftazidime-avibactam and ceftolozane-tazobactam, have enhanced activity against β-lactamase-producing organisms, particularly ESBLs, and against some carbapenemase-producing CRE. Three agents are available in the lipoglycopeptide class of antibiotics with activity against aerobic gram-positive organisms, such as *S. aureus* (including methicillin-resistant *S. aureus*), streptococci, and vancomycin-susceptible *Enterococcus faecalis*. Ceftaroline is a fifth-generation cephalosporin with a unique spectrum of activity that covers methicillin-resistant *S. aureus*. Delafloxacin is a new anionic fluoroquinolone with gram-positive (including methicillin-resistant *S. aureus*) and gram-negative activity (**Table 69**).

Antibiotics for Antibiotic-Resistant Organisms

Enterococcus faecium, *S. aureus*, *Klebsiella pneumoniae*, *Acinetobacter* species, *Pseudomonas aeruginosa*, and *Enterobacter* species are particularly problematic antibiotic-resistant organisms. This group includes ESBL and carbapenemase-producing CRE (*Klebsiella pneumoniae* carbapenemases and New Delhi metallo-β-lactamase) that destroy carbapenems. Few effective antibiotics are available to treat infections with these pathogens. However, several older, less commonly used antibiotics retain their activity. Infectious disease consultation should be considered for infections with organisms in this group.

Minocycline

Resurgence in the use of minocycline, available in intravenous and oral forms, is partly because of its activity against multidrug-resistant *Acinetobacter*. In vitro susceptibility to minocycline can be inferred from susceptibility to tetracycline; however, some tetracycline-resistant strains are sensitive to minocycline. Minocycline has been used to treat ventilator-associated pneumonia with an 80% clinical response rate and is also useful for treating infections caused by *Stenotrophomonas maltophilia*, a problematic ICU pathogen with intrinsic antibiotic resistance. The adverse effects of minocycline are similar to those of tetracycline, including photosensitivity, gastrointestinal disturbance, and skin pigmentation changes with prolonged use.

KEY POINT

- Minocycline has activity against multidrug-resistant *Acinetobacter* and *Stenotrophomonas maltophilia*.

Fosfomycin

Fosfomycin (available in the United States) is a bactericidal oral antibiotic with gram-negative and gram-positive activity (including methicillin-resistant *S. aureus* and vancomycin-resistant Enterobacteriaceae). It achieves high concentrations in the urine and may be used to treat cystitis caused by vancomycin-resistant Enterobacteriaceae and other multidrug-resistant uropathogens such as carbapenemase-producing *K. pneumoniae*.

KEY POINT

- Fosfomycin has gram-negative and gram-positive activity (including methicillin-resistant *S. aureus* and vancomycin-resistant Enterobacteriaceae) and achieves high concentrations in the urine, making it useful for treating cystitis.

Colistin

Colistin (polymyxin E) is a bactericidal agent used to treat multidrug- and pan-resistant aerobic gram-negative infections, including *P. aeruginosa*. *Proteus*, *Providencia*, *Burkholderia*, *Morganella*, and *Serratia* species are resistant to colistin. Colistin resistance has been described in some multidrug-resistant gram-negative infections (mostly carbapenemase-producing *K. pneumoniae*), leading to completely untreatable infections. Colistin can be administered by nebulized aerosol or intravenously. The most common adverse effect is nephrotoxicity (up to 50% of patients), which is usually reversible.

KEY POINT

- Nephrotoxicity occurs in up to 50% of patients treated with colistin, although it is usually reversible.

Outpatient Parenteral Antibiotic Therapy

Outpatient parenteral antibiotic therapy (OPAT) is defined as administration of at least two doses of intravenous antibiotics on different days without intervening hospitalization. Approximately 250,000 patients per year in the United States are treated with OPAT. OPAT allows patients to complete parenteral antibiotic therapy at home or in other outpatient

settings when an oral antibiotic is not appropriate or available. Bone and joint infections compose most of the infections treated with OPAT; other candidates include endocarditis, cardiac device infections, abdominal infections, skin and soft tissue infections, and antibiotic-resistant infections for which parenteral antibiotics are the only option (such as urinary tract infection).

Patients should be clinically stable and their infection improving before starting OPAT; OPAT is not appropriate if the patient's care needs would be better met in the hospital. When considering OPAT, it is important to assess the type of infection being treated, the prescribed antibiotic and dosing frequency, the planned therapy duration, the administration site, the intravenous catheter type, and the monitoring process for possible complications. Increasingly, OPAT is being started without initial hospitalization after careful medical assessment by a well-established and organized OPAT program. OPAT requires close monitoring, including antibiotic levels (vancomycin, aminoglycosides), complete blood count, creatinine level, liver chemistry tests, and coagulation tests if relevant for the antibiotic; patients receiving daptomycin therapy in particular should undergo baseline measurement of kidney function and creatine kinase level, followed by weekly monitoring. Antibiotic doses and timing should be adjusted based on monitoring results. Treatment failure may result from relapse or progression of primary infection (60% and 21%, respectively) and therapeutic complications (19%). Successful OPAT requires patient participation; supervised infectious disease OPAT programs have been shown to be safe, efficient, and clinically effective.

KEY POINT

- Bone and joint infections are the primary infections treated with outpatient parenteral antibiotic therapy (OPAT); other candidates for OPAT include serious infections (endocarditis, cardiac device infections, abdominal infections, and skin and soft tissue infections) and antibiotic-resistant infections for which parenteral antibiotics are the only option (such as urinary tract infection).

Bibliography

Central Nervous System Infections

Castelblanco RL, Lee M, Hasbun R. Epidemiology of bacterial meningitis in the USA from 1997 to 2010: a population-based observational study. Lancet Infect Dis. 2014;14:813-9. [PMID: 25104307] doi:10.1016/S1473-3099(14)70805-9

Hasbun R. Central nervous system device infections. Curr Infect Dis Rep. 2016;18:34. [PMID: 27686676] doi:10.1007/s11908-016-0541-x

Hasbun R, Rosenthal N, Balada-Llasat JM, Chung J, Duff S, Bozzette S, et al. Epidemiology of meningitis and encephalitis in the United States, 2011-2014. Clin Infect Dis. 2017;65:359-363. [PMID: 28419350] doi:10.1093/cid/cix319

McGill F, Heyderman RS, Michael BD, Defres S, Beeching NJ, Borrow R, et al. The UK joint specialist societies guideline on the diagnosis and management of acute meningitis and meningococcal sepsis in immunocompetent adults. J Infect. 2016;72:405-38. [PMID: 26845731] doi:10.1016/j.jinf.2016.01.007

Srihawan C, Castelblanco RL, Salazar L, Wootton SH, Aguilera E, Ostrosky-Zeichner L, et al. Clinical characteristics and predictors of adverse outcome in adult and pediatric patients with healthcare-associated ventriculitis and meningitis. Open Forum Infect Dis. 2016;3:ofw077. [PMID: 27419154] doi:10.1093/ofid/ofw077

Tunkel AR, Hasbun R, Bhimraj A, Byers K, Kaplan SL, Michael Scheld W, et al. 2017 Infectious Diseases Society of America's clinical practice guidelines for healthcare-associated ventriculitis and meningitis. Clin Infect Dis. 2017. [PMID: 28203777] doi:10.1093/cid/ciw861

van de Beek D, Brouwer M, Hasbun R, Koedel U, Whitney CG, Wijdicks E. Community-acquired bacterial meningitis. Nat Rev Dis Primers. 2016;2:16074. [PMID: 27808261] doi:10.1038/nrdp.2016.74

van de Beek D, Cabellos C, Dzupova O, Esposito S, Klein M, Kloek AT, et al; ESCMID Study Group for Infections of the Brain (ESGIB). ESCMID guideline: diagnosis and treatment of acute bacterial meningitis. Clin Microbiol Infect. 2016;22 Suppl 3:S37-62. [PMID: 27062097] doi:10.1016/j.cmi.2016.01.007

Venkatesan A, Tunkel AR, Bloch KC, Lauring AS, Sejvar J, Bitnun A, et al; International Encephalitis Consortium. Case definitions, diagnostic algorithms, and priorities in encephalitis: consensus statement of the international encephalitis consortium. Clin Infect Dis. 2013;57:1114-28. [PMID: 23861361] doi:10.1093/cid/cit458

Wang AY, Machicado JD, Khoury NT, Wootton SH, Salazar L, Hasbun R. Community-acquired meningitis in older adults: clinical features, etiology, and prognostic factors. J Am Geriatr Soc. 2014;62:2064-70. [PMID: 25370434] doi:10.1111/jgs.13110

Prion Diseases of the Central Nervous System

Das AS, Zou WQ. Prions: beyond a single protein. Clin Microbiol Rev. 2016;29:633-58. [PMID: 27226089] doi:10.1128/CMR.00046-15

Geschwind MD. Prion diseases. Continuum (Minneap Minn). 2015;21:1612-38. [PMID: 26633779] doi:10.1212/CON.0000000000000251

Haik S, Brandel JP. Infectious prion diseases in humans: cannibalism, iatrogenicity and zoonoses. Infect Genet Evol. 2014;26:303-12. [PMID: 24956437] doi:10.1016/j.meegid.2014.06.010

Kim MO, Geschwind MD. Clinical update of Jakob-Creutzfeldt disease. Curr Opin Neurol. 2015;28:302-10. [PMID: 25923128] doi:10.1097/WCO.0000000000000197

Knight R. Creutzfeldt-Jakob disease: a rare cause of dementia in elderly persons. Clin Infect Dis. 2006;43:340-6. [PMID: 16804850]

Skin and Soft Tissue Infections

Bystritsky R, Chambers H. Cellulitis and soft tissue infections. Ann Intern Med. 2018;168:ITC17-ITC32. [PMID: 29404597] doi:10.7326/AITC201802060

Case definitions for infectious conditions under public health surveillance. Centers for Disease Control and Prevention. MMWR Recomm Rep. 1997;46:1-55. [PMID: 9148133]

Lipsky BA, Berendt AR, Cornia PB, Pile JC, Peters EJ, Armstrong DG, et al; Infectious Diseases Society of America. 2012 Infectious Diseases Society of America clinical practice guideline for the diagnosis and treatment of diabetic foot infections. Clin Infect Dis. 2012;54:e132-73. [PMID: 22619242] doi:10.1093/cid/cis346

Liu C, Bayer A, Cosgrove SE, Daum RS, Fridkin SK, Gorwitz RJ, et al; Infectious Diseases Society of America. Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant *Staphylococcus aureus* infections in adults and children. Clin Infect Dis. 2011;52:e18-55. [PMID: 21208910] doi:10.1093/cid/ciq146

Poulakou G, Giannitsioti E, Tsiodras S. What is new in the management of skin and soft tissue infections in 2016? Curr Opin Infect Dis. 2017;30:158-171. [PMID: 28134678] doi:10.1097/QCO.0000000000000360

Stevens DL, Bisno AL, Chambers HF, Dellinger EP, Goldstein EJ, Gorbach SL, et al; Infectious Diseases Society of America. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the Infectious Diseases Society of America. Clin Infect Dis. 2014;59:e10-52. [PMID: 24973422] doi:10.1093/cid/ciu444

Thomas KS, Crook AM, Nunn AJ, Foster KA, Mason JM, Chalmers JR, et al; U.K. Dermatology Clinical Trials Network's PATCH I Trial Team. Penicillin to prevent recurrent leg cellulitis. N Engl J Med. 2013;368:1695-703. [PMID: 23635049] doi:10.1056/NEJMoa1206300

Weng QY, Raff AB, Cohen JM, Gunasekera N, Okhovat JP, Vedak P, et al. Costs and consequences associated with misdiagnosed lower extremity cellulitis. JAMA Dermatol. 2016. [PMID: 27806170] doi:10.1001/jamadermatol.2016.3816

Wong CH, Khin LW, Heng KS, Tan KC, Low CO. The LRINEC (Laboratory Risk Indicator for Necrotizing Fasciitis) score: a tool for distinguishing necrotizing fasciitis from other soft tissue infections. Crit Care Med. 2004;32:1535-41. [PMID: 15241098]

Community-Acquired Pneumonia

Eliakim-Raz N, Robenshtok E, Shefet D, Gafter-Gvili A, Vidal L, Paul M, et al. Empiric antibiotic coverage of atypical pathogens for community-acquired pneumonia in hospitalized adults. Cochrane Database Syst Rev. 2012:CD004418. [PMID: 22972070] doi:10.1002/14651858.CD004418.pub4

Jain S, Self WH, Wunderink RG; CDC EPIC Study Team. Community-acquired pneumonia requiring hospitalization [Letter]. N Engl J Med. 2015;373:2382. [PMID: 26650159] doi:10.1056/NEJMc1511751

Kolditz M, Tesch F, Mocke L, Höffken G, Ewig S, Schmitt J. Burden and risk factors of ambulatory or hospitalized CAP: a population based cohort study. Respir Med. 2016;121:32-38. [PMID: 27888989] doi:10.1016/j.rmed.2016.10.015

Lee JS, Giesler DL, Gellad WF, Fine MJ. Antibiotic therapy for adults hospitalized with community-acquired pneumonia: a systematic review. JAMA. 2016;315:593-602. [PMID: 26864413] doi:10.1001/jama.2016.0115

Mandell LA, Wunderink RG, Anzueto A, Bartlett JG, Campbell GD, Dean NC, et al; Infectious Diseases Society of America. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis. 2007;44 Suppl 2:S27-72. [PMID: 17278083]

Musher DM, Thorner AR. Community-acquired pneumonia. N Engl J Med. 2014;371:1619-28. [PMID: 25337751] doi:10.1056/NEJMra1312885

Postma DF, van Werkhoven CH, van Elden LJ, Thijsen SF, Hoepelman AI, Kluytmans JA, et al; CAP-START Study Group. Antibiotic treatment strategies for community-acquired pneumonia in adults. N Engl J Med. 2015;372:1312-23. [PMID: 25830421] doi:10.1056/NEJMoa1406330

Restrepo MI, Reyes LF, Anzueto A. Complication of community-acquired pneumonia (including cardiac complications). Semin Respir Crit Care Med. 2016;37:897-904. [PMID: 27960213]

Siemieniuk RA, Meade MO, Alonso-Coello P, Briel M, Evaniew N, Prasad M, et al. Corticosteroid therapy for patients hospitalized with community-acquired pneumonia: a systematic review and meta-analysis. Ann Intern Med. 2015;163:519-28. [PMID: 26258555] doi:10.7326/M15-0715

Tang KL, Eurich DT, Minhas-Sandhu JK, Marrie TJ, Majumdar SR. Incidence, correlates, and chest radiographic yield of new lung cancer diagnosis in 3398 patients with pneumonia. Arch Intern Med. 2011;171:1193-8. [PMID: 21518934] doi:10.1001/archinternmed.2011.15

Tick-Borne Diseases

Biggs HM, Behravesh CB, Bradley KK, Dahlgren FS, Drexler NA, Dumler JS, et al. Diagnosis and management of tickborne rickettsial diseases: Rocky Mountain spotted fever and other spotted fever group rickettsioses, ehrlichioses, and anaplasmosis - United States. MMWR Recomm Rep. 2016;65:1-44. [PMID: 27172113] doi:10.15585/mmwr.rr6502a1

Goddard J. Not all erythema migrans lesions are Lyme disease. Am J Med. 2017;130:231-233. [PMID: 27612442] doi:10.1016/j.amjmed.2016.08.020

Hu LT. Lyme disease. Ann Intern Med. 2016;164:ITC65-ITC80. [PMID: 27136224] doi:10.7326/AITC201605030

Lantos PM. Chronic Lyme disease. Infect Dis Clin North Am. 2015;29:325-40. [PMID: 25999227] doi:10.1016/j.idc.2015.02.006

Moore A, Nelson C, Molins C, Mead P, Schriefer M. Current guidelines, common clinical pitfalls, and future directions for laboratory diagnosis of Lyme disease, United States. Emerg Infect Dis. 2016;22. [PMID: 27314832] doi:10.3201/eid2207.151694

Sanchez E, Vannier E, Wormser GP, Hu LT. Diagnosis, treatment, and prevention of Lyme disease, human granulocytic anaplasmosis, and babesiosis: a review. JAMA. 2016;315:1767-77. [PMID: 27115378] doi:10.1001/jama.2016.2884

Weitzner E, McKenna D, Nowakowski J, Scavarda C, Dornbush R, Bittker S, et al. Long-term assessment of post-treatment symptoms in patients with culture-confirmed early Lyme disease. Clin Infect Dis. 2015;61:1800-6. [PMID: 26385994] doi:10.1093/cid/civ735

Urinary Tract Infections

Geerlings SE, Beerepoot MA, Prins JM. Prevention of recurrent urinary tract infections in women: antimicrobial and nonantimicrobial strategies. Infect Dis Clin North Am. 2014;28:135-47. [PMID: 24484580] doi:10.1016/j.idc.2013.10.001

Hooton TM. Clinical practice. Uncomplicated urinary tract infection. N Engl J Med. 2012;366:1028-37. [PMID: 22417256] doi:10.1056/NEJMcp1104429

Johnson JR, Russo TA. Acute pyelonephritis in adults. N Engl J Med. 2018;378:48-59. [PMID: 29298155]

Nicolle LE. Asymptomatic bacteriuria. Curr Opin Infect Dis. 2014;27:90-6. [PMID: 24275697] doi:10.1097/QCO.0000000000000019

Schaeffer AJ, Nicolle LE. Clinical practice. Urinary tract infections in older men. N Engl J Med. 2016;374:562-71. [PMID: 26863357] doi:10.1056/NEJMcp1503950

***Mycobacterium tuberculosis* Infection**

Horsburgh CR Jr, Barry CE 3rd, Lange C. Treatment of tuberculosis. N Engl J Med. 2015;373:2149-60. [PMID: 26605929] doi:10.1056/NEJMra1413919

Jamil SM, Oren E, Garrison GW, Srikanth S, Lewinsohn DM, Wilson KC, et al. Diagnosis of tuberculosis in adults and children. Ann Am Thorac Soc. 2017;14:275-278. [PMID: 28146376] doi:10.1513/AnnalsATS.201608-636CME

Lewinsohn DM, Leonard MK, LoBue PA, Cohn DL, Daley CL, Desmond E, et al. Official American Thoracic Society/Infectious Diseases Society of America/Centers for Disease Control and Prevention clinical practice guidelines: diagnosis of tuberculosis in adults and children. Clin Infect Dis. 2017;64:111-115. [PMID: 28052967] doi:10.1093/cid/ciw778

Nahid P, Dorman SE, Alipanah N, Barry PM, Brozek JL, Cattamanchi A, et al. Executive summary: official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America clinical practice guidelines: treatment of drug-susceptible tuberculosis. Clin Infect Dis. 2016;63:853-67. [PMID: 27621353] doi:10.1093/cid/ciw566

Pai M, Schito M. Tuberculosis diagnostics in 2015: landscape, priorities, needs, and prospects. J Infect Dis. 2015;211 Suppl 2:S21-8. [PMID: 25765103] doi:10.1093/infdis/jiu803

Salinas JL, Mindra G, Haddad MB, Pratt R, Price SF, Langer AJ. Leveling of tuberculosis incidence - United States, 2013-2015. MMWR Morb Mortal Wkly Rep. 2016;65:273-8. [PMID: 27010173] doi:10.15585/mmwr.mm6511a2

Nontuberculous Mycobacterial Infections

Chand M, Lamagni T, Kranzer K, Hedge J, Moore G, Parks S, et al. Insidious risk of severe Mycobacterium chimaera infection in cardiac surgery patients. Clin Infect Dis. 2017;64:335-342. [PMID: 27927870] doi:10.1093/cid/ciw754

Griffith DE, Aksamit T, Brown-Elliott BA, Catanzaro A, Daley C, Gordin F, et al; ATS Mycobacterial Diseases Subcommittee. An official ATS/IDSA statement: diagnosis, treatment, and prevention of nontuberculous mycobacterial diseases. Am J Respir Crit Care Med. 2007;175:367-416. [PMID: 17277290]

Guglielmetti L, Mougari F, Lopes A, Raskine L, Cambau E. Human infections due to nontuberculous mycobacteria: the infectious diseases and clinical microbiology specialists' point of view. Future Microbiol. 2015;10:1467-83. [PMID: 26344005] doi:10.2217/fmb.15.64

Koh WJ, Jeong BH, Kim SY, Jeon K, Park KU, Jhun BW, et al. Mycobacterial characteristics and treatment outcomes in Mycobacterium abscessus lung disease. Clin Infect Dis. 2017;64:309-316. [PMID: 28011608] doi:10.1093/cid/ciw724

Fungal Infections

Azie N, Neofytos D, Pfaller M, Meier-Kriesche HU, Quan SP, Horn D. The PATH (Prospective Antifungal Therapy) Alliance® registry and invasive fungal infections: update 2012. Diagn Microbiol Infect Dis. 2012;73:293-300. [PMID: 22789847] doi:10.1016/j.diagmicrobio.2012.06.012

Castillo CG, Kauffman CA, Miceli MH. Blastomycosis. Infect Dis Clin North Am. 2016;30:247-64. [PMID: 26739607] doi:10.1016/j.idc.2015.10.002

Farmakiotis D, Kontoyiannis DP. Mucormycoses. Infect Dis Clin North Am. 2016;30:143-63. [PMID: 26897065] doi:10.1016/j.idc.2015.10.011

Mahajan VK. Sporotrichosis: an overview and therapeutic options. Dermatol Res Pract. 2014;2014:272376. [PMID: 25614735] doi:10.1155/2014/272376

Maziarz EK, Perfect JR. Cryptococcosis. Infect Dis Clin North Am. 2016;30:179-206. [PMID: 26897067] doi:10.1016/j.idc.2015.10.006

McCarty TP, Pappas PG. Invasive candidiasis. Infect Dis Clin North Am. 2016;30:103-24. [PMID: 26739610] doi:10.1016/j.idc.2015.10.013

Pappas PG, Kauffman CA, Andes DR, Clancy CJ, Marr KA, Ostrosky-Zeichner L, et al. Executive summary: clinical practice guideline for the management of candidiasis: 2016 update by the Infectious Diseases Society of America. Clin Infect Dis. 2016;62:409-17. [PMID: 26810419] doi:10.1093/cid/civ1194

Patterson TF, Thompson GR 3rd, Denning DW, Fishman JA, Hadley S, Herbrecht R, et al. Executive summary: practice guidelines for the diagnosis and management of aspergillosis: 2016 update by the Infectious Diseases Society of America. Clin Infect Dis. 2016;63:433-42. [PMID: 27481947] doi:10.1093/cid/ciw444

Stockamp NW, Thompson GR 3rd. Coccidioidomycosis. Infect Dis Clin North Am. 2016;30:229-46. [PMID: 26739609] doi:10.1016/j.idc.2015.10.008

Wheat LJ, Azar MM, Bahr NC, Spec A, Relich RF, Hage C. Histoplasmosis. Infect Dis Clin North Am. 2016;30:207-27. [PMID: 26897068] doi:10.1016/j.idc.2015.10.009

Sexually Transmitted Infections

Bibbins-Domingo K, Grossman DC, Curry SJ, Davidson KW, Epling JW Jr, García FA, et al; US Preventive Services Task Force (USPSTF). Screening for syphilis infection in nonpregnant adults and adolescents: US Preventive Services Task Force Recommendation Statement. JAMA. 2016;315:2321–7. [PMID: 27272583] doi:10.1001/jama.2016.5824

Brunham RC, Gottlieb SL, Paavonen J. Pelvic inflammatory disease. N Engl J Med. 2015;372:2039–48. [PMID: 25992748] doi:10.1056/NEJMra1411426

Gnann JW Jr, Whitley RJ. Clinical practice. Genital herpes. N Engl J Med. 2016;375:666–74. [PMID: 27532832] doi:10.1056/NEJMcp1603178

Moi H, Blee K, Horner PJ. Management of non-gonococcal urethritis. BMC Infect Dis. 2015;15:294. [PMID: 26220178] doi:10.1186/s12879-015-1043-4

Stoner BP, Cohen SE. Lymphogranuloma venereum 2015: clinical presentation, diagnosis, and treatment. Clin Infect Dis. 2015;61 Suppl 8:S865–73. [PMID: 26602624] doi:10.1093/cid/civ756

Workowski KA, Bolan GA; Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2015. MMWR Recomm Rep. 2015;64:1–137. [PMID: 26042815]

Osteomyelitis

American College of Radiology Appropriateness Criteria. Expert Panel on Musculoskeletal Imaging: suspected osteomyelitis, septic arthritis or soft tissue infection (excluding spine and diabetic foot) https://acsearch.acr.org/list (accessed 2/2/2017)

Berbari EF, Kanj SS, Kowalski TJ, Darouiche RO, Widmer AF, Schmitt SK, et al. 2015 Infectious Diseases Society of America (IDSA) clinical practice guidelines for the diagnosis and treatment of native vertebral osteomyelitis in adults. Clin Infect Dis. 2015;61:e26–46. [PMID: 26229122] doi:10.1093/cid/civ482

Choi SH, Sung H, Kim SH, Lee SO, Lee SH, Kim YS, et al. Usefulness of a direct 16S rRNA gene PCR assay of percutaneous biopsies or aspirates for etiological diagnosis of vertebral osteomyelitis. Diagn Microbiol Infect Dis. 2014;78:75–8. [PMID: 24231384] doi:10.1016/j.diagmicrobio.2013.10.007

Conterno LO, Turchi MD. Antibiotics for treating chronic osteomyelitis in adults. Cochrane Database Syst Rev. 2013:CD004439. [PMID: 24014191] doi:10.1002/14651858.CD004439.pub3

Grigoropoulou P, Eleftheriadou I, Jude EB, Tentolouris N. Diabetic foot infections: an update in diagnosis and management. Curr Diab Rep. 2017;17:3. [PMID: 28101794] doi:10.1007/s11892-017-0831-1

Lipsky BA, Berendt AR, Cornia PB, Pile JC, Peters EJ, Armstrong DG, et al; Infectious Diseases Society of America. 2012 Infectious Diseases Society of America clinical practice guideline for the diagnosis and treatment of diabetic foot infections. Clin Infect Dis. 2012;54:e132–73. [PMID: 22619242] doi:10.1093/cid/cis346

Mears SC, Edwards PK. Bone and joint infections in older adults. Clin Geriatr Med. 2016;32:555–70. [PMID: 27394023] doi:10.1016/j.cger.2016.02.003

Fever of Unknown Origin

Cunha BA, Lortholary O, Cunha CB. Fever of unknown origin: a clinical approach. Am J Med. 2015;128:1138.e1–1138.e15. [PMID: 26093175] doi:10.1016/j.amjmed.2015.06.001

Primary Immunodeficiencies

Abbott JK, Gelfand EW. Common variable immunodeficiency: diagnosis, management, and treatment. Immunol Allergy Clin North Am. 2015;35:637–58. [PMID: 26454311] doi:10.1016/j.iac.2015.07.009

Abolhassani H, Sagvand BT, Shokuhfar T, Mirminachi B, Rezaei N, Aghamohammadi A. A review on guidelines for management and treatment of common variable immunodeficiency. Expert Rev Clin Immunol. 2013;9:561–74; quiz 575. [PMID: 23730886] doi:10.1586/eci.13.30

Audemard-Verger A, Descloux E, Ponard D, Deroux A, Fantin B, Fieschi C, et al. Infections revealing complement deficiency in adults: a French nationwide study enrolling 41 patients. Medicine (Baltimore). 2016;95:e3548. [PMID: 27175654] doi:10.1097/MD.0000000000003548

Azar AE, Ballas ZK. Evaluation of the adult with suspected immunodeficiency. Am J Med. 2007;120:764–8. [PMID: 17765042]

Frazer-Abel A, Sepiashvili L, Mbughuni MM, Willrich MA. Overview of laboratory testing and clinical presentations of complement deficiencies and dysregulation. Adv Clin Chem. 2016;77:1–75. [PMID: 27717414] doi:10.1016/bs.acc.2016.06.001

Bioterrorism

Adalja AA, Toner E, Inglesby TV. Clinical management of potential bioterrorism-related conditions. N Engl J Med. 2015;372:954–62. [PMID: 25738671] doi:10.1056/NEJMra1409755

Breman JG, Henderson DA. Diagnosis and management of smallpox. N Engl J Med. 2002;346:1300–8. [PMID: 11923491]

Hendricks KA, Wright ME, Shadomy SV, Bradley JS, Morrow MG, Pavia AT, et al; Workgroup on Anthrax Clinical Guidelines. Centers for Disease Control and Prevention expert panel meetings on prevention and treatment of anthrax in adults. Emerg Infect Dis. 2014;20. [PMID: 24447897] doi:10.3201/eid2002.130687

McFee RB. Viral hemorrhagic fever viruses. Dis Mon. 2013;59:410–25. [PMID: 24314803] doi:10.1016/j.disamonth.2013.10.003

Prentice MB, Rahalison L. Plague. Lancet. 2007;369:1196–207. [PMID: 17416264]

Thomas LD, Schaffner W. Tularemia pneumonia. Infect Dis Clin North Am. 2010;24:43–55. [PMID: 20171544] doi:10.1016/j.idc.2009.10.012

Zhang JC, Sun L, Nie QH. Botulism, where are we now? Clin Toxicol (Phila). 2010;48:867–79. [PMID: 21171845] doi:10.3109/15563650.2010.535003

Travel Medicine

Delord M, Socolovschi C, Parola P. Rickettsioses and Q fever in travelers (2004–2013). Travel Med Infect Dis. 2014;12:443–58. [PMID: 25262433] doi:10.1016/j.tmaid.2014.08.006

Franco MP, Mulder M, Gilman RH, Smits HL. Human brucellosis. Lancet Infect Dis. 2007;7:775–86. [PMID: 18045560]

Freedman DO, Chen LH, Kozarsky PE. Medical considerations before international travel. N Engl J Med. 2016;375:247–60. [PMID: 27468061] doi:10.1056/NEJMra1508815

Giddings SL, Stevens AM, Leung DT. Traveler's diarrhea. Med Clin North Am. 2016;100:317–30. [PMID: 26900116] doi:10.1016/j.mcna.2015.08.017

Hahn WO, Pottinger PS. Malaria in the traveler: how to manage before departure and evaluate upon return. Med Clin North Am. 2016;100:289–302. [PMID: 26900114] doi:10.1016/j.mcna.2015.09.008

Patterson J, Sammon M, Garg M. Dengue, Zika and chikungunya: emerging arboviruses in the New World. West J Emerg Med. 2016;17:671–679. [PMID: 27833670]

Petersen LR, Jamieson DJ, Powers AM, Honein MA. Zika virus. N Engl J Med. 2016;374:1552–63. [PMID: 27028561] doi:10.1056/NEJMra1602113

Sanford CA, Jong EC. Immunizations. Med Clin North Am. 2016;100:247–59. [PMID: 26900111] doi:10.1016/j.mcna.2015.08.018

Suwanmanee S, Luplertlop N. Dengue and Zika viruses: lessons learned from the similarities between these Aedes mosquito-vectored arboviruses. J Microbiol. 2017;55:81–89. [PMID: 28120186] doi:10.1007/s12275-017-6494-4

Weaver SC, Lecuit M. Chikungunya virus and the global spread of a mosquito-borne disease. N Engl J Med. 2015;372:1231–9. [PMID: 25806915] doi:10.1056/NEJMra1406035

Infectious Gastrointestinal Syndromes

Debast SB, Bauer MP, Kuijper EJ; European Society of Clinical Microbiology and Infectious Diseases. European Society of Clinical Microbiology and Infectious Diseases: update of the treatment guidance document for Clostridium difficile infection. Clin Microbiol Infect. 2014;20 Suppl 2:1–26. [PMID: 24118601] doi:10.1111/1469-0691.12418

DuPont HL. Acute infectious diarrhea in immunocompetent adults. N Engl J Med. 2014;370:1532–40. [PMID: 24738670] doi:10.1056/NEJMra1301069

McDonald LC, Gerding DN, Johnson S, Bakken JS, Carroll KC, Coffin SE, et al. Clinical practice guidelines for *Clostridium difficile* infection in adults and children: 2017 update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA). Clin Infect Dis. 2018 Feb 15. [Epub ahead of print] [PMID: 29462280] doi:10.1093/cid/cix1085.

Riddle MS, DuPont HL, Connor BA. ACG clinical guideline: diagnosis, treatment, and prevention of acute diarrheal infections in adults. Am J Gastroenterol. 2016;111:602–22. [PMID: 27068718] doi:10.1038/ajg.2016.126

Shane AL, Mody RK, Crump JA, Tarr PI, Steiner TS, Kotloff K, et al. 2017 Infectious Diseases Society of America clinical practice guidelines for the diagnosis and management of infectious diarrhea. Clin Infect Dis. 2017;65:e45–e80. [PMID: 29053792] doi:10.1093/cid/cix669

Surawicz CM, Brandt LJ, Binion DG, Ananthakrishnan AN, Curry SR, Gilligan PH, et al. Guidelines for diagnosis, treatment, and prevention of Clostridium difficile infections. Am J Gastroenterol. 2013;108:478–98; quiz 499. [PMID: 23439232] doi:10.1038/ajg.2013.4

Infections in Transplant Recipients

Ariza-Heredia EJ, Nesher L, Chemaly RF. Cytomegalovirus diseases after hematopoietic stem cell transplantation: a mini-review. Cancer Lett. 2014;342:1–8. [PMID: 24041869] doi:10.1016/j.canlet.2013.09.004

Fishman JA. From the classic concepts to modern practice. Clin Microbiol Infect. 2014;20 Suppl 7:4–9. [PMID: 24528498] doi:10.1111/1469-0691.12593

Fleming S, Yannakou CK, Haeusler GM, Clark J, Grigg A, Heath CH, et al. Consensus guidelines for antifungal prophylaxis in haematological

malignancy and haemopoietic stem cell transplantation, 2014. Intern Med J. 2014;44:1283-97. [PMID: 25482741] doi:10.1111/imj.12595

Lumbreras C, Manuel O, Len O, ten Berge IJ, Sgarabotto D, Hirsch HH. Cytomegalovirus infection in solid organ transplant recipients. Clin Microbiol Infect. 2014;20 Suppl 7:19-26. [PMID: 26451404]

Rubin LG, Levin MJ, Ljungman P, Davies EG, Avery R, Tomblyn M, et al; Infectious Diseases Society of America. 2013 IDSA clinical practice guideline for vaccination of the immunocompromised host. Clin Infect Dis. 2014;58:309-18. [PMID: 24421306] doi:10.1093/cid/cit816

Ullmann AJ, Schmidt-Hieber M, Bertz H, Heinz WJ, Kiehl M, Krüger W, et al; Infectious Diseases Working Party of the German Society for Hematology and Medical Oncology (AGIHO/DGHO) and the DAG-KBT (German Working Group for Blood and Marrow Transplantation). Infectious diseases in allogeneic haematopoietic stem cell transplantation: prevention and prophylaxis strategy guidelines 2016. Ann Hematol. 2016;95:1435-55. [PMID: 27339055] doi:10.1007/s00277-016-2711-1

Health Care–Associated Infections

Allegranzi B, Bischoff P, de Jonge S, Kubilay NZ, Zayed B, Gomes SM, et al; WHO Guidelines Development Group. New WHO recommendations on preoperative measures for surgical site infection prevention: an evidence-based global perspective. Lancet Infect Dis. 2016;16:e276-e287. [PMID: 27816413] doi:10.1016/S1473-3099(16)30398-X

Chenoweth CE, Saint S. Urinary tract infections. Infect Dis Clin North Am. 2016;30:869-885. [PMID: 27816141] doi:10.1016/j.idc.2016.07.007

Holland TL, Arnold C, Fowler VG Jr. Clinical management of Staphylococcus aureus bacteremia: a review. JAMA. 2014;312:1330-41. [PMID: 25268440] doi:10.1001/jama.2014.9743

Kalil AC, Metersky ML, Klompas M, Muscedere J, Sweeney DA, Palmer LB, et al. Management of adults with hospital-acquired and ventilator-associated pneumonia: 2016 clinical practice guidelines by the Infectious Diseases Society of America and the American Thoracic Society. Clin Infect Dis. 2016;63:e61-e111. [PMID: 27418577] doi:10.1093/cid/ciw353

Magill SS, Edwards JR, Bamberg W, Beldavs ZG, Dumyati G, Kainer MA, et al; Emerging Infections Program Healthcare-Associated Infections and Antimicrobial Use Prevalence Survey Team. Multistate point-prevalence survey of health care-associated infections. N Engl J Med. 2014;370:1198-208. [PMID: 24670166] doi:10.1056/NEJMoa1306801

Marston HD, Dixon DM, Knisely JM, Palmore TN, Fauci AS. Antimicrobial resistance. JAMA. 2016;316:1193-1204. [PMID: 27654605] doi:10.1001/jama.2016.11764

Meddings J, Saint S, Fowler KE, Gaies E, Hickner A, Krein SL, et al. The Ann Arbor criteria for appropriate urinary catheter use in hospitalized medical patients: results obtained by using the RAND/UCLA appropriateness method. Ann Intern Med. 2015;162:S1-34. [PMID: 25938928] doi:10.7326/M14-1304

Nuckols TK, Keeler E, Morton SC, Anderson L, Doyle B, Booth M, et al. Economic evaluation of quality improvement interventions for bloodstream infections related to central catheters: a systematic review. JAMA Intern Med. 2016;176:1843-1854. [PMID: 27775764] doi:10.1001/jamainternmed.2016.6610

Weiner LM, Fridkin SK, Aponte-Torres Z, Avery L, Coffin N, Dudeck MA, et al. Vital signs: preventing antibiotic-resistant infections in hospitals - United States, 2014. MMWR Morb Mortal Wkly Rep. 2016;65:235-41. [PMID: 26963489] doi:10.15585/mmwr.mm6509e1

Yokoe DS, Anderson DJ, Berenholtz SM, Calfee DP, Dubberke ER, Ellingson KD, et al. A compendium of strategies to prevent healthcare-associated infections in acute care hospitals: 2014 updates. Infect Control Hosp Epidemiol. 2014;35 Suppl 2:S21-31. [PMID: 25376067]

HIV/AIDS

Brown TT, Hoy J, Borderi M, Guaraldi G, Renjifo B, Vescini F, et al. Recommendations for evaluation and management of bone disease in HIV. Clin Infect Dis. 2015;60:1242-51. [PMID: 25609682] doi:10.1093/cid/civ010

Centers for Disease Control and Prevention. Preexposure prophylaxis for the prevention of HIV infection in the United States—2014. A clinical practice guideline. Available at https://stacks.cdc.gov/view/cdc/23109.

Centers for Disease Control and Prevention. Updated guidelines for antiretroviral postexposure prophylaxis after sexual, injection drug use, or other nonoccupational exposure to HIV—United States, 2016. Available at https://stacks.cdc.gov/view/cdc/38856.

Centers for Disease Control and Prevention and Association of Public Health Laboratories. Laboratory testing for the diagnosis of HIV infection: updated recommendations. Available at http://dx.doi.org/10.15620/cdc.23447. Published June 27, 2014. Available at http://www.cdc.gov/hiv/testing/laboratorytests.html.

Günthard HF, Saag MS, Benson CA, del Rio C, Eron JJ, Gallant JE, et al. Antiretroviral drugs for treatment and prevention of HIV infection in adults: 2016 recommendations of the International Antiviral Society-USA Panel. JAMA. 2016;316:191-210. [PMID: 27404187] doi:10.1001/jama.2016.8900

Kay ES, Batey DS, Mugavero MJ. The HIV treatment cascade and care continuum: updates, goals, and recommendations for the future. AIDS Res Ther. 2016;13:35. [PMID: 27826353]

Lucas GM, Ross MJ, Stock PG, Shlipak MG, Wyatt CM, Gupta SK, et al; HIV Medicine Association of the Infectious Diseases Society of America. Clinical practice guideline for the management of chronic kidney disease in patients infected with HIV: 2014 update by the HIV Medicine Association of the Infectious Diseases Society of America. Clin Infect Dis. 2014;59:e96-138. [PMID: 25234519] doi:10.1093/cid/ciu617

Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. Updated March 27, 2018. Available at https://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-arv/0

Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents. Guidelines for the prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. Updated March 7, 2018. Available at https://aidsinfo.nih.gov/guidelines/html/4/adult-and-adolescent-opportunistic-infection/0

Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission. Recommendations for use of antiretroviral drugs in pregnant HIV-1 infected women for maternal health and interventions to reduce perinatal HIV transmission in the United States. Updated March 27, 2018. Available at https://aidsinfo.nih.gov/guidelines/html/3/perinatal/0

Yarchoan R, Uldrick TS. HIV-associated cancers and related diseases. N Engl J Med. 2018;378:1029-1041. [PMID: 29539283] doi:10.1056/NEJMra1615896

Viral Infections

Cohen JI. Clinical practice: Herpes zoster. N Engl J Med. 2013;369:255-63. [PMID: 23863052] doi:10.1056/NEJMcp1302674

Gnann JW Jr, Whitley RJ. Clinical practice. Genital herpes. N Engl J Med. 2016;375:666-74. [PMID: 27532832] doi:10.1056/NEJMcp1603178

Haagmans BL, Al Dhahiry SH, Reusken CB, Raj VS, Galiano M, Myers R, et al. Middle East respiratory syndrome coronavirus in dromedary camels: an outbreak investigation. Lancet Infect Dis. 2014;14:140-5. [PMID: 24355866] doi:10.1016/S1473-3099(13)70690-X

Harper SA, Bradley JS, Englund JA, File TM, Gravenstein S, Hayden FG, et al; Expert Panel of the Infectious Diseases Society of America. Seasonal influenza in adults and children—diagnosis, treatment, chemoprophylaxis, and institutional outbreak management: clinical practice guidelines of the Infectious Diseases Society of America. Clin Infect Dis. 2009;48:1003-32. [PMID: 19281331] doi:10.1086/598513

Paules C, Subbarao K. Influenza. Lancet. 2017. [PMID: 28302313] doi:10.1016/S0140-6736(17)30129-0

Zaki AM, van Boheemen S, Bestebroer TM, Osterhaus AD, Fouchier RA. Isolation of a novel coronavirus from a man with pneumonia in Saudi Arabia. N Engl J Med. 2012;367:1814-20. [PMID: 23075143] doi:10.1056/NEJMoa1211721

Stewardship and Emerging Resistance

Barlam TF, Cosgrove SE, Abbo LM, MacDougall C, Schuetz AN, Septimus EJ, et al. Implementing an antibiotic stewardship program: guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America. Clin Infect Dis. 2016;62:e51-77. [PMID: 27080992] doi:10.1093/cid/ciw118

Deak D, Outterson K, Powers JH, Kesselheim AS. Progress in the fight against multidrug-resistant bacteria? A review of U.S. Food and Drug Administration-approved antibiotics, 2010-2015. Ann Intern Med. 2016;165:363-72. [PMID: 27239977] doi:10.7326/M16-0291

Doi Y, Paterson DL. Carbapenemase-producing Enterobacteriaceae. Semin Respir Crit Care Med. 2015;36:74-84. [PMID: 25643272] doi:10.1055/s-0035-1544208

Petrak RM, Skorodin NC, Fliegelman RM, Hines DW, Chundi VV, Harting BP. Value and clinical impact of an infectious disease-supervised outpatient parenteral antibiotic therapy program. Open Forum Infect Dis. 2016;3:ofw193. [PMID: 27807591]

Ritchie DJ, Garavaglia-Wilson A. A review of intravenous minocycline for treatment of multidrug-resistant Acinetobacter infections. Clin Infect Dis. 2014;59 Suppl 6:S374-80. [PMID: 25371513] doi:10.1093/cid/ciu613

Schmitt S, McQuillen DP, Nahass R, Martinelli L, Rubin M, Schwebke K, et al. Infectious diseases specialty intervention is associated with decreased mortality and lower healthcare costs. Clin Infect Dis. 2014;58:22-8. [PMID: 24072931] doi:10.1093/cid/cit610

Infectious Disease Self-Assessment Test

This self-assessment test contains one-best-answer multiple-choice questions. Please read these directions carefully before answering the questions. Answers, critiques, and bibliographies immediately follow these multiple-choice questions. The American College of Physicians (ACP) is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

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Successful completion of the CME activity, which includes participation in the evaluation component, enables the participant to earn up to 25 medical knowledge MOC points in the American Board of Internal Medicine's Maintenance of Certification (MOC) program. It is the CME activity provider's responsibility to submit participant completion information to ACCME for the purpose of granting MOC credit.

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CME credits and MOC points are available from the publication date of December 31, 2018, until December 31, 2021. You may submit your answer sheet or enter your answers online at any time during this period.

Directions

*Each of the numbered items is followed by lettered answers. Select the **ONE** lettered answer that is **BEST** in each case.*

Item 1

A 68-year old man is being evaluated for measures to decrease his risk of acquiring a surgical site infection; he is scheduled for coronary artery bypass graft surgery in 5 weeks for limiting chronic angina despite maximal medical therapy. Medical history includes chronic stable angina, hyperlipidemia, hypertension, and diabetes. Medications are low-dose aspirin, propranolol, isosorbide dinitrate, ranolazine, chlorthalidone, lisinopril, and atorvastatin.

On physical examination, blood pressure is 126/72 mm Hg; all other vital signs are normal. On cardiac examination, an S_4 is present. The remainder of the examination is noncontributory.

Which of the following is the most appropriate measure to prevent surgical site infection?

(A) Evaluate for *Staphylococcus aureus* nasal carriage
(B) Provide postoperative vancomycin prophylaxis for 7 days
(C) Provide preoperative vancomycin prophylaxis
(D) Shave patient's chest hair the morning of surgery

H

Item 2

A 25-year old man is evaluated in the emergency department for fever, productive cough, dyspnea, and pleuritic chest pain that began several days ago. He reports no other symptoms. Intravenous ceftriaxone and oral azithromycin are initiated, and he is hospitalized. Medical history is significant for a recent diagnosis of HIV infection, for which he began antiretroviral therapy 1 month ago. Other medications are lamivudine, abacavir, and dolutegravir.

On physical examination, temperature is 39.2 °C (102.6 °F), blood pressure is 136/84 mm Hg, pulse rate is 110/min, and respiration rate is 20/min. Oxygen saturation is 90% breathing ambient air. Cardiac examination is normal, and the lungs are clear bilaterally.

Laboratory studies at the time of HIV diagnosis showed a viral load of 95,420 copies/mL and CD4 cell count of 256/µL. The interferon-γ release assay for tuberculosis was indeterminate because of inadequate response to the positive control. One week ago, HIV viral load was 1077 copies/mL and CD4 cell count was 313/µL.

A chest radiograph shows an infiltrate in the right middle lobe and bilateral hilar enlargement.

Sputum acid-fast bacilli smear shows acid-fast bacilli; culture results are pending.

Which of the following is the most appropriate management?

(A) Await culture results
(B) Pause antiretroviral therapy
(C) Start prednisone
(D) Start rifabutin, isoniazid, ethambutol, and pyrazinamide

Item 3

A 27-year-old man is evaluated in the hospital for a 1-month history of fever, drenching night sweats, malaise, fatigue, chest pain, and a nonproductive cough. He recently completed a 7-day course of levofloxacin with no improvement in symptoms. The patient is in the military, works as a car mechanic on base, and is stationed in Bakersfield, California.

On physical examination, temperature is 37.8 °C (100.0 °F), blood pressure is 128/76 mm Hg, pulse rate is 99/min, respiration rate is 24/min, and oxygen saturation is 92% with the patient breathing room air. The remainder of the physical examination is unremarkable.

Laboratory studies:

Hemoglobin	12.4 g/dL (124 g/L)
Leukocyte count	11,900/µL (11.9×10^9/L), with 30% eosinophils, 60% neutrophils, and 10% lymphocytes
Interferon γ release assay	Negative

A chest radiograph shows a right lower lobe infiltrate and ipsilateral hilar lymphadenopathy.

Which of the following is the most likely diagnosis?

(A) Coccidioidomycosis
(B) Sarcoidosis
(C) *Streptococcus pneumoniae* pneumonia
(D) Tuberculosis

Item 4

H

A 44-year old man is evaluated in the emergency department in January for a 3-day history of dyspnea, cough, and fever. Medical history is otherwise unremarkable, and he takes no medications.

On physical examination, temperature is 38.5 °C (101.3 °F), blood pressure is 118/80 mm Hg, pulse rate is 113/min, and respiration rate is 33/min. Oxygen saturation is 89% breathing 6 L/min oxygen by nasal cannula. The patient appears uncomfortable and is oriented only to person. Breath sounds are decreased bilaterally with scattered crackles. No rash is noted.

Laboratory studies:

Leukocyte count	19,000/µL (19×10^9/L)
Platelet count	274,000/µL (274×10^9/L)
Blood urea nitrogen	36 mg/dL (12.9 mmol/L)
Creatinine	1.45 mg/dL (128 µmol/L)

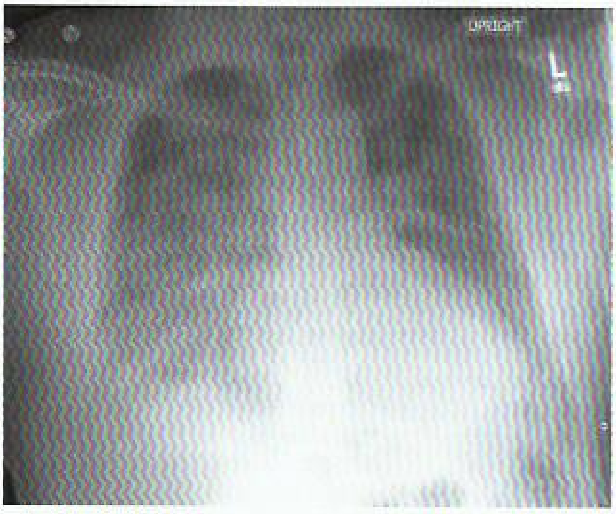
Sputum Gram stain shows 2+ polymorphonuclear cells and 1+ epithelial cells; no organisms are seen. A respiratory viral panel from a nasopharyngeal swab is positive for rhinovirus.

A chest radiograph is shown on the next page.

The patient will be transferred to the ICU.

Which of the following is the most appropriate treatment?

(A) Azithromycin
(B) Ceftazidime plus azithromycin
(C) Ceftriaxone plus levofloxacin
(D) Piperacillin-tazobactam plus ciprofloxacin



ITEM 4

Item 5

A 43-year-old man is seen in follow-up for fever up to 38.3 °C (101 °F) occurring periodically over the past 3 months. He has no associated symptoms other than fatigue. He reports no recent travel, animal exposures, or tick or insect bites. He does not eat raw meats, raw seafood, or unpasteurized dairy products. He returns for further evaluation after initial testing. Family history is negative for undiagnosed fevers. He takes no medications.

On physical examination, temperature is 37.8 °C (100.1 °F), blood pressure is 114/72 mm Hg, pulse rate is 88/min, and respiration rate is 14/min. A complete physical examination is unremarkable.

Laboratory studies:

Erythrocyte sedimentation rate	10 mm/h
Hematocrit	44%
Leukocyte count	4200/μL (4.2×10^9/L) with a normal differential
Platelet count	320,000/μL (320×10^9/L)
Alkaline phosphatase	Normal
Lactate dehydrogenase	Normal
Kidney and liver chemistry tests	Normal
Urinalysis	Normal

HIV testing is negative. An interferon-γ release assay for tuberculosis is negative. Three sets of blood cultures are negative.

A chest radiograph is normal.

Which of the following is the most appropriate diagnostic test to perform next?

(A) Bone marrow biopsy
(B) CT of the abdomen and pelvis
(C) Liver biopsy
(D) Lumbar puncture

Item 6

A 34-year-old woman is evaluated in the emergency department for a 2-day history of fever, severe headache, malaise, fatigue, dry cough, and shortness of breath. She underwent deceased-donor kidney transplantation 1 year ago; 2 weeks ago, she developed acute graft rejection and was treated with alemtuzumab. Other medications are tacrolimus, prednisone, and trimethoprim-sulfamethoxazole.

On physical examination, temperature is 37.5 °C (99.5 °F), blood pressure is 80/53 mm Hg, pulse rate is 90/min, and respiration rate is 22/min. Bibasilar crackles are heard on auscultation of the lungs.

Initial laboratory studies show a hemoglobin level of 6.9 mg/dL (69 g/L) and a leukocyte count of 4800/μL (4.8×10^9/L).

A head CT scan shows multiple acute infarcts in the frontal lobe and cerebellum without superimposed hematomas. A lumbar puncture is performed.

Cerebrospinal fluid studies:

Cell count	2 erythrocytes/hpf; 77 leukocytes/hpf, with 90% neutrophils and 10% lymphocytes
Glucose	80 mg/dL (4.4 mmol/L)
Pressure (opening)	140 mm H_2O
Protein	100 mg/dL (1000 mg/L)
Cryptococcal antigen	Negative
Gram stain	No organisms

A chest radiograph shows diffuse bilateral lung nodules.

Which of the following is the most appropriate next diagnostic test?

(A) Brain biopsy
(B) Bronchoscopy with biopsy and bronchoalveolar lavage
(C) Fungal blood culture
(D) Serum galactomannan assay

Item 7

A 19-year-old woman is evaluated in the emergency department for a 2-day history of fever, headaches, and jaundice. She vacationed in Hawaii 1 month ago and reports swimming in lakes and rivers. She was diagnosed with a flu-like illness 2 weeks ago that resolved spontaneously. She reports no history of a rash. She is sexually active with one partner. She takes no medications other than an oral contraceptive.

On physical examination, she is alert and oriented. Temperature is 38.9 °C (102 °F), blood pressure is 92/60 mm Hg, pulse rate is 124/min, and respiration rate is 24/min. Generalized lymphadenopathy, conjunctival suffusion, and scleral icterus are noted. She has photophobia, and passive neck flexion elicits resistance and discomfort. The remainder of the examination is unremarkable.

Laboratory studies:

Bilirubin, total	5.6 mg/dL (95.8 μmol/L)
Creatinine	2.3 mg/dL (203 μmol/L)
Cerebrospinal fluid	
Leukocyte count	152/μL (152×10^6/L)
Glucose	72 mg/dL (4.0 mmol/L)
Protein	78 mg/dL (780 mg/L)

Cerebrospinal fluid Gram stain is negative and culture results are pending.

H CONT.

Which of the following is the most likely cause of the patient's findings?

(A) Acute retroviral syndrome
(B) Herpes simplex virus infection
(C) Leptospirosis
(D) Neurosyphilis

H

Item 8

A 66-year-old woman is evaluated in the emergency department with a 2-day history of fever and nonbloody diarrhea occurring several times a day. She recently completed a 10-day course of cephalexin for cellulitis of the leg.

On physical examination, temperature is 39.0 °C (102.2 °F), blood pressure is 98/60 mm Hg, pulse rate is 110/min, and respiration rate is 23/min. She appears uncomfortable but is not confused. Her abdomen is distended and bowel sounds are decreased. She has tenderness and abdominal guarding to palpation. Cellulitis has resolved.

Laboratory studies:

Leukocyte count	30,000/µL (30×10^9/L) (with 80% neutrophils, 15% band forms, and 5% lymphocytes)
Albumin	2.5 mg/dL (25 g/L)
Creatinine	2.5 mg/dL (221 µmol/L) (baseline 1.0 mg/dL [88.4 µmol/L])
Lactate	2.8 mEq/L (2.8 mmol/L)

Stool polymerase chain reaction assay is positive for *Clostridium difficile* toxin gene. Abdominal imaging reveals evidence of toxic megacolon.

The patient is admitted to the ICU, and a surgical consultation is requested.

Which of the following is the most appropriate medical treatment?

(A) Fecal microbiota transplant
(B) Oral metronidazole
(C) Oral vancomycin
(D) Oral vancomycin and intravenous metronidazole
(E) Oral vancomycin and oral metronidazole

Item 9

A 44-year-old woman is evaluated for persistent fatigue, headache, myalgia, and arthralgia. Early localized Lyme disease was diagnosed 2 months ago after the patient returned from a camping trip in western New Jersey with the symptoms described and a skin eruption of erythema migrans. She was treated with a 14-day course of doxycycline with resolution of the cutaneous lesions but continuation of the other symptoms, which now are adversely affecting her work and personal life. Her only medication is ibuprofen.

On physical examination, vital signs are normal. The patient has full range of motion of the joints. No skin lesions, synovitis, or effusions are noted.

Results of laboratory studies, including a complete blood count, comprehensive metabolic panel, and lactate dehydrogenase measurement, are all within normal limits.

Which of the following is the most likely diagnosis?

(A) Anaplasmosis
(B) Babesiosis
(C) Late-stage Lyme disease
(D) Post-Lyme disease syndrome
(E) Powassan virus infection

Item 10

A 67-year-old man is evaluated for a chronic, nonhealing ulcer on his left foot of 3 months' duration. The patient states he was at a local sauna when he sustained an abrasion to the bottom of his foot after stepping on a sharp object. He subsequently developed an ulcer at the site of the injury and received several courses of antibiotics, including trimethoprim-sulfamethoxazole, doxycycline, and cephalexin, with no improvement. The ulcer continues to expand in size and deepen. Medical history is notable for hypertension and a 40-pack-year smoking history. His only medication is hydrochlorothiazide.

On physical examination, the vital signs are normal except for a temperature of 37.3 °C (99.2 °F). The legs and feet are without edema or discoloration. Pedal and popliteal pulses are symmetrical and intact. Lower extremity sensation is intact. He has a 2- × 2-cm ulcerated lesion on the plantar aspect of the metatarsal region of the great toe, with surrounding erythema, yellowish discharge, and firm edges.

Which of the following is the most likely cause of his ulcer?

(A) *Mycobacterium avium*
(B) *Mycobacterium fortuitum*
(C) *Mycobacterium kansasii*
(D) *Mycobacterium leprae*

Item 11

A 26-year-old woman is evaluated in the emergency department for lower abdominal pain with vaginal discharge. She reports no nausea or vomiting but noted vaginal bleeding after intercourse the previous night. She is sexually active, with two partners in the past 3 months, but she does not use condoms consistently. She has an intrauterine device for contraception and takes no medications.

On physical examination, vital signs are normal. Pelvic examination is shown; uterine and cervical motion tenderness are noted, but she has no adnexal tenderness or masses.

A urine pregnancy test is negative. Samples are obtained for nucleic acid amplification testing for *Neisseria gonorrhoeae* and *Chlamydia trachomatis*.

Which of the following is the most appropriate empiric treatment?

(A) Intramuscular ceftriaxone plus oral doxycycline
(B) Intravenous cefoxitin plus oral doxycycline
(C) Intravenous clindamycin plus intravenous gentamicin
(D) Oral amoxicillin-clavulanate plus oral doxycycline

H Item 12

A 72-year-old man undergoes preprocedural evaluation. He is scheduled to undergo cystoscopy and possible biopsy in follow-up for a previously diagnosed non-muscle invasive bladder cancer followed by an elective right total hip arthroplasty for chronic hip pain. He is otherwise asymptomatic. Medical history is significant for diabetes mellitus, hypertension, kidney transplantation, and osteoarthritis. Medications are metformin, amlodipine, pravastatin, prednisone, and tacrolimus.

On physical examination, vital signs are normal. External rotation of the right hip elicits pain. The examination is otherwise normal.

On microscopic urinalysis, leukocyte count is 20 to 40/hpf, erythrocyte count is 0 to 1/hpf, 2+ bacteria are present, and no squamous epithelial cells are seen. Urine culture grew 10,000 to 50,000 colony-forming units of *Proteus mirabilis*.

Kidney ultrasonography is unremarkable.

Which of the following is the primary indication for antimicrobial therapy in this patient?

(A) Cystoscopy and biopsy
(B) Diabetes mellitus
(C) Kidney transplant
(D) Total hip arthroplasty

H Item 13

A 33-year-old woman is evaluated after sustaining a needle-stick puncture in an infusion clinic, where she works as a nurse. The needle was being placed for intravenous therapy and had blood on it; it is from a patient at the clinic who is known to have HIV infection and is taking antiretrovirals, but the recent viral load is unknown. The nurse has already cleaned her wound. Medical history is unremarkable, and she takes no medications.

On physical examination, vital signs are normal, and other examination findings are noncontributory.

Which of the following is the most appropriate immediate management?

(A) Begin tenofovir and emtricitabine
(B) Begin tenofovir, emtricitabine, and dolutegravir
(C) Begin tenofovir, emtricitabine, and ritonavir-boosted darunavir
(D) Determine source patient's viral load

Item 14

A 38-year-old woman undergoes follow-up evaluation in the office. She was evaluated in the emergency department 3 nights ago with fever and flank pain following 2 days of dysuria. A urine culture and two sets of blood cultures were collected. She was given intravenous ceftriaxone and discharged with a 7-day course of ciprofloxacin. She is now asymptomatic. Medications are ciprofloxacin and an oral contraceptive.

On physical examination, vital signs and other findings are normal.

Escherichia coli susceptible to ciprofloxacin was isolated from her urine culture and one blood culture.

Which of the following is the most appropriate management?

(A) Completion of oral ciprofloxacin course
(B) Completion of oral ciprofloxacin course with follow-up blood cultures
(C) Extended oral ciprofloxacin therapy for 2 weeks
(D) Intravenous ceftriaxone
(E) Kidney ultrasonography

Item 15

A 25-year-old woman is evaluated for chronic intermittent nonbloody diarrhea with associated abdominal cramping, burping, and bloating. Symptoms began several months ago. She has a history of selective IgA deficiency with recurrent sinopulmonary infections. She has not taken antibiotics in the past 6 months.

On physical examination, temperature is 37.3 °C (99.1 °F); the vital signs are otherwise normal. On abdominal examination, bowel sounds are present with minimal diffuse tenderness to palpation.

Stool testing for occult blood is negative.

Which of the following is the most likely cause of this patient's diarrheal illness?

(A) *Clostridium difficile*
(B) Enterohemorrhagic *Escherichia coli*
(C) *Giardia lamblia*
(D) *Listeria monocytogenes*
(E) Nontyphoidal *Salmonella*

Item 16

A 28-year-old woman arrives to discuss possible recent exposure to Zika virus. She is pregnant, at 8 weeks' gestation, and feels well. Her husband returned home from Brazil 4 weeks ago; while away, he experienced a 5-day febrile illness, which was accompanied by a faint rash, headache, and myalgias, all of which resolved before he arrived home. After his return, they engaged in unprotected sexual intercourse. Her only medication is a prenatal vitamin.

On physical examination, vital signs are normal, and other examination findings are unremarkable.

Which of the following is the most appropriate test to perform next?

(A) Dengue virus IgM and IgG antibodies test
(B) Uterine ultrasonography every 3 weeks

(C) Zika virus IgM antibody test
(D) Zika virus RNA nucleic acid amplification test

H

Item 17

A 72-year-old woman is evaluated for a 2-day history of left facial droop and severe burning and stinging pain on the left ear helix and into the ear canal, with muffled hearing and tinnitus. She received the live attenuated zoster vaccine at age 60 years. She takes no medications.

On physical examination, vital signs are normal. She has a left-sided peripheral facial droop. The tympanic membrane appears normal. No rash is present. Hearing is diminished to a whisper in the left ear. The remainder of the examination is unremarkable.

Which of the following is the most likely cause of this patient's findings?

(A) *Borrelia burgdorferi*
(B) Herpes simplex virus type 1
(C) Herpes simplex virus type 2
(D) Varicella-zoster virus

Item 18

A 45-year-old man is evaluated for a 3-day history of fever, myalgia, headache, and nonproductive cough. He works as a large-animal veterinarian. Medical history is unremarkable, and he takes no medications.

On physical examination, vital signs are normal except for a temperature of 38.2 °C (100.8 °F). Oxygen saturation is 94% breathing ambient air. The examination is otherwise unremarkable.

A chest radiograph shows a patchy right lower lobe interstitial infiltrate.

Which of the following is the most likely cause of his illness?

(A) *Bacillus anthracis*
(B) *Coxiella burnetii*
(C) *Chlamydia psittaci*
(D) *Francisella tularensis*
(E) *Yersinia pestis*

H

Item 19

A 46-year-old woman is evaluated for new-onset fever and discomfort at the site of a peripherally inserted central catheter (PICC). She was hospitalized for acute pancreatitis and required the PICC for intravenous access and hydration.

On physical examination, temperature is 37.8 °C (100.1 °F), and the remaining vital signs are normal. Right brachial PICC line site is tender, without erythema. Cardiac examination is without murmurs.

Two sets of peripheral blood cultures are obtained, showing gram-positive cocci and clusters. Both sets of blood cultures are growing coagulase-negative *Staphylococcus* resistant to methicillin. Vancomycin is initiated.

Which of the following is the most appropriate additional management?

(A) Maintain PICC line and continue vancomycin for 4 weeks
(B) Maintain PICC line and perform transesophageal echocardiography
(C) Remove PICC line
(D) Remove PICC line and repeat blood cultures

Item 20

H

A 39-year-old man is evaluated in the hospital after a motorcycle accident that necessitated an open reduction and internal fixation of a femur fracture. During the emergency department evaluation, an indwelling urinary catheter was placed. Medical history is noncontributory, and he takes no medications.

On physical examination, he is alert and oriented. Vital signs are normal. The left leg is tender, with a sterile dressing over the incision.

Which of the following is the most appropriate urinary catheter management?

(A) Change catheter to an antimicrobial or antiseptic-coated catheter
(B) Initiate prophylactic antibiotics
(C) Maintain catheter placement until patient is ambulatory
(D) Remove catheter and observe for spontaneous voiding

Item 21

H

A 50-year-old woman is evaluated in the emergency department for fever and tenderness at the site of a cat bite sustained on the dorsum of her right hand 2 days ago. She indicates that she works at an animal shelter. Medical history is significant for a methicillin-resistant *Staphylococcus aureus* skin infection 6 months ago; she is up to date on all vaccinations, including rabies and tetanus. She takes no medications.

On physical examination, temperature is 38.5 °C (101.3 °F), blood pressure is 98/66 mm Hg, pulse rate is 110/min, and respiration rate is 22/min. A tender puncture wound is noted on the dorsum of the right hand; it is warm and surrounded by significant erythema. Some purulent discharge is noted from the wound.

Blood cultures are obtained.

A plain radiograph of the right hand shows no evidence of gas, foreign body, or bony involvement.

In addition to surgical consultation, which of the following antibiotic regimens is the most appropriate treatment at this time?

(A) Ampicillin-sulbactam plus vancomycin
(B) Ceftriaxone plus metronidazole
(C) Ciprofloxacin plus aztreonam
(D) Imipenem
(E) Vancomycin and clindamycin

H

Item 22

A 42-year-old man is evaluated for headache and progressive weakness. He was hospitalized yesterday with a 9-day history of fever, headache, and myalgia. He is a trail runner, and 10 days ago participated in a 10-kilometer race in North Carolina. He is not aware of any tick bite.

On physical examination, the patient appears ill. Temperature is 39.4 °C (102.9 °F), blood pressure is 102/78 mm Hg, pulse rate is 102/min, and respiration rate is 24/min. No tonsillar enlargement, cervical lymphadenopathy, hepatosplenomegaly, or skin lesion is noted.

Laboratory studies:

Leukocyte count	1500/µL (1.5×10^9/L), with 70% neutrophils and no atypical lymphocytes
Platelet count	34,000/µL (34×10^9/L)
Alanine aminotransferase	667 U/L
Aspartate aminotransferase	995 U/L

Empiric doxycycline therapy is initiated for a possible tick-borne infection. Within 24 hours, he defervesces, and within 48 hours, the leukocyte and platelet counts normalize. Serologic tests for *Rickettsia rickettsii* and *Ehrlichia chaffeensis* obtained on admission have negative results.

Which of the following is the most likely diagnosis?

(A) Heartland virus infection
(B) Human monocytic ehrlichiosis
(C) Infectious mononucleosis
(D) Rocky Mountain spotted fever

H

Item 23

A 32-year-old man is evaluated in the hospital for a 4-day history of fever and leukocytosis that began 1 week after cranial surgery and a 1-day history of worsening mental status. He experienced traumatic intracranial hemorrhage requiring a craniotomy for drainage and placement of an external ventricular drain. He remains intubated with mechanical ventilation. Medications are empiric vancomycin and cefepime, initiated 4 days ago.

On physical examination, temperature is 39.2 °C (102.5 °F), blood pressure is 108/62 mm Hg, pulse rate is 102/min, and respiration rate is 20/min. He was previously awake and able to follow simple commands, but now he is obtunded. Nuchal rigidity is noted. Other examination findings are unremarkable.

Cerebrospinal fluid (CSF) evaluation shows a leukocyte count of 134/µL (134×10^6/L) with 50% neutrophils, erythrocyte count of 10,000/µL ($10,000 \times 10^6$/L), glucose level of 35 mg/dL (1.9 mmol/L), protein level of 112 mg/dL (1120 mg/L), and elevated lactate level of 5.4 mg/dL.

Blood cultures taken at onset of fever are negative, as are CSF cultures.

A chest radiograph shows no infiltrates.

Which of the following is the most appropriate management?

(A) Continue current care
(B) Discontinue vancomycin and cefepime and begin linezolid
(C) Remove the external ventricular drain
(D) Switch to intraventricular administration of antibiotics

H

Item 24

A 19-year-old man is evaluated in the emergency department for fever, cough producing blood-tinged sputum, shortness of breath, and headache. He attended a political rally on his college campus 4 days ago. Six other people have been hospitalized with similar symptoms. Medical history is unremarkable, and he takes no medications.

On physical examination, the patient is alert and oriented. Temperature is 39.1 °C (102.4 °F), blood pressure is 98/58 mm Hg, pulse rate is 110/min, and respiration rate is 24/min. Oxygen saturation is 92% breathing oxygen 2 L/min by nasal cannula. Neurologic examination is nonfocal, and no meningeal signs are present. Dyspnea, bilateral pulmonary rhonchi, and tubular breath sounds are noted on pulmonary examination. No rash is present, and the abdomen is nontender.

Sputum Gram stain reveals many polymorphonuclear cells and abundant gram-negative coccobacilli demonstrating bipolar staining.

A chest radiograph shows bilateral patchy infiltrates.

Which of the following is the most appropriate treatment?

(A) Ceftriaxone and azithromycin
(B) Ciprofloxacin
(C) Gentamicin
(D) Piperacillin-tazobactam and levofloxacin

H

Item 25

A 39-year-old man is hospitalized for tongue pain, abdominal pain, increased weakness, and a 2-week history of malaise and fever. He reports being in good health previously. He lives in the Ohio River Valley; approximately 1 month ago, he moved his antique business from a barn to an old store in the area, after which he developed "flu-like" symptoms lasting 2 to 3 days. He says that the barn was dusty and had pigeons and bats in the rafters. He also has rheumatoid arthritis. Medications are methotrexate and prednisone.

On physical examination, the patient is lethargic. Temperature is 39.7 °C (103.5 °F), blood pressure is 90/50 mm Hg, pulse rate is 128/min, and respiration rate is 24/min. A shallow ulceration is visible on the right buccal mucosa and left lateral tongue. His neck is supple. Lungs are clear to percussion and auscultation. There is moderate hepatosplenomegaly.

Results of laboratory studies show a hemoglobin level of 9 g/dL (90 g/L), a leukocyte count of 10,500/µL (10.5×10^9/L), and a platelet count of 90,000/µL (90×10^9/L).

Posteroanterior and lateral chest radiographs are unremarkable.

Which of the following is the most appropriate treatment?

(A) Ceftriaxone and azithromycin
(B) Colchicine
(C) Itraconazole
(D) Liposomal amphotericin B

Item 26

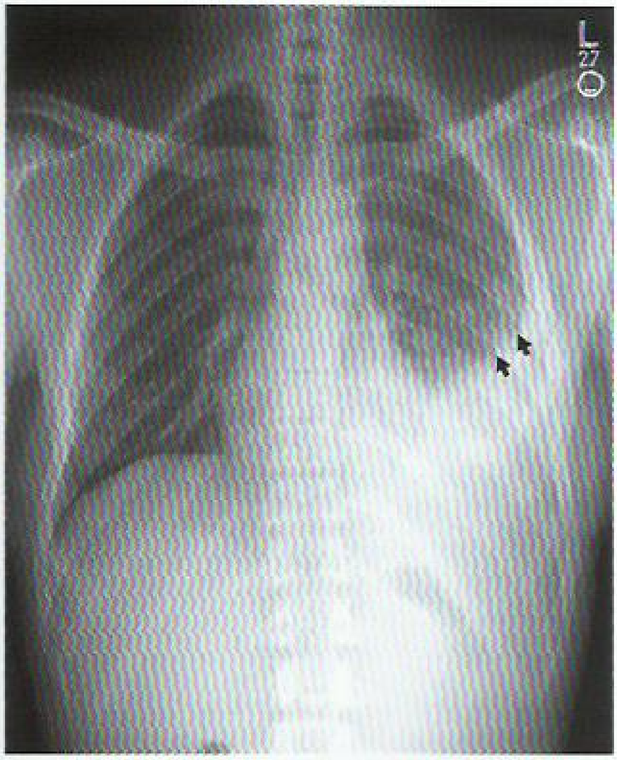
H

A 45-year-old man is evaluated in the ICU for continued daily fevers. He was hospitalized 6 days ago after 4 days of left-sided pleuritic chest pain, fever, and cough productive of yellow sputum with occasional blood streaks. He has a history of injection drug use and last injected heroin 7 days ago. Chest radiograph obtained at admission revealed a left lower lobe infiltrate. A sputum Gram stain showed gram-positive cocci in clusters. Empiric antibiotic therapy including vancomycin was begun. Sputum and two sets of blood cultures taken at admission grew methicillin-resistant *Staphylococcus aureus*, and antibiotic therapy was de-escalated to vancomycin monotherapy on hospital day 3. His only medication is vancomycin.

On physical examination, temperature is 38.5 °C (101.3 °F), blood pressure is 94/68 mm Hg, pulse rate is 118/min, and respiration rate is 28/min. Oxygen saturation is 92% breathing 6 L/min oxygen by nasal cannula. Decreased breath sounds are heard at the left lung base.

A vancomycin trough measurement is therapeutic at 15 µg/mL. Repeat blood cultures from hospital day 3 were negative at 72 hours. Repeat sputum Gram stain shows 3+ leukocytes and 1+ gram-positive cocci.

A transthoracic echocardiogram was negative for valvular vegetations. A repeat chest radiograph is shown.



Which of the following is the most appropriate management at this time?

(A) Add methylprednisolone
(B) Add piperacillin-tazobactam
(C) Perform thoracentesis
(D) Procalcitonin measurement
(E) Switch to daptomycin

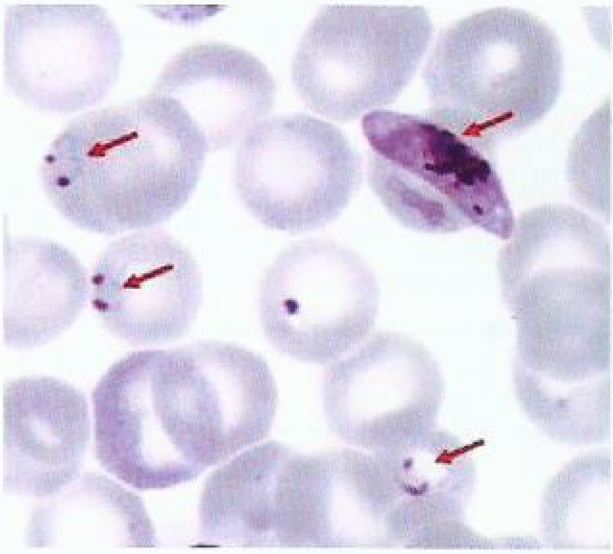
Item 27

H

A 27-year-old woman is hospitalized with a 5-day history of intermittent fever, headache, muscle pains, and abdominal cramps. She returned 8 days ago from a 1-week trip to Kenya and Tanzania. She spent time outdoors in the evening and went hiking in a wooded park. She is pregnant at 20 weeks' gestation. She declined pretravel immunizations as well as antimalarial chemoprophylaxis. Her only medication is a prenatal vitamin.

On physical examination, temperature is 39.1 °C (102.3 °F), blood pressure is 98/64 mm Hg, pulse rate is 112/min, and respiration rate is 16/min. Her conjunctivae are icteric. Cardiopulmonary examination reveals regular tachycardia. The remainder of the examination is unremarkable.

A peripheral blood smear is shown.



Which of the following is the most likely causative agent?

(A) *Plasmodium falciparum*
(B) *Plasmodium knowlesi*
(C) *Plasmodium malariae*
(D) *Plasmodium ovale*
(E) *Plasmodium vivax*

Item 28

H

A 64-year-old man is evaluated in the emergency department for acute onset of severe lower back pain that radiates down his legs, with associated numbness and fever. Medical history is significant for end-stage kidney disease, for which he receives hemodialysis. Medications are erythropoietin, iron, lisinopril, nifedipine, and sevelamer.

On physical examination, temperature is 38.6 °C (101.5 °F), blood pressure is 110/62 mm Hg, pulse rate is 114/min, and respiration rate is 20/min. The lower extremities have decreased sensation to touch, diminished reflexes, and mild weakness.

Laboratory studies show a leukocyte count of 15,450/µL (15.5×10^9/L). Blood cultures are pending.

H CONT.

MRI of the lumbar spine shows discitis in L2 to L3 with epidural abscess.

Which of the following is the most appropriate management?

(A) Await blood cultures before starting antimicrobial therapy
(B) Empiric antibiotic therapy alone
(C) Empiric antibiotic therapy and surgical drainage
(D) Surgical drainage alone

Item 29

A 19-year-old man is hospitalized with a 6 day history of lightheadedness and nightly fevers. He also reports sore throat, headache, joint and muscle aches, and a dry cough. He recalls a blotchy rash on his trunk and arms, which has resolved. He returned home 12 days ago from a trip to Vietnam, for which he did not receive specific immunizations or other prophylaxis. During the second week of his trip, he experienced 2 days of diarrhea; he has had none since, but abdominal discomfort and anorexia persist.

On physical examination, the patient is lethargic. Temperature is 39.9 °C (103.9 °F), blood pressure is 98/58 mm Hg, pulse rate is 68/min, and respiration rate is 16/min. No skin rash or evidence of jaundice is present. The abdomen is distended, with diminished bowel sounds, but nontender. Neurologic examination is nonfocal.

Which of the following is the most likely diagnosis?

(A) Brucellosis
(B) Leptospirosis
(C) Melioidosis
(D) Typhoid (enteric) fever

Item 30

A 31-year-old man arrives to establish care for newly diagnosed HIV infection. He is asymptomatic. Medical history is otherwise noncontributory, and he takes no medications.

On physical examination, vital signs are normal, and the remainder of the examination is unremarkable.

A review of his previous laboratory studies shows a normal complete blood count, and chemistries, including glucose, creatinine, and liver enzyme levels, are within normal limits. The HIV-1/2 antigen/antibody combination immunoassay is reactive. The HIV 1/2 antibody differentiation assay is positive for HIV-1 antibody, and HIV-1 RNA is quantified at 27,313 copies/mL. CD4 cell count is 455/µL.

Which of the following is the most appropriate next step in management?

(A) Genotypic viral resistance testing
(B) Glycohemoglobin level
(C) Phenotypic viral resistance testing
(D) Repeat HIV viral load and CD4 cell count in 1 month

H Item 31

A 33-year-old woman is evaluated in the emergency department in January with a 3-day history of fever, headache, stiff neck, and photophobia. She was previously well, and medical history is negative for recent travel; she takes no medications.

On physical examination, temperature is 38.5 °C (101.3 °F), blood pressure is 136/86 mm Hg, pulse rate is 100/min, and respiration rate is 18/min. The general medical examination is unremarkable. On neurologic examination, she shows photophobia, and a nondilated funduscopic examination shows no papilledema. The remainder of the examination is nonfocal.

Cerebrospinal fluid evaluation shows a leukocyte count of 324/µL (324×10^6/L) with 60% neutrophils, glucose level of 58 mg/dL (3.2 mmol/L), and protein level of 125 mg/dL (1250 mg/L). Gram stain of the cerebrospinal fluid is negative, and culture is pending.

Which of the following is the most likely cause of this patient's symptoms?

(A) Enterovirus
(B) Herpes simplex virus type 2
(C) Mumps virus
(D) West Nile virus

Item 32

A 22-year-old man returns for follow-up evaluation; he was recently diagnosed with HIV infection, and he began antiretroviral therapy 2 weeks ago. He also received influenza vaccination and the 13-valent pneumococcal conjugate vaccine at that time. He reports that he has sex with men. Medical history is notable for previous chlamydia infection and genital warts. Medications are tenofovir, emtricitabine, and dolutegravir.

On physical examination, vital signs are normal. A few small lesions consistent with warts are noted on the penis. The examination is otherwise unremarkable.

Laboratory studies:

CD4 cell count	527/µL
Hepatitis A IgG	Positive
Hepatitis A IgM	Negative
Hepatitis B surface antibody	Negative
Hepatitis B surface antigen	Positive

Which of the following is the most appropriate immunization to be given today?

(A) 23-Valent pneumococcal polysaccharide vaccine
(B) Hepatitis A vaccine
(C) Hepatitis B vaccine
(D) Human papillomavirus vaccine

Item 33

A 22-year-old man is evaluated in the emergency department 1 hour after awakening with right-sided facial weakness. He reports a 2-day history of headache but has had no fever. He lives in Minnesota and has removed two embedded ticks from himself and three from his dog over the past 3 weeks. The patient is otherwise healthy and takes no medication.

On physical examination, vital signs are normal. Nuchal rigidity and right facial nerve (cranial nerve VII) palsy are noted. Mental status is intact. Skin examination findings are shown on the next page.

H CONT.

All other physical examination findings are unremarkable. Results of laboratory studies show a leukocyte count of 11,500/µL (11.5×10^9/L).

Which of the following is the most appropriate initial management?

(A) *Borrelia burgdorferi* antibody testing
(B) Ceftriaxone administration
(C) Doxycycline administration
(D) Head CT
(E) Lumbar puncture

Item 34

A 34-year-old woman is seeking medical advice. She is pregnant at 24 weeks' gestation. Her husband returned home 1 week ago from a medical mission in the Middle East. Spores of anthrax were discovered in the hospital where he was working. Her husband, who is asymptomatic, has begun taking ciprofloxacin and will receive a vaccination series. The patient questions if she is at risk for infection. Her only medication is a prenatal vitamin.

On physical examination, vital signs are normal. The examination is unremarkable.

Which of the following is the most appropriate management?

(A) Doxycycline and vaccination
(B) Nasopharyngeal swab and anthrax blood test
(C) Raxibacumab injection
(D) No treatment

Item 35

A 27-year-old man is evaluated during a routine health maintenance visit with his internist. He asks about reducing his risk for HIV infection because he has sex with men, has multiple partners, and reports using condoms "sometimes." Medical history is unremarkable, and he takes no medications.

The physical examination is normal.

Laboratory studies show a normal serum creatinine level. A serum rapid plasma reagin test is negative. Nucleic acid amplification testing for gonorrhea and chlamydia from urine, pharynx, and rectum are all negative. An HIV test is negative.

Which of the following is the most appropriate preventive measure?

(A) Reinforce consistent condom use and avoid antiretroviral therapy
(B) Tenofovir and emtricitabine single dose before each sexual encounter
(C) Tenofovir and emtricitabine single dose after each sexual encounter
(D) Tenofovir disoproxil fumarate and emtricitabine daily

Item 36

H

A 67-year-old woman is hospitalized for an ulcer on the bottom of her right foot; it has expanded over the past 2 months. The patient has type 2 diabetes mellitus, hypertension, stage 3 chronic kidney disease, and peripheral neuropathy. Medications are insulin glargine, insulin lispro, lisinopril, and gabapentin.

On physical examination, temperature is 37.3 °C (99.1 °F); the remaining vital signs are normal. A deep 3- × 4-cm ulcer is located on the distal medial compartment of the plantar surface of the right foot. The base of the ulcer is necrotic and malodorous; a probe-to-bone test is negative. No surrounding erythema or increased warmth is noted. Both feet are warm with palpable pulses.

Erythrocyte sedimentation rate and C-reactive protein level are elevated. Results of a complete blood count are normal.

A plain radiograph reveals soft tissue swelling and ulceration; an MRI reveals findings consistent with osteomyelitis of the distal head of the first metatarsal.

Which of the following is the most appropriate management?

(A) Bone biopsy and culture
(B) Forefoot amputation
(C) Swabbing and culture of wound base
(D) Vancomycin and piperacillin-tazobactam

Item 37

A 32-year-old woman arrives to establish primary care. She is sexually active with a new male partner and reports consistent condom use. Medical history is significant for chlamydia cervicitis 5 years ago and treatment for syphilis 6 years ago. Her only medication is an oral contraceptive.

On physical examination, vital signs and the remainder of the examination are unremarkable.

A syphilis enzyme immunoassay is positive; rapid plasma reagin testing is negative. A fluorescent treponemal antibody test is positive. Nucleic acid amplification testing is negative for *Neisseria gonorrhoeae* and *Chlamydia trachomatis*. HIV antigen/antibody combination testing is negative.

Which of the following is the most appropriate management?

(A) Intramuscular benzathine penicillin, single dose
(B) Intramuscular benzathine penicillin, weekly for 3 weeks
(C) Repeat serology with *Treponema pallidum* particle agglutination assay
(D) No further testing or treatment

Item 38

A 25-year-old woman returns for counseling regarding results of HIV testing completed during a recent routine health maintenance visit. She reports no known exposure or risk factors for HIV infection. Medical history is unremarkable, and she takes no medications.

Laboratory studies show a reactive HIV-1/2 antigen/antibody combination immunoassay, a negative HIV-1/2 antibody differentiation immunoassay, and no RNA detected on HIV-1 RNA nucleic acid amplification testing.

Which of the following is the most appropriate management?

(A) Initiate combination antiretroviral therapy after counseling
(B) Order T-cell subset testing to check CD4 cell count
(C) Perform HIV genotypic resistance testing
(D) Perform Western blot HIV antibody testing
(E) Tell the patient she does not have HIV infection

Item 39

An 18-year-old man is evaluated for a 4-day history of frequent, large-volume diarrhea, with associated abdominal cramping, emesis, fever, and nausea. He is a lifeguard at a freshwater municipal pool, and several other swimmers who use the pool have recently developed similar symptoms.

On physical examination, temperature is 37.5 °C (99.5 °F); the vital signs are otherwise normal. On abdominal examination, bowel sounds are present, palpation elicits minimal tenderness, and no guarding or rebound is noted.

Modified acid-fast staining of the stool reveals oocysts that are about 5 microns in diameter.

Which of the following is the most likely cause of this patient's diarrhea?

(A) *Cryptosporidium*
(B) Enterohemorrhagic *Escherichia coli*
(C) Norovirus
(D) *Nocardia*
(E) *Vibrio parahaemolyticus*

Item 40

A 31-year-old woman undergoes consultation regarding preventive strategies for travelers' diarrhea. She is planning a 7-day vacation to Mexico. Her itinerary includes 3 days in Mexico City followed by 4 days in the Yucatan Peninsula. Medical history is significant for Crohn colitis, which is currently in remission with maintenance therapy. Medications are adalimumab and as-needed loperamide; she is allergic to aspirin.

On physical examination, vital signs are normal, and other findings are unremarkable.

Which of the following is the most appropriate preventive measure for this patient?

(A) Azithromycin
(B) Bismuth subsalicylate
(C) Ciprofloxacin
(D) Probiotics
(E) No prophylaxis

Item 41

H

An 82-year-old woman is hospitalized with hypotension and volume depletion resulting from gastroenteritis. Medical history is noncontributory, and she takes no medications.

On physical examination, temperature is 36.8 °C (98.3 °F), blood pressure is 92/66 mm Hg, pulse rate is 110/min, and respiration rate is 16/min. The remainder of the examination is unremarkable.

Because of difficulty in inserting a peripheral venous access line, an internal jugular central venous catheter will be placed for volume resuscitation.

Which of the following is the most appropriate measure to prevent catheter-related bloodstream infection in this patient?

(A) Assess catheter daily for necessity and potential removal
(B) Give one dose of vancomycin after catheter insertion
(C) Replace catheter every 7 days
(D) Use a small sterile drape when inserting the catheter

Item 42

A 36-year-old man is evaluated for a 10-day history of abdominal cramping, diarrhea, malaise, and nausea. Diarrhea is watery without mucus or blood. He returned 2 weeks ago from a 7-day trip to Lima, Peru.

On physical examination, temperature is 37.7 °C (99.9 °F); the remaining vital signs are normal. On abdominal examination, bowel sounds are present with diffuse tenderness to palpation. The abdomen is not distended; no guarding or rebound is noted.

Stool polymerase chain reaction assay is positive for *Cyclospora*.

Which of the following is the most appropriate treatment?

(A) Atovaquone
(B) Metronidazole
(C) Pyrimethamine
(D) Quinacrine
(E) Trimethoprim-sulfamethoxazole

Item 43

A 25-year-old woman is seen for counseling. She is newly pregnant at 7 weeks' gestation and has HIV infection diagnosed 6 years ago. HIV has been well controlled with an antiretroviral regimen, which she tolerates well. Medications are tenofovir disoproxil fumarate (TDF), emtricitabine, and efavirenz.

On physical examination, vital signs and other findings are normal.

Laboratory studies show HIV viral load is undetectable and the CD4 cell count is normal.

Which of the following is the most appropriate management?

(A) Continue TDF, emtricitabine, and efavirenz
(B) Pause antiretroviral therapy until after the first trimester
(C) Perform resistance testing
(D) Switch to zidovudine, lamivudine, and ritonavir-boosted lopinavir

Item 44

A 31-year-old man undergoes pretravel consultation. He plans to leave in 8 days for a safari trip to Kenya. He received yellow fever and typhoid vaccinations 18 months ago, and he is undergoing a work-related three-dose hepatitis B vaccination series. He also has a prescription for prophylactic antimalarial medication. No serum IgG antibodies to hepatitis A were detected in a recent blood test. He smokes cigarettes and occasionally drinks an alcoholic beverage.

On physical examination, vital signs are normal, and other findings are unremarkable.

Which of the following is the most appropriate pretravel management for this patient?

(A) First dose of hepatitis A vaccine with a second dose in 7 days
(B) Immune globulin
(C) Single dose of hepatitis A vaccine
(D) Single dose of hepatitis A vaccine plus immune globulin
(E) No intervention

H

Item 45

A 92-year-old man is hospitalized with a complicated urinary tract infection (UTI). He resides in a nursing home and has a chronic indwelling urinary catheter. In the nursing home, a urinalysis and urine culture were performed for possible UTI, and empiric ciprofloxacin therapy was initiated 1 day before transfer to the hospital. In the emergency department, ciprofloxacin was changed to piperacillin-tazobactam, and blood cultures were obtained. Medical history is notable for dementia, benign prostatic hyperplasia, chronic kidney disease, and recurrent UTIs. Medications are donepezil, memantine, and piperacillin-tazobactam.

On physical examination, temperature is 38.5 °C (101.3 °F), blood pressure is 108/70 mm Hg, pulse rate is 100/min, and respiration rate is 16/min. Suprapubic tenderness is noted, and the urinary catheter is draining cloudy urine. Other examination findings are noncontributory.

Laboratory studies show a leukocyte count of 15,200/µL (15.2×10^9/L) and a serum creatinine level of 1.9 mg/dL (168 µmol/L). Urinalysis reveals leukocytes too numerous to count but no erythrocytes.

Urine culture obtained from the nursing home shows more than 10^5 colony-forming units of *Escherichia coli* sensitive to piperacillin-tazobactam, gentamicin, cefepime, and meropenem (resistant to ceftriaxone, ceftazidime, cefotaxime, and ciprofloxacin); it is confirmed to be an extended-spectrum β-lactamase–producing organism. Blood cultures are pending.

No infiltrates are seen on the chest radiograph.

Which of the following is the most appropriate treatment?

(A) Add gentamicin
(B) Continue piperacillin-tazobactam
(C) Switch piperacillin-tazobactam to cefepime
(D) Switch piperacillin-tazobactam to meropenem

Item 46

A 58-year-old man is assessed for discharge from the hospital. He was admitted 3 days ago with fever and chills. He has non-Hodgkin lymphoma and a tunneled subclavian venous catheter used for chemotherapy infusion. Blood cultures at admission grew vancomycin-resistant *Enterococcus faecium*. The patient's catheter was removed, a peripherally inserted central catheter (PICC) was placed for intravenous access, and daptomycin therapy was initiated. Blood cultures are now negative, and the patient is afebrile.

The patient is ready to be discharged to complete intravenous daptomycin therapy as an outpatient. At the time of discharge, his complete blood count and comprehensive chemistry profile are normal.

Which of the following is the most appropriate weekly monitoring of his daptomycin therapy?

(A) Electrocardiography and blood glucose
(B) Hemoglobin and platelet count
(C) Serum amylase and triglycerides
(D) Serum creatinine and creatine kinase

Item 47

A 32-year-old man is evaluated for a 2-month history of painless, violaceous skin nodules with surrounding edema on the chest, back, and lower extremities. He reports that he has sex with men. Medical history is significant for AIDS, with a CD4 cell count of 54/µL. He is not following an antiretroviral therapy regimen.

On physical examination, temperature is 38.1 °C (100.5 °F), blood pressure is 135/62 mm Hg, pulse rate is 68/min, and respiration rate is 20/min. Several nodules are seen in the mouth during oral examination (shown).

Which of the following is the most likely cause of these findings?

(A) Cytomegalovirus
(B) Epstein-Barr virus
(C) Human herpes virus type 6
(D) Human herpes virus type 8

H

Item 48

A 42-year-old man is evaluated in the hospital for increased pain and drainage from a previously healed surgical wound over the left fibula. He underwent open reduction and internal fixation of a fracture 4 weeks ago. The patient has undergone incision and surgical debridement of the wound. A bone culture revealed methicillin-sensitive *Staphylococcus aureus*. Medical history is otherwise noncontributory, and his only medication is ibuprofen for pain.

On physical examination, vital signs are normal. A surgical wound over the left lateral leg is well approximated with no erythema or drainage.

A plain radiograph before debridement shows nonunion of the fracture with screws and K-wires in place.

Which of the following is the most appropriate treatment?

(A) Cefazolin
(B) Cefazolin and rifampin
(C) Ceftaroline
(D) Vancomycin and rifampin

Item 49

A 34-year-old man is evaluated immediately after a dog bite to his thigh. Medical history is notable for splenectomy 5 years ago. The patient and dog are up to date on all immunizations. He takes no medications.

On physical examination, vital signs are normal. A tiny puncture wound is located on the right mid-thigh with minimal surrounding erythema.

Which of the following is the most appropriate management?

(A) Amoxicillin-clavulanate
(B) Ciprofloxacin
(C) Metronidazole
(D) Observation

H

Item 50

A 76-year-old woman is evaluated in the hospital for recurrent diverticulitis. She has had multiple episodes of diverticulitis treated with ciprofloxacin and metronidazole over the past 18 months. During this hospitalization, an abscess was noted on a CT scan of the abdomen and pelvis, and a percutaneous drain was placed and the fluid sent for culture. Piperacillin-tazobactam is started empirically.

On physical examination, temperature is 39.2 °C (102.6 °F), blood pressure is 126/82 mm Hg, pulse rate is 100/min, and respiration rate is 15/min. She has diffuse abdominal tenderness to palpation.

Laboratory studies show a leukocyte count of 22,000/µL (22×10^9/L) and a serum creatinine level of 1.3 mg/dL (115 µmol/L).

Gram stain of the abscess fluid reveals 4+ gram-negative rods; fluid culture grows *Pseudomonas aeruginosa* resistant to ceftazidime, piperacillin-tazobactam, ciprofloxacin, meropenem, and doripenem. Blood cultures are negative.

The *Pseudomonas* isolate should be tested for susceptibility to which of the following antibiotics?

(A) Ceftolozane-tazobactam and colistin
(B) Ertapenem and tobramycin
(C) Fosfomycin
(D) Minocycline

H

Item 51

A 25-year-old woman is hospitalized with a 4-day history of fever and cough productive of brown sputum. She is at 14 weeks' gestation with her first pregnancy. Medical history is significant for mild persistent asthma. Medications are an albuterol inhaler, beclomethasone inhaler, and a prenatal vitamin.

On physical examination, temperature is 38.2 °C (100.8 °F), blood pressure is normal, pulse rate is 122/min, and respiration rate is 24/min. Oxygen saturation is 94% breathing ambient air. Crackles are heard at the left lung base on pulmonary auscultation.

Chest radiograph shows a left lower lobe infiltrate.

Which of the following is the most likely cause of pneumonia in this patient?

(A) *Escherichia coli*
(B) *Klebsiella pneumoniae*
(C) *Listeria monocytogenes*
(D) *Staphylococcus aureus*
(E) *Streptococcus pneumoniae*

Item 52

A 67-year-old woman is evaluated in December for a 2-day history of runny nose, fever, headache, myalgia, cough, and sore throat. Medical history is notable for heart failure. She lives at home with her husband and is able to eat, drink, and take her oral medications. Her medications are carvedilol and enalapril. She received a standard-dose influenza immunization in October.

On physical examination, temperature is 38.6 °C (101.5 °F), blood pressure is 145/62 mm Hg, pulse rate is 98/min, and respiration rate is 20/min. The patient has rhinorrhea, and the pharynx is erythematous. Lungs are clear to auscultation.

A chest radiograph shows no infiltrates.

A nasopharyngeal swab is positive for influenza B.

Which of the following is the most appropriate treatment?

(A) Amantadine
(B) Oseltamivir
(C) Peramivir
(D) Rimantadine

H

Item 53

A 74-year-old man is evaluated in the emergency department for new onset of confusion and 2 days of fever and rigors. Medical history is significant for diabetes mellitus, hypertension, and benign prostatic hyperplasia. Medications are lisinopril, hydrochlorothiazide, metformin, tamsulosin, and aspirin.

On physical examination, the patient is confused. Temperature is 39.1 °C (102.4 °F), blood pressure is 102/56 mm Hg, pulse rate is 88/min, and respiration rate is 22/min. Oxygen saturation is 93% breathing ambient air. Neurologic examination is nonfocal and without meningeal signs. On abdominal examination, the abdomen is soft and the urinary bladder is distended. Other examination findings are noncontributory.

Laboratory studies:

Hemoglobin	15.2 g/dL (152 g/L)
Leukocyte count	17,480/µL (17.5×10^9/L)
Blood urea nitrogen	72 mg/dL (25.7 mmol/L)
Creatinine	2.1 mg/dL (186 µmol/L)
Urinalysis (catheterized sample)	Volume 780 mL (780 µL); cloudy; 1.244 specific gravity; >100 leukocytes/hpf; 0-5 erythrocytes/hpf; 4+ bacteria

Urine culture and two sets of blood cultures are obtained.

A portable chest radiograph shows no signs of acute cardiopulmonary disease.

In addition to supportive care, which of the following is the most appropriate management?

(A) Intravenous cefepime and kidney ultrasonography
(B) Intravenous ciprofloxacin
(C) Intravenous levofloxacin and digital prostate massage
(D) Intravenous piperacillin-tazobactam and contrast-enhanced abdominal and pelvic CT

H

Item 54

A 26-year-old woman is evaluated in the emergency department for fever and low back pain that has progressed for the past 3 weeks. She injects heroin daily. Medical history is unremarkable, and she takes no medications.

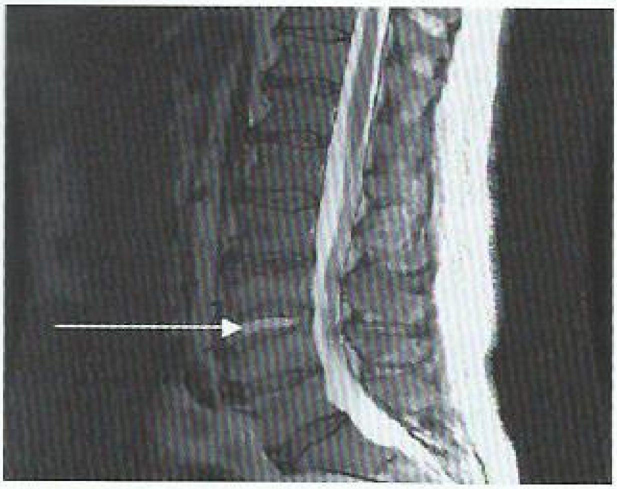
On physical examination, temperature is 38.1 °C (100.6 °F), blood pressure is 90/60 mm Hg, pulse rate is 110/min, and respiration rate is 28/min. The lower lumbar spine is tender to palpation. Neurologic examination and other physical examination findings are normal.

Aggressive fluid resuscitation is initiated. Complete blood count, metabolic profile, erythrocyte sedimentation rate, and blood culture and urinalysis are obtained.

MRI is shown (top of next column).

Which of the following is the most appropriate antibiotic management?

(A) Cefazolin and gentamicin
(B) Vancomycin
(C) Vancomycin and cefepime
(D) Withhold antibiotics while awaiting bone biopsy



ITEM 54

Item 55

A 21-year-old man is evaluated for cold symptoms beginning last week, including malaise, fatigue, swollen lymph nodes in the neck, and sore throat, which resolved before his appointment today. He has no other symptoms. He reports occasionally having sex with men, usually using condoms, but has had no known HIV exposure. Medical history is unremarkable, and he takes no medications.

On physical examination, vital signs are normal. A few shotty cervical lymph nodes are palpable, but no other lymphadenopathy is noted. No rash is present. Other examination findings are normal.

Laboratory studies show a reactive HIV-1/2 antigen/antibody combination immunoassay. The HIV-1/HIV-2 antibody differentiation immunoassay is negative. HIV-1 RNA nucleic acid amplification testing is positive, with quantification of 11,540 copies/mL.

Which of the following is the most likely diagnosis?

(A) Acute HIV infection
(B) Chronic HIV infection
(C) False-positive HIV test
(D) HIV-2 infection

Item 56

H

A 19-year-old man is evaluated at an urgent care clinic for a 3-day history of dysuria, with purulent discharge at the urethral meatus this morning. He reports no urgency, frequency, or fever. He returned last week from a spring break trip, during which he had oral sex with a new female partner. Medical history is otherwise noncontributory, he takes no medications, and he has no medication allergies.

On physical examination, vital signs are normal. Purulent discharge is noted at the urethral meatus. The examination is otherwise unremarkable.

Nucleic acid amplification testing for *Neisseria gonorrhoeae* and *Chlamydia trachomatis* is performed on a first-catch urine sample.

H CONT.

Which of the following is the most appropriate empiric treatment?

(A) Ceftriaxone plus azithromycin
(B) Doxycycline
(C) Trimethoprim-sulfamethoxazole
(D) Valacyclovir

Item 57

A 30-year-old woman undergoes predischarge evaluation 1 month after allogeneic hematopoietic stem cell transplantation for acute myeloid leukemia. The posttransplant course was complicated by prolonged neutropenia and *Escherichia coli* bacteremia. The infection and neutropenia have resolved with broad-spectrum antibiotic therapy. She received all indicated pretransplant immunizations. Medications are trimethoprim-sulfamethoxazole for pneumocystis pneumonia prophylaxis and tacrolimus.

On physical examination, vital signs are normal. The indwelling central line site appears normal without erythema, swelling, or tenderness. Lungs are clear throughout. No skin lesions are present.

Laboratory studies show a leukocyte count of 2700/µL (2.7×10^9/L) (differential of 57% polymorphonuclear cells, 30% lymphocytes, 10% monocytes, and 3% eosinophils) and a serum creatinine level of 0.7 mg/dL (61.9 µmol/L).

Pretransplant serologies were positive for cytomegalovirus, Epstein-Barr virus, varicella-zoster virus, and *Toxoplasma*.

In addition to continuing the trimethoprim-sulfamethoxazole, which of the following is the most appropriate outpatient prophylaxis for this patient?

(A) Acyclovir
(B) Ciprofloxacin
(C) Posaconazole
(D) Valganciclovir

H Item 58

A 34-year-old man is hospitalized with a 4-week history of fever, headaches, and stiff neck. He recently emigrated from Mexico, but his medical history is otherwise noncontributory, and he takes no medications.

On physical examination, the patient is alert. Temperature is 38.9 °C (102 °F), blood pressure is 92/60 mm Hg, pulse rate is 124/min, and respiration rate is 24/min. Neurologic examination is normal. Passive neck flexion elicits painful resistance.

Cerebrospinal fluid (CSF) analysis reveals a leukocyte count of 424/µL (424×10^6/L) with 92% lymphocytes, glucose level of 22 mg/dL (1.2 mmol/L), and protein level of 278 mg/dL (2780 mg/L).

Rapid point-of-care antibody screening for HIV infection is negative. CSF Gram stain and cryptococcal antigen test results are negative. Results from cultures of the CSF and blood and from the interferon-γ release assay are pending.

The chest radiograph is normal.

Which of the following is the most appropriate management?

(A) Amphotericin B and 5-fluorocytosine
(B) Rifampin, isoniazid, pyrazinamide, and ethambutol
(C) Rifampin, isoniazid, pyrazinamide, ethambutol, and dexamethasone
(D) Vancomycin, ceftriaxone, and dexamethasone

Item 59

A 25-year-old man undergoes follow-up consultation regarding a positive interferon-γ release assay. He reports working for the past year in Vietnam and having a negative tuberculin skin test before departing. He is asymptomatic. He has had no known exposure to anyone with a history of tuberculosis. He has otherwise been well and takes no medications.

On physical examination, vital signs and examination are normal.

HIV testing is negative.

Posteroanterior and lateral chest radiograph is normal.

Which of the following is the most appropriate treatment?

(A) Isoniazid and rifapentine once weekly for 24 weeks
(B) Isoniazid daily for 9 months
(C) Isoniazid, rifampin, pyrazinamide, and ethambutol for 8 weeks followed by isoniazid and rifampin for 4 months
(D) No treatment or testing

Item 60 H

A 37-year-old man is hospitalized with abdominal pain, fever, and increasing diarrhea of 3 days' duration. He underwent kidney transplantation 3 weeks ago. The postoperative course has been complicated by pneumonia and wound infection, which resolved with antibiotic treatment. The patient was seronegative for cytomegalovirus before transplantation, but the transplant donor was seropositive. Medications are prednisone, tacrolimus, mycophenolate mofetil, valganciclovir, and trimethoprim-sulfamethoxazole.

On physical examination, temperature is 38.4 °C (101.2 °F), blood pressure is 122/85 mm Hg, pulse rate is 110/min, and respiration rate is 18/min. Abdominal palpation elicits tenderness, especially in the left lower quadrant, without rebound or guarding.

Which of the following is the most likely diagnosis?

(A) *Clostridium difficile* colitis
(B) Cytomegalovirus colitis
(C) Mycophenolate adverse effect
(D) Polyoma BK virus

Item 61 H

A 22-year-old woman arrives for her annual gynecologic examination, including a Pap smear and refill of her oral contraceptive prescription. She indicates she recently became sexually active with a new partner. Medical history

H CONT

is otherwise unremarkable. Her only medication is her oral contraceptive.

On physical examination, vital signs are normal. Pelvic examination is normal. The remainder of the examination is noncontributory.

A urine pregnancy test is negative. The Pap smear is normal. Nucleic acid amplification testing is positive for *Neisseria gonorrhoeae* and negative for *Chlamydia trachomatis*. The HIV antigen/antibody combination immunoassay is negative.

Which of the following is the most appropriate treatment?

(A) Cefixime
(B) Ceftriaxone
(C) Ceftriaxone plus azithromycin
(D) Ciprofloxacin

Item 62

A 51-year-old man is evaluated in the emergency department for a 12-hour history of fever, chills, headache, and weakness. He works on his farm in Maine and spends a considerable part of most days outside, but he is not aware of any tick or mosquito bites. He has had no diarrhea, cough, or rash. The patient had his spleen surgically removed 20 years ago after being involved in a motor vehicle collision. He has had no recent travel outside of the United States, and he is up to date on all immunizations.

On physical examination, temperature is 39.6 °C (103.3 °F), blood pressure is 88/42 mm Hg, pulse rate is 135/min, respiration rate is 28/min, and oxygen saturation is 90% with the patient receiving 4 L/min of oxygen via a nasal cannula. Lethargy, scleral icterus, jaundiced skin, hepatomegaly, and lower extremity petechiae are noted.

Laboratory studies:

Haptoglobin	<8 mg/dL (80 mg/L)
Hematocrit	25%
Leukocyte count	4500/µL (4.5×10^9/L)
Platelet count	109,000/µL (109×10^9/L)
Bilirubin, total	3.9 mg/dL (66.7 µmol/L)
Creatinine	1.0 mg/dL (88.4 µmol/L)
Lactate dehydrogenase	909 U/L

A blood smear from this patient is most likely to show which of the following abnormalities?

(A) Cytoplasmic morulae in leukocytes
(B) Intraerythrocytic banana-shaped gametocytes
(C) Intraerythrocytic tetrad forms
(D) Intraneutrophilic gram-positive diplococci
(E) Schistocytes

H

Item 63

A 55-year-old man is evaluated in the hospital for antibiotic management of a diabetic foot ulcer. He was hospitalized 3 days ago for debridement of a draining great toe ulcer. A radiograph of the left foot showed osteomyelitis of the great toe. Empiric piperacillin-tazobactam was started after debridement of the ulcer, and a bone biopsy was obtained intraoperatively. Medical history is significant for diabetes mellitus with nephropathy. Medications are metformin, insulin glargine, and piperacillin-tazobactam. Today the patient is clinically improved.

On physical examination, vital signs are normal. A large, deep plantar ulcer penetrates to the bone of the left great toe with minimal surrounding erythema and no evidence of necrotic tissue.

The bone culture grows *Pseudomonas aeruginosa* (sensitive to piperacillin-tazobactam, ceftazidime, ciprofloxacin, aztreonam, and tobramycin) and *Bacteroides fragilis*.

Which of the following is the most appropriate management?

(A) Add tobramycin to piperacillin-tazobactam
(B) Switch piperacillin-tazobactam to aztreonam
(C) Switch piperacillin-tazobactam to ceftazidime
(D) Switch piperacillin-tazobactam to oral ciprofloxacin and metronidazole

Item 64

H

A 55-year-old man is hospitalized for acute diverticulitis. Seventy-two hours after initiating treatment with piperacillin-tazobactam through a percutaneously inserted central venous catheter, he becomes hypotensive and tachycardic and is transferred to the ICU. He has a 5-year history of type 2 diabetes mellitus. His only medication is metformin.

On physical examination, temperature is 40 °C (104.0 °F), blood pressure is 89/46 mm Hg, pulse rate is 136/min, respiration rate is 32/min, and oxygen saturation is 92% with the patient breathing ambient air. The patient is somnolent. The funduscopic examination is unremarkable. Abdominal examination reveals a soft, slightly tender left lower quadrant. Other examination findings are unremarkable.

A blood culture is positive for yeast.

The intravenous catheter is removed, and a replacement catheter is inserted at a different site.

Which of the following is the most appropriate management?

(A) Begin empiric therapy with an echinocandin
(B) Begin empiric therapy with fluconazole
(C) Confirm candidemia with a second positive blood culture
(D) Perform antifungal susceptibility testing before initiating therapy
(E) No additional therapy is required

Item 65

A 58-year-old man is evaluated in follow-up after being hospitalized with uncomplicated L3 vertebral osteomyelitis that presumably resulted from bacteremia during hemodialysis for end-stage kidney disease. In the hospital, a CT-guided bone biopsy identified a methicillin-susceptible *Staphylococcus aureus* infection. The patient completed 2 weeks of cefazolin antibiotic therapy and has responded with resolution of fever and improvement in pain. Other medications are sevelamer and amlodipine.

On physical examination, vital signs are normal. The lower lumbar spine is minimally tender to palpation. The remainder of the physical examination is noncontributory.

Which of the following is the most appropriate treatment?

(A) Continue cefazolin to complete 6 weeks of antibiotic therapy
(B) Continue cefazolin to complete 12 weeks of antibiotic therapy
(C) Discontinue cefazolin now
(D) Discontinue cefazolin when follow-up MRI demonstrates improvement

H

Item 66

A 40-year-old man is hospitalized for a 2-day history of diarrhea. He has five liquid bowel movements per day. One week ago, he completed a course of levofloxacin for treatment of community-acquired pneumonia.

On physical examination, temperature is 38.1 °C (100.5 °F), blood pressure is 116/70 mm Hg, pulse rate is 98/min, and respiration rate is 19/min. The abdomen is nondistended with normal bowel sounds. Moderate abdominal tenderness is present, without guarding or rebound. Mental status is normal.

Laboratory studies:

Leukocyte count	18,000/µL (18.0×10^9/L) (differential: 78% neutrophils, 3% band forms, 19% lymphocytes)
Albumin	2.8 g/dL (28 g/L)
Creatinine	1.6 mg/dL (141.4 µmol/L) (baseline, 1.0 mg/dL [88.4 µmol/L])
Lactate	Normal

Stool polymerase chain reaction assay is positive for *Clostridium difficile* toxin gene.

Which of the following is the most appropriate treatment?

(A) Fecal microbiota transplant
(B) Intravenous vancomycin
(C) Oral metronidazole
(D) Oral vancomycin
(E) Oral vancomycin and intravenous metronidazole

H

Item 67

An 18-year-old man is evaluated in the emergency department for new-onset seizures. The previous afternoon, he was evaluated in the university health service for acute onset of fever, severe myalgia, headache, and nausea; he was diagnosed with influenza and sent home with oseltamivir and ibuprofen. He received the quadrivalent meningococcal vaccine 7 months ago. Medical history is otherwise noncontributory. Other than oseltamivir and ibuprofen, he takes no medications.

On physical examination, temperature is 38.9 °C (102.0 °F), blood pressure is 90/55 mm Hg, pulse rate is 130/min, and respiration rate is 28/min. The patient is confused and lethargic. Photophobia, meningismus, and a diffuse petechial rash are present.

CT scan of the head is unremarkable.

Microscopic examination of the cerebrospinal fluid demonstrates gram-negative diplococci. Blood and cerebrospinal fluid cultures are pending.

Which of the following is the most likely bacterial agent causing this patient's meningitis?

(A) *Haemophilus influenzae*
(B) *Listeria monocytogenes*
(C) *Neisseria meningitides* group B
(D) *Streptococcus pneumoniae*

Item 68

A 28-year-old man is evaluated for anal discharge accompanied by tenesmus of 3 days' duration. He reports no abdominal pain, diarrhea, or hematochezia. He is sexually active with men and women, practices anal receptive intercourse, and uses condoms inconsistently. Medical history is unremarkable, and he takes no medications.

On physical examination, vital signs are normal. Erythema and discharge are noted in the perianal region, but no ulcers are visible. Anoscopy is not available.

Nucleic acid amplification testing for *Neisseria gonorrhoeae* and *Chlamydia trachomatis* is performed on an anal swab sample. Testing for herpes, syphilis, and HIV infections is also initiated.

Which of the following is the most appropriate treatment?

(A) Azithromycin
(B) Budesonide foam
(C) Ceftriaxone and doxycycline
(D) Ciprofloxacin

Item 69

H

A 42-year-old woman is hospitalized with dyspnea, dry cough, and fever that has been increasing over the past few days. She underwent allogeneic hematopoietic stem cell transplantation (HSCT) 7 months ago, with a recent occurrence of graft-versus-host disease of the skin and gastrointestinal tract. Donor and recipient were both cytomegalovirus seropositive before transplantation, the patient received monitoring for cytomegalovirus reactivation for 6 months after transplantation, and the cytomegalovirus nucleic acid amplification test was negative 1 month ago. Medications are prednisone, tacrolimus, trimethoprim-sulfamethoxazole, and acyclovir.

On physical examination, temperature is 38.1 °C (100.6 °F), blood pressure is 125/78 mm Hg, pulse rate is 104/min, and respiration rate is 24/min. Oxygen saturation is 88% breathing ambient air. Crackles are audible bilaterally on pulmonary examination. No lymphadenopathy is noted. The remainder of the examination is noncontributory.

Laboratory studies show a leukocyte count of 3500/µL (3.5×10^9/L), with 85% polymorphonuclear cells, 8% lymphocytes, 5% monocytes, and 2% eosinophils.

A chest radiograph shows bilateral diffuse infiltrates. Chest CT scan shows bilateral diffuse ground-glass opacities without pleural effusions.

H CONT

In addition to starting broad-spectrum antibacterial therapy, which of the following is the most appropriate initial treatment?

(A) Atovaquone
(B) Ganciclovir
(C) Liposomal amphotericin
(D) No additional therapy

H

Item 70

A 47-year-old man is hospitalized with a 1-month history of increasingly severe low back pain and a 3-day history of fever and chills. He reports injection drug use (last injected 1 week ago). Medical history is otherwise unremarkable, and he takes no medications.

On physical examination, temperature is 38 °C (100.4 °F), blood pressure is 110/76 mm Hg, pulse rate is 88/min, and respiration rate is 16/min. Neurologic examination reveals no deficits, and no murmur is heard on cardiac auscultation. Palpation of the spine elicits point tenderness over L2-L4.

Laboratory studies show an erythrocyte sedimentation rate of 98 mm/h and a leukocyte count of 18,300/µL (18.3×10^9/L).

MRI is positive for spondylodiskitis at L3-L4.

Blood samples were obtained, and empiric vancomycin was initiated.

Two sets of blood cultures are positive for methicillin-resistant *Staphylococcus aureus*, with a vancomycin minimum inhibitory concentration of 1.5 µg/mL; repeat blood cultures are pending. The vancomycin trough level is 19 µg/mL.

Transesophageal echocardiography shows no valvular vegetations.

Which of the following is the most appropriate treatment?

(A) Add gentamicin to vancomycin
(B) Add rifampin to vancomycin
(C) Change vancomycin to daptomycin
(D) Continue vancomycin

Item 71

A 28-year-old woman undergoes follow-up evaluation after a recent hospitalization for meningococcal bacteremia. Lumbar puncture results during hospitalization were negative for meningitis. She completed a course of ceftriaxone 1 week ago and reports feeling well since stopping antibiotics. Medical history is notable for gonococcal arthritis of her knee 2 years ago. She has a sister with a history of meningococcal meningitis. She takes no medications.

On physical examination, vital signs are normal. The remainder of the examination is unremarkable.

Which of the following is the most appropriate preventive measure?

(A) Intravenous immune globulin
(B) Plasma infusion
(C) Prophylactic ciprofloxacin
(D) Quadrivalent meningococcal conjugate vaccine

Item 72

H

A 33-year-old woman is evaluated for redness over her right calf at the site of a scratch that occurred 2 days ago. She has been well otherwise and takes no medications.

On physical examination, vital signs are normal. Tender erythema measuring 4 × 3 cm is noted over the right lower leg. No purulence, induration, or fluctuance is present.

Which of the following is the most appropriate treatment?

(A) Clindamycin
(B) Doxycycline
(C) Trimethoprim-sulfamethoxazole
(D) Vancomycin

Item 73

H

An 82-year-old man is admitted to the ICU with a 7-day history of fever and cough productive of green sputum. He is unable to climb the stairs to his bedroom without becoming short of breath. Medical history is remarkable for bronchiectasis and polymyalgia rheumatica. His only medication is prednisone, 10 mg/d.

On physical examination, temperature is 38.8 °C (101.8 °F), blood pressure is normal, pulse rate is 115/min, and respiration rate is 25/min. Oxygen saturation is 88% breathing ambient air. Crackles are heard in the right lung base.

A sputum Gram stain shows 3+ polymorphonuclear cells and 2+ gram-negative organisms.

A chest radiograph is shown.

Which of the following is the most appropriate treatment?

(A) Ampicillin-sulbactam and levofloxacin
(B) Aztreonam and ciprofloxacin
(C) Cefepime and ciprofloxacin
(D) Ceftriaxone and azithromycin
(E) Ceftriaxone and levofloxacin

Item 74

A 21-year-old man is hospitalized with a 3-day history of fever and cough productive of green sputum. He was in the hospital 2 months ago for giardiasis and a year ago for pneumonia. Medical history is also notable for frequent episodes of sinusitis, bronchitis, and otitis media dating back to childhood.

On physical examination, temperature is 38.2 °C (100.8 °F), blood pressure is 118/80 mm Hg, pulse rate is 108/min, and respiration rate is 24/min. Pulmonary examination reveals crackles at the right lung base.

Chest radiograph is significant for a right lower lobe consolidation, and empiric antibiotic therapy is initiated.

A sputum culture grows *Streptococcus pneumoniae.*

Which of the following is the most likely underlying diagnosis?

(A) AIDS
(B) Chronic granulomatous disease
(C) Common variable immunodeficiency
(D) Myeloperoxidase deficiency

Item 75

A 28-year-old man undergoes follow-up evaluation of an injury to his right fourth finger sustained 10 weeks ago; he is a sport fisherman and obtained the injury from a tropical fish fin. He received separate 10-day courses of cephalexin and clindamycin without response. He takes no medications.

On physical examination, vital signs are normal. Swelling is present along the dorsum of the finger, with one 2- × 3-cm erythematous, papulonodular, fluctuant lesion located between the proximal and metacarpophalangeal joints. Pain is noted along the flexor tendon.

A plain radiograph of the finger shows no evidence of bony involvement or presence of a foreign body. Surgical exploration is performed, and intraoperative tissue specimens reveal noncaseating granulomas and inflammatory granulation tissue; Gram stain is negative.

Which of the following is the most likely cause of this patient's infection?

(A) *Clostridium perfringens*
(B) Herpes simplex virus type 1
(C) *Mycobacterium marinum*
(D) *Streptococcus pyogenes*

Item 76

A 32-year-old woman is evaluated following a generalized erythematous rash that developed 1 week ago. The rash has now resolved, and she reports no additional symptoms. She was diagnosed with HIV infection and AIDS 6 months ago when she was treated for *Pneumocystis jirovecii* pneumonia. She began antiretroviral therapy and daily trimethoprim-sulfamethoxazole for secondary pneumonia prophylaxis. She stopped taking trimethoprim-sulfamethoxazole last week when the rash developed. Current therapy consists of lamivudine, abacavir, and dolutegravir.

On physical examination, vital signs are normal. No rash is noted. No lesions are present on the eyes or in the mouth. No lymphadenopathy is noted. The lungs are clear bilaterally, and the abdomen is soft and nontender.

Complete blood count with differential and liver enzyme levels are normal. CD4 cell count is 291/µL (130/µL 6 months ago). HIV quantitative RNA is undetectable (31,840 copies/mL 6 months ago); 3 months ago, the CD4 cell count was 209/µL, and viral load was undetectable.

Which of the following is the most appropriate management?

(A) Begin atovaquone
(B) Begin primaquine and clindamycin
(C) Continue current therapy
(D) Restart trimethoprim-sulfamethoxazole
(E) Switch to tenofovir, emtricitabine, and dolutegravir

Item 77

H

A 67-year-old woman is evaluated after a diagnosis of ventilator-associated pneumonia. She was transferred to the ICU 3 days ago for respiratory failure secondary to Guillain-Barré syndrome and was intubated. Yesterday, the ventilator-associated pneumonia diagnosis was made and empiric antibiotics were started. Today her antibiotic therapy was de-escalated to oxacillin after her sputum culture grew methicillin-sensitive *Staphylococcus aureus*. Blood cultures were negative. Her medications are oxacillin and low-molecular-weight heparin; she is also undergoing plasmapheresis.

On physical examination, temperature is 37.6 °C (99.6 °F), blood pressure and pulse rate are normal, and respiration rate is 15/min. Oxygen saturation is 97% breathing 40% FIO_2. Pulmonary examination reveals scattered rhonchi.

A chest radiograph shows right middle and lower lobe infiltrates without effusions.

Which of the following is the most appropriate antibiotic management?

(A) Continue antibiotic therapy for a total of 7 days
(B) Continue antibiotic therapy for a total of 14 days
(C) Continue antibiotics until extubation
(D) Obtain sputum for Gram stain and culture before stopping antibiotics

Item 78

H

A 29-year-old woman is evaluated in the emergency department in January for a 5-day history of fever, severe headaches, delusions, and paranoid behavior. Medical history is noncontributory, and she takes no medications.

On physical examination, she is confused and combative. Temperature is 37.9 °C (100.2 °F), blood pressure is 107/48 mm Hg, pulse rate is 102/min, and respiration rate is 20/min. The neck is supple. Occasionally, choreoathetoid movements of the bilateral upper extremities are observed. She has no paralysis. After the examination, she has a generalized seizure in the emergency department.

H CONT.

Lumbar puncture is performed, and results show a cerebrospinal fluid leukocyte count of 310/µL (310×10^6/L) with 94% lymphocytes, glucose level of 60 mg/dL (3.3 mmol/L), and protein level of 55 mg/dL (550 mg/L).

Cerebrospinal fluid bacterial and fungal cultures are negative. Polymerase chain reaction for herpes simplex virus is negative.

An MRI scan of the brain is normal.

Which of the following is the most likely diagnosis?

(A) Anti-N-methyl-D-aspartate receptor encephalitis
(B) Lyme meningitis
(C) Tuberculous meningitis
(D) West Nile virus encephalitis

H

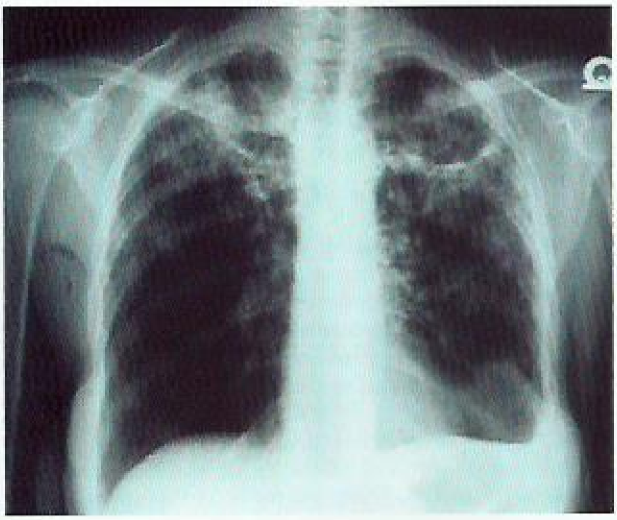
Item 79

A 45-year-old man is evaluated for extreme fatigue accompanied by a 9.1-kg (20 lb) weight loss over the past 2 months. He also has had an occasional productive cough for 1 month. He is unemployed and has been sleeping in homeless shelters for approximately 6 months. He drinks alcohol daily, consuming a fifth of vodka approximately every 2 to 3 days; he does not smoke or use illicit drugs.

On physical examination, temperature is 38.3 °C (100.9 °F), blood pressure is 110/60 mm Hg, pulse rate is 90/min, and respiration rate is 18/min. Bilateral crackles are present throughout inspiration over the upper posterior thorax. The remainder of the examination is unremarkable.

Interferon-γ release assay is positive. HIV antibody testing is negative.

The chest radiograph is shown.



Which of the following is the most appropriate management?

(A) Initiate isoniazid plus pyridoxine
(B) Initiate isoniazid, rifampin, pyrazinamide, and ethambutol
(C) Initiate piperacillin-tazobactam
(D) Obtain sputum specimen for acid-fast bacilli stain and culture

Item 80

A 19-year-old man is evaluated for multiple episodes of nonbloody diarrhea, fever, occasional vomiting, malaise, and crampy abdominal pain that began yesterday. He is a college student who adopted a pet corn snake 2 months ago; the snake is healthy.

On physical examination, temperature is 38.3 °C (100.9 °F), blood pressure is 110/60 mm Hg, pulse rate is 100/min, and respiration rate is 19/min. He appears to be in mild distress. On abdominal examination, bowel sounds are present, as is tenderness to palpation. No rebound or guarding is noted.

Stool testing for occult blood is positive.

Which of the following is the most likely cause of this patient's diarrheal illness?

(A) *Chlamydia psittaci*
(B) *Erysipelothrix rhusiopathiae*
(C) *Mycobacterium marinum*
(D) Nontyphoidal *Salmonella* species

Item 81

H

A 72-year-old woman undergoes follow-up evaluation for persistent bacteremia. She was hospitalized 12 days ago with fever and chills, which started abruptly 1 week after a cardiac catheterization procedure. Blood cultures were positive for methicillin-sensitive *Staphylococcus aureus*, and cefazolin therapy was initiated. Medical history is otherwise noncontributory, and she takes no other medications.

On physical examination, temperature is 39.4 °C (100.8 °F), blood pressure is 116/76 mm Hg, pulse rate is 92/min, and respiration rate is 16/min. A systolic murmur is present and is unchanged from previous examinations. Abdominal examination reveals right upper quadrant tenderness. The remainder of the examination is noncontributory.

Laboratory studies show an alanine aminotransferase level of 53 U/L, aspartate aminotransferase level of 58 U/L, and alkaline phosphatase level of 104 U/L.

Repeated blood cultures are positive for *S. aureus*.

A transthoracic echocardiogram shows a small aortic valve vegetation. An electrocardiogram is normal.

Which of the following is the most appropriate management?

(A) Perform abdominal CT
(B) Perform head CT
(C) Switch cefazolin to daptomycin
(D) Switch cefazolin to vancomycin

Item 82

H

A 48-year-old man is evaluated in the emergency department for skin trauma sustained in a freshwater lake 2 days ago, with abrasions and tiny lacerations over the right forearm; he developed a fever and pain at the site of trauma 1 day ago. Medical history is remarkable for cirrhosis secondary to alcohol use. He takes no medications.

On physical examination, temperature is 39.1 °C (102.4 °F), blood pressure is 100/70 mm Hg, pulse rate is 120/min, and

H CONT.

respiration rate is 25/min. The right forearm is tender and warm, with several hemorrhagic bullae noted. The remainder of the examination is unremarkable.

A plain radiograph of the right forearm shows no evidence of gas or a foreign body. Surgical exploration and debridement is performed, confirming a diagnosis of necrotizing fasciitis. Gram stain of intraoperative tissue specimens reveals gram-negative bacilli. Empiric antibiotic treatment with vancomycin plus piperacillin-tazobactam is initiated. Twenty-four hours later, the tissue culture grows *Aeromonas hydrophila*.

Which of the following is the most appropriate treatment?

(A) Ciprofloxacin plus doxycycline
(B) Linezolid plus metronidazole
(C) Nafcillin plus rifampin
(D) Vancomycin plus clindamycin

Item 83

A 33-year-old woman is evaluated 4 days after removing an embedded tick from her left arm. She reports that the tick was attached for less than 12 hours. She noticed itching at the site of tick attachment 2 days ago but otherwise has been asymptomatic. She preserved the tick in a bottle, and it is confirmed visually to be an adult black-legged deer tick (*Ixodes scapularis*).

On physical examination, vital signs are normal. A small area of induration is noted on the left arm, with no erythema, tenderness, or warmth. All other physical examination findings are unremarkable.

Which of the following is the most appropriate initial management?

(A) *Borrelia burgdorferi* polymerase chain reaction testing of the tick
(B) *Borrelia burgdorferi* serologies
(C) Doxycycline
(D) Reassurance that the risk of Lyme disease is low

Item 84

A 34-year-old man is evaluated for smallpox (variola) exposure. He feels wells. He is an Air Force surgeon and returned 2 days ago from a mission to the Middle East. Two others who accompanied him on his mission are being evaluated for a febrile illness characterized by headache, sore throat, and a vesicular rash on their faces, arms, and legs. The other men have been placed in airborne precautions because their clinical presentation is consistent with probable active variola infection. Medical history is notable for Crohn disease; he is up to date on all recommended immunizations. His only medication is infliximab.

On physical examination, vital signs are normal, and other physical examination findings are unremarkable.

A complete blood count and comprehensive metabolic profile are normal.

Which of the following is the most appropriate treatment?

(A) Airborne precautions
(B) Tecovirimat
(C) Vaccinia immune globulin
(D) Vaccinia immunization

Item 85

A 22-year-old man is evaluated in the emergency department for a 2 day history of painful rash on the left side of his posterior chest. Medical history is unremarkable, and he takes no medications.

On physical examination, temperature is 37.5 °C (99.5 °F), blood pressure is 115/62 mm Hg, pulse rate is 78/min, and respiration rate is 20/min. A vesicular rash is shown.

Which of the following is the most appropriate test to perform next?

(A) CH_{50} activity
(B) Fourth generation HIV-1/2 antigen/antibody combination immunoassay
(C) IgA measurement
(D) Quantitative immunoglobulin measurement

Item 86

A 57-year-old woman is hospitalized with a 1-month history of diminished concentration, memory, and judgment, with recent mental status fluctuations and gait disorder. Medical history is remarkable for hypertension. Medications are enalapril and hydrochlorothiazide.

On physical examination, vital signs are normal. She is somnolent but responds to verbal commands. The neck is supple. Deep-tendon reflexes are increased in the upper extremities and decreased in the lower extremities. Movement of the extremities is associated with myoclonus. The remainder of the examination is normal.

Complete blood count, comprehensive metabolic profile, thyroid studies, and vitamin B_{12} measurements are normal.

Lumbar puncture:	
Opening pressure	70 mm H_2O
Leukocyte count	4/µL (4×10^6/L)
Erythrocyte count	5/µL (5×10^6/L)
Glucose	108 mg/dL (6 mmol/L)
Protein	57 mg/dL (570 mg/L)

Gram stain of cerebrospinal fluid is negative. Polymerase chain reaction of cerebrospinal fluid for herpes simplex virus is negative.

Brain MRI shows abnormally increased T2 and FLAIR signal intensity in the putamen and head of the caudate.

Which of the following is the most likely diagnosis?

(A) Cryptococcal meningoencephalitis
(B) Sporadic Creutzfeldt-Jakob disease
(C) Tuberculous meningitis
(D) Vascular neurocognitive disorder

H

Item 87

A 74-year-old homeless woman is evaluated for hospital discharge. She was admitted 6 days ago with a diagnosis of community-acquired pneumonia, and empiric ceftriaxone and azithromycin were begun. Her fever resolved within 48 hours of admission; however, hospital discharge was delayed because of difficulty arranging posthospitalization placement. Medical history is otherwise noncontributory. She takes no other medications.

On physical examination, vital signs are normal. Oxygen saturation is 96% breathing ambient air. The remainder of the examination is unremarkable.

Sputum culture obtained at admission is growing *Streptococcus pneumoniae* sensitive to penicillin, ceftriaxone, levofloxacin, and vancomycin and resistant to erythromycin. Blood cultures obtained at admission show no growth.

The patient has been accepted into a group home and is ready for hospital discharge.

Which of the following is the most appropriate management at discharge?

(A) Continue only azithromycin
(B) Continue only ceftriaxone
(C) Stop all antibiotics
(D) Stop ceftriaxone and azithromycin and switch to amoxicillin
(E) Stop ceftriaxone and azithromycin and switch to levofloxacin

H

Item 88

A 46-year-old man is evaluated for pain and swelling of the left index finger that began 2 weeks ago. Ten weeks ago, the patient sustained a deep laceration to the finger while doing construction work. A plain radiograph at that time showed no evidence of fracture. The laceration was sutured, and the wound completely healed. History is significant for poorly controlled type 2 diabetes mellitus. Medications are metformin and glipizide.

On physical examination, vital signs are normal. A 4-cm wound along the medial aspect of the left index finger is completely healed. The finger is edematous and tender when palpated but without erythema.

Laboratory studies reveal an erythrocyte sedimentation rate of 120 mm/h, a leukocyte count of 7800/µL (7.8×10^9/L), and a serum creatinine level of 0.6 mg/dL (53.0 µmol/L).

Which of the following is the most appropriate diagnostic test to perform next?

(A) CT with contrast
(B) MRI with gadolinium
(C) Plain radiography
(D) Three-phase nuclear bone scan
(E) Ultrasonography

Item 89

H

A 42-year-old man is admitted to the ICU for nonresponsive pneumonia with a 7-day history of shortness of breath and cough. He was diagnosed with pneumonia and prescribed levofloxacin 3 days ago and has been adherent to his medication; however, his shortness of breath has worsened to the point he is unable to climb one flight of stairs. Medical history is remarkable for hospitalization 5 years ago for alcohol withdrawal and delirium tremens. He drinks a six-pack of beer every weekday and a case of beer on the weekends. His only medication is levofloxacin.

On physical examination, he is in mild respiratory distress but alert and oriented. Temperature is 38.7 °C (101.7 °F), blood pressure is normal, pulse rate is 122/min, and respiration rate is 24/min. Oxygen saturation is 89% breathing ambient air. Pulmonary auscultation reveals decreased breath sounds at the right lung base.

Laboratory studies show a leukocyte count of 18,700/µL (18.7×10^9/L) and a serum creatinine level of 2.3 mg/dL (203 µmol/L).

A chest radiograph shows a right lower lobe infiltrate.

Levofloxacin is discontinued.

In addition to initiating azithromycin, which of the following is the most appropriate antibiotic treatment?

(A) Ceftriaxone
(B) Clindamycin
(C) Metronidazole
(D) Piperacillin-tazobactam

Item 90

A 27-year-old man is evaluated in the emergency department for a 2-day history of bloody diarrhea with abdominal cramping. He reports attending a picnic 5 days before symptom onset where he ate a rare (undercooked) hamburger. Medical history is otherwise unremarkable, and he takes no medications.

On physical examination, temperature is 37.1 °C (98.8 °F), blood pressure is 120/76 mm Hg, pulse rate is 100/min, and respiration rate is 16/min. On abdominal examination, bowel sounds are present with diffuse tenderness to palpation but no guarding or rebound.

Laboratory studies:

Hematocrit	39%
Leukocyte count	18,000/µL (18.0×10^9/L) (differential: 80% neutrophils, 20% lymphocytes)
Platelet count	190,000/µL (190×10^9/L)
Creatinine	1.3 mg/dL (114.9 µmol/L)

Stool assay is positive for presence of Shiga-like toxin.

Which of the following is the most appropriate management?

(A) Ceftriaxone
(B) Ciprofloxacin
(C) Loperamide
(D) Trimethoprim-sulfamethoxazole
(E) Supportive care

H

Item 91

A 45-year-old man is hospitalized with a 5-day history of fever, bloody diarrhea, and abdominal pain. Medical history is significant for end-stage kidney disease, for which he underwent kidney transplantation 1 year ago. Medications are prednisone, mycophenolate, and tacrolimus.

On physical examination, vital signs are normal. Conjunctival pallor is present. Abdominal palpation elicits diffuse abdominal pain. The remainder of the examination is unremarkable.

Laboratory studies:

Hemoglobin	9.5 mg/dL (95 g/L)
Leukocyte count	3400/µL (3.4×10^9/L)
Platelet count	98,000/µL (98×10^9/L)
Alanine aminotransferase	99 U/L
Aspartate aminotransferase	88 U/L
Creatinine	1.5 mg/dL (133 µmol/L)

Which of the following is the most likely diagnosis?

(A) Cytomegalovirus infection
(B) *Entamoeba histolytica* infection
(C) *Salmonella enteritidis* infection
(D) *Strongyloides stercoralis* infection

H

Item 92

A 23-year-old man is evaluated for a 2-day history of erythema and drainage from a surgical incision site. He reports no fever or chills. He underwent a left inguinal hernia repair 10 days ago. Medical history is otherwise noncontributory, and he takes no medications.

On physical examination, vital signs are normal. The left inguinal incision is erythematous around the edges, is tender, and exudes a small amount of serosanguinous, cloudy drainage from a small area of incision breakdown. No induration is noted around the incision area.

Laboratory studies show a leukocyte count of 8700/µL (8.7×10^9/L).

Which of the following is the most appropriate diagnostic test to perform next?

(A) Blood culture
(B) CT of upper thigh and pelvis
(C) Gram stain and culture of incision site drainage
(D) Gram stain and culture of incision site swabbing

Item 93

A 55-year-old man is evaluated in the emergency department for a 1-week history of chills and altered mental status and a 2-week history of fever and severe headache. He has end-stage liver disease secondary to alcohol abuse. Medications are propranolol, furosemide, spironolactone, and lactulose.

On physical examination, temperature is 38.6 °C (101.5 °F), blood pressure is 110/85 mm Hg, pulse rate is 111/min, and respiration rate is 22/min. The patient is somnolent, cachectic, and jaundiced. Funduscopic examination shows no papilledema. Bibasilar crackles are heard on auscultation of the lungs. The abdomen is distended and tense. No focal neurologic findings are present.

A CT scan of the head with contrast shows cerebral atrophy. A lumbar puncture is performed.

Cerebrospinal fluid studies:

Cell count	2 erythrocytes/hpf; 98 leukocytes/hpf, with 70% neutrophils and 30% lymphocytes
Glucose	20 mg/dL (1.1 mmol/L)
Pressure, opening	180 mm H_2O
Protein	170 mg/dL (1700 mg/L)
Cryptococcal antigen titer	1:2048
Gram stain	Negative

Which of the following is the most appropriate treatment?

(A) Fluconazole
(B) Itraconazole
(C) Liposomal amphotericin B and flucytosine
(D) Micafungin

Item 94

A 64-year-old woman is evaluated for a 6-week history of right knee swelling and pain. She has had no recent injury, fevers, or chills. She retired as a horticulturist and moved from Massachusetts to Florida 3 months ago. She takes NSAIDs, which provide partial pain relief, but the swelling persists.

On physical examination, vital signs are normal. The right knee has a moderately sized effusion but no erythema or warmth. Slight pain is present on passive movement of the knee.

Results of laboratory studies show an equivocal *Borrelia burgdorferi* enzyme immunoassay of 1.07; leukocyte count and rheumatoid factor titer are within normal limits.

Which of the following is the most appropriate next diagnostic test?

(A) *Borrelia burgdorferi* IgG Western blot
(B) C6 enzyme immunoassay antibody test
(C) Polymerase chain reaction of joint fluid
(D) No further testing

Item 95

H

A 63-year-old man undergoes discharge evaluation. He was hospitalized 24 hours ago after a diagnosis of acute bacterial prostatitis, for which ciprofloxacin was initiated. His fever has resolved. Medical history is otherwise unremarkable, and he takes no other medications.

He is being discharged home to complete 6 weeks of oral ciprofloxacin therapy.

H CONT.

Which of the following is the most appropriate monitoring for this patient?

(A) Serum lipase level

(B) Serum sodium level

(C) Stool for *Clostridium difficile* toxin

(D) Symptoms of tendon or joint pain

H

Item 96

A 30-year-old man is evaluated for a 1-week history of sore throat and odynophagia. He reports no fever, nausea, vomiting, diarrhea, or other symptoms. He was recently diagnosed with HIV infection and began antiretroviral therapy 2 weeks ago. Medications are tenofovir alafenamide, emtricitabine, dolutegravir, and trimethoprim-sulfamethoxazole.

On physical examination, vital signs are normal. Oral examination findings (shown) include whitish plaques on the posterior pharynx. Lymph nodes are palpable in the anterior and posterior cervical regions bilaterally. The remainder of the examination is normal.

Laboratory studies at the time of HIV diagnosis showed a CD4 cell count of 55/µL and HIV viral load of 138,855 copies/mL.

Which of the following is the most appropriate management?

(A) Intravenous caspofungin

(B) Oral fluconazole

(C) Nystatin swish-and-swallow

(D) Upper endoscopy

(E) Valganciclovir

H

Item 97

A 47-year-old woman is evaluated in the hospital for pyelonephritis not responding to antibiotic therapy. Five days ago she was evaluated in an urgent care center for abdominal and back pain, nausea, fever, and dysuria. She was started on oral ciprofloxacin for a urinary tract infection (UTI). Symptoms did not respond to this treatment, and two days ago, she was hospitalized. Acute pyelonephritis was diagnosed, and she was treated with intravenous fluids, vancomycin, and cefepime. Since hospitalization, her clinical condition has deteriorated, with continued fever and worsening flank pain. She also has stage 2 chronic kidney disease, recurrent UTIs, and a 6-year history of poorly controlled type 2 diabetes mellitus. Medications are amoxicillin, metformin, and insulin glargine.

On physical examination, temperature is 38.2 °C (100.8 °F), blood pressure is 130/60 mm Hg, pulse rate is 106/min, and respiration rate is 22/min. Abdominal examination reveals diminished bowel sounds, bilateral costovertebral angle tenderness, and suprapubic pain. Other examination findings are unremarkable.

Laboratory studies:

Hemoglobin	11 g/dL (110 g/L)
Leukocyte count	21,000/µL (21×10^9/L) with 91% neutrophils and 9% lymphocytes
Platelet count	167,000/µL (167×10^9/L)
Creatinine	1.8 mg/mL (159 µmol/L)
Urinalysis	10 erythrocytes/hpf, leukocytes too numerous to count, many yeast forms, trace protein, and 4+ glucose

Urine culture results show 10,000 colony-forming units of *Candida glabrata*. Blood culture results are negative.

A CT scan of the abdomen with contrast shows bilateral perinephric stranding, no masses, and no renal abscesses.

Which of the following is the most likely diagnosis?

(A) Acute diverticulitis

(B) Antibiotic-resistant bacterial pyelonephritis

(C) *Candida* pyelonephritis

(D) Renal infarction

Item 98

H

A 25-year-old man is evaluated for a 3-day history of painful lesions on his penis accompanied by generalized myalgia and malaise. He has been sexually active with one female partner for the past 6 months; he does not use condoms. Medical history is unremarkable for previous genital ulcers and is otherwise noncontributory. He takes no medications but indicates he develops a rash with penicillin use.

On physical examination, vital signs are normal except for a temperature of 38.2 °C (100.8 °F). Bilateral, tender inguinal lymphadenopathy is noted. Lesions on the penile shaft are shown on the next page.

Which of the following is the most appropriate diagnostic test to perform next?

(A) Darkfield examination

(B) Direct fluorescence assay

(C) Nucleic acid amplification testing

(D) Type-specific antibody testing

ITEM 98

Item 99

A 25-year-old man is evaluated in the emergency department for left hand pain at the site of injection drug use. All of his immunizations are up to date. He takes no medications.

On physical examination, temperature is 39.3 °C (102.7 °F), blood pressure is 88/50 mm Hg, pulse rate is 110/min, and respiration rate is 26/min. A violaceous, swollen, indurated area is noted on the dorsum of the left hand at the site of recent injection drug use; it is warm to the touch and tender.

Laboratory studies:

Hematocrit	36%
Leukocyte count	25,000/µL (25×10^9/L)
Platelet count	100,000/µL (100×10^9/L)
Alanine aminotransferase	65 U/L
Aspartate aminotransferase	105 U/L
Creatinine	2.5 mg/dL (221 µmol/L)

Empiric treatment with vancomycin and piperacillin-tazobactam is initiated and he undergoes surgical debridement. Intraoperative findings confirm necrotizing fasciitis, and tissue and blood cultures grow group A *Streptococcus*.

Which of the following is the most appropriate antibiotic treatment?

(A) Continue vancomycin and piperacillin-tazobactam
(B) Change to doxycycline and ceftazidime
(C) Change to linezolid and imipenem
(D) Change to penicillin and clindamycin

Item 100

A 78-year-old woman undergoes routine evaluation. She has been feeling relatively well but experiences occasional urinary incontinence when she coughs, sneezes, or laughs. Medical history is significant for hypertension. Medications are chlorthalidone and lisinopril.

On physical examination, vital signs and other physical examination findings are normal.

On dipstick urinalysis, urine is yellow and clear, specific gravity is 1.010, pH is 7.0, and moderate leukocyte esterase and nitrites are present; the urinalysis is negative for blood or glucose but 2+ for bacteria.

Which of the following is the most appropriate management?

(A) Ciprofloxacin
(B) Cystoscopy
(C) Microscopic urinalysis
(D) Urine culture and sensitivity
(E) No further investigation or treatment

Item 101

A 52-year-old woman is evaluated in the emergency department for fever, headache, muscular pain, and a diffuse, nonpruritic rash that began on the arms. She returned 5 days ago from a 3-week trip in southern Spain. She recalls a dark, raised, scab-like lesion on her ankle that she attributed to an insect bite. Her medical history is otherwise unremarkable.

On physical examination, the patient is lethargic. Temperature is 38.7 °C (101.6 °F), blood pressure is 118/70 mm Hg, pulse rate is 82/min, and respiration rate is 16/min. Neurologic examination is nonfocal and without meningismus. A right inguinal lymph node is enlarged. A maculopapular pink rash is present on the trunk, arms, legs, palms, and soles. A black eschar is present on the right ankle that measures 1.5 × 1.5 cm. Other examination findings are normal.

Which of the following is the most likely diagnosis?

(A) Human granulocytic anaplasmosis
(B) Lyme disease
(C) Mediterranean spotted fever
(D) Rocky Mountain spotted fever

Item 102

A 24-year-old man is evaluated in the emergency department in October for a 10-day history of headaches, fever, and stiff neck. He reports camping and hiking in the woods on Nantucket Island 2 months ago. Medical history is unremarkable, and he takes no medications.

On physical examination, he is alert and oriented. Temperature is 38.3 °C (101.0 °F), blood pressure is 134/85 mm Hg, pulse rate is 104/min, and respiration rate is 20/min. Right-sided facial palsy is noted, and neck flexion elicits resistance and discomfort, but the neurologic examination is otherwise normal. No rash is present.

A lumbar puncture is performed, and cerebrospinal fluid evaluation shows a leukocyte count of 235/µL (235×10^6/L) with 84% lymphocytes. Gram stain is negative and cultures are pending.

H CONT.

Which of the following is the most likely cause of the patient's findings?

(A) *Borrelia burgdorferi*
(B) Enterovirus
(C) Herpes simplex virus type 2
(D) Varicella-zoster virus
(E) West Nile virus

H

Item 103

A 26-year-old man is hospitalized for a 3-month history of fever, night sweats, and weakness. Medical history is notable for kidney transplantation 5 years ago. Medications are prednisone and mycophenolate.

On physical examination, temperature is 38.1 °C (100.5 °F), blood pressure is 135/62 mm Hg, pulse rate is 68/min, and respiration rate is 20/min. The sclerae are pale. Cervical, supraclavicular, and axillary lymphadenopathy are noted. Abdominal examination reveals hepatosplenomegaly.

Laboratory studies:

Hemoglobin	8.4 mg/dL (84 g/L)
Leukocyte count	2300/µL (2.3×10^9/L)
Platelet count	98,000/µL (98×10^9/L)
Creatinine (stable)	1.1 mg/dL (97.2 µmol/L)

Which of the following is the most likely cause of his symptoms?

(A) Cytomegalovirus
(B) Epstein-Barr virus
(C) Herpes simplex virus type 1
(D) Polyoma BK virus

H

Item 104

A 23-year-old man is evaluated for a furuncle on the left forearm that appeared 1 day ago. Medical history is notable only for anaphylaxis with administration of trimethoprim-sulfamethoxazole. He is otherwise well and takes no medications.

On physical examination, temperature is 38.3 °C (100.9 °F), blood pressure is 124/75 mm Hg, pulse rate is 95/min, and respiration rate is 15/min. A 2- × 2-cm fluctuant lesion is present on the right forearm with 1 cm of surrounding erythema. The remainder of the examination is unremarkable.

After incision and drainage of the abscess, a culture is obtained.

Which of the following is the most appropriate additional treatment?

(A) Oral cephalexin
(B) Oral clindamycin
(C) Oral doxycycline
(D) Oral penicillin
(E) Clinical follow-up

Item 105

A 55-year-old woman undergoes annual tuberculin skin testing. An 8-mm induration is recorded after 48 hours. She reports no symptoms or exposures. She works as a clerk in an internal medicine outpatient clinic at a metropolitan hospital in New York City. Medical history is unremarkable, and she takes no medications.

On physical examination, vital signs and examination are normal.

Which of the following is the most appropriate management?

(A) Chest radiography
(B) Induce sputum for culture
(C) Initiate isoniazid for treatment of latent tuberculosis
(D) Move patient to nonpatient care areas
(E) No further testing or treatment

Item 106

A 35-year-old man is evaluated during a follow-up consultation. He was diagnosed with HIV 6 months ago; at that time, his CD4 cell count was 30/µL. He immediately began antiretroviral therapy and has been adherent to his regimen. His initial screening tests included a nonreactive tuberculin skin test (TST). He states that he has been unemployed for more than 2 years and has lived in a variety of different homeless shelters. Medications are tenofovir-emtricitabine and raltegravir.

On physical examination, vital signs and other findings are unremarkable.

Today, a repeat CD4 cell count is 100/µL and a repeat TST results in 5 mm of induration.

A posteroanterior and lateral chest radiograph is unremarkable.

Which of the following is the most appropriate management?

(A) Initiate isoniazid plus pyridoxine
(B) Initiate isoniazid, rifampin, pyrazinamide, and ethambutol
(C) Obtain an interferon-γ release assay
(D) Repeat TST in 2 weeks

Item 107

H

A 24-year-old woman is evaluated for cystitis symptoms of 4 days' duration. She reports no fever, chills, flank pain, or vaginal discharge. She has had similar symptoms three times within the past 10 months. She has been treated each time with trimethoprim-sulfamethoxazole at an urgent care center. The last episode was 5 weeks ago. She has sexual intercourse infrequently. Her only medication is an oral contraceptive.

On physical examination, vital signs and other findings are unremarkable.

On microscopic urinalysis, leukocytes are too numerous to count, erythrocyte count is 10/hpf, 4+ bacteria are present, and rare squamous epithelial cells are seen.

Which of the following is the most appropriate management?

(A) Nitrofurantoin
(B) Trimethoprim-sulfamethoxazole
(C) Urine culture plus ampicillin
(D) Urine culture plus cefpodoxime
(E) Urine culture plus ciprofloxacin

Self-Assessment Test

H

Item 108

A 41-year-old woman is evaluated in the emergency department for total loss of vision in the left eye. She also reports a 3-day history of left-sided tunnel vision and a 2-week history of sinus pain and rhinorrhea. The patient has a 20-year history of type 1 diabetes mellitus, which has been poorly controlled for the past 18 months. Medications are insulin glargine and insulin aspart.

On physical examination, temperature is 37.2 °C (99.0 °F), blood pressure is 140/66 mm Hg, pulse rate is 110/min, and respiration rate is 18/min. Left eye proptosis and chemosis are noted; the left pupil is nonreactive. The left nasal mucosa has gray-black exudate and an eschar. A 2- × 3-cm black eschar is seen on the hard palate. Neurologic examination shows occulomotor, trochlear, trigeminal, and abducens nerve (cranial nerves III, IV, V, and VI) palsy on the left.

A CT scan of the head without contrast shows a mass in the maxillary sinus with extension into the left frontal lobe and surrounding edema.

Which of the following is the most likely diagnosis?

(A) Anthrax

(B) Aspergillosis

(C) Lemierre syndrome

(D) Mucormycosis

Answers and Critiques

Item 1 Answer: A

Educational Objective: Prevent *Staphylococcus aureus* surgical site infection by evaluating for *S. aureus* nasal carriage.

The most appropriate measure to prevent surgical site infection is to evaluate for *Staphylococcus aureus* nasal carriage 2 weeks before surgery and decolonize if positive. *S. aureus* is the most common pathogen (23%) associated with surgical site infections (SSIs). SSIs after coronary artery bypass graft surgery can be serious and devastating, with mediastinitis related to *S. aureus* of particular concern. The 2016 World Health Organization guidelines recommend that patients known to be nasal carriers of *S. aureus* who are scheduled to undergo cardiothoracic or orthopedic surgery should have preoperative decolonization (mupirocin ointment for 5 days with or without chlorhexidine gluconate body wash) to decrease the risk of developing *S. aureus*–related SSI.

Data do not support extending antibiotic prophylaxis beyond 24 hours after cardiac surgery even while drains remain in place. For most other surgeries, no additional doses of antibiotic should be given postoperatively, even in cases of intraoperative spillage of gastrointestinal contents. Postoperative antibiotics are only indicated when treating an active infection.

Preoperative antibiotic prophylaxis reduces the risk of SSI by decreasing the concentration of pathogens at or around the incision site. The agent used and the timing of administration are key. For cardiac surgery, cefazolin is recommended unless a patient is known to have methicillin-resistant *S. aureus* colonization or has a severe (anaphylactic) β-lactam allergy, in which case vancomycin is used. For optimal benefit, the antibiotic should be administered 1 to 2 hours before incision. For procedures lasting more than several hours, the antibiotic should be redosed during surgery (for example, redose at 3-4 hours for cefazolin).

Preoperative shaving in the area of the planned incision increases the risk of SSI. Shaving causes microscopic abrasions of the skin, which promotes bacterial proliferation. Recommendations indicate only removing hair from the surgical site if it will interfere with the procedure, in which case clipping is preferred.

KEY POINT

- Patients undergoing cardiothoracic or orthopedic surgery should be screened for nasal carriage of *Staphylococcus aureus* and, if positive, should have preoperative decolonization.

Bibliography

Schweizer ML, Chiang HY, Septimus E, Moody J, Braun B, Hafner J, et al. Association of a bundled intervention with surgical site infections among patients undergoing cardiac, hip, or knee surgery. JAMA. 2015;313:2162-71. [PMID: 26034956] doi:10.1001/jama.2015.5387

Item 2 Answer: D

H

Educational Objective: Treat tuberculosis and immune reconstitution inflammatory syndrome in a patient with HIV.

The most appropriate management for this patient is to start rifabutin, isoniazid, ethambutol, and pyrazinamide therapy for tuberculosis. He began antiretroviral therapy 1 month ago and has responded well, with a significant decrease in viral load and increased CD4 cell count. The timing of his presentation is consistent with the immune reconstitution inflammatory syndrome (IRIS) (median 48 days), the return of a robust immune response resulting from treatment of the HIV that "unmasks" a pre-existing infection that appears like a new acute infection. This presentation is common with tuberculosis, which may present as a much more acute pulmonary illness resembling bacterial pneumonia. He had an indeterminate result on interferon-γ release assay (IGRA) because of an inadequate response to the positive control, which was the result of immunocompromise at the time of presentation; additionally, the results of IGRA testing are a poor indicator of active tuberculosis infection. He should begin four-drug antituberculous therapy while results of culture and susceptibility testing are pending. Nucleic acid amplification testing of the specimen may give information on the identification of the organisms and even the possibility of rifamycin resistance. Initial empiric treatment for tuberculosis should include a rifamycin as one of the four drugs, but rifabutin is often preferred over rifampin in patients with HIV because of fewer drug-drug interactions between rifabutin and antiretrovirals, including dolutegravir.

If this patient does have active tuberculosis, treatment is needed urgently; culture results may take weeks, so waiting would be inappropriate.

Antiretrovirals should not be stopped when IRIS occurs. Therapy should be continued while providing treatment for the newly diagnosed infection.

Prednisone can be added if IRIS is life threatening or involves the pericardium or central nervous system. None of these is the case in this patient; giving glucocorticoids without a known diagnosis increases the risk of worsening an infection that is not being directly treated.

KEY POINT

- Immune reconstitution inflammatory syndrome is the return of a robust immune response resulting from treatment of HIV that may "unmask" a pre-existing infection; when this occurs, the underlying infection should be treated while antiretroviral therapy is continued.

Bibliography

Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents. Guidelines for the prevention and treatment of opportunistic infections

in HIV infected adults and adolescents: recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. Available at https://aidsinfo.nih.gov/guidelines/html/4/adult-and-adolescent-opportunistic-infection/0. Accessed April 12, 2018.

Item 3 Answer: A

Educational Objective: Diagnose pulmonary coccidioidomycosis.

This patient has disseminated coccidioidomycosis manifesting as a pulmonary infection. The fungus *Coccidioides* is inhaled and causes an initial pulmonary infection. In endemic areas, as many as one third of cases of community acquired pneumonia (CAP) are caused by *Coccidioides* species. Healthy persons generally contain the initial infection owing to intact cell-mediated immunity; however, immunocompromised persons are at risk for dissemination. This endemic dimorphic fungal infection is known to mimic other diseases, including tuberculosis, histoplasmosis, sarcoidosis, and cancer. The patient is stationed in Bakersfield, California, an epicenter for this infection. In addition, his assignment as a car mechanic, with much of his work likely conducted outside, increases the risk of infection. Another clue is his peripheral eosinophilia. A definitive diagnosis generally is made on the basis of serology and histopathologic analysis of tissue. When coccidioidomycosis is diagnosed, first-line therapy is fluconazole to prevent progressive or disseminated disease.

Sarcoidosis is a systemic disease of unknown cause. It is slightly more frequent in black persons in their 20s and 30s, especially women. It frequently presents in the respiratory tract as bilateral hilar lymphadenopathy, with or without diffuse parenchymal lung changes. Unilateral hilar lymphadenopathy is distinctly unusual, as is eosinophilia. In addition, sarcoidosis tends to be a much more indolent process, presenting over several months to years with progressive cough and dyspnea. This patient developed symptoms acutely, over a 1-month period.

The most commonly identified organism causing CAP is *Streptococcus pneumoniae*. Suggestive clinical symptoms include fever, cough, sputum production, and dyspnea. Radiographic findings can be characterized as interstitial infiltrates, lobar consolidation, or cavitary lesions; unilateral hilar lymphadenopathy would be distinctly unusual. Finally, symptoms lasting for a month and peripheral eosinophilia are not characteristic of a bacterial lung infection.

Primary pulmonary tuberculosis may present with mid- to lower-zone unilateral infiltrates, unilateral hilar lymphadenopathy, and pleural effusions. Early in the course of the disease, laboratory findings are often normal; eosinophilia is not present. Finally, pulmonary tuberculosis is excluded by the negative interferon-γ release assay.

KEY POINT

- In endemic areas, as many as one third of cases of community-acquired pneumonia are caused by *Coccidioides* species.

Bibliography

Stockamp NW, Thompson GR 3rd. Coccidioidomycosis. Infect Dis Clin North Am. 2016;30:229-46. [PMID: 26739609] doi:10.1016/j.idc.2015.10.008

Item 4 Answer: C

H

Educational Objective: Treat community-acquired pneumonia in a hospitalized patient requiring ICU support.

The most appropriate treatment is ceftriaxone plus levofloxacin. This otherwise healthy patient presents with severe community-acquired pneumonia (CAP). The initial evaluation reveals respiratory failure (tachypnea and hypoxia), uremia, altered mentation, and multilobar infiltrates, all of which are minor criteria for severe disease based on Infectious Diseases Society of America/American Thoracic Society (IDSA/ATS) criteria. Patients with at least three minor criteria for severe disease have increased risk of mortality and are best managed in the ICU. Guideline-based recommendations for empiric therapy of CAP requiring ICU care include a third-generation cephalosporin or ampicillin-sulbactam to treat *Streptococcus pneumoniae*, gram-negative bacilli, or *Haemophilus influenzae* plus an agent active against *Legionella*, such as a macrolide or quinolone. The initial evaluation of this patient was positive for rhinovirus on a respiratory viral panel (RVP). Respiratory viruses are increasingly recognized among hospitalized patients with CAP; however, the significance of this finding is uncertain. Respiratory viruses may predispose patients to a secondary bacterial pneumonia or be present as a copathogen. Considering the severity of this patient's illness, antibiotics should be initiated and continued despite the positive RVP until a bacterial cause is excluded.

Azithromycin monotherapy is an appropriate choice for treatment of CAP in a previously healthy outpatient. Patients with more severe CAP are at risk for infections with numerous organisms, as well as with drug-resistant pathogens. For this reason, patients with CAP admitted to the ICU should receive combination therapy with an antipneumococcal β-lactam and either a macrolide or a fluoroquinolone.

Ceftazidime is a third-generation cephalosporin that is effective against *Pseudomonas* but has minimal activity against gram-positive organisms, including *S. pneumoniae*, and therefore would not be an appropriate choice, even as combination therapy with a macrolide, to treat CAP.

Piperacillin-tazobactam plus ciprofloxacin would be indicated when concern for *Pseudomonas* pneumonia is present; however, in a previously healthy patient with minimal health care interactions or previous antibiotic use, *Pseudomonas* would be an unlikely pathogen.

KEY POINT

- Guideline-based recommendations for empiric therapy of community-acquired pneumonia requiring ICU admission include a third-generation cephalosporin or ampicillin-sulbactam to treat *Streptococcus pneumoniae*, gram-negative bacilli, or *Haemophilus influenzae* plus an agent active against *Legionella*, such as a macrolide or quinolone.

Bibliography

Mandell LA, Wunderink RG, Anzueto A, Bartlett JG, Campbell GD, Dean NC, et al; Infectious Diseases Society of America. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis. 2007;44 Suppl 2:S27-72. [PMID: 17278083]

Item 5 Answer: B

Educational Objective: Evaluate fever of unknown origin.

The most appropriate diagnostic test in this patient is CT of the abdomen and pelvis. He meets the criteria for classic fever of unknown origin, which is defined by fever of 38.3 °C (100.9 °F) or greater for 3 or more weeks that remains undiagnosed after two visits in the ambulatory setting. Taking a careful, detailed history is the starting point in evaluating a patient with fever of unknown cause. The history may need to be repeated on subsequent visits because subtle clues may be revealed only later. All symptoms should be considered relevant. A history of comorbid conditions and a surgical, obstetric or gynecologic (in women), medication, travel, and social history should be elicited followed by a careful physical examination that includes full neurologic, musculoskeletal, ear-nose-throat, eye or funduscopic, skin, lymphatic, and urogenital examinations. The results of basic laboratory and imaging studies along with the history and physical examination findings are used to guide further evaluation. In this patient, the initial evaluation for infectious causes (tuberculosis, endocarditis, urinary tract infection), neoplasms (lymphoma, leukemia), and connective tissue disease is unrevealing. Therefore, the patient should undergo CT of the abdomen and pelvis (with and without contrast) to evaluate for abscess, neoplasm (hepatoma, renal cell carcinoma), splenomegaly, and lymphadenopathy. The prognosis is good for adults who remain undiagnosed after extensive evaluation.

Bone marrow biopsy is generally considered when the complete blood count is abnormal and a process involving the bone marrow (such as tuberculosis, histoplasmosis, or malignancy) is evident.

Liver biopsy is considered in the setting of abnormal liver chemistry tests and a suggested abnormality on imaging. It would not be appropriate at this time.

If signs or symptoms referable to the central nervous system are evident, imaging of the head and lumbar puncture should be considered. However, this patient has no central nervous system findings.

KEY POINT

- Initial studies for fever of unknown origin in most patients typically include a complete blood count with differential, complete metabolic profile with kidney and liver studies, at least three blood culture sets and cultures of other bodily fluids (such as urine or from other sources based on clinical suspicion), an erythrocyte sedimentation rate, tuberculosis testing, and serology for HIV; it is reasonable to perform chest imaging (radiography or CT) as initial diagnostic imaging.

Bibliography

Mulders-Manders C, Simon A, Bleeker-Rovers C. Fever of unknown origin. Clin Med (Lond). 2015;15:280-4. [PMID: 26031980] doi:10.7861/clinmedicine.15-3-280

Item 6 Answer: B

H

Educational Objective: Diagnose invasive aspergillosis.

This patient most likely has disseminated aspergillosis with lung and brain involvement. Aspergillus invades blood vessels and causes distal infarction of infected tissue. Patients with invasive pulmonary aspergillosis may have fever, cough, chest pain, and hemoptysis at presentation. Pulmonary infiltrates, nodules, or wedge-shaped densities resembling infarcts may also be seen on chest radiographs; CT scans may show a target lesion with a necrotic center surrounded by a ring of hemorrhage (halo sign). Central nervous system involvement may manifest as a brain abscess or infarction. Other sites of involvement include blood vessels in the heart, gastrointestinal tract, or skin. Risk factors for invasive or disseminated aspergillosis include profound and prolonged neutropenia and hematopoietic stem cell transplantation. The second most common risk group for invasive aspergillosis is solid organ (heart, lung, liver, kidney) transplant recipients. The infection has also increasingly been reported in patients who are critically ill and in ICUs, especially those with exposure to glucocorticoids. The most efficient way to establish a definitive diagnosis (and then initiate antifungal therapy) is with bronchoalveolar lavage (BAL) and biopsy. In patients with disseminated aspergillosis, the serum galactomannan assay has a sensitivity of less than 30% and is not very useful; in contrast, the BAL galactomannan assay has a much higher sensitivity and specificity. Therefore, BAL fluid samples should be collected for analysis, and tissue biopsy should be performed.

A brain biopsy is sometimes useful to establish a definitive diagnosis but carries a much greater risk of causing adverse effects than bronchoscopy and BAL. If the lung biopsy is negative, then a brain biopsy should be considered.

Fungal blood cultures have a low sensitivity in all invasive mold infections but especially in invasive aspergillosis, in which less than 1% of patients with infection have a positive culture.

KEY POINT

- Risk factors for invasive or disseminated aspergillosis include profound and prolonged neutropenia and stem cell and solid organ transplantation; patients have fever, cough, chest pain, and hemoptysis at presentation, and pulmonary infiltrates, nodules, or wedge-shaped densities may be seen on chest radiographs.

Bibliography

Cadena J, Thompson GR 3rd, Patterson TF. Invasive aspergillosis: current strategies for diagnosis and management. Infect Dis Clin North Am. 2016;30:125-42. [PMID: 26897064] doi:10.1016/j.idc.2015.10.015

H

Item 7 Answer: C

Educational Objective: Diagnose leptospiral meningitis.

The most likely diagnosis is leptospirosis. She presents with a biphasic illness after freshwater exposure in an area highly endemic for leptospirosis. Infection occurs by direct exposure to urine or tissues of infected animals or indirectly through contaminated water or soil. Rodents and other small mammals are the most significant sources of human disease. Leptospiral meningitis usually develops weeks after exposure, in the second phase of the illness, but may merge with the first phase in severe disease and can present with uveitis, rash, conjunctival suffusion (conjunctival redness without exudate), sepsis, lymphadenopathy, kidney injury, and hepatosplenomegaly. Subconjunctival suffusion may be subtle but is a finding that rarely occurs in other infections. The cerebrospinal fluid (CSF) findings resemble enteroviral meningitis, but empiric treatment with doxycycline should be started pending confirmation.

Most persons who develop HIV infection experience an acute symptomatic illness, referred to as acute retroviral syndrome, within a few weeks of acquiring the infection. Symptoms are most often consistent with an infectious mononucleosis with fever, malaise, lymphadenopathy, rash, and pharyngitis. Some of these patients will develop meningitis or meningoencephalitis. Meningitis caused by acute HIV infection is typically self-limited and may be clinically indistinguishable from other viral meningitis syndromes, but jaundice, kidney injury, and subconjunctival suffusion are not seen with acute HIV infection.

Patients with herpes simplex meningitis have typical meningitis symptoms, such as fever, nuchal rigidity, headache, and photophobia. Jaundice, kidney injury, and subconjunctival suffusion are not characteristic of herpes simplex meningitis.

Treponema pallidum meningitis can occur in the secondary or tertiary phase of syphilis. Headache and meningismus are common; decreased visual acuity secondary to uveitis, vitreitis, retinitis, or optic neuropathy can be seen, as well as other cranial neuropathies. The CSF usually shows a lymphocytic pleocytosis with an elevated protein level. This patient's clinical course is not compatible with syphilitic meningitis.

KEY POINT

- Leptospiral meningitis usually develops weeks after exposure, during the second phase of illness, and can present with uveitis, rash, conjunctival suffusion, sepsis, lymphadenopathy, kidney injury, and hepatosplenomegaly.

Bibliography

Londeree WA. Leptospirosis: the microscopic danger in paradise. Hawaii J Med Public Health. 2014;73:21-3. [PMID: 25478298]

H

Item 8 Answer: D

Educational Objective: Treat fulminant *Clostridium difficile* infection.

The most appropriate treatment is oral vancomycin plus intravenous metronidazole. Treatment of *Clostridium difficile* infection (CDI) should be stratified according to its severity. The Society for Healthcare Epidemiology of America and the Infectious Diseases Society of America define severe CDI by a leukocyte count ≥15,000/µL (15×10^9/L) or a serum creatinine level >1.5 mg/dL (133 µmol/L). The American College of Gastroenterology defines severe CDI by the presence of hypoalbuminemia (<3 g/dL [30 g/L]) plus leukocytosis (≥15,000/µL [15×10^9/L]) or abdominal tenderness. Fulminant CDI is defined as severe infection complicated by ileus, hypotension, shock, or toxic megacolon.

Medical therapy for fulminant CDI includes oral vancomycin plus intravenous metronidazole; vancomycin enemas may also be added if ileus is present. Complications are treated on an individual basis, although the presence of toxic megacolon requires surgical consultation to determine if emergent colectomy is indicated.

Fecal microbiota transplant is effective for treatment of recurrent episodes of CDI, but it is not recommended for an initial episode of CDI, regardless of severity.

Oral metronidazole alone for 10 days can be used for patients who present with an initial episode of nonsevere CDI when oral vancomycin or fidaxomicin is not available.

Oral vancomycin alone for 10 days is recommended for treatment of an initial episode of nonsevere and severe CDI. Oral fidaxomicin can also be used.

Oral metronidazole does not add benefit when used in addition to oral vancomycin.

KEY POINT

- Fulminant *Clostridium difficile* infections require oral vancomycin plus intravenous metronidazole; vancomycin enemas may also be added if ileus is present.

Bibliography

McDonald LC, Gerding DN, Johnson S, Bakken JS, Carroll KC, Coffin SE, et al. Clinical practice guidelines for *Clostridium difficile* infection in adults and children: 2017 update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA). Clin Infect Dis. 2018;66:987-994. [PMID: 29562266] doi:10.1093/cid/ciy149

Item 9 Answer: D

Educational Objective: Diagnose post–Lyme disease syndrome.

This patient most likely now has post–Lyme disease syndrome (PLDS). In a patient who lives in or has visited an area endemic for Lyme disease, a skin lesion consistent with erythema migrans is sufficient to make a clinical diagnosis of early localized Lyme disease. Early localized Lyme disease is treated with doxycycline for 10 to 21 days. Despite appropriate therapy, this patient continues to experience nonspecific but debilitating symptoms that have persisted for several months. She most likely has PLDS, a poorly understood sequela of Lyme disease that sometimes is misclassified as "chronic Lyme disease" despite a lack of microbiologic evidence of a persistent viable organism. PLDS is thought to be due to a disordered immunologic response to the preceding infection. Most patients slowly improve over a period of

6 months, and treatment is directed toward symptom amelioration. Randomized controlled trials have shown that patients with PLDS do not respond to prolonged courses of antibiotic therapy, and such treatment is not warranted in this population.

Anaplasma phagocytophilum, *Babesia microti*, and Powassan virus are all transmitted by the same tick vector as *Borrelia burgdorferi*, the causative spirochete of Lyme disease, and coinfections may occur. Anaplasmosis is treated with doxycycline, and the patient's previous course of treatment should have eradicated any incubating disease.

In contrast, doxycycline is not effective therapy for babesiosis. Mild babesiosis may present as a nonspecific flu-like illness, although fever typically is present. The hallmark of babesiosis is hemolytic anemia, and normal laboratory studies in this patient essentially exclude this diagnosis.

In the United States, late-stage Lyme disease most commonly presents as an inflammatory arthritis involving larger joints. The patient has no physical findings consistent with this diagnosis and had appropriate treatment to prevent progression to late-stage Lyme disease.

Powassan virus causes meningoencephalitis rather than the nonspecific symptoms manifested by this patient.

KEY POINT

- Post-Lyme disease syndrome is a poorly understood sequela of Lyme disease thought to be due to a disordered immunologic response to the preceding infection; most patients slowly improve over a 6-month course, and treatment is directed toward symptom amelioration.

Bibliography

Aucott JN. Posttreatment Lyme disease syndrome. Infect Dis Clin North Am. 2015;29:309-23. [PMID: 25999226] doi:10.1016/j.idc.2015.02.012

Item 10 Answer: B

Educational Objective: Diagnose *Mycobacterium fortuitum* infection.

This patient most likely has an infection with *Mycobacterium fortuitum*. *M. fortuitum* is one of the rapidly growing, nontuberculous mycobacteria (NTM) capable of producing chronic, nonhealing wounds anywhere the bacteria has been introduced, including skin, soft tissue, surgical sites, and occasionally on prosthetic devices. Although *M. fortuitum* is not part of the differential diagnosis of acute wound infections, NTM should always be considered in chronic wounds, especially when conventional antimicrobial therapy has been ineffective. To diagnose an NTM infection, a deep biopsy of chronic wound tissue should be performed. The biopsy specimen should be sent for histopathology to stain for bacteria, mycobacteria, and fungi, and a portion should be sent to the microbiology laboratory for similar stains and cultures.

Pulmonary disease is the most common manifestation of NTM infection, and *Mycobacterium avium* complex (MAC) infection is the most common causative species. MAC is also responsible for most cases of NTM lymphadenitis. Disseminated MAC infection develops in patients with HIV who have CD4 cell counts less than 50/µL and are not receiving MAC prophylaxis. The clinical presentation often includes fever, night sweats, weight loss, and gastrointestinal symptoms. MAC would not be responsible for a solitary, nonhealing cutaneous ulcer.

Mycobacterium kansasii most commonly causes a lung infection that mimics tuberculosis, with cough, fever, weight loss, and cavitary lung disease. Risk factors for infection include COPD, cancer, HIV, alcohol abuse, and drug-associated immunosuppression. *M. kansasii* does not cause isolated chronic skin or soft tissue infections.

Leprosy is caused by the acid-fast bacillus *Mycobacterium leprae*, a slow-growing organism. Leprosy should be considered in the setting of chronic skin lesions that fail to respond to treatment of common skin conditions or when sensory loss is observed within lesions or in extremities. This patient's rapid development of a nonhealing ulcer after an initial injury 1 month ago is not compatible with infection caused by *M. leprae*.

KEY POINT

- Rapidly growing, nontuberculous mycobacteria, such as *Mycobacterium fortuitum*, can produce chronic, nonhealing wounds that do not respond to conventional antimicrobial therapy.

Bibliography

Guglielmetti L, Mougari F, Lopes A, Raskine L, Cambau E. Human infections due to nontuberculous mycobacteria: the infectious diseases and clinical microbiology specialists' point of view. Future Microbiol. 2015;10:1467-83. [PMID: 26344005] doi:10.2217/fmb.15.64

Item 11 Answer: A

Educational Objective: Treat pelvic inflammatory disease in an outpatient.

The most appropriate treatment for this patient is a single dose of intramuscular ceftriaxone (250 mg) plus oral doxycycline (100 mg twice daily) for 14 days. The patient has risk factors for sexually transmitted infections (multiple partners and inconsistent condom use) and presents with symptoms suggesting pelvic inflammatory disease (PID). Uterine and cervical motion tenderness are sensitive findings for the diagnosis of PID; the likelihood of PID is further increased by the presence of mucopurulent cervical discharge. Antibiotic therapy should begin before diagnostic testing results are received. Although PID is a polymicrobial infection, testing only for the common sexually transmitted pathogens, *Neisseria gonorrhoeae* and *Chlamydia trachomatis*, is recommended. Although a positive result for either pathogen significantly increases the probability of PID, even if the result is negative, a treatment course for PID should be completed based on clinical findings. Women with an intrauterine device can be treated successfully with the device in place

in most cases. In addition to the diagnostic testing obtained from the cervical discharge, this patient should be screened for HIV and syphilis.

This patient has no signs of systemic toxicity or findings to suggest a potential surgical emergency, so hospitalization is not indicated. She is not pregnant and has no history suggesting she would be unable to tolerate oral therapy, so ambulatory treatment is appropriate. Intravenous cefoxitin plus doxycycline and intravenous clindamycin plus gentamicin are regimens for inpatient management of PID. Intravenous ampicillin-sulbactam plus doxycycline is an alternate regimen for hospitalized patients; however, oral amoxicillin-clavulanate is not recommended for the treatment of PID.

KEY POINT

- In patients with a high likelihood of pelvic inflammatory disease without indications for hospitalization, empiric therapy with intramuscular ceftriaxone and oral doxycycline is appropriate without waiting for microbiologic testing results.

Bibliography

Brunham RC, Gottlieb SL, Paavonen J. Pelvic inflammatory disease. N Engl J Med. 2015;372:2039-48. [PMID: 25992748] doi:10.1056/NEJMra1411426

H

Item 12 Answer: A

Educational Objective: Manage asymptomatic bacteriuria in a patient undergoing an invasive urologic procedure.

The indication for antimicrobial therapy in this patient is an invasive urologic procedure. Because urine is a sterile body fluid, the presence of significant bacteriuria is considered to be an infection. In men, either 10^5 cfu/mL of bacteria from voided urine or at least 10^2 cfu/mL of a single bacterial species from a clean intermittent catheterized sample is required to distinguish true bacteriuria from contamination. Asymptomatic bacteriuria (ASB) is diagnosed when no signs or symptoms of active infection referable to the urinary tract are present. Depending on variables such as age and genitourinary abnormalities, older adult men have an ASB prevalence of approximately 5% to 20% in the community, rising to 15% to 40% in long-term care facilities. It is important to recognize that screening for and possibly treating asymptomatic bacteriuria is supported by only two indications: pregnancy and risk mitigation before an invasive urologic procedure. The use of prophylactic antibiotics before minor noninvasive urologic interventions without mucosal bleeding does not provide any benefit and is not recommended.

Likewise, screening for and treating ASB in patients about to undergo orthopedic surgery, including total joint arthroplasty, is without proven merit because it is not a cause of postoperative surgical site infection.

Data are insufficient to advocate the routine treatment of ASB in kidney transplant recipients or patients with diabetes.

KEY POINT

- Screening for and possibly treating asymptomatic bacteriuria is supported by only two indications: pregnancy and medical clearance before an invasive urologic procedure.

Bibliography

Nicolle LE. Asymptomatic bacteriuria. Curr Opin Infect Dis. 2014;27:90-6. [PMID: 24275697] doi:10.1097/QCO.0000000000000019

H

Item 13 Answer: B

Educational Objective: Prevent HIV infection after exposure.

This patient has sustained a possible exposure to HIV and should begin postexposure prophylaxis as soon as possible with a three-drug regimen of tenofovir, emtricitabine, and dolutegravir. Significant risk factors for the exposure include that it was a hollow-bore needle with visible blood. If the source patient was known to have an undetectable viral load in blood, the risk would be reduced but not eliminated; however, the source patient's viral load is unknown at this time. Drug selection may be modified depending on the source patient's history of viral resistance, but the preferred empiric postexposure prophylaxis regimens include tenofovir disoproxil fumarate, emtricitabine, and either dolutegravir or raltegravir, and should be given for 4 weeks. The same recommendations are appropriate whether the exposure was occupational or nonoccupational. The exposed patient should be tested for HIV immediately, 4 to 6 weeks later, and 3 months after the exposure. Exposed persons should also be counseled on transmission, symptoms of acute infection, and toxicity of the medications being prescribed.

A two-drug regimen for postexposure prophylaxis (compared with pre-exposure prophylaxis) is no longer recommended.

Protease inhibitors such as darunavir, whether boosted or not, are not recommended for prophylaxis because of their higher rates of adverse effects.

Because postexposure prophylaxis must begin promptly to be most effective, it would not be appropriate to wait for results of the source patient's viral load before determining therapy. The source patient should also be tested for other blood-borne pathogens, such as hepatitis B and C.

KEY POINT

- Preferred HIV postexposure prophylaxis regimens include tenofovir disoproxil fumarate, emtricitabine, and either dolutegravir or raltegravir and are appropriate whether the exposure was occupational or nonoccupational.

Bibliography

Centers for Disease Control and Prevention. Updated guidelines for antiretroviral postexposure prophylaxis after sexual, injection drug use, or other nonoccupational exposure to HIV-United States, 2016. Available at https://stacks.cdc.gov/view/cdc/38856. Accessed November 2, 2017.

Item 14 Answer: A

Educational Objective: Manage acute pyelonephritis with bacteremia in a woman.

This patient should complete her prescribed 7-day course of oral ciprofloxacin. She has acute uncomplicated pyelonephritis, which can usually be managed with outpatient oral antimicrobial therapy. Ciprofloxacin for 1 week or levofloxacin for 5 days are the recommended first-line treatment regimens. An initial dose of a long-acting parenteral antibiotic (such as ceftriaxone or aminoglycoside) is suggested when local fluoroquinolone resistance (>10%) is a concern. When a fluoroquinolone antibiotic cannot be used or the bacterial isolate proves resistant, an alternative second-line oral antibiotic should be substituted. Available options include trimethoprim-sulfamethoxazole or the less well-studied oral β-lactam agents.

With the exception of pregnancy, follow-up microbiologic cultures and urinalysis are not required or indicated after resolution of infection.

Extending the duration of ciprofloxacin therapy beyond 7 days would be warranted for complicated pyelonephritis but should not be influenced by the discovery of the single bloodstream isolate in this otherwise healthy woman.

Transient bacteremia does not necessitate hospitalization for parenteral antimicrobial therapy except when the pathogen is found to be multidrug resistant or when complicating features are present (severe illness, obstruction, pregnancy).

In adult women with acute kidney infections, urinary tract imaging by ultrasonography or CT is not routinely performed. However, urologic imaging may be useful and is recommended in evaluating patients who do not clinically improve after 72 hours of adequate antimicrobial therapy or when complications such as obstruction or perinephric and renal abscesses are suspected. Such studies should also be considered when evaluating women who experience an excessive number of recurrent urinary tract infections.

KEY POINT

- Acute, uncomplicated pyelonephritis can usually be managed with oral outpatient antimicrobial therapy, with the fluoroquinolones ciprofloxacin and levofloxacin being the preferred, first-line agents.

Bibliography

Kumar S, Dave A, Wolf B, Lerma EV. Urinary tract infections. Dis Mon. 2015;61:45-59. [PMID: 25732782] doi:10.1016/j.disamonth.2014.12.002

Item 15 Answer: C

Educational Objective: Diagnose *Giardia lamblia* infection.

This patient with selective IgA deficiency most likely has chronic diarrhea due to a *Giardia lamblia* infection. Typical symptoms of *Giardia* include watery diarrhea that is fatty and foul smelling, bloating, crampy abdominal pain, flatulence, and nausea; fever is uncommon. In immunocompetent hosts, *Giardia* infection symptoms typically resolve within 2 to 4 weeks, but in patients with humoral immunodeficiency, such as hypogammaglobulinemia or selective IgA deficiency, *Giardia* infection may be prolonged because of impaired protection against *Giardia* adherence to the intestinal epithelium. Patients with selective IgA deficiency have impaired humoral immunity but no impairment in neutrophil, T cell, or complement function. Infectious complications of selective IgA deficiency typically include recurrent respiratory tract infections and chronic diarrhea caused by *Giardia*.

Although *Clostridium difficile* can cause recurrent disease, this patient does not have a history of recent antibiotic use or any other risk factors for *C. difficile* infection such as advanced age, chemotherapy, gastrointestinal surgery, inflammatory bowel disease, or gastric acid suppression with proton pump inhibitors.

Enterohemorrhagic *Echerichia coli* (EHEC) infection is usually spread by ingestion of undercooked meat or fecally contaminated food. EHEC typically presents with bloody acute diarrhea, crampy abdominal pain, and no fever.

Listeria monocytogenes can cause an acute gastroenteritis syndrome associated with diarrhea, emesis, fever, headache, and nonbloody watery diarrhea associated with pain in muscles and joints. But such an infection typically lasts less than 2 days. Invasive complications of infection, including bacteremia and meningitis, are seen in conditions primarily associated with cell-mediated immune dysfunction such as pregnancy, use of glucocorticoids, and extremes of age (neonates or those older than 65 years).

Nontyphoidal *Salmonella* is the most common cause of foodborne illness. Infection usually results from ingesting fecally contaminated water or food of animal origin. Symptoms are typically self-limited and include crampy abdominal pain, fever, headache, nonbloody diarrhea, nausea, and vomiting. Severe invasive disease may occur in patients with cell-mediated immunodeficiency, but the clinical presentation is not significantly altered in selective IgA deficiency.

KEY POINT

- Patients with selective IgA deficiency are susceptible to *Giardia lamblia* infection, manifesting as abdominal cramping, bloating, and chronic diarrhea.

Bibliography

Einarsson E, Ma'ayeh S, Svärd SG. An up-date on Giardia and giardiasis. Curr Opin Microbiol. 2016;34:47-52. [PMID: 27501461] doi:10.1016/j.mib.2016.07.019

Item 16 Answer: C

Educational Objective: Evaluate a patient with recent Zika virus exposure.

Testing for Zika virus IgM antibodies is the most appropriate management for this pregnant patient, who has had possible exposure to Zika virus through unprotected sexual activity. Asymptomatic pregnant women not living in an area with active Zika virus transmission who may have been exposed

more than 2 weeks previously require testing for Zika virus IgM antibodies; a positive result would indicate probable recent infection. Men who have had symptomatic or asymptomatic infection have been proven to have detectable Zika virus RNA in their semen for up to several weeks, with subsequent sexual transmission to their female partner. Under such circumstances, condoms should be used with each sexual encounter for at least 3 months. Her husband's recent viral-like illness occurring in an endemic geographic area, although unconfirmed, must be presumed to have been Zika virus infection. Evaluating her for evidence of asymptomatic infection is of paramount importance to provide counseling and investigate the possible risk of congenital Zika syndrome, of which microcephaly is the most frequent manifestation.

Patients with dengue may be asymptomatic or present with acute febrile illness associated with frontal headache, retro-orbital pain, myalgia, and arthralgia, with or without purpura, melena, or conjunctival injection. Gastrointestinal or respiratory symptoms may predominate. Severe lumbosacral pain is characteristic ("breakbone fever"). As the fever abates, a macular or scarlatiniform rash, which spares the palms and soles and evolves into areas of petechiae on extensor surfaces, may develop. The husband's symptoms are not compatible with dengue. Even if he did have dengue, he cannot transmit the infection to his wife, and testing her for dengue infection is not indicated.

Pregnant women with proven or presumptive recent Zika virus infection require serial ultrasonography every 3 to 4 weeks to assess fetal anatomy and growth. Frequent ultrasonographic monitoring may be appropriate if recent Zika infection is confirmed.

RNA nucleic acid amplification testing for the presence of Zika virus in serum and urine has a greatly diminished sensitivity if performed more than 2 weeks after symptomatic or asymptomatic exposure. In this case, Zika virus IgM antibody testing is preferred.

KEY POINT

- In patients with potential Zika virus exposure more than 2 weeks previously, testing for Zika virus IgM antibodies is necessary.

Bibliography

Petersen LR, Jamieson DJ, Powers AM, Honein MA. Zika virus. N Engl J Med. 2016;374:1552-63. [PMID: 27028561] doi:10.1056/NEJMra1602113

H Item 17 Answer: D

Educational Objective: Diagnose Ramsay Hunt syndrome caused by varicella-zoster virus infection.

Varicella-zoster virus (VZV) is the most likely cause of this patient's findings. VZV reactivation presents with pain or paresthesias in a specific dermatome; the characteristic rash develops several days later. In order of frequency, the thoracic, trigeminal, lumbar, and cervical cutaneous dermatomes are most often involved. More than 50% of cases occur in persons older than 60 years; immunocompromised patients are also at risk. Involvement of the geniculate ganglion may cause herpes zoster oticus, also known as the Ramsay Hunt syndrome, characterized by pain and vesicles in the external ear canal, ipsilateral peripheral facial palsy, and altered or absent taste. Patients may also experience hearing loss, tinnitus, and altered lacrimation. Most experts consider Ramsay Hunt syndrome to be a polycranial neuropathy, with frequent involvement of cranial nerves V, IX, and X. A vesicular rash may be absent in patients with VZV (zoster sine herpete) and should not deter physicians from ordering polymerase chain reaction testing for VZV. Acyclovir is typically prescribed for this syndrome. The live attenuated zoster vaccine has 64% efficacy that decreases to 36% after 6 years. A novel recombinant zoster vaccine, approved in 2017, has 97% efficacy and should be given to this patient.

The most common neurologic manifestation of early disseminated Lyme disease is facial nerve palsy, which may be unilateral or bilateral. Treatment of early localized disease prevents progression of infection. Untreated patients may progress to early disseminated infection. This stage typically presents as a febrile illness associated with erythema migrans at multiple sites distant from the initial tick attachment. Constitutional symptoms are common and include fever, myalgia, arthralgia, and headache. Neurologic Lyme disease without a history of tick bite, erythema migrans rash, or systemic symptoms is highly unlikely.

Bell palsy is defined as an isolated paralysis of the facial nerve that leads to complete unilateral facial paralysis. Herpes simplex virus (HSV) type 1 reactivation is the likely cause of Bell palsy in most cases. However, most cases of Bell palsy are diagnosed as "idiopathic" because it is difficult in clinical practice to prove that reactivation of HSV-1 is the cause of this peripheral neuropathy.

HSV type 2 is more commonly associated with genital ulcers, recurrent aseptic meningitis, or myelitis than with Bell palsy. Neither Lyme disease nor HSV reactivation can explain the burning and stinging ear pain, tinnitus, hearing loss, and facial palsy experienced by this patient as well as VZV reactivation can.

KEY POINT

- Varicella-zoster virus is a cause of Ramsay Hunt syndrome, which usually presents with ear pain, a vesicular rash in the external ear (although the rash may be absent), and ipsilateral peripheral facial palsy.

Bibliography

Cohen JI. Clinical practice: Herpes zoster. N Engl J Med. 2013;369:255-63. [PMID: 23863052] doi:10.1056/NEJMcp1302674

Item 18 Answer: B

Educational Objective: Diagnose Q fever pneumonia.

The most likely cause of this patient's illness is *Coxiella burnetii*. He presents with community-acquired pneumonia not requiring hospitalization, which is most frequently caused by atypical bacteria, *Streptococcus pneumoniae*, or a

viral pathogen. His occupation puts him at risk for zoonotic causes of pneumonia as well. Many zoonotic organisms can potentially cause pulmonary infection, but they can usually be differentiated based on illness severity and animal reservoir. In this patient, the relatively mild infection coupled with exposure to livestock makes *C. burnetii* the most likely culprit. *C. burnetii*, which causes Q fever pneumonia, is most frequently associated with exposure to farm animals, parturient animals in particular. High rates of seropositivity have been reported in farmers, veterinarians, and abattoir workers. Infection can occur without direct animal exposure; increased rates of Q fever pneumonia have been found among persons residing in proximity to livestock farms. Infection occurs after inhalation of aerosolized bodily fluids from infected animals. Acute pulmonary infection ranges from subclinical to severe, but it is rarely fatal. Treatment with doxycycline is indicated to decrease symptom duration and to prevent progression to chronic Q fever.

Bacillus anthracis is the causative agent of anthrax. Cutaneous anthrax is the most common naturally occurring form of the disease. In the United States, inhalation anthrax is almost exclusively of concern as an agent of bioterrorism. In endemic areas, pulmonary infection may occur after inhalation of spores from the fur or hide of infected livestock, particularly goats and cattle. Inhalation anthrax is a fulminant, often fatal infection.

Chlamydia psittaci is the causative agent of psittacosis, which typically presents as pneumonia associated with abrupt onset of fever, severe headache, and dry cough. This organism is associated with inhalation of dried bird droppings, so bird owners or breeders and poultry farmers are at particularly high risk for this infection.

Pneumonic tularemia occurs either after direct inhalation or through secondary spread of *Francisella tularensis* into the lungs. Pneumonic tularemia is characterized by a nonproductive cough, dyspnea, and substernal or pleuritic chest pain. Chest radiographs show infiltrates, hilar lymphadenopathy, and pleural effusion. In the United States, most infections are transmitted through animal exposure. Hunters are at particularly high risk for primary tularemia pneumonia through skinning and dressing of infected rabbits or other wild game.

Yersinia pestis infection of the lung causes pneumonic plague. Rodents serve as the primary reservoir for plague. Pulmonary infection occurs through droplet transmission from an infected host or secondary spread from an extrapulmonary source. Patients present with sudden high fever, pleuritic chest pain, a productive cough, and hemoptysis. Pneumonic plague is almost uniformly fatal unless recognized and treated promptly.

KEY POINT

- Many zoonotic organisms have the potential to cause pulmonary infection, but they can be differentiated based on the severity of illness and animal reservoir; relatively mild infection coupled with exposure to livestock indicates likely *Coxiella burnetii* infection.

Bibliography

Freidl GS, Spruijt IT, Borlée F, Smit LA, van Gageldonk-Lafeber AB, Heederik DJ, et al. Livestock-associated risk factors for pneumonia in an area of intensive animal farming in the Netherlands. PLoS One. 2017;12:e0174796. [PMID: 28362816] doi:10.1371/journal.pone.0174796

Item 19 Answer: D

H

Educational Objective: Treat coagulase-negative *Staphylococcus* central line–associated bloodstream infection.

The most appropriate management is to remove the peripherally inserted central catheter (PICC) and repeat blood cultures. Central line–associated bloodstream infections (CLABSIs) can occur with any type of catheter, including short-term peripheral intravenous catheters and PICCs. They are most commonly caused by coagulase-negative *Staphylococcus* followed by *S. aureus*. Coagulase-negative *Staphylococcus* is less virulent than *S. aureus* and is less likely to cause metastatic infection or endocarditis in patients without prosthetic devices or endovascular hardware (such as prosthetic heart valves) in place. Coagulase-negative *Staphylococcus* CLABSIs often resolve with removal of the catheter. Blood cultures should be repeated after catheter removal to document clearance of the organism. Alternatively, patients with coagulase-negative *Staphylococcus* CLABSIs can be treated with antibiotics for 5 to 7 days if the catheter is removed and for 10 to 14 days in combination with antibiotic lock therapy if the catheter is not removed.

Most uncomplicated CLABSIs are treated for 7 to 14 days; *S. aureus* CLABSIs may require treatment for 4 to 6 weeks after catheter removal. Shorter therapy durations (14 days) may be considered in select patients with *S. aureus* CLABSI whose catheters have been removed and who do not have diabetes mellitus, are not immunosuppressed, have no implanted prosthetic devices, have no evidence of endocarditis by echocardiography (preferably transesophageal), and have no evidence of infected thrombophlebitis; whose fever and bacteremia resolve within 72 hours of starting appropriate therapy; and whose physical examination and diagnostic tests do not suggest the presence of metastatic infection.

In patients with persistent bacteremia or endovascular hardware, transesophageal echocardiography may be pursued to evaluate for endocarditis. In patients with endovascular hardware, longer durations of antibiotics are generally required. Catheters should always be removed when endocarditis, metastatic infection, hemodynamic instability, suppurative thrombophlebitis, or persistent bacteremia is evident.

KEY POINT

- Coagulase-negative *Staphylococcus* is less virulent than *S. aureus* and is less likely to cause metastatic infection or endocarditis in patients without prosthetic devices or endovascular hardware in place (such as prosthetic heart valves) and may be treated with simple removal of the intravenous catheter.

Bibliography

Mermel LA, Allon M, Bouza E, Craven DE, Flynn P, O'Grady NP, et al. Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 update by the Infectious Diseases Society of America. Clin Infect Dis. 2009;49:1-45. [PMID: 19489710] doi:10.1086/599376

Item 20 Answer: D

Educational Objective: Prevent catheter-associated urinary tract infection by removing the catheter.

The proper management of the patient's urinary catheter is to remove it and observe the patient for spontaneous voiding. Catheters should be used for appropriate indications only, which include urinary retention and bladder outlet obstruction, measurement of urinary output in critically ill patients, perioperative use for selected surgical procedures, assistance with healing of perineal or sacral wounds in patients with incontinence, use in patients requiring prolonged immobilization, and contribution to comfort at the end of life. An indwelling urinary catheter is sometimes inserted in the emergency department during trauma evaluation; however, the need for continuing the catheter should be assessed when the initial evaluation has been completed. If this patient required prolonged immobilization (for example, multiple traumatic injuries such as pelvic fractures), continuing the indwelling urinary catheter may be appropriate. Patients should be monitored closely for their ability to void spontaneously when a catheter is removed. Bladder ultrasonography can be used to determine residual postvoid volume; if more than 200 mL remain, consider intermittent catheterization for a short amount of time rather than placing a new indwelling urinary catheter. Early removal of urinary catheters should be considered when possible and can be encouraged by reminder systems. Additionally, nurse-initiated removal protocols have been shown to be effective in limiting duration of catheterization. Catheter-associated urinary tract infection (CAUTI) prevention strategies are summarized by the acronym ABCDE: Adhere to general infection control principles, perform Bladder ultrasonography to potentially avoid catheterization, use Condom catheters or intermittent catheterization when appropriate, Do not use an indwelling catheter if criteria for use are not met, and remove catheters Early when they are no longer indicated using computerized reminders or nurse-driven removal protocols.

Antimicrobial-impregnated or antiseptic-coated catheters have not been shown to decrease CAUTIs with short-term (<14 days) catheterization. Information is scarce on their benefits with long-term urinary catheters. Early removal of the catheter is a better care strategy.

Administering antibiotics with the goal of preventing infection is not effective and promotes antibiotic-resistant bacteria and fungal CAUTIs and is not indicated in this case.

KEY POINT

- Early removal of urinary catheters should be considered when possible, and patients should be monitored for their ability to void spontaneously after catheter removal.

Bibliography

Chenoweth CE, Saint S. Urinary tract infections. Infect Dis Clin North Am. 2016;30:869-885. [PMID: 27816141] doi:10.1016/j.idc.2016.07.007

Item 21 Answer: A

Educational Objective: Treat an infected cat bite in a patient with risk factors for methicillin-resistant *Staphylococcus aureus*.

This patient should receive antibiotic treatment with ampicillin-sulbactam plus vancomycin in addition to undergoing surgical consultation. She has a cat bite-associated wound infection with accompanying low blood pressure and tachypnea and requires hospitalization. Cat bites are more likely than dog bites to cause infection because of cats' sharp, narrow teeth; infections are caused by organisms from the animal's mouth flora and the host's skin flora. This flora comprises a mix of anaerobic and aerobic organisms, including streptococci, staphylococci, and *Bacteroides*, *Fusobacterium*, *Porphyromonas*, and *Pasteurella* species. *Pasteurella* is a facultative anaerobic gram-negative rod that is the most common bacteria in a cat's mouth. Intravenous piperacillin-tazobactam, ampicillin-sulbactam, imipenem, or meropenem would address these organisms but not potential methicillin-resistant *Staphylococcus aureus* (MRSA). If pus is present, the patient has MRSA risk factors such as a previous MRSA infection or colonization within the last year, or local MRSA prevalence is high, then coverage should also include agents that target MRSA, such as vancomycin or daptomycin. Consequently, the combination of ampicillin-sulbactam and vancomycin would be the best choice for empiric antibiotic coverage because this regimen is effective against serious infections caused by MRSA and the microbiota of a cat's mouth.

Ceftriaxone and metronidazole would be effective against many of the organisms encountered in a cat bite-associated skin infection, but it would not cover the possibility of MRSA infection in this patient.

Ciprofloxacin and aztreonam also lack coverage for MRSA and some anaerobes likely to be associated with a bite wound.

Imipenem is a broad-spectrum antibiotic effective against many of the organisms associated with cat bite wounds, but it does not provide MRSA coverage.

Neither vancomycin nor clindamycin provides adequate coverage against *Pasteurella* species, so this regimen would not be effective for a cat bite-associated infection.

KEY POINT

- Cat bite-associated wound infections comprise a mix of anaerobic and aerobic organisms, including *Pasteurella* species, which require treatment with antibiotic agents such as piperacillin-tazobactam, ampicillin-sulbactam, imipenem, and meropenem; coverage for methicillin-resistant *Staphylococcus aureus* must be included in select patients who have risk factors for this infection.

Bibliography

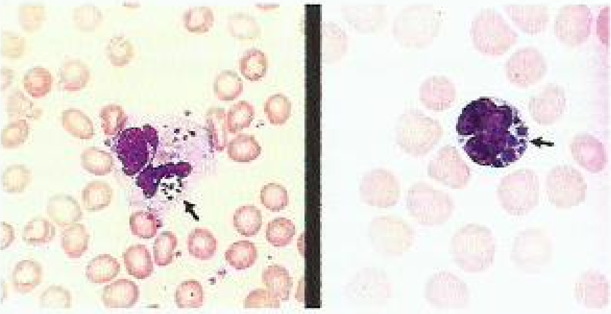
Bystritsky R, Chambers H. Cellulitis and soft tissue infections. Ann Intern Med. 2018;168:ITC17-ITC32. [PMID: 29404597] doi:10.7326/AITC201802060

H

Item 22 Answer: B

Educational Objective: Diagnose human monocytic ehrlichiosis.

This patient most likely has human monocytic ehrlichiosis (HME), a tick-borne illness primarily caused by *Ehrlichia chaffeensis*. His symptoms include a nonfocal febrile illness associated with leukopenia, thrombocytopenia, and elevated hepatic enzyme levels, all of which are characteristic of HME. His participation in outdoor activities in wooded areas places him at risk for exposure to ticks. HME is endemic in the mid-Atlantic, southern, and southeastern United States; his clinical presentation is highly suggestive of this illness. The prompt response to doxycycline is classic for a tick-borne rickettsial illness, such as HME; a lack of response within 48 hours of therapy would suggest an alternative diagnosis or a coinfection. The negative serologic results for *E. chaffeensis* do not disprove the diagnosis and should not prompt early discontinuation of doxycycline. The sensitivity of antibody testing is low in the first week of illness; seroconversion typically occurs within 2 to 4 weeks of symptom onset, and acute and convalescent titers are useful for retrospective confirmation of infection. During the acute illness, buffy-coat staining (to reveal the presence of morulae, which are basophilic inclusion bodies in the cytoplasm of monocytes representing clusters of bacteria [shown]) or polymerase chain reaction of whole blood specimens may allow an early diagnosis.



Although many infections present identically to HME, the salient feature in this patient was the rapid response to doxycycline therapy, which essentially excludes a viral process. Heartland virus, a newly described Bunyavirus transmitted by the same vector as *E. chaffeensis*, is clinically indistinguishable from HME and should be suspected when no improvement is seen within 48 hours of starting doxycycline therapy.

Infectious mononucleosis can present with fever, cytopenia, and elevated aminotransferase levels. However, other components of the infectious mononucleosis triad (fever, pharyngitis, and cervical lymphadenopathy) were absent in this patient.

The rapid response to doxycycline treatment is consistent with Rocky Mountain spotted fever (RMSF) infection. However, the pronounced leukopenia and absence of a rash more than 1 week into the illness argue against this diagnosis.

KEY POINT

- Human monocytic ehrlichiosis infection is characterized by a nonfocal febrile illness associated with leukopenia, thrombocytopenia, elevated hepatic enzyme levels, and a rapid response to tetracycline.

Bibliography

Biggs HM, Behravesh CB, Bradley KK, Dahlgren FS, Drexler NA, Dumler JS, et al. Diagnosis and management of tickborne rickettsial diseases: Rocky Mountain spotted fever and other spotted fever group rickettsioses, ehrlichioses, and anaplasmosis - United States. MMWR Recomm Rep. 2016;65:1-44. [PMID: 27172113] doi:10.15585/mmwr.rr6502a1

Item 23 Answer: C

H

Educational Objective: Treat health care–associated ventriculitis and meningitis.

The most appropriate management in this patient is removal of his ventricular drain. After drain removal, clinical monitoring for intracranial hypertension will be important. Health care-associated ventriculitis or meningitis (HCAVM) or nosocomial meningitis may present a diagnostic and treatment challenge to clinicians. It typically occurs after head trauma or a neurosurgical procedure (craniotomy, lumbar puncture) or secondary to device infection (for example, cerebrospinal fluid [CSF] shunts or drains, intrathecal pumps, deep brain stimulator). *Staphylococcus* species and enteric gram-negative bacteria are the most common causes, but up to 50% of patients can have negative cultures because more than 50% receive antibiotic therapy before CSF studies are performed, as occurred in this patient. Worsening mental status, new fever, or stiff neck in a patient who recently underwent surgery should raise the possibility of HCAVM. An elevated CSF lactate level greater than 4 mg/dL, an elevated CSF procalcitonin level, or a combination of both, may be useful in the diagnosis of health care-associated bacterial ventriculitis and meningitis in culture-negative cases. Empiric therapy should include vancomycin and a β-lactam with antipseudomonal activity (such as cefepime or meropenem) and device removal, if present.

For patients with health care-associated ventriculitis and meningitis caused by staphylococci in whom β-lactam agents or vancomycin cannot be used, treatment with linezolid, daptomycin, or trimethoprim-sulfamethoxazole is recommended with selection based on in vitro susceptibility testing. However, the priority in this patient is removing the ventricular drain, not changing the antibiotic regimen.

Intraventricular or intrathecal antimicrobial therapy should be considered for patients with health care–associated ventriculitis and meningitis in whom the

H CONT.

infection responds poorly to systemic antimicrobial therapy alone. This strategy is not appropriate in a patient with a potentially infected ventricular drain.

KEY POINT

- In patients with health care–associated ventriculitis or meningitis, device removal, if present, should accompany empiric antimicrobial therapy.

Bibliography

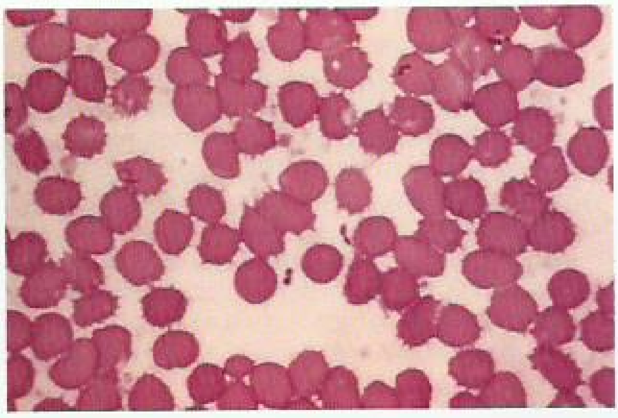
Tunkel AR, Hasbun R, Bhimraj A, Byers K, Kaplan SL, Michael Scheld W, et al. 2017 Infectious Diseases Society of America's clinical practice guidelines for healthcare-associated ventriculitis and meningitis. Clin Infect Dis. 2017. [PMID: 28203777] doi:10.1093/cid/ciw861

H

Item 24 Answer: C

Educational Objective: Treat pneumonic plague.

The most appropriate treatment is gentamicin. This patient most likely has pneumonic plague caused by the bacteria *Yersinia pestis*, one of the biologic agents classified as an A-list bioterrorism pathogen because of its high potential lethality and ease of dissemination. Sputum Gram stain (and possibly blood smear) may identify gram-negative coccobacilli demonstrating the classic bipolar staining or "safety pin" shape shown. Although most pulmonary involvement occurs through secondary hematogenous spread to the lungs from a bubo or other source, primary pneumonic plague can occur after close contact with another person with plague pneumonia, after animal exposure, or as a result of intentional aerosol release for the purpose of terrorism, as in this case. Recommended first-line treatment is either streptomycin or gentamicin.



Anthrax is caused by *Bacillus anthracis*, a gram-positive, aerobic organism. It appears as a sporulating gram-positive rod on microscopic examination. Patients with inhalational anthrax present with low-grade fever, malaise, myalgia, and headache accompanied by cough, dyspnea, and chest pain. A chest radiograph showing mediastinal widening from hemorrhagic lymphadenitis is characteristic. Ciprofloxacin, levofloxacin, moxifloxacin, or doxycycline should be provided as soon as possible after any actual or suspected case of anthrax that raises concern for a bioterrorism attack.

Ambulatory empiric therapy for community-acquired pneumonia (CAP) is directed against *Streptococcus pneumoniae*, *Haemophilus influenzae*, and atypical bacteria, even though a significant proportion of patients with CAP infected with viral pathogens do not benefit from antibiotic therapy. The combination of ceftriaxone and azithromycin would be an appropriate choice for the treatment of CAP but would be inadequate for treating plague, which requires either streptomycin or gentamicin.

When clinical concern for *Pseudomonas* is present, dual therapy with two active agents is indicated. Options include an antipseudomonal β-lactam (piperacillin-tazobactam, cefepime, or meropenem) in conjunction with either a quinolone (levofloxacin or ciprofloxacin) or an aminoglycoside. *Pseudomonas* infection should be considered in immunocompromised patients and patients with underlying structural lung disease (bronchiectasis or cystic fibrosis) or medical conditions requiring repeated courses of antibiotics. The combination of piperacillin-tazobactam and levofloxacin would be ideal for a seriously ill patient with CAP and concern for *Pseudomonas* infection but not for this patient most likely infected with *Yersinia pestis*.

KEY POINT

- First-line treatment for primary pneumonic plague is either streptomycin or gentamicin.

Bibliography

Adalja AA, Toner E, Inglesby TV. Clinical management of potential bioterrorism-related conditions. N Engl J Med. 2015;372:954-62. [PMID: 25738671] doi:10.1056/NEJMra1409755

H

Item 25 Answer: D

Educational Objective: Treat disseminated histoplasmosis.

The most appropriate treatment for this patient is liposomal amphotericin B. He has disseminated histoplasmosis, for which he has numerous risk factors. He lives in an area endemic for histoplasmosis (Ohio River Valley), and because he takes prednisone and methotrexate for his rheumatoid arthritis, he is immunosuppressed. He has had significant exposure working in an old barn with bats. He also is hypotensive and diaphoretic and has oral ulcerations and hepatosplenomegaly, which are typical of disseminated infection, as is pancytopenia. Approximately 10% of patients with histoplasmosis develop disseminated infection; if not diagnosed early, the mortality rate is greater than 90%. The treatment of choice for disseminated histoplasmosis is liposomal amphotericin B initially, with de-escalation to itraconazole for several months. A definitive diagnosis can be established by detection of the urinary antigen for histoplasmosis (95% specificity), blood cultures, or a biopsy of the oral lesions.

Ceftriaxone and azithromycin are the recommended drugs of choice for community-acquired pneumonia. The

H CONT.

patient's physical examination and chest radiograph are unremarkable, which effectively rules out pneumonia and the need for these antibiotics.

Behçet syndrome is a form of vasculitis associated with recurrent painful oral and genital ulcerations; patients also may demonstrate additional distinctive features, including hypopyon and pathergy. Central nervous system involvement can manifest as headaches, stroke, and behavioral changes. Gastrointestinal involvement may be hard to distinguish from inflammatory bowel disease. Low-dose prednisone or colchicine is used for oral or genital ulcers, and high-dose prednisone and immunomodulating agents are used for more severe disease. Behçet syndrome does not explain the patient's fever, hemodynamic instability, pancytopenia, or hepatomegaly, and colchicine therapy is not warranted.

Itraconazole is an azole triazole used to treat many endemic fungal infections, including histoplasmosis. However, it is not as effective as liposomal amphotericin B in disseminated infection. It may be used for subacute or chronic histoplasmosis, such as pulmonary histoplasmosis.

KEY POINT

- Liposomal amphotericin B is the treatment of choice for disseminated histoplasmosis.

Bibliography

Hage CA, Azar MM, Bahr N, Loyd J, Wheat LJ. Histoplasmosis: up-to-date evidence-based approach to diagnosis and management. Semin Respir Crit Care Med. 2015 Oct;36(5):729-45. doi: 10.1055/s-0035-1562899. Review. PMID: 26398539.

H

Item 26 Answer: C

Educational Objective: Evaluate a patient for complications of pneumonia (empyema).

The most appropriate management at this time is to perform thoracentesis. This patient has nonresponsive pneumonia demonstrated by persistent fever of more than 72 hours despite directed therapy (vancomycin) against the causative organism (methicillin-resistant *Staphylococcus aureus* [MRSA]). Lack of response to therapy is a poor prognostic factor and is associated with excess mortality. Antibiotic therapy failure may indicate a noninfectious cause mimicking pneumonia, antibiotic-resistant bacterial infection, infection with a nonbacterial organism, or loculated infection such as an empyema. This patient's chest radiograph shows opacification of the left heart border and hemidiaphragm, raising concern for pleural fluid adjacent to a pulmonary infiltrate. Parapneumonic pleural effusions are present in up to 40% of patients hospitalized with CAP. Determining the need for chest tube drainage requires analysis of the pleural fluid. A finding of purulent or foul-smelling material or a positive Gram stain is diagnostic of an empyema, and a pleural fluid pH less than 7.2 or a pleural fluid glucose level less than 60 mg/dL (3.33 mmol/L) is highly suggestive. Chest tube placement in addition to antibiotics is necessary to treat infection localized to the pleural space. Delayed drainage may result in ongoing fever, sepsis, or fibrosis ultimately requiring surgical intervention.

The role of glucocorticoids in CAP remains controversial. Evidence is accumulating that early administration of glucocorticoids may reduce the host inflammatory response, particularly in patients with acute respiratory distress syndrome; however, the routine use of glucocorticoids for CAP has not been established.

The addition of piperacillin-tazobactam would be indicated if a secondary hospital-acquired pulmonary infection were a concern, but the persistent fever and Gram stain showing only gram-positive cocci makes superinfection less likely.

Procalcitonin is produced by cells as a response to bacterial toxins, which result in elevated serum procalcitonin levels in bacterial infections. In viral infections, procalcitonin levels are reduced. Procalcitonin measurement is only one of several factors in determining a bacterial versus a viral cause and should be considered as adjunctive to other diagnostic tools. In this patient, there is little doubt concerning the microbiologic diagnosis, and determining the procalcitonin level will not be helpful.

Daptomycin is contraindicated for use in pulmonary infections because it binds to surfactant and does not achieve adequate levels in the alveoli.

KEY POINT

- In patients with pneumonia unresponsive to appropriate antibiotic therapy, a noninfectious cause mimicking pneumonia, antibiotic-resistant bacterial infection, infection with a nonbacterial organism, or loculated infection such as an empyema may be the cause.

Bibliography

McCauley L, Dean N. Pneumonia and empyema: causal, casual or unknown. J Thorac Dis. 2015;7:992-8. [PMID: 26150912] doi:10.3978/j.issn.2072-1439.2015.04.36

Item 27 Answer: A

H

Educational Objective: Diagnose *Plasmodium falciparum* malaria.

This pregnant woman has contracted *Plasmodium falciparum* malaria after visiting a part of the world where malaria is endemic. Her clinical presentation and peripheral blood smear showing many parasitized erythrocytes demonstrating signet ring forms, together with the absence of trophozoites and schizonts, are typical for infection with *P. falciparum*. Of returning travelers with acute and potentially life-threatening febrile diseases, *P. falciparum* malaria accounts for most infections. Furthermore, pregnant women are at increased risk of severe disease and a heightened mortality rate, which is likely related to a reduced immune response. Additionally, effects on the microvasculature and sequestering of organisms in the placenta during pregnancy are known to significantly increase the risk of miscarriage,

H CONT.

premature delivery, low-birth-weight neonates, congenital infection, and fetal demise.

Accurate identification of *P. falciparum* and *Plasmodium knowlesi* is critical because of the risk for severe and potentially lethal infection. *P. falciparum* should be suspected if the patient traveled to Africa, symptoms begin soon after return from an endemic area, and the peripheral blood smear shows a high level of parasitemia. *P. knowlesi* is a more recently recognized human pathogen; infection may be severe because of high levels of parasitemia. Examination of the peripheral blood smear reveals all stages of the parasite. The epidemiologic history is helpful because *P. knowlesi* is not encountered in Africa but rather South and Southeast Asia.

Plasmodium malariae, *Plasmodium ovale*, and *Plasmodium vivax* are all associated with a low or very low degree of parasitemia, typically less than 2%, and although the risk of recurrence is high, with the exception of *P. vivax*, the risk for severe disease is low.

KEY POINT

- *Plasmodium falciparum* infection should be suspected if the patient traveled to Africa, symptoms begin soon after return from an endemic area, and the peripheral blood smear shows a high level of parasitemia.

Bibliography

Hahn WO, Pottinger PS. Malaria in the traveler: how to manage before departure and evaluate upon return. Med Clin North Am. 2016;100:289-302. [PMID: 26900114] doi:10.1016/j.mcna.2015.09.008

H

Item 28 Answer: C

Educational Objective: Treat spinal epidural abscess.

The most appropriate treatment of this patient is empiric antibiotic therapy and surgical drainage of the abscess. Spinal epidural abscesses (SEAs) usually result from contiguous spread from infected vertebrae or intervertebral body disc spaces or from hematogenous dissemination from a distant site. SEA can be challenging to diagnose because symptoms can be mild or nonspecific and fever may not always be present. A high index of suspicion, particularly in patients with atypical or persistent back pain, will facilitate more prompt diagnosis. Symptoms may progress from back pain to accompanying neurologic symptoms, such as bowel or bladder dysfunction, lower extremity weakness, paresthesias, and, in the last stages, paralysis. MRI of the spine with contrast is the preferred imaging modality for diagnosis. Blood cultures should be performed before starting antibiotic therapy to identify the cause, and, in certain cases, cultures may avoid the need for aspiration of the spinal abscess. Medical therapy alone is often successful if no neurologic deficits are present at the time of diagnosis or if substantial complications from surgery are likely because of comorbid conditions. However, surgical drainage is recommended in patients who present with neurologic symptoms or evidence of progression or recurrence despite proper antimicrobial therapy. Serial clinical evaluations and follow-up MRI of the spine (at approximately 4-6 weeks into therapy or with any sign of clinical deterioration) are necessary adjuncts to management without surgery. Empiric parenteral antimicrobial therapy should include coverage for *Staphylococcus aureus* (accounts for approximately 50% of infections), *Streptococcus* species, and gram-negative bacilli and may be narrowed based on culture results, if available. Therapy typically lasts between 6 and 8 weeks (or until resolution of abscess on follow-up MRI) but may require modification depending on clinical and radiographic recovery.

Patients with sepsis or neurologic compromise, as in this patient, should start empiric broad-spectrum antimicrobial therapy pending blood and abscess cultures. Otherwise, empiric antimicrobial therapy may be withheld until a cause is confirmed. This patient has an indication for immediate empiric antibiotic therapy and surgical drainage.

KEY POINT

- Patients with spinal epidural abscess who also have neurologic compromise should immediately begin broad-spectrum antimicrobial therapy and undergo surgical drainage.

Bibliography

Berbari EF, Kanj SS, Kowalski TJ, Darouiche RO, Widmer AF, Schmitt SK, et al. 2015 Infectious Diseases Society of America (IDSA) clinical practice guidelines for the diagnosis and treatment of native vertebral osteomyelitis in adults. Clin Infect Dis. 2015;61:e26-46. [PMID: 26229122] doi:10.1093/cid/civ482

Item 29 Answer: D

Educational Objective: Diagnose typhoid (enteric) fever.

This patient most likely has typhoid fever, also known as enteric fever, caused by either of the typhoidal *Salmonella* strains, *S. typhi* or *S. paratyphi*. Infection is transmitted by ingestion of food or water contaminated by feces. In resource-poor areas, organisms may be spread in community food or, more frequently, by water. In developed countries, transmission is chiefly by food that has been contaminated during preparation by healthy carriers. Symptoms of enteric fever are generally nonspecific. Fever is the major manifestation, typically rising over 2 to 3 nights and persisting for several days. A pulse-temperature dissociation (relative bradycardia) is often present. A brief period of diarrhea followed by constipation, abdominal discomfort, nonproductive cough, mild confusion, and transient small blanching skin lesions (rose spots) are other clinical features. Ceftriaxone is the preferred empiric antibiotic agent, with ciprofloxacin and azithromycin as additional options if resistance is not encountered.

Human brucellosis can develop after exposure to one of four *Brucella* species through contact with viable organisms in secretions or excretions of infected animals, ingestion of undercooked meat or milk products, or, less often, inhalation. Patients experience numerous nonspecific symptoms

as well as recurring or "undulating" waves of fever, but rash, gastrointestinal symptoms, and relative bradycardia are not typical.

Humans acquire leptospirosis after contact with infected urine spread by carrier animals. Classically, illness is biphasic, beginning with a septicemic phase followed by an immune phase, which correlates with the appearance of antibodies in serum. Clinically apparent leptospirosis presents with the abrupt onset of fever, rigors, myalgias, and headache. Conjunctival suffusion in a patient with a nonspecific febrile illness should raise suspicion for the diagnosis of leptospirosis. A more severe form, known as Weil syndrome (icteric leptospirosis), consisting of jaundice, azotemia, and anemia, may also occur. Gastrointestinal symptoms are infrequent.

The gram-negative bacillus *Burkholderia pseudomallei*, found in soil and water in endemic areas such as Southeast Asia, is the causative agent of melioidosis. After acquisition through direct skin contact, ingestion, or inhalation, an acute pulmonary, septicemic, or localized suppurative infection may occur. The patient's findings are not compatible with melioidosis.

KEY POINT

- Fever is the major manifestation of typhoid fever and is often associated with a relative bradycardia; additional symptoms may include a brief period of diarrhea followed by constipation, abdominal discomfort, nonproductive cough, mild confusion, and transient small blanching skin lesions (rose spots).

Bibliography

Thwaites GE, Day NP. Approach to fever in the returning traveler. N Engl J Med. 2017;376:548-560. [PMID: 28177860] doi:10.1056/NEJMra1508435

Item 30 Answer: A

Educational Objective: Manage newly diagnosed HIV infection.

This patient needs baseline genotypic HIV resistance testing. Because of the possibility of transmitted virus having resistance mutations, it is recommended to obtain baseline resistance testing before starting an antiretroviral regimen. If the patient is ready, antiretrovirals can be started the same day, while waiting for resistance testing results, with regimen modification if necessary based on results. Virologic failure of a regimen (rebound of a suppressed viral load or failure to achieve undetectable viral load with therapy) is also an indication for resistance testing to guide the change in regimen. Genotypic testing looks for mutations in the viral genome associated with antiviral drug resistance. Phenotypic testing actually tests the virus's ability to grow in the presence of differing concentrations of the drug and is therefore more useful in the presence of multiple interacting mutations or unclear correlations of mutation and resistance, such as occurs with resistance to protease inhibitors. Genotypic testing is faster and less expensive because all that is necessary is sequencing of the respective genes for the patient's viral isolate. When significant resistance is not expected and information is needed more quickly, genotypic testing would be preferred over phenotypic testing.

Some antiretroviral agents have been associated with increased insulin resistance and risk for hyperglycemia, and assessing for this at baseline and during therapy is recommended. This patient, however, already has a normal glucose level at baseline testing, so measuring the glycohemoglobin is not necessary at this time.

All patients with HIV should begin antiretroviral therapy as soon as they are ready. Prompt initiation of therapy benefits the patient and reduces the risk of transmission to others, so waiting for repeat viral load and CD4 cell count is inappropriate and unnecessary.

KEY POINT

- Genotypic viral resistance testing is recommended immediately after a diagnosis of HIV infection to guide the selection of active agents for the antiretroviral regimen or after virologic failure of a regimen to guide adjustment of antiretroviral therapy.

Bibliography

Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in adults and adolescents living with HIV. Department of Health and Human Services. Available at https://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-arv/0. Accessed April 12, 2018.

Item 31 Answer: B

H

Educational Objective: Diagnose meningitis caused by herpes simplex virus type 2.

The most likely diagnosis in this patient is meningitis caused by herpes simplex virus (HSV) type 2. Viral meningitis is the most common cause of "aseptic" meningitis, in which cerebrospinal fluid (CSF) Gram stain and cultures are negative. Most patients have typical meningitis symptoms, such as fever, nuchal rigidity, headache, and photophobia. HSV meningitis syndromes can be related to primary infections, with central nervous system involvement as a secondary consequence, or reactivation of latent infection presenting as aseptic meningitis. HSV-2 is more commonly associated with meningitis and is the most common cause of recurrent meningitis (recurrent benign lymphocytic meningitis). HSV-1 is associated with encephalitis. HSV can cause meningitis year round. CSF findings resemble enteroviral meningitis, with lymphocytic pleocytosis, a normal glucose level, and a mildly elevated protein level as in this patient. CSF polymerase chain reaction studies may be used for diagnosing HSV and enterovirus meningitis.

Enteroviruses are the most common cause of viral meningitis, but they usually present between May and November in the Western Hemisphere, with symptoms including headache, fever, nuchal rigidity, photophobia, nausea, vomiting, myalgias, pharyngitis, maculopapular rash, and cough. This

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patient's presentation in the winter makes this an unlikely cause of her illness.

Mumps virus can cause meningitis, with typical symptoms of fever, headache, and neck stiffness. Since the advent of universal childhood vaccination for measles, mumps, and rubella, the incidence of mumps-related meningitis has dramatically decreased. Meningitis from mumps virus can occur at any point during the course of clinical mumps infection. Parotitis or orchitis may be present. The patient's clinical presentation is not consistent with mumps meningitis.

Focal motor weakness is a common finding in West Nile neuroinvasive disease (WNND), either combined with meningoencephalitis or as an isolated myelitis. In its most severe form, infection of the anterior horn cells can cause a symmetric or asymmetric flaccid paralysis, analogous to that seen with polio in the prevaccination era. The diagnosis of WNND can be confirmed through identification of the IgM antibody in CSF. West Nile virus is a mosquito-borne illness most commonly seen between June and October, making this an unlikely cause of this patient's illness.

KEY POINT

- Herpes simplex virus type 2 can cause acute aseptic meningitis year round and is the most common cause of recurrent viral meningitis.

Bibliography

Nigrovic LE. Aseptic meningitis. Handb Clin Neurol. 2013;112:1153-6. [PMID: 23622323] doi:10.1016/B978-0-444-52910-7.00035-0

Item 32 Answer: D

Educational Objective: Provide appropriate immunizations for a patient with HIV infection.

Human papillomavirus (HPV) is the most appropriate immunization for this patient at this time. He was recently diagnosed with HIV infection and has begun antiretroviral therapy. At baseline, his CD4 cell count is normal. He is in an age group for which HPV immunization is recommended, and that recommendation is the same regardless of HIV status. The presence of genital warts does not change the indication for HPV vaccination. He should begin the HPV vaccine series with the first injection today. Indications for influenza, tetanus-diphtheria-pertussis, and hepatitis A virus (HAV) vaccines are also the same for patients with HIV infection as for the general population.

Pneumococcal vaccination is important for all persons with HIV infection, regardless of CD4 cell count. As with other immunocompromised persons, patients with HIV should receive the 13-valent conjugate and 23-valent polysaccharide vaccines, in that order. This patient has already received the pneumococcal conjugate vaccine and needs the polysaccharide vaccine, but at least 8 weeks must elapse between these two vaccines to allow for better immune response in this prime-boost strategy. Therefore, giving him the pneumococcal polysaccharide vaccine at this visit would be premature.

Serum IgM antibodies to HAV are detectable at the time of symptom onset and remain detectable for approximately 3 to 6 months. Serum IgG antibodies appear in convalescence and remain detectable for decades. The presence of anti-HAV IgG in the absence of anti-HAV IgM indicates past infection or vaccination. This patient does not need vaccination against HAV.

Hepatitis B virus (HBV) surface antibody testing is negative, indicating a lack of immunity to HBV; he also has risk factors for HBV that would warrant HBV vaccination. However, the patient tested positive for hepatitis B surface antigen, indicating he already has HBV infection and would not benefit from immunization with the HBV vaccine.

KEY POINT

- Indications for influenza, tetanus-diphtheria-pertussis, hepatitis A virus, and human papillomavirus vaccines are the same for patients with HIV infection as for the general population.

Bibliography

Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents. Guidelines for the prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. Available at https://aidsinfo.nih.gov/guidelines/html/4/adult-and-adolescent-opportunistic-infection/0. Accessed April 12, 2018.

Item 33 Answer: E

H

Educational Objective: Diagnose neuroborreliosis.

This patient should undergo lumbar puncture. He has unilateral facial nerve palsy, headache, neck stiffness, and a circular rash with central clearing that is clinically consistent with erythema migrans. The presence of erythema migrans in a patient with risk factors for Lyme disease is diagnostic of infection. Neuroborreliosis occurs in 10% to 15% of patients with Lyme disease, and cranial nerve palsy, particularly of the facial nerve (cranial nerve VII), is the most common presentation. When unilateral or bilateral facial nerve palsy is present in isolation, oral doxycycline treatment for 14 to 28 days is sufficient for Lyme disease. However, when the central nervous system is involved, parenteral therapy with ceftriaxone, cefotaxime, or penicillin is recommended. In this patient, the presence of headache and nuchal rigidity raise concern for concomitant meningitis. Because confirmation of meningeal involvement would change therapy, a lumbar puncture is first necessary to determine appropriate therapy. Cerebrospinal fluid (CSF) findings in Lyme meningitis are indistinguishable from other forms of aseptic meningitis.

Testing for antibodies to *Borrelia burgdorferi* adds little to the diagnosis because the presence of erythema migrans with cranial neuropathy is sufficient for diagnosis of neuroborreliosis. Serum antibody testing for *B. burgdorferi*

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infection would be important in the absence of a compatible skin lesion or with inconsistent exposure history.

In neuroborreliosis, a delay in starting antimicrobial treatment is not associated with adverse outcomes as it is in bacterial meningitis, and empiric therapy can be deferred until CSF cell counts are available.

Performing a head CT is unnecessary because Lyme neuroborreliosis is rarely associated with intraparenchymal lesions, and thus the risk of lumbar puncture in this previously healthy, cognitively intact patient is low.

KEY POINT

- In a patient with Lyme disease and possible central nervous system involvement, positive findings on lumbar puncture can support the diagnosis of neuroborreliosis, which necessitates parenteral therapy with ceftriaxone, cefotaxime, or penicillin.

Bibliography

Halperin JJ. Neuroborreliosis. J Neurol. 2017;264:1292-1297. [PMID: 27885483] doi:10.1007/s00415-016-8346-2

Item 34 Answer: D

Educational Objective: Manage potential bioterrorism-related anthrax exposure.

Because this patient has no known direct exposure to anthrax, no treatment is necessary. In cases of proven or suspected anthrax in a family member, no specific treatment or isolation procedures are required for others in the household because spread in health care or household settings has never been demonstrated. In patients with confirmed or suspected bioterrorism-related anthrax exposure, postexposure prophylactic antibiotics, taken for 60 days, should be started as soon as possible. Ciprofloxacin, levofloxacin, and doxycycline are the approved drugs for postexposure prophylaxis in adult patients. In pregnant women, ciprofloxacin is the drug of choice, and although tetracyclines are not recommended during pregnancy, doxycycline can be used with caution when ciprofloxacin is contraindicated. Therapy can be completed with amoxicillin if the isolate is found to be penicillin susceptible. Because of the possibility that residual dormant spores may become active after antibiotics are completed, three subcutaneous injections of anthrax vaccine should be given at 2-week intervals as part of postexposure prophylaxis.

No test is available for the detection of anthrax infection in an asymptomatic person, so taking a swab or performing a blood test would provide no useful information.

The human monoclonal antibodies against anthrax toxin, raxibacumab (available only from the Centers for Disease Control and Prevention) and obiltoxaximab (FDA approved) can be combined with antibiotics for treatment of inhalation anthrax or for postexposure prophylaxis when alternative preventive therapies are not available or appropriate. In this scenario, they are not indicated for the patient or her husband who has received adequate prophylaxis for anthrax and does not have systemic disease.

KEY POINT

- Patients with no known direct exposure to anthrax do not require treatment or separation from those who may be infected.

Bibliography

Hendricks KA, Wright ME, Shadomy SV, Bradley JS, Morrow MG, Pavia AT, et al; Workgroup on Anthrax Clinical Guidelines. Centers for Disease Control and Prevention expert panel meetings on prevention and treatment of anthrax in adults. Emerg Infect Dis. 2014;20. [PMID: 24447897] doi:10.3201/eid2002.130687

Item 35 Answer: D

Educational Objective: Prevent HIV infection in persons at risk with pre-exposure prophylaxis.

The most appropriate preventive measure for this patient is daily tenofovir disoproxil fumarate and emtricitabine (TDF-FTC). He has multiple risk factors for acquiring HIV infection, including having sex with multiple partners without consistent condom use. Data support the use of pre-exposure prophylaxis (PrEP) in specific populations with ongoing high risk for infection, such as sexual partners of infected persons, men who have sex with men, and injection drug users. PrEP is recommended for persons in such groups who can adhere to the daily regimen. Efficacy has varied depending on adherence to the regimen; rates of reduction in new infections ranged from 42% to 75% and up to 92% in patients whose adherence was documented by monitoring drug blood levels. This patient is in a group shown in clinical trials to benefit from PrEP for HIV. Combination tenofovir alafenamide and emtricitabine is being studied for PrEP, but until results of these studies are known, only TDF should be used. Risk of kidney dysfunction from TDF is low, but kidney function should be checked every 6 months during PrEP. Patients taking PrEP should be counseled to continue using barrier precautions and should undergo testing for HIV, other sexually transmitted infections (STIs), and pregnancy in women, every 3 months.

TDF-FTC given as a single dose before or after each sexual exposure has not been proven effective, and because of concerns for lower effectiveness and possible selection for resistance, these methods should not be used for prevention.

Patients should be counseled regarding the need for continued barrier precautions during sex because the effectiveness of PrEP is less than 100% and to reduce transmission of other STIs. However, counseling the patient about consistent condom use without PrEP places the patient at unnecessary risk for HIV infection. PrEP and barrier protection is now the standard of prevention for men who have sex with men at risk for HIV infection.

KEY POINT

- The combination of tenofovir disoproxil fumarate plus emtricitabine taken once daily is more than 90% effective, if taken consistently, in preventing HIV acquisition.

Bibliography

Riddell J 4th, Amico KR, Mayer KH. HIV preexposure prophylaxis: A review. JAMA. 2018;319:1261-1268. [PMID: 29584848] doi:10.1001/jama.2018.1917

H

Item 36 Answer: A

Educational Objective: Evaluate osteomyelitis in a diabetic foot infection.

A bone biopsy and culture is the next step in the management of osteomyelitis for this patient. Biopsies can be accomplished by open surgical procedure or percutaneously. Confirming a microbiologic diagnosis is needed before antibiotics can be administered.

Indications for amputation include persistent sepsis, inability to tolerate antibiotic therapy, progressive bone destruction despite therapy, and bone destruction that compromises the mechanical integrity of the foot. None of these indications are present in this patient. Surgical debridement of the ulcer may be needed to remove the necrotic tissue, but this can be done at the time of bone biopsy.

With the exception of *Staphylococcus aureus*, microorganisms isolated from culture samples obtained from superficial wounds or sinus tracts correlate poorly with deep cultures from bone; therefore, this practice is of limited value. Bone biopsy with histopathologic assessment and full microbiologic studies is important for diagnosing osteomyelitis, excluding other entities (such as neoplasm), and isolating the causative pathogen(s).

Because the patient has no signs of skin or soft tissue infection or of sepsis, antibiotics are not immediately needed; furthermore, the provision of empiric antibiotics would also decrease the yield of a subsequent bone biopsy. Vancomycin and piperacillin-tazobactam might be indicated in the future, pending the results of the bone biopsy. However, a histologic and microbiologic diagnosis confirmation is needed before antibiotics can be administered.

KEY POINT

- Osteomyelitis in a patient with a diabetic foot infection and no evidence of skin or soft tissue infection or sepsis requires a bone biopsy before antibiotics are administered.

Bibliography

Lipsky BA, Berendt AR, Cornia PB, Pile JC, Peters EJ, Armstrong DG, et al; Infectious Diseases Society of America. 2012 Infectious Diseases Society of America clinical practice guideline for the diagnosis and treatment of diabetic foot infections. Clin Infect Dis. 2012;54:e132-73. [PMID: 22619242] doi:10.1093/cid/cis346

Item 37 Answer: D

Educational Objective: Manage a patient based on syphilis serology results.

This woman's serologic results are consistent with successfully treated syphilis, and no additional testing or treatment is indicated. Many laboratories use a "reverse" screening strategy, whereby a treponemal test, such as an enzyme immunoassay (EIA), is performed first and, if positive, is followed by a nontreponemal test (rapid plasma regain [RPR] or Venereal Disease Research Laboratory [VDRL] test). If the EIA is positive and the RPR or VDRL is negative, the positive result should be confirmed by a second treponemal test (such as the fluorescent treponemal antibody test performed in this patient). A positive EIA (confirmed by a second test) with a negative RPR is the expected serologic result in a patient who has been treated for syphilis. The treponemal test (EIA) remains positive indefinitely, but the nontreponemal test (RPR or VDRL) should remain negative.

If the nontreponemal test became positive again, it would indicate a new infection, and treatment, based on disease stage, would be indicated. If this patient had reported no history of treatment for syphilis, she should be treated for syphilis of unknown duration, which consists of 3 weekly doses of intramuscular benzathine penicillin. Single-dose benzathine penicillin is indicated for the treatment of primary, secondary, and early latent syphilis.

Because the positive EIA result was already confirmed by a second treponemal test, the fluorescent treponemal antibody, additional testing with another treponemal test, such as the *Treponema pallidum* particle agglutination assay, is not necessary.

KEY POINT

- In patients with previously treated syphilis, treponemal serology results will remain positive, but nontreponemal tests will be negative; these patients require no further testing or treatment.

Bibliography

Workowski KA, Bolan GA; Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2015. MMWR Recomm Rep. 2015;64:1-137. [PMID: 26042815]

Item 38 Answer: E

Educational Objective: Interpret the results of HIV testing.

This woman had a false-positive result for HIV and should be reassured she does not have HIV infection. She has no symptoms to suggest acute infection. The initial HIV combination immunoassay tests for HIV-1 or HIV-2 antibody and p24 antigen. If reactive, an HIV-1/2 antibody differentiation immunoassay is performed, which differentiates between HIV-1 and HIV-2 antibodies. If the antibody differentiation assay is reactive for HIV-1 antibody, then HIV-1 infection is confirmed. If the antibody differentiation assay is negative, then testing for HIV RNA by nucleic acid amplification is performed. A negative antibody differentiation assay with a positive HIV RNA test would indicate acute HIV infection (in the "window" period after infection but before antibody development). But if the HIV RNA assay is also negative (no HIV RNA detected), then no evidence for HIV infection exists, and the initial test was a false positive. Although

false-positive findings are rare, in a population with low pre-test probability (such as in screening), false-positive results on the initial antigen/antibody combination immunoassay may be seen with higher frequency than true-positive results; waiting for the confirmatory testing results is crucial to avoid misdiagnosis and unnecessary additional testing and treatment.

Because the patient does not have HIV infection, it would be inappropriate to begin antiretroviral therapy. Likewise, baseline HIV resistance testing is not indicated, nor would it be possible because the patient has no detectable HIV RNA to be genotyped.

It is important to assess the CD4 cell count for all persons newly diagnosed with HIV infection so the level of immunocompromise and consequent risk for opportunistic infections can be determined and prophylaxis can be started, if indicated. But this patient does not have HIV infection. Testing CD4 cell count as a surrogate for HIV infection is inappropriate because the CD4 level is neither sensitive nor specific for HIV infection.

Western blot testing for HIV is no longer performed as part of the laboratory protocol for diagnosing HIV infection because of problems with sensitivity in acute infection and with interpretation of indeterminate results.

KEY POINT

- A screening HIV test result that is positive on the initial antigen/antibody combination immunoassay but negative on the antibody differentiation immunoassay and nucleic acid amplification testing for HIV RNA represents a false-positive result.

Bibliography

Centers for Disease Control and Prevention and Association of Public Health Laboratories. Laboratory testing for the diagnosis of HIV infection: updated recommendations. Available at http://dx.doi.org/10.15620/cdc.23447. Published June 27, 2014. Accessed November 2, 2017.

Item 39 Answer: A

Educational Objective: Diagnose *Cryptosporidium* infection.

This patient has watery diarrhea associated with swimming pool exposure, and the oocysts observed microscopically represent *Cryptosporidium*. This parasitic protozoan is tolerant to chlorine and can persist for days in a chlorinated pool. *Cryptosporidium* has become the leading cause of swimming pool–related outbreaks of diarrheal illness. Swallowing infected water can result in infection. The incubation period is about 1 week, and the clinical presentation typically includes watery diarrhea, crampy abdominal pain, dehydration, fever, malaise, nausea, vomiting, and weight loss. The infection typically resolves in immunocompetent persons, but infection can be more serious and prolonged in those with immunocompromise, particularly in persons with AIDS who are not receiving combination antiretroviral therapy. Diagnosis can be established microscopically by visualization of oocysts with modified acid-fast staining. Because oocysts are shed intermittently, diagnosis may require stool antigen testing using polymerase chain reaction, enzyme immunoassay, or direct fluorescent antibody testing.

Although enterohemorrhagic *Escherichia coli* (EHEC) infection can be acquired by aspiration of contaminated swimming pool water, it typically produces bloody diarrhea. EHEC is a gram-negative rod that does not exhibit modified acid-fast staining.

Norovirus is the most common cause of gastroenteritis and is characterized by explosive vomiting and diarrhea. It is spread person to person through the fecal-oral route, leading to community outbreaks. But the virus is not visualized with modified acid-fast staining. A diagnostic assay for viral gastroenteritis with polymerase chain reaction testing is reserved for public health investigation.

Modified acid-fast staining can detect *Nocardia* species, but the organisms are filamentous branching rods. Infection usually involves the lungs, central nervous system, and skin, but not the gastrointestinal tract.

Vibrio parahaemolyticus lives in salt water and causes diarrhea, usually after consumption of undercooked shellfish, especially oysters. This gram-negative rod is not detected with a modified acid-fast stain and requires special culture media with high salt content for growth.

KEY POINT

- The protozoan *Cryptosporidium* is the most common cause of swimming pool–related outbreaks of diarrhea; diagnosis is made by microscopic examination of the stool or by stool antigen testing.

Bibliography

Wright SG. Protozoan infections of the gastrointestinal tract. Infect Dis Clin North Am. 2012;26:323-39. [PMID: 22632642] doi:10.1016/j.idc.2012.03.009

Item 40 Answer: C

Educational Objective: Prevent travelers' diarrhea in a patient with inflammatory bowel disease.

Ciprofloxacin is the most appropriate preventive measure for this patient. Travelers' diarrhea, defined as three or more loose or watery bowel movements per day associated with other signs or symptoms such as fever, abdominal pain, cramps, or blood in the stool, is the most common travel-associated infection; it has an incidence of 10% to 40% for trips lasting more than 1 week. Enterotoxigenic *Escherichia coli* is the causative agent in most cases. The risk of infection is related to certain geographic travel destinations (South and Southeast Asia, Central and South America, the Middle East and sub-Saharan Africa) as well as individual characteristics. Persons with chronic inflammatory bowel disease (Crohn and ulcerative colitis) or who are immunocompromised (HIV, organ transplantation, those taking immunosuppressant medications) are particularly susceptible. Although most

diarrheal episodes are self-limited and resolve within a few days, they can sometimes be protracted and severe, causing significant volume depletion and electrolyte imbalance. In some persons, chronic diarrhea or irritable bowel syndrome may persist for many months after the initial travel diarrhea episode has subsided. Prevention strategies generally focus on advice for avoiding potentially contaminated water and food, but studies have not conclusively proven these measures to be significantly effective. Prophylactic administration of systemic antibiotics has been determined to be highly effective in preventing infection, but it should only be offered to those at greatest risk for complications should infection occur. Nevertheless, in these higher risk persons, the duration of antibiotic administration should not extend beyond 2 to 3 weeks in an effort to decrease the chances of medication-related adverse effects or the development of drug resistance. The fluoroquinolone antibiotics (ciprofloxacin or norfloxacin) are the preferred drugs.

The macrolide antibiotic azithromycin is a highly effective agent for the treatment of various bacterial pathogens causing enterocolitis, but it has not been adequately evaluated as a prophylactic medication.

More than two thirds of persons who took bismuth subsalicylate to prevent diarrhea while traveling found it effective. However, it requires multiple daily doses, has potential adverse effects, and would be contraindicated in this woman with an aspirin allergy.

Probiotics have been proposed for the prevention and treatment of numerous medical disorders, but proven benefit has been limited to only a handful of disorders; travelers' diarrhea is not one of them.

Even though the risk of infection is less than 50%, this woman has Crohn colitis, so not recommending chemoprophylaxis may place her at undue risk.

KEY POINT

- Persons with chronic inflammatory bowel disease or who are immunocompromised are most susceptible to severe travelers' diarrhea or complications, and prophylaxis (fluoroquinolones preferred) should be provided to these patients.

Bibliography

Steffen R, Hill DR, DuPont HL. Traveler's diarrhea: a clinical review. JAMA. 2015;313:71-80. [PMID: 25562268] doi:10.1001/jama.2014.17006

H Item 41 Answer: A

Educational Objective: Prevent central line–associated bloodstream infection.

This patient's central venous catheter (CVC) should be assessed daily for continued necessity and potential removal. Approximately 250,000 central line–associated bloodstream infections (CLABSIs) occur in the United States every year, with 80,000 occurring in the ICU. CLABSIs increase length of hospital stay up to 24 days and have an attributable mortality rate of 35%. Approximately 55% of patients in the ICU and 24% of those in other units have a central line. Antimicrobial resistance is a problem for most CLABSI pathogens. The risk of CLABSI can be reduced by routinely incorporating the CVC bundle as part of patient care. The CVC insertion bundle includes hand hygiene; use of full barrier precautions (including a large full-body sterile drape to cover the patient during catheter insertion) and personal protective equipment (mask, cap, sterile gown, and gloves); chlorhexidine skin antisepsis; selection of optimal catheter type (such as selecting the minimum number of ports or lumens needed) and site; sterile dressing; and daily review of line necessity with prompt removal of unnecessary catheters. The daily review of line necessity and documentation can be achieved with multidisciplinary rounds, daily reminders, and automated alerts. These practices are important for decreasing the risk of developing CLABSIs. Just as with the insertion bundle, a maintenance bundle helps decrease the risk of introducing organisms during use of the catheter. Components of the maintenance bundle include daily review of line necessity with prompt removal of unnecessary catheters, hand hygiene before manipulation of the intravenous system, care of injection ports, and proper monitoring of catheter site dressing and dressing changes.

Guidelines recommend against routinely replacing CVCs (or arterial catheters) and administering antimicrobial prophylaxis for short-term or tunneled catheter insertion. Neither practice has been shown to decrease central line–associated infections. In fact, routinely changing central catheters may increase the risk of infection by introducing bacteria from the skin at the time of insertion.

KEY POINT

- Central venous catheters should be assessed daily for continued necessity and removed promptly when they are no longer needed.

Bibliography

Marschall J, Mermel LA, Fakih M, Hadaway L, Kallen A, O'Grady NP, et al; Society for Healthcare Epidemiology of America. Strategies to prevent central line-associated bloodstream infections in acute care hospitals: 2014 update. Infect Control Hosp Epidemiol. 2014;35:753-71. [PMID: 24915204] doi:10.1086/676533

Item 42 Answer: E

Educational Objective: Treat *Cyclospora* parasitic infection.

This patient has travel-associated *Cyclospora* infection and should be treated with trimethoprim-sulfamethoxazole. *Cyclospora* protozoan infections are typically acquired after consumption of fecal-contaminated food or water, particularly in countries where the parasite is endemic, such as Peru, Guatemala, Haiti, and Nepal. *Cyclospora* infections may also be acquired through consumption of fresh produce imported from tropical areas. The incubation period is approximately 1 week (range, 2 days to ≥2 weeks). The clinical presentation usually consists of crampy abdominal pain, anorexia, bloating, decreased appetite, fatigue, flatulence, low-grade fever,

malaise, nausea, watery diarrhea, and weight loss. Persons with HIV infection may have more severe symptoms associated with wasting.

Diagnosis can be established microscopically by visualization of oocysts with modified acid-fast staining; fluorescence microscopy can be used as well. Several stool specimens may be required because *Cyclospora* oocysts may be shed intermittently and at low levels, even in persons with profuse diarrhea. Polymerase chain reaction assays appear to have the greatest sensitivity for the diagnosis of a *Cyclospora* infection.

The recommended treatment is one double-strength tablet of trimethoprim-sulfamethoxazole taken orally twice daily for 7 to 10 days. The Centers for Disease Control and Prevention states no effective alternative treatments have been identified for persons who are allergic to or cannot tolerate trimethoprim-sulfamethoxazole; observation and symptomatic care is recommended for those patients.

Atovaquone has activity against protozoans such as *Pneumocystis jirovecii*, *Toxoplasma*, *Plasmodium*, and *Babesia*, but not *Cyclospora*.

Metronidazole has activity against some protozoans, including *Giardia*, *Entamoeba*, and *Trichomonas*, but not *Cyclospora*.

Pyrimethamine has activity against protozoans such as *Toxoplasma*, *Pneumocystis jirovecii*, and *Isospora belli*, but not *Cyclospora*.

Quinacrine can be used to treat *Giardia* but is not effective against *Cyclospora*.

KEY POINT

- *Cyclospora* infection is treated with oral trimethoprim-sulfamethoxazole.

Bibliography

Wright SG. Protozoan infections of the gastrointestinal tract. Infect Dis Clin North Am. 2012;26:323-39. [PMID: 22632642] doi:10.1016/j.idc.2012.03.009

Item 43 Answer: A

Educational Objective: Prevent perinatal transmission of HIV.

This pregnant woman with well-controlled HIV infection should continue the same antiretroviral regimen. Antiretroviral therapy during pregnancy is crucial and significantly decreases the risk of perinatal transmission of HIV to the baby. Although most transmission in untreated women occurs at the time of delivery, in utero transmission also occurs, and maintaining therapy throughout pregnancy or starting therapy immediately is important to significantly reduce the risk. Although concerns have been raised regarding the safety of efavirenz and tenofovir disoproxil fumarate in pregnancy, more recent data demonstrate the safety of these agents, including in the first trimester. A woman whose HIV is well controlled and is found to be pregnant should continue the same regimen unless another reason exists to change it.

Pausing antiretroviral therapy would result in rebound of viral replication and viremia, which would significantly increase the risk of in utero transmission of HIV to the developing fetus.

Testing for HIV drug resistance can be genotypic (looking for specific mutations associated with resistance to specific drugs) or phenotypic (assessing whether HIV can replicate in the presence of achievable levels of specific drugs). Resistance testing should always be done before an initial drug regimen is chosen and when treatment failure occurs, as indicated by failure to suppress viral load or an increase in viral load that was previously suppressed. Resistance testing is unnecessary at this time because no virologic failure is evident that would necessitate changing therapy. Moreover, it would not be possible to perform resistance testing in a patient with an undetectable viral load because not enough virus is present to test. A viral load level greater than 500 copies/mL is usually necessary to successfully perform resistance testing.

Zidovudine, lamivudine, and ritonavir-boosted lopinavir is a valid alternative for treating HIV; it was previously a preferred regimen in pregnancy. However, changing this patient's therapy, which is well tolerated and controls her HIV infection well, is unnecessary and would only risk new adverse effects, poor adherence (because of more pills or more frequent dosing), or treatment failure.

KEY POINT

- Antiretroviral therapy during pregnancy is crucial and significantly decreases the risk of perinatal transmission of HIV to the baby.

Bibliography

Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission. Recommendations for the use of antiretroviral drugs in pregnant women with HIV infection and interventions to reduce perinatal HIV transmission in the United States. Available at https://aidsinfo.nih.gov/guidelines/html/3/perinatal/0. Accessed April 12, 2018.

Item 44 Answer: C

Educational Objective: Prevent acute hepatitis A infection.

This patient should be given a single dose of hepatitis A vaccine. Worldwide, hepatitis A is the most common cause of acute viral hepatitis. Infection with this human-only RNA picornavirus is spread primarily through the fecal-oral route. Rates of endemicity are highest in developing nations, where hygiene and sanitary measures are less than optimal. Since the availability of effective hepatitis A vaccines in the mid-1990s, this enteric virus has been designated the leading cause of infection and death among vaccine-preventable diseases. Infected adolescents and adults usually present with fever, malaise, nausea, and anorexia, with more than 70% exhibiting jaundice. Most infection is benign and resolves uneventfully. Rarely, patients may experience fulminant hepatitis and acute liver failure. However, hepatitis A does

not become a chronic disease. Either of the two inactivated cell culture–produced vaccines that have become part of the recommended routine childhood vaccine schedule can be used. In addition to avoiding potentially contaminated food and water, vaccination is also strongly advised for those planning to travel to areas that pose significant risk of infection. Ideally, vaccination should occur at least 2 to 4 weeks before departure. Nevertheless, a single dose of vaccine given any time before travel provides adequate protection in otherwise healthy persons. Depending on the particular vaccine product used, a second dose is administered between 6 to 18 months later.

Another dose of vaccine administered 7 days after the first would have no immunologic boosting effect.

Passive immunization with intramuscular immune globulin adds no benefit when administered alone or in combination with vaccination for most healthy patients when time before travel is short. However, to optimally guard against infection, immune globulin is recommended with vaccination in persons with chronic liver disease or other chronic medical conditions, immunocompromised states, and older adults if travel is scheduled in less than 2 weeks. Immune globulin alone would also be warranted in persons who are allergic to or decline vaccination and in children younger than 12 months for whom the vaccine is not approved.

Providing no intervention would place this traveler at undue risk of acquiring hepatitis A infection.

KEY POINT

- Hepatitis A vaccination should ideally occur 2 to 4 weeks before travel to an endemic region; however, a single dose of the vaccine given any time before travel provides adequate protection to otherwise healthy persons.

Bibliography

Fiore AE, Wasley A, Bell BP; Advisory Committee on Immunization Practices (ACIP). Prevention of hepatitis A through active or passive immunization: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep. 2006;55:1-23. [PMID: 16708058]

H

Item 45 Answer: D

Educational Objective: Treat multidrug-resistant urinary tract infection.

Antibiotic therapy should be switched from piperacillin-tazobactam to meropenem. This patient has a complicated urinary tract infection (UTI), defined by the presence of a chronic indwelling urinary catheter. The pattern of antibiotic susceptibility of *Escherichia coli* from the urine culture suggests an extended-spectrum β-lactamase (ESBL)–producing organism. ESBL-producing gram-negative organisms are capable of hydrolyzing higher generation cephalosporins that have an oxyimino side chain, including cefotaxime, ceftazidime, ceftriaxone, and cefepime. Laboratory identification of ESBLs is difficult because they are a heterogeneous group of enzymes. The carbapenem class of antibiotics (imipenem, meropenem, doripenem, ertapenem) is the preferred class of agents for treating infections with ESBL-producing organisms.

Adding gentamicin would provide no benefit. Additionally, this patient has kidney disease; thus, aminoglycosides should be avoided if at all possible.

On laboratory testing, ESBL-producing gram-negative organisms may appear susceptible to piperacillin-tazobactam; however, susceptibility breakpoints do not always reflect clinical success. Thus, piperacillin-tazobactam may be insufficient to treat infections with ESBL-producing organisms. An exception is uncomplicated UTI, in which piperacillin-tazobactam may be effective because high concentrations of the antibiotic are achievable in urine.

The oxyimino cephalosporins (such as cefepime) should not be used, even if an ESBL-producing organism appears to be susceptible on laboratory testing. Treatment failures are common, even with higher doses, so carbapenems are the preferred antibiotic.

KEY POINT

- The carbapenem class of antibiotics (imipenem, meropenem, doripenem, ertapenem) is the preferred class of agents for treating infections with extended-spectrum β-lactamase–producing organisms.

Bibliography

Kaye KS, Pogue JM. Infections caused by resistant gram-negative bacteria: epidemiology and management. Pharmacotherapy. 2015;35:949-62. [PMID: 26497481] doi:10.1002/phar.1636

Item 46 Answer: D

Educational Objective: Monitor for adverse effects of daptomycin therapy in an outpatient.

Patients receiving outpatient daptomycin therapy should undergo baseline measurement of kidney function and creatine kinase (CK) followed by weekly monitoring. Patients should also be screened for symptoms of myopathy. Daptomycin is commonly used for outpatient parenteral antibiotic therapy (OPAT) because of its safety profile, ease of administration (once daily), and good activity against gram-positive bacteria, including vancomycin-resistant enterococci and methicillin-resistant *Staphylococcus aureus*. However, daptomycin is known to cause elevated levels of CK and can contribute to the development of myopathy during therapy. Daptomycin should be discontinued in asymptomatic patients if CK levels increase to greater than 10 times the upper limit of normal or the CK level is greater than 5 times the upper limit of normal with symptoms of myopathy. Concomitant treatment with statins (particularly simvastatin and atorvastatin) may increase the chance of developing an elevated CK level; it is suggested that statins be discontinued if possible during daptomycin treatment. If statins cannot be discontinued, or if kidney dysfunction is evident, the CK level should be monitored more

frequently than once weekly. Likewise, the creatinine level should also be monitored because daptomycin dosing may require adjustment (lower dose or dosing interval of every other day), and CK may require more frequent monitoring if the creatinine level increases.

Daptomycin use does not require electrocardiographic monitoring, and it has no effect on the bone marrow (for example, erythrocyte or platelet suppression), pancreas, lipid levels, or blood glucose level; so weekly amylase, triglyceride, glucose, and hemoglobin measurements and platelet count monitoring are unnecessary (although periodic leukocyte counts may be necessary in some patients for monitoring of the primary infection). It is important for patients undergoing OPAT to have close follow-up to monitor for any adverse effects from antibiotic therapy (including development of vascular access infections) as well as resolution of the infection being treated.

KEY POINT

- Patients receiving daptomycin therapy should undergo baseline measurement of kidney function and creatine kinase level followed by weekly monitoring.

Bibliography

Cervera C, Sanroma P, González-Ramallo V, García de la María C, Sanclemente G, Sopena N, et al; DAPTODOM Investigators. Safety and efficacy of daptomycin in outpatient parenteral antimicrobial therapy: a prospective and multicenter cohort study (DAPTODOM trial). Infect Dis (Lond). 2017;49:200-207. [PMID: 27820968] doi:10.1080/23744235.2016.1247292

Item 47 Answer: D

Educational Objective: Identify the cause of Kaposi sarcoma.

This patient has Kaposi sarcoma caused by human herpes virus (HHV) type 8. It is found primarily in men who have sex with other men and who have AIDS. This patient's clinical presentation is typical for Kaposi sarcoma, with painless violaceous skin nodules with oral involvement. The treatment for Kaposi sarcoma includes antiretroviral therapy, local therapies (radiation therapy, intralesional chemotherapy, cryotherapy, or topical retinoids), and systemic therapies such as interferon or chemotherapy.

Cytomegalovirus (HHV-5) infections are most commonly asymptomatic, but they can also present with a mononucleosis-like syndrome and may reactivate in patients with cellular immunodeficiency such as AIDS or in those who have had a solid organ or bone marrow transplantation. Cytomegalovirus does not cause skin nodules but can present with retinitis (in AIDS), pneumonia, hepatitis, adrenalitis, pancytopenia, gastritis, or colitis.

Epstein-Barr virus (EBV) (HHV-4) is the main cause of infectious mononucleosis presenting with fever, exudative pharyngitis, cervical lymphadenopathy, and splenomegaly. EBV reactivation is associated with the development of T-cell and B-cell lymphomas, Hodgkin and Burkitt lymphoma, nasopharyngeal carcinoma, and posttransplant lymphoproliferative disease in solid organ transplantation.

Human herpes virus type 6 causes roseola infantum, febrile seizures in children, and cytomegalovirus-seronegative and EBV-seronegative mononucleosis. It does not cause skin nodules. Recipients of bone marrow transplantation may also develop encephalitis, hepatitis, pneumonia, rash, graft-versus-host disease, and delayed engraftment.

KEY POINT

- Kaposi sarcoma can develop in patients with AIDS infected with human herpes virus type 8, presenting with painless violaceous skin nodules with oral involvement.

Bibliography

De Paoli P, Carbone A. Kaposi's sarcoma herpesvirus: twenty years after its discovery. Eur Rev Med Pharmacol Sci. 2016;20:1288-94. [PMID: 27097948]

Item 48 Answer: B

H

Educational Objective: Treat osteomyelitis associated with orthopedic hardware.

Cefazolin and rifampin are appropriate therapy for treatment of methicillin-sensitive *Staphylococcus aureus* (MSSA) osteomyelitis associated with orthopedic hardware. Identification of the causative pathogen, administration of adequate antimicrobials for a prolonged duration, surgical debridement (if warranted), and removal of orthopedic prosthetic devices (if feasible) influence the success of osteomyelitis treatment. Optimal management of this patient's infection includes hardware removal; however, this is not possible because the fracture has not yet healed. Hardware-associated infections caused by *S. aureus* are difficult to eradicate because of the biofilm that forms on the hardware. First-line treatment of MSSA osteomyelitis consists of a β-lactam agent such as cefazolin; a randomized controlled trial and systematic review of the literature have demonstrated that if infected hardware cannot be removed, the addition of rifampin increases the chances of therapeutic success compared with an antistaphylococcal agent alone.

Although cefazolin has activity against MSSA as well as good bone penetration, it would not be an appropriate therapeutic option for the treatment of hardware-associated osteomyelitis without the addition of rifampin.

Ceftaroline has coverage for MSSA, methicillin-resistant *S. aureus*, and Enterobacteriaceae, but it is unnecessarily broad coverage for the treatment of this patient's MSSA infection.

Vancomycin, a bacteriostatic agent, is less effective than β-lactam agents for the treatment of MSSA and is typically restricted to patients with drug intolerance or allergy.

KEY POINT

- Rifampin should be used in combination with another antistaphylococcal agent when managing *Staphylococcus aureus* osteomyelitis in the setting of orthopedic hardware if the hardware cannot be removed.

Bibliography

Kim BN, Kim ES, Oh MD. Oral antibiotic treatment of staphylococcal bone and joint infections in adults. J Antimicrob Chemother. 2014;69:309-22. [PMID: 24072167] doi:10.1093/jac/dkt374

Item 49 Answer: A

Educational Objective: Treat an immunocompromised patient after a dog bite.

The most appropriate management for this patient would be administration of amoxicillin-clavulanate. Because of asplenia, he is immunodeficient and should receive prophylactic antibiotic therapy after the dog bite, even without evidence of infection. Infections typically result from the host's skin flora and the animal's mouth flora. This flora is a mix of aerobic and anaerobic organisms, including staphylococci, streptococci, *Bacteroides* species, *Porphyromonas* species, *Fusobacterium* species, *Capnocytophaga canimorsus*, and *Pasteurella* species. *C. canimorsus* is a gram-negative bacillus that can cause overwhelming sepsis in patients with functional or anatomic asplenia who have experienced a dog bite or scratch. Because of its activity against pathogens associated with animal bite wounds, a 3- to 5-day course of amoxicillin-clavulanate is recommended for patients who are immunosuppressed (including patients with cirrhosis and asplenia); have wounds with associated edema, lymphatic or venous insufficiency, or crush injury; have wounds involving a joint or bone; have deep puncture wounds; or have moderate to severe injuries, especially when involving the face, genitalia, or hand. If a patient is allergic to penicillin, a combination of trimethoprim-sulfamethoxazole or a fluoroquinolone or doxycycline plus clindamycin or metronidazole can be used.

Because these infections are typically polymicrobial, consisting of aerobic and anaerobic bacteria, neither ciprofloxacin nor metronidazole alone would be adequate. Ciprofloxacin lacks anaerobic bacterial coverage, and metronidazole lacks aerobic activity.

Because of this the patient's immunodeficiency, observation alone would not be recommended by the Infectious Diseases Society of America guidelines.

KEY POINT

- Amoxicillin-clavulanate is recommended for patients with animal bites who are immunosuppressed (including patients with cirrhosis and asplenia); have wounds with associated edema, lymphatic or venous insufficiency, or crush injury; have wounds involving a joint or bone; have deep puncture wounds; or have moderate to severe injuries, especially when involving the face, genitalia, or hand.

Bibliography

Stevens DL, Bisno AL, Chambers HF, Dellinger EP, Goldstein EJ, Gorbach SL, et al. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the infectious diseases society of America. Clin Infect Dis. 2014;59:147-59. [PMID: 24947530] doi:10.1093/cid/ciu296

Item 50 Answer: A

Educational Objective: Treat multidrug-resistant intra-abdominal infection.

The *Pseudomonas* isolate should be tested for susceptibility to ceftolozane-tazobactam and colistin. This patient has an intra-abdominal infection caused by carbapenem-resistant (meropenem and doripenem) *Pseudomonas aeruginosa*. The antimicrobial options for treating carbapenem-resistant organisms are limited. Ceftolozane-tazobactam consists of a newer antipseudomonal cephalosporin combined with a β-lactamase inhibitor. It has activity against some extended-spectrum β-lactamase (ESBL)-producing gram-negative organisms as well as carbapenem-resistant strains of *Pseudomonas*. Its efficacy is reduced in patients whose creatinine clearance rate is 50 mL/min or less. Ceftolozane-tazobactam is approved to treat complicated urinary tract infections and complicated intra-abdominal infections. For complicated intra-abdominal infections, ceftolozane-tazobactam must be paired with metronidazole because it lacks antianaerobic activity. This patient's penicillin allergy is not an anaphylactic reaction, so it is reasonable to consider a cephalosporin in her treatment.

Colistin is an older antimicrobial agent that has made a resurgence because of its bactericidal activity against pan-resistant gram-negative organisms (including carbapenem-resistant, gram-negative organisms). Half of patients who are administered colistin develop nephrotoxicity, which limits the drug's usefulness in many cases. Kidney function should be closely monitored during administration, and colistin should be dose adjusted for patients with kidney disease. Paresthesias are a commonly reported neurotoxicity. Unfortunately, colistin resistance has been reported and appears to be increasing.

Ertapenem is a non-antipseudomonal carbapenem, so it would not be an option for this patient. Likewise, tobramycin is an aminoglycoside, which has poor activity and penetration into abscesses and would not be a consideration for this patient.

Fosfomycin is used to treat urinary tract infections caused by several multidrug-resistant organisms (such as vancomycin-resistant enterococci, methicillin-resistant *Staphylococcus aureus*, and resistant *Klebsiella pneumoniae*). Fosfomycin has poor tissue penetration and is not indicated for infections other than uncomplicated urinary tract infections.

Minocycline is another older antimicrobial agent that has been used recently to treat multidrug-resistant *Acinetobacter* as well as *Stenotrophomonas maltophilia* infections, but it does not have activity against *Pseudomonas*.

KEY POINT

- Ceftolozane-tazobactam is a newer antipseudomonal cephalosporin combined with a β-lactamase inhibitor that can be used in the treatment of multidrug-resistant intra-abdominal infection.

Bibliography

Morrill HJ, Pogue JM, Kaye KS, LaPlante KL. Treatment options for carbapenem-resistant Enterobacteriaceae infections. Open Forum Infect Dis. 2015;2:ofv050. [PMID: 26125030] doi:10.1093/ofid/ofv050

H

Item 51 Answer: E

Educational Objective: Evaluate community-acquired pneumonia in a pregnant patient.

Streptococcus pneumoniae is the most likely cause of this patient's community-acquired pneumonia (CAP). Pneumonia is the most common cause of fatal nonobstetric infection in pregnancy. The microbiology of CAP in pregnancy is similar to that seen in the general population. Among patients requiring hospitalization, the most common pathogens are *S. pneumoniae*, *Haemophilus influenzae*, and atypical organisms, including *Legionella* species, *Chlamydia pneumoniae*, and *Mycoplasma pneumoniae*. Empiric treatment of pregnant patients is similar to that in nonpregnant adults, although quinolones and tetracyclines are relatively contraindicated because of the potential for teratogenic effects. In addition to these common bacterial causes of CAP, pregnant women are at increased risk for serious viral pneumonia from influenza virus and varicella-zoster virus, so it is recommended that pregnant women receive seasonal influenza vaccination.

Gram-negative bacteria, including *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Acinetobacter* species, *Escherichia coli*, and *Enterobacter* species, are rarely implicated in CAP, including among pregnant women hospitalized for pneumonia. Most patients with CAP caused by gram-negative bacteria have a predisposing risk factor, such as bronchiectasis, cystic fibrosis, or COPD, and develop severe pneumonia necessitating admission and care in the ICU.

Pregnancy causes a decrease in T-cell function, and pregnant women are at increased risk for severe *Listeria* infections, including meningitis and sepsis. However, *Listeria* rarely causes pulmonary infection and would be an unlikely cause of infection in this patient.

Staphylococcus aureus is an increasingly recognized cause of CAP, with risk factors including antecedent viral infection or injection drug use. Maternal *S. aureus* infection can occur perinatally, related to delivery, surgery, or indwelling lines, but remains a rare cause of CAP in the prenatal period.

KEY POINT

- The microbiology of community-acquired pneumonia in pregnancy is similar to that seen in the general population; among patients requiring hospitalization, the most common pathogens are *Streptococcus pneumoniae*, *Haemophilus influenzae*, and atypical organisms, including *Legionella* species, *Chlamydia pneumoniae*, and *Mycoplasma pneumoniae*.

Bibliography

Mehta N, Chen K, Hardy E, Powrie R. Respiratory disease in pregnancy. Best Pract Res Clin Obstet Gynaecol. 2015;29:598-611. [PMID: 25997564] doi:10.1016/j.bpobgyn.2015.04.005

Item 52 Answer: B

Educational Objective: Treat influenza virus infection with a neuraminidase inhibitor.

The most appropriate treatment for this patient is the neuraminidase inhibitor oseltamivir. During a confirmed local influenza outbreak, infection can be reliably diagnosed on the basis of clinical criteria alone. When confirmation is needed, rapid antigen tests of respiratory samples from nasopharyngeal swabs detect influenza A and B. Positive test results are highly specific. However, sensitivity ranges from 40% to 80%. Detection of viral nucleic acid by polymerase chain reaction (PCR) is rapid, has high sensitivity and specificity, and can determine the type and subtype of influenza virus. Annual influenza vaccination is the most effective intervention for preventing influenza and is recommended for all persons 6 months or older. Only a few randomized trials have assessed the efficacy of influenza vaccines in older individuals. These trials suggest that the vaccines are approximately 60% effective against influenza in adults 65 years and older. Nevertheless, immunization is likely to prevent hospitalization in older adults. Neuraminidase inhibitors have activity against influenza A and B. They can be given orally (oseltamivir), intranasally (zanamivir), or intravenously (peramivir). Antiviral therapy is recommended for severe disease, including all hospitalized patients or those with confirmed or suspected influenza infection at high risk for complications. Older adult patients (older than ≥65 years), young children, pregnant women, and patients with chronic medical conditions (especially chronic lung disease and heart disease) are at higher risk for severe primary influenza complications such as superimposed bacterial pneumonia caused by *Streptococcus pneumoniae* or *Staphylococcus aureus* and death.

M2 inhibitors, such as amantadine and rimantadine, were the first agents introduced for influenza treatment, but they are only active against influenza A. Therefore, these agents would be ineffective against this patient's infection with influenza B.

Antiviral therapy should be started within 48 hours of symptom onset in patients with a positive rapid influenza test because it decreases recovery time, hospitalization rates, and complications. Because this patient can be treated as an outpatient, either oseltamivir or zanamivir would be appropriate choices. Intravenous peramivir is typically reserved for patients who cannot tolerate or are otherwise incapable of taking inhaled or enteral agents.

KEY POINT

- Neuraminidase inhibitors (oseltamivir, zanamivir, peramivir) are indicated for the treatment of influenza A and B and can be administered through various routes (oral, intranasal, intravenous).

Bibliography

Uyeki TM. Influenza. Ann Intern Med. 2017;167:ITC33-ITC48. [PMID: 28869984] doi:10.7326/AITC201709050

H

Item 53 Answer: A

Educational Objective: Manage urinary tract infections in men.

This patient should be given intravenous cefepime and fluids and should undergo kidney ultrasonography. According to the 2016 Critical Care Congress Third International Consensus Definition of Sepsis and Septic Shock (Sepsis-3), this man is septic. The probable source of his severe infection is the urinary tract (UTI), likely acute prostatitis, which is the most significant cause of bacteremia in older adult men. The prompt administration of adequate antimicrobial therapy is the most important factor in decreasing morbidity, mortality, and length of hospital stay in patients with sepsis. Cefepime is an appropriate choice because it possesses dependable bactericidal activity against common urinary pathogens as well as potentially drug-resistant organisms, including *Pseudomonas*. In addition to antimicrobial therapy and supportive medical care, men with febrile UTIs require anatomic assessment of the upper and lower urinary tract by either kidney ultrasonography or CT with contrast (more sensitive, but contraindicated with kidney disease) to determine the need for source control. When acute prostatitis is the presumed diagnosis, imaging generally is unnecessary, but assurance that this patient with sepsis does not have a prostatic abscess may prove beneficial if his fever persists beyond 72 hours.

The empiric use of ciprofloxacin or other fluoroquinolone antibiotics in a hospitalized patient with a complicated UTI is no longer recommended because several strains of *Escherichia coli* and other Enterobacteriaceae have become resistant to these agents.

Detection of a boggy and tender prostate gland on gentle digital rectal examination would suggest a prostate focus of infection, but vigorous prostate massage is not indicated in acute prostatitis because of a lack of diagnostic or therapeutic benefit and possibility of facilitating bacteremia.

The β-lactam and β-lactamase inhibitor, piperacillin-tazobactam, would be an adequate initial antibiotic selection but should be avoided in a patient with an undocumented penicillin allergy, even if he has tolerated cephalosporin medications.

KEY POINT

- Men with febrile urinary tract infections require prompt antimicrobial therapy and anatomic assessment of the upper and lower urinary tract.

Bibliography

Schaeffer AJ, Nicolle LE. Clinical practice. Urinary tract infections in older men. N Engl J Med. 2016;374:562-71. [PMID: 26863357] doi:10.1056/NEJMcp1503950

H

Item 54 Answer: C

Educational Objective: Treat vertebral osteomyelitis in a patient with signs of sepsis.

The patient has vertebral osteomyelitis and clinical findings suggestive of sepsis; empiric antibiotic therapy to cover the most likely pathogens should be initiated. A diagnosis of vertebral osteomyelitis should be considered in patients reporting worsening back or neck pain without an alternate explanation. Local tenderness over the site of spinal infection is frequently detected. Radicular pain, motor weakness, and sensory changes may be present. Common sources of hematogenous osteomyelitis are distant foci of infection (for example, skin and soft tissue, genitourinary, gastrointestinal), intravascular catheters, and infective endocarditis. Hematogenous osteomyelitis is typically monomicrobial, and *Staphylococcus aureus* is the most commonly isolated pathogen; however, aerobic, gram-negative bacilli cause disease in many patients. Certain patient-specific conditions are associated with less common bacterial organisms, including *Salmonella* osteomyelitis in persons with sickle cell disease and *Pseudomonas aeruginosa* bone infection in injection drug users. Lengthy parenteral antimicrobial therapy is the mainstay of treatment. An antistaphylococcal agent with methicillin-resistant *S. aureus* (MRSA) coverage (vancomycin) and a β-lactam with antipseudomonal coverage (cefepime) is an appropriate empiric regimen for suspected osteomyelitis in this patient who uses injection drugs.

Cefazolin does not provide coverage for MRSA, and aminoglycosides, such as gentamicin, have poor penetration into bone.

Vancomycin alone would not provide coverage for gram-negative organisms, which should be included in the empiric therapy for this patient.

Although microbiologic confirmation of the bacterial cause should always be sought, withholding antibiotics in a patient likely to have sepsis (fever, hypotension, tachycardia) is not appropriate. If the patient has positive blood cultures, a presumptive microbiologic diagnosis of vertebral osteomyelitis can usually be made. However, because injection drug users have frequent bacteremia and the patient's bloodstream infection may be unrelated to the vertebral osteomyelitis, some experts would recommend pursuing bone biopsy, even in patients with positive blood cultures.

KEY POINT

- When sepsis is suspected among patients with osteomyelitis, empiric antibiotic therapy should begin, even when the microbial cause of the infection has not yet been determined.

Bibliography

Berbari EF, Kanj SS, Kowalski TJ, Darouiche RO, Widmer AF, Schmitt SK, et al. 2015 Infectious Diseases Society of America (IDSA) clinical practice guidelines for the diagnosis and treatment of native vertebral osteomyelitis in adults. Clin Infect Dis. 2015;61:e26-46. [PMID: 26229122] doi:10.1093/cid/civ482

Item 55 Answer: A

Educational Objective: Diagnose acute HIV infection.

This patient has acute HIV infection. His recent nonspecific viral symptoms are consistent with the acute

retroviral syndrome, although they are not diagnostic. Regardless of the presence or absence of symptoms, his HIV testing results support a diagnosis of acute HIV infection. His initial HIV-1/2 antigen/antibody combination immunoassay is reactive, indicating further testing is needed. The HIV-1/HIV-2 antibody differentiation assay is negative, indicating the absence of antibody to HIV; however, the RNA assay is positive for HIV-1 RNA. This finding indicates the patient does not have antibodies to HIV but does demonstrate the presence of virus by nucleic acid amplification testing. The initial combination immunoassay was reactive because of the presence of HIV p24 antigen rather than antibody, which indicates acute infection with HIV before antibody development. The ability to detect acute infection is a key advantage of and improvement in current HIV testing, allowing for earlier detection of infection, faster initiation of treatment, and, consequently, reduced risk of transmission.

In chronic HIV infection, the HIV antibody differentiation immunoassay would have demonstrated antibody to HIV, either HIV-1 (usually) or HIV-2 (rarely). Because no antibody was detected but HIV RNA is present, infection is still in the acute phase before antibody development.

Because the HIV-1 RNA assay was positive at a significant level, the initial HIV antigen/antibody immunoassay result was not a false positive. Although false-positive HIV RNA testing can occur, it is usually at a very low, barely detectable level. This patient's level is substantial, and he has known risk factors and consistent symptoms for acute HIV infection, increasing his pretest probability and making a positive result much more likely a true positive.

HIV-2 infection is rare in the United States. It is ruled out in this patient by the negative HIV-2 antibody result on the HIV-1/HIV-2 antibody differentiation assay.

KEY POINT

- On testing for HIV infection, a positive result on HIV-1/2 antigen/antibody combination immunoassay is followed by testing with the HIV-1/HIV-2 antibody differentiation immunoassay; a negative antibody differentiation immunoassay but a positive follow-up HIV-1 nucleic acid amplification test is diagnostic of acute HIV infection.

Bibliography

Centers for Disease Control and Prevention and Association of Public Health Laboratories. Laboratory testing for the diagnosis of HIV infection: updated recommendations. Available at http://dx.doi.org/10.15620/cdc.23447. Published June 27, 2014. Accessed November 2, 2017.

H

Item 56 Answer: A

Educational Objective: Treat urethritis with empiric therapy.

The most appropriate treatment is ceftriaxone plus azithromycin. The patient has dysuria and evidence of mucopurulent urethral discharge, which are consistent with urethritis. Because he is being evaluated in an urgent care setting and may not return for follow-up, empiric therapy is appropriate. A single intramuscular dose of ceftriaxone (250 mg) plus a single oral dose of azithromycin (1 g) will treat *Neisseria gonorrhoeae* and *Chlamydia trachomatis*, the most common causes of urethritis. Diagnostic testing results are still important in case the patient does not respond to empiric therapy and for disease reporting and contact tracing. This man should also be offered HIV and syphilis testing and undergo counseling regarding the use of condoms for all sexual encounters, including oral sex. Some concern exists that sexually active persons, particularly young persons, may believe that oral sex is "safe" and does not pose a risk of sexually transmitted infection (STI) transmission. Most STIs can be acquired through oral sex; the risk of acquiring HIV infection may be lower, but precise data on the relative risk of STI acquisition from specific types of sexual activity are not available.

Doxycycline for 7 days is an alternate therapy for *C. trachomatis*; however, it should be used only when a macrolide allergy precludes the use of azithromycin. It also will not reliably treat *N. gonorrhoeae*.

Trimethoprim-sulfamethoxazole is not an effective treatment for urethritis. Trimethoprim-sulfamethoxazole can potentially be used for empiric therapy for cystitis; however, men with cystitis should not have purulent urethral discharge. Additionally, symptoms of bladder irritation, including increased frequency and urgency, are generally present.

Herpes simplex virus can present as urethritis, and penile ulcers may not be present on physical examination; however, this clinical presentation is less common and should only be considered if the infection fails to respond to treatment for the more common causes of urethritis. Therefore, valacyclovir is not the most appropriate initial empiric therapy for this patient.

KEY POINT

- In a patient with clinical signs and symptoms of urethritis, treatment with ceftriaxone and azithromycin provides appropriate empiric therapy without waiting for microbiologic testing results.

Bibliography

Workowski KA, Bolan GA; Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2015. MMWR Recomm Rep. 2015;64:1-137. [PMID: 26042815]

Item 57 Answer: C

Educational Objective: Prevent opportunistic fungal infections after hematopoietic stem cell transplantation.

Posaconazole is the most appropriate prophylactic therapy for this patient after hospital discharge. Patients who undergo allogeneic hematopoietic stem cell transplantation (HSCT) usually experience a period of prolonged neutropenia after the pretransplant myeloablative conditioning

regimen. This prolonged, severe neutropenia is a significant risk factor for invasive bacterial and fungal infections, and prophylaxis for both is indicated. The risk of invasive fungal infection remains elevated, however, even after recovery of neutrophils for the first few months after allogeneic HSCT and even later in the setting of graft-versus-host disease. Therefore, although this patient is doing well and her neutrophil count has recovered, antifungal prophylaxis should be provided in addition to continuing trimethoprim-sulfamethoxazole therapy. Posaconazole provides activity against *Candida* and *Aspergillus* and other moulds that are the cause of an increasing proportion of invasive fungal infections after HSCT.

Acyclovir is used to reduce reactivation of herpes simplex virus during periods of neutropenia, but its administration is no longer needed. Additionally, this patient is seropositive for varicella-zoster virus because of immunization, so varicella-zoster prophylaxis is unnecessary. Finally, acyclovir has no role in preventing reactivation of Epstein-Barr virus or cytomegalovirus, two other infections for which this patient is at risk.

Ciprofloxacin is a preferred agent for antibacterial prophylaxis during neutropenia because it has activity against most of the gram-negative bacteria of greatest concern. But with resolution of neutropenia and completion of therapy for known infection, continued antibacterial therapy should be avoided to lessen toxicities and complications such as *Clostridium difficile* colitis.

Valganciclovir is used to prevent or treat cytomegalovirus infection. This patient is at risk for reactivation cytomegalovirus because of her positive serology. However, because of the leukopenia that is a common toxicity of valganciclovir, a strategy of monitoring for cytomegalovirus and starting pre-emptive therapy only when indicated is preferred over prophylaxis after HSCT.

KEY POINT

- In patients who have undergone hematopoietic stem cell transplantation, the risk of invasive fungal infection remains elevated for the first few months, even after recovery of neutrophil counts, so antifungal prophylaxis should be continued during this time.

Bibliography

Ullmann AJ, Schmidt-Hieber M, Bertz H, Heinz WJ, Kiehl M, Krüger W, et al; Infectious Diseases Working Party of the German Society for Hematology and Medical Oncology (AGIHO/DGHO) and the DAG-KBT (German Working Group for Blood and Marrow Transplantation). Infectious diseases in allogeneic haematopoietic stem cell transplantation: prevention and prophylaxis strategy guidelines 2016. Ann Hematol. 2016;95:1435-55. [PMID: 27339055] doi:10.1007/s00277-016-2711-1

H Item 58 Answer: C

Educational Objective: Treat suspected tuberculous meningitis.

The most appropriate management for this patient is four-drug antituberculous therapy (rifampin, isoniazid, pyrazinamide, and ethambutol) plus dexamethasone. Meningitis can be defined as either acute or chronic. The symptoms of acute meningitis typically progress over hours, sometimes days, whereas chronic meningitis generally progresses over 4 or more weeks. Tuberculosis and fungal infection are the most common causes of chronic meningitis. Tuberculous meningitis should be suspected in patients from highly endemic countries who have basilar lymphocytic meningitis associated with cranial neuropathies (particularly involving cranial nerve VI) and hypoglycorrhachia. A history of tuberculosis exposure, an abnormal chest radiograph, a positive tuberculin skin test, and a positive interferon-γ release assay may be clues to the diagnosis, but these can be absent. Cerebrospinal fluid (CSF) acid-fast bacilli stains and cultures are insensitive and may take up to 6 weeks to grow. Patients with a high suspicion for tuberculosis should be treated empirically with rifampin, isoniazid, pyrazinamide, and ethambutol pending culture results and clinical improvement. Adjunctive dexamethasone decreases mortality, especially in patients with normal mental status and no neurologic deficits; it should be started concomitantly with antituberculous therapy.

The most common fungal meningitis in the United States is cryptococcal meningitis. Cryptococcus is inhaled and causes an initial pulmonary infection. Risk factors for dissemination include AIDS, organ transplantation, glucocorticoid treatment, diabetes mellitus, liver dysfunction, and kidney injury. The central nervous system is the most common site of disseminated cryptococcosis. CSF analysis may resemble that of tuberculous meningitis, although monocytes may predominate and the opening pressure is often greater than 200 mm H_2O. An India ink preparation of the CSF will demonstrate cryptococcal organisms in up to 80% of patients with a high organism burden, such as patients with HIV infection, but is only 50% sensitive in patients without HIV. The CSF assay for cryptococcal antigen is highly sensitive and specific for the diagnosis of meningitis and can be obtained soon after lumbar puncture results are available. Recommended induction therapy for cryptococcal meningitis includes amphotericin B and 5-fluorocytosine but is not indicated in this patient who is at low risk for this infection.

Bacterial meningitis is an acute infection with progression of symptoms over hours to days. This patient has chronic lymphocytic meningitis with an extremely low CSF glucose level and a negative CSF Gram stain, making bacterial meningitis unlikely. Initiating vancomycin, ceftriaxone, and dexamethasone is not the most appropriate management.

KEY POINT

- Tuberculosis and cryptococcus are the most common causes of chronic meningitis; empiric treatment for tuberculous meningitis includes four-drug antituberculous therapy (rifampin, isoniazid, pyrazinamide, and ethambutol) plus dexamethasone.

Bibliography

Prasad K, Singh MB, Ryan H. Corticosteroids for managing tuberculous meningitis. Cochrane Database Syst Rev. 2016;4:CD002244. [PMID: 27121755] doi:10.1002/14651858.CD002244.pub4

Item 59 Answer: B

Educational Objective: Treat a patient with latent tuberculosis infection.

The most appropriate management for this patient is to initiate self-administered treatment with isoniazid. He has traveled to a high-risk area for *Mycobacterium tuberculosis*. Before departing for Vietnam, he had a negative tuberculin skin test; however, he returned with a positive screening result for tuberculosis. Because the chest radiograph is negative, he requires treatment for latent tuberculosis rather than treatment with the four-drug regimen for active tuberculosis. Several treatment options exist, and the regimen chosen should be based on comorbidities, knowledge of the drug-susceptibility data from the source patient, and possible drug interactions. Self-administered isoniazid for 9 months is approved for the treatment of latent tuberculosis by the Centers for Disease Control and Prevention for patients with and without HIV infection. In patients being treated for latent tuberculosis who have normal baseline aminotransferase levels and no risk factors for liver disease, routine testing of aminotransferase levels during treatment is unnecessary.

Once-weekly isoniazid and rifapentine only needs to be administered for 12 weeks, not 24 weeks. This regimen must be administered as directly observed therapy (that is, a health care worker directly observes the ingestion of a medication), as are all intermittent therapies. The 12-week regimen can be used instead of 9 months of isoniazid alone for healthy adult patients, including those with HIV coinfection who are not taking antiretroviral agents. It is not recommended for patients suspected of having rifampin- or isoniazid-resistant tuberculosis strains or for patients who are pregnant or plan to become pregnant while taking these agents.

Treatment of active tuberculosis usually consists of multiple drugs for 6 to 9 months administered in two phases: initial and continuation. The core first-line antituberculous agents are isoniazid, rifampin, pyrazinamide, and ethambutol. These agents are administered for 8 weeks as part of the initiation phase. Isoniazid and rifampin are then continued for 4 or 7 months as part of the continuation phase. This patient does not have active tuberculosis (absent symptoms and a normal chest radiograph) and does not require therapy with four antituberculosis drugs.

This patient has latent tuberculosis infection, as detected by the positive interferon-γ release assay. Providing no treatment would put him at risk of developing active disease or exposing close contacts who may then become ill.

KEY POINT

- Prophylactic treatment with isoniazid is recommended for persons with latent tuberculosis infection, determined by a newly positive tuberculosis screening test but no signs or symptoms of active disease; 9 months of daily isoniazid can be self-administered.

Bibliography

Nahid P, Dorman SE, Alipanah N, Barry PM, Brozek JL, Cattamanchi A, et al. Executive summary: Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America clinical practice guidelines: treatment of drug-susceptible tuberculosis. Clin Infect Dis. 2016;63:853-67. [PMID: 27621353] doi:10.1093/cid/ciw566

Item 60 Answer: A

H

Educational Objective: Diagnose *Clostridium difficile* colitis after transplantation.

The most likely diagnosis is colitis caused by *Clostridium difficile*. *C. difficile* infection is the most common cause of health care–associated colitis, and antibiotic use is the most significant risk factor. The patient presents within the first month after solid organ transplantation; this is a time when the most likely infections are nosocomial and similar to those in patients who have had other surgeries. This patient has recently completed antimicrobial treatment for pneumonia and wound infection, increasing his risk for *C. difficile* colitis, which is common in transplant recipients during this time frame. Testing for *C. difficile* colitis and providing treatment would be appropriate at this time. Polymerase chain reaction assays to detect the genes responsible for production of toxins A and B are very sensitive and are increasingly used in the diagnosis of *C. difficile* colitis.

The other concern of most significance in this patient would be cytomegalovirus infection, most likely manifesting as colitis in this scenario. Being a cytomegalovirus-seronegative recipient of an organ from a cytomegalovirus-seropositive donor puts the patient at significant risk for developing cytomegalovirus disease, most commonly in the gastrointestinal tract or as a nonspecific febrile illness. However, because of this risk, he is already receiving prophylaxis with valganciclovir, which significantly lowers the rate of occurrence. His presentation being so early after transplantation also makes cytomegalovirus less likely, because infection most often occurs in the "middle" period, 1 to 6 months after transplantation.

Mycophenolate toxicities include diarrhea, cytopenias, and infection. Although diarrhea is a common adverse effect of mycophenolate, the additional presence of fever and abdominal pain makes this an unlikely cause. *C. difficile* infection must be considered first and ruled out.

Polyoma BK virus causes a nephropathy after transplantation, not diarrhea, and usually occurs later than the first month after transplantation. Definitive diagnosis requires kidney biopsy. When polyoma BK nephropathy occurs, immunosuppression should be reduced to the minimum level necessary to avoid rejection.

KEY POINT

- The first month after solid organ transplantation is when the most likely infections are nosocomial and similar to those in patients who have had other surgeries; patients who have recently completed antimicrobial treatment are particularly at increased risk for *Clostridium difficile* colitis.

Bibliography

Fishman JA. From the classic concepts to modern practice. Clin Microbiol Infect. 2014;20 Suppl 7:4-9. [PMID: 24528498] doi:10.1111/1469-0691.12593

Item 61 Answer: C

Educational Objective: Treat *Neisseria gonorrhoeae* infection.

The most appropriate treatment is ceftriaxone plus azithromycin. This sexually active young woman presented for an annual Pap smear and renewal of oral contraceptives. She was appropriately screened for *Chlamydia trachomatis* and *Neisseria gonorrhoeae* infection using nucleic acid amplification testing. The U.S. Preventive Services Task Force recommends this screening for all sexually active women younger than 25 years. If the patient were older than 25 years, she should be tested because of her new sexual partner. Her screening results are positive for *N. gonorrhoeae*. Even without symptoms or findings on pelvic examination, she should be treated; a significant number of persons with *N. gonorrhoeae* infection are asymptomatic without evidence of cervicitis. Intramuscular ceftriaxone (250 mg) is the preferred therapy for treatment of *N. gonorrhoeae* infection, along with a single dose of oral azithromycin (1 g). Although this regimen is given empirically when *C. trachomatis* and *N. gonorrhoeae* coinfection is suspected (for example, empiric therapy for cervicitis), because of increasing minimum inhibitory concentrations (MIC) to ceftriaxone among *N. gonorrhoeae* isolates in the United States, azithromycin is used even when *C. trachomatis* infection is not present; this combination will increase the success of treatment of the *N. gonorrhoeae* infection.

Oral cefixime does not achieve adequate levels to exceed the MIC of many *N. gonorrhoeae* isolates, so this option should only be used if ceftriaxone is unavailable. In this circumstance, a single dose of oral azithromycin should be administered with the cefixime.

Ciprofloxacin was previously recommended for the treatment of *N. gonorrhoeae* infections; however, the prevalence of fluoroquinolone resistance among *N. gonorrhoeae* isolates has increased, and this antibiotic is no longer recommended.

KEY POINT

- Because of increasing minimum inhibitory concentrations to ceftriaxone among *Neisseria gonorrhoeae* isolates in the United States, this agent should be combined with a single dose of azithromycin.

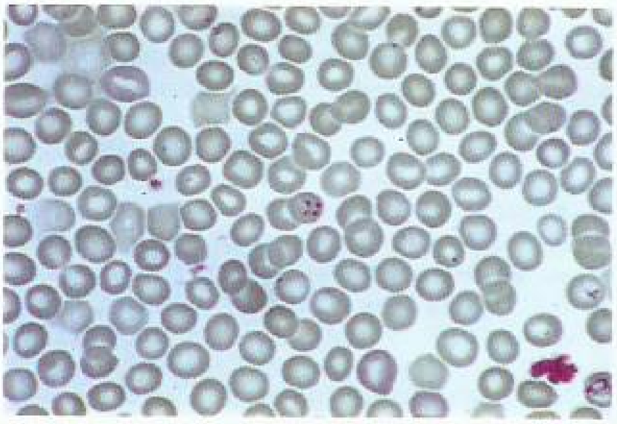
Bibliography

Workowski KA, Bolan GA; Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2015. MMWR Recomm Rep. 2015;64:1-137. [PMID: 26042815]

Item 62 Answer: C

Educational Objective: Diagnose babesiosis.

This patient's blood smear is most likely to show intraerythrocytic tetrad forms. He has a life-threatening illness characterized by fever and hemolysis and has no spleen. Given his residence in the northeastern United States and his outdoor vocation, severe babesiosis is likely. *Babesia* species are transmitted by the same tick that causes Lyme disease; infection also can be acquired through transfusion of infected erythrocytes outside of the endemic region. Asplenia is a major risk factor for fulminant *Babesia* infection, as is older age, HIV infection, or other immunocompromising conditions. Clinical manifestations are variable, with most relating to severe hemolytic anemia. Infection can be diagnosed by visualization of intraerythrocytic parasites, which appear as either ring forms or tetrads, with the latter often described as having the Maltese cross appearance shown. Complications, including acute respiratory distress syndrome, disseminated intravascular coagulation, heart failure, kidney failure, and coma, are associated with severe anemia (hematocrit level <30%) and parasitemia (exceeding 10%) and are indications for exchange transfusion.



Morulae, basophilic inclusion bodies composed of clusters of bacteria, can be seen in the cytoplasm of monocytes and neutrophils of patients with ehrlichiosis and anaplasmacytosis, respectively. These tick-borne infections cause fever, leukopenia, and thrombocytopenia but are not associated with hemolytic anemia.

Both malaria and babesiosis cause a hemolytic anemia and may present with ring-shaped parasitic inclusions inside erythrocytes. However, banana-shaped gametocytes are seen only with *Plasmodium falciparum* malaria, and the absence of a compatible travel history excludes this diagnosis.

Asplenic patients are at risk for overwhelming pneumococcal sepsis with a high bacterial burden; gram-positive diplococci may be visualized inside neutrophils on buffy coat stain. Although leukopenia and thrombocytopenia are common with fulminant infection, hemolytic anemia is not a feature of pneumococcal sepsis.

Schistocytes are a manifestation of microangiopathic hemolytic anemia caused by a thrombotic microangiopathy (TMA), such as hemolytic uremic syndrome or thrombotic thrombocytopenic purpura. Although both these syndromes

can cause fever, hemolysis, and thrombocytopenia, the absence of acute kidney injury in this patient excludes a TMA.

KEY POINT

- Babesiosis can be diagnosed by visualization of intraerythrocytic parasites in a ring or tetrad form on a blood smear.

Bibliography

Akel T, Mobarakai N. Hematologic manifestations of babesiosis. Ann Clin Microbiol Antimicrob. 2017;16:6. [PMID: 28202022] doi:10.1186/s12941-017-0179-z

H

Item 63 Answer: D

Educational Objective: **Manage conversion of intravenous antimicrobial therapy to oral antimicrobial therapy.**

This patient's therapy should be switched from intravenous piperacillin-tazobactam to oral ciprofloxacin and metronidazole. He has a diabetic foot ulcer and osteomyelitis of the left great toe caused by *Pseudomonas aeruginosa* and *Bacteroides fragilis*. Ciprofloxacin and metronidazole have excellent bioavailability and will penetrate bone adequately with oral administration. Continuing intravenous therapy offers no advantage for this patient, and intravenous therapy has risks that include developing a venous catheter–associated bloodstream infection. Intravenous-to-oral antibiotic switching should be considered in patients who have an intact and functioning gastrointestinal tract, whose clinical status is improving, and who are not being treated for an infection for which parenteral therapy is preferred (for example, endocarditis or meningitis). Common infectious scenarios for which a switch from intravenous to oral therapy should be considered include community-acquired pneumonia, bacterial peritonitis, pyelonephritis, septic arthritis, and skin and soft tissue infections. When switching from a parenteral to an oral antibiotic agent, the bioavailability of the oral antibiotics must be considered.

A second antipseudomonal agent is not required for this patient's osteomyelitis. He also has kidney disease, which should discourage use of an aminoglycoside. Therefore, adding tobramycin while continuing intravenous antibiotic therapy would not be the best management for this patient who can de-escalate to oral therapy.

Although aztreonam and ceftazidime have good antipseudomonal activity, neither agent has any anaerobic activity to cover *B. fragilis*.

KEY POINT

- Intravenous-to-oral antibiotic switching should be considered in patients who have an intact and functioning gastrointestinal tract, whose clinical status is improving, and who are not being treated for an infection for which parenteral therapy is preferred.

Bibliography

Cyriac JM, James E. Switch over from intravenous to oral therapy: A concise overview. J Pharmacol Pharmacother. 2014;5:83-7. [PMID: 24799810] doi:10.4103/0976-500X.130042

H

Item 64 Answer: A

Educational Objective: **Manage candidemia with empiric antifungal therapy.**

This patient has candidemia. Candidemia occurs most frequently in the presence of an intravascular catheter and may lead to focal organ involvement or disseminated infection as a consequence of hematogenous spread. Risk factors for candidemia and other forms of systemic candidiasis include neutropenia, malignancies, organ transplantation, broad-spectrum antimicrobial agents, immunosuppressive agents, chemotherapeutic agents, intravascular catheters, hemodialysis, parenteral nutrition, and major abdominal surgery. Because systemic candidiasis has a high mortality rate, therapy should be initiated promptly when it is suspected or diagnosed. The finding of yeast in the blood culture is enough to initiate empiric antifungal therapy until the fungal identification is definitive. An echinocandin (anidulafungin, caspofungin, or micafungin) is recommended as empiric therapy for most patients with candidemia. If the *Candida* species is azole susceptible, the patient may be de-escalated to fluconazole to complete the 14-day course of therapy.

Fluconazole is not recommended as initial management for this patient. Several *Candida* species, such as *C. glabrata*, *C. auris*, and *C. krusei*, are known to be intrinsically resistant to azoles.

Systemic candidiasis is usually diagnosed by a positive culture from blood or a normally sterile body site. A positive blood culture should not be treated as a contaminant, and empiric therapy should be instituted immediately, particularly in seriously ill patients such as this one. *Candida* isolated from blood cultures should always prompt a search for the source.

Central venous catheters should be removed as soon as possible in patients with candidemia; however, removal of an implicated catheter is not sufficient treatment for candidemia. All patients must be treated with antifungal drugs.

KEY POINT

- A positive blood culture for *Candida* species should not be treated as a contaminant, and empiric therapy with an echinocandin should be instituted immediately.

Bibliography

Pappas PG, Kauffman CA, Andes DR, Clancy CJ, Marr KA, Ostrosky-Zeichner L, et al. Executive summary: clinical practice guideline for the management of candidiasis: 2016 update by the Infectious Diseases Society of America. Clin Infect Dis. 2016;62:409-17. [PMID: 26810419] doi:10.1093/cid/civ1194

Item 65 Answer: A

Educational Objective: **Treat vertebral osteomyelitis.**

This patient has a confirmed diagnosis of methicillin-susceptible *Staphylococcus aureus* osteomyelitis and should

complete a 6-week course of antibiotics. Although there are no randomized controlled trials regarding the optimal duration of antibiotic therapy for osteomyelitis, a treatment course of 2 weeks is inadequate. For this patient, vertebral osteomyelitis at a single level, not associated with epidural abscess or hardware, has a favorable prognosis; older age, comorbidities, and infection with *S. aureus* are unfavorable factors. However, there is no evidence that antibiotics beyond 6 weeks will enhance therapeutic success. In a recently published clinical trial comparing 6 weeks to 12 weeks of antibiotics for vertebral osteomyelitis, cure rates were not significantly different between the treatment groups. Several retrospective studies have found similar results.

Prolonged courses of antibiotics place the patient at risk for adverse events, including drug-resistant pathogens and *Clostridium difficile*–associated diarrhea.

Cefazolin should not be discontinued now because the patient has only completed 2 weeks of treatment, and 6 weeks is considered the therapeutic minimum.

Monitoring of inflammatory markers during treatment can assist in assessing the success of therapy. Routine follow-up MRI is not recommended in patients who respond clinically. Follow-up MRI may suggest progressive infection and lead to unnecessary additional intervention. Follow-up MRI is indicated with clinical deterioration or if a concomitant epidural or paraspinal abscess was present that was managed medically.

KEY POINT

- The recommended duration of antibacterial therapy for acute vertebral osteomyelitis is 6 weeks.

Bibliography

Berbari EF, Kanj SS, Kowalski TJ, Darouiche RO, Widmer AF, Schmitt SK, et al. 2015 Infectious Diseases Society of America (IDSA) clinical practice guidelines for the diagnosis and treatment of native vertebral osteomyelitis in adults. Clin Infect Dis. 2015;61:e26-46. [PMID: 26229122] doi:10.1093/cid/civ482

Item 66 Answer: D

Educational Objective: Treat severe *Clostridium difficile* infection.

This patient has severe *Clostridium difficile* infection (CDI) and should receive oral vancomycin therapy. All patients with confirmed CDI require antimicrobial treatment, but optimal management depends on whether the episode represents the initial presentation or a recurrence, as well as the severity of the illness. The American College of Gastroenterology defines severe disease by the presence of hypoalbuminemia (<3 g/dL [30 g/L]) plus leukocytosis (leukocyte count ≥15,000/µL [15×10^9/L]) or abdominal tenderness. The Society for Healthcare Epidemiology of America and the Infectious Diseases Society of America guidelines define severe disease by a serum creatinine level >1.5 mg/dL (133 µmol/L) or leukocyte count ≥15,000/µL (15×10^9/L). Oral vancomycin for 10 days is recommended for the initial episode of a severe CDI infection. Oral fidaxomicin may also be used.

Fecal microbiota transplantation has been advocated as a treatment approach for patients with multiple relapses of CDI. The rationale is that exogenous feces will restore the normal colonic microbiota. Fecal microbiota transplantation is not recommended for an initial episode of CDI.

Intravenous vancomycin is not recommended for treatment of CDI because vancomycin delivered intravenously is not excreted into the large intestine and has no effect on CDI.

Oral metronidazole for 10 days can be used for patients who have an initial episode of nonsevere CDI when neither oral vancomycin nor fidaxomicin is available, but not in this patient with severe disease.

Oral vancomycin plus intravenous metronidazole is recommended for an initial episode of severe infection complicated (that is, fulminant disease) by ileus, hypotension, shock, or toxic megacolon. Fulminant CDI is often associated with ileus limiting colonic transit of orally dosed medications; therefore, a vancomycin enema through a rectal tube should be considered to maximize colonic luminal concentrations.

KEY POINT

- Oral vancomycin (or fidaxomicin) therapy is recommended for the treatment of an initial episode of severe *Clostridium difficile* infection.

Bibliography

McDonald LC, Gerding DN, Johnson S, Bakken JS, Carroll KC, Coffin SE, et al. Clinical practice guidelines for *Clostridium difficile* infection in adults and children: 2017 update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA). Clin Infect Dis. 2018;66:987-994. [PMID: 29562266] doi:10.1093/cid/ciy149

Item 67 Answer: C

Educational Objective: Diagnose serogroup B *Neisseria meningitides* in a patient who received the quadrivalent meningococcal vaccine.

Neisseria meningitides serogroup B is the most likely cause of this patient's meningitis. Bacterial meningitis classically presents with fever, nuchal rigidity, and altered mental status. However, all three symptoms may not be present in many patients with confirmed disease. Other clinical manifestations that suggest bacterial meningitis include photophobia and headache. Serogroup B *N. meningitides* accounts for 40% of all bacterial meningitis infections in the United States because the quadrivalent conjugate vaccine (ACYW 135) does not include group B. College students are at higher risk for developing meningococcal meningitis because of risk factors such as living in dormitories, sharing drinks, and kissing multiple partners. Clinical findings that support the diagnosis of meningococcal meningitis include severe myalgia, rapid progression, hemodynamic instability, and early appearance of a petechial or hemorrhagic rash in a previously well person. Finally, the finding of gram-negative diplococci on cerebrospinal fluid (CSF) examination strongly supports the diagnosis.

H CONT.

Prevalence of *Haemophilus influenzae* meningitis has decreased in the pediatric age group since the advent of the type B conjugate vaccine, and it is an uncommon cause of meningitis in adults. Adult patients with functional or anatomic asplenia are at greatest risk. Gram stain of the CSF would show small pleomorphic gram-negative coccobacilli, which is not consistent with this patient's findings.

Listeria monocytogenes is responsible for meningitis primarily in immunosuppressed patients with decreased cell mediated immunity, owing to medications or medical conditions, as well as in the very old or very young. *L. monocytogenes* appears as gram positive rods and coccobacilli, which are not consistent with this patient's findings. *Streptococcus pneumoniae* is the most common bacterial cause of meningitis in adults of all ages followed by *N. meningitidis*. Since the introduction of the pneumococcal conjugate vaccine in 2000, the rate of pneumococcal meningitis has decreased by about one third, and the greatest reduction is seen in children younger than 5 years. *S. pneumoniae* is a gram positive diplococcus and is an unlikely cause of this patient's meningitis.

KEY POINT

- The quadrivalent meningococcal vaccine does not include coverage for serogroup B *Neisseria meningitides*, which now accounts for 40% of all meningitis infections in the United States.

Bibliography

van de Beek D, Brouwer M, Hasbun R, Koedel U, Whitney CG, Wijdicks E. Community acquired bacterial meningitis. Nat Rev Dis Primers. 2016;2:16074. [PMID: 27808261] doi:10.1038/nrdp.2016.74

Item 68 Answer: C

Educational Objective: Treat proctitis in a patient at risk for sexually transmitted infection.

Ceftriaxone and doxycycline should be given empirically to patients with clinical evidence of proctitis who are at risk for sexually transmitted infections (STIs). The differential diagnosis of proctitis in this patient includes *Chlamydia trachomatis* (including the lymphogranuloma venereum serovars), *Neisseria gonorrhoeae*, syphilis, and herpes simplex virus (HSV) infection. In those who also have diarrhea (proctocolitis), *Campylobacter*, *Shigella*, and *Entamoeba histolytica* should be considered as well. In this patient with proctitis, diagnostic evaluation should include nucleic acid amplification testing (NAAT) of a rectal swab specimen for *N. gonorrhoeae*, *C. trachomatis*, and HSV-1 and HSV-2 (even if ulcers are not visible on external examination) as well as serologic testing for syphilis. If anoscopy is not available to further elucidate the most likely diagnosis, initial empiric therapy for *N. gonorrhoeae* and *C. trachomatis* should be prescribed pending diagnostic testing results. If the NAAT is positive for *C. trachomatis*, further testing for lymphogranuloma venereum should be performed, and consultation with an expert in STIs should be sought.

For initial empiric therapy of proctitis, azithromycin would not provide adequate coverage for the possibility of *N. gonorrhoeae* infection.

This patient could have inflammatory bowel disease; however, considering his high risk for STI and the acute nature of his symptoms, an STI is far more likely, and the use of a topical glucocorticoid preparation is not appropriate.

Although it may provide coverage for some of the enteric pathogens implicated in proctocolitis, ciprofloxacin cannot be used as part of empiric therapy for *N. gonorrhoeae* because of high rates of resistance.

KEY POINT

- Ceftriaxone and doxycycline should be given empirically to patients with clinical evidence of proctitis who are at risk for sexually transmitted infections.

Bibliography

Workowski KA, Bolan GA; Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2015. MMWR Recomm Rep. 2015;64:1-137. [PMID: 26042815]

Item 69 Answer: B

H

Educational Objective: Treat pneumonia after hematopoietic stem cell transplantation.

Ganciclovir for cytomegalovirus is the most appropriate empiric treatment in this patient at this time. The risk of cytomegalovirus reactivation is related to serologic status of the donor and recipient and is unlikely when donor and recipient are both negative. Cytomegalovirus disease after transplantation may manifest as a nonspecific febrile illness; may cause leukopenia and thrombocytopenia; or may cause organ specific disease, most often pneumonitis, colitis, esophagitis, or hepatitis. This patient is at significant risk for cytomegalovirus infection and has a clinical presentation consistent with cytomegalovirus pneumonia, specifically her presenting symptoms and radiographic findings of diffuse bilateral lung involvement. Although it has been more than 6 months from her hematopoietic stem cell transplantation (HSCT), her recent graft-versus-host disease increases infection risk. She is not receiving cytomegalovirus prophylaxis at this time; her acyclovir therapy is effective prophylaxis for herpes simplex virus and varicella-zoster virus but not for cytomegalovirus. Cytomegalovirus pneumonia after HSCT is associated with poor prognosis and significant mortality. Treatment with ganciclovir should be started while proceeding with the diagnostic evaluation, including nucleic acid amplification testing and bronchoscopy.

Atovaquone is an appropriate treatment for *Pneumocystis jirovecii* pneumonia. Although this patient is at risk for *P. jirovecii* and her presentation is consistent with it, she is taking trimethoprim-sulfamethoxazole, which is effective as prophylaxis, making this infection unlikely.

Liposomal amphotericin would provide broad-spectrum antifungal coverage in this patient who is at risk for fungal infection. However, her presentation and

H CONT.

radiographic findings are not consistent with invasive fungal infection, which is more likely to demonstrate nodules on CT. Moreover, the toxicity of amphotericin would preclude its use empirically in this setting.

KEY POINT

- Cytomegalovirus disease after transplantation may manifest as a nonspecific febrile illness; may cause leukopenia and thrombocytopenia; or may cause organ-specific disease, most often pneumonitis, colitis, esophagitis, or hepatitis; ganciclovir therapy should be initiated empirically in patients who present with signs and symptoms of cytomegalovirus infection.

Bibliography

Ariza-Heredia EJ, Nesher L, Chemaly RF. Cytomegalovirus diseases after hematopoietic stem cell transplantation: a mini-review. Cancer Lett. 2014;342:1-8. [PMID: 24041869] doi:10.1016/j.canlet.2013.09.004

H

Item 70 Answer: D

Educational Objective: Treat methicillin-resistant *Staphylococcus aureus* bacteremia.

The most appropriate management is to continue the vancomycin. Endocarditis and vertebral osteomyelitis are two important complications of *Staphylococcus aureus* bacteremia. Vancomycin is the preferred antimicrobial agent for treatment of bacteremia with methicillin-resistant *S. aureus* (MRSA). An alternative to vancomycin should be considered if the organism is not susceptible or if no clinical or microbiologic (such as persistent bacteremia) response occurs despite adequate source control. Daptomycin is an acceptable alternative if the isolate is susceptible. *S. aureus* with a vancomycin minimum inhibitory concentration (MIC) of 2 µg/mL or less is considered susceptible; intermediate susceptibility is defined as an MIC of 4 to 8 µg/mL. Vancomycin should not be used in the treatment of MRSA bacteremia when the vancomycin MIC is greater than 2 µg/mL because clinical failures have been reported. At MICs close to 2 µg/mL, clinical response (that is, clearance of bacteremia and resolution of fever and leukocytosis) should guide whether to continue vancomycin or change to daptomycin. Source control and appropriate antibiotic therapy are important for improving clinical outcomes. When using vancomycin to treat MRSA bacteremia, a trough level of 15 to 20 µg/mL should be targeted. At trough levels greater than 20 µg/mL, the risk for adverse effects increases without an increase in clinical benefit.

Adding rifampin or gentamicin to vancomycin has not been shown to improve outcomes of MRSA bacteremia and should be avoided. Combination therapy also increases the risk for adverse events (nephrotoxicity with gentamicin, hepatotoxicity and drug interactions with rifampin). Combination therapy is sometimes considered with prosthetic device infections, and an infectious diseases specialist should be consulted for guidance in such cases.

KEY POINT

- When treating methicillin-resistant *Staphylococcus aureus* bacteremia, vancomycin should be used only if the minimum inhibitory concentration is 2 µg/mL or less.

Bibliography

Choo EJ, Chambers HF. Treatment of methicillin-resistant Staphylococcus aureus bacteremia. Infect Chemother. 2016;48:267-273. [PMID: 28032484] doi:10.3947/ic.2016.48.4.267

Item 71 Answer: D

Educational Objective: Prevent infection in patients with terminal complement deficiency.

The most appropriate preventive measure for this patient is immunization with the quadrivalent meningococcal conjugate vaccine. A personal history of recurrent *Neisseria* infection or history of infection in multiple family members suggests a deficiency in one of the terminal complement components that make up the membrane attack complex (MAC). The MAC comprises C5 to C9, and a deficiency in any of these constituents leads to an impaired ability to combat *Neisseria* infections, particularly *N. meningitidis*. Patients are at risk for recurrent meningococcal infection, often caused by unusual serogroups. For unclear reasons, infection in this population is often uncharacteristically mild. Evaluation for terminal complement deficiency is performed by quantitation of total hemolytic complement (CH_{50}). If the CH_{50} is low, more specific testing for individual components of the MAC may be performed. Immunization is the mainstay of infection prevention in patients with defects in terminal complement. The Advisory Committee on Immunization Practices recommends use of a conjugate quadrivalent meningococcal vaccine as well as a vaccine active against serogroup B meningococcal infection, with a booster of the conjugate quadrivalent meningococcal vaccine given every 5 years for adults with terminal complement deficiency. These patients should also receive both pneumococcal (polysaccharide and conjugate) and *Haemophilus influenzae* type B vaccines.

Intravenous immune globulin does not have appreciable levels of complement and would not be useful for infection prevention in a patient with terminal complement deficiency.

Although plasma is rich in complement, plasma infusion is not a feasible long-term approach to repletion of complement levels. Additionally, such treatment would be associated with an increased risk of bloodborne diseases and the potential development of antibody against the missing component.

Prophylactic ciprofloxacin has a role in reducing the risk of meningococcal disease after close exposure to an infected person, but no data support using chronic prophylactic antibiotics in patients with terminal complement deficiencies. Instead, patients should be counseled to be vigilant

for development of fever, rash, headache, or other symptoms concerning for *Neisseria* infection.

KEY POINT

- Immunization with the quadrivalent meningococcal conjugate vaccine is the mainstay of infection prevention in patients with terminal complement deficiency.

Bibliography

Audemard-Verger A, Descloux E, Ponard D, Deroux A, Fantin B, Fieschi C, et al. Infections revealing complement deficiency in adults: a French nationwide study enrolling 41 patients. Medicine (Baltimore). 2016;95:e3548. [PMID: 27175654] doi:10.1097/MD.0000000000003548

H

Item 72 Answer: A

Educational Objective: Treat a patient with mild nonpurulent cellulitis.

The most appropriate treatment for this patient is clindamycin. Treatment of skin and soft tissue infections is guided by categorizing the infection as purulent or nonpurulent and by grading the severity of the infection as mild, moderate, or severe. This patient has a nonpurulent cellulitis without systemic signs of infection (mild infection). Nonpurulent infections are typically caused by streptococci, and outpatient treatment with an oral agent active against streptococci, including clindamycin, penicillin, cephalexin, or dicloxacillin, is recommended.

After incision and drainage, trimethoprim-sulfamethoxazole or doxycycline would be appropriate empiric therapy for moderate-severity (systemic signs of infection present) purulent skin infections (such as a furuncle or carbuncle) in which the usual cause is *Staphylococcus aureus* (including methicillin-resistant strains [MRSA]).

Because of the increased likelihood of MRSA contributing to infection, intravenous vancomycin would be appropriate to include for empiric treatment of severe purulent skin infections. Severe infections are those that do not improve with incision and drainage plus oral antibiotics or that have specific systemic signs of infection, including temperature greater than 38 °C (100.4 °F), heart rate greater than 90/min, respiration rate greater than 24/min, abnormal leukocyte count (>12,000/µL [12×10^9/L] or <4000/µL [4×10^9/L]), or infection in immunocompromised patients. Intravenous vancomycin is also appropriate for severe nonpurulent necrotizing skin infections (in addition to coverage of gram-negative bacilli and anaerobes). In select patients with cellulitis of moderate severity, vancomycin is recommended for coverage of streptococci and MRSA. These would include cellulitis in patients who are injection drug users, those with nasal MRSA colonization or extracutaneous MRSA infection, or those whose infection is associated with penetrating trauma.

KEY POINT

- Nonpurulent cellulitis without systemic signs of infection is usually caused by streptococci, which can be treated with an oral agent such as clindamycin, penicillin, cephalexin, or dicloxacillin.

Bibliography

Stevens DL, Bisno AL, Chambers HF, Dellinger EP, Goldstein EJ, Gorbach SL, et al; Infectious Diseases Society of America. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the Infectious Diseases Society of America. Clin Infect Dis. 2014;59:e10-52. [PMID: 24973422] doi:10.1093/cid/ciu444

Item 73 Answer: C

H

Educational Objective: Treat community-acquired pneumonia caused by *Pseudomonas aeruginosa*.

The most appropriate empiric treatment regimen for this patient is cefepime and ciprofloxacin. *Pseudomonas aeruginosa* is an uncommon cause of community-acquired pneumonia (CAP), reported in 1% to 8% of patients in various case series. However, it is important to recognize risk factors predisposing patients to this organism because standard treatment regimens for CAP require modification when *Pseudomonas* is suspected. Risk factors for *Pseudomonas* infection include structural lung disease (such as bronchiectasis, COPD, and cystic fibrosis) and frequent COPD exacerbations requiring repeated courses of antibiotics or glucocorticoids. This patient has bronchiectasis, glucocorticoid use, and the presence of gram-negative bacilli on sputum Gram stain as risk factors for *Pseudomonas* infection. Initial treatment with an appropriate antibiotic regimen has been shown to decrease mortality in patients with CAP caused by *Pseudomonas*. For this reason, the use of two agents with antipseudomonal activity is advocated for empiric therapy, with de-escalation when culture and sensitivity results become available. Even in patients with risk factors for *Pseudomonas* infection, it is important to continue treatment with a combination that is also active against *Streptococcus pneumoniae* and *Legionella* species until culture results are available. Recommended regimens include dual therapy with an antipseudomonal, antipneumococcal β-lactam (such as cefepime or piperacillin-tazobactam) or an antipseudomonal carbapenem (such as imipenem or meropenem) and an antipseudomonal quinolone (ciprofloxacin or levofloxacin). The combination of cefepime and ciprofloxacin meets these requirements.

Neither ceftriaxone nor ampicillin-sulbactam is active against *Pseudomonas* and should not be used when this organism is a concern. Although levofloxacin is effective against quinolone-susceptible *Pseudomonas*, administration of a single antipseudomonal agent is not recommended because of the high rates of antibiotic resistance.

The combination of aztreonam and ciprofloxacin provides double coverage against *Pseudomonas*; however, it is inactive against *S. pneumoniae* and therefore is inappropriate for initial empiric therapy.

KEY POINT

- In patients with community-acquired pneumonia and risk factors for *Pseudomonas aeruginosa* infection, the use of dual therapy with antipseudomonal, antipneumococcal β-lactam, or an antipseudomonal carbapenem, and antipseudomonal quinolone agents is recommended for initial empiric therapy.

Bibliography

Cillóniz C, Gabarrús A, Ferrer M, Puig de la Bellacasa J, Rinaudo M, Mensa J, et al. Community-acquired pneumonia due to multidrug- and non-multidrug-resistant Pseudomonas aeruginosa. Chest. 2016;150:415-25. [PMID: 27060725] doi:10.1016/j.chest.2016.03.042

Item 74 Answer: C

Educational Objective: Diagnose common variable immunodeficiency.

This patient has common variable immunodeficiency (CVID). The history of recurrent sinopulmonary and gastrointestinal infections in a young patient should trigger an investigation for an underlying immunodeficiency. CVID refers to a heterogeneous group of disorders that are linked by the presence of low levels of IgG and IgA and an impaired ability to produce antibody to antigenic stimuli. Clinically, patients with CVID are at increased risk for recurrent respiratory tract infections with encapsulated organisms such as *Streptococcus pneumoniae* and *Haemophilus influenzae* as well as *Mycoplasma pneumoniae*. These patients may also develop chronic diarrhea because of enteroviruses, norovirus, or *Giardia*. Based on this patient's history of previous infection with several of these pathogens, further evaluation with quantitative immunoglobulin levels is warranted. Diagnosis of CVID is important; patients with CVID benefit from replacement therapy with exogenous immune globulin. In addition to recurrent infection, patients with CVID are at increased risk for autoimmune diseases, bronchiectasis, enteropathy, and lymphoma.

Patients with advanced HIV infection or AIDS have low levels of CD4 cells and are at risk for opportunistic infections typically controlled through cellular immunity. Mucocutaneous candidiasis infection is one of the most common manifestations of HIV infection. *Cryptococcus* infection typically manifests as subacute or chronic meningitis. *Pneumocystis jirovecii* pneumonia is a common complication in patients with HIV infection who have not received prophylaxis. *Toxoplasma gondii* can cause encephalitis. Tuberculosis and *Mycobacterium avium* complex infection are the most common mycobacterial infections in patients with AIDS. Cytomegalovirus usually manifests as retinitis, esophagitis or colitis, and polyradiculitis or encephalitis. The nature of this patient's infections and history dating back to childhood make advanced AIDS an unlikely diagnosis.

Chronic granulomatous disease (CGD), which is usually diagnosed in childhood, is caused by a defect in neutrophil oxidation. A history of recurrent or unusually severe infections or infections with *Aspergillus* species, *Staphylococcus aureus*, *Burkholderia cepacia* complex, *Serratia marcescens*, or *Nocardia* species suggests the diagnosis. This patient's frequent episodes of sinusitis, bronchitis, otitis media, and giardiasis are not characteristic of CGD.

Myeloperoxidase is an intraleukocytic enzyme that plays a role in the destruction of fungal organisms. Complete deficiency of myeloperoxidase is rare, and most patients with this syndrome remain asymptomatic. This patient's recurrent episodes of infection since childhood are not compatible with myeloperoxidase deficiency.

KEY POINT

- Patients with common variable immunodeficiency are at increased risk of recurrent respiratory tract infections with encapsulated organisms (*Streptococcus pneumoniae*, *Haemophilus influenzae*), and they may develop chronic diarrhea because of enteroviruses, norovirus, or *Giardia*.

Bibliography

Abbott JK, Gelfand EW. Common variable immunodeficiency: diagnosis, management, and treatment. Immunol Allergy Clin North Am. 2015;35:637-58. [PMID: 26454311] doi:10.1016/j.iac.2015.07.009

Item 75 Answer: C

Educational Objective: Diagnose *Mycobacterium marinum* skin infection.

The most likely cause of this patient's infection is *Mycobacterium marinum*. *M. marinum* is found worldwide in freshwater and saltwater aquatic environments, including swimming pools. Skin infections have typically been reported after skin trauma and contact with fish tanks ("fish tank granuloma"), fish, or shellfish. Hobbies and occupations predisposing to infection include aquatic sports enthusiasts, fishermen, seafood workers, and owners of fish tanks. The incubation period is usually less than 1 month, and the clinical course is often insidious. Infection usually manifests initially as a violaceous or erythematous papule or nodule that may ulcerate at the site of inoculation. Lesions may be solitary or multiple; occasionally, a sporotrichoid distribution along the lymphatic vessels may develop. The upper extremities, including the hands, fingers, or elbows, are commonly involved. Diagnosis is often delayed and is established by isolation of the organism from culture of a biopsy, aspirate, or drainage specimen. Granulomas may be present and provide evidence of potential mycobacterial infection.

This patient's course of infection is indolent and inconsistent with the more acute presentations of *Streptococcus pyogenes* and *Clostridium perfringens* skin and soft tissue infections. Additionally, Gram stain of the intraoperative specimen would have revealed bacterial organisms, and infections secondary to these organisms would have responded to the antibiotics already administered.

Herpes simplex virus type 1 can cause a painful infection of the finger (herpetic whitlow), manifesting as grouped vesicles on an erythematous base. Infection occurs when the virus is inoculated through breaks in the skin. Even without treatment, these infections usually resolve within several weeks and would not be expected to persist for months in an immunocompetent patient.

KEY POINT

- *Mycobacterium marinum* is found worldwide in freshwater and saltwater aquatic environments, typically causing indolent skin or soft tissue infection and usually appearing as papules on extremities after contact and trauma from fish tanks, fish, or shellfish.

Bibliography

Aubry A, Chosidow O, Caumes E, Robert J, Cambau E. Sixty-three cases of Mycobacterium marinum infection: clinical features, treatment, and antibiotic susceptibility of causative isolates. Arch Intern Med. 2002;162:1746-52. [PMID: 12153378]

Item 76 Answer: C

Educational Objective: Discontinue *Pneumocystis* pneumonia prophylaxis in HIV infection.

This patient should discontinue taking trimethoprim-sulfamethoxazole regardless of whether it caused the reported rash the previous week, but she should continue her current antiretroviral regimen. The patient initially presented 6 months ago with *Pneumocystis jirovecii* pneumonia and was diagnosed with HIV and AIDS. Following successful treatment of the pneumonia and initiation of antiretroviral therapy, appropriate secondary prophylaxis was initiated with daily trimethoprim-sulfamethoxazole. She demonstrated an excellent response to antiretrovirals with achievement of undetectable viral load and rising CD4 cell count. Her CD4 cell count has now been higher than 200/µL for more than 3 months, meeting criteria for safe discontinuation of prophylaxis for *Pneumocystis*. Studies have shown that *Pneumocystis* prophylaxis, whether primary or secondary, can be safely discontinued in patients with this level of immune reconstitution.

Atovaquone would be an acceptable alternative to trimethoprim-sulfamethoxazole for prophylaxis of *Pneumocystis*, but this patient no longer requires *Pneumocystis* prophylaxis with any agent.

Primaquine and clindamycin is an appropriate alternative regimen to trimethoprim-sulfamethoxazole for treatment of *Pneumocystis* pneumonia but not for prophylaxis. However, this patient has no evidence of active pneumonia, so treatment is not indicated.

The patient has continued taking her previously prescribed antiretroviral regimen, and the rash resolved, so the rash was unlikely caused by these agents. With the excellent response to this regimen and no apparent adverse effects, the current regimen should be continued rather than switching regimens.

KEY POINT

- Patients with HIV who are taking antiretroviral therapy and achieve CD4 cell counts greater than 200/µL for more than 3 months may safely discontinue prophylaxis for *Pneumocystis jirovecii* infection.

Bibliography

Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents. Guidelines for the prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. Available at https://aidsinfo.nih.gov/guidelines/html/4/adult-and-adolescent-opportunistic-infection/0. Accessed April 12, 2018.

Item 77 Answer: A

Educational Objective: Treat ventilator-associated pneumonia for 7 days.

H

The recommended treatment duration for ventilator-associated pneumonia (VAP) is 7 days. VAP is defined as pneumonia developing 48 hours after endotracheal intubation. The most significant VAP risk factor is intubation and mechanical ventilation. Early onset (<5 days after hospitalization or intubation) generally results from antimicrobial-sensitive organisms (*Streptococcus pneumoniae*, *Haemophilus influenzae*, *Staphylococcus aureus*, and antibiotic-susceptible gram-negative bacteria); late onset (≥5 days after hospitalization or intubation) is more likely with multidrug-resistant organisms (MDROs), including *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Acinetobacter* species, *Stenotrophomonas maltophilia*, *Burkholderia cepacia*, and methicillin-resistant *S. aureus*. The recommended therapy duration for VAP is 7 days. A longer antibiotic duration does not improve outcomes, leads to the emergence of antibiotic-resistant organisms, and can increase the risk for adverse effects from antibiotic exposure.

Sputum Gram stain and culture are unnecessary for influencing the timing to stop antibiotics; the implicated organism may remain (colonizing) after treatment has been completed and the patient has improved clinically. Persistence of the infecting organism is not an indication to continue antibiotic therapy.

Antibiotics should not be continued until extubation. The antibiotic therapy duration is the same for patients who are successfully extubated during treatment and patients who remain intubated after 7 days of antibiotic therapy as long as clinical improvement occurs. If the patient does not improve clinically (resolution of fever, decrease in oxygenation and suction requirements) or initially improves and then worsens during treatment, the patient should be evaluated to identify development of infectious complications (pleural effusion, empyema, superinfection, antibiotic resistance) or noninfectious complications.

KEY POINT

- Ventilator-associated pneumonia should be treated with a 7-day course of antibiotics; longer courses contribute to the emergence of antibiotic resistance, increase the risk for antibiotic-related adverse effects, and do not improve outcomes.

Bibliography

Kalil AC, Metersky ML, Klompas M, Muscedere J, Sweeney DA, Palmer LB, et al. Management of adults with hospital-acquired and ventilator-associated

Answers and Critiques

pneumonia: 2016 clinical practice guidelines by the Infectious Diseases Society of America and the American Thoracic Society. Clin Infect Dis. 2016;63:e61-e111. [PMID: 27418577] doi:10.1093/cid/ciw353

H

Item 78 Answer: A

Educational Objective: Diagnose anti-*N*-methyl-D-aspartate receptor encephalitis.

The most likely diagnosis is anti-*N*-methyl-D-aspartate receptor (anti-NMDAR) encephalitis. Anti-NMDAR encephalitis has emerged as an increasingly common cause of encephalitis. Anti-NMDAR encephalitis is associated with ovarian teratomas in more than 50% of patients with the disease because of antibody production to a tumor protein that cross-reacts with neuronal tissue. In patients without evidence of teratoma, an inciting antigenic stimulus is rarely identified. The diagnosis is suggested by the presence of choreoathetosis, psychiatric symptoms, seizures, and autonomic instability; detection of anti-NMDAR antibody in serum confirms it. Anti-NMDAR encephalitis should be suspected in young women presenting with encephalitis associated with changes in mood and behavior when initial evaluation for other causes, including herpes simplex virus infection, is negative. Anti-NMDAR encephalitis treatment can include tumor removal (if present), intravenous glucocorticoids, intravenous immune globulin, plasmapheresis, and rituximab.

The most common central nervous system manifestation of Lyme disease is lymphocytic meningitis that may be indistinguishable from viral meningitis with fever, headache, and meningismus. An inflammatory encephalomyelitis may very rarely be observed. Lyme meningitis usually occurs in the summer and fall; it is often associated with peripheral facial palsy and is not associated with altered mental status, psychiatric symptoms, choreoathetosis, or seizure as seen in this patient.

Tuberculous meningitis is a subacute febrile illness with a predilection for inflammatory changes at the base of the brain. After a 2- to 3-week prodromal period, patients often manifest meningismus and varying degrees of cranial nerve and long-tract signs. Tuberculosis is unlikely in this patient because of the lack of chronicity, normal glucose level in cerebrospinal fluid, absence of cranial nerve and long-track signs, and lack of evidence of basilar meningitis on MRI.

West Nile neuroinvasive disease may present with meningitis, encephalitis, or myelitis, either singly or as overlap syndromes in the endemic months between June and October. Limb weakness, which may be symmetric or involve a single extremity, is characteristic. A nonspecific viral exanthema may be found in less than 50% of patients. MRI may show focal lesions of the thalami, basal ganglia, and spinal cord in some patients.

KEY POINT

- When other causes of encephalitis have been ruled out in a patient presenting with associated changes in mood and behavior, anti-*N*-methyl-D-aspartate receptor encephalitis should be suspected.

Bibliography

Dalmau J, Graus F. Antibody-mediated encephalitis. N Engl J Med. 2018;378:840-851. [PMID: 29490181] doi:10.1056/NEJMra1708712

Item 79 Answer: D

H

Educational Objective: Diagnose active tuberculosis infection.

The most appropriate management for this patient is to obtain a sputum specimen and perform acid-fast bacilli (AFB) staining and culture. The patient appears to have active pulmonary tuberculosis, based on an indolent course of cough, fever, fatigue, and weight loss and a posteroanterior chest radiograph showing bilateral upper lobe cavitary infiltrates and a left pleural effusion. Although it is essential to initiate antimicrobial therapy promptly, it is important to verify the microbiologic diagnosis of *Mycobacterium tuberculosis* infection first by submitting three sputum specimens for AFB staining and culture. If the AFB stain is positive, nucleic acid amplification testing (NAAT) can be used to differentiate *M. tuberculosis* from other types of mycobacteria, allowing for early initiation of treatment. It is also important to perform susceptibility testing because the frequency of antimicrobial resistance (for isoniazid and rifampin) is increasing.

The tuberculin skin test (TST) and interferon-γ release assay (IGRA) are the initial diagnostic studies used to evaluate for tuberculosis infection. However, neither test can distinguish between latent and active tuberculosis. Latent tuberculosis infection is diagnosed when an asymptomatic patient has a positive TST or IGRA result without clinical evidence of active tuberculosis infection by history, physical examination, or chest imaging. Because this patient has active tuberculosis, treatment for latent tuberculosis with isoniazid plus pyridoxine would not be appropriate. This regimen should only be used in patients with latent tuberculosis.

For active tuberculosis infection, the Centers for Disease Control and Prevention recommends initiating four-drug therapy with isoniazid, rifampin, pyrazinamide, and ethambutol for 8 weeks. In susceptible isolates, isoniazid and rifampin should then be continued for 18 weeks. This treatment regimen is appropriate only after *M. tuberculosis* infection has been confirmed with positive stain and NAAT.

Piperacillin-tazobactam would be an appropriate antibiotic choice if pneumococcus, *Klebsiella pneumoniae*, or *Pseudomonas aeruginosa* were the likely pathogens. However, the presentation of an indolent infection, a positive IGRA, and evidence of fibrocavitary disease in the upper lobes is highly suspicious for pulmonary tuberculosis, not acute bacterial pneumonia.

KEY POINT

- The microbiologic diagnosis of tuberculosis should be verified by acid-fast bacilli staining of sputum samples and nucleic acid amplification testing before initiating antituberculous therapy.

Bibliography

Lewinsohn DM, Leonard MK, LoBue PA, Cohn DL, Daley CL, Desmond E, et al. Official American Thoracic Society/Infectious Diseases Society of America/Centers for Disease Control and Prevention clinical practice guidelines: diagnosis of tuberculosis in adults and children. Clin Infect Dis. 2017;64:111-115. [PMID: 28052967] doi:10.1093/cid/ciw778

Item 80 Answer: D

Educational Objective: Diagnose nontyphoidal *Salmonella* infection.

The most likely diagnosis is nontyphoidal *Salmonella* infection. This patient's fever and nonbloody diarrhea are most likely caused by nontyphoidal *Salmonella*, with infection resulting from contact with a colonized snake. Nontyphoidal *Salmonella* infection usually results from ingesting fecally contaminated water or food of animal origin, including poultry, beef, eggs, and milk. Intestinally colonized reptiles and amphibians are asymptomatic and intermittently shed the organism in their feces, creating the potential for fecal-oral route transmission. Handling infected snakes, turtles, iguanas, frogs, or toads or anything in the enclosures in which they live can result in infection. Surfaces contaminated by feces may also serve as a source of infection. The incubation period is usually less than 3 days, and symptoms typically include crampy abdominal pain, diarrhea (not usually visibly bloody), fever, headache, nausea, and vomiting.

Infection with *Chlamydia psittaci* is typically acquired by inhaling the organism in feces from a pet bird. The incubation period is about 1 week and the clinical presentation usually consists of chills, dry cough, fever, headache, and myalgia. Diarrhea may be present but is much less common. Chest radiograph abnormalities are common.

Erysipelothrix rhusiopathiae is a bacterium that infects animals such as fish, swine, and poultry. Human infection is usually occupationally acquired in butchers, fish handlers, and veterinarians. Localized cutaneous violaceous lesions of the fingers and hands are a classic finding, although more diffuse cutaneous infections, bacteremia, and even infective endocarditis can develop.

Mycobacterium marinum is a nontuberculous mycobacterium found worldwide in freshwater and saltwater aquatic environments. Skin infections result from skin trauma and contact with fish tanks ("fish tank granuloma"), fish, or shellfish. Persons predisposed to infection include aquatic sports enthusiasts, fish tank owners, fishermen, and seafood workers. The clinical course is often insidious, manifesting initially as a violaceous or erythematous papule or nodule at the site of inoculation, which may ulcerate. Lesions may be solitary or multiple; occasionally a sporotrichoid distribution along lymphatic vessels may develop. *M. marinum* does not cause diarrhea.

KEY POINT

- Nontyphoidal *Salmonella* is commonly carried asymptomatically by reptiles and amphibians and transferred from the animals' feces to people; human symptoms include crampy abdominal pain, fever, nonbloody diarrhea, and vomiting.

Bibliography

Mermin J, Hutwagner L, Vugia D, Shallow S, Daily P, Bender J, et al; Emerging Infections Program FoodNet Working Group. Reptiles, amphibians, and human Salmonella infection: a population based, case-control study. Clin Infect Dis. 2004;38 Suppl 3:S253-61. [PMID: 15095197]

Item 81 Answer: A

H

Educational Objective: Evaluate persistent *Staphylococcus aureus* bacteremia.

An abdominal CT is the most appropriate next step in the evaluation and management of this patient. Bacteremia persisting more than 72 hours after the start of appropriate antimicrobial therapy suggests a complicated infection, requiring additional evaluation with a longer treatment course. Endocarditis and vertebral osteomyelitis are two important complications of *Staphylococcus aureus* bacteremia. Patients with abdominal pain or flank pain should undergo abdominal CT to evaluate for the presence of metastatic infection of the liver, spleen, or kidney; psoas abscess; or other intra-abdominal source. This patient has aortic valve endocarditis, persistent *S. aureus* bacteremia and fever, new right upper quadrant pain, and abnormal liver chemistry tests, which are concerning for development of liver abscess. Metastatic infections are not uncommon with *S. aureus* bacteremia and require a careful history and physical examination to identify where to look and what tests to perform next. New right upper quadrant pain with liver chemistry test abnormalities should prompt investigation with imaging studies such as CT, which can also evaluate the spleen, kidney, and pararenal structures that may be seeded during bacteremia. Transesophageal echocardiography (TEE) will also need to be performed because of this patient's fever and persistent bacteremia. Development of a perivalvular abscess is a possibility, especially if conduction abnormalities are present on the electrocardiogram. Compared with transthoracic echocardiography, perivalvular abscesses are better visualized with TEE.

Several neurologic complications can arise from *S. aureus* endocarditis, including brain abscess, stroke, and meningitis. Neurologic symptoms can be the presenting signs in *S. aureus* endocarditis (for example, a patient presenting with stroke who has a heart murmur and unexplained fever should be evaluated for endocarditis). New neurologic symptoms that develop during the course of treatment for endocarditis should always be evaluated (such as with head CT). This patient has no neurologic symptoms, so a head CT is not indicated.

Daptomycin is rarely used to treat methicillin-sensitive *S. aureus* (MSSA) infections except in patients with multiple antibiotic allergies that preclude the use of β-lactams or glycopeptides. Persistent bacteremia is likely a failure of source control and requires careful investigation for possible sources of metastatic infection and drainage if amenable.

Cefazolin is more rapidly bactericidal than vancomycin and is preferred over vancomycin for treatment of MSSA. Therefore, switching would be inappropriate.

KEY POINT

- *Staphylococcus aureus* bacteremia persisting more than 72 hours after the start of appropriate antimicrobial therapy suggests a complicated infection requiring additional evaluation; endocarditis, osteomyelitis, and intra-abdominal infections are important sites of metastatic infection.

Bibliography

Tong SY, Davis JS, Eichenberger E, Holland TL, Fowler VG Jr. Staphylococcus aureus infections: epidemiology, pathophysiology, clinical manifestations, and management. Clin Microbiol Rev. 2015;28:603-61. [PMID: 26016486] doi:10.1128/CMR.00134-14

H Item 82 Answer: A

Educational Objective: **Treat necrotizing skin infection caused by *Aeromonas hydrophila*.**

The most appropriate treatment for this patient is ciprofloxacin plus doxycycline. This patient has *Aeromonas hydrophila*-associated skin and soft tissue infection. *Aeromonas* species are found in aquatic environments, including fresh water and brackish water, and grow best during warmer months. Lacerations and puncture wounds sustained in these environments can result in wound infection. *Aeromonas* infections of the skin and soft tissue and of the bloodstream are more likely to occur in patients with underlying immunocompromising conditions, such as cirrhosis and cancer, and are more common in men. Necrotizing fasciitis caused by this gram-negative bacillus requires surgery, supportive care, and antibiotics. Pending culture data, empiric therapy for necrotizing skin infections typically consists of broad-spectrum antibiotics such as vancomycin plus piperacillin-tazobactam. When the diagnosis of *A. hydrophila* infection is established, doxycycline plus ciprofloxacin or ceftriaxone is recommended.

The combination of linezolid and metronidazole, although effective against aerobic gram-positive organisms, such as staphylococci and enterococci as well as many anaerobes, is not active against *Aeromonas*.

Nafcillin and rifampin would be active against methicillin-susceptible *S. aureus*, particularly prosthetic joint infections, but is not active against *A. hydrophila*.

Vancomycin plus clindamycin would be effective in necrotizing fasciitis with associated toxic shock caused by methicillin-resistant *S. aureus* but would not be active against *A. hydrophila*.

KEY POINT

- Lacerations and puncture wounds sustained in fresh and brackish water environments can result in necrotizing infection with *Aeromonas hydrophila*; this infection should be treated with surgery, supportive care, and antibiotics with gram-negative coverage, such as doxycycline plus ciprofloxacin.

Bibliography

Stevens DL, Bisno AL, Chambers HF, Dellinger EP, Goldstein EJ, Gorbach SL, et al. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the infectious diseases society of America. Clin Infect Dis. 2014;59:147-59. [PMID: 24947530] doi:10.1093/cid/ciu296

Item 83 Answer: D

Educational Objective: **Manage a tick bite.**

The most appropriate initial management for this patient is reassurance that the risk of Lyme disease is low. In selected patients at high risk, doxycycline prophylaxis has been shown to decrease the risk of Lyme disease if given within 72 hours of tick removal, assuming that the tick has been attached for greater than 36 hours. Knowledge of the epidemiology of Lyme disease in the area of practice is important for making informed decisions about prophylaxis. Even in endemic regions, such as the northeastern and upper midwestern United States, few vector ticks are infected with *Borrelia burgdorferi*. Most patients in highly endemic areas do not develop symptomatic infection after a tick bite because bacterial transmission rarely occurs unless the vector tick has fed for at least 36 hours. In the subset of patients from highly endemic areas seen within 72 hours of tick removal in whom attachment with an *Ixodes* species tick for greater than 36 hours can be substantiated, a single dose of doxycycline (200 mg) has been shown to decrease the risk of developing infection. This patient was exposed to the tick that transmits Lyme disease. However, given the short duration of attachment, her risk for infection is negligible. Furthermore, she is beyond the 72-hour window during which prophylaxis has been shown to be beneficial. The most appropriate management is reassurance, with the caveat that she return for evaluation if she develops a rash, fever, or other suggestive symptoms within a month of the exposure.

Diagnostic testing with polymerase chain reaction to confirm tick infection is not routinely available and not informative because of the low risk of transmission, even if *B. burgdorferi* is identified in the vector.

Checking *B. burgdorferi* titers similarly has low yield because antibodies may not be present during the early stages of infection, and paired serologic testing with a subsequent convalescent specimen in the absence of symptoms is not cost effective.

KEY POINT

- In patients at high risk, doxycycline prophylaxis has been shown to decrease the risk of Lyme disease if started within 72 hours of tick removal, assuming that the tick has been attached for at least 36 hours.

Bibliography

Ogden NH, Lindsay LR, Schofield SW. Methods to prevent tick bites and Lyme disease. Clin Lab Med. 2015;35:883-99. [PMID: 26593263] doi:10.1016/j.cll.2015.07.003

Item 84 Answer: D

Educational Objective: Evaluate a patient with potential smallpox exposure.

This man has potentially been exposed to variola and requires active vaccinia immunization to prevent the development of smallpox. Ideally, vaccinia vaccination should be administered no more than 7 days (but preferably within 3) after the presumed exposure. In 1980, the World Health Organization declared that smallpox had been eradicated worldwide. However, because of its ease of deliberate airborne spread, highly contagious nature, and expected significant morbidity and mortality, smallpox has been identified as a member of the A list of potential agents of bioterrorism. Because routine childhood vaccinia immunization is no longer required or recommended in the United States, most of the population is not immune. Smallpox vaccines are available in the event of exposure. Although none of these vaccines contains the actual variola virus, when properly administered the vaccines elicit a significant protective immune response. Although serious adverse events are a greater risk after administration of any live virus vaccine, including those containing vaccinia, persons at high risk for complications from replication-component vaccines are also at higher risk for severe smallpox. Unless the patient is severely immunodeficient (within 4 months of bone marrow transplantation, HIV infection with CD4 cell counts <50/µL, or severe combined immunodeficiency), the vaccine should be given. This patient's use of infliximab would not exclude him from vaccination.

The core protein cysteine protease inhibitor tecovirimat, which has proven activity against members of the orthopox genus, has been approved for the treatment of smallpox in the event of a potential outbreak.

Airborne precautions after potential exposure would only be indicated if fever or other signs of active infection occurred.

Vaccinia immune globulin, available from the Centers for Disease Control and Prevention, consists of pooled human antibodies and is indicated for the treatment of severe vaccinia virus vaccine complications or when vaccination is contraindicated.

KEY POINT

- Vaccinia immunization is appropriate in the event of possible exposure to smallpox (variola).

Bibliography

Petersen BW, Damon IK, Pertowski CA, Meaney-Delman D, Guarnizo JT, Beigi RH, et al. Clinical guidance for smallpox vaccine use in a postevent vaccination program. MMWR Recomm Rep. 2015;64:1-26. [PMID: 25695372]

Item 85 Answer: B

Educational Objective: Evaluate a young patient with herpes zoster for HIV infection.

The most appropriate test to perform next is a fourth generation HIV-1/2 antigen/antibody combination immunoassay. This test combines an immunoassay for HIV antibody with a test for HIV p24 antigen. This improves the ability of the test to detect early HIV infection because p24 antigen becomes detectable a week before antibody in acute infection. Detection of antigen may help diagnose patients as early as 2 weeks after infection. This patient's painful vesicular rash distributed over a thoracic dermatome is classic for infection with varicella-zoster virus. Older adults and immunocompromised patients, including patients with HIV infection, are at increased risk. Severe or recurrent varicella-zoster virus infections or infection at a young age should prompt an evaluation for HIV infection.

Patients with terminal complement component deficiencies usually present with recurrent, invasive infections with encapsulated bacteria such as *Neisseria meningitides*, *Haemophilus influenzae*, and *Streptococcus pneumoniae*. These patients should be screened for complement deficiency by assaying for CH_{50} activity. If CH_{50} activity is normal, alternate pathway function should be assessed with an alternative complement pathway (AH_{50}) assay. If results of either assay are abnormal, specific component concentrations should be determined.

Selective IgA deficiency is one of the most common B-cell immunodeficiencies. Inheritance may be autosomal dominant or recessive; most cases are sporadic. Patients with selective IgA deficiency may be asymptomatic or present with recurrent sinopulmonary infections (otitis media, sinusitis, pneumonia) or gastrointestinal infections (giardiasis). Other common manifestations include inflammatory bowel disease; celiac disease; an increased frequency of autoimmune disorders, including rheumatoid arthritis, systemic lupus erythematosus, and chronic active hepatitis; and allergic disorders, including asthma, allergic rhinitis, and food allergies.

Common variable immunodeficiency involves B- and T-cell abnormalities and results in clinically significant immune dysregulation. The primary manifestation is hypogammaglobulinemia, and recurrent respiratory infections are a common presentation in adults. The gastrointestinal tract is frequently involved and causes malabsorption or chronic diarrhea. Infection with *Giardia*, *Campylobacter*, or *Yersinia* species may occur, as may opportunistic infections. Concurrent autoimmune disorders occur in up to 25% of patients. The risk for malignancy is increased, including gastrointestinal cancers and non-Hodgkin lymphoma. Patients also have a poor or an absent response to protein and polysaccharide vaccines. Serum immunoglobulin levels are usually low, circulating B cells may be normal or low, and T-cell function varies. The diagnosis is made by confirming low levels of total IgG and IgA or IgM, as well as by a poor antibody response to vaccines.

KEY POINT

- Infection with varicella-zoster virus in a young patient should prompt testing for HIV infection.

Bibliography

Cohen JI. Clinical practice: Herpes zoster. N Engl J Med. 2013;369:255-63. [PMID: 23863052] doi:10.1056/NEJMcp1302674

Item 86 Answer: B

Educational Objective: Diagnose sporadic Creutzfeldt-Jakob disease.

This patient most likely has sporadic Creutzfeldt-Jakob disease (sCJD). This is the most common form of prion disease and has no evidence of environmental risk factors. Involvement of several neurologic systems and a rapid onset of apparent dementia are classic manifestations of prion disease. On physical examination, ataxia, myoclonus, and a rapidly progressive dementia are present. MRI abnormalities are not specific for sCJD and vary with the clinical syndrome. Patients with increased T2 signal in the caudate and putamen are more likely to have early dementia and shorter survival. No simple, noninvasive assay is available to diagnose sCJD; however, the presence of T-tau or 14-3-3 protein in cerebrospinal fluid (CSF) can be suggestive. The definitive diagnostic test is a brain biopsy demonstrating widespread spongiform changes with gliosis. No definitive treatment exists for any prion disease, and most are rapidly fatal.

Cryptococcal meningitis may present initially with altered mentation. Cryptococcal meningitis can be seen in apparently immunocompetent persons; however, it is likely that most patients who develop this infection have some underlying immune deficiency. Lumbar puncture may show a high opening pressure, and the CSF typically shows a lymphocytic pleocytosis. The patient's findings are not compatible with this diagnosis.

Tuberculous meningitis may present with waxing and waning mental status changes. However, the CSF in tuberculous meningitis frequently shows high protein (>500 mg/dL [5000 mg/L]) and low glucose (<40 mg/dL [2.22 mmol/L]) levels. Additionally, MRI may reveal basilar pachymeningitis and occasional tuberculomas, which are not seen in this patient.

Vascular neurocognitive disorder (VND) is the term now used to describe cognitive impairment of any degree resulting from cerebrovascular disease. The diagnosis is made when neuroimaging or clinical history reveals evidence of a stroke or subclinical cerebrovascular disease that is responsible for impairment of at least one cognitive domain. The absence of infarcts on MRI and rapid progression of this patient's symptoms are not compatible with VND.

KEY POINT

- Sporadic Creutzfeldt-Jakob disease is the most common form of prion disease, involving several neurologic systems and rapid progression of apparent dementia.

Bibliography

Kim MO, Geschwind MD. Clinical update of Jakob-Creutzfeldt disease. Curr Opin Neurol. 2015;28:302-10. [PMID: 25923128] doi:10.1097/WCO.0000000000000197

Item 87 Answer: C

Educational Objective: Choose the appropriate treatment duration for uncomplicated community-acquired pneumonia.

The most appropriate management for this patient at discharge is to discontinue her antibiotics. She had pneumococcal pneumonia requiring hospitalization for treatment and stabilization. Her clinical status rapidly improved with appropriate empiric therapy. The Infectious Diseases Society of America/American Thoracic Society guidelines recommend an antibiotic treatment duration for uncomplicated community-acquired pneumonia of 5 to 7 days. A recent randomized trial found no difference in clinical response between patients treated for 5 days compared with control patients who received a median of 10 days of antibiotic therapy. This study was limited to immunocompetent patients who did not require admission to the ICU and who defervesced at least 48 hours before antibiotic discontinuation; short-course therapy has not been validated in patients with complicated infection, including those at risk for *Staphylococcus aureus* or *Pseudomonas* infection. Short-course therapy offers the advantages of minimizing the risk of adverse effects, lowering cost, and potentially decreasing length of hospital stay. Because this patient completed more than 5 days of therapy during hospitalization, no further antibiotics are indicated at discharge.

Under the same circumstances, azithromycin would be contraindicated because the isolate was resistant to erythromycin, indicating a class effect of macrolide resistance.

Continuing ceftriaxone would necessitate either continued inpatient intravenous treatment or placement of an indwelling intravenous line for outpatient therapy, both unnecessary interventions.

The management of patients who have clinically responded before completing 5 days of inpatient therapy can be challenging, especially if cultures are negative. Antibiotic de-escalation from parenteral to oral formulations is appropriate when patients have clinically improved. If this patient had been ready for discharge before completing 5 days of therapy, transition to oral amoxicillin would have been appropriate for completing the antibiotic course.

Although levofloxacin is active against this patient's infection, it is overly broad therapy for a penicillin-sensitive strain of *Streptococcus pneumoniae*.

KEY POINT

- In patients with uncomplicated community-acquired pneumonia not requiring ICU admission, a short course of antibiotic therapy (5-7 days) is sufficient.

Bibliography

Uranga A, España PP, Bilbao A, Quintana JM, Arriaga I, Intxausti M, et al. Duration of antibiotic treatment in community-acquired pneumonia: a multicenter randomized clinical trial. JAMA Intern Med. 2016;176:1257-65. [PMID: 27455166] doi:10.1001/jamainternmed.2016.3633

H **Item 88 Answer: C**

Educational Objective: Diagnose osteomyelitis using radiography.

Plain radiography is the appropriate initial diagnostic test for a patient with suspected osteomyelitis. This patient presents with pain and swelling in his finger after a traumatic injury that has healed. The clinical examination is not consistent with a skin and soft tissue infection (lack of erythema); however, inflammatory markers are elevated, so osteomyelitis due to a contiguous spread of organisms introduced by the injury should be considered. Cortical bone loss must be greater than 50% for a plain radiograph to show findings diagnostic of osteomyelitis, so plain radiography is not sufficiently sensitive to exclude this diagnosis. However, plain radiography is much less expensive than the other available imaging modalities and can be quite specific for bone infection if findings are positive, so this test should be done first. The utility of plain radiography in this patient may be higher because a film was taken at the time of the injury, and subtle changes may be apparent when compared.

If the plain radiograph is not diagnostic, a gadolinium-enhanced MRI would be the next imaging test to pursue. A contrast-enhanced CT can be performed if MRI is contraindicated (for example, because of the presence of hardware). A three-phase bone scan could be ordered with a labeled leukocyte scan, but it should only be done if an MRI or a CT with contrast cannot be obtained. Ultrasonography has limited utility in the diagnosis of osteomyelitis.

With the exception of ultrasonography, all these imaging modalities are expensive and, depending on the technique, unnecessarily expose the patient to contrast agents and excessive radiation; the clinician should always consult with the radiologist if the best imaging modality to confirm the suspected diagnosis is in question.

KEY POINT

- Plain radiography is the most cost-effective diagnostic test that can confirm a suspected case of osteomyelitis, but it is not sufficiently sensitive to exclude the diagnosis.

Bibliography

Beaman FD, von Herrmann PF, Kransdorf MJ, Adler RS, Amini B, Appel M, et al; Expert Panel on Musculoskeletal Imaging. ACR Appropriateness Criteria® suspected osteomyelitis, septic arthritis, or soft tissue infection (excluding spine and diabetic foot). J Am Coll Radiol. 2017;14:S326-S337. [PMID: 28473089] doi:10.1016/j.jacr.2017.02.008

H **Item 89 Answer: D**

Educational Objective: Treat aspiration pneumonia.

In addition to starting azithromycin for empiric coverage of atypical organisms, piperacillin-tazobactam is the most appropriate antibiotic treatment for this patient. He requires ICU admission for severe, progressive community-acquired pneumonia (CAP) after outpatient therapy with levofloxacin has failed to improve his infection. Levofloxacin was an appropriate empiric treatment choice for CAP in this patient, considering his history of heavy alcohol use, which increases the risk of infection with Enterobacteriaceae, including *Klebsiella* species. Antibiotic treatment failure can result from poor adherence, a noninfectious cause of symptoms (such as pulmonary embolism), a nonbacterial infection (such as histoplasmosis), lack of source control (as with empyema), or infection with a resistant organism. The patient's history of heavy alcohol use suggests the possibility of aspiration pneumonia, whereby normal oropharyngeal organisms gain access to the lower airways and cause infection. Other risk factors for aspiration pneumonia include poor dentition, gastroesophageal reflux, dysphagia, vomiting, and reduced consciousness, as can be seen in patients with alcoholism, illicit drug use, or seizures. The localization to the right lower lobe is also consistent with aspiration because this area is dependent when patients are lying supine. In community-dwelling patients with aspiration pneumonia, the most common organisms are anaerobic bacteria, such as microaerophilic streptococci, *Fusobacterium*, *Peptostreptococcus*, and *Prevotella* species; however, Enterobacteriaceae may also be present. Therefore, an empiric agent active against anaerobic organisms and gram-negative bacteria is indicated; piperacillin-tazobactam meets these criteria.

Ceftriaxone has adequate coverage against Enterobacteriaceae (as well as other more common flora such as *Streptococcus pneumoniae*) but has limited activity against anaerobic organisms. Therefore, this agent would not be ideal when aspiration pneumonia is a concern.

Clindamycin is active against gram-positive anaerobic organisms but not against gram-negative agents, such as *Fusobacterium* or *Prevotella*. It also lacks activity against other aerobic gram-negative bacilli, such as *Haemophilus influenzae*.

Metronidazole has excellent activity against anaerobic gram-negative rods but limited utility against anaerobic gram-positive cocci and streptococcal species, so it would not be appropriate as empiric therapy for aspiration pneumonia.

KEY POINT

- In community-dwelling patients with aspiration pneumonia, the most common organisms are anaerobic bacteria, such as microaerophilic streptococci, *Fusobacterium*, *Peptostreptococcus*, and *Prevotella* species as well as Enterobacteriaceae.

Bibliography

DiBardino DM, Wunderink RG. Aspiration pneumonia: a review of modern trends. J Crit Care. 2015;30:40-8. [PMID: 25129577] doi:10.1016/j.jcrc.2014.07.011

Item 90 Answer: E

Educational Objective: Treat enterohemorrhagic *Escherichia coli* infection with supportive care.

This patient has a diarrheal infection caused by enterohemorrhagic *Escherichia coli* (EHEC) and should receive supportive care and monitoring for the development of complications, such as hemolytic-uremic syndrome (HUS). EHEC strains such as *E. coli* O157:H7 and O104:H4 produce a Shiga-like toxin that can cause hemorrhagic colitis; consequently, EHEC is also referred to as Shiga toxin–producing *E. coli* (STEC). Supportive care typically consists of oral hydrations salts; salty liquids such as chicken soup are also effective. Bismuth subsalicylate compounds can help reduce the number of bowel movements.

E. coli infection is typically foodborne, with outbreaks often associated with consumption of a contaminated food source. Beef is commonly responsible when the intestinal contents from an infected animal contaminate the meat during processing. Consumption of fewer than 100 organisms can result in symptoms.

Although EHEC does not invade the mucosa, inflammation is caused by toxin release. The clinical presentation usually consists of abdominal pain, bloody diarrhea, and leukocytosis; fever is often absent or low grade. HUS complicates less than 10% of EHEC infections, manifesting as microangiopathic hemolytic anemia, thrombocytopenia, and kidney injury. It is more commonly seen in children than adults.

Diagnostic testing depends on laboratory protocol. Some laboratories routinely plate all stool samples on media capable of detecting *E. coli* O157:H7; other laboratories restrict testing to only grossly bloody stools or to clinician request. Considering this variability, the laboratory should be notified when STEC is a concern to ensure appropriate testing is performed.

Antibiotics (such as ceftriaxone, ciprofloxacin, and trimethoprim-sulfamethoxazole) and antimotility agents (such as loperamide) are usually not administered to patients with EHEC because they do not provide clinical benefit and their use is associated with an increased risk for HUS.

KEY POINT

- Primary enterohemorrhagic *Escherichia coli* infections should receive supportive care; administration of antibiotics or antimotility medications is associated with increased risk for hemolytic uremic syndrome.

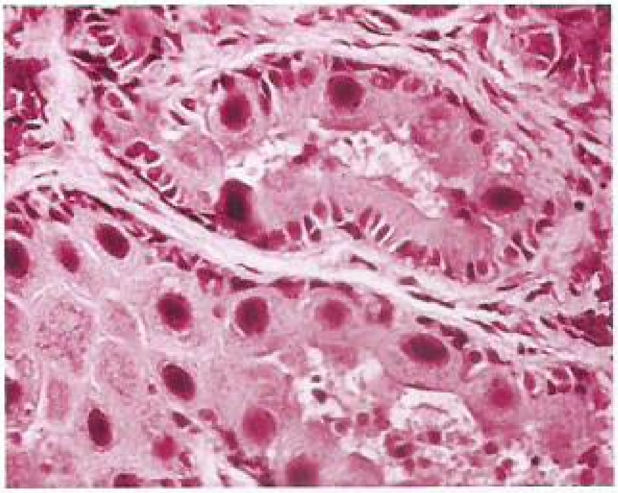
Bibliography

Freedman SB, Xie J, Neufeld MS, Hamilton WL, Hartling L, Tarr PI, et al; Alberta Provincial Pediatric Enteric Infection Team (APPETITE). Shiga toxin-producing Escherichia coli infection, antibiotics, and risk of developing hemolytic uremic syndrome: a meta-analysis. Clin Infect Dis. 2016;62:1251-1258. [PMID: 26917812] doi:10.1093/cid/ciw099

H Item 91 Answer: A

Educational Objective: Diagnose cytomegalovirus infection in a solid organ transplant recipient with colitis.

The most likely diagnosis in this patient is cytomegalovirus infection. Approximately 60% to 90% of adults have latent cytomegalovirus infection, with reactivation of disease common in persons who are immunosuppressed (patients with AIDS, transplant recipients, patients taking glucocorticoids). Cytomegalovirus is an important pathogen in kidney transplant recipients, and the risk of cytomegalovirus infection depends on the serologic status of the kidney donor and recipient at the time of transplantation. The highest risk occurs when a seronegative recipient (one who has never had a cytomegalovirus infection) receives a kidney from a seropositive donor. Cytomegalovirus can cause retinitis (especially in persons with AIDS), pneumonitis, hepatitis, bone marrow suppression, colitis with bloody diarrhea, esophagitis, and adrenalitis. This patient recently received a kidney transplant; he has bone marrow suppression (leukopenia and thrombocytopenia), hepatitis (elevated aminotransferase levels), and bloody diarrhea consistent with cytomegalovirus reactivation. Diagnosis relies on isolation of the virus from bodily fluids, such as urine; detection of cytomegalovirus pp65 antigen in leukocytes; cytopathic demonstration of "owl's eye" intracellular inclusions from tissue biopsy (colon in this case) (shown); polymerase chain reaction; and serologic assays. Antiviral treatment is typically indicated in cases of disease reactivation in immunocompromised patients and occasionally in immunocompetent hosts with severe disease. Valganciclovir is the first-line agent and is also used as prophylaxis or pre-emptive therapy in certain transplant patients.



Entamoeba histolytica and *Salmonella enteritidis* can cause bloody diarrhea, but neither presents with pancytopenia. Therefore, they are unlikely possibilities in a solid organ transplant recipient. Furthermore, *E. histolytica* would not cause elevated aminotransferase levels in the absence of a liver abscess.

Strongyloides stercoralis is the only parasite that has an autoinfection route (ability to complete its life cycle entirely within the human host) resulting in an increasing burden of parasites that can survive for decades in patients. Disseminated strongyloidiasis after solid organ transplantation

H CONT.

can present with abdominal pain and diarrhea, but it is usually nonbloody. Furthermore, disseminated *Strongyloides* infection may present with sepsis with colonic bacteria, serpiginous rash, meningitis, or eosinophilic pneumonia. All patients scheduled for solid organ transplantation are now screened with a *Strongyloides* antibody and treated with ivermectin to decrease the incidence of this infection.

KEY POINT

- Latent cytomegalovirus infection is present in 60% to 90% of adults, and patients who are immunosuppressed may experience disease reactivation with retinitis, pneumonitis, hepatitis, bone marrow suppression, colitis with bloody diarrhea, esophagitis, or adrenalitis.

Bibliography

Angarone M, Ison MG. Diarrhea in solid organ transplant recipients. Curr Opin Infect Dis. 2015;28:308-16. [PMID: 26098506] doi:10.1097/QCO.0000000000000172

H

Item 92 Answer: C

Educational Objective: Evaluate surgical site infection.

Gram stain and culture of the drainage from the incision site is the most appropriate test to perform next. Most surgical site infections (SSIs) occur within 30 days of surgery (90 days for surgery involving placement of an implant). The major sources of organisms causing SSIs are from the patient's skin and possibly the alimentary tract or female genital tract, depending on the type of surgery. The organism most often isolated is *Staphylococcus aureus*, followed by coagulase-negative staphylococci, *Escherichia coli*, *Enterococcus faecalis*, and *Pseudomonas aeruginosa*. SSIs are categorized as superficial incisional, deep incisional, and organ/deep organ space infections. A superficial incisional infection involves the underlying soft tissue and presents with inflammatory changes at the incision site (erythema, tenderness), with or without purulent drainage, and few if any systemic signs of infection, such as fever. Such incisions may require reopening to determine the extent of infection, allow complete drainage, and obtain proper specimens for Gram stain and culture to guide antibiotic therapy. Obtaining a culture is important to identify the pathogen involved and obtain antibiotic sensitivity information to determine if antibiotic-resistant organisms are present. Wound drainage fluid, purulent fluid, or infected tissue is the best culture source. Deep tissue or wound cultures are preferable to superficial wound swab cultures, which are more likely to reflect skin or wound colonization and do not necessarily yield the causative pathogen. The most narrow-spectrum oral antibiotic should be used whenever possible.

Deep incisional (involving fascia and/or muscle layers) SSIs usually present with some systemic signs of infection, such as fever and leukocytosis. These infections are managed with debridement and antibiotic therapy guided by results of deep-tissue cultures. Bacteremia may occur with deep or organ space infections, and blood cultures should be considered in such circumstances but are unnecessary in patients with a superficial site infection such as this one.

CT is useful in cases of organ or deep space (tissue deep to the fascia) SSIs to identify abscesses and plan necessary drainage procedures. Imaging, such as ultrasonography or CT, does not provide additional information needed to manage this type of SSI.

A superficial swab of the incision site is likely to pick up skin flora and make interpreting the culture results difficult.

KEY POINT

- A superficial incisional infection involves the underlying soft tissue and presents with inflammatory changes at the incision site (erythema, tenderness), with or without purulent drainage, and few if any systemic signs of infection such as fever; therapy is guided by Gram stain and culture of the wound.

Bibliography

Garner BH, Anderson DJ. Surgical site infections: an update. Infect Dis Clin North Am. 2016;30:909-929. [PMID: 27816143] doi:10.1016/j.idc.2016.07.010

Item 93 Answer: C

Educational Objective: Treat cryptococcal meningitis.

This patient should be treated with liposomal amphotericin B and flucytosine. *Cryptococcus neoformans* is inhaled and causes an initial pulmonary infection. Healthy persons generally contain the initial infection because of intact cell-mediated immunity; however, immunocompromised persons are at risk for dissemination. Risk factors for dissemination include AIDS, organ transplantation, glucocorticoid treatment, diabetes mellitus, liver dysfunction, and kidney injury. The central nervous system is the most common site of disseminated cryptococcosis. The patient most likely has cryptococcal meningitis, as evidenced by the classic triad of headache, fever, and positive cryptococcal antigen titer in the cerebrospinal fluid (CSF). Because the mortality rate may approach 60% in patients without HIV with cryptococcal meningitis, it is imperative that the appropriate antifungal regimen of liposomal amphotericin B and flucytosine be initiated as soon as possible and continued for a minimum of 2 weeks. In addition, although no papilledema or focal neurologic findings are noted, the CSF opening pressure is elevated, and the patient may require serial lumbar punctures.

Fluconazole, an azole antifungal agent, has in vitro and in vivo activity against *C. neoformans*, but it is recommended as de-escalation therapy after the patient has received at least 2 weeks of amphotericin B and flucytosine and is clinically stable. Fluconazole should be continued for at least 2 months after diagnosis, assuming the patient improves and clinical disease manifestations respond to therapy.

Itraconazole, an azole antifungal agent, has some activity in vitro against *C. neoformans*. It is not recommended for

primary therapy because of a lack of data. It may be used as an alternative agent and as suppressive therapy or prophylaxis if fluconazole is not available.

Micafungin, an echinocandin antifungal agent, is the drug of choice for candidemia and invasive candidiasis but has no activity against *C. neoformans*.

KEY POINT

- Combination therapy with liposomal amphotericin B and flucytosine is the treatment of choice for cryptococcal meningitis.

Bibliography

Maziarz EK, Perfect JR. Cryptococcosis. Infect Dis Clin North Am. 2016;30:179-206. [PMID: 26897067] doi:10.1016/j.idc.2015.10.006

Item 94 Answer: A

Educational Objective: Diagnose late disseminated Lyme disease.

This patient should have IgG Western blotting to detect antigens to *Borrelia burgdorferi*. She has symptoms of monoarticular arthritis, which has a broad differential diagnosis. Her presentation is most compatible with late disseminated Lyme disease; her previous residence in a Lyme-endemic area and her occupation, with its increased likelihood of tick exposure, increase the probability of this diagnosis. Onset of symptoms of Lyme arthritis typically occurs months, and sometimes years, after the initial infection. Involvement of large joints, particularly the knees, is common. Confirmatory serologic testing using a two-tiered diagnostic approach is required for definitive diagnosis of late disseminated Lyme disease. The initial test is a Lyme enzyme immunoassay antibody titer. This test is very sensitive, and, in a patient suspected of having late disseminated Lyme disease, a negative result essentially excludes the diagnosis. In patients with a positive or equivocal result, as with this patient, a second-tier test is necessary to confirm the diagnosis. Early in the course of infection, both IgM and IgG Western blots are recommended because IgM antibody production predates IgG development. After 4 weeks or more of symptoms, IgG antibody is presumed to be positive, and thus a positive IgM Western blot with a negative IgG likely represents a false-positive result. For this reason, the testing algorithm from the Centers for Disease Control and Prevention specifies that when signs and symptoms are present for more than 30 days, only a confirmatory IgG Western blot should be performed.

The C6 antibody corresponds to a highly conserved protein common to all *Borrelia* strains. Testing using this assay may have a role in diagnosis of infections that occurred outside of the United States. For domestically acquired infections, this test is not currently recommended to replace either component of the conventional two-tier algorithm.

The sensitivity of synovial polymerase chain reaction is low, and this method is not recommended as an initial diagnostic test for Lyme arthritis.

KEY POINT

- Confirmatory serologic testing using a two-tiered diagnostic approach that includes enzyme immunoassay and IgG Western blotting (and, early in the course of disease, IgM Western blotting) is required for definitive diagnosis of late disseminated Lyme disease.

Bibliography

Arvikar SL, Steere AC. Diagnosis and treatment of Lyme arthritis. Infect Dis Clin North Am. 2015;29:269-80. [PMID: 25999223] doi:10.1016/j.idc.2015.02.004

Item 95 Answer: D

H

Educational Objective: Monitor for ciprofloxacin adverse effects.

This patient should be monitored for tendon or joint pain. Fluoroquinolones (such as ciprofloxacin and delafloxacin) are associated with the development of tendinitis and tendon rupture. Most tendinitis occurrences (90%) involve the Achilles tendon and are more common in men and persons older than 60 years. Tendon rupture occurs in 40% of patients and is more common in women. Additional risk factors include concomitant glucocorticoid treatment and solid organ transplantation. Tendinitis can occur anytime during treatment and up to 6 months after discontinuation of the antibiotic. Patients should be counseled to immediately report tendon pain, swelling, or inflammation and stop taking the fluoroquinolone. Other adverse effects involve the nervous system and include headache, dizziness, insomnia, and alteration in mood. Peripheral neuropathy usually occurs early in therapy; symptoms can last years after fluoroquinolone discontinuation and may be irreversible. Another important adverse effect of fluoroquinolones is the potential for QT prolongation and the development of serious arrhythmias. Fluoroquinolones should be avoided in patients with known QT prolongation, risk factors for torsades de pointes, or concomitant administration of other medications that prolong the QT interval. The FDA advises restricting fluoroquinolone use in uncomplicated infections.

The gastrointestinal effects of fluoroquinolones (anorexia, nausea, vomiting, mild abdominal discomfort) do not include pancreatitis, so monitoring the serum lipase level is unnecessary; regardless, the serum lipase level would not be measured unless the patient had symptoms compatible with acute pancreatitis.

Fluoroquinolones are associated with hypoglycemia and hyperglycemia but not with disturbances in sodium level. Therefore, sodium levels do not require monitoring. Hypoglycemia occurs most often in older adult patients with diabetes mellitus but can occur in patients without diabetes. Hyperglycemia has also been associated with the use of fluoroquinolones. Patients should be monitored closely for signs and symptoms of disordered glucose regulation, but monitoring of glucose levels is not recommended in most patients without diabetes.

H CONT.

Stool should be tested for *Clostridium difficile* toxin or with polymerase chain reaction assays to detect the genes responsible for production of toxins only if the patient develops diarrhea.

KEY POINT

- Fluoroquinolone antibiotics such as ciprofloxacin are associated with the development of tendinitis and tendon rupture, so patients should be counseled to report tendon or joint pain and swelling.

Bibliography

Lewis T, Cook J. Fluoroquinolones and tendinopathy: a guide for athletes and sports clinicians and a systematic review of the literature. J Athl Train. 2014;49:422-7. [PMID: 24762232] doi:10.4085/1062-6050-49.2.09

H

Item 96 Answer: B

Educational Objective: Treat *Candida* esophagitis.

Oral fluconazole is the most appropriate management for this patient's likely esophageal candidiasis; he should be treated presumptively and followed for response. The diagnosis of oropharyngeal candidiasis is usually made clinically; although whitish plaques are often prominent, oral candidiasis may also present as diffuse erythema without plaques. The presence of oral candidiasis and painful swallowing symptoms indicates likely esophageal involvement. The preferred treatment is oral fluconazole regardless if the disease is isolated to the oral cavity or extends into the esophagus; however, esophageal involvement warrants a more prolonged course (14-21 days rather than 7-14 days). Clinical response is usually apparent within a few days.

Because this patient is able to swallow pills, oral therapy is appropriate, and intravenous therapy is unnecessary. Additionally, fluconazole has higher rates for complete resolution without relapse of disease than the echinocandins and is preferred therapy unless resistance is documented, which would not be expected in a patient who has not been taking long-term azole therapy.

Topical agents such as nystatin are less effective than systemic fluconazole for oropharyngeal candidiasis and are especially ineffective for esophageal disease.

If presumptive treatment for candida esophagitis is ineffective in improving symptoms, then upper endoscopy is indicated to better define the cause.

Cytomegalovirus esophagitis is seen in immunocompromised patients and rarely occurs in patients with an intact immune system. Although herpes simplex virus (HSV) esophagitis can be seen in immunocompetent and immunocompromised patients, it is much more likely to be found in an immunocompromised person. These viral infections usually manifest as esophageal ulcerative lesions rather than plaques. Biopsies of the ulcer should be performed to confirm cytomegalovirus and HSV. Treatment of cytomegalovirus with valganciclovir (or HSV with acyclovir) would not be appropriate without first seeing evidence for it on endoscopy.

KEY POINT

- The preferred treatment for oropharyngeal candidiasis, including esophageal disease, is oral fluconazole, although esophageal involvement warrants a more prolonged treatment course.

Bibliography

Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents. Guidelines for the prevention and treatment of opportunistic infections in HIV infected adults and adolescents: recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. Available at https://aidsinfo.nih.gov/guidelines/html/4/adult-and-adolescent-opportunistic-infection/0. Accessed April 12, 2018.

Item 97 Answer: C

H

Educational Objective: Diagnose invasive candidiasis.

This patient has *Candida* pyelonephritis, a form of invasive candidiasis. She has several risk factors for candidiasis, such as recently taking broad-spectrum antibiotics, uncontrolled diabetes mellitus, and a history of recurrent urinary tract infections. These risk factors, in combination with the findings of yeast, leukocytes, and erythrocytes in the urine, is classic for this infection. Although the urine culture only grew 10,000 colony-forming units of *Candida glabrata*, the colony count may not correlate with active infection in *Candida* infections of the urinary tract. Thus, antifungal therapy with an echinocandin should be initiated immediately. After identification of the species, the antifungal agent may be de-escalated to an oral azole if the *Candida* species is susceptible to azoles. The total duration should be 10 to 14 days of antifungal therapy.

Acute diverticulitis may present with the same manifestations this patient had. However, the bilateral flank pain and the lack of abdominal pain make diverticulitis less likely. In addition, the urinalysis results showing leukocytes too numerous to count and the classic CT scan finding of perinephric stranding point to a kidney infection.

Antibiotic-resistant bacterial pyelonephritis is a possibility and could explain her progressive symptoms despite appropriate antibiotic therapy for pyelonephritis. However, this diagnosis is excluded by the patient's urine culture, which showed only *Candida* species.

Patients with acute kidney infarction typically present with acute flank pain or generalized abdominal pain, often associated with nausea and vomiting and, less commonly, with fever; hematuria is present in one third of patients. Over half of kidney infarctions are cardioembolic, and atrial fibrillation is commonly found in patients with this diagnosis. A contrast-enhanced CT scan will show a wedge-shaped perfusion defect. This patient's normal abdominal

H CONT.

contrast-enhanced CT scan and urinalysis argue against kidney infarction.

KEY POINT

- In patients with invasive candidiasis, antifungal therapy with an echinocandin should be initiated immediately, followed by de-escalation to an oral azole if the identified *Candida* species is susceptible; the total duration of antifungal therapy should be 10 to 14 days.

Bibliography

Pappas PG, Kauffman CA, Andes DR, Clancy CJ, Marr KA, Ostrosky-Zeichner L, et al. Executive summary: clinical practice guideline for the management of candidiasis: 2016 update by the Infectious Diseases Society of America. Clin Infect Dis. 2016;62:409-17. [PMID: 26810419] doi:10.1093/cid/civ1194

H

Item 98 Answer: C

Educational Objective: Diagnose primary herpes simplex virus genital infection.

The patient's presentation is most consistent with primary genital infection with herpes simplex virus (HSV), and nucleic acid amplification testing (NAAT) for HSV-1 and HSV-2 is the preferred method to confirm the diagnosis. HSV is the most common cause of genital ulcer disease in the United States. The epidemiology of primary genital HSV infections has shifted, and up to half are now caused by HSV-1 rather than HSV-2. However, HSV-1 is less able to establish latency in the genital region, so most recurrent genital infections are caused by HSV-2. NAAT is highly sensitive and specific for HSV. Regardless of type, the initial treatment of primary genital HSV infection is the same (acyclovir, valacyclovir, or famciclovir), but patients with HSV-1 primary genital infection can be counseled that they are less likely to experience recurrent genital ulcers. This patient must also be counseled regarding the natural history of his infection, the need to inform sexual partners of his diagnosis, and the need to avoid sexual contact when ulcers are present. He should be screened for other sexually transmitted infections (STIs), including gonorrhea, chlamydia, syphilis, and HIV, and counseled on the use of condoms to reduce the risk of STI transmission.

Darkfield examination is the appropriate diagnostic test if genital ulcer disease caused by syphilis is suspected. Although syphilitic chancres may appear in multiples and are often accompanied by regional lymphadenopathy, single ulcers are far more common and appear as deeper ulcers with raised regular borders. Syphilitic chancres are generally painless.

Type-specific serologic testing for HSV-1 and HSV-2 should not be used to confirm the diagnosis of genital ulcer disease, especially when ulcers are present. Patients may have evidence of HSV infection on the basis of serologic testing with genital ulcers resulting from another cause.

Direct fluorescence assay testing of the ulcer is not as sensitive as NAAT. Viral culture is a better option if NAAT testing is unavailable.

For all diagnostic tests, sensitivity is improved by obtaining the sample by rotating the swab firmly on the ulcer base after a vesicle is unroofed or from a lesion that has been ulcerated for less than 24 hours.

KEY POINT

- Nucleic acid amplification testing is the most appropriate diagnostic choice for confirming genital ulcer disease caused by herpes simplex virus.

Bibliography

Gnann JW Jr, Whitley RJ. Clinical practice. Genital herpes. N Engl J Med. 2016;375:666-74. [PMID: 27532832] doi:10.1056/NEJMcp1603178

Item 99 Answer: D

H

Educational Objective: Treat a patient with necrotizing fasciitis and toxic shock syndrome secondary to group A *Streptococcus*.

The antibiotic treatment should be switched from vancomycin and piperacillin-tazobactam to penicillin and clindamycin. This patient has necrotizing fasciitis (NF) secondary to group A *Streptococcus* (GAS) infection (usually *Streptococcus pyogenes*). Additionally, he has toxic shock syndrome, which occurs in approximately 50% of patients with GAS NF. A definitive diagnosis of toxic shock syndrome is established by isolation of the organism from a sterile site (blood and tissue), hypotension, and the presence of multiorgan involvement (in this case, kidney, liver, bone marrow [thrombocytopenia]). Surgical debridement is the primary treatment for GAS NF. The Infectious Diseases Society of America (IDSA) also recommends penicillin plus clindamycin for antibiotic treatment of GAS NF. Although *S. pyogenes* is susceptible to penicillin, clindamycin is added because of its ability to suppress streptococcal toxin production. More studies are needed to establish the exact role of intravenous immune globulin in this setting, and it is not recommended by the IDSA in the latest guidelines.

Doxycycline plus a third-generation cephalosporin, such as ceftazidime, ceftriaxone, or cefotaxime, is recommended by the IDSA for treatment of *Vibrio vulnificus*-associated necrotizing skin and soft tissue infections. This combination would not treat GAS NF adequately because it does not include a protein synthesis inhibitor to suppress toxin production.

Empiric therapy for necrotizing skin and soft tissue infections should address the possibility of mixed aerobic and anaerobic organisms, including methicillin-resistant *Staphylococcus aureus*. Vancomycin or linezolid plus imipenem or meropenem, or piperacillin-tazobactam, or metronidazole plus ceftriaxone, is recommended. When culture results are available, however, antibiotic stewardship principles would advocate discontinuing vancomycin and piperacillin-tazobactam and initiating targeted therapy consisting of penicillin and clindamycin against *S. pyogenes*. The combination of linezolid and imipenem would be too broad in its coverage after the culture results reveal GAS.

KEY POINT

- In patients with necrotizing fasciitis caused by group A *Streptococcus*, the combination of penicillin and clindamycin is indicated for antimicrobial therapy after surgical debridement.

Bibliography

Stevens DL, Bisno AL, Chambers HF, Dellinger EP, Goldstein EJ, Gorbach SL, et al. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the infectious diseases society of America. Clin Infect Dis. 2014;59:147-59. [PMID: 24947530] doi:10.1093/cid/ciu296

H

Item 100 Answer: E

Educational Objective: Manage asymptomatic bacteriuria.

No treatment or further investigation is indicated in this asymptomatic older woman who has bacteriuria discovered on a routine dipstick urinalysis. Although commonly performed, analysis of the urine is not warranted, except when evaluating a patient who presents with clear signs or symptoms of a urinary tract infection (UTI), and may lead to unnecessary administration of antibiotics. Incontinence without urgency or dysuria is not unexpected in many older women. The prevalence of asymptomatic bacteriuria (ASB) is as low as 1% to 5% in healthy premenopausal women (2%-10% in pregnant women) and up to 100% in patients with long-term indwelling urinary catheters. However, most ASB occurs in older adult women and men, with a respective prevalence of 11% to 16% and 4% to 19% in the community, increasing to 25% to 50% and 15% to 40% in long-term care facilities. Except in specific patient groups, well-designed studies have proven that although persons with bacteriuria are at increased risk for symptomatic UTIs, ASB treatment does not decrease the frequency of symptomatic infections or improve other outcomes. ASB is associated with a higher prevalence of potentially dangerous antibiotic-resistant strains in women who progress to an active UTI. Except in pregnant women, who have a known increased prevalence of ASB, which has been demonstrated to lead to serious complications, routine screening for infection in women without symptoms is unwarranted. Screening and treatment are also indicated before invasive urologic procedures. The presence of pyuria accompanying ASB is not an indication for antimicrobial treatment.

This patient does not require treatment for her asymptomatic bacteruria; additionally, fluoroquinolone antibiotics are no longer recommended for the treatment of symptomatic lower UTIs because of the significant rise in *Escherichia coli* isolates resistant to this class of agents.

Cystoscopy is recommended in the evaluation of microscopic hematuria for all patients older than 35 years or those with risk factors for urologic malignancy. Cystoscopy would possibly be warranted in patients with recurring symptomatic UTIs but is not indicated in this patient.

Culture and sensitivity testing as well as microscopic urinalysis are not necessary in women presenting with classic lower UTI symptoms, including frequency, urgency, and dysuria, without manifestations of systemic or upper tract disease. Urinalysis and urine culture are not indicated as part of routine health surveillance in asymptomatic patients and should not be performed. They are not necessary in this patient with asymptomatic bacteruria.

KEY POINT

- No treatment is indicated for asymptomatic bacteriuria in otherwise healthy, nonpregnant patients.

Bibliography

Nicolle LE. Urinary tract infections in the older adult. Clin Geriatr Med. 2016;32:523-38. [PMID: 27394021] doi:10.1016/j.cger.2016.03.002

Item 101 Answer: C

Educational Objective: Diagnose Mediterranean spotted fever.

This patient most likely has Mediterranean spotted fever caused by *Rickettsia conorii*. Most rickettsial infections are transmitted by arthropod vectors. Outdoor activities, especially during the spring and summer months, present the greatest opportunity for infection. Mediterranean spotted fever is one of the most severe forms of the spotted fever group of rickettsial diseases likely to be contracted during international travel. Signs and symptoms of illness usually begin following an incubation period of 2 to 14 days after a tick bite, which frequently goes unnoticed. The risk of infection is greatest in northern and southern Europe but also occurs in Africa, India, and the Middle East. Characteristically, fever, myalgia, and headache mark the onset of infection followed shortly by the appearance of a maculopapular and oftentimes petechial rash, generally beginning on the ankles and wrists and typically involving the palms and soles. A distinct eschar (shown) is classically present

at the site of inoculation along with the development of localized regional lymphadenopathy. Disease is usually mild to moderate; however, vascular dissemination can lead to severe complications, of which neurologic manifestations are the most common. Laboratory findings are nonspecific, but diagnosis may be aided by polymerase chain reaction and serologic assays. A 7- to 10-day course of doxycycline is the treatment of choice.

Anaplasma phagocytophilum, the causative agent of human granulocytic anaplasmosis, can be found worldwide and is transmitted by various *Ixodes* tick species. However, rash is a very uncommon clinical manifestation (<10%).

Lyme disease in Europe mainly results from infection with *Borrelia garinii* or *Borrelia afzelii*, transmitted by *Ixodes ricinus* ticks. In nearly 75% of infected persons, it presents with an erythema migrans rash at the site of inoculation.

Rocky Mountain spotted fever, caused by *R. rickettsii*, is the most common rickettsial infection but is geographically restricted to certain areas of the United States, Central and South America, Mexico, and Canada. Eschar formation at the site of tick attachment is rare.

KEY POINT

- Mediterranean spotted fever characteristically presents with fever, myalgia, and headache followed shortly by the appearance of a maculopapular and oftentimes petechial rash; a distinct black eschar is also classically present at the site of inoculation.

Bibliography

Parola P, Paddock CD, Socolovschi C, Labruna MB, Mediannikov O, Kernif T, et al. Update on tick-borne rickettsioses around the world: a geographic approach. Clin Microbiol Rev. 2013;26:657-702. [PMID: 24092850] doi:10.1128/CMR.00032-13

Item 102 Answer: A

Educational Objective: Diagnose Lyme meningitis.

Lyme disease, caused by infection with *Borrelia burgdorferi*, is the most common vector-borne infection in the United States. The first stage involves localized symptoms occurring 1 to 4 weeks after infection. This early stage is usually characterized by erythema migrans present in 60% to 80% of localized infections. Untreated patients may progress to early disseminated infection, typically presenting as a febrile illness associated with erythema migrans at multiple sites distant from the initial tick attachment. Focal cardiac or neurologic symptoms may also occur in early disseminated disease, typically 2 to 10 weeks after the development of the erythema migrans rash. The most common neurologic manifestation of early disseminated Lyme disease is facial nerve palsy, which may be unilateral or bilateral. Because the cerebrospinal fluid (CSF) findings closely resemble those of other viral infections (enterovirus, herpes simplex virus, varicella-zoster virus, West Nile virus), the "rule of 7s" was derived and validated to accurately classify a patient at low risk for having Lyme disease (headache duration <7 days, <70% mononuclear cells, and absence of a seventh facial nerve palsy). Nantucket Island is a highly endemic area for Lyme disease; the patient's history of camping 2 months before meningitis onset is consistent with the diagnosis of *Borrelia burgdorferi* infection. The treatment is intravenous ceftriaxone.

Aseptic meningitis caused by herpes simplex virus type 2, West Nile virus, or enterovirus would include a normal neurologic examination. The presence of right-sided facial palsy in this patient makes these unlikely causes.

Varicella-zoster virus can also present with a facial palsy, but this condition usually occurs as part of the Ramsay-Hunt syndrome (with vesicular rash of the external ear). Ramsay-Hunt syndrome is usually seen in young immunosuppressed persons (those with AIDS) or in older adults.

The normal mental status excludes West Nile virus encephalitis as does the presence of facial palsy.

KEY POINT

- For patients presenting with aseptic meningitis and cerebrospinal fluid findings typical for viral infection, the "rule of 7s" can classify a patient at low risk for having Lyme disease (headache duration <7 days, <70% mononuclear cells, and absence of a seventh facial nerve palsy).

Bibliography

Shapiro ED. Clinical practice. Lyme disease. N Engl J Med. 2014;370:1724-31. [PMID: 24785207] doi:10.1056/NEJMcp1314325

Item 103 Answer: B

Educational Objective: Diagnose Epstein-Barr virus infection in a kidney transplant recipient.

This patient's symptoms are most likely caused by infection with Epstein-Barr virus (EBV). He most likely has posttransplant lymphoproliferative disorder (PTLD). His clinical presentation of fever, pancytopenia, generalized lymphadenopathy, and hepatosplenomegaly is consistent with this diagnosis, considering his kidney transplantation and immunosuppressive therapy. PTLD risk is higher in patients with a history of pre-existing EBV infection treated with lymphocyte-depleting agents and in those receiving sirolimus and tacrolimus compared with those receiving mycophenolate and cyclosporine. PTLD can range from a benign monoclonal gammopathy to a malignant lymphoma. PTLD should be considered in any patient presenting with fever and lymphadenopathy or an extranodal mass; treatment includes reduction of immunosuppression and rituximab or other chemotherapy.

Although numerous viral infections can complicate transplantation, cytomegalovirus is the most significant. The risk for reactivation is related to serologic status of the donor and recipient and is most likely in seronegative recipients from a seropositive donor; it is unlikely when donor and recipient are both negative. Like EBV, cytomegalovirus can

H CONT.

reactivate and cause pancytopenia, hepatitis, pneumonitis, esophagitis, colitis, or adrenalitis in solid-organ transplant recipients. Cytomegalovirus reactivation is also associated with organ rejection, secondary infection, and an increased risk for graft loss and death. However, cytomegalovirus does not cause generalized lymphadenopathy or hepatosplenomegaly. Cytomegalovirus-seropositive transplant recipients or cytomegalovirus-negative recipients with positive donors should receive prophylactic valganciclovir or undergo routine monitoring for cytomegalovirus viremia.

Herpes simplex virus can also reactivate in the setting of immunosuppressive therapy, but it would be more likely to present with oral or genital ulcers.

Polyoma BK virus reactivation occurs in approximately 5% of kidney transplant recipients and can cause kidney allograft dysfunction or loss. It can present with a gradual, asymptomatic increase in the serum creatinine level with tubulointerstitial nephritis or, less commonly, with ureteral stenosis. Patients may have polyoma BK virus on polymerase chain reaction of the urine or serum or may have polyoma BK virus inclusion-bearing epithelial cells called "decoy cells." The treatment is to reduce immunosuppression. This patient's stable serum creatinine level argues against this diagnosis.

KEY POINT

- Posttransplant lymphoproliferative disorder caused by Epstein-Barr virus can present several years after transplantation with fever, pancytopenia, generalized lymphadenopathy, and hepatosplenomegaly.

Bibliography

Petrara MR, Giunco S, Serraino D, Dolcetti R, De Rossi A. Post-transplant lymphoproliferative disorders: from epidemiology to pathogenesis-driven treatment. Cancer Lett. 2015;369:37-44. [PMID: 26279520] doi:10.1016/j.canlet.2015.08.007

H

Item 104 Answer: C

Educational Objective: Treat a patient with a moderate-severity purulent skin infection who is allergic to trimethoprim-sulfamethoxazole.

Empiric therapy with oral doxycycline is the most appropriate treatment for this patient after incision and drainage. Treatment of skin and soft tissue infections is guided by categorizing the infection as purulent or nonpurulent and by grading the severity of the infection as mild, moderate, or severe. The patient has a purulent skin infection (furuncle) of moderate severity (systemic signs of infection present, including fever and tachycardia). These infections are typically caused by methicillin-resistant *Staphylococcus aureus* (MRSA). Recommended treatment is incision and drainage and outpatient treatment with an oral agent active against MRSA. Oral trimethoprim-sulfamethoxazole or doxycycline is recommended by the Infectious Diseases Society of America (IDSA) for moderate-severity purulent skin infections; however, the patient has a known allergy to trimethoprim-sulfamethoxazole, eliminating it as an option. Culture of the purulent material will allow for identification of the microbial agent and a reassessment of pathogen-directed therapy.

Mild (no evidence of systemic signs of infection), nonpurulent skin infections are typically caused by streptococci, and empiric outpatient treatment with an oral agent such as clindamycin, penicillin, cephalexin, or dicloxacillin would be appropriate according to recommendations from the IDSA.

Incision and drainage alone with clinical follow-up is recommended by the IDSA for patients with mild purulent infections. However, in a 2017 randomized clinical trial of patients with skin abscess measuring 5 cm or less who underwent incision and drainage, higher cure rates were observed among those who received antibiotic therapy than those who received placebo. Because this patient has systemic signs of infection, he would be considered to have at least a moderate purulent skin and soft tissue infection and would, therefore, require antibiotics in addition to incision and drainage.

KEY POINT

- Purulent skin infections with systemic signs of infection should be managed with incision and drainage followed by empiric oral therapy with trimethoprim-sulfamethoxazole or doxycycline.

Bibliography

Stevens DL, Bisno AL, Chambers HF, Dellinger EP, Goldstein EJ, Gorbach SL, et al. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the Infectious Diseases Society of America. Clin Infect Dis. 2014;59:147-59. [PMID: 24947530] doi:10.1093/cid/ciu296

Item 105 Answer: E

Educational Objective: Evaluate the results of a tuberculin skin test.

This patient has a negative tuberculin skin test (TST), so no treatment or further management is recommended. The criteria for a positive reaction have been established by the Centers for Disease Control and Prevention (CDC) based on the patient's risks for tuberculosis. A TST reaction of 5 mm or greater should be considered positive in persons at high risk, including patients with HIV, patients with recent known contact with a person with active tuberculosis, persons with chronic fibrotic changes on chest radiography consistent with old tuberculosis, patients who have undergone solid organ transplantation, and other persons who are immunosuppressed (patients taking prednisone >15 mg/d or a tumor necrosis factor-α antagonist). A TST reaction of 10 mm or greater should be considered positive in recent (<5 years) arrivals from high-prevalence countries, injection drug users, residents or employees of high-risk congregate settings (prisons and jails, nursing homes, and other long-term facilities for older adults), hospitals and other health care facilities (which would include this patient), homeless shelters, mycobacteriology laboratory personnel, persons

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with clinical conditions that put them at high risk for active disease, and children younger than 4 years or those exposed to adults in high-risk categories. In patients with no risk factors for tuberculosis, 15 mm or greater should be considered a positive result.

Because latent and active tuberculosis were ruled out in this patient, a chest radiograph is unnecessary.

Sputum induction for culture is not indicated in the absence of clinical signs or symptoms of active infection and without testing results indicating tuberculosis infection.

Because the patient did not have evidence of latent tuberculosis, isoniazid treatment is not indicated. Isoniazid should not be initiated empirically without evidence of infection.

Because the TST is considered negative and the chest radiograph is normal, latent and active tuberculosis have been ruled out in this patient, and she does not need to be removed from her work area.

KEY POINT

- The criteria for a positive tuberculin skin test reaction have been established by the Centers for Disease Control and Prevention based on the patient's risks for tuberculosis; in patients with no risk factors for tuberculosis, 15 mm or greater should be considered a positive result.

Bibliography

Lewinsohn DM, Leonard MK, LoBue PA, Cohn DL, Daley CL, Desmond E, et al. Official American Thoracic Society/Infectious Diseases Society of America/Centers for Disease Control and Prevention clinical practice guidelines: diagnosis of tuberculosis in adults and children. Clin Infect Dis. 2017;64:111-115. [PMID: 28052967] doi:10.1093/cid/ciw778

Item 106 Answer: A

Educational Objective: Treat latent tuberculosis infection in a patient who is HIV positive.

The most appropriate management for this patient is daily isoniazid plus pyridoxine. He has HIV, and a tuberculin skin test (TST) produces a 5-mm induration, which is considered positive in patients who are immunocompromised. Because the chest radiograph was negative, he should be treated as having latent tuberculosis infection (LTBI) with 9 months of isoniazid therapy. Pyridoxine is added to LTBI treatment in patients at risk for peripheral neuropathy (such as patients with HIV, diabetes, uremia, alcoholism, malnutrition, and pregnancy). It cannot be determined if the patient's tuberculosis infection is newly acquired or long standing because the previous negative TST was performed when his CD4 cell count was extremely low.

Because this patient has no evidence of active infection, four-drug antituberculous therapy is not necessary.

Routine use of a TST and interferon-γ release assay (IGRA) is not recommended. In certain circumstances, however, using a second test when the result of the initial test is negative might be helpful when the risk of infection or progression is increased or risk for poor outcome exists, such as in children younger than 5 years who have been exposed to a patient with active tuberculosis or in patients with HIV infection. Use of a second test for diagnosing infection when the result of the first test is negative can also be considered when the suspicion of tuberculosis is strong based on clinical presentation or radiographic imaging. Conversely, using both tests when the result of the initial test is positive might be helpful when a suspected false-positive result is obtained in a person at low risk for infection and progression to active disease. This patient is at high risk for tuberculosis and has a positive TST; therefore, additional testing with IGRA is not necessary.

Repeating the TST would not provide additional information. The Centers for Disease Control and Prevention recommends initiating antituberculous prophylaxis in patients who are HIV positive who have a TST induration of 5 mm or greater.

KEY POINT

- A 5-mm induration on tuberculin skin testing is considered positive in persons who are immunocompromised, including those with HIV; if no other signs of tuberculosis infection are present, treatment for latent tuberculosis infection should be initiated with isoniazid.

Bibliography

Lewinsohn DM, Leonard MK, LoBue PA, Cohn DL, Daley CL, Desmond E, et al. Official American Thoracic Society/Infectious Diseases Society of America/Centers for Disease Control and Prevention clinical practice guidelines: diagnosis of tuberculosis in adults and children. Clin Infect Dis. 2017;64:111-115. [PMID: 28052967] doi:10.1093/cid/ciw778

Item 107 Answer: E

H

Educational Objective: Treat recurrent cystitis in women.

The most appropriate management of this patient is urine culture plus ciprofloxacin. This young woman has a classic presentation and typical dipstick urinalysis findings of a lower urinary tract infection (UTI). Urine cultures are not generally necessary to confirm the diagnosis; however, culture and susceptibility testing are indicated when infection is recurrent. Recurrent UTI is defined as three episodes of UTI in the preceding 12 months or two episodes in the preceding 6 months. Recurrent UTI is common in women. A recurrent UTI may be a relapse or reinfection. Relapse is defined as an infection caused by the same strain (by repeat culture) as the initial UTI and occurs within 2 weeks of completing initial therapy. Reinfection is diagnosed if the UTI is caused by a different strain than that causing the initial infection or if a sterile urine culture was documented between episodes. Most recurrences are reinfections. While awaiting results, she should begin empiric treatment with ciprofloxacin twice daily for 7 days. Although fluoroquinolone antibiotics are no longer recommended as first-line agents for the treatment of cystitis because of increasing concerns for potential adverse effects and uropathogen antimicro-

H CONT.

bial resistance development, ciprofloxacin and levofloxacin are the preferred antimicrobial agents when trimethoprim-sulfamethoxazole local resistance rates are high (>20%) or the patient has been treated with an antibiotic for a UTI within the previous 3 months. Having recently received antibiotics defines this patient's UTI as complicated, warranting 7 to 10 days of treatment with a fluoroquinolone antibiotic.

Nitrofurantoin, trimethoprim-sulfamethoxazole, fosfomycin, and oral β-lactams are not recommended as first-line empiric oral therapy in complicated cystitis because of concerns regarding resistance to these agents. In the case of culture-proven sensitivity, these agents can be used in the treatment of complicated UTI.

Ampicillin and amoxicillin are no longer acceptable UTI treatment options because more than one third of community-acquired *Escherichia coli* harbor resistance to this agent.

KEY POINT

- Ciprofloxacin and levofloxacin are the preferred antimicrobial agents for the treatment of recurrent cystis when trimethoprim-sulfamethoxazole local resistance rates are high or the patient has been treated with an antibiotic for a urinary tract infection within the previous 3 months.

Bibliography

Gupta K, Hooton TM, Naber KG, Wullt B, Colgan R, Miller LG, et al; Infectious Diseases Society of America. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: A 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. Clin Infect Dis. 2011;52:e103-20. [PMID: 21292654] doi:10.1093/cid/ciq257

H

Item 108 Answer: D

Educational Objective: **Diagnose rhinocerebral mucormycosis.**

This patient has mucormycosis (rhinocerebral form), which has a mortality rate of 60% to 80%. Various organisms are responsible for causing mucormycosis, with *Rhizopus* and *Mucor* species being the most common. Patients with uncontrolled diabetes or ketoacidosis have a unique susceptibility. Other risk factors include immunocompromise from hematologic malignancies, organ transplantation, and cancer chemotherapy. The most common presentation is rhinocerebral. This is a rapidly fatal infection that spreads from the sinuses retro-orbitally to the central nervous system. Symptoms and signs include headache, epistaxis, and ocular findings, including proptosis, periorbital edema, and decreased vision. A pathognomonic finding on physical examination is the presence of a black eschar on the nose or palate. Mucormycosis is diagnosed by tissue biopsy and culture. The most important step in managing any form of mucormycosis is early, extensive, and repeated debridement of infected and necrotic tissue. The drug of choice is high-dose liposomal amphotericin B.

Cutaneous anthrax is the most common type of anthrax in the United States and results after causative microorganisms are introduced into a skin abrasion or open wound. Cutaneous lesions are initially pruritic and painless and subsequently progress to vesicular lesions surrounded by nonpitting edema. The lesions then become hemorrhagic or necrotic, and satellite lesions may form. Finally, a central black eschar can develop and usually resolves over 6 weeks. Anthrax does not cause rhinocerebral infection.

Rhinocerebral aspergillosis has a similar presentation to mucormycosis. A helpful clue to the correct diagnosis is the propensity of rhinocerebral aspergillosis to occur in patients with neutropenia, typically secondary to hematologic malignancy. In contrast, mucormycosis occurs most commonly in those with diabetes mellitus, especially with ketoacidosis, and typically is distinguished by the presence of the characteristic eschar. A biopsy is necessary to establish the correct diagnosis, which is important because treatment of the two conditions is different.

Lemierre syndrome (jugular vein suppurative thrombophlebitis) is a rare complication of acute pharyngitis that involves septic thrombosis of the internal jugular vein and bacteremia, typically involving *Fusobacterium necrophorum*. Lemierre syndrome should be considered in patients with antecedent pharyngitis and persistent fever despite antibiotic treatment. Soft-tissue CT of the neck with contrast typically shows a jugular vein thrombus with surrounding tissue enhancement. This disorder is not associated with necrotic involvement of the nose and sinuses.

KEY POINT

- Rhinocerebral mucormycosis is a rapidly fatal infection that spreads from the sinuses retro-orbitally to the central nervous system in immunocompromised patients, especially those with uncontrolled diabetes or ketoacidosis; a pathognomonic finding on physical examination of the nose or palate is the presence of a black eschar.

Bibliography

Farmakiotis D, Kontoyiannis DP. Mucormycoses. Infect Dis Clin North Am. 2016;30:143-63. [PMID: 26897065] doi:10.1016/j.idc.2015.10.011

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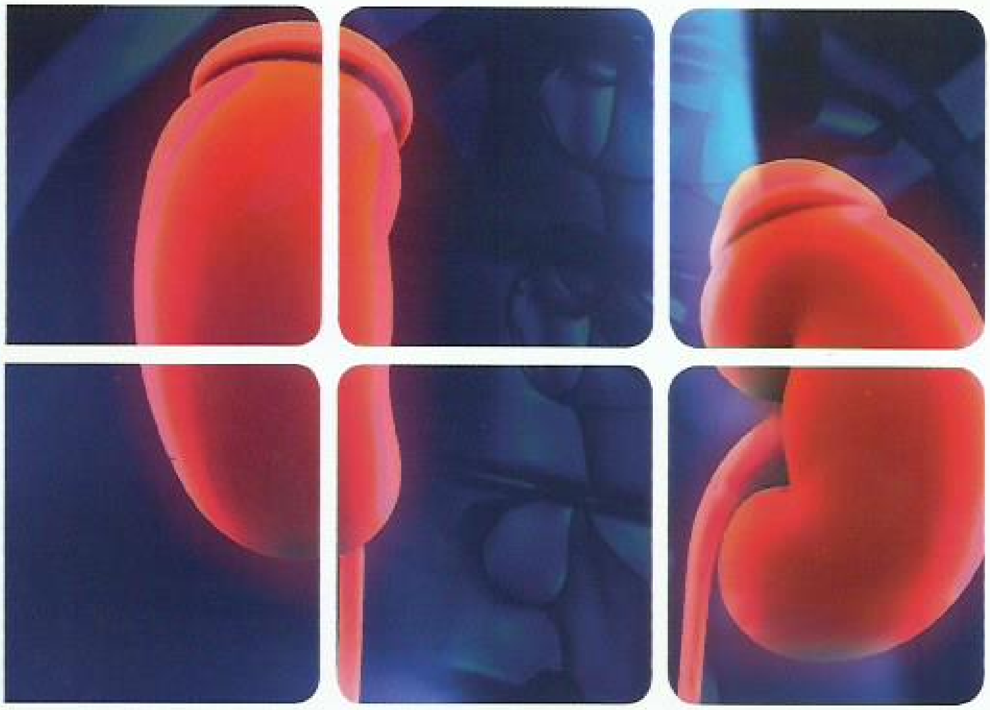

Nephrology

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Medical Knowledge Self-Assessment Program®

Nephrology

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Welcome to the Nephrology Section of MKSAP 18!

In these pages, you will find updated information on the clinical evaluation of kidney function, fluids and electrolytes, acid-base disorders, hypertension, chronic tubulointerstitial nephritis, glomerular diseases, kidney manifestations of deposition diseases, genetic disorders and kidney disease, acute kidney injury, kidney stones, the kidney in pregnancy, and chronic kidney disease. All of these topics are uniquely focused on the needs of generalists and subspecialists *outside* of nephrology.

The core content of MKSAP 18 has been developed as in previous editions—all essential information that is newly researched and written in 11 topic areas of internal medicine—created by dozens of leading generalists and subspecialists and guided by certification and recertification requirements, emerging knowledge in the field, and user feedback. MKSAP 18 also contains 1200 all-new peer-reviewed, psychometrically validated, multiple-choice questions (MCQs) for self-assessment and study, including 108 in Nephrology. MKSAP 18 continues to include *High Value Care* (HVC) recommendations, based on the concept of balancing clinical benefit with costs and harms, with associated MCQs illustrating these principles and HVC Key Points called out in the text. Internists practicing in the hospital setting can easily find comprehensive *Hospitalist*-focused content and MCQs, specially designated in blue and with the H symbol.

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Sincerely,

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The learning objectives of MKSAP 18 are to:

- Close gaps between actual care in your practice and preferred standards of care, based on best evidence
- Diagnose disease states that are less common and sometimes overlooked and confusing
- Improve management of comorbid conditions that can complicate patient care
- Determine when to refer patients for surgery or care by subspecialists
- Pass the ABIM Certification Examination
- Pass the ABIM Maintenance of Certification Examination

Target Audience

- General internists and primary care physicians
- Subspecialists who need to remain up to date in internal medicine
- Residents preparing for the certifying examination in internal medicine
- Physicians preparing for maintenance of certification in internal medicine (recertification)

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Nephrology High Value Care Recommendations

The American College of Physicians, in collaboration with multiple other organizations, is engaged in a worldwide initiative to promote the practice of High Value Care (HVC). The goals of the HVC initiative are to improve health care outcomes by providing care of proven benefit and reducing costs by avoiding unnecessary and even harmful interventions. The initiative comprises several programs that integrate the important concept of health care value (balancing clinical benefit with costs and harms) for a given intervention into a broad range of educational materials to address the needs of trainees, practicing physicians, and patients.

HVC content has been integrated into MKSAP 18 in several important ways. MKSAP 18 includes HVC-identified key points in the text, HVC-focused multiple choice questions, and, for subscribers to MKSAP Digital, an HVC custom quiz. From the text and questions, we have generated the following list of HVC recommendations that meet the definition below of high value care and bring us closer to our goal of improving patient outcomes while conserving finite resources.

High Value Care Recommendation: A recommendation to choose diagnostic and management strategies for patients in specific clinical situations that balance clinical benefit with cost and harms with the goal of improving patient outcomes.

Below are the High Value Care Recommendations for the Nephrology section of MKSAP 18.

- The random (spot) urine protein-creatinine ratio and albumin-creatinine ratio are sufficiently accurate for screening and monitoring proteinuria.
- Urinalysis should not be used for detection of bladder cancer in asymptomatic patients.
- Ultrasonography is the most commonly used imaging modality in the evaluation of the kidneys and upper urinary tract because of its safety, cost effectiveness, and availability.
- Obtaining blood pressure measurements outside of the clinical setting for diagnostic confirmation is recommended before starting treatment.
- Non-dialytic palliative therapy is a reasonable option for elderly patients with end-stage kidney disease and multiple comorbidities, with treatment focusing on symptom management and quality of life.
- Use of the potassium exchange resin, sodium polystyrene sulfonate, is controversial; its effectiveness is limited, and it produces adverse gastrointestinal effects.
- Initial antihypertensive treatment for black patients with or without diabetes mellitus includes a thiazide diuretic or calcium channel blocker.
- Kidney biopsy is required to diagnose and classify lupus nephritis, which guides therapy.
- Kidney ultrasonography, rather than other imaging modalities, should be obtained for suspected urinary tract obstruction or when the underlying cause of acute kidney injury is unclear.
- Normal pregnancy is associated with decreased blood pressure, increased glomerular filtration rate with decreased serum creatinine, and increased proteinuria.
- In properly selected individuals, peritoneal dialysis allows patients to preserve their independence and offers outcomes similar to those seen with hemodialysis (see Item 19).
- Patients with newly diagnosed primary membranous glomerulopathy are observed for 6 to 12 months while on conservative therapy to allow time for possible spontaneous remission before initiating immunosuppression (see Item 38).
- Nonpharmacologic therapy alone is especially useful for prevention of hypertension, including in adults with elevated blood pressure, and for management of high blood pressure in adults with milder forms of hypertension (see Item 105).
- There is no benefit in starting renal replacement therapy (RRT) in asymptomatic patients or at an arbitrary estimated glomerular filtration rate cutoff compared with careful clinical management and initiating RRT for symptoms or metabolic abnormalities that are refractory to medical treatment (see Item 108).

Nephrology

Clinical Evaluation of Kidney Function

Assessment of Kidney Function

The kidney selectively removes waste while retaining needed substrate, maintains fluid and electrolyte homeostasis, and regulates blood pH. Glomerular filtration rate (GFR) measures total nephron filtration of blood and therefore correlates closely with toxin removal and overall kidney function. Early loss of kidney function is difficult to detect because nephron loss is not initially accompanied by GFR changes due to compensation through hypertrophy and hyperfiltration. Other markers of disordered glomerular filtration, such as proteinuria and hematuria, are also indicators of kidney disease that may precede any evidence of reduced filtration.

Biochemical Markers of Kidney Function

Although numerous methods for estimating kidney function are available (**Table 1**), serum creatinine and serum cystatin C are the primary biomarkers used to estimate GFR.

Serum Creatinine

Serum creatinine is the most extensively used measure of kidney function. Creatinine is freely filtered by the glomerulus, without metabolism or reabsorption. Therefore, changes in serum creatinine primarily reflect changes in GFR. However, the relationship of serum creatinine to GFR is nonlinear; significant losses in kidney function at higher GFR may be masked by only small changes in serum creatinine, and small filtration changes at lower GFR are associated with large changes in serum creatinine (**Figure 1**). Creatinine is also secreted into urine by the proximal tubule, and the contribution of secretion to total creatinine excretion increases as GFR declines. Therefore, when measured creatinine clearance is used to estimate GFR, secreted creatinine will contribute to overestimation of true GFR. With complete loss of kidney function (anuria), serum creatinine typically increases by about 1.0 mg/dL (88.4 µmol/L) per day in patients with average muscle mass.

Creatinine is a metabolite of creatine, which is mostly present in skeletal muscle. Persons with higher muscle mass (such as younger people, men, and black persons) have a higher serum creatinine compared with less muscular persons with the same GFR. Loss of muscle mass seen with aging, muscle wasting, malnutrition, or amputation will result in lower serum creatinine despite stable GFR. In persons with decreased muscle mass, serum creatinine therefore tends to overestimate the GFR.

Some medications reduce proximal tubule secretion of creatinine. Such drugs include cimetidine, trimethoprim, cobicistat, and dolutegravir. Resulting increases in serum creatinine occur despite stable GFR. Reassessment of the serum creatinine level 1 week after identification of the increase will confirm the drug's effect.

Serum Cystatin C

Cystatin C is produced by all nucleated cells, freely filtered by glomeruli, and catabolized by tubules. Compared with serum creatinine, serum cystatin C levels are less affected by age, sex, or muscle mass but may be increased by acute disease (such as malignancy, inflammation, or HIV infection). Changes in serum cystatin C may identify small decreases in kidney function better than serum creatinine. Formulas using cystatin C to estimate GFR are helpful for patients in whom creatinine-based GFR may be inaccurate.

Blood Urea Nitrogen

Blood urea nitrogen (BUN) is a product of protein metabolism. Levels increase with reduced GFR and with increased urea reabsorption caused by renal hypoperfusion. BUN is also affected by protein intake and by changes in catabolic rate as caused by glucocorticoids, starvation, or stress. Persons with liver disease have abnormally low levels. BUN may be useful in detecting renal hypoperfusion because elevation of BUN from increased reabsorption is disproportionate to the rise in serum creatinine level.

Estimation of Glomerular Filtration Rate

Creatinine-based formulas are used to estimate GFR by adjusting for factors that affect serum creatinine and creatinine clearance. These formulas take into account the effects of age, race, sex, and muscle mass (estimated by weight) on serum creatinine levels (see Table 1).

The Chronic Kidney Disease Epidemiology (CKD-EPI) Collaboration creatinine equation is the most widely used method for estimating GFR and is the most accurate equation for most persons, particularly when GFR >60 mL/min/1.73 m^2. A newer CKD-EPI creatinine-cystatin C equation is the most accurate when serum cystatin creatinine-cystatin C is known. CKD-EPI equations presume standard body surface area and therefore require adjustment for very large or small persons.

The Modification of Diet in Renal Disease (MDRD) study equation does not accurately estimate high GFRs. It performs similarly to the CKD-EPI equation at GFRs

TABLE 1. Methods for Estimating Kidney Function

Method	Applications	Considerations
Serum Creatinine		
	Most frequently used assessment of kidney function	Nonlinear relationship with GFR Nonkidney effects on blood levels (muscle mass, drugs affecting secretion)
Serum Cystatin C		
	More accurate in elderly population and patients with cirrhosis due to their low muscle mass More accurate in those with an increase in muscle mass Sensitive to mild changes in GFR	Levels are affected by diabetes mellitus, thyroid disease, inflammation, glucocorticoid use, malignancy, HIV infection
Chronic Kidney Disease Epidemiology (CKD-EPI) Collaboration Equation[a]		
CKD-EPI Creatinine		
Variables include serum creatinine, age, race, and gender: $eGFR = 141 \times \min(S_{Cr}/\kappa, 1)^{\alpha}$ $\times \max(S_{Cr}/\kappa, 1)^{-1.209}$ $\times 0.993^{Age}$ $\times 1.018$ [if female] $\times 1.159$ [if black]	More accurate than MDRD and CGE equations in elderly population and in those with eGFR >60 mL/min/1.73 m^2	Preferred formula for calculating creatinine-based eGFR
CKD-EPI Cystatin C		
Variables include serum cystatin C, age, and gender: $eGFR = 133 \times \min(S_{Cr}/\kappa, 1)^{-0.499}$ $\times \max(S_{Cr}/\kappa, 1)^{-1.328}$ $\times 0.996^{Age}$ $\times 0.932$ [if female]	Can be used as confirmatory test for CKD. May be more accurate than creatinine-based equation in those with muscle wasting, chronic illness, or high muscle mass.	Helpful in estimating GFR in those taking drugs that affect creatinine secretion (such as cobicistat, dolutegravir, bictegravir, trimethoprim, and cimetidine)
CKD-EPI Creatinine-Cystatin C		
Equation uses same variables as CKD-EPI creatinine but different exponents and includes serum cystatin C: $eGFR = 135 \times \min(S_{Cr}/\kappa, 1)^{\alpha}$ $\times \max(S_{Cr}/\kappa, 1)^{-0.601}$ $\times \min(S_{Cys}/0.8, 1)^{-0.375}$ $\times \max(S_{Cys}/0.8, 1)^{-0.711}$ $\times 0.995^{Age}$ $\times 0.969$ [if female] $\times 1.08$ [if black]	Creatinine-cystatin C combination provides most accurate eGFR in most patient populations	—
Modification of Diet in Renal Disease (MDRD) Study Equation[a]		
Variables include serum creatinine, age, race, and gender: $eGFR = 175 \times (S_{Cr})^{-1.154}$ $\times (age)^{-0.203}$ $\times 0.742$ [if female] $\times 1.212$ [if black]	Similar accuracy as CKD-EPI when eGFR is 15-60 mL/min/1.73 m^2	Most accurate (but similar to CKD-EPI) when eGFR is 15-60 mL/min/1.73 m^2 Underestimates GFR when GFR >60 mL/min/1.73 m^2

(Continued on the next page)

TABLE 1. Methods for Estimating Kidney Function *(Continued)*

Method	Applications	Considerations
Creatinine Clearance (CrCl)		
$U_{Cr}V/S_{Cr} = U_{Cr}$ (mg/dL) × 24-hour urine volume (mL/24 h)/S_{Cr} (mg/dL) × 1440 (min/24 h)	Useful in pregnancy, extremes of age and weight, amputees, malnourished and cirrhotic patients (situations where creatinine is low so CKD-EPI and MDRD will overestimate GFR)	Overestimates GFR 10%-20% Overestimation worsens with lower GFR (due to increased ratio of creatinine secretion to filtration) Over- or undercollection limits accuracy
Cockcroft-Gault Equation (CGE)		
Variables include serum creatinine, body weight, age, and gender: CrCl = (140 − age) × (weight in kg) × (0.85 if female)/(72 × S_{Cr})	Improved accuracy when age is <65 years	Most accurate when eGFR is 15-60 mL/min/1.73 m² Underestimates GFR in obesity Overestimates GFR when BMI <25
Radionuclide Kidney Clearance Scanning		
Iothalamate GFR scan or diethylenetriamine pentaacetic acid (DTPA) GFR scan	Useful in kidney donor evaluation if eGFR is borderline for donation or other times when accurate prediction is essential	Most precise method; expensive

CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; GFR = glomerular filtration rate; S_{Cr} = serum creatinine (mg/dL); S_{Cys} = serum cystatin C (mg/L); U_{Cr} = urine creatinine (mg/dL).

$\alpha = -0.329$ for females, −0.411 for males; $\kappa = 0.7$ for females, 0.9 for males; min = minimum of S_{Cr}/κ or 1; max = maximum of S_{Cr}/κ or 1.

[a]Mathematical equations recommended by the National Kidney Foundation Kidney Disease Outcomes Quality Initiative for estimation of GFR.

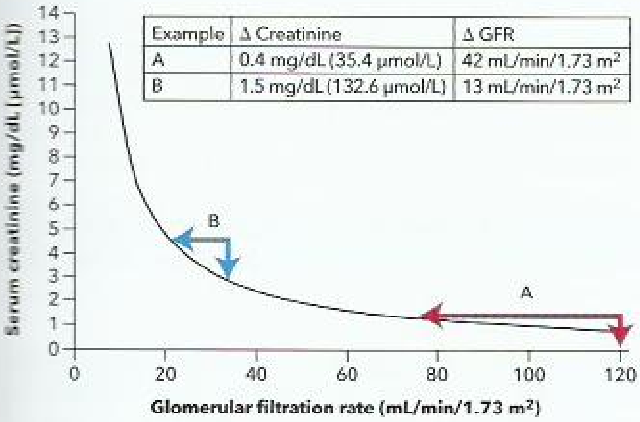


FIGURE 1. The relationship between serum creatinine and glomerular filtration rate (GFR). Example A illustrates that a small increase in the serum creatinine level in the reference range (in this case, 0.8 to 1.2 mg/dL [70.7-106.1 μmol/L]) reflects a relatively large change in GFR (120 to 78 mL/min/1.73 m²). Example B illustrates that a relatively greater increase in the serum creatinine level (in the high range of 3.0 to 4.5 mg/dL [265.2-398 μmol/L]) reflects a proportionately smaller change in GFR (35 to 22 mL/min/1.73 m²).

<60 mL/min/1.73 m². Clinical laboratories that use the MDRD do not report GFRs >60 mL/min/1.73 m²; therefore, physicians may not be aware of the presence of kidney disease. However, an increasing serum creatinine level, proteinuria, or other urine abnormalities should alert the clinician to the presence of kidney disease despite high GFR. The MDRD study equation also requires adjustment for large or small body surface area.

The Cockcroft-Gault equation (CGE) is the least accurate method. It remains in use for drug dosing because it was used in pharmacokinetic studies for most medications.

Creatinine clearance obtained by using 24 hour urine collection is a better measure of GFR than serum creatinine, but it is not recommended for routine estimation of GFR because it is affected by the accuracy of collection and by creatinine secretion.

Radionuclide imaging provides the most accurate measurement of GFR and is the gold standard in research. It is useful for accurate determination of GFR during evaluation of kidney donors, evaluation of recipients for other organs, or assessment of the differential GFR of each kidney before nephrectomy.

KEY POINTS

- Serum creatinine changes nonlinearly with glomerular filtration rate (GFR), and significant losses in kidney function at higher GFR may cause only small changes in serum creatinine.
- The Chronic Kidney Disease Epidemiology (CKD-EPI) Collaboration equation is the most widely used equation to estimate glomerular filtration rate (GFR); it is the most accurate equation for most persons, particularly in the elderly and those with a GFR >60 mL/min/1.73 m².

Interpretation of the Urinalysis

Urine dipstick and urine microscopy are indicated in the evaluation of both acute and chronic kidney disease (**Table 2**). Analysis is best performed on a fresh specimen within 30 to 60 minutes of voiding. Midstream collection is preferred with a clean catch in women and uncircumcised men.

Urine Dipstick

See Table 2 for details on urine dipstick.

Specific Gravity

Specific gravity measures hydration status and reflects the kidney's ability to concentrate urine.

pH

Low urine pH may occur in persons eating high-protein diets. High alkaline pH ≥7.0 can occur in strict vegetarians and in persons with infections caused by urea-splitting organisms. Urine pH may be inappropriately high in some forms of renal tubular acidosis (type 1 distal) but may be appropriately low in others (type 4 distal).

TABLE 2. Findings on Urinalysis

	Normal Range	Comments
Dipstick		
Specific gravity	1.005-1.030	Low: dilute urine from excess hydration; impaired urine concentration (diabetes insipidus; sickle cell nephropathy; acute tubular injury) High: volume depletion; renal hypoperfusion; excretion of hypertonic solute (glycosuria; contrast dye)
pH	5.0-6.5	Low/acidic: high protein diets; increases risk for uric acid and cystine calculi; type 4 distal RTA; some type 2 proximal RTA High/alkaline: urease-splitting organisms (most commonly *Proteus* species; other potential organisms include *Escherichia coli* and *Pseudomonas*, *Klebsiella*, and some staphylococcal species); low acid ingestion; type 1 distal RTA; some type 2 RTA; increases risk for struvite and calcium phosphate calculi
Blood/heme pigments	None	Positive: hemoglobin or myoglobin; absence of erythrocytes suggests myoglobinuria or intravascular hemolysis False positive: alkaline urine (pH >9)
Protein	None to trace	Dipsticks primarily detect albumin; concentration dependent (trace positive can be normal in a concentrated specimen); not sufficiently sensitive to detect moderately increased albuminuria Graded as trace (10-30 mg/dL), 1+ (30 mg/dL), 2+ (100 mg/dL), 3+ (300 mg/dL), 4+ (>1000 mg/dL)
Glucose	None	Positive: plasma glucose exceeds ~180 mg/dL (10.0 mmol/L); proximal tubule defect (Fanconi syndrome); pregnancy (lower excretion threshold)
Ketones	None	Detects acetone and acetoacetic acid, not β-hydroxybutyrate Positive: diabetic ketoacidosis; starvation; vomiting; pregnancy
Leukocyte esterase	None	Enzyme found in leukocytes; indicates pyuria (possibly from UTI); positive test requires ≥5 leukocytes/hpf
Nitrites	None	Produced by bacteria from nitrates Positive: suggests UTI Negative: does not rule out UTI (specific but not sensitive)
Microscopic		
Erythrocytes	0-2/hpf	Urine microscopy should be performed to evaluate erythrocyte morphology
Leukocytes	0-4/hpf	The presence of any leukocytes may be abnormal depending on clinical circumstances
Squamous epithelial cells	<15/hpf	Increased epithelial cells indicates contamination
Casts	None or hyaline	Hyaline casts: indicative of poor kidney perfusion Granular casts: acute tubular injury Erythrocyte casts: glomerular bleeding/glomerulonephritis Leukocyte casts: infection; acute interstitial nephritis
Crystals (see Table 3)	None	Most common are calcium oxalate, calcium phosphate, uric acid, and struvite

RTA = renal tubular acidosis; UTI = urinary tract infection.

Blood

Dipsticks detect peroxidase activity of blood and free heme pigments (hemoglobin and myoglobin). Three or more erythrocytes result in a positive test (1+ blood). A positive test in the absence of erythrocytes in the urine sediment may indicate myoglobinuria (due to rhabdomyolysis) or hemoglobinuria (due to intravascular hemolysis, transfusion, or shear stress related to mechanical heart valve and perivalvular leak). False-positive tests may occur with other substances with peroxidase activity, including peroxidase-expressing bacteria and drugs such as rifampin or chloroquine. Ascorbic acid can cause a false-negative result. Medications (rifampin, phenytoin) or food (beets) can cause red-colored urine that is heme negative.

Protein

Although various proteins may be present in urine, the dipstick preferentially detects albumin. Because dipsticks are dependent on urine concentration, false negatives may result from dilute urine and false positives from highly concentrated urine. Because moderately increased albuminuria (microalbuminuria) may go undetected by dipstick, direct quantification of albuminuria and/or proteinuria using a random (spot) protein-creatinine ratio or albumin-creatinine ratio or a 24-hour urine collection is required in high-risk patients. False-positive tests can occur with highly alkaline urine specimens.

Glucose

Glucosuria typically occurs when plasma glucose exceeds 180 mg/dL (10.0 mmol/L). Glucosuria in the absence of hyperglycemia suggests proximal tubular dysfunction, as seen with myeloma or exposure to drugs (including tenofovir disoproxil fumarate and sodium-glucose cotransporter-2 inhibitors such as empagliflozin and canagliflozin). Glucosuria may be present in normal pregnancy due to changes in tubular threshold for glucose reabsorption.

Ketones

Ketonuria is most commonly seen in starvation, diabetic ketoacidosis, and alcoholic ketoacidosis. Urine ketones are also seen in salicylate toxicity and isopropyl alcohol poisoning. Urine dipstick detects acetone and acetoacetate but not β-hydroxybutyrate; therefore, in diabetic ketoacidosis and alcoholic ketoacidosis where β-hydroxybutyrate is the primary ketone, the dipstick underestimates ketone excretion. False-positive tests may occur with drugs containing sulfhydryl groups, such as captopril.

Leukocyte Esterase and Nitrites

Leukocyte esterase is an enzyme present in leukocytes. A positive test suggests pyuria (≥5 leukocytes/hpf).

A positive nitrite test signifies the presence of gram-negative bacteria (*Escherichia coli*; *Klebsiella*, *Enterobacter*, *Citrobacter*, and *Proteus* species) capable of converting urine nitrates into nitrites. The test is falsely negative if there is inadequate contact time for urine nitrates with the bacteria. The nitrite test is negative in urinary tract infection (UTI) caused by nonconverting organisms (*Enterococcus*, *Staphylococcus*, *Streptococcus*, or *Haemophilus* species).

The presence of both leukocyte esterase and nitrites on urine dipstick is highly predictive of a UTI; conversely, the absence of both has a high negative predictive value for a UTI.

Bilirubin

Bilirubin should be absent from the urine when serum levels are normal. Conjugated, water-soluble bilirubin is excreted in the urine in severe liver disease or obstructive hepatobiliary disease.

Urobilinogen

Gut bacteria produce urobilinogen through metabolism of bilirubin. Urobilinogen is then absorbed via portal circulation and excreted in urine. Increased urobilinogen is associated with hemolytic anemia or parenchymal liver disease. Decreased levels are seen with severe cholestasis and obstructive disease.

KEY POINTS

- Because moderately increased albuminuria (microalbuminuria) may go undetected by dipstick, direct quantification using a random (spot) protein-creatinine ratio or albumin-creatinine ratio or a 24-hour urine collection is required in high-risk patients.
- The urine nitrite test is negative in urinary tract infections caused by nonconverting organisms (*Enterococcus*, *Staphylococcus*, *Streptococcus*, or *Haemophilus* species).
- The presence of both leukocyte esterase and nitrites on urine dipstick is highly predictive of a urinary tract infection (UTI); conversely, the absence of both has a high negative predictive value for a UTI. HVC

Urine Microscopy

Microscopic assessment of urine sediment (**Figure 2**) is indicated for patients with abnormalities on dipstick and in those with acute kidney injury, newly diagnosed chronic kidney disease, or suspected glomerulonephritis. See Table 2 for details on urine microscopy.

Erythrocytes

Erythrocyte morphology may indicate their origin (see Figure 2). Isomorphic erythrocytes (round and of consistent size) suggest a nonglomerular origin as a result of infection, mass, cyst, or stone. Glomerular bleeding may be associated with erythrocyte fragmentation, leading to dysmorphic appearances with significant variability. Acanthocytes, a form of dysmorphic erythrocytes characterized by vesicle-shaped protrusions, are most suggestive of a glomerular source of bleeding and should result in prompt

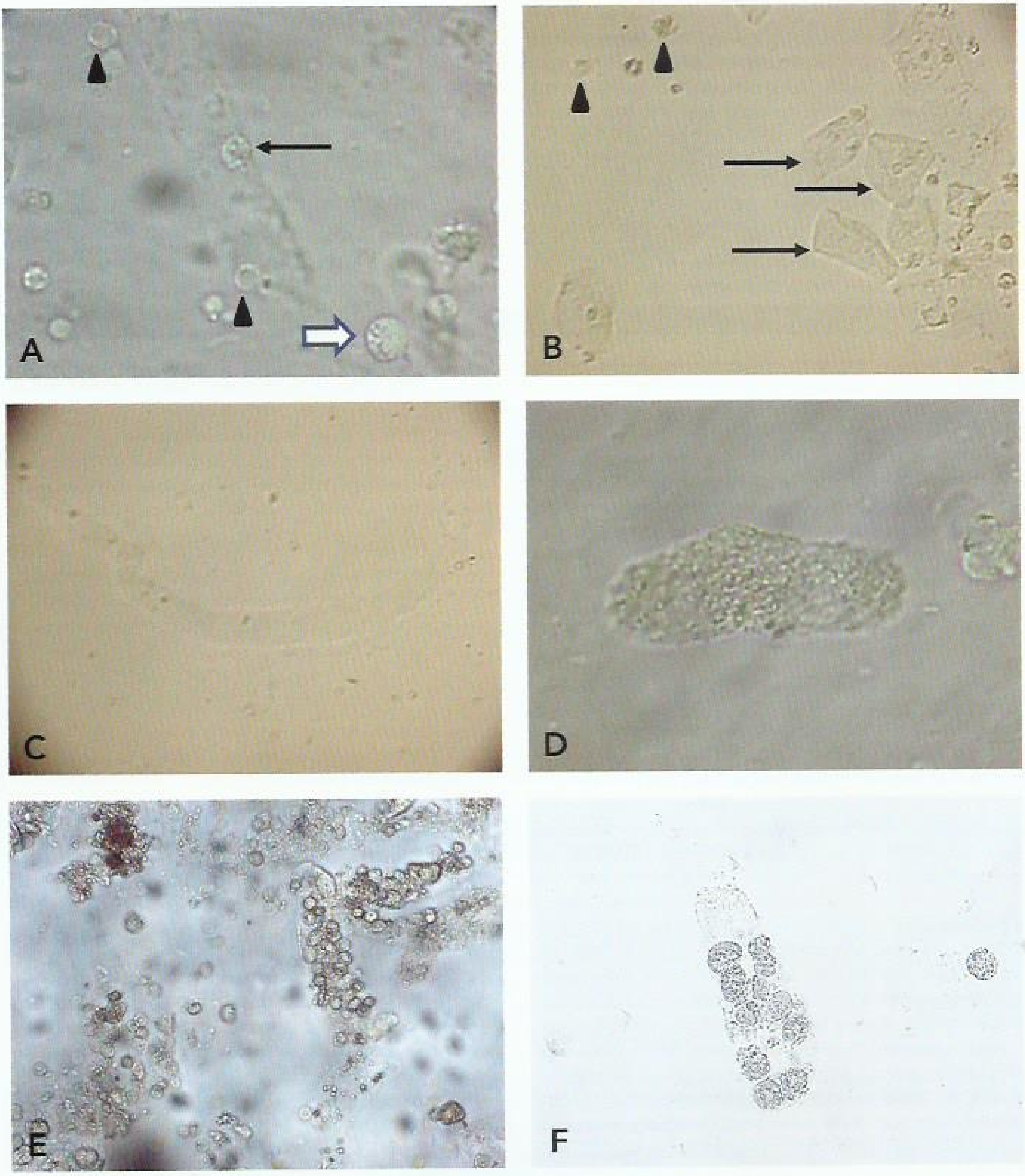


FIGURE 2. Findings on urine microscopy. **A**, Erythrocytes (*black arrowheads*). Also shown is a leukocyte (*black arrow*) embedded in a cast, as well as a tubular cell (*white arrow*). **B**, Leukocytes (*black arrowheads*): Note the large relative size of squamous epithelial cells (*black arrows*). **C**, Hyaline cast. **D**, Granular cast. **E**, Erythrocyte cast. **F**, Leukocyte cast.

evaluation for glomerulonephritis (**Figure 3**). See Clinical Evaluation of Hematuria for more information.

Leukocytes

The presence of ≥5 leukocytes in the urine sediment indicates pyuria, which is most commonly caused by a UTI. Sterile pyuria is the presence of urine leukocytes in the setting of negative urine culture; common causes include vaginitis and cervicitis in women, prostatitis in men, acute interstitial nephritis (AIN), kidney stones, kidney transplant rejection, and, less commonly, UTIs due to organisms that do not grow by standard culture techniques (*Chlamydia* species, *Mycobacterium tuberculosis*, *Ureaplasma urealyticum*). The absence of leukocytes does not rule out AIN.

Eosinophils

Urine eosinophils suggest interstitial nephritis, atheroembolic disease, glomerulonephritis, small-vessel vasculitis, UTI, prostatic disease, or parasitic infections. Poor sensitivity and specificity limit the utility of urine eosinophils in the diagnosis of interstitial nephritis.

Epithelial Cells

Renal tubular, transitional, and squamous epithelial cells may be seen on urinalysis (see Figure 2). Renal tubular epithelial cells are round with central nuclei and are 1.5 to 3 times larger than leukocytes. Their presence in the context of granular casts suggests acute tubular necrosis. Transitional epithelial cells are slightly larger than renal tubular epithelial cells and may be binucleate; they originate anywhere from the renal pelvis to the proximal urethra. Squamous epithelial cells are the largest epithelial cells, and are flat and irregular with small central nuclei; they are derived from the distal urethra or external genitalia, and their presence in large numbers (>15/hpf) denotes contamination by genital secretions.

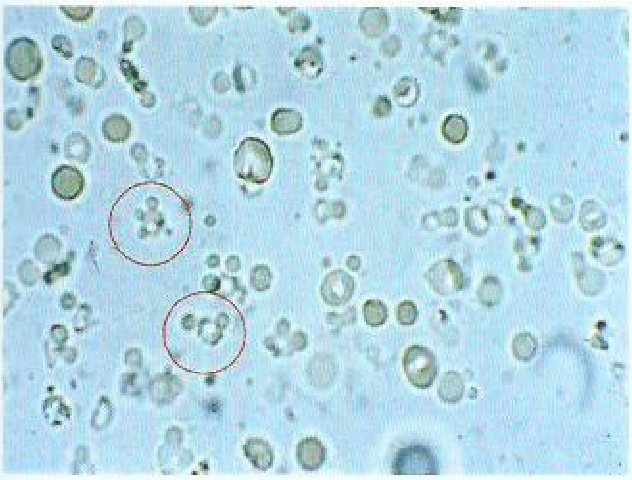


FIGURE 3. Urine microscopy demonstrating acanthocytes, indicated in the red circles. Acanthocytes, a form of dysmorphic erythrocytes characterized by vesicle-shaped protrusions, are most suggestive of glomerular bleeding.

Courtesy of J. Charles Jennette, MD.

Casts

The backbone of all urine casts is a matrix composed of Tamm-Horsfall protein (uromodulin). These cylindrical casts form in the distal tubular lumen. Any cells or debris in casts were present in the tubule at the time of cast formation, therefore originating from a more proximal part of the nephron. Erythrocyte casts are highly suggestive of glomerulonephritis. Leukocyte casts may be present in AIN and infections (pyelonephritis). Pigmented or granular (muddy brown) casts contain tubular cell debris (**Figure 4**) and are present in acute tubular necrosis. The severity of acute kidney injury correlates with the number of casts and presence of renal tubular epithelial cells.

Crystals

Crystalluria results from the supersaturation of solutes in concentrated urine. These solutes are derived from metabolic disorders, inherited diseases, or drugs. **Table 3** describes features of common crystals. Certain drugs can crystallize in concentrated urine and when used in high doses, including sulfadiazine, sulfamethoxazole, intravenous acyclovir, methotrexate, and atazanavir.

KEY POINTS

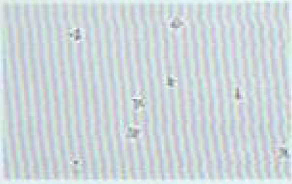
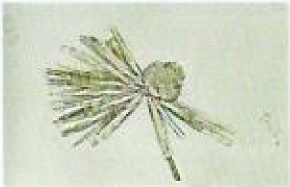
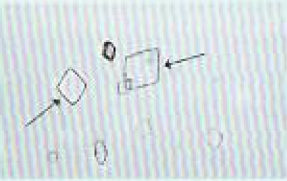
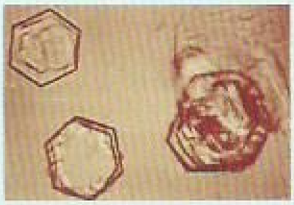
- Isomorphic erythrocytes suggest a nonglomerular origin of blood; dysmorphic erythrocytes, particularly acanthocytes, suggest a glomerular origin.
- Erythrocyte casts are highly suggestive of glomerulonephritis, leukocyte casts may be present in acute interstitial nephritis and infections, and granular (muddy brown) casts are present in acute tubular necrosis.

Measurement of Albumin and Protein Excretion

Assessment for urine protein is indicated in patients with any suspected kidney disease. Concurrent increased serum creatinine or abnormal findings on urine sediment raise concern for active kidney disease in any patient with proteinuria.

FIGURE 4. Tubular injury (for example, acute tubular necrosis) may lead to deposition of pigmented epithelial tubular debris in the proteinaceous matrix of the cast, with the formation of pigmented or granular (muddy brown) casts.

TABLE 3. Urine Crystals

Type	Morphology	Associated Conditions	Image
Calcium oxalate	Envelope; dumbbell; needle	Hypercalciuria; hyperoxaluria; ethylene glycol poisoning	
Calcium phosphate	Prism; needle; star-like clumps	Distal renal tubular acidosis; urine pH >6.5; tumor lysis syndrome; acute phosphate nephropathy	
Uric acid	Rhomboid; needle; rosette; barrels; hexagonal plates	Hyperuricemia; gout; diabetes mellitus; obesity; tumor lysis syndrome; urine pH <6.0	
Struvite (magnesium ammonium phosphate)	Coffin-lid	Alkaline urine due to chronic urinary tract infection with urease-producing organisms	
Cystine	Hexagonal	Cystinuria	

Assays to detect protein in the urine include urine dipstick, random (spot) urine protein-creatinine ratio or albumin-creatinine ratio, and 24-hour urine collections. Due to the challenges of 24-hour urine collections, the random urine albumin-creatinine ratio and protein-creatinine ratio have been widely adopted. Both random tests adequately determine the presence of albuminuria, but the urine protein-creatinine ratio also detects nonalbumin proteins. Random collections correlate well with timed collections and are sufficiently accurate for screening and monitoring proteinuria despite inaccuracies due to diurnal fluctuations of urine protein and interindividual differences in urine creatinine excretion. **Table 4** outlines the definitions of proteinuria and albuminuria as well as normal values.

Urine albumin, when present at high levels, indicates glomerular injury; conversely, the absence of albuminuria essentially excludes most glomerular diseases. Smaller proteins are filtered at the level of the glomerulus but are reabsorbed by the proximal tubule; their presence in urine generally indicates tubulointerstitial disease. Light chains present at high levels, such as in monoclonal gammopathy, are detected on urine protein electrophoresis or free light chain assay.

Transient, nonpathologic, usually small elevations in urine protein can occur with acute illness or fever, rigorous exercise, and pregnancy. Orthostatic proteinuria is a benign proteinuria that increases when the patient is upright but decreases when the patient is recumbent. This condition is more common in adolescents but should be considered in those up to age 30 years. Split urine collection (daytime versus nighttime collection that includes first morning void) can evaluate this diagnosis.

ACP recommends against screening for chronic kidney disease, including screening for proteinuria in asymptomatic adults without risk factors for chronic kidney disease, because there is no evidence of benefit from early treatment to outweigh the harms of screening, including false-positive results and unnecessary testing and treatment. However, screening

TABLE 4. Definitions of Proteinuria and Albuminuria

Total Urine Protein			
Urine Collection Method	**Normal**	**Clinical Proteinuria**	
24-Hour Excretion	<150 mg/24 h	≥150 mg/24 h	
Spot Urine Protein-Creatinine Ratio[a]	≤150 mg/g ≈ ≤150 mg/24 h	>150 mg/g ≈ >150 mg/24 h	
Urine Albumin			
Urine Collection Method	**Normal[b]**	**Moderately Increased Albuminuria (Microalbuminuria)[b,c]**	**Severely Increased Albuminuria (Macroalbuminuria)[b,c]**
24-Hour Excretion	<30 mg/24 h	30-300 mg/24 h	>300 mg/24 h
Conventional Spot Urine Dipstick[d]	Negative	Negative	Positive
Albumin-Specific Spot Urine Dipstick[e]	<3.0 mg/dL Negative	≥3.0 mg/dL Positive	Positive
Spot Urine Albumin-Creatinine Ratio[a]	<30 mg/g ≈ <30 mg/24 h	30-300 mg/g = 30-300 mg/24 h	>300 mg/g = >300 mg/24 h

[a]Because of the difficulty of obtaining a 24-hour urine collection, urine protein-creatinine ratio or urine albumin-creatinine ratio on random (spot) urine samples is used to estimate 24-hour excretion. Measurement of either urine protein or albumin concentration in a sample is divided by the creatinine concentration of the same sample to derive a unitless value. These ratios correlate well with the 24-hour excretion of protein or albumin. Although these calculations are technically dimensionless, they may be expressed by different laboratories with their units of calculation, such as mg/g (mg protein or albumin/g creatinine) or with units to reflect the proportional 24-hour excretion amount (mg or g protein or albumin/g creatinine).

[b]Chronic kidney disease classification categories A1, A2, and A3 correspond to normal (or mildly increased), moderately increased, and severely increased albuminuria, respectively.

[c]The newer terminology of "moderately increased albuminuria" and "severely increased albuminuria" has been adopted due to the finding that even relatively low levels of urine protein have been associated with significant cardiovascular risk and risk of progression of underlying kidney disease.

[d]Conventional urine dipsticks are more sensitive for detection of albumin than non-albumin proteins; the detection limit is approximately 30 mg/dL, although they are not highly accurate for determining the degree of albuminuria if present.

[e]Urine dipsticks designed specifically to detect small amounts of albuminuria. Similar to conventional urine dipsticks, these dipsticks detect albumin above a concentration threshold but are sensitive to the presence of albumin at lower levels and can be used to indicate the presence of moderately increased albuminuria.

for proteinuria may be considered in high-risk patients, such as hypertensive, diabetic, and older patients.

In patients with diabetes mellitus, urine albumin screening is recommended due to its ability to detect early disease. The American Diabetes Association recommends yearly assessment in patients with type 2 diabetes, and assessment after 5 years of disease in patients with type 1 diabetes. Because there is no evidence that monitoring proteinuria levels in patients taking ACE inhibitors or angiotensin receptor blockers is beneficial or that reduced proteinuria levels translate into improved outcomes, ACP recommends against testing for proteinuria in adults with or without diabetes who are currently taking an ACE inhibitor or an angiotensin receptor blocker.

Urine protein electrophoresis can characterize proteins, allowing for classification of the proteinuria as glomerular or tubular. It also detects monoclonal gammopathy, although it is less sensitive than light chain assay.

KEY POINTS

HVC
- The random (spot) urine protein-creatinine ratio and albumin-creatinine ratio correlate with 24-hour urine collections and are sufficiently accurate for screening and monitoring proteinuria.
- High urine albumin levels indicate glomerular injury; the absence of albuminuria excludes most glomerular diseases.

Clinical Evaluation of Hematuria

Hematuria is defined as the presence of ≥3 erythrocytes/hpf in the urine sediment and may be microscopic (detectable only on urine testing) or macroscopic (grossly visible). Hematuria is most often of nonglomerular origin. A glomerular origin is suggested by concurrent proteinuria, presence of dysmorphic erythrocytes, increased serum creatinine or decrease in estimated GFR (eGFR), or systemic signs and symptoms. Evaluation of hematuria is outlined in **Figure 5**.

Urinalysis should not be used for cancer screening in asymptomatic adults. However, a single incidental finding of hematuria is sufficient to warrant further investigation. Evaluation should be pursued even in patients with bleeding diatheses or those taking antiplatelet or anticoagulation therapy. If menstruation, viral illness, vigorous exercise, or some other benign cause is suspected, urinalysis should be repeated after the cause is resolved. If infection is confirmed, urinalysis should be repeated after treatment to document resolution of hematuria.

In a patient with asymptomatic microscopic hematuria, it is important to assess kidney function, erythrocyte morphology, and urine protein to evaluate for a nephrologic cause, particularly glomerulonephritis. The absence of proteinuria generally rules out a glomerular process; exceptions include very mild glomerular disease (most often IgA nephropathy) or thin glomerular basement membrane disease related to a type

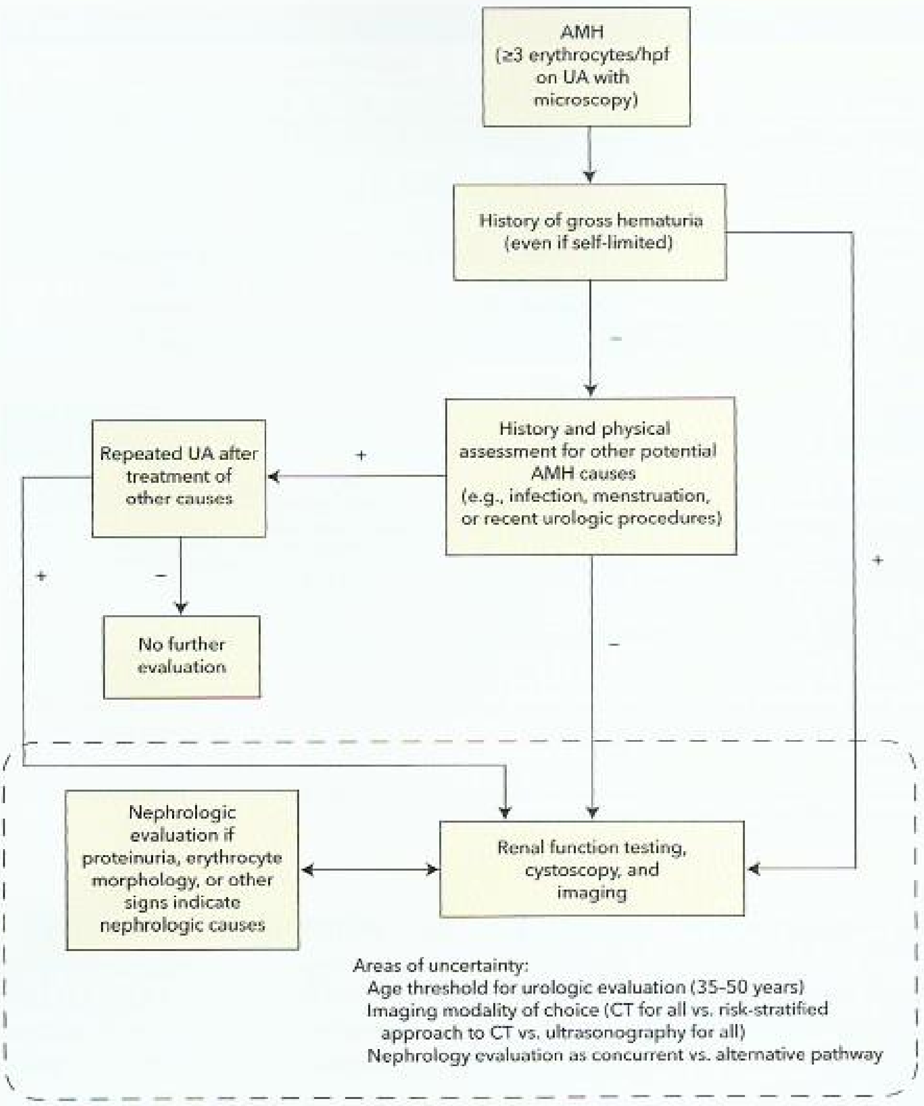


FIGURE 5. Summary of the American College of Physicians recommendations for the evaluation of patients with hematuria.
AMH = asymptomatic microscopic hematuria;
UA = urinalysis.

Reprinted with permission from Nielsen M, Qaseem A; High Value Care Task Force of the American College of Physicians. Hematuria as a marker of occult urinary tract cancer: advice for high-value care from the American College of Physicians. Ann Intern Med. 2016;164:488-97. [PMID: 26810935] Copyright 2016, American College of Physicians.

IV collagen defect that may present as isolated hematuria. Systemic signs and symptoms raise suspicion for nephrologic disease, particularly those associated with rheumatologic disorders and rapidly progressive glomerulonephritis.

Macroscopic hematuria should prompt urology referral even if self-limited, with further evaluation of nephrologic disease and malignancy as indicated.

H If a nephrologic cause of hematuria is not suggested, hematuria may indicate a malignancy. The American Urological Association (AUA) guidelines recommend that patients older than 35 years or those with risk factors for malignancy undergo evaluation for malignancy. Although CT urography (contrast CT with kidney-specific imaging) has the highest sensitivity and specificity for renal malignancy, noncontrast helical CT is more appropriate if a kidney stone is suspected. Ultrasonography is a reasonable first imaging step because of availability, lower cost, and no ionizing radiation. MRI with contrast is useful when CT contrast studies cannot be performed. Cystoscopy is indicated when imaging is negative. ACP and the AUA recommend against obtaining urine cytology in the initial evaluation of hematuria. H

KEY POINTS

- Urinalysis should not be used for detection of bladder cancer in asymptomatic patients. HVC
- Hematuria requires thorough evaluation because of potentially life-threatening causes, such as rapidly progressive glomerulonephritis and urinary tract malignancy.
- Evaluation of nonglomerular hematuria in patients older than 35 years or those with risk factors for urologic malignancy includes CT urography unless contraindicated; if imaging is negative, cystoscopy should be performed.

Imaging Studies

Ultrasonography is the most commonly used kidney imaging modality. It is easily available, safe, and relatively inexpensive. Ultrasonography can demonstrate hydronephrosis, kidney

size and cortical thickness, echogenicity, and presence of cysts and tumors. Absence of hydronephrosis quickly rules out obstruction in most cases. Echogenicity is the ability of a tissue to "bounce back" or return the ultrasound signal and is recognized as brighter shades on the sonogram image. Echogenicity is nonspecific but implies acute or chronic parenchymal disease. Additionally, ultrasonography can measure pre- and postvoid bladder residual, for evaluation of bladder dysfunction or outlet obstruction. Ultrasonography is also useful for uncomplicated nephrolithiasis; a positive ultrasound may be adequate for initial diagnosis. Ultrasonography is less useful in evaluating diseases (including stones) of the mid or distal ureter. Doppler ultrasonography may detect renal artery stenosis or renal vein thrombosis, but is highly user dependent.

CT is appropriate for patients with a nondiagnostic ultrasound or a more complicated presentation. Noncontrast helical CT is the gold standard for diagnosis of nephrolithiasis, and is appropriate for evaluating renal colic. Most stones can be detected, including small stones and those in the distal ureter not detected on ultrasound. It may provide information regarding stone composition and, because the entire urinary tract and abdomen is visualized, alternative diagnoses may be suggested.

CT urography (contrast-enhanced kidney-specific CT) is the test of choice for patients with unexplained hematuria and allows characterization of renal tumors and cysts. CT with contrast is valuable for imaging the renal vasculature. The use of contrast confers risk for contrast-induced nephropathy, particularly in patients with an eGFR <50 mL/min/1.73 m^2.

MRI with contrast is an alternative for evaluation of renal masses and cysts when CT cannot be performed. MR angiography for detection of renal artery stenosis, and venography for detection of renal vein thrombosis, can be performed with or without gadolinium-based contrast, although contrast provides optimal imaging. MR angiography and CT angiography have mostly replaced standard angiography of renal arteries. Due to concerns for nephrogenic systemic fibrosis (NSF), gadolinium contrast must be avoided in patients with an eGFR <30 mL/min/1.73 m^2. In life-threatening situations in which benefit outweighs the risk for NSF, MRI is performed with low doses of stable gadolinium agents. See MKSAP 18 Dermatology for more information on NSF.

Radionuclide imaging provides the most accurate measurement of GFR and is the gold standard in research (see Estimation of Glomerular Filtration Rate).

KEY POINTS

HVC
- Ultrasonography is the most commonly used imaging modality in the evaluation of the kidneys and upper urinary tract because of its safety, cost effectiveness, and availability.
- CT urography is the test of choice for patients with unexplained hematuria and allows characterization of renal tumors and cysts; noncontrast helical CT is the gold standard for diagnosis of nephrolithiasis, and CT with contrast is valuable in imaging the renal vasculature.

Kidney Biopsy

H

Clinical and laboratory features are often insufficient for definitive diagnosis of kidney disease. Kidney biopsy may therefore be essential for diagnosis and management. Indications include glomerular hematuria, severely increased albuminuria, acute or chronic kidney disease of unclear cause (in the absence of atrophic kidneys), and kidney transplant dysfunction or monitoring. AIN and atheroembolic disease may require biopsy for diagnosis because they frequently present only with increased serum creatinine. Classes of lupus nephritis are also distinguished through biopsy.

Percutaneous kidney biopsy with ultrasonography or CT guidance is most common. Open or laparoscopic surgical biopsy is performed when percutaneous biopsy is not possible. Contraindications to percutaneous biopsy include the uncooperative patient, bleeding diatheses (including antiplatelet use or anticoagulation), uncontrolled hypertension, poor kidney visualization, atrophic kidneys, and active UTI. Solitary kidney and pregnancy require weighing of risks and benefits.

The most common risks of biopsy are bleeding and injury to surrounding organs. The most common major complications (occurring in <3% of cases) are need for transfusion or angiography with or without embolization, as well as hemodynamic instability. Minor complications include pain and hematuria. Kidney loss and death are very rare complications. H

KEY POINT

- Indications for kidney biopsy include glomerular hematuria, severely increased albuminuria, kidney disease of unclear cause, and kidney transplant dysfunction or monitoring.

Fluids and Electrolytes

Osmolality and Tonicity

The osmolality of a solution is determined by the number of solutes per kilogram. In serum or plasma, osmolality can be measured by freezing point depression or calculated using the following formula:

$$2 \times [Na^+] + \text{Glucose (mg/dL)}/18 + \text{Blood Urea Nitrogen (mg/dL)}/2.8 + \text{Ethanol if present (mg/dL)}/4.6$$

If using international units: $2 \times [Na^+]$ + Urea (mmol/L) + Glucose (mmol/L) + Ethanol (mmol/L)

Normal serum osmolality is between 275 and 295 mOsm/kg H_2O. The difference between measured osmolality and calculated osmolality (the osmolal gap) should be <10 mOsm/kg H_2O. A greater value suggests the presence of a low-molecular-weight alcohol. Because water moves freely between the intracellular and extracellular spaces based on the osmotic gradient, the osmolality of both compartments is virtually identical.

Tonicity is effective osmolality due to solutes that are not freely permeable across the cell membrane. Differences in tonicity determine the distribution of water between body compartments. The major solute determining plasma tonicity is sodium. Because urea and ethanol are freely permeable across the cell membrane, they do not contribute to tonicity or the movement of water.

Osmolality is tightly controlled within a narrow range by thirst and antidiuretic hormone (ADH; also known as vasopressin). ADH stimulates reabsorption of water in the collecting duct of the kidney. Increases in tonicity stimulate both thirst and ADH. As long as there is access to water, appropriate thirst, normal control of ADH, and a functioning nephron, serum osmolality should be maintained in the normal range. Disorders of osmolality reflect impaired water homeostasis. Because the body will defend volume status over tonicity, volume depletion (a decrease in total body sodium content) will stimulate ADH such that at any given osmolality, volume depletion will result in an exaggerated ADH response.

H Disorders of Serum Sodium

Hyponatremia

Hyponatremia is defined as a serum sodium concentration <135 mEq/L (135 mmol/L). Evaluation begins with measurement of serum osmolality. Hyponatremia is then identified as hypertonic (osmolality >295 mOsm/kg H_2O), isotonic (osmolality 275-295 mOsm/kg H_2O), or hypotonic (osmolality <275 mOsm/kg H_2O) (**Figure 6**).

Evaluation

Symptoms caused by hyponatremia depend on both the rapidity and degree of decline in serum sodium. Acute hyponatremia in <48 hours provides inadequate time for the brain to adapt. A sudden drop in serum sodium causes water to move into the brain, producing cerebral edema and possible headaches, seizures, or death. More chronic declines that allow cells to regulate their volume by decreasing intracellular electrolytes may be asymptomatic.

Hypertonic Hyponatremia

Hypertonic hyponatremia (osmolality >295 mOsm/kg H_2O) results from an increased concentration of effective osmotic solute (typically glucose). The increase in osmolality pulls water out of cells, diluting the sodium. For every 100 mg/dL (5.6 mmol/L) increase in glucose, serum sodium decreases by 1.6 to 2.2 mEq/L (1.6-2.2 mmol/L).

Isotonic (Pseudo) Hyponatremia

Isotonic (pseudo) hyponatremia (osmolality 275-295 mOsm/kg H_2O) is a laboratory artifact. Normally, plasma is 93% water (in which solutes are dissolved) and 7% solids (proteins and lipids). The normal sodium concentration in the water phase is 154 mEq/L (154 mmol/L) (hence, normal saline has a sodium concentration of 154 mEq/L [154 mmol/L]). The lower normal value (around 140 mEq/L [140 mmol/L]) is approximately 7% less because electrolytes are reported as a concentration per liter of plasma/serum. Conditions such as severe hypertriglyceridemia or multiple myeloma that increase the solid phase decrease the sodium concentration in plasma.

Hypotonic Hyponatremia

Hypotonic hyponatremia (osmolality <275 mOsm/kg H_2O) reflects excess water for the sodium present and is further categorized by volume status into hypovolemic, hypervolemic, or isovolemic.

In hypovolemic hypotonic hyponatremia, renal sodium and water reabsorption are stimulated by sympathetic outflow, angiotensin, aldosterone, and ADH, leading to urine sodium concentration <20 mEq/L (20 mmol/L) and urine osmolality

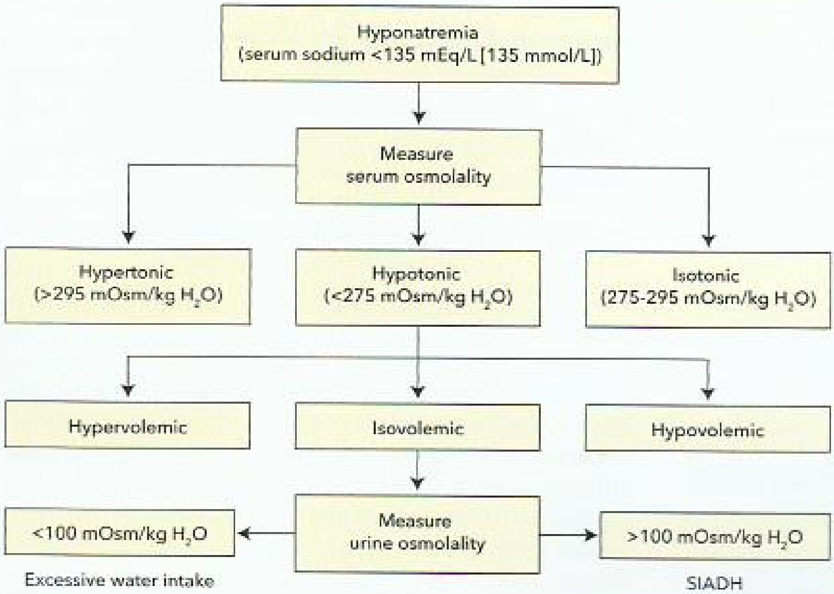


FIGURE 6. Evaluation of hyponatremia. SIADH = syndrome of inappropriate antidiuretic hormone secretion.

>300 mOsm/kg H_2O (except if taking diuretics). Common causes of volume depletion include gastrointestinal losses, excessive sweating, or renal salt wasting from diuretics.

In hypervolemic hypotonic hyponatremia resulting from heart failure or cirrhosis, effective circulating blood volume is inadequate despite total volume overload, resulting in similar urine chemistries.

Isovolemic hypotonic hyponatremia is secondary either to impaired dilution of urine or to water intake that exceeds the kidney's ability to excrete dilute urine. Urine osmolality distinguishes between these two entities. Urine osmolality <100 mOsm/kg H_2O indicates excessive water intake, as seen with psychogenic polydipsia or poor solute intake. Because the kidney cannot excrete pure water, a minimal solute concentration of 50 mOsm/kg H_2O is required. If solute intake is low while liquid intake remains high (as seen in beer potomania or chronic low food intake), water excretion is limited by available urinary solute.

Isovolemic hypotonic hyponatremia with urine osmolality >100 mOsm/kg H_2O can occur in patients with late-stage chronic kidney disease because of impairment of urine dilution, causing hyponatremia after excessive dietary fluid intake. Urine osmolality >100 mOsm/kg H_2O also occurs in isovolemic hypotonic hyponatremia due to the syndrome of inappropriate antidiuretic hormone secretion (SIADH) (**Table 5**). Medications are the most common cause of SIADH, with antidepressants and thiazide diuretics being the most common. 3,4-Methylenedioxymethamphetamine (ecstasy) is increasingly recognized as a cause of hyponatremia. This drug stimulates ADH and, because of the frequently associated fever and dry mouth, induces thirst. Hyponatremia has also been reported in inexperienced marathon runners who overhydrate. Of note, hyponatremia associated with thiazide diuretics, ecstasy, or extreme exertion occurs more frequently in women. A frequent finding in SIADH is a low serum urate level (<4.0 mg/dL [0.24 mmol/L]). Cortisol and thyroid hormone are required to suppress ADH; therefore, deficiencies of these hormones should be evaluated.

TABLE 5. Causes of the Syndrome of Inappropriate Antidiuretic Hormone Secretion

Cause	Examples
Drugs*	Thiazide diuretics
	Selective serotonin reuptake inhibitors
	Phenothiazines
	Haloperidol
	Clofibrate
	Carbamazepine
	Cyclophosphamide
	Tricyclic antidepressants
	Valproic acid
	Bromocriptine
	3,4-Methylenedioxymethamphetamine (ecstasy)
Malignancy	Small cell carcinoma
	Squamous cell carcinoma of the head and neck
Central nervous system disease	—
Pulmonary disease	—
Endocrine disorders	Glucocorticoid deficiency
	Myxedema
Idiopathic	—
Endurance exercise (marathon running)	—

*Drugs are the most common cause.

Management

Treatment of hypotonic hyponatremia is determined by the underlying pathogenesis. In patients with volume overload, treatment is targeted to the underlying disease process along with water restriction. In hypovolemia, volume expansion with isotonic saline will suppress ADH, thereby increasing water excretion with correction of the hyponatremia.

Treatment of isovolemic hypotonic hyponatremia is determined by the severity of symptoms and the rapidity of the decline.

Symptomatic patients with isovolemic hypotonic hyponatremia and an acute decrease in serum sodium should be treated with a 100-mL bolus of 3% saline to increase the serum sodium by 2.0 to 3.0 mEq/L (2.0-3.0 mmol/L). This is usually adequate to decrease cerebral edema and relieve symptoms. If symptoms persist, the bolus can be repeated once or twice at 10-minute intervals as long as the serum sodium can be measured. If the acute decline in sodium is secondary to excess water intake, fluid restriction will rapidly correct the hyponatremia. Because it is often not possible to determine the acuity of the hyponatremia, some authorities recommend limiting the sodium increase in this population by using either hypotonic solutions or desmopressin.

In isovolemic hypotonic hyponatremia with a more chronic (>48 hours) decline in serum sodium, overly aggressive treatment can result in neuronal damage and osmotic demyelination. The serum sodium should not be increased >8.0 to 10 mEq/L (8.0-10 mmol/L) in 24 hours. If there is significant neurologic impairment (for example, seizures or coma), sodium can be acutely increased 2.0 to 4.0 mEq/L (2.0-4.0 mmol/L) using a bolus of 3% saline as long as the total increase remains ≤10 mEq/L (10 mmol/L) in 24 hours. Administration of potassium will also increase plasma sodium because it enters cells, increasing intracellular osmolality and causing water to move from the extracellular space into the intracellular space, thus raising the plasma sodium concentration.

In patients with asymptomatic isovolemic hypotonic hyponatremia or with only mild to moderate symptoms (headache, lethargy), water restriction is safe and effective.

H CONT.

However, limiting fluid intake to <800 mL/24 h is often intolerable. If water restriction is not adequate, therapy is targeted at blocking ADH activity or increasing water excretion. Demeclocycline inhibits ADH action and can be used chronically but is frequently associated with photosensitivity and gastrointestinal symptoms. Tolvaptan, an ADH antagonist, is effective and usually well tolerated, but it is cost-prohibitive and its use is limited to 1 month because of potential liver toxicity. Loop diuretics can be used adjunctively to limit urine concentration, along with increased oral sodium intake. Oral urea, 15 to 30 g/d, is also effective in increasing water excretion, although its use is often limited by unpalatable taste. H

KEY POINTS

- Hyponatremia is divided into three categories: hypertonic (osmolality >295 mOsm/kg H_2O), isotonic (osmolality 275-295 mOsm/kg H_2O), or hypotonic (osmolality <275 mOsm/kg H_2O); hypotonic hyponatremia is further categorized by volume status (hypovolemic, hypervolemic, or isovolemic).
- Treatment of acute symptomatic isovolemic hypotonic hyponatremia consists of a 100-mL bolus of 3% saline; if the acute decline in serum sodium is secondary to excess water intake, fluid restriction will rapidly correct the hyponatremia.
- Overly aggressive treatment of chronic isovolemic hypotonic hyponatremia can result in neuronal damage and osmotic demyelination; therefore, serum sodium should not be increased >8.0 to 10 mEq/L (8.0-10 mmol/L) in 24 hours.

H Hypernatremia

Hypernatremia is defined as a serum sodium concentration >145 mEq/L (145 mmol/L). Although less common than hyponatremia, hypernatremia is often seen in hospitalized patients and is associated with increased mortality in the critically ill.

Hypernatremia can be divided into three broad categories: inappropriate intake/administration of hypertonic solutions; loss of hypotonic fluids; and excessive water loss due to defects in ADH release or action. A detailed history and physical examination combined with measurement of urine electrolytes and osmolality help distinguish the pathogenesis of hypernatremia.

Evaluation

The most common cause of hypernatremia is loss of hypotonic body fluids with inadequate water replacement because of lack of access or absence of thirst (adipsia). Hypotonic losses may result from diarrhea, the respiratory tract, excessive sweating, or renal losses from osmotic diuresis (such as with glucosuria). If the losses are nonrenal, urine osmolality will be elevated to >600 mOsm/kg H_2O. In osmotic diuresis, urine osmolality is usually between 300 and 600 mOsm/kg H_2O. Hypotonic losses with inadequate replacement result in intravascular volume depletion with orthostasis or frank hypotension.

Hypertonic hypernatremia can also occur with administration of excessive quantities of hypertonic saline or sodium bicarbonate, or with salt ingestion. The acute increase in sodium causes water to move out of cells, causing shrinkage and neurologic findings. Symptoms can range from lethargy to seizures and coma. Physical examination frequently reveals intravascular volume overload with elevated jugular venous pressure and pulmonary crackles.

Less commonly, hypernatremia may be secondary to either an inadequate release (central diabetes insipidus) or action of ADH (nephrogenic diabetes insipidus). Common symptoms are polydipsia and polyuria. Urine osmolality <300 mOsm/kg H_2O in a hypernatremic patient confirms the diagnosis. An increase in urine osmolality after a dose of desmopressin (ADH analogue) distinguishes between central and nephrogenic diabetes insipidus. Because solute loss is not excessive, hypernatremia from water loss is usually associated with minimal symptoms unless the sodium increases acutely.

Management

Management of hypernatremia is determined by the underlying pathogenesis. When secondary to acute hypertonic gains, treatment of hypernatremia needs to rapidly restore normal sodium concentration. Water can be administered as 5% dextrose, along with intravenous loop diuretics, to abrogate the volume overload. If available, hemodialysis can be considered.

If hypernatremia has occurred over >24 hours, the brain adapts by uptake of electrolytes and other osmotically active solutes. Therefore, to prevent cerebral edema during water infusion, the correction should be <10 mEq/L/24 h (10 mmol/L/d). The change in the serum sodium for each liter of infusate can be calculated using the formula:

$$(\text{Infusate Sodium}) - (\text{Serum Sodium}) \div (\text{Total Body Water} + 1)$$

If possible, water should be administered orally or by means of a nasogastric tube. Because dextrose-containing solutions may cause glycosuria and increased free water losses, it is important to monitor serum glucose and maintain it below 180 mg/dL (10 mmol/L). In the presence of hemodynamic compromise due to intravascular volume depletion, replacement fluid should be isotonic saline; otherwise, a hypotonic solution (half [0.45%] or quarter [0.22%] normal saline) can be used.

In patients with diabetes insipidus, the first step is determining whether the defect is secondary to a defect in ADH secretion or an ADH action. Central diabetes insipidus can be treated with intranasal or oral desmopressin, a synthetic analogue of vasopressin. Nephrogenic diabetes insipidus is more difficult to treat. Therapy is aimed at limited solute intake to decrease the amount of free water that the kidney can excrete and induction of mild volume depletion using a thiazide diuretic to increase salt and water reabsorption proximal to the collecting duct. H

KEY POINTS

- The most common cause of hypernatremia is loss of hypotonic body fluids with inadequate water replacement because of lack of access or adipsia.
- Treatment of hypernatremia secondary to acute hypertonic gains is aggressive, with rapid restoration of normal sodium concentration.
- If hypernatremia has occurred over >24 hours, correction should be <10 mEq/L/24 h (10 mmol/L/d) to prevent cerebral edema.

H Disorders of Serum Potassium

Hypokalemia

Hypokalemia is defined as a serum potassium level <3.5 mEq/L (3.5 mmol/L). It can be divided into disorders of internal balance (movement of potassium between the intracellular and extracellular compartments) and disorders of external balance (potassium intake and output) (**Figure 7**). Serum potassium >3.0 mEq/L (3.0 mmol/L) is usually asymptomatic. Because the ratio of intracellular to extracellular potassium is the major determinant of the membrane potential of electrically active tissue, symptoms of hypokalemia include weakness or paralysis, decreased gastrointestinal motility or ileus with nausea, and cardiac arrhythmias. Electrocardiographic (ECG) manifestations include ST-segment depression, decreased T-wave amplitude, and increased U-wave amplitude. Severe hypokalemia can cause rhabdomyolysis.

Evaluation

The cause of hypokalemia can usually be determined from the history and simple laboratory evaluation. Rarely, hypokalemia is spurious, as can occur in leukemia when delayed sample processing allows large numbers of metabolically active leukocytes to take up potassium. In addition to leukocytosis, a clue to pseudohypokalemia is the lack of signs and symptoms associated with hypokalemia.

Hypokalemia can occur secondary to disordered internal balance. Insulin or β_2-agonists shift potassium into cells, causing an acute, transient, and modest hypokalemia that is usually asymptomatic. Ingestion of soluble barium or cesium salts, which block potassium exit from cells, can produce severely symptomatic hypokalemia with levels below 2.0 mEq/L (2.0 mmol/L). Increased cell production after repletion of vitamin B_{12} or folate in deficient individuals can also cause hypokalemia. Hypokalemic periodic paralysis, either an inherited autosomal dominant disorder or an acquired disorder seen in hyperthyroid patients usually of Japanese descent, may present with severe muscle weakness and paralysis.

Most cases of hypokalemia are due to disordered external balance with total body potassium depletion, secondary either to lack of potassium intake or to increased potassium excretion. Because the kidney can almost cease potassium excretion, only a severely compromised diet can cause hypokalemia. The major determinants of renal potassium secretion are distal tubular flow rate and aldosterone, both of which increase sodium reabsorption, increasing the electronegativity of the tubule lumen and promoting potassium secretion.

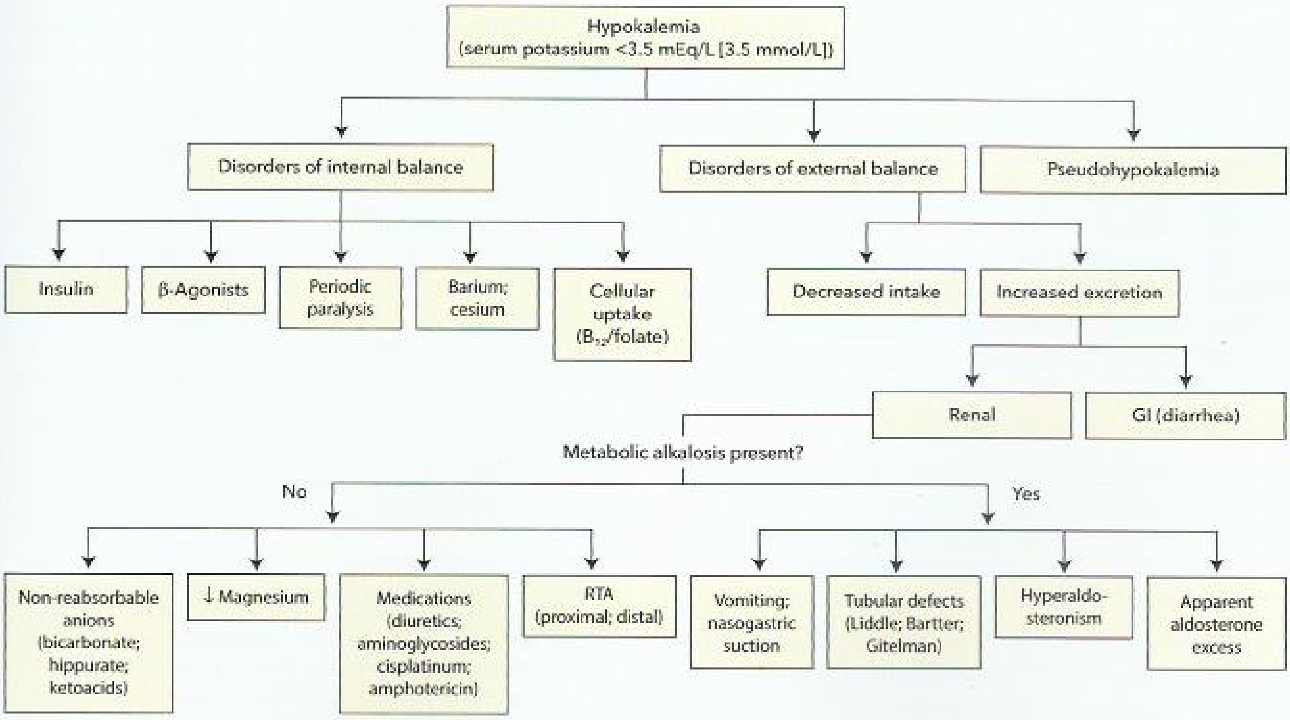


FIGURE 7. Causes of hypokalemia. GI = gastrointestinal; RTA = renal tubular acidosis.

Under normal conditions, distal flow and aldosterone levels are inversely related, thus preventing disruptions in potassium homeostasis by changes in intravascular volume.

The gold standard to distinguish between renal and extrarenal causes of total body potassium depletion is a 24-hour urine potassium <30 mEq/24 h (30 mmol/d); however, this test is often impractical. The preferred alternative is a spot urine potassium-creatinine ratio. A value <13 mEq/g identifies hypokalemia secondary to lack of intake, transcellular shifts, or gastrointestinal losses.

Gastrointestinal losses are usually caused by diarrhea or laxative abuse. Frequently, a concomitant metabolic acidosis is present. Renal potassium wasting may be caused by numerous disorders, including medications (most commonly diuretics), delivery of non-reabsorbable anions to the distal tubule (such as bicarbonate), aldosterone excess, hypomagnesemia, and tubular defects (see Figure 7).

Hyperaldosteronism is associated with hypertension and a metabolic alkalosis. Hypomagnesemia can cause potassium wasting, and renal potassium wasting also occurs in inherited tubular defects, including Liddle, Bartter, and Gitelman syndromes. In Liddle syndrome, increased sodium reabsorption in the distal nephron causes hypertension, metabolic alkalosis, and potassium wasting. Bartter and Gitelman syndromes are caused by mutations in transporters that mimic the effects of diuretics on the tubule. Finally, proximal and distal renal tubular acidosis is associated with potassium wasting.

Management

The total body potassium deficit is difficult to predict and can be up to 200 mEq (200 mmol) for each mEq/L decrease in plasma potassium. In patients with neuromuscular or cardiac symptoms, it is important to increase the potassium promptly. Intravenous potassium can be safely infused at 20 mEq/h (20 mmol/h). Infusion through a central vein can be increased to 40 mEq/h (40 mmol/h) with close monitoring. For mild hypokalemia (2.5-3.5 mEq/L [2.5-3.5 mmol/L]), oral supplementation using potassium chloride or potassium bicarbonate is usually adequate. Concurrent hypomagnesemia must be corrected to prevent ongoing potassium losses. In patients with potassium wasting, potassium-sparing diuretics can be helpful. When significant hypokalemia is secondary to acute transcellular shifts, total body potassium is normal and excessive potassium replacement may cause rebound hyperkalemia.

KEY POINTS

- Symptoms of hypokalemia include weakness or paralysis, decreased gastrointestinal motility or ileus with nausea, and cardiac arrhythmias; electrocardiographic manifestations include ST-segment depression, decreased T-wave amplitude, and increased U-wave amplitude.
- In patients with hypokalemia and neuromuscular or cardiac symptoms, intravenous potassium (20 mEq/h [20 mmol/h]) can be used to increase the potassium promptly; oral supplementation is usually adequate for mild cases.

Hyperkalemia

Hyperkalemia is defined by a serum potassium level >5.0 mEq/L (5.0 mmol/L). Levels >6.0 mEq/L (6.0 mmol/L) can cause fatal arrhythmias. Slow increases in potassium are better tolerated than abrupt increases. Signs and symptoms of hyperkalemia are manifested in electrically active tissue and include muscle weakness and ECG abnormalities.

Evaluation

Initial evaluation of hyperkalemia requires a history and physical examination, review of all medications, assessment of kidney function, and an ECG. Initial ECG manifestations include peaked precordial T waves and a shortened QT interval. With progression of hyperkalemia, lengthening of the PR interval, loss of the P wave, widening of the QRS complex, a sine wave pattern, and asystole may occur (**Figure 8**). However, ECG findings do not always correlate with the serum potassium level and do not necessarily progress in an orderly fashion.

During the clotting process, cells are disrupted with the release of intracellular potassium, and pseudohyperkalemia may occur in serum specimens when there are extreme elevations of leukocytes or platelets. In these cases, repeating a plasma specimen will be normal. A tight tourniquet or excessively clenched fist during blood draw can also cause local potassium release.

Hyperkalemia may be caused by transcellular shifts, as occur in states of insulin deficiency or hypertonicity or with the use of β_2-adrenergic blockers. Rapid breakdown of cells such as that seen in rhabdomyolysis or in tumor lysis from treatment of leukemias and lymphomas can acutely raise serum potassium levels.

Hyperkalemia usually results from increased intake with decreased renal excretion. Hyperkalemia frequently occurs with

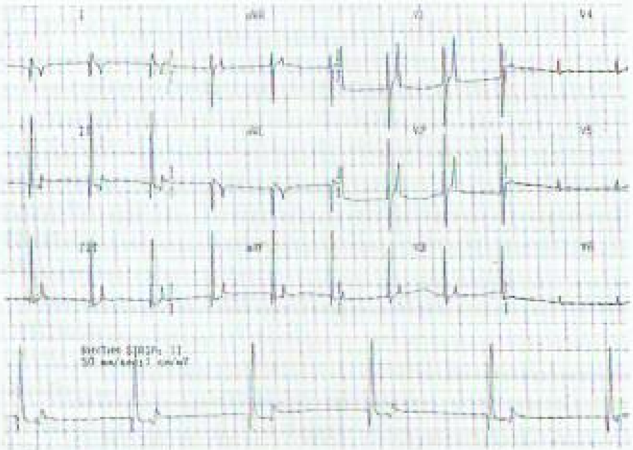


FIGURE 8. This electrocardiogram demonstrates tall, peaked T waves and decreased P waves, which are characteristic of hyperkalemia. T-wave peaking begins with mild to moderate elevations of serum potassium (5.5-7.0 mEq/L [5.5-7.0 mmol/L]) and tends to persist with more severe hyperkalemia. As serum potassium levels increase to above 7.0 to 8.0 mEq/L (7.0-8.0 mmol/L), decreases in P-wave amplitude and widening of the QRS complex are seen. With serum potassium levels above 9.0 to 10.0 mEq/L (9.0-10.0 mmol/L), the waveform will become sinusoidal, and cardiac arrest may follow.

H CONT.

oliguric acute or chronic kidney disease with a glomerular filtration rate (GFR) <20 mL/min/1.73 m². Potassium-sparing diuretics (amiloride, triamterene, spironolactone) also commonly cause hyperkalemia through decreased excretion. Other medications that decrease potassium excretion include trimethoprim and pentamidine (by blocking the epithelial sodium channel) and NSAIDs (by decreasing renin). Hypoaldosteronism caused by inhibitors of the renin-angiotensin system, heparin, type 4 renal tubular acidosis (often seen in early diabetic nephropathy), or primary adrenal insufficiency also cause hyperkalemia, especially in the presence of excess potassium intake.

Management

Elevation in the serum potassium level >6.5 mEq/L (6.5 mmol/L), or >6.0 mEq/L (6.0 mmol/L) with ECG changes, should be promptly treated. Treatment is directed at stabilizing the cardiac membrane, shifting potassium into cells, and removing potassium from the body. Intravenous administration of calcium gluconate (100 mg) quickly antagonizes the effects of hyperkalemia on the cardiac membrane. Its duration of action is relatively short and therefore is never definitive therapy. Intravenous administration of insulin alone if serum glucose is >250 mg/dL (13.9 mmol/L) or with 10% dextrose will drive potassium into cells, and is effective for up to 6 hours. Potassium can also be shifted into cells using high-dose nebulized albuterol. Sodium bicarbonate therapy has fallen out of favor because it does not promote redistribution of potassium.

Definitive treatment of severe hyperkalemia must include removal of potassium from the body. In patients without severe kidney disease, loop diuretics can be effective. Use of the potassium exchange resin sodium polystyrene sulfonate is controversial; its effectiveness is limited, and it produces adverse gastrointestinal effects. Hemodialysis is the treatment of choice in patients with severe hyperkalemia and oliguric kidney disease.

In chronic hyperkalemia, limiting potassium intake may be beneficial. Increased sodium intake along with a thiazide or loop diuretic will increase potassium excretion. In hypoaldosteronism, fludrocortisone will normalize the potassium; however, it may cause elevated blood pressure and edema, and long-term effects of fludrocortisone are unknown. All potentially causative medications should be discontinued if possible. If necessary, newer potassium binders (such as patiromer) may allow continuation of essential medications. H

KEY POINTS

- Intravenous administration of calcium gluconate quickly antagonizes the effects of hyperkalemia on the cardiac membrane, but its duration of action is relatively short.
- Definitive treatment of severe hyperkalemia must include removal of potassium from the body; loop diuretics can be effective in patients without severe kidney disease, and hemodialysis is the treatment of choice in patients with severe hyperkalemia and oliguric kidney disease.

Disorders of Serum Phosphate

Hypophosphatemia

Hypophosphatemia is defined as a serum phosphate level <2.7 mg/dL (0.87 mmol/L). Phosphate (PO_4) is found primarily within bone and the intracellular space. Phosphate is required for metabolic pathways involved in energy production, cellular repair, and enzymatic activity. Mild hypophosphatemia is rarely symptomatic. Levels <2.0 mg/dL (0.65 mmol/L) are associated with muscle weakness. Severe hypophosphatemia (<1.0 mg/dL [0.32 mmol/L]) is associated with life-threatening symptoms, including delirium, seizures, coma, heart failure, respiratory failure, rhabdomyolysis, and hemolysis.

Evaluation

Hypophosphatemia results from transcellular shifts, decreased intake, or increased excretion. Movement of phosphorous into cells occurs with respiratory alkalosis, insulin treatment, or refeeding of starved individuals. Medications that bind phosphate in the gut (calcium, antacids) can decrease effective intake. Because the kidney can decrease phosphate excretion to very low levels, low dietary phosphate rarely causes hypophosphatemia without coexisting malnutrition. Increased excretion may be caused by diarrhea or renal wasting. Excretion of >100 mg of phosphate in a 24-hour urine collection or a fractional excretion of phosphate (FE_{PO_4}) >5% suggests renal wasting. FE_{PO_4} is calculated as follows:

$$FE_{PO_4} = (U_{PO_4} \times P_{Cr})/(P_{PO_4} \times U_{Cr}) \times 100$$

(where Cr = creatinine, P = plasma, PO_4 = phosphate, U = urine)

Renal losses of phosphate are seen in hyperparathyroidism and in proximal tubular dysfunction.

Management

Mild decreases in serum phosphate can be treated with oral sodium or potassium phosphate. Levels <2.0 mg/dL (0.65 mmol/L) should be treated with intravenous sodium phosphate. Calcitriol is sometimes required to increase intestinal absorption of phosphate.

KEY POINTS

- Severe hypophosphatemia (<1.0 mg/dL [0.32 mmol/L]) is associated with life-threatening symptoms, including delirium, seizures, coma, heart failure, respiratory failure, rhabdomyolysis, and hemolysis.
- Mild hypophosphatemia can be treated with oral sodium or potassium phosphate; levels <2.0 mg/dL (0.65 mmol/L) should be treated with intravenous sodium phosphate.

Hyperphosphatemia

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Hyperphosphatemia is defined by a serum phosphate level >4.5 mg/dL (1.45 mmol/L). Causes include cellular lysis with release of phosphate, excessive intake, and/or decreased renal

excretion. Symptoms are usually related to co-occurring hypocalcemia. Acute elevations in phosphate can cause precipitation of calcium phosphate in the kidney, resulting in phosphate nephropathy.

Evaluation

Hyperphosphatemia from reduced renal excretion does not occur due to reduced GFR unless patients have severe chronic kidney disease. Hypoparathyroidism decreases excretion through increased phosphate tubular reabsorption; hypocalcemia is often present. Rare defects in the action of fibroblast growth factor-23 (such as in tumoral calcinosis) also increase tubular reabsorption of phosphate.

Because phosphate is primarily an intracellular anion, widespread cellular damage as occurs in rhabdomyolysis and tumor lysis syndrome increases serum phosphate, especially if the GFR is decreased. Excessive phosphate intake rarely causes hyperphosphatemia because the kidney rapidly excretes phosphate. However, phosphate-containing cathartics can cause acute elevations in serum phosphate, especially in patients with reduced GFR.

Management

If kidney function is adequate, serum phosphate levels should normalize in 12 to 24 hours. If necessary, phosphate excretion can be increased with intravenous saline. In patients with acute kidney injury, dialysis may be necessary. Because many foods contain phosphate, dietary phosphate restriction is difficult. Therefore, patients with chronic hyperphosphatemia must often use agents that bind phosphate in the gut.

KEY POINTS

- Causes of hyperphosphatemia include cellular lysis with release of phosphate, excessive intake, and/or decreased renal excretion from decreased glomerular filtration rate or increased tubular reabsorption (hypoparathyroidism).
- If kidney function is adequate in patients with hyperphosphatemia, serum phosphate levels should normalize in 12 to 24 hours; if necessary, phosphate excretion can be increased with intravenous saline, and dialysis can be initiated for those with acute kidney injury.

Disorders of Serum Magnesium

There are approximately 24 grams of magnesium in the body, with 99% residing intracellularly and within bone. Magnesium is essential for protein and nucleic acid synthesis, cell adhesion, enzyme reactions, and modulating channel activity.

Hypomagnesemia

Hypomagnesemia is defined by a serum magnesium level <1.7 mg/dL (0.7 mmol/L). Symptoms usually do not develop until serum magnesium is <1.2 mg/dL (0.5 mmol/L). Symptoms include tremors, fasciculations, muscle weakness, carpopedal spasm, Chvostek (contraction of the ipsilateral facial muscles by tapping the facial nerve) and Trousseau (carpopedal spasm after inflation of blood pressure cuff above systolic blood pressure) signs, and seizures. Hypomagnesemia also appears to potentiate cardiac arrhythmogenicity due to hypokalemia, myocardial ischemia, and various drugs. In addition, hypomagnesemia causes hypokalemia due to renal potassium wasting, and it causes hypocalcemia by impeding parathyroid hormone release and action.

Evaluation

Hypomagnesemia results from decreased gastrointestinal absorption or increased renal secretion. History and physical examination often delineate the cause. More than 10 mg of magnesium in a 24-hour urine collection or a fractional excretion of magnesium (FE_{Mg}) >2% suggests renal wasting in the setting of hypomagnesemia. FE_{Mg} is calculated by using the following formula:

$$FE_{Mg} = ([U_{Mg} \times P_{Cr}]/[(0.7 \times P_{Mg}) \times U_{Cr}]) \times 100$$

(where Cr = creatinine, Mg = magnesium, P = plasma, U = urine. Magnesium is multiplied by 0.7 because only 70% of the magnesium is filtered.)

Causes of decreased magnesium absorption include severe malnutrition, diarrhea, and malabsorption. The use of proton pump inhibitors has become an important cause of hypomagnesemia, with most reported cases occurring after prolonged use; hypomagnesemia rapidly reverses upon discontinuation of the drug.

Hypomagnesemia from renal losses occurs with diuretics, cisplatin, aminoglycosides, or calcineurin inhibitors. Vascular endothelial growth factor inhibitors used in cancer treatment can cause significant magnesium wasting. Other causes of urine losses include volume expansion, alcohol ingestion, and diabetic ketoacidosis.

Management

If significant symptoms are present, 4 grams of magnesium sulfate should be infused over 12 hours and repeated if necessary. Less severe symptoms can be treated with 1 to 2 grams of intravenous magnesium sulfate. Importantly, half of acutely infused intravenous magnesium is excreted by the kidney; therefore, slow-release oral magnesium or nasogastric tube delivery may be better to replete mild to moderate degrees of hypomagnesemia.

KEY POINTS

- Significant symptoms of hypomagnesemia usually develop when the serum magnesium level is <1.2 mg/dL (0.50 mmol/L); these include tremors, fasciculations, muscle weakness, carpopedal spasm, Chvostek and Trousseau signs, seizures, and cardiac arrhythmogenicity.
- Treatment of significant symptoms of hypomagnesemia includes magnesium sulfate infusions; less severe symptoms can be treated with infusion or with slow-release oral magnesium.

Hypermagnesemia

Hypermagnesemia is defined by a serum magnesium level of >2.4 mg/dL (0.99 mmol/L).

Evaluation

Hypermagnesemia occurs infrequently and most commonly results from excessive intake in the setting of decreased kidney function. Numerous medications such as antacids and laxatives contain magnesium, and magnesium sulfate can be used in the treatment of refractory asthma and remains the treatment of choice for prevention of preeclampsia.

Symptoms of hypermagnesemia do not occur until levels are >5.0 mg/dL (2.1 mmol/L). Early symptoms include loss of deep tendon reflexes, progressing to flaccid paralysis at higher levels. Hypermagnesemia also results in hypotension from vascular relaxation. Laboratory analysis often shows hypocalcemia.

Management

Prevention is the key to management of hypermagnesemia. Hypermagnesemia is usually self-limited; magnesium-containing agents should be limited or avoided in individuals with kidney disease. Magnesium-containing medications should be discontinued, and magnesium excretion can be enhanced with saline diuresis. For more severe symptoms, intravenous calcium will antagonize the effects of magnesium.

KEY POINTS

- Early symptoms of hypermagnesemia include loss of deep tendon reflexes, progressing to flaccid paralysis at higher levels.
- For patients with hypermagnesemia, all magnesium-containing medications should be discontinued, and magnesium excretion can be enhanced with saline diuresis; for more severe symptoms, intravenous calcium will antagonize the effects of magnesium.

Acid-Base Disorders

Overview

Acid-base balance is essential to appropriate function of the human body. Hydrogen ions are maintained within narrow limits and determine pH (**Table 6**). Alterations of acid-base balance can have dire consequences; therefore, any change in pH results in a predictable response to limit that change.

TABLE 6. Physiologic Levels of Tests Used in the Assessment of Acid-Base Status

	pH	P_{CO_2}	Bicarbonate
Arterial blood	7.37-7.44	36-44 mm Hg (4.8-5.9 kPa)	22-26 mEq/L (22-26 mmol/L)
Venous blood	7.32-7.38	42-50 mm Hg (5.6-6.7 kPa)	23-27 mEq/L (23-27 mmol/L)

Causes of acid-base disorders can be determined by using blood gas results (pH, P_{CO_2}), serum bicarbonate measurements, and the serum anion gap. Arterial blood provides the most accurate measurement, although venous blood gases may be useful in following response to therapy. Venous gases are least useful in patients with shock, due to lower pH and higher P_{CO_2} values than in arterial gases.

Primary acid-base disorders are classified according to the underlying mechanism (metabolic or respiratory) and their effect on acid-base balance (acidosis or alkalosis) (**Figure 9**). Expected compensatory response to the primary disorder is then assessed (**Table 7**). A mixed acid-base disorder is present when measured values fall outside the range of the predicted compensatory response. The primary disorder is usually reflected by the blood pH, although a normal pH may occur in the context of a mixed disorder. Appropriate compensation may result in near-normal pH.

KEY POINTS

- Primary metabolic acidosis is defined by low serum bicarbonate and primary metabolic alkalosis by elevated serum bicarbonate.
- In primary respiratory acidosis, arterial P_{CO_2} is above the normal range; in primary respiratory alkalosis, P_{CO_2} is below normal.

Metabolic Acidosis

General Approach

Metabolic acidosis is detected by low pH and low serum bicarbonate. A stepwise approach to assessment supports appropriate diagnosis of the underlying acid-base disorder. First, both pH and P_{CO_2} are needed to confirm the primary disorder

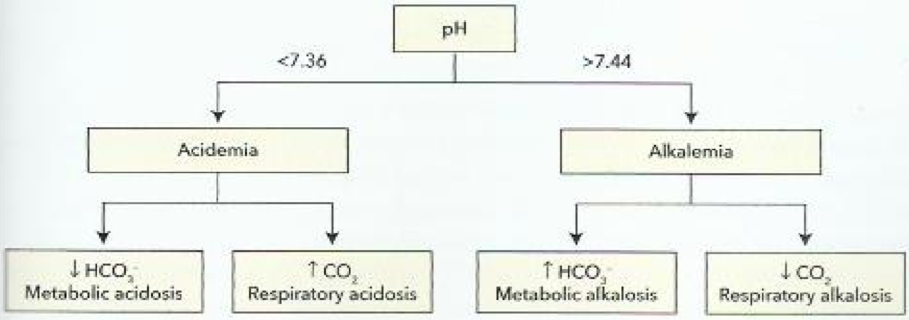

FIGURE 9. Classification of primary acid-base disorders.

TABLE 7. Compensation in Acid-Base Disorders

Condition	Expected Compensation
Metabolic acidosis	Maximally compensated: expected $PCO_2 = (1.5)[HCO_3] + 8 \pm 2$ (Winter's formula)
	Measured PCO_2 > expected: complicating primary respiratory acidosis
	Measured PCO_2 < expected: complicating primary respiratory alkalosis
Metabolic alkalosis	For each ↑ 1.0 mEq/L (1.0 mmol/L) in $[HCO_3]$, PCO_2 ↑ 0.7 mm Hg (0.09 kPa)
Respiratory acidosis	Acute: 1.0 mEq/L (1.0 mmol/L) ↑ $[HCO_3]$ for each 10 mm Hg (1.3 kPa) ↑ in PCO_2
	Chronic: 3.5 mEq/L (3.5 mmol/L) ↑ $[HCO_3]$ for each 10 mm Hg (1.3 kPa) ↑ in PCO_2
	$[HCO_3]$ < expected value: complicating metabolic acidosis
	$[HCO_3]$ > expected value: complicating metabolic alkalosis
Respiratory alkalosis	Acute: 2.0 mEq/L (2.0 mmol/L) ↓ $[HCO_3]$ for each 10 mm Hg (1.3 kPa) ↓ in PCO_2
	Chronic: 4.0-5.0 mEq/L (4.0-5.0 mmol/L) ↓ $[HCO_3]$ for each 10 mm Hg (1.3 kPa) ↓ in PCO_2
	$[HCO_3]$ < expected value: complicating metabolic acidosis
	$[HCO_3]$ > expected value: complicating metabolic alkalosis

H CONT.

because low serum bicarbonate may be a compensatory response to respiratory alkalosis.

Next, the serum anion gap is calculated to assess whether the low serum bicarbonate is due to loss of serum bicarbonate (no anion gap) or is a result of unmeasured anion (anion gap acidosis). The anion gap is calculated as follows:

$$\text{Anion Gap} = \text{Serum Sodium (mEq/L)} - (\text{Serum Chloride [mEq/L]} + \text{Serum Bicarbonate [mEq/L]})$$

The normal reference range for the anion gap is 8.0 to 10 mEq/L ± 2 mEq/L (8.0-10 mmol/L ± 2 mmol/L). In normal subjects, negatively charged albumin is a major contributor to the anion gap. Therefore, changes in albumin need to be taken into account. This is most important in the context of a low albumin wherein failure to correct the anion gap will result in underestimation of the true anion gap. The albumin-corrected anion gap (with normal albumin being 4.0 g/dL [40 g/L]) is calculated as follows:

$$\text{Albumin-Corrected Anion Gap} = \text{Anion Gap} + 2.5 \times (\text{Normal Albumin} - \text{Measured Albumin [g/dL]})$$

If the corrected anion gap is increased, patients should next be assessed for coexistent normal anion gap acidosis or metabolic alkalosis. One method for detection of a coexistent additional acid-base disorder is to assess the ratio of the amount of anion gap abnormality (Δ anion gap) to the amount of bicarbonate abnormality (Δ bicarbonate), or the "delta-delta (Δ-Δ) ratio."

$$\Delta\text{-}\Delta \text{ Ratio} = \Delta \text{ Anion Gap}/\Delta \text{ Bicarbonate} = (\text{Anion Gap} - 12)/(25 - \text{Bicarbonate})$$

A ratio of <0.5 to 1 may reflect the presence of concurrent normal anion gap metabolic acidosis, whereas a ratio of >2 may indicate the presence of metabolic alkalosis.

Patients with metabolic acidosis due to acute or chronic kidney disease may have either a normal anion gap or an increased anion gap, depending on severity of loss of nephron mass. When the glomerular filtration rate (GFR) decreases to <45 mL/min/1.73 m², decreased urine ammonium excretion leads to a normal anion gap metabolic acidosis, often associated with hyperkalemia. When the GFR decreases to <15 mL/min/1.73 m², retention of sulfates, phosphates, and organic acids results in an increased anion gap metabolic acidosis. H

KEY POINTS

- Metabolic acidosis is detected by low pH and low serum bicarbonate levels.
- When metabolic acidosis is present, the anion gap is useful in assessing whether the decreased serum bicarbonate is due to an unmeasured organic anion (increased anion gap metabolic acidosis) or to a loss of bicarbonate (normal anion gap metabolic acidosis).
- Metabolic acidosis due to acute or chronic kidney disease may have either a normal anion gap or an increased anion gap, depending on severity of nephron loss.

Increased Anion Gap Metabolic Acidosis

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Increased anion gap metabolic acidosis occurs when unmeasured anions accumulate. Lactic acidosis is the most common cause (**Table 8**). Less common causes include ketoacidosis (diabetic, alcoholic, or starvation), acute or chronic kidney injury, or poisoning (methanol, ethylene glycol, salicylate, or propylene glycol). The plasma osmolal gap may assist in identifying a cause. The plasma osmolal gap is the difference between the measured and calculated plasma osmolality. The calculated plasma osmolality is determined as follows:

$$\text{Plasma Osmolality (mOsm/kg } H_2O) = (2 \times \text{Serum Sodium [mEq/L]}) + \text{Plasma Glucose (mg/dL)}/18 + \text{Blood Urea Nitrogen (mg/dL)}/2.8$$

A high osmolal gap (>10 mOsm/kg H_2O) indicates the presence of unmeasured osmoles such as methanol or ethylene glycol, which are metabolized to organic acids, thereby increasing the anion gap. A high osmolal gap is also seen in

TABLE 8. Causes of Lactic Acidosis

Condition	Cause	Clinical and Laboratory Manifestations	Treatment	Comments
Lactic Acidosis	**See below.**	**Serum lactate level >4.0 mEq/L (4.0 mmol/L)**	**Treat underlying cause; sodium bicarbonate when arterial pH is <7.1 to raise pH to 7.2**	**Most common cause of increased anion gap metabolic acidosis**
Type A lactic acidosis	Tissue hypoperfusion	Multisystem organ dysfunction typically present	Correct cause of hypoperfusion	—
Type B lactic acidosis				
Propofol	Propofol >4 mg/kg/h for >24 h	Rhabdomyolysis; hyperlipidemia; cardiogenic shock	Discontinue propofol; hemodialysis	Seen with continuous infusion, not bolus dosing
Metformin	Metformin use in patients with impaired kidney function	More likely to occur in those with acute kidney injury	Hemodialysis	Avoid in those with eGFR <30 mL/min/1.73 m²
HIV nucleoside reverse transcriptase inhibitor	Mitochondrial toxicity	Type B lactic acidosis	Discontinue medication; supportive care	Risk factors: female sex, pregnancy, obesity, poor liver function, lower CD4 count; mostly: ddI, d4T > AZT; rare: TFV, ABC, FTC, 3TC
Hematologic malignancy	Thought to be due to anaerobic metabolism in cancer cells	Type B lactic acidosis; hypoglycemia	Treat underlying malignancy	Portends very poor prognosis; seen in high-grade B-cell lymphomas
D-Lactic acidosis	Short-bowel syndrome[a]; undigested carbohydrates in the colon are metabolized to D-lactate by bacteria	Intermittent confusion; slurred speech; ataxia; increased anion gap metabolic acidosis with normal serum lactate level	Antibiotics (e.g., metronidazole or neomycin) directed toward bowel flora; restriction of dietary carbohydrates	Diagnosis requires measurement of D-lactate because D-isomer is not measured by conventional assays for serum lactate

3TC = lamivudine; ABC = abacavir; AZT = zidovudine; d4T = stavudine; ddI = didanosine; eGFR = estimated glomerular filtration rate; FTC = emtricitabine; TFV = tenofovir.

[a]After jejunoileal bypass or small-bowel resection.

pseudohyponatremia, in which plasma osmolality is normal while calculated osmolality is low. The patient's history should guide further testing for unmeasured anions.

Diabetic ketoacidosis usually presents with an increased anion gap metabolic acidosis due to accumulation of β-hydroxybutyrate and acetoacetate, although it may present with a normal anion gap due to excretion of ketoacids. Compensatory hyperventilation is characterized by increased tidal volume rather than increase in respiratory rate. Urine dipstick assays for ketones detect acetoacetate using the nitroprusside assay; however, β-hydroxybutyrate is the dominant ketoacid in diabetic ketoacidosis, so urine dipstick results can be falsely negative or underestimate the total ketone load (see MKSAP 18 Endocrinology and Metabolism).

Alcoholic ketoacidosis occurs in patients with chronic ethanol abuse who typically have a history of recent binge drinking, little food intake, and persistent vomiting. Liver chemistry test abnormalities may be present due to concomitant alcoholic hepatitis. Treatment with intravenous saline and intravenous glucose typically results in rapid resolution of ketones due to induction of insulin secretion and suppression of glucagon release. For patients with chronic malnutrition related to alcohol use, thiamine should be administered before glucose to decrease the risk of precipitating Wernicke encephalopathy.

Medication and toxin exposures that cause increased anion gap acidosis are described in Table 9.

KEY POINTS

- Lactic acidosis is defined as a serum lactate level >4.0 mEq/L (4.0 mmol/L); management includes treatment of the underlying cause and sodium bicarbonate when arterial pH is <7.1.
- Ethylene glycol or methanol ingestion should be suspected in patients with an increased anion gap acidosis associated with a serum bicarbonate level <10 mEq/L (10 mmol/L) and a plasma osmolal gap >10 mOsm/kg H_2O.

Normal Anion Gap Metabolic Acidosis

Normal anion gap metabolic acidoses most often result from gastrointestinal bicarbonate losses (diarrhea), kidney bicarbonate losses (type 2 renal tubular acidosis), or inability of the kidney to adequately excrete acid (types 1 and 4 renal tubular acidosis; chronic kidney disease). Although a patient history

TABLE 9. Medication and Toxin Exposures that Cause Increased Anion Gap Acidosis

Condition	Cause	Clinical and Laboratory Manifestations	Treatment	Comments
Ethylene glycol ingestion	Glycolic acid accumulation; calcium oxalate precipitation in renal tubules and crystals in the urine	Neurotoxicity/inebriation; AKI and flank pain due to precipitation of calcium oxalate in kidneys; hypocalcemic symptoms; cardiovascular collapse; pulmonary edema Serum bicarbonate level <10 mEq/L (10 mmol/L); plasma osmolal gap >10 mOsm/kg H_2O	Fomepizole IV hydration Hemodialysis: in severe acidemia, very large ingestions, severe CNS depression, AKI, systemic collapse Pyridoxine and thiamine: in suspected ethylene glycol toxicity Sodium bicarbonate	Found in antifreeze, solvents, cosmetics May be difficult to differentiate from methanol ingestion
Methanol ingestion	Formic acid accumulation	CNS damage; optic nerve/eye damage with blindness; inebriation less prominent than with ethylene glycol; papilledema; mydriasis; afferent pupillary defect; abdominal pain; pancreatitis Serum bicarbonate level <10 mEq/L (10 mmol/L); plasma osmolal gap >10 mOsm/kg H_2O	Fomepizole Hemodialysis: in severe acidemia, very large ingestions, severe CNS depression, any visual impairment Folic acid: in suspected methanol toxicity Sodium bicarbonate	Found in windshield-washing fluid, commercial solvents, paints, some antifreezes May be difficult to differentiate from ethylene glycol ingestion 80%-90% mortality rate with methanol ingestion; permanent blindness may occur
Salicylate toxicity	Salicylate anion accumulation; ingestion of as little as 10 grams of aspirin in adults	Respiratory alkalosis; tinnitus; nausea/vomiting; impaired mental status; cerebral edema and fatal brainstem herniation; tachypnea; low-grade fever; noncardiogenic pulmonary edema; hepatic injury; with severe intoxication, lactic acidosis or ketoacidosis	Bicarbonate infusion: alkalinization mitigates CNS toxicity; aim for urine pH >7.5 Hemodialysis: in AKI, impaired mental status, cerebral edema, serum salicylate levels >100 mg/dL with acute ingestion and levels >60 mg/dL with chronic ingestion, refractory acidemia, pulmonary edema	Toxicity can develop from ingestion or mucocutaneous exposure to salicylate preparations such as methyl salicylate (oil of wintergreen)
Propylene glycol toxicity	Large doses of propylene glycol (a solvent used for IV medications), most commonly lorazepam diluted in propylene glycol (80%)	AKI; anion gap metabolic acidosis with increased plasma osmolal gap; toxicity when propylene glycol levels >25 mg/dL or plasma osmolal gap >10 mOsm/kg H_2O	Discontinue the IV infusion Hemodialysis	Monitor acid-base status and serum osmolality when lorazepam doses >1 mg/kg/d; unlikely to develop if 24-h lorazepam dose is limited to <166 mg/d
Pyroglutamic (5-oxoproline) acidosis	Resulting from chronic acetaminophen ingestion; most common in critically ill patients, those with poor nutrition, liver disease, or CKD, and in vegetarians	Impaired mental status; on urine testing for organic anions, high concentrations of urine pyroglutamate (5-oxoproline)	Discontinue acetaminophen Consider *N*-acetylcysteine to regenerate depleted glutathione stores	Female preponderance (80%); genetic factors may play a role

AKI = acute kidney injury; CKD = chronic kidney disease; CNS = central nervous system; IV = intravenous.

H CONT.

may elucidate the cause, the urine anion gap may help to narrow down the cause.

The kidneys should increase acid excretion in response to acidemia. This is achieved primarily by increased tubular production of ammonia (NH_3) and secretion of protons, resulting in increased urine ammonium (NH_4^+). The amount of urine ammonium reflects the ability of the kidneys to respond appropriately to acidemia and indicates if the kidney is a cause of the acidosis. Because urine ammonium is difficult to obtain, the urine anion gap is used as a surrogate to assess kidney acid excretion:

$$\text{Urine Anion Gap} = (\text{Urine Sodium} + \text{Urine Potassium}) - \text{Urine Chloride}$$

In patients with gastrointestinal losses of bicarbonate (diarrhea; laxative abuse) or those exposed to an acid load, urine NH_4^+ should increase. Ammonium cation excretion results in proportionately less excretion of sodium and

potassium (the predominant urine cations). Chloride anion excretion continues with ammonium cation excretion to maintain electrical neutrality. In the context of increased urine NH_4^+ production, therefore, the urine anion gap will be negative (less than zero). A positive urine anion gap in a patient with acidemia suggests the presence of a distal renal tubular acidosis. Proton secretion in the distal nephron generates NH_4^+, and in distal renal tubular acidosis there is a defect in this proton secretion. Therefore, urine NH_4^+ will be low, with proportionately greater sodium and potassium excretion resulting in a positive urine anion gap.

The urine anion gap, together with serum potassium levels and urine pH, can help further distinguish the causes of normal anion gap metabolic acidosis (**Table 10**).

Type 2 (Proximal) Renal Tubular Acidosis

The primary defect in type 2 (proximal) renal tubular acidosis (RTA) is failure of the proximal tubule to adequately absorb filtered bicarbonate, resulting in bicarbonate loss and acidosis. Type 2 RTA is usually accompanied by other evidence of proximal tubular dysfunction, including Fanconi syndrome (glycosuria, phosphaturia, aminoaciduria, hypouricemia). As blood bicarbonate levels decrease, less bicarbonate is filtered and eventually the resorptive threshold is reached, such that serum bicarbonate levels stabilize (around 12-14 mEq/L [12-14 mmol/L]). Because the distal nephron functions appropriately in type 2 RTA, urine can still be acidified to a pH <5.5 and NH_4^+ production will be normal, usually making the urine anion gap negative. Hypokalemia is also often present due to increased distal tubular potassium secretion. This occurs because sodium accompanies bicarbonate to the distal tubule, where sodium is reabsorbed in exchange for potassium.

Alkali replacement is the mainstay of treatment for type 2 RTA. Thiazide diuretics may help by causing mild volume depletion with subsequent aldosterone-driven proximal reabsorption of sodium and bicarbonate.

Type 1 (Hypokalemic Distal) Renal Tubular Acidosis

In type 1 (hypokalemic distal) RTA, a distal tubular defect results in impaired excretion of hydrogen ions by the distal nephron (hence, low urine ammonium and positive urine anion gap) with inability to acidify urine below a pH of 6.0. Serum bicarbonate may fall below 10 mEq/L (10 mmol/L) as levels fail to stabilize as is seen with type 2 (proximal) RTA; despite lower filtered bicarbonate, continued impairment in acid excretion will worsen the acidosis.

The most common causes include Sjögren syndrome and other tubulointerstitial diseases, including reflux uropathy and obstructive uropathy. Type 1 RTA can also be caused by medications such as amphotericin B and lithium and has been described in dysproteinemias, sickle cell disease, and Wilson disease.

Urinary potassium wasting in the setting of diminished proton secretion underlies the development of hypokalemia. Hypercalciuria and hyperphosphatemia are frequent in untreated type 1 RTA due to increased calcium and phosphate release from bone due to buffering of acid. Reduced tubular calcium resorption in the context of acidosis exacerbates hypercalciuria. Increased proximal reabsorption of citrate in the context of acidosis and hypokalemia causes hypocitraturia. Citrate usually inhibits calcium crystallization; therefore, hypocitraturia, in addition to hypercalciuria, increases the risk of calcium phosphate stones and nephrocalcinosis.

Treatment consists of potassium citrate, 1 mEq/kg/d (which is subsequently metabolized to bicarbonate), with the dose titrated to response.

Type 4 (Hyperkalemic Distal) Renal Tubular Acidosis

Type 4 (hyperkalemic distal) RTA is caused by aldosterone deficiency or resistance. Primary adrenal insufficiency (Addison disease) may cause aldosterone deficiency. Hyporeninemic hypoaldosteronism is a more common cause and may occur in the presence of various kidney diseases, most often diabetic nephropathy. Aldosterone resistance can occur in those with tubulointerstitial disease, including urinary obstruction, sickle cell disease, medullary cystic kidney disease, and kidney transplant rejection. Drug-induced type 4 RTA can be caused by numerous drugs that reduce aldosterone production, including ACE inhibitors, angiotensin receptor blockers, heparin, and cyclooxygenase-2 inhibitors.

Type 4 RTA is associated with a positive urine anion gap but a urine pH <5.5 (see Table 10). Hyperkalemia decreases NH_3 production (and therefore NH_4^+), resulting in a positive

TABLE 10. Diagnostic Approach to Normal Anion Gap Metabolic Acidosis

Diagnosis	Urine Anion Gap $(U_{Na} + U_K) - U_{Cl}$	Serum Potassium	Urine pH
Ammonium chloride ingestion (acid load)	Negative	Normal	<5.5
Diarrhea and acidosis	Negative	Normal	<5.5
Type 2 (proximal) RTA[a]	Negative	Decreased	Variable[b]
Type 1 (hypokalemic distal) RTA	Positive	Decreased	>5.5
Type 4 (hyperkalemic distal) RTA	Positive	Increased	<5.5

RTA = renal tubular acidosis; U_{Cl} = urine chloride; U_K = urine potassium; U_{Na} = urine sodium.

[a]Type 2 (proximal) RTA is often associated with Fanconi syndrome (glycosuria, phosphaturia, aminoaciduria, hypouricemia).

[b]Patients with type 2 (proximal) RTA have normal distal renal tubular function and can acidify the urine once the serum bicarbonate drops to a point at which the filtered load of bicarbonate can be normally reabsorbed.

H CONT.

urine anion gap. Even if the distal nephron is able to decrease urine pH appropriately, reduced NH_4^+ excretion will lead to insufficient acid excretion, generating a metabolic acidosis.

Treatment is focused on correcting the underlying cause if possible; offending medications should be discontinued when identified. Because many patients are also hypertensive and volume expanded, thiazide or loop diuretics may help increase bicarbonate and decrease serum potassium. Fludrocortisone can be used to replace mineralocorticoids in hyporeninemic hypoaldosteronism in those without hypertension or heart failure. Use of the potassium exchange resin sodium polystyrene sulfonate is controversial because its effectiveness is limited. The newer cation-exchanger patiromer is effective.

Mixed Forms of Renal Tubular Acidosis

Topiramate inhibits carbonic anhydrase in both proximal and distal tubules, causing the acquired form of RTA. Due to consequent high urine pH (>6.0) and hypocitraturia, topiramate is associated with increased risk for calcium phosphate stones. Rare hereditary carbonic anhydrase deficiencies also result in combined proximal and distal RTAs. H

KEY POINTS

- In type 2 (proximal) renal tubular acidosis, failure of the proximal tubule to adequately absorb filtered bicarbonate causes bicarbonate loss; treatment consists of alkali replacement and a thiazide diuretic.
- In type 1 (hypokalemic distal) renal tubular acidosis, impaired distal hydrogen ion excretion causes citrate reabsorption and increases the risk for nephrocalcinosis; treatment consists of potassium citrate.
- In type 4 (hyperkalemic distal) renal tubular acidosis, aldosterone deficiency or resistance causes hyperkalemia and decreased NH_4^+ excretion; treatment includes correction of the underlying cause and treatment of hyperkalemia.

H Metabolic Alkalosis

Metabolic alkalosis with high blood pH results either from a loss of acid or from administration or retention of bicarbonate (alkali). Metabolic alkalosis occurs in two phases: a generation phase in which the primary disorder (such as vomiting or the accumulation of alkali) occurs, and a maintenance phase in which typical renal compensatory excretion of excess bicarbonate is ineffective. The metabolic alkalosis generation phase usually involves the gastrointestinal (GI) tract (in vomiting-induced acid loss) or the kidney (typically a mineralocorticoid effect, either primary or in response to intravascular volume depletion, with resulting sodium and bicarbonate retention at the expense of acid and potassium secretion). Conditions that contribute to maintenance of metabolic alkalosis include volume contraction, ineffective arterial blood volume, hypokalemia, chloride depletion, and decreased glomerular filtration.

Symptoms of metabolic alkalosis are usually related to the underlying disorder. Coexisting hypokalemia markedly increases the risk for cardiac arrhythmias. Severe metabolic alkalosis (serum bicarbonate >50 mEq/L [50 mmol/L]) can cause hypocalcemia, hypoventilation, and hypoxemia, with potential neurologic consequences (seizures, delirium, stupor).

Thorough history and physical examination, including assessment of blood pressure and volume status, are essential to identifying the likely cause (**Figure 10**). Laboratory evaluation is based on urine chloride rather than urine sodium. Urine sodium can be high during appropriate compensatory urine bicarbonate excretion because sodium is the primary cation excreted with bicarbonate. Urine sodium measurement may also be misleading with diuretic use.

The most common causes of metabolic alkalosis are associated with chloride depletion: vomiting, nasogastric suction, and diuretic use. Although upper GI losses are far more common, lower GI chloride-secretory diarrheas (villous adenoma, congenital chloridorrhea) can rarely cause chloride depletion with bicarbonate retention. A "contraction alkalosis" results from loss of extracellular fluid containing low amounts of bicarbonate, leaving a contracted extracellular volume around a constant amount of existing circulating bicarbonate.

In patients with low urine chloride (<15 mEq/L [15 mmol/L]), normal/low intravascular volume, and normal/low extracellular volume, treatment consists of saline administration plus repletion of potassium (saline-responsive metabolic alkalosis) while addressing the primary cause of the alkalosis. In contrast, those with a low urine chloride (<15 mEq/L [15 mmol/L]) and normal/low intravascular volume but with an increased extravascular volume (heart failure, cirrhosis) have secondary hyperaldosteronism with sodium and bicarbonate retention manifested by edema; treatment is tailored to improving effective arterial blood volume and diuresis.

Mineralocorticoid excess presents with a high urine chloride (>15 mEq/L [15 mmol/L]) with elevated blood pressure and hypokalemia without volume overload (saline-resistant metabolic alkalosis). The lack of an overt increase in extravascular volume is often described as "aldosterone escape": after initial sodium retention, sodium balance is attained through spontaneous diuresis that returns vascular volume toward normal. Mineralocorticoid excess is treated with potassium repletion and treatment of the underlying condition.

Rarely, patients may have clinical features consistent with saline-responsive metabolic alkalosis but with a urine chloride of >15 mEq/L (15 mmol/L); ongoing diuretic use can present this way. Two autosomal recessive genetic conditions, Bartter and Gitelman syndromes, result in disordered renal sodium and chloride transporters and clinically mimic loop diuretic

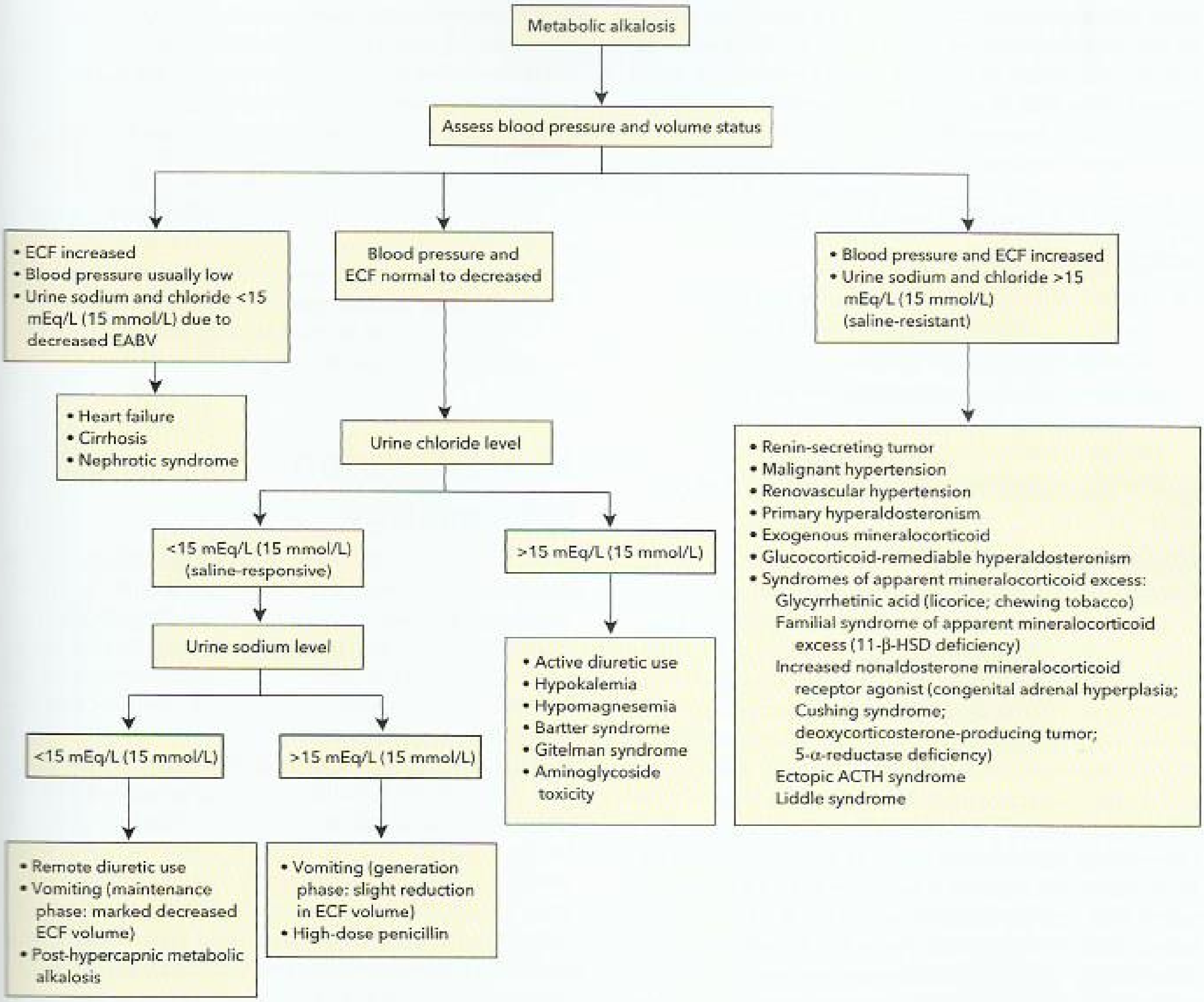

FIGURE 10. Assessment of metabolic alkalosis. ACTH = adrenocorticotropic hormone; EABV = effective arterial blood volume; ECF = extracellular fluid; HSD = hydroxysteroid dehydrogenase.

and thiazide diuretic use, respectively. These diagnoses should be considered only after urine diuretic screening.

KEY POINTS

- The most common causes of metabolic alkalosis are associated with chloride depletion: vomiting, nasogastric suction, and diuretic use.
- In metabolic alkalosis, blood pressure, volume status, and urine chloride are critical to identify the likely cause and to determine treatment.

Respiratory Acidosis

Respiratory acidosis is characterized by retention of arterial CO_2 (hypercapnia). The most common causes are inadequate ventilation (decreased central respiratory drive, thoracic neuromuscular dysfunction, musculoskeletal disorders), impaired arterial alveolar gas exchange (pneumonia, pulmonary edema, interstitial lung diseases), and airway obstruction (COPD, status asthmaticus, upper airway obstruction).

With acute respiratory acidosis, excess CO_2 is initially buffered by water, leading to formation of hydrogen ions and bicarbonate. Thus, the acute arterial blood gas reveals increased P_{CO_2}, decreased pH, and a slight increase in bicarbonate. Over 3 to 5 days, compensatory increases in renal acid excretion (with bicarbonate reabsorption) reach a new steady state (see Table 7).

Clinical manifestations of respiratory acidosis are complicated by frequently associated hypoxemia. Symptoms are predominantly neurologic, including headache, anxiety, blurred vision, and tremor. Severe acidosis can cause confusion, somnolence, or seizures. Chronic respiratory acidosis may have milder neurologic effects such as memory loss, inattentiveness, or irritability. Cardiovascular manifestations include

H CONT.

vasodilation and tachycardia that may evolve to cardiac arrhythmias and decreased cardiac output. Renal vasoconstriction with enhanced sodium retention occurs in severe respiratory acidosis, typically in those with severe lung disease and right-sided heart failure.

Treatment involves correcting the underlying mechanism if possible, and may necessitate mechanical ventilation to reduce CO_2 and oxygen supplementation. H

KEY POINTS

- In respiratory acidosis, arterial blood gases demonstrate elevated P_{CO_2} (hypercapnia), decreased pH, and increased bicarbonate.
- Symptoms of acute respiratory acidosis are predominantly neurologic and can include confusion, somnolence, or seizures; chronic respiratory acidosis may result in memory loss, inattentiveness, or irritability.

H Respiratory Alkalosis

Respiratory alkalosis is defined by a reduction in arterial P_{CO_2} (hypocapnia) due to increased ventilation. The most common causes of respiratory alkalosis are an enhanced respiratory drive (sepsis, hepatic failure, anxiety, iatrogenic hyperventilation, pregnancy, nicotine, salicylate intoxication, subarachnoid hemorrhage), hypoxemia, and pulmonary disease with stimulation of thoracic stretch receptors (pneumonia, acute respiratory distress syndrome, pulmonary embolism).

Acute hypocapnia leads to a rapid increase in arterial pH. However, immediate compensatory diffusion of hydrogen ions from intracellular stores, and subsequent reduction in serum bicarbonate through regeneration of CO_2, limits the magnitude of alkalosis. The typical arterial blood gas in this setting demonstrates a decrease in P_{CO_2}, an increase in pH, and a slight decrease in bicarbonate. Over 2 to 3 days, bicarbonate levels decrease further as compensatory kidney excretion of bicarbonate reaches a new steady state (see Table 7).

Respiratory alkalosis may cause increased cellular lactic acid production. Increases in negatively charged albumin may cause a mildly increased anion gap and decreased ionized calcium (from enhanced albumin binding). Finally, severe hypophosphatemia can occur due to a shift of phosphate from extracellular to intracellular fluid.

Clinical presentation includes underlying tachypnea and neurologic findings such as lightheadedness, numbness and paresthesias, cramps, confusion, and, rarely, seizures. An important consideration is the potential for salicylate intoxication, which in its early phases presents with mental status changes, respiratory alkalosis, and an increased anion gap metabolic acidosis.

Treatment of respiratory alkalosis is directed at correction of the primary disorder. Treatment of salicylate intoxication includes forced diuresis, urine alkalization, or hemodialysis. For anxiety-induced or psychogenic hyperventilation, increasing inspired P_{CO_2} by closed bag rebreathing may be effective. In rare circumstances of severe alkalemia (pH >7.55) with hemodynamic instability, arrhythmias, or altered mental status, strategies to reduce bicarbonate include acetazolamide or controlled mechanical hypoventilation. H

KEY POINTS

- Respiratory alkalosis is associated with a decrease in P_{CO_2}, an increase in pH, and a slight decrease in bicarbonate.
- Salicylate intoxication presents in the early phase with mental status changes, respiratory alkalosis, and an increased anion gap metabolic acidosis; treatment includes forced diuresis, urine alkalization, or hemodialysis.

Hypertension

Epidemiology

In the United States, hypertension is second only to smoking as a risk factor for death and disability. In 2010, hypertension was the leading cause of death and disability-adjusted life years worldwide. The prevalence of hypertension varies based on the cut point used to define hypertension, with the prevalence increasing from 32% to 46% when the cutoff is changed from a blood pressure (BP) ≥140/90 mm Hg to ≥130/80 mm Hg. Prevalence increases as the population ages, such that in individuals without hypertension at age 45 years, the 40-year risk for developing hypertension is 93% for black adults, 92% for Hispanic adults, 86% for white adults, and 84% for Chinese adults. Overall, persons free of hypertension at 55 years have a 90% lifetime risk for developing hypertension. Although several clinical trials have revealed that treatment of hypertension with antihypertensive medications reduces cardiovascular events, hypertension control to a BP <140/90 mm Hg is achieved in only 50% of the U.S. population.

Consequences of Sustained Hypertension

End-Organ Injury

Exposure to chronic BP elevation and, in some cases, to hypertensive emergency (defined as severely elevated BP with symptoms or signs of acute target-organ damage) can significantly injure multiple organs.

Eye

Chronically elevated BP can lead to elevated arteriolar pressure, resulting in hypertensive retinopathy, which manifests as vasoconstriction and arteriolar narrowing (visualized as "arteriovenous nicking" or "copper wiring" on funduscopic examination), endothelial damage and retinal hemorrhage (or "flame hemorrhages"), and choroidopathy. Optic neuropathy may result from ischemia to the nerve fiber secondary to

fibrinoid necrosis of vessels, manifesting as "cotton wool spots" or optic disc pallor.

Hypertensive emergency can lead to papilledema, resulting from leakage, ischemia, and fibrinoid necrosis of arterioles supplying the optic disc, causing optic nerve hemorrhage and swelling. Loss of visual acuity and blindness can occur.

Medium to Large Vessels

Long-standing hypertension can damage the vascular endothelium and, combined with elevated cholesterol and especially in the presence of diabetes mellitus, lead to peripheral vascular disease, including aortic aneurysms.

Hypertensive emergency may cause aortic aneurysmal rupture or aortic wall dissection.

Brain

Arteriosclerosis related to long-standing hypertension can cause distal ischemia, including transient ischemic attacks, lacunar infarctions, cerebrovascular accidents, and vascular neurocognitive disorder.

Hypertensive emergency has serious manifestations such as hemorrhagic stroke or subarachnoid hemorrhage from cerebral aneurysmal rupture, resulting in paralysis or fatality.

Heart

Left ventricular hypertrophy can occur as a compensatory mechanism, resulting in diastolic dysfunction, and can eventually lead to heart failure.

Hypertensive emergency can lead to acute myocardial infarction.

Kidney

Injury to the renal vasculature results in arteriosclerosis and atherosclerosis and, ultimately, hypertensive nephrosclerosis and chronic kidney disease (CKD). Hypertension is a major cause of CKD and end-stage kidney disease (ESKD), especially in black persons. Additionally, uncontrolled hypertension can increase the rate of CKD progression in patients with other underlying CKD causes, such as diabetic nephropathy.

Hypertensive emergency can cause acute kidney injury (AKI), with arteriolar proliferation (onion skinning), fibrinoid necrosis, and features of thrombotic microangiopathy.

Clinical Impact

Hypertension is one of the most significant but modifiable risk factors for cardiovascular disease, stroke, ESKD, and overall mortality. Systolic is more important than diastolic BP as an independent risk factor for coronary events, heart failure, stroke, and ESKD. Data suggest that BP-related cardiovascular disease, kidney disease, and vascular death risk is evident before development of hypertension per se; risk increases progressively throughout ranges of BP that were previously recognized as normal and are now referred to as "elevated blood pressure." Therefore, a large proportion of the U.S. population has BP below the traditional threshold for pharmacologic treatment but high enough to signify future risk. Worldwide, approximately 50% of strokes and of ischemic heart disease events are attributable to high BP, equivalent to 7.6 million premature deaths (13.5% of total) and 92 million disability-adjusted life-years (6% of total).

KEY POINTS

- Chronic elevation of blood pressure can lead to significant injury in multiple organs, including the eyes, blood vessels, brain, heart, and kidneys; hypertensive emergency is defined as severely elevated blood pressure and acute target-organ damage.
- Worldwide, approximately 50% of strokes and of ischemic heart disease events are attributable to high blood pressure.

Blood Pressure Measurement

Proper Technique

Repeat BP determinations with proper technique are necessary before making clinical decisions regarding management. Smoking, caffeinated beverages, or exercise within 30 minutes before BP measurements should be avoided. A properly calibrated and validated instrument using the oscillometric method (manual or calibrated automated device) should be employed. The patient should be quietly seated in a chair for ≥5 minutes, with the back supported, feet on the floor, legs uncrossed, and the arm bared and supported on a flat surface, with the upper arm at the heart level. The cuff size should be appropriately chosen to ensure that the bladder encircles at least 80% of the upper arm. Two common reasons for an elevated BP office reading include using a cuff that is too small or measuring the BP before the patient has rested in a seated position. At least two measurements should be taken and averaged, about 2 minutes apart; the process should be repeated if the initial measurements differ by more than 5 mm Hg. Office BP measurement(s) and the expected BP target should be communicated to the patient orally and in writing to increase awareness and adherence.

Auscultatory Blood Pressure Monitoring

The sphygmomanometer is placed on the arm with the lower cuff edge about 2 to 3 cm above the antecubital fossa. A stethoscope is placed over the brachial artery in the antecubital fossa. The cuff is inflated at least 30 mm Hg above the point at which the palpated brachial pulse disappears (estimated systolic BP). Systolic BP is recorded at the point at which the first sound is heard (or onset of the first Korotkoff sound), and diastolic BP is recorded at the point the sound disappears (or disappearance of all Korotkoff sounds).

Electronic Blood Pressure Monitoring

Electronic devices use the same oscillometric method as manual cuffs and may reduce the inter-individual variability of manual measurements. However, proper calibration is

essential for accurate measurements, especially if used by the patient at home. In general, electronic devices underestimate systolic BP and overestimate diastolic BP compared with intra-arterial measurements, which is more of a problem than with nonautomated devices.

Ambulatory Blood Pressure Monitoring

Ambulatory blood pressure monitoring (ABPM) is an electronic BP measuring device that can be worn continuously for periods of 24 hours or longer and programmed to measure and record BP every 15 to 60 minutes during daytime wakefulness and nighttime sleep. Average 24-hour, daytime, and nighttime systolic and diastolic BP are also generally reported. Normal BP by ABPM includes a 24-hour average BP <115/75 mm Hg; daytime average BP <120/80 mm Hg; and nighttime average BP <100/65 mm Hg. ABPM provides valuable information supplementary to office BP in the evaluation of scenarios such as the following:

- Suspected white coat hypertension (BP measures higher in the office)
- Suspected masked hypertension (BP measures lower in the office)
- Suspected episodic hypertension
- Apparent treatment-resistant hypertension
- Hypotensive symptoms with antihypertensive medication treatment
- Autonomic dysfunction
- Possible nondipping (<10% nocturnal decrease in BP, which is associated with increased risk for cardiovascular events). Presence of nondipping can be evaluated in patients at high risk for future cardiovascular events, such as in those with CKD, diabetes with microvascular complications, and history of previous myocardial infarction or stroke.

ABPM is clinically helpful in these scenarios and is a better prognosticator of both end-organ damage (such as left ventricular hypertrophy) and hard outcomes (such as cardiovascular death) compared with office or home BP measurements.

Home Blood Pressure Monitoring

Home BP monitoring refers to the measurement of BP at home by the patient, often by using an electronic BP device. Observational data show that home systolic and diastolic BP readings are more predictive of cardiovascular death than office readings, but less predictive than ABPM average readings. The advantage of home BP monitoring over ABPM is that home monitoring is more readily available, less expensive, and less time consuming in that the patient does not have to come to the office to have the device put on and then return the device after the 24-hour period of monitoring. In addition, home BP monitoring encourages patients to play an active role in their own BP management and be more aware of the need for adherence to lifestyle modifications and antihypertensive medications. However, unlike ABPM, which provides information regarding continuous BP measurements during awake and asleep periods as well as during ambulatory and exertion periods, home BP measurements can only be taken during awake hours and when the patient is at rest. Home BP monitoring can provide additional information ancillary to office BP in the following ways:

- Assess response to lifestyle modifications or treatment with antihypertensive medications
- Improve patient adherence
- Evaluate for white coat and masked hypertension

Several issues should be considered to ensure accuracy of home BP measurements. First, upper arm cuffs are preferred over newer devices that measure BP more distally, such as at the wrist, given that systolic BP is higher and diastolic lower in distal arteries, and finger measurements are generally not accurate. Second, education should be given regarding the proper use of the device, frequency and timing of measurements, and avoidance of self-adjustment of antihypertensive medications based on home BP. The patient should be instructed to sit in a comfortable position with legs uncrossed and back supported, and to place the left arm raised and supported to the level of the heart. The cuff should be wrapped snuggly around the upper part of the bare arm, and BP should be measured after at least 5 minutes of rest. BP readings and times of measurement should be recorded and a running list brought to office visits for evaluation and to assist with hypertension management. The device should be brought to the office initially and periodically to validate accuracy of readings. Those with home self-measured BP averaging ≥130/80 mm Hg are considered hypertensive.

KEY POINTS

- Repeat blood pressure measurements using proper technique are necessary before making clinical decisions regarding management.
- Ambulatory blood pressure monitoring can be used to evaluate for white coat, masked, episodic, or treatment-resistant hypertension; hypotensive symptoms with antihypertensive medication treatment; autonomic dysfunction; and dipping status.
- Home blood pressure monitoring can be used to assess response to lifestyle modifications or treatment, improve patient adherence, and evaluate for white coat or masked hypertension.

Definitions

The 2017 high BP guideline from the American College of Cardiology (ACC), the American Heart Association (AHA), and nine other organizations provides new BP definitions

and recommendations (http://hyper.ahajournals.org/). This guideline is an update to the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7). The new definitions of BP are listed in **Table 11**.

KEY POINT

- According to the 2017 high blood pressure guideline from the American College of Cardiology, the American Heart Association, and nine other organizations, hypertension is defined as blood pressure ≥130/80 mm Hg.

Screening and Diagnosis

The U.S. Preventive Services Task Force (USPSTF) recommends screening for hypertension in adults ≥18 years of age to identify those at increased risk for cardiovascular disease from hypertension and to begin early interventions to decrease this risk. Adults aged 18 to 39 years with a BP <130/85 mm Hg and without cardiovascular risk factors should be rescreened every 3 to 5 years. Those aged ≥40 years and persons at increased risk for hypertension (for example, those who have BP that is 130-139/85-89 mm Hg, are overweight, or are black) should be screened annually.

A diagnosis of hypertension (BP ≥130/80 mm Hg) should be based on an average of two or more elevated systolic and/or diastolic BP measurements obtained on two or more occasions. Out-of-office automated monitoring or self-monitoring of BP measurements is recommended to confirm hypertension diagnosis. Compared with a single measurement, multiple measurements over time have better positive predictive values for hypertension diagnosis. More recent evidence regarding the prevalence of white coat and masked hypertension suggests that confirmation of elevated BP with 24-hour ABPM (≥125/75 mm Hg) or self-measured home BP monitoring (≥130/80 mm Hg) may be prudent for hypertension diagnosis.

KEY POINTS

- The U.S. Preventive Services Task Force recommends screening for hypertension in adults ≥18 years of age to identify those at increased risk for cardiovascular disease from hypertension and to begin early interventions to decrease this risk.
- A diagnosis of hypertension should be based on an average of two or more elevated systolic and/or diastolic blood pressure measurements obtained on two or more occasions; obtaining measurements outside of the clinical setting for diagnostic confirmation is recommended before starting treatment. HVC

Evaluation of the Patient with Newly Diagnosed Hypertension

Initial evaluation of a patient with newly diagnosed hypertension includes a complete history, physical examination, and screening laboratory studies to address the following:

- Establish whether a familial pattern of hypertension is present.
- Rule out secondary, potentially reversible, causes.
- Identify and eliminate modifiable factors that can elevate BP.
- Assess for the presence of other cardiovascular risk factors.
- Assess for end-organ damage.
- Identify potential barriers to lifestyle modification for lowering BP.

History

A complete history should be elicited to identify a personal history of the following: stroke or myocardial infarction, thyroid disease, kidney disease, obstructive sleep apnea, and additional cardiovascular risk factors. Family history should be explored for a genetic pattern of hypertension and premature history of cardiovascular disease.

A complete review of the systems is warranted, especially to elicit the presence of episodic palpitations, headaches, or

TABLE 11. Definitions of Blood Pressure for Adults

Definitions[a]	Office-Based Readings (mm Hg)[a]	24-Hour Ambulatory Readings (mm Hg)[b]	Self-Recorded Readings (mm Hg)[b]
Normal	<120/80	<115/75	<120/80
Elevated Blood Pressure	120-129/<80	—	—
Hypertension, Stage 1	130-139/80-89	≥125/75	≥130/80
Hypertension, Stage 2	≥140/90	≥130/80	≥135/85
White Coat Hypertension	≥130/80	<125/75	<130/80
Masked Hypertension	<130/80	≥125/75	≥130/80

[a]Based on Whelton PK, Carey RM, Aronow WS, Casey DE Jr, Collins KJ, Dennison Himmelfarb C, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2018;71:e127-e248. [PMID: 29146535]

[b]The corresponding thresholds of 24-hour ambulatory and self-recorded home blood pressure readings are provided as a guide and should be interpreted with caution, given that they are based on European, Australian, and Asian populations, with few available data in U.S. populations.

sweating (which may suggest pheochromocytoma); visual changes (to assess end-organ damage); or gross hematuria (which may suggest underlying kidney glomerular disease). Behavioral and psychosocial contributors to hypertension should also be explored, including a sedentary routine, illicit drug use, excessive alcohol, tobacco smoking, high dietary sodium intake, and emotional stress.

A complete list of prescription and nonprescription medications, including complementary and alternative medications (herbals) and illicit drugs, is of utmost importance because many medications can result in reversible BP elevations (**Table 12**). If the patient is taking any drugs that may result in BP elevation, the drug should be discontinued and BP remeasured in 1 month.

Physical Examination

Physical examination should focus on the following:

- Measure BP accurately in both arms.
- Measure body weight and calculate BMI to ascertain cardiovascular risk.
- Recognize target organ damage: eye examination (retinopathy or papilledema); volume status (elevated jugular venous pressure or lower extremity edema suggesting heart failure or CKD); peripheral vascular examination (unequal pulses in all extremities, carotid or abdominal bruits suggesting vascular disease); cardiac examination (laterally displaced point of maximal impulse or S_4 gallop suggestive of left ventricular hypertrophy).
- Identify abnormalities that suggest potential secondary causes (tachycardia for pheochromocytoma; abdominal bruit for renovascular hypertension; enlarged thyroid gland suggestive of thyroid disease; violaceous abdominal striae or "buffalo hump" fat pad suggesting Cushing syndrome).

Testing

Initial testing is performed to identify common secondary causes, assess for other cardiovascular risk factors, and detect end-organ damage.

- Baseline electrocardiography (ECG) to assess for left ventricular hypertrophy (end-organ damage) or previous silent myocardial infarction.
- Blood laboratory studies: complete blood count, serum creatinine, estimated glomerular filtration rate (GFR), serum sodium, potassium, calcium, bicarbonate, fasting glucose, lipid panel, thyroid-stimulating hormone.
- Urinalysis with microscopic examination; in addition, urine albumin-creatinine ratio in patients with diabetes mellitus and in those with a high clinical suspicion for underlying CKD, such as a positive family history or presence of other end-organ damage (left ventricular hypertrophy on ECG).

TABLE 12. Drugs That Can Raise Blood Pressure

Drug/Drug Class	Potential Mechanisms
Prescription Drugs	
Antidepressants: monoamine oxidase inhibitors; selective serotonin reuptake inhibitors; serotonin-norepinephrine reuptake inhibitors	Adrenergic stimulation
Calcineurin inhibitors: cyclosporine A; tacrolimus	Vasoconstriction; sympathetic excitation; sodium retention
Contraceptives: estrogens; progesterones	Sodium retention; increased renin-angiotensin system activity
Glucocorticoids	Sodium retention; weight gain
Erythropoietin-stimulating agents	Vasoconstriction
NSAIDs	Sodium retention
Sympathomimetics (methylphenidate)	Adrenergic stimulation
Vascular endothelial growth factor antagonists	Endothelial dysfunction; vasoconstriction
Nonprescription Drugs	
Anabolic steroids	Sodium retention
Caffeine	Adrenergic stimulation
Ethanol	Adrenergic stimulation
Glycyrrhizic acid (in some licorice, cough drops, chewing tobacco)	Mineralocorticoid activity; sodium retention
Herbal supplements: ephedra; 1,3-dimethylamine; synephrine; *N*-methylamine; *Citrus aurantium*; *Caulophyllum thalictroides*	Sympathomimetic
Illicit drugs: amphetamines; cocaine; 3,4-methylenedioxymethamphetamine (ecstasy)	Sympathomimetic
NSAIDs	Sodium retention
Sympathomimetic nonprescription drugs: decongestants (phenylephrine, pseudoephedrine); appetite suppressants; vigilance enhancers	Sympathomimetic

- Echocardiography is not routinely recommended but may be helpful in suspected white coat hypertension in which presence of left ventricular hypertrophy would necessitate treatment with antihypertensive medication, even in the absence of elevated home BP. Echocardiography may also be used to detect hypertrophy in the presence of left bundle branch block on ECG or to assess baseline wall function in persons with a known history of ischemic heart disease.

More extensive diagnostic testing can be pursued if the history, physical examination, or initial testing raises suspicion for secondary causes (**Table 13**).

KEY POINTS

- Initial evaluation of patients with newly diagnosed hypertension includes a complete history, physical examination, and screening laboratory studies to assess for a familial pattern, secondary causes, other cardiovascular risk factors, end-organ damage, and modifiable lifestyle factors.
- Baseline electrocardiography is appropriate for all patients with newly diagnosed hypertension.

Primary Hypertension

Pathogenesis

Ninety percent of patients with hypertension are identified as having primary (essential) hypertension, in which no secondary underlying etiology can be found. The pathogenesis is still not completely understood, but potential mechanisms include abnormal kidney sodium handling, increased activity of the renin-angiotensin system, and elevated sympathetic tone.

In general, hypertension is a complex polygenic disorder in which many genes or combinations may influence BP. Many genetic variants affect the distal tubular sodium transport and may result in excess sodium retention, leading to hypertension. Genetic polymorphisms involving oxidative stress, mediators of vascular smooth muscle tone, and vasoactive mechanisms have also been implicated. However, associated genetic variants have only small effects, such that the collective effect of all identified BP loci account for only about 3.5% of BP variability. Monogenic forms, in which single gene mutations explain the underlying pathophysiology of hypertension, are less common and include such diseases as glucocorticoid-remediable aldosteronism, Liddle disease, and Gordon syndrome.

TABLE 13. Secondary Causes of Hypertension

Underlying Cause	Diagnostic Testing
Kidney disease	Serum creatinine; estimated glomerular filtration rate; urinalysis with microscopic examination; urine albumin-creatinine ratio; kidney ultrasonography
Renovascular disease	Renal duplex Doppler ultrasonography; CT or MR angiography; renal artery angiography
Obstructive sleep apnea	Polysomnography
Pheochromocytoma	Plasma fractionated metanephrines; 24-hour urine metanephrines and catecholamines
Hypo- or hyperthyroidism	Thyroid-stimulating hormone; free thyroxine
Primary hyperparathyroidism	Intact parathyroid hormone; serum calcium and phosphorus
Gordon syndrome (pseudohypoaldosteronism type II)	Clinical diagnosis; family history; aldosterone and renin levels; electrolytes
Aortic coarctation	Blood pressure measurements in arms and legs; CT or MR angiography; transthoracic echocardiography
Conditions Associated with Hypokalemia	**Diagnostic Testing**
High aldosterone conditions: Primary hyperaldosteronism: adrenal adenoma (rarely carcinoma or ectopic); bilateral adrenal hyperplasia Familial hyperaldosteronism type I (glucocorticoid-remediable aldosteronism; >50% normokalemic), type II, or type III Secondary hyperaldosteronism: renal artery stenosis; renin-secreting tumor	Serum sodium and potassium concentrations; plasma aldosterone concentration/plasma renin activity ratio; saline suppression test; CT imaging; adrenal vein sampling; genetic testing
Cushing syndrome	Dexamethasone suppression test; 24-hour urine cortisol excretion; salivary cortisol
Congenital adrenal hyperplasia	Clinical diagnosis
Apparent mineralocorticoid excess	Clinical diagnosis; aldosterone and renin levels; electrolytes
Liddle syndrome	Clinical diagnosis; family history; aldosterone and renin levels; electrolytes

Dietary factors have been implicated as contributors to hypertension development. Populations with low sodium intake have lower BP than those with high intake. Habitual high sodium intake along with low potassium intake seen in a modern diet is a critical factor contributing to the worldwide high prevalence of hypertension. This is especially true for those with salt sensitivity, common in black patients, older adults, and those with CKD or diabetes mellitus, in which an increase in sodium intake leads to a disproportionate increase in BP.

Positive correlations are also found between BP and physical inactivity, being overweight or obese, excess alcohol intake, hyperuricemia, and insulin resistance.

KEY POINT

- Habitual high sodium intake along with low potassium intake is a critical factor contributing to the worldwide high prevalence of hypertension.

Management

General Approach

Treatment recommendations for specific populations are elaborated upon in their respective sections. Importantly, consideration must be given to individual patient characteristics and circumstances to tailor management.

The 2017 ACC/AHA BP guideline provides treatment recommendations, including the following:

- Nonpharmacologic therapy is recommended for those with elevated BP (systolic BP between 120-129 mm Hg and diastolic BP <80 mm Hg) or stage 1 hypertension (systolic BP between 130-139 mm Hg or diastolic BP between 80-89 mm Hg) and a 10-year cardiovascular risk of <10%.
- Nonpharmacologic and drug treatment is recommended for those with BP ≥130/80 mm Hg and clinical cardiovascular disease or a 10-year cardiovascular risk ≥10% to a BP goal of <130/80 mm Hg.
- Nonpharmacologic and drug treatment is recommended for those with no cardiovascular disease and a 10-year cardiovascular risk of <10% for stage 2 hypertension (≥140/90 mm Hg).
- Adults with stage 2 hypertension and an average BP that is 20/10 mm Hg above their BP target should be treated with a combination of two first-line antihypertensive drugs of different classes.
- The target systolic BP goal for noninstitutionalized, ambulatory community-dwelling patients who are ≥65 years of age is <130 mm Hg.
- The target BP for patients with hypertension and diabetes mellitus is <130/80 mm Hg.
- The target BP for patients with hypertension and CKD is <130/80 mm Hg.

Lifestyle Modifications

Lifestyle modifications and cardiovascular risk factors should be addressed in all patients with elevated BP or hypertension, even if pharmacologic treatment is necessary. Several nonpharmacologic interventions have been shown to have efficacy in reducing BP (**Table 14**). The best evidence for BP lowering effects in individuals with elevated BP or hypertension exists for weight loss, the Dietary Approaches to Stop Hypertension (DASH) diet, and dietary sodium reduction. Of the lifestyle interventions tested in clinical trials, weight reduction was most efficacious, followed by sodium reduction. Although difficult to achieve, a combination of lifestyle modifications (such as DASH combined with a low sodium diet alone or in combination with weight loss) had BP-lowering effects greater than or equal to those of single-drug therapy in hypertensive patients. Other nonpharmacologic interventions supported by evidence include potassium supplementation (preferably in dietary modification), increased physical activity, and moderation in alcohol consumption. Controlled trials of an increase in magnesium or calcium intake revealed less robust BP-lowering effects. Regardless of BP effects, tobacco cessation should be encouraged given that smoking is a significant risk factor for cardiovascular disease.

Based on the level of evidence for behavioral therapies, transcendental meditation, yoga, and biofeedback had modest, mixed, or no consistent BP-lowering effects. More data

TABLE 14. Efficacy of Lifestyle Modifications for Reducing Blood Pressure

Approach	Recommendation	Effect on Systolic Blood Pressure
Reduce weight	BMI <25	5 to 10 mm Hg reduction per 10-kg (22-lb) weight loss
Reduce dietary sodium	1500 to 2400 mg/d	2 to 8 mm Hg reduction
Consume DASH (Dietary Approaches to Stop Hypertension) diet	Fruits; vegetables; low-fat dairy; whole grains; legumes; low saturated fat and sodium; high potassium, magnesium, and calcium	8 to 14 mm Hg reduction
Increase potassium intake	4700 mg/d	Variable reductions
Moderate alcohol consumption	Men: ≤2 drinks per day; women: ≤1 drink per day	2 to 4 mm Hg reduction
Exercise	30 min/d, most days (not consistently independent of weight loss)	4 to 9 mm Hg reduction
Alternative approaches	Device-guided breathing; yoga; meditation; biofeedback; acupuncture	Variable reductions

support efficacy of device-guided breathing than acupuncture among the noninvasive procedures and devices that were evaluated.

It is imperative to tailor lifestyle modifications to the individual patient while considering patient needs, patient support systems and resources, and readiness for behavioral change.

KEY POINTS

- The 2017 high blood pressure guideline from the American College of Cardiology, the American Heart Association, and nine other organizations recommends a blood pressure goal of <130/80 mm Hg in most adult patient populations.
- Lifestyle modifications (weight loss, diet, dietary sodium reduction) and cardiovascular risk factors should be addressed in all patients with elevated blood pressure and hypertension.

Pharmacologic Therapy

Clinical trials data suggest that antihypertensive medication therapy can be associated with up to a 40% reduction in stroke, 25% reduction in myocardial infarction, and 50% reduction in heart failure. In addition to lifestyle modification, treatment with antihypertensive medications should be initiated in patients with stage 1 hypertension and clinical cardiovascular disease or a 10-year cardiovascular risk ≥10% and in all patients with stage 2 hypertension.

Clinical trial evidence reveals that lowering BP is more important than the class of antihypertensive drug used to achieve control. Head-to-head trials of antihypertensive medications revealed comparable effects on cardiovascular outcomes, except that for preventing heart failure, initial therapy with a thiazide diuretic was more effective than a calcium channel blocker (CCB) or ACE inhibitor, and an ACE inhibitor was more effective than a CCB. The primary agents recommended are those that were shown to reduce clinical events and include a thiazide diuretic, CCB, ACE inhibitor, or angiotensin receptor blocker (ARB) for hypertension in the general nonblack population, including those with diabetes. In black patients, initial antihypertensive therapy should include a thiazide diuretic or a CCB (see Specific Populations, Black Patients).

There are not enough good quality head-to-head randomized trials comparing other antihypertensive classes (β-blockers, central- or peripheral-acting α-blockers, vasodilators, aldosterone receptor antagonists, or loop diuretics) to the four drug classes mentioned. Therefore, these drug classes are not recommended as first-line therapy but can be used in specific populations (β-blockers for post-myocardial infarction or heart failure; aldosterone receptor blockers for heart failure; loop diuretics for advanced CKD) or as add-on therapy for resistant hypertension.

See **Table 15** for more information on frequently used antihypertensive medications.

Diuretics

Initial antihypertensive treatment may include thiazide diuretics, which act by inhibiting the sodium-chloride cotransporter in the distal renal tubule. Although hydrochlorothiazide is the most commonly used thiazide diuretic, chlorthalidone is

TABLE 15. Frequently Used Antihypertensive Medications

Class/Agent	Common Side Effects/Contraindications
Thiazide diuretics (e.g., hydrochlorothiazide; chlorthalidone)	Hypokalemia; hyponatremia; hyperlipidemia; hyperuricemia; hyperglycemia. Avoid in gout unless patient is on urate-lowering therapy.
ACE inhibitors (e.g., captopril; lisinopril; enalapril; benazepril)	Hyperkalemia; cough. Avoid use with angiotensin receptor blockers or direct renin inhibitors. Avoid in pregnancy.
Angiotensin receptor blockers (e.g., candesartan; losartan; valsartan; irbesartan)	Hyperkalemia. Avoid use with ACE inhibitors or direct renin inhibitors. Avoid in pregnancy.
Calcium channel blockers	
Dihydropyridines (e.g., amlodipine; felodipine; nifedipine)	Pedal edema; headache; flushing.
Non-dihydropyridines (e.g., diltiazem; verapamil)	Constipation. Avoid in HFrEF. Avoid routine use with β-blockers (heart block, bradycardia). Drug interactions (*CYP3A4* major substrate and moderate inhibitor).
β-Blockers (e.g., atenolol; metoprolol tartrate; metoprolol succinate; labetalol)	Fatigue; bronchospasm; sexual dysfunction; hyperglycemia.
Potassium channel openers (vasodilators) (e.g., hydralazine; minoxidil)	Edema. Hydralazine: lupus-like syndrome. Minoxidil: hypertrichosis.
α-Blockers (e.g., prazosin)	Orthostatic hypotension; dizziness.
Central α-agonists (e.g., clonidine, oral or patch)	Fatigue; depression; rebound hypertension.
Potassium-sparing diuretics (e.g., spironolactone; amiloride; eplerenone)	Hyperkalemia. Avoid if GFR <45 mL/min/1.73 m^2. Spironolactone: gynecomastia.

GFR = glomerular filtration rate; HFrEF = heart failure with reduced ejection fraction.

preferred due to a prolonged half-life, which allows once-daily dosing, and evidence from trials demonstrating efficacy in reducing cardiovascular events. Loop diuretics are preferred in patients with symptomatic heart failure or CKD with an estimated GFR <30 mL/min/1.73 m^2 (see Kidney Disease, Management).

Suboptimal BP therapy in patients with difficult-to-control hypertension is frequently the result of not including a diuretic medication, which ensures that extracellular volume expansion is prevented or treated. This is particularly important in sodium-retentive, edematous conditions such as heart failure, liver cirrhosis, or CKD. Even in the absence of edematous conditions, persistent intravascular volume expansion without apparent edema can still contribute to hypertension that appears resistant to treatment. In addition, diuretic medication should be prescribed in adequate doses, with dosing frequency tailored appropriately to the diuretic half-life. For example, loop diuretics such as furosemide should be dosed at least twice to three times daily, and higher doses should be used in patients with low GFR.

Potassium-sparing diuretics, such as aldosterone receptor antagonists (spironolactone or eplerenone) or epithelial sodium channel blockers (amiloride), are weaker diuretics. These are often used in liver cirrhosis, heart failure, or resistant hypertension. Caution and close monitoring are advised when these medications are prescribed concomitantly with other drug classes that also raise the serum potassium, such as ACE inhibitors, ARBs, or direct renin inhibitors, and in patients with reduced GFR.

Calcium Channel Blockers

There are two classes of CCBs: dihydropyridines (amlodipine, felodipine, nifedipine) and nondihydropyridines (diltiazem, verapamil). No data support the use of one class over the other for hypertension management, although long-acting dihydropyridines are usually chosen. Nondihydropyridines have more pronounced cardiac effects such as diminished cardiac contractility (negative inotropy) and atrioventricular nodal blockade, and caution should be taken in prescribing these medications concomitantly with β-blockers or in patients with heart failure with severely reduced ejection fraction, sick sinus syndrome, or second- or third-degree atrioventricular block. Additionally, short-acting nifedipine was associated with mortality if used immediately after acute myocardial infarction due to profound hypotension and sympathetic activation. Finally, there may be an increased risk for myopathy if a CCB (especially nondihydropyridines) is used concomitantly with a high-dose statin.

Renin-Angiotensin System Agents

Renin angiotensin system (RAS) agents are ACE inhibitors, ARBs, and direct renin inhibitors (such as aliskiren). Clinical trials reported similar efficacy of ACE inhibitors and ARBs on reducing BP, progression of albuminuria and CKD, and risk for cardiovascular events. Therefore, neither agent is preferred over the other.

Dry cough is a side effect of ACE inhibitors but is generally not reported with ARBs. Angioedema, a life-threatening condition, is a complication of both ACE inhibitors and renin inhibitors. Patients with a compelling indication for RAS inhibition who develop angioedema can be treated with an ARB with very careful monitoring, given a low but possible risk for occurrence. There are less outcomes data on the effects of aliskiren, although similar BP-lowering effect is expected. RAS agents should not be used in combination, and they are contraindicated in pregnancy.

Combination Therapy

Combination therapy with more than one drug class (separately or as a single-dose pill) may be necessary to control BP. The 2017 ACC/AHA BP guideline recommends combination therapy with two first-line antihypertensive drugs of different classes for adults with stage 2 hypertension and an average BP of 20/10 mm Hg above their BP target (typically ≥150/90 mm Hg). There are no definitive recommendations for best drug combinations, but some data suggest an ACE inhibitor/CCB combination may be more efficacious than an ACE inhibitor/thiazide diuretic combination. Using a thiazide diuretic/CCB combination is also an option.

Combined use of any RAS drug classes (ACE inhibitors, ARBs, and direct renin inhibitors) is not recommended; several clinical trials (ONTARGET, NEPHRON-D, ALTITUDE) have revealed more adverse events with these combinations (hyperkalemia, hypotension, AKI), without additional cardiovascular or renal benefits.

Assessment of Efficacy and Medication Titration

Adherence and response to treatment should be assessed 4 weeks after treatment initiation or sooner, based on the urgency for BP lowering. Further assessments are necessitated until target is achieved. Three strategies are possible for dose titration:

1. Maximize the first medication dose before adding a second.
2. Add a second medication before reaching the maximum dose of the first.
3. Start with two medication classes separately or as fixed-dose combinations.

There are no randomized controlled trials comparing these strategies; therefore, the strategy should be tailored to the individual patient, dose-related side effects, and adherence patterns. Generally, there is diminishing return in BP lowering if dose is titrated up from 50% to 100% of maximum. Also, it is unlikely that increasing the dose from 50% to 100% of maximum will result in an additional >5 mm Hg BP reduction; an additional agent may therefore need to be added. Finally, titration to maximum doses may more commonly result in side effects and reduce adherence.

KEY POINTS

- In addition to lifestyle modification, pharmacologic therapy should be initiated in patients with stage 1 hypertension and clinical cardiovascular disease or a 10-year cardiovascular risk ≥10% and in all patients with stage 2 hypertension.
- A thiazide diuretic, calcium channel blocker, ACE inhibitor, or angiotensin receptor blocker is recommended as initial therapy for hypertension in the general nonblack population, including those with diabetes mellitus.
- Combination therapy with two first-line antihypertensive drugs of different classes is recommended for adults with stage 2 hypertension and an average blood pressure (BP) that is 20/10 mm Hg above their BP target.

White Coat Hypertension

White coat hypertension refers to elevated BP measured in the office, but out-of-office BP averages that are not elevated (see Table 11). In adults with untreated systolic BP >130 mm Hg but <160 mm Hg or diastolic BP >80 mm Hg but <100 mm Hg, it is reasonable to screen for white coat hypertension using either daytime ABPM or home BP monitoring. Before white coat hypertension is diagnosed, the reliability of out-of-office measurements must be confirmed; for example, the patient's home BP monitor should be calibrated against the office sphygmomanometer or, preferably, BP should be measured by ABPM.

The prevalence of white coat hypertension is approximately 13% and as high as 35% in some hypertensive populations. The risk for conversion of white coat hypertension to sustained hypertension is estimated to be about 1% to 5% per year by ABPM or home BP monitoring. Incidence of conversion is higher with older age, obesity, or black race. Additionally, such patients may have a slightly higher cardiovascular risk compared with normotensive patients, but a lower risk than in those with masked or sustained hypertension. Optimal management of such patients is uncertain. A 3-month trial of lifestyle modifications is suggested in those with suspected white coat hypertension. If this does not result in a decrease of daytime ABPM or home BP to <130/80 mm Hg, then initiation of an antihypertensive drug should be considered. Screening echocardiography may also be considered to evaluate for left ventricular hypertrophy, the presence of which necessitates treatment with antihypertensives.

KEY POINT

- Lifestyle modifications and careful monitoring should be considered for patients with white coat hypertension due to increased risk for future development of hypertension and slightly higher cardiovascular risk compared with normotensive patients.

Masked Hypertension

Masked hypertension is defined as BP that is normal in the office but elevated in the ambulatory setting (see Table 11). It is associated with an increased prevalence of target organ damage and risk of cardiovascular disease, stroke, and mortality compared with normotension. In adults with elevated office BP (120-129/<80 mm Hg) but not meeting the criteria for hypertension or with end-organ damage such as left ventricular hypertrophy, screening for masked hypertension with daytime ABPM or home BP is reasonable.

The prevalence of masked hypertension varies from 10% to 26% in population-based surveys and from 14% to 30% in normotensive clinic populations. A 3-month trial of lifestyle modifications should be considered in suspected cases of masked hypertension. Antihypertensive treatment should be initiated if daytime ABPM or home BP is still ≥130/80 mm Hg.

KEY POINT

- Masked hypertension is associated with an increased risk for sustained hypertension and cardiovascular disease; after a 3-month trial of lifestyle modifications, antihypertensive medication should be initiated if daytime ambulatory or home blood pressure is still ≥130/80 mm Hg.

Resistant Hypertension

Resistant hypertension is defined as BP that remains above goal despite concurrent use of three antihypertensive agents of different classes, or BP at goal but requiring four or more medications. One of these medications must be a diuretic to make the diagnosis. A prevalence of 2% to 10% is reported in the general population, but can be as high as 40% in patients with CKD. Risk factors include older age, male sex, black race, diabetes, and higher BMI.

Before the diagnosis is made, a systematic approach to BP control should include ensuring accuracy of BP readings, optimizing medication selection and dosing, and addressing potential secondary and reversible causes of hypertension. The importance of out-of-office BP measurements (home or ABPM) as a part of evaluation to rule out white coat hypertension and to confirm resistance is increasingly recognized. Behaviors that could lead to high BP, including excessive sodium consumption, should be reviewed, and use of recreational drugs and prescription or nonprescription medications (such as complementary and alternative medications) that may exacerbate hypertension should be excluded. Adherence to antihypertensive medications, including correct frequency and dosage, should be confirmed, and potential reasons for nonadherence, such as medication side effects, should be addressed.

The cornerstone of management includes a low sodium diet and treatment with an appropriate diuretic with attention to dosage and dosing frequency (see Diuretics). Patients should be treated with a combination of medications from different

classes: a RAS blocker (either an ACE inhibitor, an ARB, or a direct renin inhibitor), a calcium antagonist, a diuretic, and possibly a β-blocker. Recent trials support the efficacy of adding a low-dose aldosterone receptor antagonist (spironolactone or eplerenone) for treatment of resistant hypertension. If additional agents are needed for BP control or the patient is intolerant of the aforementioned agents, then vasodilators (hydralazine or minoxidil), α-blockers (doxazosin, prazosin) or central sympathetic agonists (clonidine) can be added.

KEY POINTS

- Resistant hypertension is defined as blood pressure (BP) that remains above goal despite the concurrent use of three antihypertensive agents of different classes, or BP at goal but requires four or more medications; one of the medications must be a diuretic to make the diagnosis.
- Management of resistant hypertension includes accurate out-of-office blood pressure (BP) measurement, addressing behaviors that contribute to high BP, avoiding drugs that exacerbate hypertension, reducing dietary sodium, and ensuring appropriate diuretic dose and frequency.

H Secondary Hypertension

In about 10% of adults with hypertension, a specific and remediable cause can be identified for hypertension. Diagnostic testing for secondary causes of hypertension can be pursued if a high clinical suspicion exists following history, physical examination, and initial laboratory testing (see Table 13). Factors that raise pretest probability for secondary hypertension include hypertension onset at <30 years of age, abrupt onset or worsening BP if previously well controlled, drug resistance, clinical features indicating a secondary process, presence of target organ damage disproportionate to hypertension duration or severity, diastolic hypertension onset in those aged ≥65 years, and unprovoked or excessive hypokalemia.

Kidney Disease

Pathophysiology and Epidemiology

Hypertension develops in the setting of both AKI and CKD. Underlying parenchymal kidney disease is an important cause of hypertension, and up to 85% of patients with CKD have high BP. Hypertension prevalence increases with GFR decline. Additionally, chronic uncontrolled hypertension is a leading cause of CKD and of CKD progression to ESKD. BP elevation in glomerular disease is primarily attributed to fluid overload, as evidenced by suppression of the RAS and increased release of atrial natriuretic peptide. In acute vascular diseases affecting the kidney (vasculitis or scleroderma renal crisis), elevated BP is thought to result from ischemia-induced activation of the RAS. Endothelial vascular injury, increased sympathetic tone, and impaired nitric oxide synthesis are also implicated.

Clinical Manifestations

Underlying kidney disease is suggested by an elevated serum creatinine concentration and/or an abnormal urinalysis or albuminuria. Patients can present with other evidence of hypertension end-organ damage (such as left ventricular hypertrophy) and edema, but the absence of either does not exclude kidney disease as hypertension etiology.

Diagnosis

Initial evaluation of hypertension in all patients includes assessment of serum creatinine and estimated GFR, urinalysis with microscopic examination to exclude hematuria and/or proteinuria, and urine albumin-creatinine ratio in those with diabetes mellitus or family history of kidney disease. Abnormalities in any of these tests can signify underlying kidney disease. In those with a normal serum creatinine but a high suspicion for certain kidney diseases, such as a positive family history of autosomal dominant polycystic disease, kidney ultrasonography can be undertaken.

Management

The 2017 ACC/AHA BP guideline recommends a BP target of <130/80 mm Hg for patients with hypertension and CKD. An ACE inhibitor or an ARB is a preferred drug for treatment of hypertension for patients with stage G3 CKD or higher or for those with stage G1 or G2 CKD with albuminuria (albumin-creatinine ratio ≥300 mg/g).

Kidney function and serum potassium should be reassessed 2 to 3 weeks after medication initiation. An increase in serum creatinine of 25% to 30% is acceptable, but the dose may need to be lowered or medication discontinued if more severe decline in kidney function is observed; in such cases, bilateral renovascular disease should also be considered.

Given that sodium retention and volume overload are major contributory factors in the hypertension of CKD, dietary sodium restriction to <2000 mg/d and addition of a diuretic are both essential for control of BP, especially in advanced CKD. The following factors addressing appropriate dose and dosing interval for diuretics should be considered:

- Higher doses of diuretics are required in patients with CKD due to decreased GFR.
- Thiazide diuretics may be less effective if the estimated GFR is <30 mL/min/1.73 m²; although there are no head-to-head trials, it seems preferable to use chlorthalidone instead of hydrochlorothiazide in patients with CKD due to a longer half-life.
- For an estimated GFR <20 to 30 mL/min/1.73 m², a loop diuretic can be used effectively, with more frequent dosing interval (for example, furosemide should be dosed at least two to three times daily).
- The combination of a thiazide and a loop diuretic can be used to augment diuresis, with careful monitoring.
- Volume overload refractory to medical management in those with stage G5 CKD (estimated GFR <15 mL/min/1.73 m²) may necessitate dialysis.

Renovascular Hypertension

Pathophysiology and Epidemiology

Prevalence of renovascular hypertension is higher in white than black populations. Pathogenesis involves renal hypoperfusion as a result of renal artery stenosis, with subsequent release of renin and angiotensin resulting in systemic vasoconstriction, sodium retention, and hypertension. Disease can be unilateral or bilateral. Parenchymal kidney damage with loss of kidney function can occur.

There are two types of renovascular disease: (1) atherosclerotic renovascular disease, which usually occurs in patients >45 years of age, especially in those with diffuse atherosclerosis, but can also be isolated to the kidney; and (2) fibromuscular dysplasia, a nonatherosclerotic disorder that usually affects the mid and distal portions of the renal artery and usually occurs in young persons, particularly women.

Clinical Manifestations

Patients with atherosclerotic renovascular disease often have other manifestations of atherosclerosis, including the presence of coronary artery, cerebrovascular, or peripheral vascular disease. Bruits may be auscultated, especially a systolic-diastolic abdominal bruit that lateralizes to one side. Clinical suspicion should be high in patients who present with onset of severe hypertension after age 55 years, recurrent flash pulmonary edema, refractory heart failure, AKI after initiation of an ACE inhibitor/ARB, or AKI after control of BP to target. Asymmetry in kidney sizes of >1.5 cm on imaging or the presence of a unilateral small kidney ≤9 cm also increases likelihood of renovascular disease.

Abrupt onset of hypertension at an age <35 years suggests fibromuscular dysplasia.

Diagnosis

Routine testing for renovascular disease may not change management because recent data suggest that medical therapy may be as beneficial as invasive procedures, especially for those with atherosclerotic renovascular disease. However, in young patients with resistant hypertension and a high clinical suspicion for fibromuscular dysplasia, renal artery imaging may be considered. Plasma renin activity, captopril renal scintigraphy, and selective renal vein renin measurements are no longer recommended as diagnostic tests given the availability of more sensitive and specific imaging tests.

Renal duplex Doppler ultrasonography is a reasonable imaging modality if performed by experienced sonographers. MR or CT angiography have higher diagnostic utility but are potentially harmful in patients with severe CKD given the risk for contrast nephropathy and gadolinium-induced nephrogenic systemic fibrosis. A stenosis >75% in one or both renal arteries or >50% with post-stenotic dilatation suggests the diagnosis. Renal intra-arterial angiography is the gold standard and can be considered if other noninvasive tests are negative, clinical suspicion is high, and an invasive procedure is being considered. It is not recommended as a routine test due to adverse risks, such as contrast nephropathy and cholesterol emboli.

Management

Three large randomized trials (STAR, ASTRAL, and CORAL) failed to show that renal artery angioplasty confers additional benefit above optimal medical therapy in patients with atherosclerotic renovascular disease and stable kidney function. Medical therapy in those suspected of having atherosclerotic renovascular disease includes treatment of underlying cardiovascular risk factors (such as hypercholesterolemia) and an ACE inhibitor or ARB. Patients who may benefit from percutaneous angioplasty and stenting or surgical intervention include those who present with a short hypertension duration; are refractory to medical therapy; have severe hypertension or recurrent acute flash pulmonary edema; have AKI following treatment with an ACE inhibitor or ARB; or have progressive impaired kidney function thought to result from bilateral renovascular disease or unilateral stenosis affecting a solitary functioning kidney. Patients with advanced CKD or with proteinuria >1000 mg/24 h are less likely to benefit from revascularization.

In young persons with fibromuscular dysplasia, studies have suggested that angioplasty alone may improve BP and even cure hypertension.

Primary Hyperaldosteronism

A triad of resistant hypertension, metabolic alkalosis, and hypokalemia (including in patients treated with low-dose thiazide diuretics) should raise suspicion for primary aldosteronism (see Table 13). Primary hyperaldosteronism, in which aldosterone production cannot be suppressed with sodium loading, is the most common cause of secondary hypertension in middle-aged adults and an important cause of resistant hypertension. Screening for primary hyperaldosteronism is recommended if any of the following are present: resistant hypertension, hypokalemia (spontaneous or substantial, if diuretic induced), incidentally discovered adrenal mass, family history of early-onset hypertension, or stroke at age <40 years. Calculation of plasma aldosterone concentration (PAC)/plasma renin activity (PRA) ratio is used for screening, with a very high ratio of PAC/PRA suggestive of the diagnosis. Confirmatory diagnostic testing is needed with a saline suppression test.

PAC and PRA are usually suppressed in other disorders with hypokalemia and hypertension, including Cushing syndrome, syndrome of apparent mineralocorticoid excess, familial hyperaldosteronism type I (glucocorticoid-remediable aldosteronism), and Liddle syndrome (see Table 13). Renal artery stenosis and renin-secreting tumors generate high PRA and, therefore, lower PAC, with subsequent lowering of the PAC/PRA ratio, to usually <10. See MKSAP 18 Endocrinology and Metabolism for details.

Pheochromocytomas

Pheochromocytomas are rare catecholamine-secreting neoplasms of the adrenal medulla or sympathetic ganglia that occur in <0.2% of patients with hypertension. Presence of the

H CONT following characteristics raises clinical suspicion and may prompt testing: resistant hypertension; hypertension onset that is new or at a young age; paroxysmal hypertension; episodic tachycardia, headaches, and sweating; history of familial syndromes; adrenal adenoma found incidentally on imaging with or without hypertension; or pressor response during invasive procedures or anesthesia. Diagnostic tests include plasma fractionated metanephrines and 24-hour urine metanephrines and catecholamines. Positive test results should be followed by imaging to locate the tumor. Definitive treatment is surgical resection. See MKSAP 18 Endocrinology and Metabolism for details. H

KEY POINTS

- The 2017 high blood pressure guideline from the American College of Cardiology, the American Heart Association, and nine other organizations recommends a target blood pressure of <130/80 mm Hg in patients with hypertension and chronic kidney disease.
- Treatment of hypertension in patients with chronic kidney disease includes an ACE inhibitor or angiotensin receptor blocker, dietary sodium restriction to <2000 mg/d, and addition of a diuretic as needed to control intravascular volume.
- Medical therapy for renovascular disease, including treatment of underlying cardiovascular risk factors and use of an ACE inhibitor or angiotensin receptor blocker, may be as beneficial as invasive procedures.
- Primary hyperaldosteronism is the most common cause of secondary hypertension in middle-aged adults and an important cause of resistant hypertension; the plasma aldosterone concentration/plasma renin activity ratio is used for screening.

Hypertensive Urgency

Hypertensive urgency is defined as severely elevated BP—often a systolic BP ≥180 mm Hg and/or diastolic BP ≥110 mm Hg—in a patient without obvious signs or symptoms of acute or impending change in target organ damage or dysfunction. Patients are often asymptomatic or present with a mild headache in an ambulatory setting. The most important aspect of initial management is a focused history and physical examination to exclude the presence of acute end-organ damage in the setting of severely elevated BP, which would raise concern for hypertensive emergency. Referral to an emergency department may be required for further diagnostic testing to rule out target organ damage. See MKSAP 18 Pulmonary and Critical Care Medicine for information on hypertensive emergencies.

Management is very challenging and includes the assessment of imminent risk of cardiovascular events from severe hypertension versus risk of adverse sequelae from rapid BP reduction. These may include AKI, myocardial infarction, or stroke resulting from decreased perfusion to organs and limited time for autoregulation to maintain perfusion. Therefore, recommendations regarding the rapidity of BP lowering in this setting are controversial and not based on strong evidence. Generally, systolic BP may be lowered in patients with imminent risk of target organ damage but without a compelling condition (aortic dissection, preeclampsia, or pheochromocytoma crisis) by no more than 25% within the first hour, then to <160/100 mm Hg within the next 2 to 6 hours, then cautiously to target during the following 24 to 48 hours. Choice of antihypertensive medication should be tailored to the specific patient. If there is concern for imminent end-organ damage, faster-acting antihypertensive agents, such as oral clonidine, can be given to lower BP. Several hours of observation in the ambulatory setting may be required to ensure that the patient remains asymptomatic and that BP is decreasing before discharge. In patients in whom hypertensive urgency developed because of medication nonadherence, antihypertensive medications can be resumed slowly and in a stepwise fashion, with care not to drop the BP precipitously. Close follow-up of such patients is necessary, and further management can include home monitoring of BP.

KEY POINTS

- Hypertensive urgency is defined as severely elevated blood pressure (BP)—often a systolic BP ≥180 mm Hg and/or diastolic BP ≥110 mm Hg—in a patient without obvious signs or symptoms of acute end-organ damage.
- Management of hypertensive urgency in patients with imminent risk of target organ damage but without a compelling condition includes lowering the systolic blood pressure by no more than 25% within the first hour, then to <160/100 mm Hg within the next 2 to 6 hours, then cautiously to target during the following 24 to 48 hours.

Specific Populations

Women

Hypertension prevalence is lower in women <50 years of age compared with men, but prevalence increases with older age and eventually becomes similar in both sexes. Women, particularly if premenopausal, are at a lower risk than men for hypertension complications, such as coronary artery disease, stroke, and left ventricular hypertrophy. Clinical trials suggest that women derive similar relative benefits from antihypertensive treatment as men, and recommendations for BP targets and agents are the same.

Women of childbearing age who anticipate pregnancy should not be prescribed RAS agents (ACE inhibitors, ARBs, or direct renin inhibitors) because of the risk for urogenital developmental abnormalities; these agents are contraindicated in pregnant women. Instead, transition to methyldopa, nifedipine, and/or labetalol during pregnancy is a reasonable choice. See The Kidney in Pregnancy for more information.

Oral contraceptives may be associated with modest increases in BP, which usually resolve with discontinuation; women prescribed these medications should be monitored. Hormone replacement therapy consists of much lower estrogen doses and is not associated with elevated BP.

Patients with Diabetes Mellitus

The 2017 ACC/AHA BP guideline recommends a BP goal of <130/80 mm Hg for patients with diabetes. First-line therapy in nonblack patients with diabetes includes a thiazide diuretic, CCB, ACE inhibitor, or ARB; ACE inhibitors or ARBs are reasonable choices in the presence of albuminuria. In black patients with diabetes, a thiazide diuretic or CCB is recommended as initial therapy.

The American Diabetes Association (ADA) recommends that most patients with diabetes and hypertension should be treated to a BP goal of 140/90 mm Hg; lower systolic and diastolic BP targets, such as 130/80 mm Hg, may be appropriate for individuals at high risk of cardiovascular disease if they can be achieved without undue treatment burden. The ADA also recommends an ACE inhibitor or ARB, at the maximum tolerated dose indicated for BP treatment, as first-line treatment for hypertension in patients with diabetes and albuminuria.

Black Patients

Although hypertension is more prevalent in black patients and correlates with a higher risk for cardiovascular and kidney outcomes, current recommendations for target BP are similar in black patients to those in other racial groups. The difference in management is with regard to the agent used. In general, ACE inhibitors are less efficacious in lowering BP in black patients than are CCBs. Additionally, a landmark trial (ALLHAT) revealed that in black patients, a thiazide diuretic was more effective in improving cardiovascular outcomes compared with an ACE inhibitor, and there was a higher risk of stroke with use of an ACE inhibitor as initial therapy compared with a CCB. Therefore, in the absence of CKD or heart failure, initial antihypertensive treatment should include a thiazide diuretic or CCB in black patients. If CKD is present, initial or add-on therapy should include an ACE inhibitor or ARB, especially in those with proteinuria, as illustrated by the AASK study. Choice of antihypertensive medication in patients with heart failure should be in accordance with appropriate guidelines.

Older Patients

Prevalence of hypertension increases with age and is as high as 60% to 80% in patients >65 years of age. A wide pulse pressure and isolated systolic hypertension (>160 mm Hg with diastolic <90 mm Hg) are common.

According to the 2017 ACC/AHA BP guideline, the target systolic BP goal for noninstitutionalized, ambulatory community-dwelling patients who are ≥65 years of age is <130 mm Hg. In those with a high burden of comorbidity and limited life expectancy, clinical judgement, patient preference, and an assessment of risk-benefit ratio should be considered for decisions about the intensity of BP control and antihypertensive medication choice.

On the other hand, a 2017 guideline from the American College of Physicians and American Academy of Family Physicians (http://annals.org/aim/article/2598413/pharmacologic-treatment-hypertension-adultsaged-60-years-older-higher-versus) addressed the treatment of hypertension in patients ≥60 years of age, including three recommendations:

- Initiate treatment in patients ≥60 years of age with a systolic BP persistently ≥150 mm Hg to achieve a target systolic BP <150 mm Hg to reduce the risk for mortality, stroke, and cardiac events.
- Consider initiating or intensifying pharmacologic treatment in patients ≥60 years of age with a history of stroke or transient ischemic attack to achieve a target systolic BP <140 mm Hg to reduce the risk for recurrent stroke.
- Consider initiating or intensifying pharmacologic treatment in some patients ≥60 years of age at high cardiovascular risk, based on individualized assessment, to achieve a target systolic BP <140 mm Hg to reduce the risk for stroke or cardiac events.

Regarding antihypertensive class, nonblack older patients without CKD can be treated with a thiazide diuretic, CCB, or ACE inhibitor or ARB, similar to patients <65 years of age. Care must be taken in initiating antihypertensive medications at lower doses with close monitoring of BP and attention to adverse events, given that older patients are more prone to drug-drug interactions, hyponatremia from thiazide diuretics, and orthostatic hypotension when treated with diuretics, vasodilators, α-blockers, and central acting drugs (such as clonidine).

KEY POINTS

- Women of childbearing age who anticipate pregnancy should not be prescribed renin-angiotensin system agents because of the risk for urogenital developmental abnormalities; these agents are contraindicated in pregnant women.
- In the absence of chronic kidney disease, first-line therapy of hypertension in nonblack patients with diabetes is similar to treatment of patients without diabetes: a thiazide diuretic, calcium channel blocker, ACE inhibitor, or angiotensin receptor blocker.
- Initial antihypertensive treatment for black patients with or without diabetes mellitus includes a thiazide diuretic or calcium channel blocker.
- The 2017 ACC/AHA BP guideline recommends a target systolic BP goal of <130 mm Hg for noninstitutionalized, ambulatory community-dwelling patients who are ≥65 years, whereas the American College of Physicians and American Academy of Family Physicians recommend a target systolic BP goal of <150 mm Hg in patients ≥60 years of age.

Chronic Tubulointerstitial Nephritis

Epidemiology and Pathophysiology

Tubulointerstitial nephritis (TIN) is characterized by damage to the renal tubules and interstitium, resulting in tubulointerstitial edema and progressive fibrosis and tubular atrophy. TIN can be acute or chronic. Acute interstitial nephritis is commonly due to allergic drug reactions or infection and can cause acute kidney injury within days to weeks. It is characterized by inflammation of the renal interstitium and tubules, which is generally reversible after the offending drug is removed or the underlying disease is treated (see Acute Kidney Injury). Chronic TIN (CTIN) causes a slow decline in kidney function over months and years and is characterized by interstitial scarring, fibrosis, and tubular atrophy. Acute interstitial nephritis can progress to CTIN over time. CTIN can also develop in the setting of chronic primary glomerular disease, vascular diseases, and ischemia secondary to atherosclerosis and hypertension. Causes of CTIN are listed in **Table 16**.

Diagnosis and Evaluation

CTIN is often asymptomatic until severe loss of kidney function occurs. Presenting symptoms include polyuria and nocturia due to renal concentrating defects.

A careful history with a review of medications should be performed to determine the cause of CTIN (see Table 16). A thorough physical examination may provide clues to the diagnosis and may reveal hypertension, but often no characteristic findings exist. Urinalysis may be normal or demonstrate pyuria and/or proteinuria <1500 mg/24 h. See **Table 17** for other laboratory manifestations of CTIN. Kidney ultrasound may show small kidneys. Kidney biopsy may be necessary to establish a definitive diagnosis.

KEY POINTS

- Chronic tubulointerstitial nephritis is characterized by interstitial scarring, fibrosis, and tubular atrophy and results in a slow decline in kidney function over months and years.
- Features of chronic tubulointerstitial nephritis include polyuria and nocturia due to renal concentrating defects; hypertension; and a urinalysis that is normal or demonstrates pyuria and/or proteinuria <1500 mg/24 h.

Causes

See Table 16 for a list of causes of CTIN.

Immunologic Diseases

Sjögren Syndrome

Kidney involvement in Sjögren syndrome may include interstitial nephritis, distal (type 1) renal tubular acidosis (RTA), and glomerulonephritis. Nephrolithiasis, nephrocalcinosis, and progressive kidney disease may also occur.

Sarcoidosis

Kidney involvement in sarcoidosis is common and can manifest as nephrocalcinosis from hypercalcemia and hypercalciuria, obstructive uropathy, and TIN due to granulomatous interstitial nephritis. Urine findings of TIN include impaired urine concentration, mild proteinuria, and sterile pyuria. Kidney recovery is usually incomplete.

Systemic Lupus Erythematosus

The TIN that may occur in systemic lupus erythematosus is often associated with concurrent glomerular disease but can also be the only manifestation of lupus nephritis. The severity of TIN is a useful predictor of hypertension, progressive kidney disease, and kidney failure.

IgG4-Related Disease

IgG4-related disease can be associated with a TIN with an abundant IgG4-positive plasma cell interstitial infiltration. Other laboratory findings include decreased serum complement levels and peripheral eosinophilia.

Infections

Infections associated with acute interstitial nephritis and CTIN include bacterial (such as brucellosis and tuberculosis), viral, fungal, and parasitic infections.

In immunosuppressed patients with transplanted organs, BK polyoma virus can cause interstitial nephritis. Diagnosis of BK virus nephropathy can be difficult to distinguish from acute cellular rejection. The most important treatment intervention is to decrease immunosuppressive therapy.

Chronic pyelonephritis resulting from chronic infections or vesicoureteral reflux is a common cause of CTIN. Patients can present with fever, chills, dysuria, flank or back pain, and hypertension. Kidney manifestations include distal tubular dysfunction, pyuria, and leukocyte casts. Persistent chronic pyelonephritis can progress to localized xanthogranulomatous pyelonephritis, which is characterized by a destructive mass that invades the renal parenchyma and is associated with urinary tract obstruction, infection, nephrolithiasis, diabetes mellitus, and/or immunosuppression.

Malignancy

Lymphoproliferative disorders such as lymphoma and leukemia can infiltrate the kidney, causing TIN. Presenting features include proteinuria, sterile pyuria, and enlarged kidneys. Plasma cell dyscrasias such as multiple myeloma can cause TIN in the form of myeloma cast nephropathy, Fanconi syndrome, or interstitial light chain deposition.

TABLE 16. Causes of Chronic Tubulointerstitial Nephritis
Immunologic Diseases
Anti-tubular basement membrane antibody-mediated tubulointerstitial nephritis
Sarcoidosis
Sjögren syndrome
Systemic lupus erythematosus
IgG4-related disease
Tubulointerstitial nephritis with uveitis[a]
Toxic Causes
Balkan endemic nephropathy/aristolochic acid nephropathy (urologic evaluation is indicated due to increased risk of transitional cell carcinoma)
Heavy metal nephropathy (e.g., lead, cadmium, mercury, arsenic, bismuth, chromium, copper, gold, iron, uranium)
Hereditary Tubulointerstitial Nephritis
Medullary cystic kidney disease
Mitochondrial disorders
Nephronophthisis
Infection-Related Causes
Polyoma BK virus (most commonly post-kidney transplantation)
Brucellosis
Cytomegalovirus
Epstein-Barr virus
Hantavirus
HIV
Hepatitis B virus
Fungal infections
Legionella species
Mycobacterium tuberculosis
Toxoplasmosis
Chronic pyelonephritis
Malignancy-Related Causes
Leukemia
Lymphoma
Malignancy-associated monoclonal gammopathies (e.g., multiple myeloma, plasmacytoma)
Medication-Induced Causes
Analgesic nephropathy (e.g., acetaminophen, aspirin, caffeine, or NSAID combinations)
Sodium phosphate (phosphate nephropathy)
Orlistat; high doses of vitamin C (oxalate nephropathy)
Calcineurin inhibitors (cyclosporine, tacrolimus)
Lithium
Cyclooxygenase-2 inhibitors (celecoxib)
NSAIDs
Proton pump inhibitors (esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole)
H_2 blockers (famotidine, ranitidine, nizatidine, cimetidine)
Allopurinol
HIV medications (indinavir, abacavir, tenofovir)

(Continued on the next page)

TABLE 16. Causes of Chronic Tubulointerstitial Nephritis *(Continued)*

Medication-Induced Causes
Diuretics (triamterene, furosemide, thiazides)
Anticonvulsants (e.g., phenytoin, carbamazepine, phenobarbital, valproate)
5-Aminosalicylates (mesalamine)
Antibiotics (cephalosporins, fluoroquinolones, penicillins, rifampin, sulfonamides)
Antineoplastics (cisplatin, carboplatin, cyclophosphamide, ifosfamide, nitrosoureas)
Prolonged exposure to any medication that can cause acute interstitial nephritis
Secondary Tubulointerstitial Injury Due to Glomerular and Vascular Disorders
Hypertensive nephrosclerosis
Urinary Tract Obstruction
Obstructive uropathy
Nephrolithiasis
Reflux disease

[a]Tubulointerstitial nephritis with uveitis is an uncommon immune-mediated syndrome with the combination of tubulointerstitial nephritis and uveitis associated with autoimmune disorders, including hypoparathyroidism, thyroid disease, IgG4-related disease, and rheumatoid arthritis.

TABLE 17. Laboratory Manifestations of Chronic Tubulointerstitial Nephritis

Abnormality[a]	Causes
Decline in GFR	Obstruction of tubules; damage to microvasculature; interstitial fibrosis and sclerosis of glomeruli
Proximal tubular damage (Fanconi syndrome)	Incomplete absorption and kidney wasting of glucose, phosphate, uric acid, bicarbonate, and amino acids
Normal anion gap metabolic acidosis	Proximal and distal RTA; decreased ammonia production
Polyuria and isosthenuria	Decreased concentrating and diluting ability
Proteinuria	Decreased tubular protein reabsorption (usually <1500 mg/24 h)
Hyperkalemia	Defect in potassium secretion (type 4 [hyperkalemic] distal RTA)
Hypokalemia	Defect in potassium reabsorption (type 1 [hypokalemic] distal RTA)
Anemia	Injury to erythropoietin-producing cells in the kidney

GFR = glomerular filtration rate; RTA = renal tubular acidosis.

[a]The degree of these abnormalities depends on the extent and location of injury.

Medications

Analgesics

Analgesic nephropathy is a chronic progressive TIN thought to be due to the long term use of combinations of phenacetin (banned since 1983) with aspirin, caffeine, acetaminophen, or NSAIDs. It can also occur with the individual drugs. When severe, analgesic nephropathy is associated with renal papillary necrosis, which manifests as gross hematuria, flank pain, and, occasionally, obstruction and infection.

Patients with analgesic nephropathy are typically women over the age of 45 years with a history of heavy analgesic use, low back pain or chronic musculoskeletal pain, and kidney disease with low-grade proteinuria, sterile pyuria, and anemia. CT may demonstrate microcalcifications at the papillary tips.

Calcineurin Inhibitors

The calcineurin inhibitors cyclosporine and tacrolimus can cause CTIN, in part via renal vasoconstriction. In kidney transplant recipients, cyclosporine- or tacrolimus-induced CTIN can be similar to chronic rejection. Clinical features of calcineurin inhibitor–induced TIN include hypertension and metabolic abnormalities from tubular dysfunction, including hyperkalemia, hyperuricemia, metabolic acidosis from type 4 (hyperkalemic distal) RTA, hypophosphatemia, hypomagnesemia, and hypercalciuria. Thrombotic microangiopathy might further contribute to both acute and chronic nephrotoxicity. Risk factors for CTIN are duration of exposure and cumulative dose.

Lithium

Lithium causes several kidney disorders, including distal tubular dysfunction (type 1 hypokalemic distal RTA), nephrogenic diabetes insipidus, and CTIN. CTIN from long-term lithium use can occur in up to 15% to 20% of patients. Risk factors for CTIN include advanced age, duration of lithium exposure, the cumulative dose, and repeated episodes of lithium toxicity with high serum levels. Lithium nephropathy is characterized by cystic dilation of the distal tubules with formation of microcysts. Kidney dysfunction can progress to end-stage kidney disease even with discontinuation of lithium. Amiloride can attenuate lithium-induced nephrogenic diabetes insipidus by blocking distal tubular reabsorption of lithium.

Antineoplastic Agents

Multiple chemotherapy agents can cause TIN, including cisplatin, carboplatin, cyclophosphamide, ifosfamide, and nitrosoureas (particularly streptozotocin and semustine). Newer

biologic agents such as immune checkpoint inhibitors have also been implicated.

Lead

Lead can result in tubular dysfunction and CTIN. Occupational exposure to lead occurs from welding, smelting, the battery industry, and mining. Toxicity may also develop after months to years of exposure to lead in water, soil, paint, or food products. Lead nephropathy should be considered in any patient with a history of lead exposure, hypertension, gout, and progressive kidney disease. Gout is common because lead reduces urine excretion of uric acid. The clinical diagnosis of lead nephropathy is based on history of exposure, evidence of kidney dysfunction, and blood lead levels. Levels may be normal if high-level lead exposure has abated.

Hyperuricemia

Both acute and chronic uric acid nephropathy can cause TIN from deposition of uric acid in renal tubules and interstitium. Clinical findings include elevated serum creatinine, bland urine sediment, mild proteinuria, and elevated serum urate levels. Kidney biopsy is necessary for definitive diagnosis.

Obstruction

Obstructive uropathy from prostate disease, malignancy, nephrolithiasis, pelvic radiation, medications such as methysergide, and retroperitoneal fibrosis can cause CTIN and progressive kidney dysfunction. RTA, hyperkalemia, and mild proteinuria are common.

KEY POINT

- Causes of chronic tubulointerstitial nephritis include various immunologic diseases, infections, malignancy, medications, lead, hyperuricemia, and obstruction.

Management

Management of acute and chronic TIN involves treating the underlying cause: discontinuing offending agents, administering immunosuppressive therapy for immunologic or drug-related allergic causes, treating infection and malignancy, and relieving obstruction. Treatment of lead nephropathy consists of EDTA chelation therapy or oral succimer, which can slow the progression of chronic kidney disease. In patients with CTIN and progressive kidney disease, management includes control of blood pressure and treatment of proteinuria and metabolic abnormalities (see Chronic Kidney Disease).

KEY POINT

- Management of chronic tubulointerstitial nephritis involves treating the underlying cause: discontinuing offending agents, administering immunosuppressive therapy for immunologic or drug-related allergic causes, treating infection and malignancy, and relieving obstruction.

Glomerular Diseases

Epidemiology and Pathophysiology

Glomerular diseases are the third leading cause of end-stage kidney disease (ESKD) in the United States, accounting for approximately 10,000 incident cases of ESKD per year and trailing only diabetes mellitus and hypertension. The term *glomerular disease* encompasses a wide array of conditions with etiologies that span autoimmune disease, malignancy-associated conditions, sequelae of infection, genetic mutations, and medication toxicities. These diseases are classified as either primary (idiopathic), in which the glomerular injury is an intrinsic process generally limited to the kidney, or secondary, in which the glomerular lesion is the result of a systemic disease with kidney involvement as one of many possible manifestations.

The normal, noninflamed glomerulus forms a tight barrier, largely due to the slit diaphragms that connect podocyte (visceral epithelial cell) foot processes on the outside surface of the glomerular basement membrane (**Figure 11**). When healthy, this filtration barrier prevents passage of blood and protein into the urinary filtrate. Glomerular diseases involve injury of the glomerular filter with subsequent passage of protein (proteinuria) and, in the setting of glomerulonephritis, blood (hematuria) into the urine. These urinary abnormalities are the earliest manifestation of a glomerular lesion. If the injury responsible for the hematuria and proteinuria goes unchecked, the result is scarring of the glomerular filters (glomerulosclerosis) with subsequent decline in kidney function that manifests as elevated serum creatinine.

Most etiologies of glomerular disease are diagnosed via kidney biopsy. No formal guidelines exist for the indications to perform a kidney biopsy in any age group. The decision to pursue a kidney biopsy should be individualized for each patient, but, in general, a kidney biopsy appears justified for

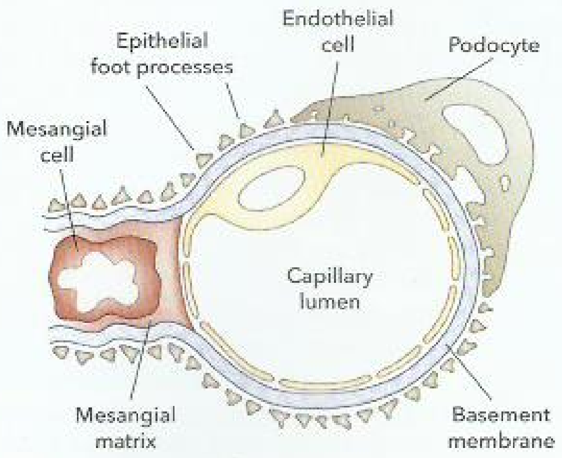

FIGURE 11. The podocyte, a visceral epithelial cell, sits on the outside surface of the glomerular basement membrane.

patients with two or more of the following four findings: hematuria, proteinuria >1000 mg/24 h, reduced kidney function (glomerular filtration rate <60 mL/min/1.73 m²), and/or positive serologies for systemic diseases with known potential for kidney involvement (for example, hepatitis B or C virus infection, systemic lupus erythematosus, and ANCA seropositivity).

Clinical Manifestations of Glomerular Disease

The two main categories of glomerular disease are the nephrotic and nephritic syndromes, each of which has a distinct clinical presentation.

The Nephrotic Syndrome

Clinical manifestations of the nephrotic syndrome stem from ongoing loss of protein, principally albumin, into the urine. This urinary loss of albumin causes hypoalbuminemia; in response, the liver increases its production of several proteins, including cholesterols, leading to hyperlipidemia. The resulting hallmark features of the nephrotic syndrome include the following:

- Urine protein excretion >3500 mg/24 h or a urine protein-creatinine ratio >3500 mg/g (nephrotic-range proteinuria)
- Hypoalbuminemia (usually <3.0 g/dL [30 g/L])
- Hypercholesterolemia
- Edema

Edema is typically most severe in the lower extremities. Many patients report periorbital edema upon awakening. Severe fluid retention can lead to pulmonary edema, pulmonary effusions, and anasarca. Despite avid salt and water retention, hypertension occurs only in a minority of patients.

Two explanations have been proposed for the edema seen in the nephrotic syndrome. The "underfill hypothesis" argues that low serum albumin concentrations lead to a reduction in intravascular oncotic pressure and a resultant shift of plasma from the capillary lumen to the interstitium. Further, the consequent intravascular depletion activates the renin-angiotensin system, which promotes salt and water retention throughout the nephron, exacerbating the edema. In contrast, the "overfill hypothesis" argues that sodium is primarily retained at the collecting duct, triggered by the abnormally filtered proteins themselves. Both hypotheses may be correct, and both provide a rationale for edema management in patients with the nephrotic syndrome. First, resolution of edema is only attainable long term by remission of proteinuria; lending support to the overfill hypothesis, edema will often subside when proteinuria has fallen but before albumin has returned to normal range. Second, diuretics are crucial to control the symptoms of edema, blocking the reabsorption of sodium (and water) at various points in the nephron.

The nephrotic syndrome is a hypercoagulable state due to urinary losses of protein. In addition to albuminuria, patients with the nephrotic syndrome lose in their urine a number of low-molecular-weight anticoagulants (for example, antithrombin III, protein S) and fibrinolytics (for example, plasminogen). Hepatic overproduction of proteins, as an intrinsic response to hypoalbuminemia, leads not only to hyperlipidemia but also to increased levels of procoagulants (for example, factor V, factor VIII, fibrinogen). As a result, patients with the nephrotic syndrome are at increased risk for lower extremity, pulmonary, and renal vein thrombosis. Clots are most often seen in patients with membranous glomerulopathy, but any patient with nephrotic-range proteinuria and significant hypoalbuminemia (usually <2.5 g/dL [25 g/L]) should be considered at risk.

Severe albuminuria should be treated with renin-angiotensin system blocking drugs to control blood pressure and reduce proteinuria. Hyperlipidemia should be treated with cholesterol-lowering medications. Edema should be managed with diuretics and dietary sodium restriction. This combination of renin-angiotensin system blocking drugs, cholesterol-lowering medications, and diuretics is generally considered conservative therapy for most forms of glomerular disease. A general strategy for edema management in a newly diagnosed patient with the nephrotic syndrome is to start with a loop diuretic, with a goal weight loss of 1 to 2 kg (2.2-4.4 lb) per week. In severe cases of edema when loop diuretics have been maximally uptitrated and weight loss/edema control is insufficient, it is often necessary to add a second diuretic (a thiazide diuretic and/or potassium-sparing diuretic) that works distal to the loop of Henle. In patients taking high doses of loop diuretics, increased delivery of salt and water to the distal portions of the nephron can lead to hypertrophy of these segments and overabsorption of sodium, undermining the effects of the loop diuretic.

The Nephritic Syndrome

The nephritic syndrome, also termed glomerulonephritis, can present as a number of clinical variants. Common features are hematuria (microscopic or macroscopic) and proteinuria, with the more severe variants typically including hypertension, edema, and kidney dysfunction (elevated serum creatinine). The glomerular hematuria seen in the nephritic syndrome can be distinguished from other causes of urinary tract bleeding by the presence of either dysmorphic erythrocytes (resulting from passage through a damaged glomerular basement membrane) or erythrocyte casts on urine microscopy (see Clinical Evaluation of Kidney Function).

The mildest forms of the nephritic syndrome are asymptomatic, microscopic hematuria with or without proteinuria, often discovered on routine laboratory assessment. Recurrent gross hematuria, in which macroscopic hematuria occurs several days after an upper respiratory infection or physical exertion, is a classic presentation of IgA nephropathy, particularly in younger patients. This nephritic presentation also usually

follows a benign clinical course without associated chronic kidney disease.

On the other hand, the term *acute glomerulonephritis* is used to denote the more classical nephritic syndrome presentation, with variable degrees of kidney dysfunction, hypertension, edema, proteinuria, and hematuria. The most severe form of the nephritic syndrome is termed *rapidly progressive glomerulonephritis*, in which patients experience a rapid decline of kidney function over days or weeks that will progress to ESKD if untreated.

KEY POINTS

- The hallmark features of the nephrotic syndrome include a urine protein excretion >3500 mg/24 h or a urine protein-creatinine ratio >3500 mg/g, hypoalbuminemia, hypercholesterolemia, and edema.
- Common features of the nephritic syndrome are hematuria (with dysmorphic erythrocytes or erythrocyte casts) and proteinuria; hypertension, edema, and kidney dysfunction may also occur.

Conditions Associated With the Nephrotic Syndrome

Focal Segmental Glomerulosclerosis

Epidemiology and Pathophysiology

Focal segmental glomerulosclerosis (FSGS) is the most common form of the nephrotic syndrome in black patients and, in certain parts of the world, has replaced membranous glomerulopathy as the leading cause of the nephrotic syndrome in white patients. The prevalence of FSGS in the United States is more than 20,000 patients, with a yearly incidence of approximately 5000 newly diagnosed cases per year. In the United States, FSGS currently accounts for up to 40% of primary nephrotic syndromes in adults. Worldwide, the incidence of FSGS has been estimated at nearly 1 in 100,000 people per year.

FSGS stems from abnormalities in the podocyte. Podocyte detachment and death lead to the segmental sclerosis that is the hallmark histopathology of FSGS. The podocyte injury in FSGS, in turn, can stem from immunologic, genetic, and/or hyperfiltration causes. Immunologic injury is considered the main pathogenic mechanism behind primary forms of FSGS, with leukocytes producing a soluble circulating factor that directly targets podocytes. This mechanism is supported by cases of FSGS recurring almost immediately after kidney transplantation and responding briskly to plasmapheresis, although to date definitive identification of such a circulating factor has yet to occur. Identified genetic causes of FSGS are chiefly mutations in podocyte-specific proteins (for example, nephrin, podocin, formin). These mutations are more commonly found in infants, young (<25 years of age) patients who do not respond to glucocorticoid therapy, and patients with a family history of ESKD. Individuals of African ancestry carry approximately a five times higher risk of FSGS than those of European descent, likely mediated in large part by variants in the *APOL1* gene (see Genetic Disorders and Kidney Disease). The third major cause of podocyte injury, hyperfiltration, causes a large proportion of secondary FSGS cases. This hyperfiltration form of FSGS is seen classically in obese patients but also can manifest in patients with a history of premature birth or solitary kidney. Finally, a drug-induced FSGS can occur as a rare complication of some commonly used treatments, including lithium, interferon, and pamidronate.

Clinical Manifestations

All patients with FSGS have proteinuria. Primary forms of FSGS usually present with nephrotic-range proteinuria and can be accompanied by the full nephrotic syndrome, including severe edema, whereas secondary forms typically have asymptomatic subnephrotic proteinuria. Any form of FSGS can present with reduced glomerular filtration rate, particularly when diagnosed late in the disease course.

Diagnosis

FSGS is diagnosed by kidney biopsy. On light microscopy, glomerulosclerosis (scarring of glomeruli) is seen in a focal (<50%) and segmental (affecting a portion but not the entirety of individual glomeruli) distribution (**Figure 12**). Histologic variants of FSGS include classic (or "not otherwise specified") FSGS, perihilar variant, glomerular tip lesion variant, cellular variant, and collapsing variant. The collapsing variant is often resistant to treatment and therefore carries the worst long-term prognosis, whereas the tip lesion usually responds to glucocorticoids and is unlikely to progress to ESKD.

Treatment and Prognosis

For all patients with FSGS, conservative therapy includes renin-angiotensin system blocking drugs to control proteinuria,

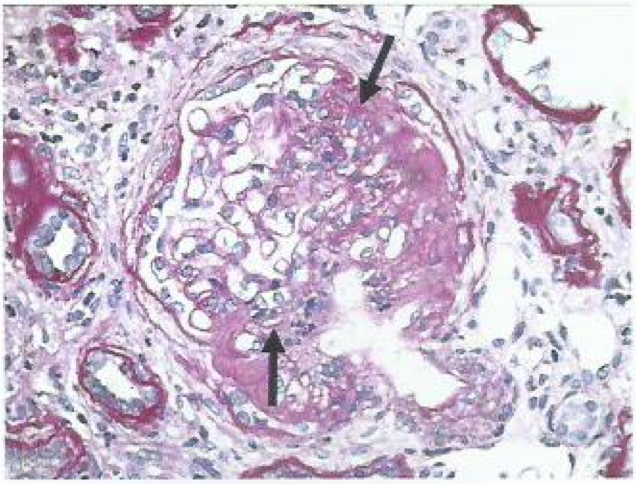

FIGURE 12. Light microscopy in focal segmental glomerulosclerosis shows scarring (arrows) in some, but not all, glomeruli in a segmental distribution, as demonstrated by this glomerulus.

Courtesy of Glen Markowitz, MD.

cholesterol-lowering medication, and edema management. Such conservative therapy measures suffice for FSGS patients with subnephrotic proteinuria.

When nephrotic-range proteinuria is present and if a primary form of FSGS is suspected, high-dose glucocorticoids remain the mainstay of initial therapy. Other immunosuppressants, including calcineurin inhibitors, mycophenolate mofetil, alkylating agents, and rituximab, have been reported to provide some benefit as second-line agents for patients who either do not respond to glucocorticoids or whose proteinuria relapses when glucocorticoids are tapered off.

Approximately 50% of patients with FSGS progress to ESKD within 10 years of diagnosis; this poor prognosis is rooted in low rates of treatment response.

Membranous Glomerulopathy

Epidemiology and Pathophysiology

Membranous glomerulopathy (membranous nephropathy) is a leading cause of the nephrotic syndrome in white adults. Epidemiology has remained constant over the past several decades. Disease occurs at an approximate rate of 1 case per 100,000 persons per year, with a peak incidence between 30 and 50 years of age. Approximately 75% of cases are considered primary; the remaining 25% are considered secondary to systemic diseases such as systemic lupus erythematosus, hepatitis B virus infection, and solid tumors.

In the past decade, target antigens and their associated autoantibodies responsible for the development of primary membranous glomerulopathy cases have been identified. The M-type phospholipase A2 receptor (PLA2R) is the specific podocyte antigen responsible for eliciting immune complex formation with circulating autoantibodies in most primary cases. Anti-PLA2R antibodies are detected in approximately 75% of primary cases and are rarely found in secondary forms. Additional alternative podocyte autoantigens have been reported in patients with primary membranous glomerulopathy, potentially filling in the missing gaps in PLA2R antibody–negative disease. Membranous glomerulopathy occurs when circulating antibodies permeate the glomerular basement membrane and, in the subepithelial space, form immune complexes with epitopes on podocyte membranes.

Clinical Manifestations

Patients typically describe slowly progressive edema, and laboratory testing reveals proteinuria, hypoalbuminemia, and hyperlipidemia, most often with preserved kidney function. Patients with membranous glomerulopathy are particularly prone to thrombotic complications. These clots include lower extremity, pulmonary, and renal vein thromboses; they can occur in up to 25% of patients and are most likely to occur within the first 2 years of diagnosis. The risk of clotting increases when serum albumin is <2.8 g/dL (28 g/L) and is highest when serum albumin is <2.2 g/dL (22 g/L).

Diagnosis

The diagnosis of membranous glomerulopathy is traditionally made by kidney biopsy, although FDA approval of serologic testing for anti-PLA2R antibodies in 2015 has introduced the possibility of diagnosing the disease noninvasively.

The hallmark biopsy finding is the presence of subepithelial immune deposits that alter the glomerular capillary wall, classically accompanied by intervening "spikes" of glomerular basement membrane extending between the immune deposits in more advanced cases. In addition to serologic testing for anti-PLA2R antibodies, the biopsy can be stained for the PLA2R antigen, which typically yields a higher sensitivity (>80%) than antibody testing in the serum. This testing is used not to make a diagnosis of membranous glomerulopathy but to help distinguish primary from secondary forms of the disease. Such a distinction is crucial because secondary forms are expected to remit if the underlying systemic disease responsible for the lesion is successfully treated. Notably, in patients with membranous glomerulopathy aged 65 years and older, malignancies have been detected in up to 25% within 1 year of their biopsy diagnosis. Therefore, age- and sex-appropriate cancer screening is recommended for all patients at the time of their diagnosis, even those with PLA2R positivity.

Treatment and Prognosis

Patients with newly diagnosed primary forms of membranous glomerulopathy are usually observed for 6 to 12 months on conservative therapy (renin-angiotensin system blockade, cholesterol-lowering medication, and edema management) before initiating a course of immunosuppression for patients with persistent nephrotic-range proteinuria. The observation period allows patients a chance to achieve spontaneous remission, which occurs in approximately 30% within 1 to 2 years of diagnosis. Patients who remain nephrotic have the option of two first-line immunosuppressive regimens: (1) a combination of glucocorticoids and alkylating agents, which achieves remission in approximately 75% to 80% of patients within 12 months, or (2) calcineurin inhibitors (cyclosporine or tacrolimus), which have reported remission rates of 70% to 75% in the first year of therapy. Relapse rates are higher in patients treated with calcineurin inhibitors than alkylating agents. Recent reports also suggest that rituximab may have efficacy in membranous glomerulopathy. Treatment of secondary forms of membranous glomerulopathy should be aimed at the underlying systemic disease or etiology (for example, resection of a tumor in malignancy-associated membranous glomerulopathy, treatment of hepatitis B in viral-associated membranous glomerulopathy).

Progression to ESKD depends on remission of proteinuria: The 10-year incidence of ESKD in patients who undergo complete or partial remission of proteinuria ranges from 0 to 10%, compared with a >50% incidence of ESKD in patients who maintain nephrotic-range proteinuria.

Minimal Change Glomerulopathy

Epidemiology and Pathophysiology

Minimal change glomerulopathy (MCG; also known as minimal change disease) is the most common cause of the nephrotic syndrome in children (>90% of cases). For this reason, unless clinical and serologic evidence suggests the presence of a disease other than MCG, a kidney biopsy is not performed in children with the nephrotic syndrome unless they do not respond to glucocorticoid therapy. In adults, biopsy series have shown that MCG is the cause of up to 10% to 15% of cases of the nephrotic syndrome, with a greater representation in older patients (≥65 years of age) and elderly patients (≥80 years of age).

The pathophysiology of MCG is not well understood. Similar to FSGS, MCG is a podocytopathy; the presumed model of injury is immunologic, in which a circulating factor (produced by B or T cells) alters podocyte function, resulting in massive proteinuria. The rapid response of most cases (>90%) of MCG to nonspecific immunosuppression (usually glucocorticoids) fits this model of a circulating factor–inducing disease. Most cases of MCG are primary, but the disease is associated with various conditions, including malignancies (Hodgkin lymphoma, non-Hodgkin lymphoma, thymoma), medications (NSAIDs, lithium), infections (strongyloides, syphilis, mycoplasma, ehrlichiosis), and atopy (pollen, dairy products).

Clinical Manifestations

The classic presentation of MCG is sudden-onset nephrotic syndrome. Microscopic hematuria is present in 10% to 30% of adult cases. Up to 25% of adults with MCG may also have acute kidney injury (AKI), more commonly occurring in older patients with hypertension, low serum albumin levels, and heavy proteinuria.

Diagnosis

MCG is diagnosed with kidney biopsy demonstrating normal glomerular histology on light microscopy, negative immunofluorescence staining for immunoglobulin and complement proteins, and complete effacement of the podocyte foot processes on electron microscopy.

Treatment and Prognosis

The 2012 Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline for Glomerulonephritis recommends glucocorticoids as first-line therapy for children and adults with MCG, with remission achieved in more than 90% of children and 80% to 90% of adults. Time-to-response is prolonged in adults compared with children, and adults are not considered to have glucocorticoid-resistant disease until they have not responded to 16 weeks of glucocorticoid therapy. After an initial course of glucocorticoids, patients are subdivided into categories: glucocorticoid-sensitive MCG, glucocorticoid-dependent MCG, infrequently relapsing MCG, frequently relapsing MCG, and glucocorticoid-resistant MCG. Treatment of glucocorticoid-dependent, frequently relapsing, and glucocorticoid-resistant MCG has included calcineurin inhibitors, mycophenolate mofetil, alkylating agents, and rituximab, with variable results.

Diabetic Nephropathy

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Epidemiology and Pathophysiology

Diabetes mellitus is the leading cause of chronic kidney disease (CKD) and ESKD worldwide. In the United States, diabetes accounts for over 50,000 new cases of ESKD requiring dialysis each year. Diabetic nephropathy, defined as clinical evidence of kidney injury in response to chronic, long-standing hyperglycemia, has a 10% incidence over 25 years among patients with type 1 diabetes and a 12% incidence over 25 years among patients with type 2 diabetes.

Advanced glycation end products are felt to be the primary mediator of injury in diabetic nephropathy, activating signaling cascades that promote mesangial cell synthesis of profibrogenic cytokines, including platelet-derived growth factor and transforming growth factor β.

Clinical Manifestations

Diabetic nephropathy manifests initially as moderately increased albuminuria (microalbuminuria). Over time, progressive proteinuria is followed by a decline in glomerular filtration rate, with progression to later stages of CKD and ESKD. When proteinuria is severe, it is typically accompanied by hypoalbuminemia, and many patients present with edema befitting a classic picture of the nephrotic syndrome.

Kidney disease due to diabetes is often accompanied by extrarenal microvascular complications of diabetes, including retinopathy and peripheral neuropathy, as well as macrovascular complications, such as peripheral vascular disease, coronary artery disease, and stroke.

Diagnosis

The American Diabetes Association recommends yearly assessment of albuminuria in patients with type 2 diabetes, and assessment after 5 years of disease in patients with type 1 diabetes. The diagnosis of diabetic nephropathy is usually made clinically in the presence of hallmark features: proteinuric CKD in a patient with long-standing diabetes and evidence of other (microvascular and/or macrovascular) complications of disease. If the clinical presentation is not entirely consistent with diabetic nephropathy, a kidney biopsy is performed. The biopsy finding of nodular mesangial sclerosis with glomerular and tubular basement thickening, in the absence of immune deposits, is the classic description of diabetic nephropathy.

Treatment and Prognosis

The cornerstone of treatment of diabetic nephropathy involves glycemic control and blood pressure control. Blockade of the renin-angiotensin system with an ACE inhibitor or angiotensin receptor blocker (ARB) is recommended, typically to the maximal tolerated dose, because these agents both reduce blood pressure and levels of

H CONT. proteinuria, which, along with glycemic control, are the most important modifiable risk factors for progression of diabetic nephropathy to ESKD. Combined use of any two of the three renin-angiotensin system drug classes (ACE inhibitor, ARB, and direct renin inhibitor) is not recommended given the results of several clinical trials that revealed more adverse events with these combinations (hyperkalemia, hypotension, AKI), without additional cardiovascular or renal benefits. Combining ACE inhibitors or ARBs with mineralocorticoid receptors (spironolactone or eplerenone) has been shown in small studies to be a safe and effective antiproteinuric strategy in diabetic nephropathy, but the risk for hyperkalemia should be considered.

The 2017 high blood pressure guideline from the American College of Cardiology (ACC), the American Heart Association (AHA), and nine other organizations recommends a blood pressure target of <130/80 mm Hg for patients with hypertension and diabetes mellitus and/or CKD. The American Diabetes Association recommends that most patients with diabetes and hypertension should be treated to a systolic blood pressure goal of <140 mm Hg and a diastolic blood pressure goal of <90 mm Hg; lower systolic and diastolic blood pressure targets, such as 130/80 mm Hg, may be appropriate for individuals at high risk of cardiovascular disease, if they can be achieved without undue treatment burden. H

KEY POINTS

- Initial treatment of focal segmental glomerulosclerosis is high-dose glucocorticoids; other immunosuppressants (calcineurin inhibitors, mycophenolate mofetil, alkylating agents, rituximab) may provide some benefit for patients who do not respond to glucocorticoids or relapse when glucocorticoids are tapered off.
- Newly diagnosed primary membranous glomerulopathy is typically treated with conservative therapy for 6 to 12 months before initiating immunosuppression for patients with persistent nephrotic-range proteinuria.
- Minimal change glomerulopathy (MCG) is initially treated with glucocorticoids; treatment options for glucocorticoid-dependent, frequently relapsing, and glucocorticoid-resistant MCG include calcineurin inhibitors, mycophenolate mofetil, alkylating agents, or rituximab.
- The American Diabetes Association recommends yearly assessment of albuminuria in patients with type 2 diabetes mellitus, and assessment after 5 years of disease in patients with type 1 diabetes mellitus.
- The cornerstone of treatment of diabetic nephropathy involves glycemic control and renin-angiotensin system blockade using either an ACE inhibitor or an angiotensin receptor blocker.

Conditions Associated With the Nephritic Syndrome

Rapidly Progressive Glomerulonephritis

Epidemiology and Pathophysiology

Rapidly progressive glomerulonephritis (RPGN; also known as crescentic glomerulonephritis) is not a specific disease; rather, RPGN is a clinical entity that can be caused by multiple diseases and manifests as (1) at least a 50% decline in glomerular filtration rate over a short period (usually days to weeks) with (2) pathology findings of extensive glomerular crescents (**Figure 13**). Crescents signal focal rupture of the glomerular capillary walls, the most severe glomerular damage that can be seen on light microscopy. This rupture allows accumulation of fibrin and fibronectin in the urinary space, where they activate de-differentiated glomerular parietal epithelial cells to proliferate, surround, and compress the glomerular tuft.

Clinical Manifestations

RPGN typically presents with macroscopic or microscopic hematuria, erythrocyte casts, varying ranges of proteinuria, and AKI that can lead rapidly to dialysis dependence.

Diagnosis

The diagnosis of all forms of glomerulonephritis is traditionally made by kidney biopsy, which can distinguish among the three major categories of glomerulonephritis (**Table 18**) and their associated etiologies. Serologic testing (for example, ANCA, anti-glomerular basement membrane antibodies, antinuclear antibodies) aids in the diagnosis. An alternative classification scheme for glomerulonephritis is based on low versus normal complement levels (**Table 19**). Although any form of glomerulonephritis can display an aggressive disease course that would fit the definition of an RPGN, the most common etiologies seen in RPGN cases are ANCA-associated

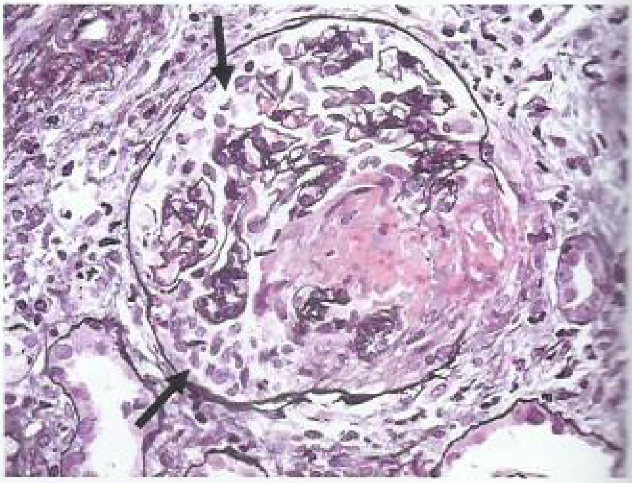

FIGURE 13. A glomerular crescent (*arrows*), named for its moon-shaped appearance, signals focal rupture of the glomerular capillary walls.

Courtesy of Glen Markowitz, MD.

TABLE 18. Categorization of Glomerulonephritis Based on Immunofluorescence Microscopy Findings

Immunofluorescence Staining Pattern		
Granular	**Pauci-immune**	**Linear**
Lupus nephritis	ANCA-associated GN	Anti-GBM antibody disease
Infection-related GN		
IgA nephropathy		
MPGN		
Cryoglobulinemic GN		

GBM = glomerular basement membrane; GN = glomerulonephritis; MPGN = membranoproliferative glomerulonephritis.

TABLE 19. Categorization of Glomerulonephritis Based on Serum Complement Levels

Low Serum C3 and/or C4 Levels	Normal Serum C3 and C4 Levels
Lupus nephritis	IgA nephropathy
Infection-related GN	ANCA-associated GN
MPGN	Anti-GBM antibody disease
Cryoglobulinemic GN	

GBM = glomerular basement membrane; GN = glomerulonephritis; MPGN = membranoproliferative glomerulonephritis.

glomerulonephritis, lupus nephritis, and anti–glomerular basement membrane glomerulonephritis.

Treatment and Prognosis

Treatment is based on the specific etiology of RPGN. If untreated, RPGN is expected to progress to dialysis dependence in a matter of days to weeks. If treated early, lesions can often be reversed, although CKD is often a lingering consequence.

Anti–Glomerular Basement Membrane Antibody Disease

Epidemiology and Pathophysiology

Anti–glomerular basement membrane (anti-GBM) antibody disease is a rare form of RPGN with an incidence of less than one case per million per year. Anti-GBM antibody disease accounts for about 20% of RPGN cases in adults. The lesion is more frequently seen in white patients and has a bimodal age and gender distribution, with peak incidences in young men in the second and third decades of life and in older women in the sixth and seventh decades of life. More than half of patients with anti-GBM antibody disease present with RPGN and pulmonary hemorrhage. About one third of patients present with isolated glomerulonephritis. Notably, up to one third of patients have concurrent circulating ANCA (usually antimyeloperoxidase [MPO]) antibodies.

Circulating anti-GBM antibodies target the alpha-3 chain of type IV collagen. When anti-GBM antibodies bind rapidly and tightly to the GBM, they incite an intense inflammatory response that translates to the typically fulminant nature of this disease.

Clinical Manifestations

The presentation of anti-GBM antibody disease is similar to that of other forms of RPGN previously described, with macroscopic or microscopic hematuria, erythrocyte casts, varying ranges of proteinuria, and usually moderate to severe AKI. Lung involvement (Goodpasture syndrome) occurs in >50% of patients; hemoptysis can be a presenting symptom, although shortness of breath or cough should also raise suspicion for a pulmonary-renal syndrome even in the absence of hemoptysis.

Diagnosis

Kidney biopsy in anti-GBM disease shows a crescentic glomerulonephritis on light microscopy and pathognomonic linear staining for IgG along the glomerular capillaries, indicative of antibodies directed against the GBM. Serologic testing for anti-GBM antibodies is performed at the time of diagnosis. The serologic test is done by indirect immunofluorescence or direct enzyme-linked immunoassay (ELISA), with sensitivity ranging from 60% to 100%; therefore, a kidney biopsy to confirm diagnosis is recommended unless contraindicated. Even with a renal biopsy diagnosis, antibody levels should be measured because their titers can be followed to assess efficacy of therapy.

Treatment and Prognosis

Outcomes in anti-GBM disease are based largely on the degree of AKI at the time of diagnosis and treatment. In an oft-cited series, patients with anti-GBM disease who presented with serum creatinine <5.65 mg/dL (500 µmol/L) had, at 10 years, a <5% overall mortality and a <20% risk for ESKD. In contrast, patients who presented with dialysis-dependent kidney failure had a 35% mortality rate within the first year of diagnosis, and only 8% were able to be taken off dialysis during this time. Treatment for anti-GBM disease consists of plasmapheresis, pulse glucocorticoids (high doses of intravenous glucocorticoids over a short period of time) followed by oral prednisone, and cyclophosphamide.

ANCA-Associated Glomerulonephritis

See MKSAP 18 Rheumatology for more information on ANCA-associated vasculitis.

Epidemiology and Pathophysiology

ANCA-associated glomerulonephritis (pauci-immune crescentic glomerulonephritis) accounts for more than half of all RPGN cases and has a particularly high prevalence in patients >65 years of age presenting with AKI and active urinary sediment. ANCA are autoantibodies that target proteins within neutrophil granules and monocyte lysosomes. There are two types of vasculitis-associated ANCA: p-ANCA (perinuclear) is directed against the neutrophil enzyme myeloperoxidase (MPO), and c-ANCA (cytoplasmic) is directed against the neutrophil proteinase 3 (PR3).

Clinical Manifestations

Most patients with ANCA-associated glomerulonephritis report a vasculitic prodrome of malaise, arthralgia, myalgia, and flu-like symptoms that can include fever. Kidney involvement can produce dark brown (tea-colored) urine, and laboratory studies will confirm the presence of hematuria, proteinuria, and AKI. Lung and sinus involvement often occurs in ANCA-associated glomerulonephritis, with patients reporting hemoptysis and/or epistaxis.

Diagnosis

Serologic testing for ANCA using enzyme-linked immunosorbent assay is usually performed at the time of presentation if RPGN is suspected. Light microscopy of the kidney biopsy shows a crescentic glomerulonephritis, but immunofluorescence shows a paucity or absence of immune-type deposits. Foci of necrosis or cellular crescents are highlighted by immunofluorescence staining for fibrinogen.

Treatment and Prognosis

The initial treatment of organ-threatening disease is an area of ongoing controversy. Typical induction therapy consists of glucocorticoids combined with either cyclophosphamide or rituximab. Plasmapheresis is reserved for patients with evidence of alveolar hemorrhage or severe kidney failure. Other induction options include cyclophosphamide- or rituximab-based therapies. After remission is induced, maintenance therapy is usually continued for at least 12 to 24 months using rituximab, azathioprine, or mycophenolate mofetil.

Patients with c-ANCA/anti-PR3 have a significantly higher rate of relapse than patients with p-ANCA/anti-MPO, particularly if there is a history of lung or sinus involvement. ANCA-associated glomerulonephritis is associated with an approximately 20% mortality rate within the first year of diagnosis and results in ESKD in up to 25% of surviving patients within the first 4 years after diagnosis.

KEY POINTS

- Rapidly progressive glomerulonephritis can be caused by multiple diseases; it is characterized by at least a 50% decline in glomerular filtration rate over a short period with pathology findings of extensive glomerular crescents.
- More than half of patients with anti–glomerular basement membrane antibody disease have lung involvement manifesting as hemoptysis, shortness of breath, or cough.
- Treatment of anti–glomerular basement membrane antibody disease consists of plasmapheresis, pulse glucocorticoids followed by oral prednisone, and cyclophosphamide.
- ANCA-associated glomerulonephritis is characterized by a prodrome of malaise, arthralgia, myalgia, and flu-like symptoms; dark brown (tea-colored) urine, hematuria, proteinuria, acute kidney injury, hemoptysis, and epistaxis may occur.

Immune Complex–Mediated Glomerulonephritis

The glomerulonephritides with granular immunofluorescence microscopy staining patterns all fall under the umbrella category of immune complex–mediated glomerulonephritis, with antigen-antibody complexes depositing in the kidney at various locations and in various patterns (see Table 18). Immune complex deposition activates the classic complement pathway as a co-player in glomerular inflammation, injury, and, if unchecked, scarring. For this reason, most immune complex–mediated glomerulonephritides are associated with low levels of C3 and/or C4 (see Table 19). IgA nephropathy, which usually presents with normal C3 and C4 levels, is an exception due to the chronic, gradual nature of the disease: complement consumption is at a rate slow enough for hepatic production to replace complement proteins. In rare hyper-acute cases of IgA nephropathy that fulfill criteria for RPGN, however, complement levels are usually depressed.

IgA Nephropathy

Epidemiology and Pathophysiology

IgA nephropathy (IgAN) is the most common primary glomerular disease worldwide, diagnosed in up to 10% of all kidney biopsies done in the United States and approximately one third of all kidney biopsies in Asian countries, where the disease is the leading cause of ESKD. In contrast, IgAN is very rare among patients of African ancestry. IgAN can be diagnosed at any age, particularly because a significant subgroup of patients is asymptomatic, but is most commonly diagnosed in youth or early adulthood, with a 2:1 male-to-female ratio. In the United States, the overall incidence of IgAN is estimated at 2.5 cases per 100,000 person-years, with a prevalence of approximately 80,000 individuals.

In IgAN, there is defect in IgA1-producing cells leading to hypogalactosylation of the hinge region of IgA1. Blood levels of galactose-deficient IgA1 (Gd-IgA1) are elevated in patients with IgAN. Patients then develop antibodies directed against Gd-IgA1 to form immune complexes that accumulate in the glomerular mesangium.

Clinical Manifestations

IgAN can present with any of the manifestations of the nephritic syndrome. The mildest presentation, seen in up to one third of patients, is asymptomatic microscopic hematuria with or without proteinuria, usually discovered incidentally as part of a routine examination. Recurrent gross hematuria, in which macroscopic hematuria occurs in the setting of an upper respiratory infection (synpharyngitic hematuria) is a common presentation in younger patients; it usually portends a benign clinical course with recurrent episodes of gross hematuria without progression to CKD. IgAN can also present as an acute glomerulonephritis or an even more aggressive RPGN, with variable degrees of AKI, hypertension, edema, proteinuria, and hematuria.

Diagnosis

The diagnosis of IgAN may be suspected clinically but can only be made by kidney biopsy showing dominant mesangial immune deposits of IgA with C3, and occasionally IgG or IgM. In some centers, patients with microscopic hematuria, normal kidney function, and proteinuria <500 mg/24 h are given an empiric diagnosis of IgAN without a biopsy because the disease course is expected to be mild in these cases. In other centers, patients with microscopic hematuria that is deemed to be glomerular in origin (that is, presence of dysmorphic erythrocytes or erythrocyte casts in the urine sediment) elicits a biopsy regardless of kidney function or proteinuria.

Treatment and Prognosis

There are no current standard care therapies for IgAN other than conservative, nonimmunomodulatory therapies. Antiproteinuric therapy using an ACE inhibitor or ARB is a hallmark for treating IgAN; it is usually coupled with lipid-lowering therapy and fish oil, although the efficacy of the latter two as specific IgAN therapies is unproven. The use of immunosuppression in IgAN remains controversial. In the United States, it is common for most patients with IgAN who progress to ESKD to have done so despite long-term renin-angiotensin system blockade and at least one course of immunosuppressive therapy.

Approximately one third of patients with IgAN will have a benign long-term course, with continued microscopic hematuria but little to no proteinuria and no evidence of kidney dysfunction. The disease progresses to CKD or ESKD in the remainder of patients, with up to 40% reaching ESKD within 15 years of diagnosis. The recent Oxford histopathology classification of IgAN provides evidence that advanced disease chronicity, manifesting as >50% tubular atrophy and interstitial fibrosis on kidney biopsy, is the most reliable predictor of progression to ESKD. Among clinical parameters, proteinuria ≥1000 mg/24 h has been shown to be a risk factor for progression.

IgA Vasculitis

IgA vasculitis (Henoch-Schönlein purpura) can present with the classic tetrad of rash, arthralgia, abdominal pain, and kidney disease. Considered a systemic version of IgAN, this vasculitis is often diagnosed empirically in the pediatric setting, because the differential diagnosis of vasculitis in children is extremely limited. In adults, the diagnosis should be confirmed with tissue biopsy (kidney or skin), because the presentation of IgA vasculitis can also fit with a non-IgA form of vasculitis. Skin biopsy is usually adequate to make the diagnosis when lesions less than 24 hours old in appearance are sampled. Kidney involvement in IgA vasculitis typically is more severe in adults than in children, with higher rates of AKI and the nephrotic syndrome. Treatment includes glucocorticoids and, in cases of associated RPGN, cyclophosphamide.

See MKSAP 18 Rheumatology for more information.

Lupus Nephritis

See MKSAP 18 Rheumatology for more information on systemic lupus erythematosus.

Epidemiology and Pathophysiology

Kidney involvement in systemic lupus erythematosus (SLE), generally termed lupus nephritis (LN), is a major contributor to SLE-associated morbidity and mortality. Up to 50% of patients with SLE will have clinically evident kidney disease at presentation; during follow-up, kidney involvement occurs in up to 75% of patients. LN has been shown to affect clinical outcomes in SLE both directly via target organ damage and indirectly through complications of therapy.

The immune deposits that incite LN are primarily complexes of anti-double-stranded DNA antibodies directed against nucleosomal antigens. A smaller fraction of autoantibodies can also bind directly to chromatin in the glomerular basement membrane (GBM) and mesangium. These immune complexes, when deposited in the mesangium and subendothelial space, are proximal to the GBM and are in communication with the systemic circulation. Subsequent activation of the classical complement pathway, triggered by the DNA/anti-DNA antibody complex formation, generates the potent chemoattractants, C3a and C5a, which elicit an influx of neutrophils and mononuclear cells. The pattern on light microscopy is a proliferative glomerulonephritis that can be mesangial (class II), focal endocapillary (class III), or diffuse endocapillary (class IV) (**Table 20**). Endocapillary proliferation refers to an increased number of inflammatory cells within glomerular capillary lumina, causing luminal narrowing or obliteration. Immune complex deposits in the subepithelial space can also activate complement but only locally; C3a and C5a are separated from the circulation by the GBM, and hence no influx of inflammatory cells occurs into this space. The injury in this class V LN (membranous) is limited to the glomerular epithelial cells, the primary clinical manifestation is proteinuria, and the histologic pattern on light microscopy is similar to primary membranous nephropathy.

Clinical Manifestations

Typically, patients with SLE initially present with evidence of non–kidney organ involvement (malar rash, arthritis, oral ulcers). After a diagnosis of SLE is confirmed, evidence of kidney disease, if present, usually emerges within the first 3 years of diagnosis. Kidney involvement in SLE first manifests with proteinuria and/or microscopic hematuria on urinalysis; this eventually progresses to reduction in kidney function. Early in the course of disease, it is unusual for patients to present with decreased kidney function, except for very aggressive cases of LN that present as RPGN. The symptoms of kidney involvement tend to correlate with laboratory abnormalities. For example, patients with nephrotic-range proteinuria can present with edema. When kidney function is impaired, elevated blood pressure is a common clinical finding.

TABLE 20. Classification of Lupus Nephritis with Associated Presentation and Treatment Options

ISN/RPS Class	Biopsy Findings	Clinical Features	Treatment	
			Induction Phase	Maintenance Phase
Class I: minimal mesangial LN	No LM abnormalities; isolated mesangial IC deposits on IF and/or EM	Normal urine or microscopic hematuria	Conservative, nonimmunomodulatory therapy (e.g., RAS blockade)	Not applicable
Class II: mesangial proliferative LN	Mesangial hypercellularity or matrix expansion with mesangial IC deposits on IF and/or EM	Microscopic hematuria and/or low-grade proteinuria	Conservative, nonimmunomodulatory therapy (e.g., RAS blockade)	Not applicable
Class III: focal LN	<50% of glomeruli on LM display segmental (<50% of glomerular tuft) or global (>50% of glomerular tuft) endocapillary and/or extracapillary proliferation or sclerosis; mesangial and focal subendothelial IC deposits on IF and EM	Nephritic urine sediment and subnephrotic proteinuria	Pulse IV glucocorticoids followed by tapering doses of oral glucocorticoids *and* IV cyclophosphamide for 6 doses (high-dose monthly vs. low-dose bimonthly) *or* Mycophenolate mofetil for 6 months	Lowest tolerable amount of oral glucocorticoids *and* Mycophenolate mofetil (tapered down every 3-6 months assuming stable disease) *or* Azathioprine (tapered down every 3-6 months assuming stable disease)
Class IV: diffuse LN	≥50% of glomeruli on LM display endocapillary and/or extracapillary proliferation or sclerosis; class IV-S denotes that ≥50% of affected glomeruli have segmental lesions; class IV-G denotes that ≥50% of affected glomeruli have global lesions; mesangial and diffuse subendothelial IC deposits on IF and EM	Nephritic and nephrotic syndromes; hypertension; reduced kidney function	Pulse IV glucocorticoids followed by tapering doses of oral glucocorticoids *and* IV cyclophosphamide for 6 doses (high-dose monthly vs. low-dose bimonthly) *or* Mycophenolate mofetil for 6 months	Lowest tolerable amount of oral glucocorticoids *and* Mycophenolate mofetil (tapered down every 3-6 months assuming stable disease) *or* Azathioprine (tapered down every 3-6 months assuming stable disease)
Class V: membranous LN[a]	Diffuse thickening of the glomerular capillary walls on LM with subepithelial IC deposits on IF and EM, with or without mesangial IC deposits	Nephrotic syndrome	Pulse IV glucocorticoids followed by tapering doses of oral glucocorticoids *and* IV cyclophosphamide for 6 doses (high-dose monthly vs. low-dose bimonthly) *or* Cyclosporine *or* Tacrolimus *or* Mycophenolate mofetil for 6 months	Lowest tolerable amount of oral glucocorticoids *and* Mycophenolate mofetil (tapered down every 3-6 months assuming stable disease) *or* Azathioprine (tapered down every 3-6 months assuming stable disease)
Class VI: advanced sclerosing LN	>90% of glomeruli on LM are globally sclerosed with no residual activity	Advanced CKD or ESKD with varying degrees of hematuria and/or proteinuria	Conservative, nonimmunomodulatory therapy (e.g., RAS blockade) with preparation for renal replacement therapy	Not applicable

CKD = chronic kidney disease; EM = electron microscopy; ESKD = end-stage kidney disease; IC = immune complex; IF = immunofluorescence; ISN/RPS = International Society of Nephrology/Renal Pathology Society; IV = intravenous; LM = light microscopy; LN = lupus nephritis; RAS = renin-angiotensin system.

[a]Class V may coexist with class III or class IV, in which case both classes are diagnosed.

Diagnosis

The diagnosis of LN is suspected by changes in laboratory parameters (elevated serum creatinine, hematuria and/or proteinuria, low serum complements) but can only be made definitively by kidney biopsy. The classic pattern of LN is an immune complex–mediated glomerulonephritis with a varied pathology that includes six distinct classes of disease (see Table 20). On immunofluorescence microscopy, the glomerular deposits in LN stain dominantly for IgG with co-deposits of IgA, IgM, C3, and C1q in a "full house" pattern. On electron microscopy, tubuloreticular inclusions, which represent "interferon footprints" in the glomerular endothelial cell cytoplasm, are essentially pathognomonic for LN.

Treatment and Prognosis

The current approach to treating LN is guided by histologic findings with appropriate consideration of presenting clinical parameters and the degree of kidney function impairment (see Table 20). Important recent changes in the management of LN include the preferential use of mycophenolate mofetil over cyclophosphamide as induction therapy for LN classes III, IV, and V based on similar efficacy rates and a more favorable side-effect profile with mycophenolate mofetil (in particular, the non-impact on fertility of mycophenolate mofetil compared with cyclophosphamide in a young patient population with childbearing potential). The landmark ALMS trial showed only a 56% response rate in the mycophenolate arm (compared with a 53% response rate in the cyclophosphamide arm).

Up to 30% of patients with LN will progress to ESKD within 10 years of diagnosis, depending in large part on the response to the initial course of immunosuppression. Severity of disease at the time of diagnosis as well as black race, Hispanic ethnicity, and socioeconomic status have also been reported to influence outcomes in LN.

Infection-Related Glomerulonephritis

Epidemiology and Pathophysiology

Infection-related glomerulonephritis (IRGN) results from a recently resolved infection or an infection that is ongoing at the time of development of glomerulonephritis. IRGN is preferred to the formerly used term "postinfectious glomerulonephritis," which adequately described classic poststreptococcal glomerulonephritis but did not address the increasingly recognized forms of glomerulonephritis that are manifestations of ongoing infection and nonstreptococcal infectious agents. Diabetes is the most common comorbidity (malignancy, immunosuppression, AIDS, alcoholism, and injection drug use are other recognized comorbidities), and older age is a key risk factor. Patients over 65 years of age account for about one third of IRGN cases in the developed world.

The incidence of poststreptococcal glomerulonephritis has declined throughout most of the world due to improvements in infection control and sanitation. The entity, however, remains a health concern in developing countries: More than 450,000 cases of poststreptococcal glomerulonephritis occur worldwide annually, resulting in approximately 5000 deaths, with >95% of these cases in less developed countries. In industrialized countries, much of the burden of IRGN has shifted from children to adults, with a decrease in IRGN attributed to streptococcal infections and an increase in IRGN cases associated with *Staphylococcus aureus* and gram-negative bacteria.

In the classical view of the pathogenesis of IRGN, antibodies directed at bacterial antigens form immune complexes in the circulation that subsequently deposit in the glomerulus. Additionally, however, antibodies directed at bacterial antigens planted within glomeruli can result in *in situ* formation of glomerular immune complexes.

Clinical Manifestations

The variable presentation of IRGN ranges from asymptomatic microscopic hematuria to RPGN. Proteinuria is usually subnephrotic.

In classic poststreptococcal glomerulonephritis, symptomatic patients (typically children) present with an acute nephritic syndrome of hematuria, proteinuria, hypertension, edema, and, in some cases, kidney dysfunction. The urine sediment is active with dysmorphic erythrocytes, erythrocyte casts, and leukocyturia. Hypocomplementemia is very common, with decreased C3 in up to 90% of cases. There is usually a latent period (1 to 2 weeks after upper respiratory infections; 2 to 4 weeks after skin infections) between the resolution of the streptococcal infection and the onset of the nephritic syndrome. Serologic markers of a recent streptococcal infection, including elevated antistreptolysin O, antistreptokinase, anti-hyaluronidase, and antideoxyribonuclease B antibody levels, are often detected. In adults, most cases of IRGN are no longer poststreptococcal, and the glomerulonephritis often coexists with the triggering infection. Low complement levels may be absent in these peri-infectious cases.

Diagnosis

The diagnosis of IRGN can be made clinically in the appropriate setting (for example, classic nephritic presentation with low complements and clear evidence of a recent infection), although the only definitive way to make the diagnosis is by kidney biopsy. The most common finding on light microscopy is a proliferative glomerulonephritis with significant presence of infiltrating neutrophils. On electron microscopy, the classic finding in poststreptococcal glomerulonephritis is hump-shaped subepithelial electron dense deposits, although these are not required for the diagnosis of IRGN.

Treatment and Prognosis

Treatment is typically supportive and aimed at the infectious etiology, although in some cases with severe proliferative glomerulonephritis on biopsy, a trial of glucocorticoids is used.

In children, prognosis for complete recovery is excellent, and treatment usually is supportive and aimed at the infecting organism. The prognosis of the newly recognized forms

of IRGN (for example, due to *S. aureus* and gram-negative organisms) in adults is different, with more patients developing severe kidney dysfunction and progressing to CKD and sometimes ESKD.

Membranoproliferative Glomerulonephritis

Epidemiology and Pathophysiology

Membranoproliferative glomerulonephritis (MPGN) is a rare form of chronic glomerulonephritis diagnosed primarily in children and young adults. The name stems from its pattern of glomerular injury. The entity is divided into immune complex forms of MPGN (mediated by antigen-antibody interactions triggering the classical complement pathway) versus complement-mediated forms of MPGN (also termed C3 glomerulopathies, due to a hyperactive alternative complement pathway). An immune-complex MPGN, with or without cryoglobulinemia, is the classic form of kidney involvement seen in patients with hepatitis C virus infection. The alternative complement pathway abnormalities that drive the C3 glomerulopathies are either mutations in regulators (for example, complement factor H) or activators (for example, complement factor B) of the alternative pathway, or antibodies directed at regulator or activator complement proteins.

Clinical Manifestations

Although MPGN can rarely present as an acute and severe form of glomerulonephritis, the more common presentation is a chronic glomerulonephritis that initially manifests with microscopic hematuria and subnephrotic proteinuria. As disease progresses, proteinuria can reach nephrotic range, and kidney dysfunction ensues.

Diagnosis

The diagnosis of MPGN is made by kidney biopsy. The distinction between immune complex and complement-mediated MPGN is based on immunofluorescence microscopy, in which the absence of immunoglobulin staining signals an antibody-independent manner of triggering complement and hence alternative pathway hyperactivity.

Treatment and Prognosis

Currently, treatment of MPGN is nonspecific and includes immunosuppression (for example, glucocorticoids) when nephrotic-range proteinuria and/or kidney dysfunction is present. The advent of complement-targeting therapies such as the C5 monoclonal antibody, eculizumab, may bring disease-specific therapy for the complement-mediated forms of MPGN.

The overall prognosis of MPGN as a chronic form of glomerulonephritis is poor, with >50% of patients progressing to ESKD within 15 years of diagnosis.

Cryoglobulinemia

Cryoglobulinemia can be associated with the nephritic syndrome. Of the three types of cryoglobulins, kidney involvement is typically due to type II cryoglobulins.

See MKSAP 18 Hematology and Oncology for details on cryoglobulinemia; MKSAP 18 Rheumatology for information on cryoglobulinemic vasculitis; and Kidney Manifestations of Deposition Diseases in MKSAP 18 Nephrology for information on kidney involvement in cryoglobulinemia.

Collagen Type IV–Related Nephropathies

Type IV collagen is an integral component of the glomerular basement membrane. Structural defects in this protein due to genetic variations can result in a hereditary form of glomerulonephritis, discussed in more detail in Genetic Disorders and Kidney Disease.

KEY POINTS

- Treatment of IgA nephropathy consists of conservative therapy using an ACE inhibitor or angiotensin receptor blocker.
- Kidney biopsy is required to diagnose and classify lupus nephritis, which guides therapy.
- Treatment of classes I and II lupus nephritis (LN) includes conservative therapy with an ACE inhibitor or angiotensin receptor blocker; classes III, IV, and V LN may require aggressive immunosuppressive therapy; and class VI LN may be treated with conservative therapy.
- Infection-related glomerulonephritis results from a recently resolved infection or an infection that is ongoing at the time of development of glomerulonephritis; in industrialized countries, clinical disease is seen more often in adults and is associated with *Staphylococcus aureus* and gram-negative bacteria.
- Treatment of membranoproliferative glomerulonephritis is nonspecific and includes immunosuppression when nephrotic-range proteinuria and/or kidney dysfunction is present.

Kidney Manifestations of Deposition Diseases

Overview

Various kidney diseases are associated with deposition of immunoglobulin (Ig) and non-Ig proteins. On electron microscopy, these deposits can be unstructured or organized into fibrils or tubules (**Figure 14**). Monoclonal Ig deposits may be caused by myeloma, Waldenström macroglobulinemia, or chronic lymphocytic leukemia, or by the clonal expansion of Ig-secreting cells that do not meet the strict definition of these disorders, which has been termed *monoclonal gammopathy of renal significance* (MGRS). The pathological findings associated with monoclonal Ig deposition can include proliferative glomerulonephritis, AL amyloid, type 1 cryoglobulinemia, and, occasionally, immunotactoid and fibrillary glomerulopathy. Polyclonal Ig deposits include

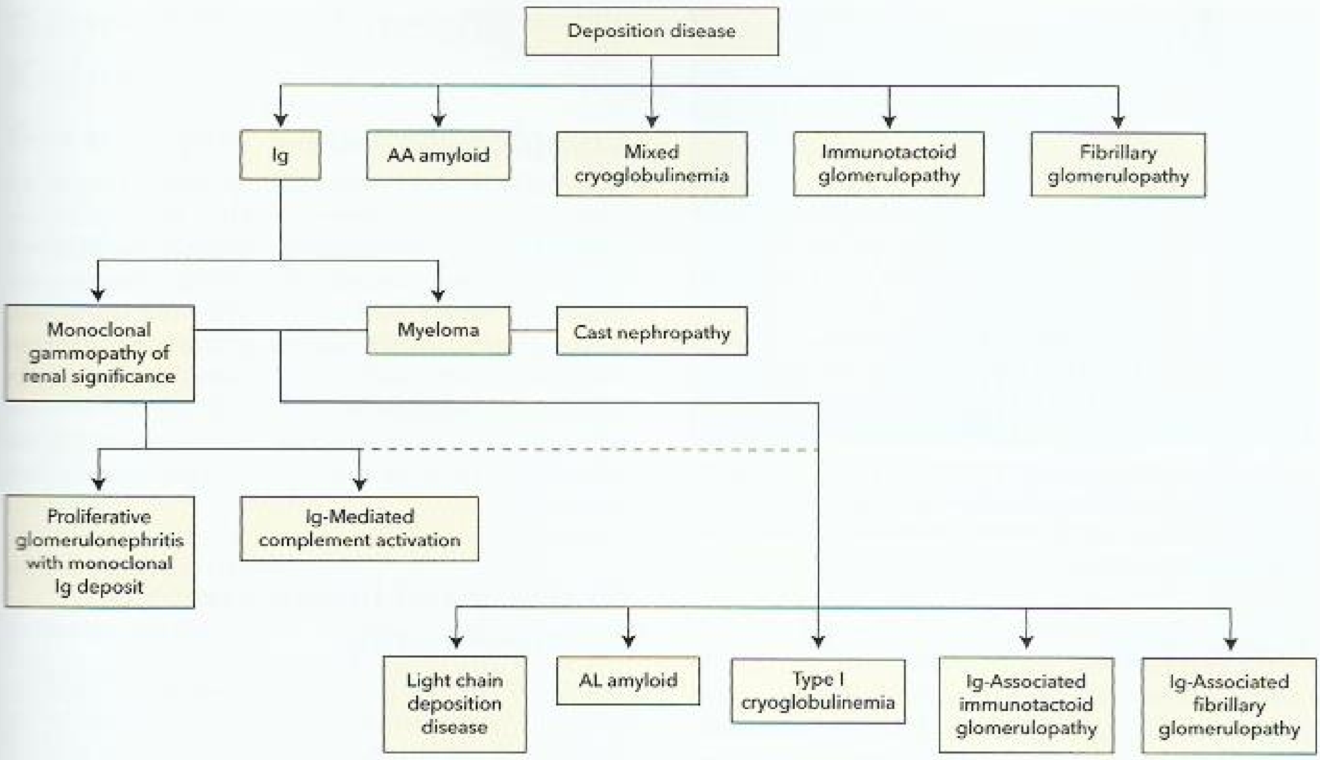

FIGURE 14. Deposition diseases can be divided into five major categories: immunoglobulin (Ig)-related disease, amyloid, cryoglobulinemia, immunotactoid glomerulopathy, and fibrillary glomerulopathy. Ig-related disease can be further divided into multiple myeloma and monoclonal gammopathy of renal significance (MGRS). Although some histopathological findings occur more commonly in either multiple myeloma (such as cast nephropathy) or MGRS, most have been reported in either disorder.

mixed cryoglobulinemia, whereas non-Ig proteins contribute to AA amyloid and to most cases of immunotactoid and fibrillary glomerulopathy.

Monoclonal Immunoglobulin–Associated Kidney Disease

A wide array of renal lesions can be caused by clonal expansion of Ig-secreting cells. If there are greater than 10% plasma cells on bone marrow biopsy or the presence of an extramedullary plasmacytoma, a diagnosis of multiple myeloma can be made. However, as noted above, paraproteinemia caused by clonal expansion of Ig-secreting cells that do not meet the strict definition of myeloma, Waldenström macroglobulinemia, or chronic lymphocytic leukemia can be associated with nephrotoxicity. Although some of the findings noted pathologically occur more frequently with either MGRS or myeloma, except for myeloma cast nephropathy seen exclusively with myeloma, all the renal lesions can occur in each of these disorders. Because filtered light chains are endocytosed by proximal tubule cells and are nephrotoxic, patients may present with proximal tubular dysfunction with Fanconi syndrome; common features include glycosuria, phosphaturia, and normal anion gap metabolic acidosis. Kidney function may be normal or abnormal.

Myeloma Cast Nephropathy

Myeloma cast nephropathy occurs in the presence of a markedly increased concentration of free light chains and is always associated with multiple myeloma. Light chains are freely filtered by the glomerulus and combine with secreted Tamm-Horsfall protein to form obstructing casts. These tubular casts have a characteristic fractured appearance on microscopic examination. Patients with cast nephropathy present with acute or slowly progressive kidney injury. Serum free light chains are extremely elevated. Treatment is aimed at reducing the concentration of free light chains using chemotherapy. Plasmapheresis may also be beneficial in selected patients.

Monoclonal Gammopathy of Renal Significance

Monoclonal gammopathy of renal significance (MGRS) is characterized by kidney damage caused by monoclonal Ig that is secreted by a B cell or plasma cell clone not meeting diagnostic criteria for multiple myeloma or a lymphoproliferative disorder. All pathological findings associated with the clonal expansion of Ig-secreting cells can be seen in both myeloma and MGRS. The underlying pathology is likely determined by the characteristics of

the secreted protein. Entities associated with MGRS include proliferative glomerulonephritis with monoclonal Ig deposits (PGNMID), C3 glomerulopathy with monoclonal gammopathy, AL amyloid, type 1 cryoglobulinemia, fibrillary glomerulonephritis, and immunotactoid glomerulopathy.

Kidney manifestations of MGRS are usually caused by deposition of monoclonal Ig light chains. Patients can present with both nephrotic and subnephrotic proteinuria, hematuria, and elevated serum creatinine.

Kidney biopsy is necessary to make the diagnosis. In addition to evaluating for underlying myeloma and chronic lymphocytic leukemia, further testing may include serum and urine protein electrophoresis, immunofixation, measurement of free light chains, and bone marrow biopsy. Because treatment is aimed at eradication of the expanded clonal line, it is important that the care of patients with MGRS be coordinated with a myeloma specialist.

Amyloidosis

Amyloidosis is a disorder characterized by the fibrillary deposition of insoluble amyloid proteins that form β-pleated sheets, which exhibit green birefringence on polarizing microscopy when stained with Congo red. Amyloid fibrils are approximately 10 nm in diameter, as opposed to the larger microtubules seen in fibrillary glomerulonephritis and immunotactoid glomerulopathy. Although amyloid can be made up of numerous proteins, kidney disease is most commonly caused by AL amyloid or AA amyloid. AL amyloid is composed of monoclonal λ (most commonly) or κ light chains produced by either MGRS or myeloma; AA amyloid is formed by serum amyloid A protein, an acute phase reactant produced in various inflammatory diseases such as rheumatoid arthritis, inflammatory bowel disease, chronic osteomyelitis, and familial Mediterranean fever. Patients with renal amyloid frequently present with nephrotic-range proteinuria. Less commonly, amyloid can affect only the renal vasculature or tubular-interstitium and have minimal or no proteinuria. Treatment is aimed at the underlying disease.

Monoclonal Immunoglobulin Deposition Disease

Monoclonal light chains (usually κ) or heavy chains can be deposited in the kidney and manifest as proteinuria and kidney failure. Unlike AL amyloid, these proteins do not form β-pleated sheets and do not stain with Congo red. These deposits can be limited to the basement membrane, giving a microscopic appearance similar to that of diabetic nodular sclerosis (light chain deposition disease), or can activate complement and induce a proliferative glomerulonephritis (PGNMID). In some cases, an underlying plasma cell dyscrasia or lymphoproliferative disorder can be identified, but criteria for myeloma or chronic lymphocytic leukemia are often absent.

Cryoglobulinemia

Of the three types of cryoglobulinemia, kidney involvement occurs most frequently with type II (mixed Ig) cryoglobulinemia and is usually associated with hepatitis C virus infection. Patients can present with a nephritic picture: elevated serum creatinine, hypertension, proteinuria, and hematuria. Membranoproliferative glomerulonephritis is usually noted on biopsy. Occasionally, a rapidly progressive glomerulonephritis with crescent formation can occur. A palpable purpuric rash is frequently present on the lower extremities. Because hepatitis C is the predominant cause, treatment is aimed at eradication of the virus.

Fibrillary and Immunotactoid Glomerulopathy

Although rare, both fibrillary and immunotactoid glomerulopathy are becoming increasingly recognized causes of kidney disease. These diseases are caused by glomerular deposition of microtubular structures that are larger than amyloid (20 nm in fibrillary glomerulopathy and >30 nm in immunotactoid glomerulopathy) and do not stain with Congo red. Proteinuria, frequently in the nephrotic range, and hematuria are common. Although the pathogenesis of these entities is unknown, both have been associated with paraproteinemia. Treatment is usually unsuccessful, and kidney outcomes are poor.

KEY POINTS

- Patients with myeloma cast nephropathy present with acute or slowly progressive kidney injury and have extremely elevated serum free light chains; treatment is aimed at reducing the concentration of free light chains using chemotherapy.
- Diseases causing monoclonal gammopathy of renal significance can present with either nephrotic or subnephrotic proteinuria, hematuria, and elevated serum creatinine; kidney biopsy is necessary to make the diagnosis, and treatment is aimed at eradication of the expanded clonal line.
- Kidney disease in amyloidosis is most commonly caused by AL amyloid composed of monoclonal λ or κ light chains or AA amyloid formed by serum amyloid A protein; patients frequently present with nephrotic-range proteinuria, and treatment is aimed at the underlying disorder.
- Kidney involvement in cryoglobulinemia occurs most frequently with type II (mixed) cryoglobulins and is usually associated with hepatitis C virus infection; treatment is directed at eradication of hepatitis C virus.

Genetic Disorders and Kidney Disease

Genetic Cystic Kidney Disorders

Genetic cystic kidney disorders are categorized in **Table 21**.

Autosomal Dominant Polycystic Kidney Disease

Autosomal dominant polycystic kidney disease (ADPKD) is the leading genetic cause of end-stage kidney disease (ESKD) and the fourth leading cause of ESKD. ADPKD manifests as large kidneys with multiple kidney cysts (**Figure 15**). Genetic mutations in *PKD1* and *PKD2*, which encode for proteins that regulate differentiation and proliferation of renal tubular epithelial cells, account for approximately 85% and 15% of cases, respectively. More than 90% of mutations are inherited as an autosomal dominant trait, with spontaneous germline mutations accounting for the remaining cases.

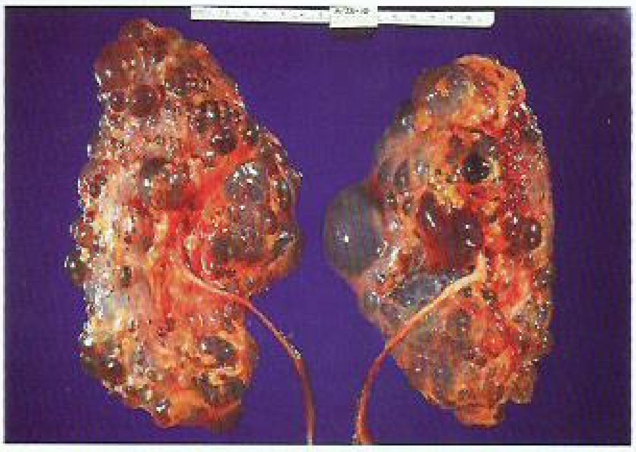

FIGURE 15. Autosomal dominant polycystic kidney disease with multiple bilateral cysts, which replace the normal smooth architecture of the kidneys and lead to markedly increased kidney size.

Image from the CDC Public Health Image Library.

Screening and Diagnosis

Ultrasonography is the most common and least costly screening method for ADPKD. Ultrasonography criteria for diagnosing ADPKD are based on the number of visible cysts, the patient's age, and a family history of ADPKD. Direct DNA sequencing of the *PKD1* and *PKD2* genes is increasingly used to confirm diagnosis or, in some cases, is performed in lieu of imaging. Gene linkage testing, which identifies DNA markers in several members of a family, can also be used in patients with a family history of ADPKD.

Clinical Manifestations

Early in the disease, there are generally no symptoms. Diagnosis is therefore often delayed in patients without a known family history of ADPKD. The first sign of ADPKD is often hypertension; other early signs and symptoms include hematuria (macroscopic or microscopic), pain or bloating in the back or abdomen, urinary tract infection, or kidney stones. In patients without a family history, these presentations usually lead to imaging studies that reveal ADPKD. CT or MRI may be used to evaluate for complications in patients with known ADPKD, such as bleeding into a cyst or a suspected kidney stone.

Extrarenal manifestations include hepatic cysts (detected in >80% of patients over their lifetime), mitral valve prolapse, inguinal and umbilical hernias, and intracranial aneurysms (detected in 5%-10% of patients, with a strong familial pattern).

Management

Patients with ADPKD have a >50% chance of progressing to ESKD by age 70 years. No disease-specific therapies currently exist; therefore, management is focused on controlling blood pressure and addressing complications of disease. Vasopressin blockade with tolvaptan in patients with ADPKD has been shown in two randomized clinical trials to delay the need for

TABLE 21. Genetic Cystic Kidney Disorders

Disorder	Inheritance	Gene(s)	Features/Comments
Autosomal dominant polycystic kidney disease	AD	*PKD1* *PKD2*	Most common inherited kidney disorder (5% of ESKD cases); intracranial cerebral aneurysm; mitral valve prolapse; hepatic cysts; diverticulosis
Autosomal recessive polycystic kidney disease	AR	*PKHD1*	Causes ESKD in infancy or childhood; hepatic fibrosis; portal hypertension; homozygous mutations cause complete loss of function: severe cystic kidney disease, oligohydramnios, pulmonary hypoplasia, Potter syndrome (limb deformities, typical facial appearance, pulmonary hypoplasia)
Tuberous sclerosis complex	AD	*TSC1* *TSC2*	Characterized by benign hamartomas; epilepsy, brain tumors, developmental delay, autism, and lung disease may also occur; renal angiomyolipomas are common; kidney cysts may develop
Nephronophthisis	AR	Multiple (13)	Most common genetic cause of ESKD detected in childhood/adolescence; interstitial fibrosis; renal medullary cysts; a renal concentrating defect and/or salt wasting; retinitis pigmentosa

AD = autosomal dominant; AR = autosomal recessive; ESKD = end-stage kidney disease.

dialysis from 6 to 9 years. However, tolvaptan carries an FDA-mandated safety warning about the possibility of irreversible liver injury, and it has not been approved by the FDA for use in ADPKD.

The Guidelines for the Management of Patients with Unruptured Intracranial Aneurysms from the American Heart Association/American Stroke Association recommend that patients with a history of ADPKD, particularly those with a family history of intracranial aneurysm, should be offered screening by CT angiography or MR angiography. This is a class I recommendation (should be performed because benefit greatly exceeds risk) based on level B evidence (data derived from a single randomized trial or nonrandomized studies).

Tuberous Sclerosis Complex

Tuberous sclerosis complex (TSC) is a genetic disorder with mutations in the tumor-suppressing genes *TSC1* or *TSC2* and resulting tumors in many organs, primarily in the brain, eyes, heart, kidney, skin, and lungs. Although TSC is most frequently diagnosed in the pediatric population, mild disease may escape detection until adulthood. Nearly 1 million people worldwide are estimated to have TSC, with approximately 50,000 in the United States.

Renal angiomyolipomas occur in 75% of patients with TSC and can be detected by CT, ultrasonography, or MRI. Renal cell carcinoma occurs in 1% to 2% of adults with TSC, and therefore screening with abdominal MRI is recommended every 1 to 3 years. Kidney cysts may also develop. The features of TSC that most strongly affect quality of life are generally associated with the brain: seizures, developmental delay, intellectual disability, and autism.

Therapy is rarely needed for the kidney manifestations of TSC. Surgery or related interventions (radiofrequency ablation, selective arterial embolization) may be required for large or hemorrhagic angiomyolipomas.

KEY POINTS

- Autosomal dominant polycystic kidney disease is characterized by large kidneys with multiple kidney cysts, hypertension, hematuria, pain or bloating in the back or abdomen, urinary tract infection, or kidney stones.
- No disease-specific therapies currently exist for autosomal dominant polycystic kidney disease; therefore, management is focused on controlling blood pressure and addressing complications of disease.
- Kidney manifestations of tuberous sclerosis complex include renal angiomyolipomas, renal cell carcinoma, and cysts; surgery or related interventions may be required for large or hemorrhagic angiomyolipomas.

Genetic Noncystic Kidney Disorders

Genetic noncystic kidney disorders are categorized in **Table 22**.

Collagen Type IV-Related Nephropathies

Type IV collagen is an integral component of the glomerular basement membrane (GBM). Structural defects in this protein, due to genetic variations, can result in manifestations spanning from GBM thinning to progressive glomerular injury.

Hereditary Nephritis

Hereditary nephritis (Alport syndrome) is a glomerular disease associated with sensorineural hearing loss and characteristic ocular findings that include corneal dystrophies, microcornea, arcus, iris atrophy, cataracts, spontaneous lens rupture, spherophakia, and anterior lenticonus. There are three genetic variants: X-linked (80%), autosomal recessive (15%), and autosomal dominant (5%). Females with the X-linked variant can be asymptomatic carriers or can develop kidney disease depending on activity of the X chromosome in somatic renal cells. The disease has a prevalence of 0.4% among U.S. adults.

Diagnosis has traditionally been made by kidney biopsy with electron microscopy; the hallmark finding is prominent thickening and lamellation of the GBM in a "basket-weave" appearance. In patients with a clearly documented family history and abnormal urinary findings, diagnosis is increasingly being made by genetic testing. Genetic testing is also the most reliable way to identify heterozygote carriers of type IV collagen mutations. Proteinuria, hypertension, and chronic kidney disease (CKD) usually progress to ESKD between the late teenage years and the fourth decade of life. Management is supportive, including blood pressure control via renin-angiotensin system blockade.

Thin Glomerular Basement Membrane Disease

Thin glomerular basement membrane disease (benign familial hematuria) is associated with type IV collagen variants causing GBM thinning, which results in hematuria without significant proteinuria or ensuing glomerulosclerosis. Up to 5% of the population may be affected. Although diagnosis can be made using electron microscopy of kidney biopsy material, thin glomerular basement membrane disease is usually a clinical diagnosis based on benign presentation and course (normal kidney function with microscopic hematuria and little or no proteinuria) and positive family history of similarly benign phenotype (family history of isolated hematuria without kidney failure). The disease has excellent long-term prognosis with rare progression to CKD. Management is supportive.

Fabry Disease

Fabry disease is an X-linked recessive inborn error of glycosphingolipid metabolism caused by deficiency of α-galactosidase A. The gene responsible for α-galactosidase is located on the long arm of the X chromosome, with almost 200 mutations identified. The enzyme deficiency leads to defective storage of sphingolipid and progressive endothelial

TABLE 22. Genetic Noncystic Kidney Disorders

Disorder	Inheritance	Gene(s)	Features/Comments
Autosomal dominant tubulointerstitial kidney disease (also called medullary cystic kidney disease or uromodulin-associated kidney disease)	AD	*UMOD; REN; MUC1; HNF1B*	Rare; medullary cysts may or may not be present; slow progression to ESKD; bland urine sediment; may be associated with gout and anemia
Collagen type IV-related nephropathies			
Hereditary nephritis (Alport syndrome)	X-linked	*COL4A5*	Sensorineural hearing loss; lenticonus (conical deformation of the lens)
	AD or AR	*COL4A3*	Similar phenotype as X-linked with some variability
	AD or AR	*COL4A4*	Similar to *COL4A3*
Thin glomerular basement membrane disease (benign familial hematuria)	Primarily AD	*COL4A3; COL4A4*	Microscopic or macroscopic hematuria
Hereditary nephrotic syndromes			
Congenital nephropathy (Finnish type)	AR	*NEPH1; NEPH2*	Severe perinatal nephrotic syndrome; ESKD; kidney transplantation is only treatment
Familial FSGS	AR or AD	*NEPH2; ACTN4; TRPC6; INF2; APOL1*	The nephrotic syndrome; ESKD; should be considered in FSGS patients who are infants, are young (<25 years) and steroid-resistant, or have family history of ESKD
Denys-Drash syndrome	AR	*WT1*	Cause of pediatric nephrotic syndrome; associated with urogenital abnormalities
Fabry disease	X-linked	*GLA*	Progressive kidney disease; premature coronary artery disease; severe neuropathic pain; telangiectasias; angiokeratomas
APOL1 nephropathy	AR	*APOL1*	High-risk genotypes present in ~13% of black persons; account for a large fraction of nondiabetic kidney disease in black persons

AD = autosomal dominant; *APOL1* = apolipoprotein 1; AR = autosomal recessive; ESKD = end-stage kidney disease; FSGS = focal segmental glomerulosclerosis.

accumulation, causing abnormalities in the skin, eye, kidney, heart, brain, and peripheral nervous system.

Fabry disease should be considered as a cause of CKD of unknown etiology in young adulthood. Diagnosis can be made by kidney biopsy but also can be made noninvasively with measurement of leukocyte enzymatic activity and subsequent genetic confirmation. Screening for the disease is recommended for family members of affected patients. Enzyme replacement therapy with recombinant human α-galactosidase A is available.

Apolipoprotein L1 Nephropathy

Black persons develop kidney failure at rates four to five times higher than white persons. Recently, genetic variants in the apolipoprotein L1 (*APOL1*) gene were discovered that explain a large fraction of this health disparity. Two risk alleles for kidney disease (G1 and G2) have been identified in the *APOL1* gene. The transmission of disease risk is consistent with recessive inheritance: The high-risk *APOL1* genotype can be G1/G1, G1/G2, or G2/G2. Approximately 12% to 15% of black persons inherit a high-risk *APOL1* genotype; this accounts for a large fraction of nondiabetic kidney disease in black persons. High-risk *APOL1* alleles are unusually prevalent possibly because they conferred a survival advantage in sub-Saharan Africa by enhancing innate immunity against African trypanosomal disease (African sleeping sickness).

Persons with a high-risk *APOL1* genotype have an approximately 10-fold increased risk for focal segmental glomerulosclerosis, a 7-fold increased risk for hypertension-attributed ESKD, and, among those with HIV infection, a 29-fold increased risk for HIV-associated nephropathy. In addition, the *APOL1* risk genotype is associated with an increased risk for progression to CKD in other nondiabetic kidney diseases, including lupus nephritis and primary membranous nephropathy.

KEY POINTS

- Hereditary nephritis (Alport syndrome) is a glomerular disease associated with sensorineural hearing loss and characteristic ocular findings; proteinuria, hypertension, and chronic kidney disease usually progress to end-stage kidney disease between the late teenage years and the fourth decade of life.
- Thin glomerular basement membrane disease (benign familial hematuria) results in hematuria without significant proteinuria or ensuing glomerulosclerosis, with rare progression to chronic kidney disease.

(Continued)

KEY POINTS *(continued)*

- Fabry disease should be considered as a cause of chronic kidney disease of unknown etiology in young adulthood; treatment with recombinant human α-galactosidase A is available.
- High-risk *APOL1* genotype confers increased risk for chronic kidney disease in black persons, including an approximately 10-fold increased risk for focal segmental glomerulosclerosis, a 7-fold increased risk for hypertension-attributed end-stage kidney disease, and a 29-fold increased risk for HIV-associated nephropathy among those with HIV infection.

Acute Kidney Injury

Definition

Acute kidney injury (AKI) is characterized by a sudden decrease in kidney function resulting in an increase in serum creatinine concentration and the accumulation of nitrogenous excretory products over a course of hours to days. AKI is commonly accompanied by decreased urine output, fluid retention, metabolic acidosis, hyperkalemia, and hyperphosphatemia. The Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group definitions for AKI are described in **Table 23**. Multiple studies have shown a correlation between more severe stages of AKI and worse clinical outcomes.

AKI is associated with high morbidity, mortality, and health care costs. Patients with AKI have an increased risk for developing chronic kidney disease (CKD) and end-stage kidney disease (ESKD). Likewise, patients with pre-existing CKD are at an increased risk for developing acute-on-chronic kidney failure. Given its substantial morbidity and mortality, AKI care should be focused on prevention, early recognition and diagnosis, and management of complications.

TABLE 23. KDIGO Definition of Acute Kidney Injury[a]

Stage	Serum Creatinine Criteria	Urine Output Criteria
1	Increase in S_{Cr} to 1.5 to 1.9 times baseline within 7 days or ≥0.3 mg/dL (26.5 µmol/L) within 48 h	<0.5 mL/kg/h for 6 to 12 h
2	Increase in S_{Cr} to 2 to 2.9 times baseline	<0.5 mL/kg/h for ≥12 h
3	Increase in S_{Cr} to 3 times baseline or ≥4.0 mg/dL (356.6 µmol/L) or initiation of RRT or, in patients <18 years, a decrease in eGFR <35 mL/min/1.73 m²	<0.3 mL/kg/h for ≥24 h or anuria for ≥12 h

eGFR = estimated glomerular filtration rate; KDIGO = Kidney Disease: Improving Global Outcomes; RRT = renal replacement therapy; S_{Cr} = serum creatinine.

[a]The KDIGO definition is based on the RIFLE (Risk, Injury, Failure, Loss, and ESKD) and AKIN (Acute Kidney Injury Network) criteria.

KEY POINT

- The Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group defines acute kidney injury by any of the following: increase in serum creatinine by ≥0.3 mg/dL (26.5 µmol/L) within 48 hours; an increase in serum creatinine to ≥1.5 times baseline over 7 days; or a urine volume <0.5 mL/kg/h for 6 hours.

Epidemiology and Pathophysiology

The reported incidence of AKI varies markedly depending on the definition of AKI applied and the patient population studied. The incidence of AKI based on the KDIGO definition is estimated to be 21% of all hospital admissions, with 11% requiring dialysis support. In the ICU, AKI affects >50% of patients. Mortality varies depending on the severity of AKI, underlying cause, and patient population. Critically ill patients with AKI in the context of multiorgan failure have been reported to have mortality rates >50%, especially when dialysis therapy is required.

AKI can be divided into prerenal, intrinsic, and postrenal causes (**Table 24**). Prerenal AKI (prerenal azotemia) is caused by decreased renal perfusion. The integrity of renal tissue is preserved, and tubular and glomerular function remains normal. Intrinsic AKI is caused by structural damage to the renal parenchyma. Postrenal AKI refers to AKI caused by urinary tract obstruction. Prerenal AKI and acute tubular necrosis (ATN) account for approximately 65% to 75% of AKI cases in hospitalized patients. H

KEY POINT

- Prerenal acute kidney injury and acute tubular necrosis account for approximately 65% to 75% of acute kidney injury cases in hospitalized patients.

Clinical Manifestations

Patients with AKI can be asymptomatic until extreme loss of kidney function occurs, and patients with mild to moderate AKI are often diagnosed by laboratory studies only. Patients with AKI can also present with oliguria (urine output <500 mL/d or <0.3 mL/kg/h) or anuria (urine output <50 mL/d). Severe AKI can lead to symptoms from volume overload, electrolyte abnormalities, anemia, platelet dysfunction, and uremia. Uremic symptoms include nausea, vomiting, anorexia, weight loss, fatigue, muscle cramps, restless legs, mental status changes, pruritus, asterixis, seizures, and pericarditis. H

KEY POINT

- Patients with acute kidney injury (AKI) can be asymptomatic until extreme loss of kidney function occurs; severe AKI can lead to symptoms from volume overload, electrolyte abnormalities, anemia, platelet dysfunction, and uremia.

TABLE 24. Causes of Acute Kidney Injury

Cause	Examples
Prerenal	
Volume depletion	Renal losses; GI fluid losses; hemorrhage; burns
Decreased cardiac output	Heart failure; massive pulmonary embolus; acute coronary syndrome
Systemic vasodilation	Sepsis; cirrhosis; anaphylaxis; anesthesia
Intrarenal vasoconstriction	Drugs (NSAIDs, COX-2 inhibitors, amphotericin B, calcineurin inhibitors, contrast agents); hypercalcemia; hepatorenal syndrome
Efferent arteriolar vasodilation	Renin inhibitors; ACE inhibitors; ARBs
Intrinsic	
Acute tubular necrosis	Ischemic: prolonged prerenal AKI; abdominal compartment syndrome
	Drug-induced: aminoglycosides; vancomycin; polymyxins; lithium; amphotericin B; pentamidine; cisplatin; foscarnet; tenofovir; cidofovir; carboplatin; ifosfamide; zoledronate; contrast agents; sucrose; immune globulins; mannitol; hydroxyethyl starch; dextran; NSAIDs; synthetic cannabinoids; amphetamines
	Pigment: rhabdomyolysis; intravascular hemolysis
Acute interstitial nephritis	Drug-induced: cephalosporins; penicillin; methicillin; fluoroquinolones; sulfonamides; rifampin; NSAIDs; COX-2 inhibitors; proton pump inhibitors; 5-aminosalicylates; indinavir; abacavir; allopurinol; phenytoin; triamterene; furosemide; thiazide diuretics; phenytoin; carbamazepine; Chinese herb nephropathy
	Infection: pyelonephritis; viral nephritides; leptospirosis; *Legionella*; *Mycobacterium tuberculosis*
	Autoimmune: Sjögren syndrome; sarcoidosis; SLE; TINU syndrome; IgG4-related disease
	Malignancy: lymphoma; leukemia; multiple myeloma
Acute glomerulonephritis	Infection-related glomerulonephritis; cryoglobulinemia; RPGN; IgA; lupus nephritis; renal vasculitis; anti-GBM antibody disease
Acute vascular syndromes	Macrovascular: renal artery occlusion; renal vein thrombosis; polyarteritis nodosa
	Microvascular:
	Disease-associated TMA: HUS; atypical HUS; TTP; HELLP; scleroderma renal crisis; hypertensive emergency
	Drug-induced TMA: quinine; cancer therapies (gemcitabine, mitomycin, bevacizumab, bortezomib, sunitinib); calcineurin inhibitors (cyclosporine, tacrolimus); drugs of abuse (cocaine, ecstasy, intravenous extended-release oxymorphone)
	Other drugs: clopidogrel; cyclosporine; tacrolimus; anti-angiogenesis drugs; interferon; mTOR inhibitors
	Atheroembolic disease
Intratubular obstruction	Paraprotein: myeloma
	Crystals: TLS; sulfonamides; triamterene; ciprofloxacin; ethylene glycol; acyclovir; indinavir; atazanavir; methotrexate; orlistat; large doses of vitamin C; sodium phosphate purgatives
Postrenal	
Upper tract obstruction	Nephrolithiasis; blood clots; external compression
Lower tract obstruction	BPH; neurogenic bladder; blood clots; cancer; urethral stricture

AKI = acute kidney injury; ARB = angiotensin receptor blocker; BPH = benign prostatic hyperplasia; COX = cyclooxygenase; GBM = glomerular basement membrane; GI = gastrointestinal; HELLP = hemolysis, elevated liver enzymes, and low platelets; HUS = hemolytic uremic syndrome; mTOR = mammalian target of rapamycin; RPGN = rapidly progressive glomerulonephritis; SLE = systemic lupus erythematosus; TINU = tubulointerstitial nephritis and uveitis; TLS = tumor lysis syndrome; TMA = thrombotic microangiopathy; TTP = thrombotic thrombocytopenic purpura.

Diagnosis

The diagnosis of AKI is based on increased levels of serum creatinine and blood urea nitrogen (BUN). The most reliable way to distinguish AKI from CKD is knowledge of previous serum creatinine levels; documentation of similarly elevated creatinine levels for ≥3 months suggests that the kidney failure is chronic. However, serum creatinine and BUN concentrations can be increased by multiple factors independent of kidney function, limiting their specificity for diagnosis of AKI (**Table 25**). Furthermore, serum creatinine is not a sensitive marker of kidney injury in patients with sepsis, liver disease, muscle wasting, or fluid overload and does not provide any information regarding the cause of AKI. BUN can also be normal in patients with AKI who are malnourished or have liver disease. Moreover, the rise in serum creatinine is delayed 24 to 36 hours after the onset of injury and decline in glomerular filtration rate (GFR).

A thorough patient history, physical examination, and analysis of laboratory and image findings are necessary to

TABLE 25. Selected Examples of Causes of Elevated Blood Urea Nitrogen and Serum Creatinine Without Acute Kidney Injury

Elevated Blood Urea Nitrogen
Gastrointestinal bleeding
Protein loading, including albumin infusions
Catabolic steroids
Tetracycline antibiotics
Elevated Serum Creatinine
Medications that block creatinine secretion: cimetidine; trimethoprim; cobicistat; dolutegravir
Creatine ethyl ester (an aid for athletic performance and for muscle development for body builders)
Substances that interfere with creatinine assay: acetoacetate; cefoxitin; flucytosine

CONT.

identify the AKI as prerenal, intrinsic, or postrenal. The history focuses on identifying potential nephrotoxic medications (including over-the-counter medications, herbal products, and recreational drugs), recent exposure to iodinated contrast agents, predisposing conditions for AKI, and urinary obstructive symptoms (see Table 24). Physical examination focuses on volume status, signs of systemic illness that might impair kidney function, and evidence of urinary obstruction (such as a palpable bladder or flank pain). Laboratory evaluation includes BUN and creatinine concentrations, electrolytes, complete blood count, and assessment of the urine (urine indices, urinalysis, and microscopic evaluation of the urine sediment) (**Table 26**).

In patients with oliguria, the fractional excretion of sodium (FE_{Na}) can help distinguish between prerenal AKI and ATN. FE_{Na} measures the ratio of sodium excreted (urine sodium × volume) to sodium filtered (serum sodium × GFR) and is calculated as follows:

$$(U_{Sodium} \times P_{Creatinine})/(U_{Creatinine} \times P_{Sodium}) \times 100\%$$

In prerenal AKI, decreased renal perfusion increases sodium and water reabsorption, resulting in a decrease in urinary sodium excretion and FE_{Na} <1%. However, FE_{Na} <1% can occur with other causes of AKI that are not prerenal but have intact tubular function: contrast nephropathy, pigment nephropathy, glomerulonephritis, and early obstruction. FE_{Na} >2% suggests impaired tubular ability to reabsorb sodium and is consistent with ATN. However, FE_{Na} may be >2% in patients with prerenal AKI who have urinary sodium loss due to diuretics, adrenal insufficiency, or from bicarbonaturia in severe metabolic alkalosis. FE_{Na} may also be >2% in prerenal patients with CKD as a result of impaired tubular function.

In the setting of diuretics, the fractional excretion of urea (FE_{Urea}) can be used to diagnose prerenal AKI, with FE_{Urea} <35% suggesting the diagnosis. FE_{Urea} is calculated as follows:

$$(U_{Urea} \times P_{Creatinine})/(U_{Creatinine} \times P_{Urea}) \times 100\%$$

Ultrasonography of the kidneys and bladder should be obtained for suspected urinary tract obstruction or when the underlying cause of AKI is unclear. Kidney size may help distinguish between AKI and CKD because diminished kidney size and cortical thinning suggest CKD. Kidney size can be normal in patients with CKD from infiltrative disorders such as diabetes mellitus, HIV-associated nephropathy, amyloidosis, or multiple myeloma. Kidney biopsy should be considered in patients with AKI from no apparent cause, suspected glomerulonephritis, or unexplained systemic disease.

TABLE 26. Diagnostic Findings in Acute Kidney Injury

Condition	BUN-Creatinine Ratio	Urine Osmolality (mOsm/kg H_2O)	Urine Sodium (mEq/L [mmol/L])	FE_{Na}	Urinalysis and Microscopy
Prerenal	>20:1	>500	<20	<1%	Specific gravity >1.020; normal or hyaline casts
Acute tubular necrosis	10-15:1	~300	>40	>2%[a]	Specific gravity ~1.010; pigmented granular (muddy brown) casts and tubular epithelial cells
Acute interstitial nephritis	Variable	Variable, ~300	Variable	Variable	Mild proteinuria; leukocytes; erythrocytes; leukocyte casts; eosinophiluria
Acute glomerulonephritis	Variable	Variable	Variable	Variable	Proteinuria; dysmorphic erythrocytes; erythrocyte casts
Intratubular obstruction	Variable	Variable	Variable	Variable	Crystalluria or Bence-Jones proteinuria
Acute vascular syndromes	Variable	Variable	Variable	Variable	Variable hematuria
Postrenal	Variable	Variable	Variable	Variable	Variable; bland

BUN = blood urea nitrogen; FE_{Na} = fractional excretion of sodium.

[a]FE_{Na} can be low in contrast-induced nephropathy and pigment nephropathy.

KEY POINTS

- In patients with oliguria, the fractional excretion of sodium (FE_{Na}) can help distinguish between prerenal acute kidney injury (AKI) and acute tubular necrosis (ATN); FE_{Na} <1% indicates prerenal AKI, and FE_{Na} >2% is consistent with ATN.
- In the setting of diuretics, the fractional excretion of urea (FE_{Urea}) can be used to diagnose prerenal acute kidney injury, with FE_{Urea} <35% suggesting the diagnosis.
- Ultrasonography of the kidneys and bladder should be obtained for suspected urinary tract obstruction or when the underlying cause of acute kidney injury is unclear.

Causes

AKI can be divided into prerenal, intrinsic, and postrenal causes.

Prerenal Acute Kidney Injury

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See Table 24 for the causes of prerenal AKI.

Prerenal AKI (prerenal azotemia) is caused by underperfusion of the kidney with a subsequent decrease in GFR, which is reversible with appropriate therapy. Renal hypoperfusion can occur due to intravascular volume depletion, decreased effective arterial circulation, renal vasoconstriction, and/or medications. Patients may have a history of acute hemorrhage, loss of gastrointestinal fluids, heart failure, decompensated liver disease, sepsis, or recent diuretic or NSAID use. Physical signs of hypovolemia include hypotension, tachycardia, orthostasis, and decreased skin turgor. Patients with heart failure or cirrhosis have physical examination findings supporting these conditions.

In prerenal AKI, the kidney responds by reabsorbing urea, sodium, and water, often resulting in a BUN-creatinine ratio >20:1; however, a normal BUN-creatinine ratio does not exclude prerenal AKI. Other laboratory values that support a diagnosis of prerenal AKI are listed in Table 26. Prerenal AKI due to hypovolemia can be distinguished from ATN by the renal response to a fluid challenge. If serum creatinine recovers to baseline with fluid repletion, the cause of AKI is likely to be prerenal.

Drug-induced prerenal AKI typically results from decreased blood flow to the kidney or intraglomerular hemodynamic alterations. Diuretics can cause prerenal AKI from volume depletion. Drugs affecting vasodilatation of the afferent arterioles or vasoconstriction of the efferent arterioles can cause prerenal AKI, especially in the setting of volume depletion, decreased effective arterial circulation, or CKD. NSAIDs, including cyclooxygenase-2 inhibitors, cause AKI by diminishing the renal vasodilatory effect of prostaglandins. ACE inhibitors and angiotensin receptor blockers (ARBs) prevent efferent vasoconstriction by inhibiting angiotensin II. Calcineurin inhibitors such as cyclosporine and tacrolimus can cause prerenal AKI from afferent and efferent vasoconstriction.

Management of prerenal AKI includes discontinuing nephrotoxins and increasing renal perfusion by treating the underlying cause, such as correcting volume deficits. If prerenal AKI is not recognized and treated in a timely fashion, prolonged renal hypoperfusion will result in ATN and progressive intrinsic kidney failure. H

KEY POINT

- Prerenal acute kidney injury is caused by underperfusion of the kidney with a subsequent decrease in glomerular filtration rate, which is reversible with discontinuing nephrotoxins and treating the underlying cause.

Intrinsic Kidney Diseases

Intrinsic AKI occurs from structural damage to the renal tubules, interstitium, glomerulus, or vascular structures, or intratubular obstruction (see Table 24).

Acute Tubular Necrosis

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ATN due to ischemia, nephrotoxins, and/or sepsis is the most common cause of AKI in hospitalized patients. A patient history of sepsis or nephrotoxin exposure along with assessment of hemodynamics and volume status can aid in the diagnosis. Laboratory values suggestive of ATN include a BUN-creatinine ratio <10 to 15:1, an FE_{Na} >2%, and a urine osmolality of approximately 300 mOsm/kg H_2O (see Table 26), reflecting the failure to maximally dilute or concentrate urine (isosthenuria). Urine sediment is characterized by many tubular epithelial cells and coarse granular (muddy brown) casts (**Figure 16**).

Unlike prerenal AKI, ATN does not rapidly improve with restoration of intravascular volume and blood flow to the kidneys. Treatment is supportive because no pharmacologic therapies exist. Complete or partial renal recovery can take days to weeks.

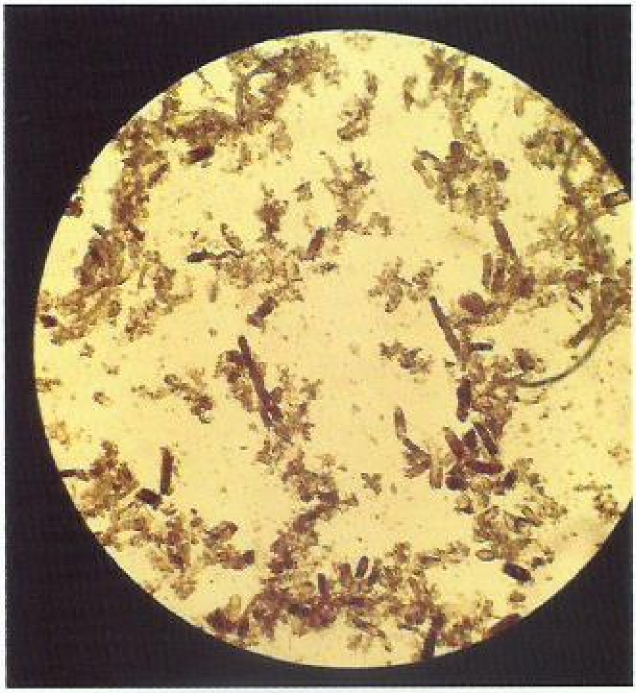

FIGURE 16. Urine sediment showing multiple coarse, granular (muddy brown) casts characteristic of acute tubular necrosis.

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Compared with oliguric ATN, patients with nonoliguric ATN are thought to have less severe kidney injury and a better renal prognosis. Patients with baseline CKD are less likely to recover kidney function compared with patients with baseline normal kidney function. Patients with severe ATN who require acute dialysis may recover kidney function or progress to dialysis-dependent ESKD.

Ischemic Acute Tubular Necrosis

Severe ischemia due to prolonged hypotension or prolonged prerenal state can cause ATN (see Table 24). The ischemic injury leads to cytokine release, oxygen-free radical and enzyme production, endothelial activation and leukocyte adhesion, activation of coagulation, and apoptosis. GFR declines due to renal vasoconstriction, tubular back leak of filtrate into the bloodstream, and tubular obstruction from sloughed cellular debris. Ischemic ATN is mostly reversible but can result in permanent kidney failure.

Normotensive ischemic ATN can occur without overt hypotension in conditions with impaired renal autoregulation. These conditions include older age, hypertension, atherosclerotic or renovascular disease, and CKD. Patients with hypertension can develop normotensive ischemic ATN if their blood pressure is decreased to a value lower than what they are accustomed to but within normal range. Management involves treating any potential volume deficits and decreasing antihypertensive medications to allow the blood pressure to increase to baseline levels.

Drug-Induced Acute Tubular Necrosis

Drug-induced ATN can be a consequence of prolonged hemodynamic alterations or direct tubular injury (see Table 24). The drugs associated with prerenal AKI can cause ATN from prolonged hypoperfusion. Early recognition and prompt discontinuation of the drug are essential for renal recovery. The risk of drug-induced ATN increases in the elderly and in patients with decreased effective arterial circulation, CKD, or concomitant nephrotoxin exposure.

Osmotic nephrosis is a form of tubular injury due to hyperosmolar substances such as sucrose-containing intravenous immunoglobulin, mannitol, hydroxyethyl starch, dextran, and contrast media. It is characterized by vacuolization and swelling of the renal proximal tubular cells with resultant tubular obstruction and damage.

Contrast agents can cause nonoliguric ATN primarily through renal vasoconstriction. The serum creatinine increases within 24 to 48 hours after contrast administration. Aminoglycosides cause nonoliguric ATN through direct tubular toxicity with an increase in serum creatinine occurring 5 to 7 days after initiation of therapy. Hypomagnesemia, hypokalemia, hypocalcemia, and hypophosphatemia can be seen. Cisplatin causes ATN through direct tubular toxicity, renal vasoconstriction, and inflammation. Hypomagnesemia with urinary magnesium wasting is common. Amphotericin B causes dose-related AKI through both renal vasoconstriction and direct tubular toxicity. It can be associated with potassium and magnesium wasting, metabolic acidosis due to type 1 (distal) renal tubular acidosis, and nephrogenic diabetes insipidus. Lipid-based preparations decrease the risk for nephrotoxicity. Vancomycin nephrotoxicity occurs in the setting of high trough levels (>15 mg/L), high vancomycin dose (≥4 g/d), prolonged duration of therapy, and/or concomitant nephrotoxic drugs (for example, an aminoglycoside or piperacillin-tazobactam). Certain types of synthetic cannabinoids used as recreational drugs have been associated with ATN.

Pigment Nephropathy

Heme pigment released from myoglobin or hemoglobin can cause AKI through intravascular volume depletion (seen in rhabdomyolysis), renal vasoconstriction, direct proximal tubular injury, and tubular obstruction. In rhabdomyolysis, myoglobin is released in the circulation from damaged skeletal muscle. Major causes of rhabdomyolysis include trauma, drugs and toxins, seizures, metabolic and electrolyte disorders, endocrinopathies (diabetic ketoacidosis, hyperglycemic hyperosmolar syndrome, hypothyroidism), and exercise. Rhabdomyolysis-induced AKI is more likely to occur with serum creatine kinase levels >5000 U/L. In addition to elevated serum creatine kinase and serum creatinine levels, hyperkalemia, hypocalcemia, hyperphosphatemia, hyperuricemia, metabolic acidosis, increased lactate dehydrogenase concentration, and increased aspartate and alanine aminotransferase levels can occur. Urinary findings include FE_{Na} <1% (due to renal vasoconstriction), myoglobinuria, pigmented (red) granular casts, and a positive urine dipstick for blood with absence of erythrocytes.

In addition to correcting the underlying cause, prevention and management of AKI involve aggressive intravenous isotonic fluid resuscitation aimed at maintaining urine output >200 to 300 mL/h. Limited studies suggest that alkalinization of the urine with intravenous bicarbonate to increase the urine pH >6.5 may prevent tubular cast formation. If urine alkalinization is used, it should be discontinued if the patient develops symptomatic hypocalcemia or alkalosis, or if urine pH does not increase to >6.5 after several hours. Dialysis may be necessary for severe electrolyte and acid-base abnormalities. Most patients have partial or complete renal recovery.

Heme pigment nephropathy is less common and occurs when large amounts of heme pigment are released into circulation due to intravascular hemolysis. Causes include glucose-6-phosphate dehydrogenase (G6PD) deficiency, drug reactions, hemolysis related to cardiopulmonary bypass circuits, transfusion of stored red blood cells, paroxysmal nocturnal hemoglobinuria, malaria, certain poisonings, and snakebites. In addition to elevated serum creatinine concentration, other laboratory abnormalities include anemia, increased lactate dehydrogenase, and decreased haptoglobin. Urinary findings include FE_{Na} <1%, hemoglobinuria, pigmented granular casts, and urine dipstick positive for blood with no erythrocytes. Both myoglobinuria and hemoglobinuria can cause tea-colored urine; however, only hemoglobin causes a reddish brown color of centrifuged serum.

because it is too large to be effectively filtered in kidneys. Treatment of hemoglobinuria involves treating the underlying cause as well as volume repletion with intravenous fluids.

Acute Interstitial Nephritis

Acute interstitial nephritis (AIN) is a common cause of AKI characterized by inflammation and edema of the interstitium. The classic clinical presentation of fever, rash, and peripheral eosinophilia occurs in only 10% to 30% of patients with AIN. Urinary findings can include eosinophiluria by Hansel stain, leukocytes, erythrocytes, and leukocyte casts (see Table 26). Urine eosinophils are neither sensitive nor specific for AIN; AIN can still occur in their absence, and eosinophiluria can occur in other causes of AKI such as acute glomerulonephritis, atheroembolic disease, pyelonephritis, cystitis, and prostatitis.

Drug-induced AIN, especially due to antibiotics, is the most common cause of AIN and should be considered in any patient with AKI, a characteristic urinalysis, and history of any drug exposure. Other causes include infections, systemic diseases such as autoimmune disorders, and idiopathic cases (see Table 24). Typically, the serum creatinine gradually increases 7 to 10 days after drug exposure but can increase much sooner following repeat exposure of the drug.

Drug-induced AIN from NSAIDs, including selective cyclooxygenase-2 inhibitors, is usually not associated with fever, rash, or eosinophilia and develops 6 to 18 months after drug exposure. AIN from NSAIDs can be associated with the nephrotic syndrome due to minimal change glomerulopathy or membranous glomerulopathy. Proton pump inhibitors are also associated with AIN without fever, rash, and eosinophilia. The onset of AIN is variable but typically occurs 10 to 11 weeks after exposure. Proton pump inhibitors are thought to be a risk factor for the development of CKD.

Renal recovery from drug-induced AIN is usually complete if the drug is stopped immediately after the onset of kidney injury but may take weeks to several months. Irreversible interstitial fibrosis can develop after 2 weeks of continued exposure. Kidney biopsy should be considered if there is no improvement in kidney function after 5 to 7 days of drug discontinuation. Early glucocorticoid administration may limit damage associated with drug-induced AIN.

Acute Glomerulonephritis

Acute glomerulonephritis with AKI results from immune-mediated damage to glomeruli. Urinary findings include proteinuria, dysmorphic erythrocytes, and erythrocyte casts (see Table 26). Constitutional signs and symptoms are often present. Serologic assays and kidney biopsy identify most causes. Early recognition is extremely important because, without treatment, it can be fatal and result in irreversible kidney damage. See Glomerular Diseases for more information.

Acute Vascular Syndromes

Macrovascular (large and medium vessel) or microvascular (small vessel) disease can cause AKI (see Table 24).

Examples of macrovascular disease include severe abdominal aortic disease, major renal artery occlusion, and renal vein thrombosis. Acute renal arterial occlusion and acute renal vein thrombosis cause acute renal infarction and present as abdominal or flank pain, elevated serum lactate dehydrogenase levels, and hematuria. Treatment usually consists of anticoagulation and supportive care.

AKI can also occur from polyarteritis nodosa, a systemic vasculitis that affects medium and occasionally small arteries at branching points. It causes microaneurysms that subsequently rupture, resulting in hemorrhage, thrombosis, and organ ischemia and infarction. AKI results from renovascular ischemic changes and renal artery vasculitis. See MKSAP 18 Rheumatology for more information.

Patients with atherosclerotic disease who undergo an invasive vascular procedure such as vascular surgery or angiography are at increased risk for atheroemboli-induced AKI (cholesterol emboli). Atheroembolic events can occur spontaneously or several days to weeks after manipulation of the aorta. Plaque rupture causes cholesterol embolization to distal small- and medium-sized arteries, resulting in ischemia with end-organ damage. In addition to the kidneys, atheroemboli can affect the arteries in the skin, muscle, gastrointestinal tract, liver, eyes, and central nervous system. Physical examination findings may include livedo reticularis (lacy network of bluish red vessels, usually seen on legs), Hollenhorst plaques on funduscopic examination (yellow refractile body within arteriole), ulcerations, and blue toes from ischemia (**Figure 17**). Laboratory findings can include low serum complements,

FIGURE 17. Blue toe syndrome presents as a cyanotic toe with necrosis of the skin caused by occlusion of the small vessels from cholesterol emboli, as seen in atheroembolic acute kidney injury.

peripheral eosinophilia, and eosinophiluria; urinalysis may be unremarkable or can have proteinuria, microscopic hematuria, or erythrocyte casts. Treatment of atheroemboli is supportive and consists of risk factor reduction: aspirin, statins, and hypertension management. The use of anticoagulants for treatment of cholesterol emboli is controversial because anticoagulants and thrombolytics can induce atheroemboli. Renal prognosis is poor.

AKI from microvascular disease can present as thrombotic microangiopathy (TMA) with microangiopathic hemolytic anemia, thrombocytopenia, and glomerular capillary thrombosis. Diseases that can lead to TMA include thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, the HELLP (hemolysis, elevated liver enzymes, and low platelets) syndrome, hypertensive emergency, scleroderma renal crisis, complement-mediated TMA, and drug-induced TMA. Urine may show hematuria, erythrocyte casts, and/or proteinuria. Treatment of TMA is based on the underlying cause. Drug-induced TMA is treated by discontinuation of the drug.

Intratubular Obstruction

Intratubular obstruction can cause AKI through precipitation of either protein or crystals within the tubular lumen. Examples include monoclonal light chain deposition in multiple myeloma, calcium oxalate deposition from ethylene glycol ingestion, crystals from drugs, and uric acid from tumor lysis syndrome (see Table 24).

In multiple myeloma, AKI from light chain cast nephropathy is the most common type of kidney disease. Cast nephropathy is due to direct tubular toxicity and obstruction from the precipitation of filtered free light chains. See Kidney Manifestations of Deposition Diseases for more information.

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Ethylene glycol intoxication causes AKI from intratubular precipitation of calcium oxalate crystals, which can be seen on urine microscopy. Ethylene glycol should be suspected in a patient with a history of ingestion and whose laboratory studies demonstrate an increased anion gap metabolic acidosis and osmolal gap. Treatment consists of supportive care, the antidote fomepizole, and hemodialysis if needed. Orlistat, a gastrointestinal lipase inhibitor used to induce clinically significant weight loss by fat malabsorption, has also been associated with intratubular calcium oxalate deposition and AKI. High doses of vitamin C, which is metabolized to oxalate, can also lead to AKI from calcium oxalate precipitation in the tubules.

Drugs associated with crystal-induced AKI are listed in Table 24. Urinary findings include hematuria, pyuria, and crystals. AKI is usually reversed after discontinuation of the drug. Predisposing factors include volume depletion, CKD, and changes in urine pH. Correction of volume depletion with intravenous fluids is critical for both the prevention and treatment of crystal-induced AKI. Bolus intravenous acyclovir can cause acyclovir crystal deposition in the tubules, which can be prevented by prior intravenous fluid administration and slow rate of drug infusion. Because crystals from sulfonamide antibiotics and methotrexate are more likely to form in acidic urine, urinary alkalinization can prevent crystal deposition. Crystals from protease inhibitors can cause AKI from both crystal deposition and nephrolithiasis.

Acute phosphate nephropathy is a potentially irreversible cause of AKI due to phosphate-containing bowel preparations. A transient severe increase in serum phosphate in the setting of volume depletion causes acute and chronic tubular injury from tubular and interstitial precipitation of calcium phosphate crystals. AKI can present days to months after exposure. Predisposing factors include volume depletion, CKD, older age, NSAIDs, and hypertension treated with ACE inhibitors, ARBs, or diuretics. H

KEY POINTS

- Acute tubular necrosis due to ischemia, nephrotoxins, and/or sepsis is the most common cause of acute kidney injury in hospitalized patients; a history of sepsis or nephrotoxin exposure along with hemodynamic and volume status assessment can aid in the diagnosis.
- Drug-induced acute interstitial nephritis is associated with a gradual increase in serum creatinine 7 to 10 days after drug exposure; renal recovery is usually complete if the drug is stopped immediately after the onset of kidney injury.
- In atheroemboli-induced acute kidney injury, plaque rupture causes cholesterol embolization to distal small- and medium-sized arteries, resulting in ischemia with end-organ damage; treatment is supportive.
- Acute kidney injury from microvascular disease can present as thrombotic microangiopathy (TMA); conditions that can lead to TMA include thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, the HELLP (hemolysis, elevated liver enzymes, and low platelets) syndrome, hypertensive emergency, scleroderma renal crisis, complement-mediated TMA, and drug-induced TMA.
- Intratubular obstruction causes of acute kidney injury include monoclonal light chain deposition in multiple myeloma; calcium oxalate deposition from ethylene glycol ingestion, orlistat, and high doses of vitamin C; crystals from drugs; and uric acid from tumor lysis syndrome.

Postrenal Disease

Postrenal AKI can occur from obstruction anywhere from the renal pelvis to the external urethral meatus (see Table 24). Upper urinary tract obstruction (at the level of the ureters or renal pelvis) must be bilateral or affect a single functioning kidney to cause AKI. Obstruction of urinary flow leads to hydronephrosis and eventual renal parenchymal damage. If postrenal AKI is not treated promptly, the obstruction can predispose the patient to urinary tract infections and urosepsis, and it can also lead to CKD and ESKD.

Postrenal AKI should be suspected in patients with a history of benign prostatic hyperplasia, diabetes, nephrolithiasis,

pelvic malignancies, abdominal or pelvic surgeries, or retroperitoneal adenopathy. Patients can present with anuria, oliguria, polyuria, or normal urine output. Symptoms of lower tract obstruction include abdominal fullness or pain, urinary frequency, urgency, hesitancy, nocturia, overflow incontinence, and incomplete voiding. Acute nephrolithiasis may present with flank pain and hematuria. Urine chemistries can be variable with obstruction (see Table 26).

Lower urinary tract obstruction can be diagnosed by placement of a urinary catheter with return of a large volume of urine or an elevated postvoid residual volume by ultrasound. Ultrasonography can yield false-negative results in the early stages of hydronephrosis or obstruction from encasement of the ureter or kidney, as seen in retroperitoneal disease. Noncontrast CT is indicated for suspected nephrolithiasis. Treatment focuses on removing the obstruction. Renal prognosis depends upon the severity and duration of the obstruction. Renal recovery is generally good if the obstruction is relieved within 1 to 2 weeks.

KEY POINT

- Postrenal acute kidney injury can occur from obstruction anywhere from the renal pelvis to the external urethral meatus; diagnosis can be made via ultrasonography or noncontrast CT, with generally good renal recovery if the obstruction is relieved within 1 to 2 weeks.

Specific Clinical Settings

Contrast-Induced Nephropathy

Contrast-induced nephropathy (CIN) is a common cause of reversible AKI in the hospital. CIN is defined as an increase in serum creatinine within 24 to 48 hours following contrast exposure. The pathogenesis is not completely understood, but CIN is thought to be due to ATN from contrast-induced vasoconstriction, decreased renal blood flow, medullary hypoxia, oxidative stress, and direct tubular cytotoxicity. AKI tends to be nonoliguric, with an FE_{Na} <1%. The urinary sediment may be bland or show classic ATN findings. Risk factors include CKD, diabetic nephropathy, conditions of decreased renal perfusion (heart failure, hypovolemia, hypotension), multiple myeloma, concomitant nephrotoxins, high contrast dose, hyperosmolar contrast, and intra-arterial contrast administration.

Preventive strategies for patients at high risk for CIN include minimizing the amount of contrast, using low or iso-osmolar contrast, discontinuing nephrotoxins, and administering either intravenous isotonic saline or sodium bicarbonate. A randomized controlled trial demonstrated that oral acetylcysteine was no more effective than placebo for the prevention of CIN. Statins have been shown in observational studies and several randomized controlled trials to prevent CIN by acting as stabilizers of the endothelium and free radical scavengers in a model of ischemic nephropathy. Further studies are needed to establish their benefit. There is no role for prophylactic hemodialysis or hemofiltration following contrast exposure. Treatment of CIN is supportive.

Cardiorenal Syndrome

Cardiorenal syndrome (CRS) is a disorder of the heart and kidneys whereby acute or long-term dysfunction in one organ induces acute or long-term dysfunction in the other. CRS is characterized by the triad of concomitant decreased kidney function, diuretic-resistant heart failure with congestion, and worsening kidney function during heart failure therapy. The decreased kidney function in CRS is thought to be due to neurohumoral activation, increased intra-abdominal pressure leading to venous congestion and increased renal venous pressure, reduced renal perfusion, and right ventricular dysfunction. CRS can be classified into five types (**Table 27**).

Management is challenging because treatment directed toward improving cardiac function (diuretics, ACE inhibitor/ARB, vasodilators, and inotropes) can worsen kidney function. Ultrafiltration has been used for volume overload refractory to diuretics. Current evidence does not support the use of ultrafiltration over intensive diuretic management. Decreased kidney function in patients with heart failure is an independent risk factor for all-cause mortality.

Hepatorenal Syndrome

Hepatorenal syndrome (HRS) is a reversible functional kidney impairment that occurs in the setting of portal hypertension due to liver cirrhosis, severe alcoholic hepatitis, or acute liver failure. HRS is characterized by increased renal vasoconstriction and peripheral arterial vasodilation. Tubular function is preserved with the absence of significant hematuria and proteinuria, as well as lack of renal histological changes.

Type 1 HRS is a clinical diagnosis made after exclusion of other causes of kidney dysfunction. It is characterized by a rise in serum creatinine of at least 0.3 mg/dL (26.5 µmol/L) and/or ≥50% from baseline within 48 hours, bland urinalysis, and

TABLE 27. Classification of Cardiorenal Syndrome

Type	Definition
Type 1	Acute worsening of cardiac function (acute heart failure; acute coronary syndrome; cardiogenic shock) leading to acute kidney injury
Type 2	Chronic abnormalities in cardiac function leading to progressive chronic kidney disease
Type 3	Acute worsening of kidney function leading to acute cardiac dysfunction
Type 4	Primary chronic kidney disease leading to cardiac injury (left ventricular remodeling and dysfunction; diastolic dysfunction; acute heart failure; acute coronary syndrome)
Type 5	Systemic condition (such as diabetes mellitus, sepsis, amyloidosis) causing both cardiac and kidney dysfunction

H CONT.

normal findings on kidney ultrasound. It is also supported by a lack of improvement in kidney function after withdrawal of diuretics and 2 days of volume expansion with intravenous albumin. Often, patients also have low urine sodium, low FE_{Na}, and oliguria. Type 2 HRS is defined as a more gradual decline in kidney function associated with refractory ascites.

Patients with HRS have an overall poor prognosis without liver transplantation. General management includes discontinuing diuretics, restricting sodium, restricting water in hyponatremic patients, and searching for precipitating factors. Therapeutic interventions include treatment with vasoconstrictors and albumin, placement of a transjugular intrahepatic portosystemic shunt in select patients, renal replacement therapy, and liver transplant. Renal replacement therapy is usually reserved for patients with severe AKI who are liver transplant candidates.

Tumor Lysis Syndrome

Tumor lysis syndrome (TLS) is characterized by the rapid lysis of malignant cells leading to hyperuricemia, hyperkalemia, hyperphosphatemia, hypocalcemia, and AKI. TLS typically occurs after initiation of chemotherapy in hematologic malignancies with high cell turnover rate, rapid growth rate, or high tumor bulk (acute lymphoblastic leukemia, Burkitt lymphoma, acute myeloid leukemia); however, it can also occur spontaneously. AKI occurs from deposition of uric acid and/or calcium phosphate crystals in the renal tubules.

Management of TLS requires the initiation of preventive measures in high-risk patients prior to cytotoxic therapy, as well as the timely initiation of supportive care for patients who develop TLS. Treatment of established TLS includes intravenous hydration, urate-lowering therapy, management of hyperkalemia and hyperphosphatemia, and renal replacement therapy in refractory cases. Patients at risk for or presenting with TLS require aggressive volume expansion to achieve a urine output of at least 80 to 100 $mL/m^2/h$. Urinary alkalinization is no longer recommended because the high urine pH can cause an increase in calcium phosphate crystal deposition. Allopurinol, a competitive inhibitor of xanthine oxidase, prevents the formation of new uric acid and is recommended as prophylaxis for patients at intermediate risk for TLS (those with highly chemotherapy-sensitive solid tumors); it has no effect on existing serum urate levels. Rasburicase, a recombinant urate oxidase that makes uric acid more soluble in urine with rapid reduction in serum urate levels, is given to patients at high risk of TLS or those with TLS. Rasburicase is contraindicated in patients with G6PD deficiency. H

Abdominal Compartment Syndrome

Abdominal compartment syndrome is defined as a sustained intra-abdominal pressure (IAP) >20 mm Hg associated with at least one organ dysfunction. Abdominal compartment syndrome occurs in the setting of abdominal surgery, trauma, hemoperitoneum, retroperitoneal bleed, ascites, bowel obstruction, ileus, and pancreatitis. It can also occur from capillary leak from massive fluid resuscitation or sepsis. Increasing IAP causes hypoperfusion and ischemia of the intestines and other peritoneal and retroperitoneal structures, leading to hemodynamic, respiratory, neurologic, and kidney impairment. Renal vein compression and renal artery vasoconstriction cause oliguric AKI.

Abdominal compartment syndrome is diagnosed by measuring IAP; measurement of bladder pressure with an indwelling catheter is the standard methodology. Management includes supportive therapy, abdominal compartment decompression, and correction of positive fluid balance.

KEY POINTS

- Preventive strategies for patients at high risk for contrast-induced nephropathy include minimizing the amount of contrast, using low or iso-osmolar contrast, discontinuing nephrotoxins, and administering intravenous isotonic saline or sodium bicarbonate.
- Cardiorenal syndrome is characterized by the triad of concomitant decreased kidney function, diuretic-resistant heart failure with congestion, and worsening kidney function during heart failure therapy.
- Hepatorenal syndrome occurs in the setting of portal hypertension due to liver cirrhosis, severe alcoholic hepatitis, or acute liver failure and is characterized by increased renal vasoconstriction and peripheral arterial vasodilation.
- Acute kidney injury in the setting of tumor lysis syndrome (TLS) occurs from deposition of uric acid and/or calcium phosphate crystals in the renal tubules; management of TLS requires preventive measures in high-risk patients prior to cytotoxic therapy, and timely supportive care for established TLS.
- Abdominal compartment syndrome is defined as a sustained intra-abdominal pressure >20 mm Hg associated with at least one organ dysfunction; in this setting, renal vein compression and renal artery vasoconstriction cause oliguric acute kidney injury.

Management

General Considerations

In most cases of AKI, treatment of the underlying medical condition and discontinuation of nephrotoxic medications lead to improvement in kidney function. No specific pharmacologic therapy is effective in established ATN. Supportive measures include optimizing hemodynamics and renal perfusion, preventing further kidney injury, treating AKI complications, and providing appropriate nutrition. Diuretics can be used for volume overload. Bicarbonate can be administered to correct metabolic acidosis. Dietary potassium, magnesium, and phosphate should be restricted. Phosphate binders may be required to prevent severe hyperphosphatemia. In patients with severe AKI, initiation of renal replacement therapy may be the only option.

Renal Replacement Therapy

Renal replacement therapy (RRT) is used to manage the urgent complications of severe AKI, including hyperkalemia, metabolic acidosis, volume overload refractory to diuretics, uremic manifestations, and dialyzable toxins. Options for RRT for AKI include intermittent hemodialysis (IHD), continuous renal replacement therapy (CRRT), "hybrid" therapies such as prolonged intermittent renal replacement therapy (PIRRT), and peritoneal dialysis (PD). IHD, CRRT, and PIRRT are extracorporeal therapies that require vascular access in the form of a large-bore, double-lumen central venous catheter; PD requires the placement of an intra-abdominal dialysis catheter.

IHD, typically delivered 3 to 6 times a week for 3 to 5 hours per session, allows for rapid correction of electrolyte disturbances and rapid removal of drugs or toxins. The main disadvantage of IHD is the risk for hypotension caused by the rapid solute and volume removal. Furthermore, rapid solute removal from the intravascular space can cause cerebral edema and increased intracranial pressure, limiting this therapy in patients with head trauma or hepatic encephalopathy. CRRT represents a variety of dialysis modalities developed specifically to manage critically ill patients with AKI who cannot tolerate IHD due to hemodynamic instability. CRRT is administered 24 hours a day and removes solutes and fluid much more slowly than IHD, resulting in better hemodynamic tolerance. PIRRT removes solutes and fluid more slowly than IHD but more quickly than CRRT and is administered 8 to 12 hours daily. PD is not as effective as the other forms of RRT but may be useful when the other types of RRT are unavailable or vascular access cannot be obtained.

Randomized clinical trials have not shown a survival benefit of CRRT over IHD or PIRRT for critically ill AKI patients. IHD is typically chosen for patients who are hemodynamically stable, whereas CRRT or PIRRT is chosen for patients who are unstable, are fluid overloaded, and/or have sepsis and multiorgan failure. IHD is favored in patients who need rapid solute removal, such as those with severe hyperkalemia or drug intoxications. CRRT is preferred in patients with cerebral edema because IHD may worsen neurologic status by compromising cerebral perfusion pressure. Transitions in therapy are common depending on the changing needs of the patient.

KEY POINTS

- In most cases of acute kidney injury, treatment of the underlying medical condition and discontinuation of nephrotoxic medications leads to improvement in kidney function.
- Renal replacement therapy is used to manage the urgent complications of severe acute kidney injury, including hyperkalemia, metabolic acidosis, volume overload refractory to diuretics, uremic manifestations, and dialyzable toxins.

Kidney Stones

Overview

Approximately 7% to 11% of the U.S. population will develop nephrolithiasis, and 50% will have recurrent disease. Risk factors for developing kidney stones include male gender, increased age, white race, obesity, diabetes mellitus, the metabolic syndrome, decreased fluid intake, chronic diarrheal states, and Roux-en-Y gastric bypass.

Clinical Manifestations

Although kidney stones may be asymptomatic and diagnosed as an incidental finding on imaging, the typical presentation is waxing and waning "colicky" flank pain that radiates to the groin. Stone movement may result in pain migration to the lateralized genitalia. The patient frequently finds it difficult to achieve a comfortable position. Nausea, vomiting, and dysuria may also be present. Microscopic hematuria is usually noted, although its absence does not exclude a stone.

Similar symptoms may be present with pyelonephritis and acute abdominal processes, which need to be considered. In addition, the ureteral passage of blood clots can mimic renal colic pain.

KEY POINT

- Kidney stones typically present with waxing and waning "colicky" flank pain that radiates to the groin; nausea, vomiting, and dysuria may also be present.

Diagnosis

Nephrolithiasis should be considered in all patients who present with flank pain. Costovertebral angle tenderness may be present. Microscopic examination of the urine for hematuria, leukocytes that may indicate infection, pH measurement, and crystals is mandatory but nonspecific. The presence of crystals may help to identify the type of stone. A complete blood count and complete metabolic panel should be obtained to exclude infection and acute kidney injury, and to screen for common metabolic causes of stone disease.

Definitive diagnosis is made with imaging. Noncontrast helical CT is the gold standard modality because of its high sensitivity and specificity. Although less sensitive than CT, kidney ultrasonography is less expensive, has no radiation exposure, and can be used in pregnant women or when CT is unavailable. Plain abdominal radiography has a low sensitivity and should not be ordered except to follow the stone burden in established disease.

KEY POINT

- Noncontrast helical CT is the gold standard modality to diagnose nephrolithiasis because of its high sensitivity and specificity; kidney ultrasonography, although less sensitive than CT, is less expensive and has no radiation exposure and can be used if CT is unavailable and in pregnant women.

Types of Kidney Stones

See **Table 28** for details on kidney stones and Table 3 in Clinical Evaluation of Kidney Function for images of crystals.

Calcium

Eighty percent of kidney stones contain calcium; most are composed of calcium oxalate, and the remainder are composed of calcium phosphate or a combination of the two.

Calcium oxalate stones are associated with hypercalciuria, hyperoxaluria, and hypocitraturia. Up to 50% of patients with recurrent stones have elevated 24-hour urine calcium levels. This increase may be secondary to elevated serum calcium as seen in hyperparathyroidism, sarcoidosis, or excessive vitamin D intake, but is more frequently idiopathic. Hyperoxaluria can be primary or can occur secondary to increased dietary oxalate intake; malabsorption syndrome due to the binding of gastrointestinal calcium to fatty acids, allowing for increased absorption of oxalate; decreased dietary calcium; and high vitamin C intake. Rous en Y gastric bypass surgery is associated with hyperoxaluria and an increase risk of stone formation. The weight loss drug orlistat, by inducing fat malabsorption, is also associated with hyperoxaluria and the formation of calcium oxalate stones. Because citrate prevents calcium crystal formation, low urine levels are associated with increased stone formation. Citrate excretion is decreased in the presence of metabolic acidosis, as occurs with chronic diarrhea and distal renal tubular acidosis.

Calcium phosphate stones occur when there is persistently elevated urine pH and are therefore commonly associated with distal renal tubular acidosis and hyperparathyroidism. In addition, the use of carbonic anhydrase inhibitors such as acetazolamide or topiramate, by raising urine pH and decreasing citrate excretion, are associated with increased incidence of calcium phosphate stones. Imaging may reveal nephrocalcinosis.

TABLE 28. Kidney Stone Risk Factors and Therapy

Stone Type	Risk Factors	Therapy
Calcium oxalate	Hypercalciuria; hyperoxaluria; hypocitraturia	Increase fluids Decrease sodium intake Thiazide diuretics Low oxalate diet Potassium citrate or bicarbonate
Calcium phosphate	Elevated urine pH; distal renal tubular acidosis; hyperparathyroidism	Increase fluids Decrease sodium intake Thiazide diuretics Treat hyperparathyroidism Potassium citrate or bicarbonate
Uric acid	Low urine pH; diarrhea; metabolic syndrome; gout; hyperuricosuria	Increase fluids Potassium citrate or bicarbonate Allopurinol
Struvite	Chronic urinary tract infections with urea-splitting organism	Treat infection Urologic intervention
Cystine	Cystinuria; low urine pH	Increase fluids Potassium citrate or bicarbonate Acetazolamide Penicillamine Tiopronin

Struvite

Struvite stones occur in the presence of urea-splitting bacteria such as *Proteus*, *Klebsiella*, or, less frequently, *Pseudomonas* species. These bacteria split urea into ammonium, which markedly increases urine pH and results in the precipitation of magnesium ammonium phosphate (struvite). The pH of the urine will be >7.5. Struvite stones commonly produce staghorn calculi (stones that bridge two or more renal calyces) and occur most frequently in older women with chronic urinary tract infections. Because struvite stones are large and grow rapidly, they do not pass into the ureter to cause pain typical of smaller stones. Signs and symptoms typically are related to the underlying infection. Because of their association with infections, there is significant morbidity and mortality associated with these stones.

Uric Acid

Uric acid stones (<10% of stones) develop in the presence of a persistently acidic urine, which decreases the solubility of uric acid. In addition, some individuals overproduce uric acid, resulting in increased urine uric acid; both gout and increased urine uric acid are associated with uric acid stones, but hyperuricosuria is not required for uric acid stone formation. Chronic diarrhea, resulting in metabolic acidosis and low urine volume, is a common cause of uric acid stones. The metabolic syndrome is also associated with uric acid stone formation. Uric stones are radiolucent but are visualized on ultrasound and CT.

Cystine

Cystine stones (1%-2% of stones) result from cystinuria, an autosomal recessive disease that presents at a young age. These stones are recognized by characteristic hexagonal crystals in the urine. They may also form staghorn calculi, and are less radio-opaque then calcium-containing stones.

KEY POINTS

- Eighty percent of kidney stones contain calcium; most are composed of calcium oxalate, which is associated with hypercalciuria, hyperoxaluria, and hypocitraturia.

(Continued)

KEY POINTS *(continued)*

- Struvite stones commonly produce staghorn calculi and occur most frequently in older women with chronic urinary infections; because of their association with infections, there is significant morbidity and mortality associated with these stones.
- Uric acid stones form in persistently acidic urine and are associated with chronic diarrhea, the metabolic syndrome, and gout.
- Cystine stones result from cystinuria, an autosomal recessive disease that presents at a young age; these stones produce characteristic hexagonal crystals in the urine.

H Management

Acute management of symptomatic nephrolithiasis is aimed at pain management and facilitation of stone passage. Pain can be relieved by NSAIDs and opioids as needed. Stone passage decreases with size. Only 50% of stones >6 mm will pass, and stones >10 mm are extremely unlikely to pass spontaneously. Medications, including tamsulosin, nifedipine, silodosin, and tadalafil, appear to increase the rate of spontaneous passage for most stones and can be considered for stones <10 mm.

Urologic intervention is required in all patients with evidence of infection, acute kidney injury, intractable nausea or pain, and stones that fail to pass. This may necessitate shock wave lithotripsy, ureteroscopy with laser ablation, or percutaneous nephrolithotomy.

Patients should strain their urine to collect stone fragments for chemical analysis if the type of stone is unknown. In addition to the initial evaluation previously described, a 24-hour urine for measurement of volume, calcium, oxalate, citrate, uric acid, and sodium should be collected on all recurrent stone formers.

Increased fluid intake is the most important intervention to prevent recurrent disease regardless of stone composition. Urine output should be >2500 mL/d to decrease urine solute concentration.

Other interventions should be based on findings in the metabolic workup and stone analysis (see Table 28). If hypercalciuria is present, calcium excretion can be decreased by the use of thiazide diuretics. Because calcium excretion parallels sodium excretion, limiting sodium intake will also lower urine calcium. Unless excessive, dietary calcium should not be restricted because this will increase oxalate absorption. Oxalate excretion can be decreased by limiting foods high in oxalate such as nuts, cocoa, spinach, rhubarb, and beets. Potassium citrate or potassium bicarbonate will increase urinary citrate excretion. An additional benefit of potassium citrate is a decrease in renal calcium excretion, possibly related to preventing calcium release from bone.

In patients with uric acid stones, management consists of increasing the solubility of uric acid by alkalinizing the urine with potassium citrate or bicarbonate; allopurinol can be beneficial if uric acid excretion is elevated.

Urinary cystine excretion can be reduced by limiting sodium intake and by alkalizing the urine to a pH >7.0. If unsuccessful, additional interventions may be required.

Struvite stones typically require urologic intervention. Before any surgical procedure, it is important that active infection be treated with antibiotics to avert sepsis. To prevent recurrent stone formation, all stone fragments must be removed from the kidney. In patients unable to undergo surgery, the urease inhibitor acetohydroxamic acid may reduce urine alkalinity and decrease stone growth; however, this is best used as an adjunct to urologic intervention. H

KEY POINTS

- Acute management of symptomatic nephrolithiasis includes pain management and facilitation of stone passage.
- Urologic intervention is required in all patients with evidence of infection, acute kidney injury, intractable nausea or pain, and stones that fail to pass.
- Increased fluid intake to >2500 mL/d is the most important intervention to prevent recurrent kidney stones, regardless of stone composition.

The Kidney in Pregnancy

Normal Physiologic Changes in Pregnancy

Pregnancy is a state of volume expansion and vasodilation. Sodium and water retention increase plasma volume, augmenting renal blood flow and increasing glomerular filtration rate (GFR) by up to 50%. With the GFR increase, serum creatinine levels decrease. Therefore, high normal serum creatinine levels may indicate significant kidney impairment. Despite the volume expansion, blood pressure begins to decrease in the first trimester and reaches the nadir in the second trimester due to peripheral vasodilation.

Proteinuria increases, with the upper limit of normal increasing from 100 mg/24 h (in nonpregnant) to approximately 200 mg/24 h. Values >300 mg/24 h are considered abnormal. Prepartum proteinuria may also worsen during pregnancy, making pregnancy-related changes difficult to distinguish from a flare of an underlying kidney disease or development of preeclampsia.

Due to increased renal vascular and interstitial volume, kidney size may increase by 1 to 1.5 cm. Physiologic hydronephrosis and hydroureter, due in part to external compression of the ureters, are common in pregnancy, increase as pregnancy advances, and may take weeks to resolve postpartum. The dilated collecting system can lead to urinary stasis, which increases the risk for pyelonephritis. Therefore, screening for asymptomatic bacteruria at least once in early pregnancy is recommended, and treatment is indicated.

Respiratory alkalosis due to progesterone-induced hyperventilation commonly decreases P_{CO_2} to 27 to 32 mm Hg. Renal compensation results in serum bicarbonate levels between 18

and 20 mEq/L (18-20 mmol/L), with a serum pH of approximately 7.45.

Changes in antidiuretic hormone response to osmolality (reset osmostat) cause mild hyponatremia (decrease in serum sodium of 4-5 mEq/L [4-5 mmol/L]) with a decrease in serum osmolality by 8 to 10 mOsm/kg H_2O. No treatment is indicated. Rarely, transient gestational diabetes insipidus can develop due to excessive metabolism of antidiuretic hormone by placental vasopressinase.

KEY POINTS

- Pregnancy is associated with decreased blood pressure, increased glomerular filtration rate with decreased serum creatinine, and increased proteinuria.
- Dilatation of the urinary system during pregnancy increases the risk for pyelonephritis; therefore, screening for asymptomatic bacteriuria at least once in early pregnancy is recommended, and treatment is indicated.

Hypertension in Pregnancy

Chronic Hypertension

The American College of Obstetricians and Gynecologists (ACOG) defines chronic hypertension as a systolic blood pressure (BP) ≥140 mm Hg or diastolic BP ≥90 mm Hg starting before pregnancy or before 20 weeks of gestation or persists longer than 12 weeks postpartum. It is associated with worse maternal and fetal outcomes. Hypertension first recognized during pregnancy before 20 weeks' gestation usually indicates chronic hypertension. The lower BP measurements associated with physiologic changes of pregnancy can mask hypertension during the first trimester.

To avoid overtreatment of hypertension and associated fetal risk, the 2013 ACOG Taskforce on Hypertension in Pregnancy recommends treating persistent systolic BP ≥160 mm Hg or diastolic ≥105 mm Hg in women with chronic hypertension, and maintaining BP at 120-160/80-105 mm Hg. However, these goals remain controversial, with some suggesting lower targets. Antihypertensive treatment reduces the risk of progression to severe hypertension by 50% compared with placebo but has not been shown to prevent preeclampsia, preterm birth, being small for gestational age, or infant mortality. Any evidence of end-organ damage requires treatment, even with lower BPs. All antihypertensive medications cross the placenta; drug selection is based on safety profiles.

Renin-angiotensin system agents (ACE inhibitors, angiotensin receptor blockers, and direct renin inhibitors) are all contraindicated due to teratogenicity, even early in pregnancy, and should be stopped prior to conception. If conception has already occurred, they should be stopped immediately and the mother counseled regarding possible fetal effects.

First-line therapy includes methyldopa and labetalol, which have been used safely and extensively in pregnancy. Methyldopa monotherapy may be insufficient, in which case it can be replaced with labetalol. Calcium channel blockers can be added; nifedipine has been used most extensively. The β-blockers metoprolol and pindolol have also been used in pregnancy, but atenolol and propranolol may have adverse fetal effects. Diuretics must be used with caution because they may induce oligohydramnios if started during pregnancy.

Gestational Hypertension

Gestational hypertension first manifests after 20 weeks of pregnancy without proteinuria or other end-organ damage (features of preeclampsia) and resolves within 12 weeks of delivery. Preeclampsia occurs in approximately one third of cases. Hypertension persisting beyond 12 weeks postpartum is considered chronic hypertension. Gestational hypertension can recur in subsequent pregnancies and is associated with an approximately fourfold risk for development of chronic hypertension.

KEY POINTS

- Chronic hypertension precedes pregnancy or is present before 20 weeks' gestation.
- The 2013 American College of Obstetricians and Gynecologists Taskforce on Hypertension in Pregnancy recommends treating persistent systolic blood pressure (BP) ≥160 mm Hg or diastolic BP ≥105 mm Hg in women with chronic hypertension.
- Renin-angiotensin system agents (ACE inhibitors, angiotensin receptor blockers, and direct renin inhibitors) are contraindicated in pregnancy due to teratogenicity; they must be stopped prior to conception or stopped immediately if conception has already occurred.
- First-line therapy of chronic hypertension in pregnancy includes methyldopa and labetalol.
- Gestational hypertension first manifests after 20 weeks of pregnancy without proteinuria or other end-organ damage and resolves within 12 weeks of delivery.

Preeclampsia

Preeclampsia is defined by new-onset hypertension and proteinuria (≥300 mg/24 h from a timed collection or ≥300 mg/g by urine protein-creatinine ratio) that occurs after 20 weeks of pregnancy (**Table 29**). New-onset hypertension with new-onset end-organ damage (such as liver or kidney injury, pulmonary edema, cerebral or visual symptoms, or thrombocytopenia) is also diagnostic of preeclampsia. Severe preeclampsia is identified by persistent systolic BP >160 mm Hg or diastolic BP >110 mm Hg and end-organ damage. Eclampsia is the presence of seizures in context of preeclampsia without other cause. The HELLP (hemolysis, elevated liver enzymes, low platelets) syndrome is a life-threatening state complicating 10% to 20% of preeclampsia cases. Risk factors for preeclampsia include prior preeclampsia (with an approximate 20% recurrence rate), nulliparity, diabetes mellitus, advanced maternal age, multiple gestation, and family history.

The pathophysiology of preeclampsia is poorly understood. Abnormal placental vascular development and generalized endothelial dysfunction occur. Two angiogenic and antiangiogenic factors, soluble fms-like tyrosine kinase-1

TABLE 29. Diagnostic Criteria for Preeclampsia

Blood pressure	≥140 mm Hg systolic or ≥90 mm Hg diastolic on two occasions at least 4 hours apart after 20 weeks of gestation in a woman with a previously normal blood pressure
	≥160 mm Hg systolic or ≥110 mm Hg diastolic; hypertension can be confirmed within a short interval (minutes) to facilitate timely antihypertensive therapy
and	
Proteinuria	≥300 mg/24 h urine collection (or this amount extrapolated from a timed collection)
	or
	Urine protein-creatinine ratio ≥300 mg/g
	Dipstick reading of 1+ (used only if other quantitative methods are not available)
Or, in the absence of proteinuria, new-onset hypertension with the new onset of any of the following:	
Thrombocytopenia	Platelet count <100,000/µL (100 × 10^9/L)
Kidney dysfunction	Serum creatinine concentrations >1.1 mg/dL (97.2 µmol/L) or a doubling of the serum creatinine concentration in the absence of other kidney disease
Impaired liver function	Elevated blood concentrations of liver aminotransaminases to twice the normal concentration
Pulmonary edema	—
Cerebral or visual symptoms	—

With permission from American College of Obstetricians and Gynecologists; Task Force on Hypertension in Pregnancy. Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. Obstet Gynecol. 2013;122(5):1122-31. [PMID: 24150027]

(sFlt-1) and soluble endoglin (sEng), are elevated in women with preeclampsia; their role in treatment and diagnosis continues to be elucidated.

Symptoms of preeclampsia include rapid weight gain due to edema, nausea, vomiting, abdominal pain (particularly concerning if in the right upper quadrant, signifying possible HELLP syndrome), headaches, altered mental status, and blurred vision. If untreated, preeclampsia ultimately leads to maternal end-organ damage and fetal growth retardation, and it may cause maternal and/or fetal death.

Low dose (81 mg/d) aspirin started after 12 weeks of pregnancy reduces the rate of preeclampsia in women at high risk. Antihypertensive medications do not prevent preeclampsia but reduce complications of stroke, heart failure, and kidney injury. Most experts initiate treatment at BP >150-160/100-110 mm Hg, although there is no consensus.

Definitive treatment of preeclampsia is delivery. Maternal risk for complications diminishes in the hours after delivery, although proteinuria may take months to resolve. Maternal benefits must be weighed against neonatal risks for a preterm delivery, but severe preeclampsia is an indication for immediate delivery regardless of gestational age. Mild preeclampsia may be managed conservatively, with maternal and fetal monitoring and treatment of hypertension. In all cases, close attention to hypertension is recommended in the postpartum period.

KEY POINTS

- Preeclampsia is defined by new-onset hypertension and proteinuria that occurs after 20 weeks of pregnancy.
- Low-dose (81 mg/d) aspirin started after 12 weeks of pregnancy reduces rates of preeclampsia in women at high risk.
- Definitive treatment of preeclampsia is delivery.

Chronic Kidney Disease in Pregnancy

Chronic kidney disease (CKD) complicates management of pregnancy; the obstetric literature notes a serum creatinine cutoff of >1.4 mg/dL (124 µmol/L) as that at which complications are of most concern. Proteinuria may also increase risk, but reduced GFR has greater impact. Complications include preeclampsia, acute kidney injury, progression of CKD, end-stage kidney disease, preterm delivery, gestational hypertension, intrauterine growth retardation, and fetal loss. Preconception counseling regarding these risks is essential.

Pregnancy is uncommon in women receiving dialysis, which is frequently associated with infertility. Levels of β-human chorionic gonadotropin (β-hCG) may increase with dialysis in the absence of pregnancy; therefore, ultrasonography is usually necessary to confirm pregnancy. Pregnancy in the context of dialysis is associated with very high risk of preeclampsia and fetal loss, although live birth rates have improved to 60% to 80%. To optimize fetal outcomes, hemodialysis frequency and dose are increased to improve BP and volume status.

Pregnancy in women with kidney transplants is more common than in those receiving dialysis due to increased fertility after transplant. Outcomes are improved with better allograft function (serum creatinine <1.5 mg/dL [132.6 µmol/L]) and stable immunosuppression; transplant patients should await 1 to 2 years with a stable allograft before attempting conception. No immunosuppressive medication has been extensively studied in pregnancy, and all have some associated risk. Although calcineurin inhibitors (tacrolimus and cyclosporine) have been used safely, mycophenolate mofetil is teratogenic and needs to be replaced 3 to 6 months prior to conception

with azathioprine, which has an extensive history of use in pregnancy. Sirolimus is contraindicated due to fetal toxicity. Glucocorticoids increase risk for pregnancy-induced hypertension and diabetes.

KEY POINTS

- Women with chronic kidney disease (CKD) have a greater risk for preeclampsia, acute kidney injury, progression of CKD, end-stage kidney disease, preterm delivery, gestational hypertension, intrauterine growth retardation, and fetal loss.
- Kidney transplant recipients should wait at least 1 to 2 years after transplantation with a stable allograft and stable immunosuppression before attempting conception.
- The immunosuppressive medications mycophenolate mofetil and sirolimus used in kidney transplant recipients are teratogenic and must be discontinued prior to attempting conception.

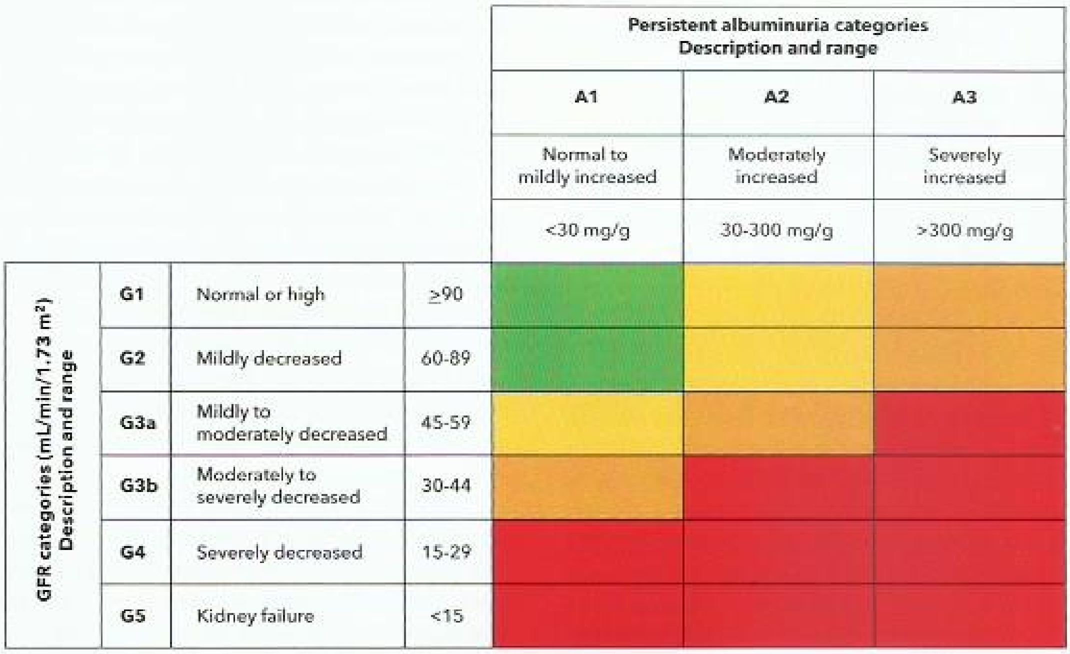
Chronic Kidney Disease

Definition and Staging

Chronic kidney disease (CKD) is defined as abnormal kidney structure or function present for >3 months. CKD is stratified into stages 1 to 5 based on the level of estimated glomerular filtration rate (eGFR). Stages G1 and G2 do not have reductions in eGFR and therefore are defined by the presence of anatomical defects or markers of kidney damage such as albuminuria, hematuria, or electrolyte abnormalities. Because albuminuria is associated with increased renal and cardiovascular morbidity and mortality, the Kidney Disease: Improving Global Outcomes (KDIGO) group further subdivides the eGFR based kidney stages by degree of albuminuria (**Figure 18**). This dual eGFR and albuminuria staging algorithm provides a means for predicting which patients are at highest risk for developing progressive CKD into end-stage kidney disease (ESKD), defined as CKD stage G5 treated with chronic dialysis or kidney transplantation.

Epidemiology and Pathophysiology

CKD, defined by either albuminuria or eGFR <60 mL/min/1.73 m², affects approximately 15% of the U.S. adult population. About 50% of patients with prevalent CKD have stage G3 disease or worse; the other 50% have CKD due to the presence of albuminuria. The prevalence of CKD is heavily influenced by age and has increased severalfold in elderly persons over the past 20 years. The largest increase over time, as assessed by the National Health and Nutrition Examination Survey (NHANES), is in stage G3 disease. In the United States, the prevalence of



Green: low risk (if no other markers of kidney disease, no CKD); Yellow: moderately increased risk; Orange: high risk; Red: very high risk.

FIGURE 18. The Kidney Disease: Improving Global Outcomes (KDIGO) chronic kidney disease staging system. Prognosis of chronic kidney disease by glomerular filtration rate and albuminuria category. CKD = chronic kidney disease; GFR = glomerular filtration rate.

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CKD stage G3 or worse is 0.3% in those aged 20 to 39 years, 3.3% in those aged 40 to 59 years, and 22.6% in those aged ≥60 years. In contrast, the prevalence of albuminuria is less age dependent. Approximately 6% of persons aged 40 to 59 years have a urine albumin-creatinine ratio ≥30 mg/g, compared with 8.5% of those aged ≥60 years. Advanced CKD, defined by stages G4 or G5, is present in <1% of the population. Compared with men, women have a slightly higher prevalence of both eGFR <60 mL/min/1.73 m² (7.9% versus 6.4%) and albuminuria (10.9% versus 8.8%).

CKD results from various etiologies that cause chronic damage to the glomeruli, tubulointerstitium, or both. Glomerular damage is reflected by proteinuria or albuminuria. Although a large degree of tubulointerstitial damage (both chronic inflammation and fibrosis) can exist subclinically and thus go unnoticed, eventually the underlying structural abnormalities affect kidney function, and GFR falls below normal levels.

Not all patients with CKD progress to ESKD. The most important predictors of progression are the baseline level of eGFR and the degree of albuminuria/proteinuria. eGFR trajectory over time also adds prognostic value for ESKD and cardiovascular outcomes. Patients with diabetic CKD usually progress faster than those without diabetes. The rate of eGFR decline ranges between -3 and -6 mL/min/1.73 m² per year in patients who have type 2 diabetes with high albuminuria. Renal risk variants in the apolipoprotein L1 (*APOL1*) gene are prevalent in black persons and are associated with higher rates of ESKD and progression of CKD, regardless of diabetes status (see Genetic Disorders and Kidney Disease).

Screening

CKD is typically asymptomatic except in advanced stages (G4, G5). Controversy exists regarding screening patients for CKD. The U.S. Preventive Services Task Force (USPSTF) and the American College of Physicians recommend against screening for CKD in asymptomatic adults with or without risk factors for CKD. In contrast, the American Society of Nephrology advises screening all adults for CKD, including, but not limited to, those with a family history of kidney disease or adults with risk factors for CKD (diabetes, hypertension, or cardiovascular disease).

Clinical Manifestations

CKD is typically asymptomatic except in advanced stages (G4, G5). When eGFR falls below 30 mL/min/1.73 m², numerous alterations in metabolic pathways, including 1,25-dihydroxyvitamin D production and erythrocyte production, become altered due to the lack of nephron mass and loss of 1α-hydroxylase and erythropoietin synthesis. Moderate to severe CKD can also result in impaired ability to excrete salt and water, and may manifest as edema. CKD in a patient with nephrotic-range proteinuria may also result in edema or anasarca.

When CKD progresses to ESKD, several nonspecific ("uremic") symptoms can occur such as fatigue, nausea, loss of appetite, insomnia, irritability, difficulty concentrating, confusion, or pruritus. Uremia can also induce serositis, including pleuritis and pericarditis. However, a large proportion of patients with CKD stage G5 manifest few or only intermittent uremic symptoms, for unexplained reasons. Although rarely seen today due to increased awareness and the widespread availability of dialysis, patients who have prolonged uremia that is untreated with renal replacement therapy may develop "uremic frost," which appears as chalky whitish skin and is due to crystallized urea deposits and other nitrogenous waste products that evaporated from sweat (**Figure 19**).

Diagnosis

CKD may be clinically suspected, or it may be incidentally detected on a basic chemistry panel that includes serum creatinine. Initial assessment of GFR includes establishing eGFR based on serum creatinine using the Chronic Kidney Disease Epidemiology (CKD-EPI) Collaboration creatinine equation. If confirmation of GFR is required because of conditions that affect serum creatinine independent of GFR (such as extremes of muscle mass or diet), cystatin C should be measured to employ the CKD-EPI creatinine-cystatin equation, or GFR should be measured directly using a clearance procedure. Initial assessment of albuminuria includes a random urine albumin-creatinine ratio. If confirmation of albuminuria is required because of diurnal variation or conditions affecting creatinine excretion, the albumin excretion rate should be

FIGURE 19. Uremic frost presenting as powdery deposits of urea and uric acid salts on the skin in a patient with untreated chronic kidney disease.

measured from a timed urine collection. See Clinical Evaluation of Kidney Function for more information.

Diagnosis of CKD requires a low eGFR confirmed at least 3 months after initial assessment, or persistent proteinuria or albuminuria. Kidney biopsy is used to determine the etiology of CKD when a glomerulonephritis, unexplained tubulointerstitial disease, or severe proteinuria is likely based upon clinical history, urine sediment, and laboratory results and/or antibody tests. Kidney biopsy is not indicated in the presence of shrunken kidneys (<9 cm), which generally indicate chronic irreversible disease. Occasionally, patients are noted to have "medical kidney disease" on imaging (such as ultrasound revealing hyperechoic kidneys). Urinalysis done for other nonspecific reasons may detect previously undiagnosed hematuria or proteinuria, which may suggest the presence of CKD and should prompt close observation or additional evaluation depending on the clinical scenario. There is currently a lack of evidence regarding the use of urinalysis as a routine screening test for CKD.

Patients who experience acute kidney injury (AKI) can have slow recovery; studies have demonstrated that kidney function can continue to recover for up to 1 year after an initial episode of AKI. Therefore, although diagnosis of CKD requires at least 3 months of persisting abnormalities in structure or function, a diagnosis of CKD after AKI may be premature in some patients between 3 and 12 months after the AKI episode.

KEY POINTS

- Chronic kidney disease is defined as abnormal kidney structure or function present for >3 months.
- Staging of chronic kidney disease is based on estimated glomerular filtration rate and albuminuria.
- The U.S. Preventive Services Task Force and the American College of Physicians recommend against screening for chronic kidney disease (CKD) in asymptomatic adults with or without risk factors for CKD, whereas the American Society of Nephrology advises screening all adults for CKD, including, but not limited to, those with a family history of kidney disease or adults with risk factors for CKD (diabetes, hypertension, or cardiovascular disease).

Complications and Management

According to KDIGO guidelines, referral to a nephrologist is indicated for evaluation and management of CKD in the presence of the following: AKI or an abrupt, sustained fall in GFR; GFR <30 mL/min/1.73 m^2; persistent albuminuria (>300 mg/g); progression of CKD; erythrocyte casts; >20 erythrocytes/hpf that is sustained and not readily explained; hypertension refractory to treatment with four or more antihypertensive agents; persistent abnormalities of serum potassium; recurrent or extensive nephrolithiasis; or hereditary kidney disease.

A kidney failure risk equation (KFRE) has been developed and validated. The KFRE uses four variables (age, sex, eGFR, and albuminuria) to predict 2-year and 5-year risk for ESKD in patients with CKD stages G3 to G5. The KFRE performs well across age, sex, race, and presence/absence of diabetes. The use of this equation is consistent with KDIGO guidelines, which recommend integration of risk prediction in the evaluation and management of CKD.

Cardiovascular Disease

Cardiovascular disease is the leading cause of death among patients with CKD. The risk for cardiovascular-related death in patients with CKD stages G3 and G4 is 4 to 5 times higher than the risk for progression to ESKD. Mortality risk increases with decreasing eGFR and increasing albuminuria. Unfortunately, many landmark clinical trials that guide the prevention or treatment of cardiovascular disease did not include patients with advanced CKD, and the findings may not be generalizable to patients with CKD. However, most post-hoc analyses of randomized controlled trials that had participants with some degree of CKD demonstrated efficacy regardless of baseline CKD status, including for interventions such as percutaneous coronary interventions. Thus, experts recommend against withholding otherwise efficacious therapies from those with CKD due to unsubstantiated concerns of lack of efficacy or harm. These also include coronary angiography or thrombolysis and/or platelet antagonists for patients with acute coronary syndromes or acute strokes and contrast-based CT studies for patients with high pretest probability of pulmonary embolism or aortic dissection.

Hypertension

Both KDIGO and the 2017 high blood pressure guideline from the American College of Cardiology (ACC), the American Heart Association (AHA), and nine other organizations recommend a blood pressure target of <130/80 mm Hg in patients with CKD.

An ACE inhibitor or an angiotensin receptor blocker is a preferred drug for treatment of hypertension for patients with stage G3 CKD or higher or for those with stage G1 or G2 CKD with albuminuria (albumin-creatinine ratio ≥300 mg/g). These medications may also slow the progression of CKD in some patients. Thiazide diuretics are a cornerstone of hypertension treatment but may lose efficacy with severe CKD. Loop diuretics therefore serve an important role in managing salt and water retention associated with proteinuria and CKD. Dietary sodium chloride restriction is essential for blood pressure control in most forms of CKD, and KDIGO recommends restricting sodium intake to <2000 mg/d.

See Hypertension for more information.

Dyslipidemia

Elevated LDL cholesterol and triglyceride levels with low HDL cholesterol levels are common among patients with CKD. Conflicting data exist on the effect of treating dyslipidemia in

reducing proteinuria and in slowing the progression of CKD. Statins have been shown to reduce cardiovascular and all-cause mortality in patients with CKD, although large trials have failed to demonstrate a mortality benefit for statins in patients with dialysis-dependent ESKD (unless initiated pre-dialysis). KDIGO guidelines recommend treatment with a statin in all patients aged ≥50 years with non-dialysis-dependent CKD and in adults aged 18 to 49 years with non-dialysis–dependent CKD and any one of the following: coronary disease, diabetes mellitus, prior ischemic stroke, or a >10% estimated risk of coronary death or nonfatal myocardial infarction. Statins are also recommended for adult kidney transplant recipients.

Dyslipidemia associated with the nephrotic syndrome helps maintain plasma oncotic pressure but, over time, may hasten the progression of glomerular injury. Dyslipidemia in the nephrotic syndrome requires aggressive treatment to prevent atherosclerotic disease, especially in patients with existing cardiovascular risk factors and in younger patients to prevent premature cardiovascular disease. See Glomerular Diseases for more information on the nephrotic syndrome.

Coronary Artery Disease

There is a significantly increased prevalence of coronary artery disease (CAD) among patients with CKD compared with the general population. This is partly explained by the high prevalence of shared risk factors/comorbidities such as diabetes or hypertension. However, CKD is independently associated with CAD, and this association strengthens with declining eGFR and rising albuminuria. Despite high cardiovascular mortality among patients with CKD, these patients may be less likely to undergo coronary revascularization procedures, possibly because of the increased risk for contrast-induced nephropathy (see Special Considerations, Imaging Contrast Agents).

In patients with CKD, serum biomarkers for myocardial ischemia such as cardiac troponins may be chronically elevated due to decreased renal clearance. Serial troponin measurements and other markers such as creatine kinase-MB can help distinguish acute ischemia from stable elevations.

KEY POINTS

- Both the Kidney Disease: Improving Global Outcomes group and the 2017 high blood pressure guideline from the American College of Cardiology (ACC), the American Heart Association (AHA), and nine other organizations recommend a target blood pressure of <130/80 mm Hg in patients with hypertension and chronic kidney disease.
- Treatment of hypertension in patients with chronic kidney disease includes an ACE inhibitor or angiotensin receptor blocker, dietary sodium restriction to <2000 mg/d, and addition of a diuretic as needed to control vascular volume.

(Continued)

KEY POINTS *(continued)*

- The Kidney Disease: Improving Global Outcomes guidelines recommend treatment with a statin in all patients with non-dialysis–dependent chronic kidney disease (CKD) who are over 50 years of age and in adults 18 to 49 years of age with non-dialysis–dependent CKD and any one of the following: coronary disease, diabetes mellitus, prior ischemic stroke, or a >10% estimated risk of coronary death or nonfatal myocardial infarction.

Chronic Kidney Disease-Mineral and Bone Disorder

As kidney function declines, the normal homeostasis of calcium and phosphorus levels by the kidney becomes compromised, resulting in alterations in bone mineralization. The term *chronic kidney disease-mineral and bone disorder* (CKD-MBD) encompasses these changes. The KDIGO guidelines for CKD-MBD are available at kdigo.org.

Calcium and Phosphorus Homeostasis

Three hormones are largely responsible for regulating calcium and phosphorus homeostasis: parathyroid hormone (PTH), vitamin D, and fibroblast growth factor 23 (FGF-23). PTH is the most important regulator of calcium and phosphorus concentrations. PTH has three separate mechanisms to increase serum calcium: It stimulates osteoclasts to resorb bone, stimulates hydroxylation of 25-hydroxyvitamin D in the kidneys, and stimulates tubular reabsorption of calcium (**Figure 20**). Concurrently, PTH induces renal phosphorus excretion.

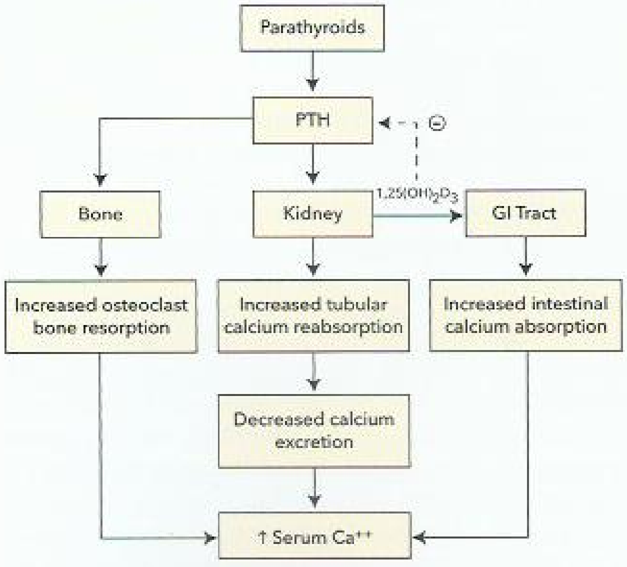

FIGURE 20. Overview of the metabolic systems that maintain calcium homeostasis. Parathyroid hormone (PTH) stimulates increased 1,25-dihydroxyvitamin D_3 [$1,25(OH)_2D_3$] synthesis by the kidneys, and $1,25(OH)_2D_3$ causes feedback suppression of PTH production. Ca^{++} = ionized calcium; GI = gastrointestinal; $1,25(OH)_2D_3$ = 1,25-dihydroxyvitamin D_3; PTH = parathyroid hormone; ↑ = increased.

FGF-23 is a peptide secreted by osteocytes and osteoclasts. It acts on the kidney to induce phosphaturia and downregulates 1α-hydroxylase to inhibit synthesis of 1,25 dihydroxyvitamin D. FGF-23 rises in stage G3a CKD, preceding PTH elevation. As GFR falls and PTH rises, PTH directly stimulates further FGF-23 production by osteocytes, resulting in a massive increase of FGF-23 blood levels, upwards of 100-fold from normal. Initially, the high FGF-23 serves to increase renal phosphorus excretion and helps maintain normal phosphorus levels as GFR declines.

As CKD progresses, increased FGF-23 and decreased nephron mass reduce the conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D by renal tubular cells. Reduction in 1,25-dihydroxyvitamin D levels results in lower intestinal absorption of calcium and phosphorus in the gut, mitigating phosphorus retention but also contributing to hypocalcemia, especially late in CKD. Reduced 1,25-dihydroxyvitamin D levels also increase PTH production by the parathyroid glands, and hypocalcemia is a potent stimulus for further increases in PTH levels.

Increased plasma PTH as a result of CKD is referred to as *secondary hyperparathyroidism*. Increased PTH levels result in reduced calcium excretion, increased calcium absorption from the gut, increased phosphorus excretion by the kidneys, and activation of osteoclast bone resorption. Early in CKD, the PTH-induced increase in renal phosphorus excretion enables normal phosphorus levels despite reduced renal excretory capacity. However, as CKD progresses, the kidney is unable to compensate for the increased release of phosphorus from bone, and phosphorus levels rise. This results in a vicious cycle as hyperphosphatemia stimulates PTH production.

If secondary hyperparathyroidism cannot be adequately controlled, tertiary hyperparathyroidism can ensue. Tertiary hyperparathyroidism is the result of the prolonged PTH stimulation needed to maintain eucalcemia. This prolonged stimulation results in increased calcium levels and severe hyperparathyroid hyperplasia with elevated PTH levels that are no longer responsive to the plasma calcium concentration.

Laboratory Abnormalities

Serum calcium and phosphorus levels typically remain in the normal range until the eGFR drops below 20 to 30 mL/min/1.73 m^2 (stages G4-G5), at which point the ability of elevated FGF-23 and PTH levels to promote phosphorus excretion becomes overwhelmed, and hyperphosphatemia develops. Progressive decline in 1,25-dihydroxyvitamin D levels results in reduced intestinal calcium absorption, and hyperphosphatemia promotes precipitation of calcium and phosphorus in extraskeletal tissues, leading to hypocalcemia.

In addition to reduced conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D, patients with CKD also have a higher prevalence of 25-hydroxyvitamin D deficiency. KDIGO guidelines recommend that patients with an eGFR <60 mL/min/1.73 m^2 (stage G3-G5) be evaluated for 25-hydroxyvitamin D deficiency and supplemented as per guidelines for the general population.

PTH levels are often elevated in patients with an eGFR <60 mL/min/1.73 m^2 (stage G3-G5) and progressively increase with worsening CKD. KDIGO guidelines recommend measuring intact PTH levels in these patients to aid in the detection and management of secondary hyperparathyroidism and its complications.

Vascular Calcification

An increased prevalence of arterial calcification, including the coronary arteries, has been noted in patients with CKD; the burden of calcification is highest in patients with ESKD. Arterial calcification reduces vascular compliance and likely contributes to the increased prevalence of left ventricular hypertrophy observed in patients with CKD. Arterial calcification is also strongly associated with cardiovascular and all-cause mortality; KDIGO guidelines therefore suggest treating patients with CKD and arterial calcification as is appropriate for patients in the highest category of cardiovascular risk, although treatments specifically targeted at reducing vascular calcification have not been shown to improve clinical outcomes.

Renal Osteodystrophy

Renal osteodystrophy refers to alteration of bone morphology in patients with CKD, which occurs as part of the systemic disorder of CKD-MBD. Four main types of histologic changes in bone can occur as part of renal osteodystrophy and are discussed in this section. KDIGO guidelines recommend a bone biopsy if knowledge of the type of renal osteodystrophy will affect treatment decisions in patients with CKD stages G3a to G5. This recommendation is based on the growing experience with osteoporosis medications in patients with CKD, low bone mineral density, and a high risk of fracture. The lack of ability to perform a bone biopsy may not justify withholding antiresorptive therapy from patients at high risk of fracture.

Osteitis Fibrosa Cystica

Osteitis fibrosa cystica is due to abnormally high bone turnover that can occur after prolonged exposure of bone to sustained high levels of PTH in secondary hyperparathyroidism. It is associated with an increased number and activity of osteoblasts and osteoclasts and expansion of osteoid surfaces, resulting in an increased risk for fracture. Patients can be asymptomatic or have bone pain. Classic skeletal changes on radiograph include subperiosteal resorption of bone, most prominently at the phalanges of the hands, and radiolucent bone cysts of the long bones.

Adynamic Bone Disease

Adynamic bone disease occurs when there is a lack of bone cell activity and a markedly reduced rate of bone turnover. Histopathologic abnormalities include decreased osteoclast activity with an increase in osteoid, resulting in an increased risk for fracture. Patients have suppressed PTH levels (due to chronic illness or aggressive treatment with vitamin D

analogues) or skeletal resistance to PTH from down-regulation of the bone PTH receptor due to high circulating PTH levels. Patients may be asymptomatic or have bone pain. Adynamic bone disease should be excluded prior to bisphosphonate therapy because these drugs can cause and/or worsen the disease by inhibiting osteoclast activity.

Osteomalacia

Osteomalacia is characterized by decreased mineralization of osteoid at sites of bone turnover, with increased risk of fracture. The most common symptoms include bone pain and tenderness. Although patients with CKD are at increased risk for osteomalacia, CKD does not cause osteomalacia per se; vitamin D deficiency caused by coexisting factors such as intestinal malabsorption due to gastrointestinal disorders or restricted access to sunlight is often present.

Osteoporosis

Patients with CKD have many causes of reduced bone density. Current KDIGO guidelines indicate that in patients with CKD stages G3a to G5 with evidence of CKD-MBD and/or risk factors for osteoporosis, bone mineral density testing is suggested to assess fracture risk if results will affect treatment decisions.

Management

In patients with CKD stages G3a to G5, treatment of CKD-MBD is based on serial assessments of phosphorus, calcium, and PTH levels. Current KDIGO guidelines recommend that in patients with CKD stages G3a to G5, elevated phosphorus levels should be lowered *toward* the normal range, not into the normal range, because there is an absence of data showing that efforts to maintain phosphorus in the normal range are of benefit and safety concerns. Thus, treatment should be aimed at overt hyperphosphatemia, and decisions to start phosphate-lowering treatment should be based solely on progressively or persistently elevated serum phosphorus levels.

KDIGO guidelines recommend avoiding hypercalcemia. Mild and asymptomatic hypocalcemia (for example, in the context of calcimimetic treatment) can be tolerated to avoid inappropriate calcium loading. KDIGO guidelines also now recommend restricting the dose of calcium-based phosphate binders (calcium carbonate and calcium acetate) in CKD stages G3a to G5, rather than restriction only in those with hypercalcemia. This change was based on published trials suggesting that exposure to exogenous calcium is harmful in terms of vascular calcification in all stages of CKD, along with data suggestive of lower mortality risk with non–calcium-containing phosphate binders (sevelamer and lanthanum) versus calcium-containing binders.

For patients with CKD stages G3a to G5 who are not on dialysis, optimal PTH levels are not known. Previously, patients with PTH levels above the upper normal limit were targeted for management. The 2016 KDIGO update suggests that patients with levels of intact PTH "*progressively rising or persistently above the upper normal limit* for the assay be evaluated for modifiable factors, including hyperphosphatemia, hypocalcemia, high phosphate intake, and vitamin D deficiency." KDIGO guidelines recommend against routine use of calcitriol and vitamin D analogues to lower PTH levels in patients with CKD stages G3a to G5 not on dialysis, because trials of these agents failed to demonstrate improvements in clinically relevant outcomes. Instead, these agents should be reserved for patients with CKD stages G4 to G5 with severe and progressive hyperparathyroidism.

In patients on dialysis, KDIGO guidelines recommend use of calcimimetics, calcitriol, or vitamin D analogues, or a combination of calcimimetics and calcitriol or vitamin D analogues, to lower PTH levels. This recommendation was largely due to the EVOLVE (EValuation Of Cinacalcet Hydrochloride Therapy to Lower CardioVascular Events) trial and several secondary analyses of data from this trial. The EVOLVE trial evaluated the effect of cinacalcet versus placebo in hemodialysis patients by using a composite end point of all-cause mortality, nonfatal myocardial infarction, hospitalization for unstable angina, heart failure, and peripheral vascular events. Although the primary analysis demonstrated a nonsignificant reduction in the primary composite end point with cinacalcet, multiple sensitivity analyses demonstrated statistically significant reductions in the composite end point, including in those aged ≥65 years. Given these mostly positive but mixed findings, the KDIGO Work Group listed calcimimetic therapy among the acceptable treatment options while still recognizing the utility and efficacy of active vitamin D compounds.

Tertiary hyperparathyroidism does not respond to phosphate binders or calcitriol therapy, and patients often require parathyroidectomy for definitive treatment.

KEY POINTS

- Chronic kidney disease–mineral and bone disorder is defined by the changes to the normal homeostasis of calcium and phosphorus levels as kidney function declines, resulting in alterations in bone mineralization.
- According to current Kidney Disease: Improving Global Outcomes (KDIGO) guidelines, management of chronic kidney disease–mineral and bone disorder focuses upon normalizing serum phosphorus, avoiding hypercalcemia, and addressing modifiable factors.

Anemia

Anemia in the setting of CKD is common, and its prevalence increases as CKD progresses into stages G4 and G5. Most often normocytic, anemia in CKD largely results from lack of erythropoietin production due to the decline in functional renal mass. Other contributors include erythropoietin resistance, neocytolysis (decreased survival time of erythrocytes), and iron deficiency.

Although modest declines in hemoglobin are well tolerated, concern for inducing or contributing to the development

of left ventricular hypertrophy has been the key driver in the belief that higher hemoglobin values are beneficial. Moreover, observational data suggest that higher hemoglobin values are associated with better outcomes in patients with CKD and ESKD. However, several large randomized controlled trials conducted in the past 15 to 20 years demonstrated no benefit or increased harm regarding some cardiovascular events in groups randomly assigned to higher hemoglobin targets via erythropoiesis-stimulating agents (ESAs). Moreover, these trials revealed only modest improvements in fatigue and no benefit in physical functioning with higher hemoglobin targets. The mechanisms underlying the lack of benefit or harm for the higher hemoglobin groups are not well understood but may include off-target effects of ESAs on extrarenal organs. Thus, current KDIGO recommendations are to consider ESAs for patients with CKD who have hemoglobin concentrations <10 g/dL (100 g/L). Black box warnings for use of ESAs include the risk for increased mortality and/or tumor progression in patients with active malignancy, increased risk for thromboembolic events in postsurgical patients not receiving anticoagulant therapy, and increased risk for serious cardiovascular events when ESAs are administered to patients with hemoglobin values >11 g/dL (110 g/L) or with a history of stroke.

All patients with CKD and anemia should have iron profiles assessed, including total iron-binding capacity and ferritin levels. KDIGO recommendations suggest maintaining transferrin saturation levels of >30% and serum ferritin levels of >500 ng/mL (500 µg/L) using either oral or intravenous iron supplementation. Inadequate iron stores will contribute to ESA hyporesponsiveness. Blood transfusions can be used in patients with severe anemia or modest anemia with symptoms; however, the goal is to minimize the number of erythrocyte transfusions in patients with CKD and ESKD due to concerns for iron overload and sensitization to HLA antigens, which may lead to allosensitization and increased waiting times for kidney transplantation.

KDIGO guidelines for the diagnosis and management of CKD-related anemia can be found at kdigo.org.

Metabolic Acidosis

Metabolic acidosis frequently occurs in patients with CKD due to defective acid excretion (resulting in reduced bicarbonate generation), most commonly due to impaired ammoniagenesis. Untreated metabolic acidosis can lead to muscle loss (due to increased muscle proteolysis) and bone loss (due to increased bone resorption and impaired bone formation). In early CKD, metabolic acidosis is typically a normal anion gap hyperchloremic metabolic acidosis. As eGFR declines, organic and inorganic anions are retained, and an increased anion gap metabolic acidosis develops.

Large observational studies have shown a strong association between lower serum bicarbonate levels and both increased progression of CKD and mortality. Alkali therapy, most commonly sodium bicarbonate or sodium citrate, can delay the progression of CKD. Therefore, KDIGO guidelines recommend starting alkali therapy when the serum bicarbonate is chronically <22 mEq/L (22 mmol/L). The alkali salt therapy dose should be titrated to achieve a serum bicarbonate level within the normal range; excessive alkali therapy in the setting of a reduced eGFR may induce a metabolic alkalosis, which is associated with increased mortality. Despite the administration of excess sodium, alkali salts are not associated with volume expansion, even among patients with chronic heart failure or overt edema, most likely because the accompanying anion is not chloride.

Nephrotoxins

Two major issues exist regarding drug administration in patients with CKD: 1) Renally excreted drugs require dose adjustment to avoid accumulation and potential side effects; and 2) Reduced functional nephron mass increases the probability that a potentially nephrotoxic drug will cause nephrotoxicity.

Conceptually, it is useful to compartmentalize nephrotoxic medications by their main site of action. For example, several medications, including NSAIDs, calcineurin inhibitors, and ACE inhibitors/angiotensin receptor blockers, can have effects on glomerular blood flow. Patients with AKI who are on NSAIDs should have the medications immediately discontinued. For patients with CKD, the American Society of Nephrology recommends the avoidance of NSAIDs, including cyclooxygenase-2 inhibitors, due to the risk of worsening kidney function. ACE inhibitors or angiotensin receptor blockers are the cornerstone of treatment for patients with CKD; however, during episodes of acute illness and/or volume depletion, these drugs increase the risk for AKI due to their effects on intraglomerular pressure. Drugs that cause glomerular injury, tubular injury, or tubulointerstitial nephritis are reviewed in Acute Kidney Injury.

Emerging literature suggests that proton pump inhibitors, in addition to their classic association with acute interstitial nephritis/AKI, may contribute to the development and progression of CKD. The association is robust and has been confirmed in three independent cohorts. These studies used careful comparators, including the use of H_2 blockers, and adjusted for numerous potential confounding variables, including chronic NSAID use.

Proteinuria

The severity of proteinuria is strongly associated with adverse clinical outcomes, including progression of CKD to ESKD, cardiovascular morbidity, and mortality. It is unclear whether proteinuria is simply a marker of the underlying severity of kidney damage and disease, or if proteinuria itself activates inflammatory pathways and contributes to tubulointerstitial fibrosis. Although dual renin-angiotensin system blockade via combinations of ACE inhibitors, angiotensin receptor blockers, or direct renin inhibitors have been shown to decrease

proteinuria, several clinical trials have revealed that use of combination renin-angiotensin system antagonism results in more adverse events (hyperkalemia, hypotension, AKI) without additional cardiovascular or renal benefits.

Protein Restriction

In animal models, protein-restricted diets have been shown to slow the progression of kidney disease by reducing glomerular filtration pressure, thereby preventing progressive injury and fibrosis. However, in the Modification of Diet in Renal Disease study, no definitive benefit was seen in renal outcomes in patients randomly assigned to the low protein (0.6 g/kg/d) group. Although there is insufficient evidence to recommend routine use of low protein diets to slow progression of CKD, high protein diets may precipitate or exacerbate symptoms of uremia in patients with stage G5 CKD. Small studies suggest that low protein diets might delay the onset of symptomatic uremia and the need for renal replacement therapy in patients with stage G5 CKD not yet on dialysis.

KEY POINTS

- Erythropoiesis-stimulating agents are associated with an increased risk for serious cardiovascular events when administered to patients with hemoglobin values >11 g/dL (110 g/L) or a history of stroke.
- Kidney Disease: Improving Global Outcomes (KDIGO) guidelines recommend treatment of metabolic acidosis with alkali therapy in patients with chronic kidney disease when the serum bicarbonate is chronically <22 mEq/L (22 mmol/L).
- ACE inhibitors and angiotensin receptor blockers decrease proteinuria and slow progression of proteinuric kidney diseases, but use of both drug classes in combination results in more adverse events without additional cardiovascular or renal benefits.

Special Considerations

Imaging Contrast Agents

H

Intravenous iodinated contrast can cause contrast-induced nephropathy (CIN), and risk for CIN increases with increasing severity of CKD. Patients with CKD should receive intravenous hydration with isotonic saline or bicarbonate-containing solutions before and after receiving contrast unless there is evidence of frank pulmonary edema. See Acute Kidney Injury for more information on CIN.

Gadolinium contrast used in MRI is associated with risk for nephrogenic systemic fibrosis (NSF) and must be avoided in patients with an eGFR <30 mL/min/1.73 m². In life-threatening situations in which benefit outweighs the risk for NSF, MRI is performed with low doses of stable gadolinium agents. Prior nephrology consult should be obtained to assess risks of gadolinium administration and guide the use of dialysis in advanced CKD and ESKD. In those with severe CKD who require gadolinium, daily dialysis for 3 days appears to be effective at clearing the gadolinium and reducing the risk for NSF. See MKSAP 18 Dermatology for more information on NSF. H

Vaccination

Patients with CKD are at increased risk for infections that can be prevented by vaccination; however, these patients also have impaired immune responses to vaccines. The Centers for Disease Control and Prevention guidelines state that vaccinations in patients with CKD may be more effective when performed before the need for chronic dialysis or kidney transplantation. Patients with CKD should otherwise receive vaccinations according to guidelines, with a few exceptions:

- Patients with advanced CKD near dialysis dependence or those with ESKD on hemodialysis should be vaccinated against hepatitis B virus.
- Patients with CKD (stage not specified) or the nephrotic syndrome should receive the 23- and 13-valent pneumococcal vaccines, with revaccination with the 23-valent vaccine after a minimum of 5 years.
- Influenza vaccine should be administered annually to patients with CKD, but patients with ESKD should only receive the inactivated influenza vaccine due to risks associated with the live vaccines in immunocompromised patients.

Vascular Access

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Patients with advanced CKD may ultimately require renal replacement therapy; for those who choose hemodialysis, timely vascular access creation is essential. Referral to an experienced surgeon many months before dialysis is critical because arteriovenous fistula placement can be technically challenging and may require several months for full maturation. Arteriovenous fistulas have superior clinical outcomes compared with arteriovenous grafts and tunneled catheters.

Protecting the nondominant arm veins is paramount and involves limiting phlebotomy and intravenous catheters in that arm. Peripherally inserted central venous catheters should be avoided in patients with an eGFR <60 mL/min/1.73 m². A recent study demonstrated that peripherally inserted central catheters placed before or after hemodialysis initiation were independently associated with approximately 15% to 20% lower likelihoods of transition to any working fistula or graft. Avoidance of subclavian venous catheters helps to limit subclavian stenosis, which could impair the proper functioning of an arteriovenous fistula or arteriovenous graft used for dialysis. H

Older Patients

CKD stages G1 through G3a in elderly patients without albuminuria is of minimal clinical importance; some may refer to this mild decrement in eGFR as normal aging. For elderly

persons with progressing or severe CKD necessitating discussions about renal replacement therapy and/or referral for evaluation for kidney transplantation, a patient-centered approach is preferred. Comorbid medical conditions, functional status, expected outcomes, and patient preferences regarding goals of care should be considered. For patients aged ≥80 years at the start of hemodialysis treatment, data demonstrate better survival among those who received pre-hemodialysis nephrology care that followed a planned management pathway, those who had a good nutritional status, and those with an arteriovenous fistula as vascular access for hemodialysis at the time of hemodialysis initiation.

KEY POINTS

- Gadolinium contrast used in MRI is associated with the risk for nephrogenic systemic fibrosis and must be avoided in patients with an estimated glomerular filtration rate <30 mL/min/1.73 m².
- In patients with chronic kidney disease, peripherally inserted central venous catheters and subclavian venous catheters should be avoided in the nondominant arm veins for possible future dialysis vascular access.

End-Stage Kidney Disease

H

CKD stage G5 is defined as an eGFR <15 mL/min/1.73 m², and ESKD is defined as CKD stage G5 treated with chronic dialysis or kidney transplantation. About 10% of patients with CKD stage G3 progress to ESKD, but most die from cardiovascular disease or infection before they progress to advanced CKD.

Patients with an eGFR <30 mL/min/1.73 m² should be educated about renal replacement therapy (RRT) treatment options, including hemodialysis, peritoneal dialysis, and kidney transplantation. Patients with advanced age or multiple comorbidities may not want any of these life-sustaining options. There has been increasing support of "kidney supportive care," which involves services aimed at improving the quality of life for patients with advanced CKD. It includes aligning treatment with a patient's goals through culturally sensitive shared decision-making and advance care planning, along with treating symptoms resulting from uremia, hypervolemia, hyperkalemia, and/or acidosis. For patients amenable to RRT, studies demonstrate no benefit in starting RRT in asymptomatic patients or at a specific eGFR cutoff compared with watchful waiting and initiating RRT for symptoms or metabolic abnormalities that are refractory to medical treatment. For the elderly and frail patients, physicians need to balance the management of symptoms with optimal care, with less emphasis being placed on maximizing long-term health outcomes, such as survival. Care should align with patient preferences and maximize the patient's quality of life. **Table 30** compares goals of care for patients with ESKD treated with standard dialysis versus kidney supportive care.

Dialysis

Patients who choose hemodialysis should be referred for arteriovenous fistula creation in a timely manner to allow for arteriovenous fistula maturation. Arteriovenous grafts for hemodialysis and peritoneal dialysis catheters for peritoneal dialysis can be placed weeks before starting RRT but ideally should be planned months in advance. Tunneled dialysis catheters can be placed within days or the same day prior to starting hemodialysis but are associated with increased risk for bloodstream infections and death. Therefore, arteriovenous fistula or arteriovenous graft is preferred.

Hemodialysis

Hemodialysis achieves clearance of blood solutes by convection and diffusion against a concentration gradient provided

TABLE 30. Goals of Care for Patients with End-Stage Kidney Disease Treated with Dialysis Versus Kidney Supportive Care

Issue	Current Disease-Focused Metrics for Conventional Delivery of Dialysis Care	Kidney Supportive Care
Vascular access	Creation and maintenance of an AVF; avoid central venous catheters as much as possible	Central venous catheter acceptable if patient chooses hemodialysis
Dialysis adequacy	Target small solute clearance based on current standards, intensifying the dialysis prescription as needed to achieve targets	Lower clearance acceptable if changes in dialysis prescription increase demands inconsistent with patient preference; may involve fewer hemodialysis sessions or more frequent but shorter sessions
Cardiovascular disease	Treat cardiovascular risk factors, potentially targeting BP and dyslipidemia	Tolerate hypertension to avoid symptoms; no indication for dyslipidemia treatment
Mineral and bone disorder	Dietary counseling; binders to control hyperphosphatemia; vitamin D analogues with or without calcimimetics for secondary hyperparathyroidism	Limited restrictions; more permissive hyperphosphatemia and hyperparathyroidism
Nutrition	Encourage dietary protein intake while limiting potassium, sodium, and phosphorus intake	Reduce dietary restrictions
Laboratory monitoring	Routine monthly laboratory tests	Minimal necessary

AVF = arteriovenous fistula; BP = blood pressure.

by dialysate flowing opposite to blood flow and separated by a semipermeable dialyzer membrane. Hemodialysis is commonly performed three times per week for 3- to 4-hour treatment sessions at an outpatient dialysis unit. Frequent and/or longer treatments provide better control of volume status and serum electrolytes. Some patients perform hemodialysis at home four to five times per week but with shorter treatment sessions.

Peritoneal Dialysis

Peritoneal dialysis utilizes an indwelling catheter to perform exchanges of dialysate with a specified solute concentration and osmolality into the peritoneum, which serves as a semipermeable membrane and allows for diffusion of solutes and osmosis of water. Dialysate needs to be exchanged about three to five times per day to maintain a high concentration gradient and maintain adequate solute clearance. Patients can perform these exchanges during the day, or a cycler can be used to exchange the fluid overnight while the patient sleeps; these options provide greater autonomy because the patient can work or perform activities during the day, rather than the need to be present at a hemodialysis unit three times per week. Clinical outcomes are similar for patients on peritoneal dialysis compared with hemodialysis, although patients starting RRT who have residual renal function may have better outcomes with peritoneal dialysis. Furthermore, residual renal function is preserved longer in peritoneal dialysis compared with hemodialysis and, although small, helps maintain adequate solute clearance and euvolemia.

Peritonitis is an important complication because repeated infections can cause peritoneal fibrosis and reduce the efficacy of the dialysis treatments. Dialysis-associated peritoneal peritonitis is infrequent, with an average of one episode every 2 to 3 years. It is usually caused by gram-positive skin flora and less commonly by gram-negative intestinal flora. Proper skin hygiene and sterile technique when handling the peritoneal dialysis catheter are critical in preventing peritonitis.

Non-dialytic Palliative Therapy

Some patients with CKD stage G5/ESKD may choose not to initiate RRT, or patients already on RRT may decide to discontinue treatment. Palliative care and hospice services play an important role in caring for these patients. Non-dialytic therapy is a reasonable treatment option for elderly patients with ESKD and multiple comorbidities. Treatment focuses on symptom management and results in less hospitalization with similar or better quality of life compared with patients on RRT. For patients who withdraw from RRT, death usually occurs within 2 weeks. Recent studies have shown that the withdrawal rate from dialysis is approximately 3 per 100 person-years of dialysis, and this rate is increasing over time. H

KEY POINTS

- Clinical outcomes are similar for patients on peritoneal dialysis compared with hemodialysis, although patients starting renal replacement therapy who have residual renal function may have better outcomes with peritoneal dialysis.
- Non-dialytic palliative therapy is a reasonable option for elderly patients with end-stage kidney disease and multiple comorbidities, with treatment focusing on symptom management and quality of life. HVC

Kidney Transplantation

Kidney transplantation is the preferred treatment for ESKD. It improves life expectancy and quality of life, and provides a significant cost savings to the health care system compared with dialysis. However, demand far exceeds supply, and waiting lists for deceased-donor kidneys are several years long in most regions of the United States.

Referral

Patients should be referred to a kidney transplant center for evaluation when the eGFR is <20 mL/min/1.73 m^2. Early referral is important because preemptive kidney transplants (transplants before needing dialysis) are associated with improved clinical outcomes compared with receiving a transplant after starting dialysis. Early referral also allows adequate time to identify suitable living donors; if no living donor is available, early listing is essential to begin the waiting process for a deceased-donor kidney.

Patients and donors undergo extensive health screening to identify issues that may affect the safety and/or outcome of the transplant. In the potential recipient, these include active malignancy, coronary ischemia, or active infections. An adequate social support system and financial resources are also important to ensure medication adherence and long-term survival of the transplanted allograft. Donors are screened for intrinsic kidney disease, hypertension, and diabetes to ensure there is minimal risk related to reduced renal mass resulting from donation nephrectomy.

Patients are generally managed by a transplant nephrologist for at least the first 6 months posttransplant and are then comanaged with a general nephrologist and/or internist, especially for comorbidities.

Immunosuppressive Therapy

Immunosuppressive medications are required to prevent allograft rejection. Induction therapy is started perioperatively with polyclonal anti–T-cell antibodies (thymoglobulin) or monoclonal anti–interleukin-2 receptor antibody (basiliximab). Calcineurin inhibitors with pulse glucocorticoids are started at this time as well.

Long-term maintenance therapy for most patients includes a combination of calcineurin inhibitors (tacrolimus or cyclosporine), antimetabolites (mycophenolate mofetil or azathioprine), and glucocorticoids. However, some patients

with well-matched allografts can discontinue glucocorticoids. Doses of these medications are highest immediately posttransplant and are gradually decreased over the next several months to minimize side effects (**Table 31**), including long-term nephrotoxicity, while maintaining adequate immunosuppression.

Risks of Transplantation

Immediately posttransplant, patients need to be monitored for acute rejection and postoperative complications. Thereafter, minimizing risk for infection and medication side effects becomes the focus while maintaining adequate immunosuppression to prevent acute and chronic rejection.

Infection

Immunosuppression significantly increases the risk for infection. Within the first month after surgery, the most common infectious complications are similar to other surgical patients and include urinary tract infections and wound infections. Afterward, opportunistic infections become more prevalent.

Cytomegalovirus (CMV) is an important pathogen, and the risk for infection depends on the serologic status of the donor and recipient at the time of transplant. The highest risk occurs when a seropositive donor kidney is transplanted into a seronegative recipient. Most patients receive prophylaxis against CMV with valganciclovir during the first 6 to 12 months; however, CMV infections can occur after the medication is discontinued. Signs and symptoms include fever, pneumonitis, hepatitis, and gastroenteritis/colitis.

TABLE 31. Common Side Effects of Medications Used for Chronic Maintenance Immunosuppression After Kidney Transplantation

Class	Medication	Common Side Effects
Calcineurin inhibitor	Cyclosporine	Hypertension; decreased GFR; dyslipidemia; hirsutism; gingival hyperplasia
	Tacrolimus	New-onset diabetes mellitus; decreased GFR; hypertension; gastrointestinal symptoms
Antimetabolite	Mycophenolate mofetil	Diarrhea; nausea/vomiting; leukopenia; anemia
	Azathioprine	Leukopenia; hepatitis; pancreatitis
mTOR inhibitor	Sirolimus; everolimus	Proteinuria; dyslipidemia; new-onset diabetes mellitus; anemia; leukopenia
Glucocorticoid	Prednisone	Osteopenia, osteoporosis, osteonecrosis; hypertension; edema; new-onset diabetes mellitus; glaucoma; cataracts

GFR = glomerular filtration rate; mTOR = mammalian target of rapamycin.

Prophylaxis against *Pneumocystis jirovecii* pneumonia with trimethoprim-sulfamethoxazole is most commonly used, but atovaquone can be used for sulfa-allergic or hyperkalemic patients.

Polyoma BK virus uniquely affects kidney transplant patients, only rarely occurring with other organ transplants or in other immunosuppressed states. The most common clinical manifestation is an acute or indolent rise in serum creatinine due to tubulointerstitial nephritis or ureteral stenosis. Treatment requires reduction in the immunosuppression dose, but this must be balanced against the risk of allograft rejection.

Cancer

Because kidney transplant recipients are at higher risk for developing cancer, it is important to screen recipients for the presence of active malignancy prior to transplant.

Immunosuppressive medications increase the risk for several forms of malignancy, with non-melanoma skin cancers being the most common. Transplant patients therefore should be screened regularly for skin cancer and other age- and sex-appropriate cancer.

Posttransplant lymphoproliferative disorders can occur with long-term immunosuppression. These malignancies are caused by uncontrolled B-lymphocyte proliferation associated with Epstein-Barr virus infection and impaired T-cell surveillance. Treatment involves reduction in immunosuppression and administration of the anti–B-cell monoclonal antibody rituximab. Additionally, calcineurin inhibitors may be switched to the mammalian target of rapamycin inhibitor sirolimus because of its antiproliferative effects.

Kaposi sarcoma is also common and is associated with human herpesvirus 8 infection. Treatment involves reduction in immunosuppression dosing and switching to a sirolimus-based regimen.

Special Considerations in Transplant Recipients

Acute Kidney Injury

AKI is a common posttransplant complication and can occur immediately posttransplant or any time in the future. Acute rejection should always be part of the differential diagnosis, because early recognition and treatment are associated with better long-term outcomes. Posttransplant AKI may also be due to renal vasoconstriction from calcineurin inhibitor toxicity, calcineurin inhibitor–induced thrombotic microangiopathy, BK nephropathy, acute tubular necrosis, acute interstitial nephritis, or volume depletion/prerenal causes.

Disease Recurrence

Glomerular diseases can recur in the transplant allograft. Focal segmental glomerulosclerosis is one of the most common forms of glomerular disease to recur posttransplant and can occur within a few days to weeks after transplantation. Focal segmental glomerulosclerosis and thrombotic microangiopathy should be treated aggressively if disease recurrence is seen in the transplanted kidney, because these conditions are associated with high

rates of graft failure. Patients with lupus or ANCA vasculitis should have quiescent disease for several months preceding transplantation to reduce risk for disease recurrence posttransplant. Diabetic nephropathy and IgA nephropathy can affect allograft function after transplant but are unlikely to cause graft failure.

Cardiovascular Disease

Cardiovascular disease is the leading cause of death in kidney transplant recipients (about 50% of deaths). Kidney transplantation, despite restoration of kidney function, should be treated as a cardiovascular disease equivalent for purposes of risk factor modification.

Calcineurin inhibitors induce hypertension by activating the sodium chloride cotransporter in the distal convoluted tubule of the kidney. Therefore, thiazide diuretics may be efficacious in these patients. Dyslipidemia is a common side effect of calcineurin inhibitors, sirolimus, and glucocorticoids. Treatment with a statin improves cardiac outcomes; however, statins have drug-drug interactions with calcineurin inhibitors and can increase toxicities of both drugs.

Bone Disease

Secondary and tertiary hyperparathyroidism, common in patients with ESKD, can persist for several months posttransplant; continuation of vitamin D analogues or calcimimetics may be warranted if the patient is hypercalcemic. Additionally, hypophosphatemia secondary to hyperparathyroidism is common posttransplant due to renal phosphorus wasting. Long-term glucocorticoids can cause osteopenia, osteoporosis, and osteonecrosis. Calcineurin inhibitors induce magnesium wasting. See Chronic Kidney Disease–Mineral and Bone Disorder for more information.

Vaccination

Most transplant centers do not recommend immunization within the first 3 to 6 months posttransplant due to increased immunosuppression and therefore decreased likelihood of developing long-term immunity from the vaccine. Influenza vaccine, however, may be administered within 1 month of transplant in the setting of an influenza outbreak. Live attenuated vaccines are generally contraindicated in transplant recipients.

KEY POINTS

- Patients should be referred to a kidney transplant center for evaluation when the estimated glomerular filtration rate is <20 mL/min/1.73 m^2.
- Preemptive kidney transplants are associated with improved clinical outcomes compared with transplantation after dialysis.
- Within the first month following kidney transplantation, the most common infectious complications are similar to other surgical patients and include urinary tract infections and wound infections; afterward, opportunistic infections (such as cytomegalovirus, *Pneumocystis jirovecii*, and polyoma BK virus) become more prevalent.

(Continued)

KEY POINTS *(continued)*

- Immunosuppression of kidney transplant recipients increases the risk for several malignancies, including non-melanoma skin cancers, Kaposi sarcoma, and posttransplant lymphoproliferative disorders; regular screening for skin cancer and other age- and sex-appropriate cancer is recommended.

Complications of End-Stage Kidney Disease

Cardiovascular Disease

Sudden cardiac death is the leading cause of death in ESKD. This population is at increased risk due to rapid shifts of serum electrolytes during dialysis and chronic volume overload that contribute to left ventricular hypertrophy and cardiac fibrosis. Uremic toxins also contribute to left ventricular hypertrophy and cardiac fibrosis and may play a role in arrhythmogenesis. Avoiding rapid changes in serum potassium during dialysis may help limit arrhythmias, and adherence to dietary salt and fluid restriction may help limit volume overload. However, intradialytic hypotension induced by rapid volume removal during dialysis may cause cardiovascular and central nervous system injury due to organ hypoperfusion. Vascular calcification is accelerated by uremic toxins, chronic inflammation, and calcium-based medications/vitamin D analogues. Limiting medications that raise serum calcium and achieving adequate clearance during dialysis may help delay the progression of atherosclerosis. KDGIO guidelines recommend continuing a statin if a patient with CKD progresses to ESKD, but statins should not be newly started if progression to ESKD has already occurred.

Infection

Infection is the second leading cause of death in ESKD. Patients are at increased risk due to a relatively immunosuppressed state from chronic inflammation and frequent exposure to the health care environment. Tunneled dialysis catheters increase the risk for bacteremia, and empiric antibiotics should be administered while waiting for blood culture results in patients with suspected bacteremia. Tunneled catheters should be removed immediately for severe sepsis, evidence of metastatic infection, evidence of an exit-site or tunnel infection, persistent fever, or bacteremia despite antibiotics. Exchange of the catheter over a guidewire may be an option for clinically stable patients without a tunnel infection or for patients who clear the bacteremia within 48 hours of antibiotic administration. Antibiotic lock therapy consists of the instillation of a highly concentrated antibiotic solution into an intravascular catheter lumen to treat catheter-related bloodstream infections. Antibiotic lock therapy with vancomycin and/or ceftazidime is an alternative option for stable patients with less virulent organisms such as *Staphylococcus epidermitis*, but catheter salvage should not be attempted for *Staphylococcus aureus* infections and some gram-negative organisms.

Acquired Cystic Kidney Disease

Acquired cystic kidney disease is common among patients with severe CKD and ESKD. Cysts are usually detected during routine kidney ultrasonography or incidentally found on abdominal CT or MRI. These cysts are at increased risk for transformation into renal cell carcinoma, but routine screening is not recommended for most patients. A high index of suspicion is warranted for patients with new gross hematuria or unexplained flank pain. For cysts that are highly suspicious for malignancy, partial nephrectomy and nephron-sparing approaches are indicated for less severe stages of CKD. For patients with advanced CKD or ESKD, radical nephrectomy is the most prudent option.

KEY POINT

- Complications of end-stage kidney disease include cardiovascular disease, infection, and acquired cystic kidney disease.

Bibliography

Clinical Evaluation of Kidney Function

Corapi KM, Chen JL, Balk EM, Gordon CE. Bleeding complications of native kidney biopsy: a systematic review and meta-analysis. Am J Kidney Dis. 2012;60:62-73. [PMID: 22537423]

Davis R, Jones JS, Barocas DA, Castle EP, Lang EK, Leveillee RJ, et al; American Urological Association. Diagnosis, evaluation and follow-up of asymptomatic microhematuria (AMH) in adults: AUA guideline. J Urol. 2012;188:2473-81. [PMID: 23098784]

Fähling M, Seeliger E, Patzak A, Persson PB. Understanding and preventing contrast-induced acute kidney injury. Nat Rev Nephrol. 2017;13:169-180. [PMID: 28138128]

Inker LA, Schmid CH, Tighiouart H, Eckfeldt JH, Feldman HI, Greene T, et al; CKD-EPI Investigators. Estimating glomerular filtration rate from serum creatinine and cystatin C. N Engl J Med. 2012;367:20-9. [PMID: 22762315]

Ix JH, Wassel CL, Stevens LA, Beck GJ, Froissart M, Navis G, et al. Equations to estimate creatinine excretion rate: the CKD epidemiology collaboration. Clin J Am Soc Nephrol. 2011;6:184-91. [PMID: 20966119]

Levey AS, Fan L, Eckfeldt JH, Inker LA. Cystatin C for glomerular filtration rate estimation: coming of age [Editorial]. Clin Chem. 2014;60:916-9. [PMID: 24871681]

Margulis V, Sagalowsky AI. Assessment of hematuria. Med Clin North Am. 2011;95:153-9. [PMID: 21095418]

Moyer VA; U.S. Preventive Services Task Force. Screening for bladder cancer: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2011;155:246-51. [PMID: 21844550]

Nielsen M, Qaseem A; High Value Care Task Force of the American College of Physicians. Hematuria as a marker of occult urinary tract cancer: advice for high-value care from the American College of Physicians. Ann Intern Med. 2016;164:488-97. [PMID: 26810935]

Subramaniam RM, Suarez-Cuervo C, Wilson RF, Turban S, Zhang A, Sherrod C, et al. Effectiveness of prevention strategies for contrast-induced nephropathy: a systematic review and meta-analysis. Ann Intern Med. 2016;164:406-16. [PMID: 26830221]

Fluids and Electrolytes

Adrogué HJ, Madias NE. Hypernatremia. N Engl J Med. 2000;342:1493-9. [PMID: 10816188]

Agus ZS. Hypomagnesemia. J Am Soc Nephrol. 1999;10:1616-22. [PMID: 10405219]

Ahamed S, Anpalahan M, Savvas S, Gibson S, Torres J, Janus E. Hyponatraemia in older medical patients: implications for falls and adverse outcomes of hospitalisation. Intern Med J. 2014;44:991-7. [PMID: 25039672]

Almond CS, Shin AY, Fortescue EB, Mannix RC, Wypij D, Binstadt BA, et al. Hyponatremia among runners in the Boston Marathon. N Engl J Med. 2005;352:1550-6. [PMID: 15829535]

Felsenfeld AJ, Levine BS. Approach to treatment of hypophosphatemia. Am J Kidney Dis. 2012;60:655-61. [PMID: 22863286]

Greenlee M, Wingo CS, McDonough AA, Youn JH, Kone BC. Narrative review: evolving concepts in potassium homeostasis and hypokalemia. Ann Intern Med. 2009;150:619-25. [PMID: 19414841]

Hoorn EJ, Betjes MG, Weigel J, Zietse R. Hypernatraemia in critically ill patients: too little water and too much salt. Nephrol Dial Transplant. 2008;23:1562-8. [PMID: 18065827]

Huang CL, Kuo E. Mechanism of hypokalemia in magnesium deficiency. J Am Soc Nephrol. 2007;18:2649-52. [PMID: 17804670]

Jain G, Ong S, Warnock DG. Genetic disorders of potassium homeostasis. Semin Nephrol. 2013;33:300-9. [PMID: 23953807]

Mohmand HK, Issa D, Ahmad Z, Cappuccio JD, Kouides RW, Sterns RH. Hypertonic saline for hyponatremia: risk of inadvertent overcorrection. Clin J Am Soc Nephrol. 2007;2:1110-7. [PMID: 17913972]

Moritz ML, Kalantar-Zadeh K, Ayus JC. Ecstasy-associated hyponatremia: why are women at risk? Nephrol Dial Transplant. 2013;28:2206-9. [PMID: 23804804]

Palmer BF. Regulation of potassium homeostasis. Clin J Am Soc Nephrol. 2015;10:1050-60. [PMID: 24721891]

Regolisti G, Cabassi A, Parenti E, Maggiore U, Fiaccadori E. Severe hypomagnesemia during long-term treatment with a proton pump inhibitor. Am J Kidney Dis. 2010;56:168-74. [PMID: 20493607]

Sterns RH, Silver SM. Complications and management of hyponatremia. Curr Opin Nephrol Hypertens. 2016;25:114-9. [PMID: 26735146]

Acid-Base Disorders

Gennari FJ. Pathophysiology of metabolic alkalosis: a new classification based on the centrality of stimulated collecting duct ion transport. Am J Kidney Dis. 2011;58:626-36. [PMID: 21849227]

Kraut JA, Kurtz I. Toxic alcohol ingestions: clinical features, diagnosis, and management. Clin J Am Soc Nephrol. 2008;3:208-25. [PMID: 18045860]

Kraut JA, Madias NE. Metabolic acidosis of CKD: an update. Am J Kidney Dis. 2016;67:307-17. [PMID: 26477665] doi:10.1053/j.ajkd.2015.08.028

Kraut JA, Nagami GT. The serum anion gap in the evaluation of acid-base disorders: what are its limitations and can its effectiveness be improved? Clin J Am Soc Nephrol. 2013;8:2018-24. [PMID: 23833313]

Madias NE. Renal acidification responses to respiratory acid-base disorders. J Nephrol. 2010;23 Suppl 16:S85-91. [PMID: 21170892]

Melcescu E, Phillips J, Moll G, Subauste JS, Koch CA. 11Beta-hydroxylase deficiency and other syndromes of mineralocorticoid excess as a rare cause of endocrine hypertension. Horm Metab Res. 2012;44:867-78. [PMID: 22932914]

Raimondi GA, Gonzalez S, Zaltsman J, Menga G, Adrogué HJ. Acid-base patterns in acute severe asthma. J Asthma. 2013;50:1062-8. [PMID: 23947392]

Rastegar M, Nagami GT. Non-anion gap metabolic acidosis: a clinical approach to evaluation. Am J Kidney Dis. 2017;69:296-301. [PMID: 28029394]

Treger R, Pirouz S, Kamangar N, Corry D. Agreement between central venous and arterial blood gas measurements in the intensive care unit. Clin J Am Soc Nephrol. 2010;5:390-4. [PMID: 20019117]

Vichot AA, Rastegar A. Use of anion gap in the evaluation of a patient with metabolic acidosis. Am J Kidney Dis. 2014;64:653-7. [PMID: 25132207]

Hypertension

ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). JAMA. 2002;288:2981-97. [PMID: 12479763]

Appel LJ, Wright JT Jr, Greene T, Agodoa LY, Astor BC, Bakris GL, et al; AASK Collaborative Research Group. Intensive blood-pressure control in hypertensive chronic kidney disease. N Engl J Med. 2010;363:918-29. [PMID: 20818902]

Braam B, Taler SJ, Rahman M, Fillaus JA, Greco BA, Forman JP, et al. Recognition and management of resistant hypertension. Clin J Am Soc Nephrol. 2017;12:524-535. [PMID: 27895136]

Brook RD, Appel LJ, Rubenfire M, Ogedegbe G, Bisognano JD, Elliott WJ, et al; American Heart Association Professional Education Committee of the Council for High Blood Pressure Research, Council on Cardiovascular and Stroke Nursing, Council on Epidemiology and Prevention, and Council on Nutrition, Physical Activity. Beyond medications and diet: alternative

approaches to lowering blood pressure: a scientific statement from the american heart association. Hypertension. 2013;61:1360-83. [PMID: 23608661]

Eckel RH, Jakicic JM, Ard JD, de Jesus JM, Houston Miller N, Hubbard VS, et al; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2013 AHA/ACC guideline on lifestyle management to reduce cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2014;63:2960-84. [PMID: 24239922]

Fried LF, Emanuele N, Zhang JH, Brophy M, Conner TA, Duckworth W, et al; VA NEPHRON-D Investigators. Combined angiotensin inhibition for the treatment of diabetic nephropathy. N Engl J Med. 2013;369:1892-903. [PMID: 24206457]

Pierdomenico SD, Cuccurullo F. Prognostic value of white-coat and masked hypertension diagnosed by ambulatory monitoring in initially untreated subjects: an updated meta analysis. Am J Hypertens. 2011;24:52-8. [PMID: 20847724]

Qaseem A, Wilt TJ, Rich R, Humphrey LL, Frost J, Forciea MA; Clinical Guidelines Committee of the American College of Physicians and the Commission on Health of the Public and Science of the American Academy of Family Physicians. Pharmacologic treatment of hypertension in adults aged 60 years or older to higher versus lower blood pressure targets: a clinical practice guideline from the American College of Physicians and the American Academy of Family Physicians. Ann Intern Med. 2017;166:430-437. [PMID: 28135725]

Siu AL; U.S. Preventive Services Task Force. Screening for high blood pressure in adults: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2015;163:778-86. [PMID: 26458123]

Stergiou GS, Asayama K, Thijs L, Kollias A, Niiranen TJ, Hozawa A, et al; International Database on HOme blood pressure in relation to Cardiovascular Outcome (IDHOCO) Investigators. Prognosis of white-coat and masked hypertension: International Database of HOme blood pressure in relation to Cardiovascular Outcome. Hypertension. 2014;63:675-82. [PMID: 24420553]

Whelton PK, Carey RM, Aronow WS, Casey DE Jr, Collins KJ, Dennison Himmelfarb C, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2017. [PMID: 29146535]

Yusuf S, Teo KK, Pogue J, Dyal L, Copland I, Schumacher H, et al; ONTARGET Investigators. Telmisartan, ramipril, or both in patients at high risk for vascular events. N Engl J Med. 2008;358:1547-59. [PMID: 18378520]

Chronic Tubulointerstitial Nephritis

François H, Mariette X. Renal involvement in primary Sjögren syndrome. Nat Rev Nephrol. 2016;12:82-93. [PMID: 26568188]

Hutchison CA, Batuman V, Behrens J, Bridoux F, Sirac C, Dispenzieri A, et al; International Kidney and Monoclonal Gammopathy Research Group. The pathogenesis and diagnosis of acute kidney injury in multiple myeloma. Nat Rev Nephrol. 2011;8:43-51. [PMID: 22045243]

Lazarus B, Chen Y, Wilson FP, Sang Y, Chang AR, Coresh J, et al. Proton pump inhibitor use and the risk of chronic kidney disease. JAMA Intern Med. 2016;176:238-46. [PMID: 26752337]

Saeki T, Kawano M. IgG4-related kidney disease. Kidney Int. 2014;85:251-7. [PMID: 24107849]

Shah S, Carter-Monroe N, Atta MG. Granulomatous interstitial nephritis. Clin Kidney J. 2015;8:516-23. [PMID: 26413275]

Shirali AC, Perazella MA. Tubulointerstitial injury associated with chemotherapeutic agents. Adv Chronic Kidney Dis. 2014;21:56-63. [PMID: 24359987]

Stefanovic V, Toncheva D, Polenakovic M. Balkan nephropathy. Clin Nephrol. 2015;83:64-9. [PMID: 25725245]

Glomerular Diseases

Almaani S, Meara A, Rovin BH. Update on lupus nephritis. Clin J Am Soc Nephrol. 2017;12:825-835. [PMID: 27821390]

Fogo AB, Lusco MA, Najafian B, Alpers CE. AJKD Atlas of Renal Pathology: membranoproliferative glomerulonephritis. Am J Kidney Dis. 2015;66:e19-20. [PMID: 26300204]

Geetha D, Specks U, Stone JH, Merkel PA, Seo P, Spiera R, et al; Rituximab for ANCA-Associated Vasculitis Immune Tolerance Network Research Group. Rituximab versus cyclophosphamide for ANCA-associated vasculitis with renal involvement. J Am Soc Nephrol. 2015;26:976-85. [PMID: 25381429]

Glassock RJ. Antiphospholipase A2 receptor autoantibody guided diagnosis and treatment of membranous nephropathy: a new personalized medical approach [Editorial]. Clin J Am Soc Nephrol. 2014;9:1341-3. [PMID: 25035274]

Glassock RJ, Alvarado A, Prosek J, Hebert C, Parikh S, Satoskar A, et al. Staphylococcus-related glomerulonephritis and poststreptococcal glomerulonephritis: why defining "post" is important in understanding and treating infection-related glomerulonephritis. Am J Kidney Dis. 2015;65:826-32. [PMID: 25890425]

Hogan JJ, Markowitz GS, Radhakrishnan J. Drug-induced glomerular disease: immune-mediated injury. Clin J Am Soc Nephrol. 2015;10:1300-10. [PMID: 26092827]

Maas RJ, Deegens JK, Smeets B, Moeller MJ, Wetzels JF. Minimal change disease and idiopathic FSGS: manifestations of the same disease. Nat Rev Nephrol. 2016;12:768-776. [PMID: 27748392]

Magistroni R, D'Agati VD, Appel GB, Kiryluk K. New developments in the genetics, pathogenesis, and therapy of IgA nephropathy. Kidney Int. 2015;88:974-89. [PMID: 26376134]

Markowitz GS, Bomback AS, Perazella MA. Drug-induced glomerular disease: direct cellular injury. Clin J Am Soc Nephrol. 2015;10:1291-9. [PMID: 25862776]

Sethi S, Haas M, Markowitz GS, D'Agati VD, Rennke HG, Jennette JC, et al. Mayo Clinic/Renal Pathology Society Consensus Report on pathologic classification, diagnosis, and reporting of GN. J Am Soc Nephrol. 2016;27:1278-87. [PMID: 26567243]

Kidney Manifestations of Deposition Diseases

Alpers CE, Kowalewska J. Fibrillary glomerulonephritis and immunotactoid glomerulopathy. J Am Soc Nephrol. 2008;19:34-7. [PMID: 18045849]

Bridoux F, Leung N, Hutchison CA, Touchard G, Sethi S, Fermand JP, et al; International Kidney and Monoclonal Gammopathy Research Group. Diagnosis of monoclonal gammopathy of renal significance. Kidney Int. 2015;87:698-711. [PMID: 25607108]

Heher EC, Rennke HG, Laubach JP, Richardson PG. Kidney disease and multiple myeloma. Clin J Am Soc Nephrol. 2013;8:2007-17. [PMID: 23868898]

Rosner MH, Edeani A, Yanagita M, Glezerman IG, Leung N; American Society of Nephrology Onco-Nephrology Forum. Paraprotein-related kidney disease: diagnosing and treating monoclonal gammopathy of renal significance. Clin J Am Soc Nephrol. 2016;11:2280-2287. [PMID: 27526705]

Genetic Disorders and Kidney Disease

Chapman AB, Devuyst O, Eckardt KU, Gansevoort RT, Harris T, Horie S, et al; Conference Participants. Autosomal-dominant polycystic kidney disease (ADPKD): executive summary from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. Kidney Int. 2015;88:17-27. [PMID: 25786098]

Eckardt KU, Alper SL, Antignac C, Bleyer AJ, Chauveau D, Dahan K, et al; Kidney Disease: Improving Global Outcomes. Autosomal dominant tubulointerstitial kidney disease: diagnosis, classification, and management--a KDIGO consensus report. Kidney Int. 2015;88:676-83. [PMID: 25738250]

El Dib R, Gomaa H, Carvalho RP, Camargo SE, Bazan R, Barretti P, et al. Enzyme replacement therapy for Anderson-Fabry disease. Cochrane Database Syst Rev. 2016;7:CD006663. [PMID: 27454104]

Friedman DJ, Pollak MR. Apolipoprotein L1 and kidney disease in African Americans. Trends Endocrinol Metab. 2016;27:204-215. [PMID: 26947522]

Hall G, Gbadegesin RA. Translating genetic findings in hereditary nephrotic syndrome: the missing loops. Am J Physiol Renal Physiol. 2015;309:F24-8. [PMID: 25810439]

Savige J, Storey H, Il Cheong H, Gyung Kang H, Park E, Hilbert P, et al. X-Linked and autosomal recessive alport syndrome: pathogenic variant features and further genotype-phenotype correlations. PLoS One. 2016;11:e0161802. [PMID: 27627812]

Acute Kidney Injury

Durand F, Graupera I, Ginès P, Olson JC, Nadim MK. Pathogenesis of hepatorenal syndrome: implications for therapy. Am J Kidney Dis. 2016;67:318-28. [PMID: 26500178]

Grodin JL, Stevens SR, de Las Fuentes L, Kiernan M, Birati EY, Gupta D, et al. Intensification of medication therapy for cardiorenal syndrome in acute decompensated heart failure. J Card Fail. 2016;22:26-32. [PMID: 26209004]

Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO Clinical Practice Guideline for Acute Kidney Injury. Kidney inter., Suppl. 2012;2: 1-138.

Mehta RL, Cerdá J, Burdmann EA, Tonelli M, Garcia-Garcia G, Jha V, et al. International Society of Nephrology's 0by25 initiative for acute kidney injury (zero preventable deaths by 2025): a human rights case for nephrology. Lancet. 2015;385:2616–43. [PMID: 25777661]

Patel DM, Connor MJ Jr. Intra-abdominal hypertension and abdominal compartment syndrome: an underappreciated cause of acute kidney injury. Adv Chronic Kidney Dis. 2016;23:160–6. [PMID: 27113692]

Pendergraft WF 3rd, Herlitz LC, Thornley-Brown D, Rosner M, Niles JL. Nephrotoxic effects of common and emerging drugs of abuse. Clin J Am Soc Nephrol. 2014;9:1996–2005. [PMID: 25035273]

Raghavan R, Eknoyan G. Acute interstitial nephritis - a reappraisal and update. Clin Nephrol. 2014;82:149–62. [PMID: 25079860]

Wichmann JL, Katzberg RW, Litwin SE, Zwerner PL, De Cecco CN, Vogl TJ, et al. Contrast-induced nephropathy. Circulation. 2015;132:1931–6. [PMID: 26572669]

Wilson FP, Berns JS. Tumor lysis syndrome: new challenges and recent advances. Adv Chronic Kidney Dis. 2014;21:18–26. [PMID: 24359983]

Kidney Stones

Eisner BH, Goldfarb DS, Pareek G. Pharmacologic treatment of kidney stone disease. Urol Clin North Am. 2013;40:21–30. [PMID: 23177632]

Fink HA, Wilt TJ, Eidman KE, Garimella PS, MacDonald R, Rutks IR, et al. Medical management to prevent recurrent nephrolithiasis in adults: a systematic review for an American College of Physicians Clinical Guideline. Ann Intern Med. 2013;158:535–43. [PMID: 23546565]

Shoag J, Tasian GE, Goldfarb DS, Eisner BH. The new epidemiology of nephrolithiasis. Adv Chronic Kidney Dis. 2015;22:273–8. [PMID: 26088071]

Tan JA, Lerma EV. Nephrolithiasis for the primary care physician. Dis Mon. 2015;61:434–41. [PMID: 26362879]

The Kidney in Pregnancy

American College of Obstetricians and Gynecologists. Hypertension in Pregnancy. Report of the American College of Obstetricians and Gynecologists Task Force on Hypertension in Pregnancy. Obstet Gynecol. 2013;122:1122–31. [PMID: 24150027]

Cheung KL, Lafayette RA. Renal physiology of pregnancy. Adv Chronic Kidney Dis. 2013;20:209–14. [PMID: 23928384]

Coscia LA, Constantinescu S, Davison JM, Moritz MJ, Armenti VT. Immunosuppressive drugs and fetal outcome. Best Pract Res Clin Obstet Gynaecol. 2014;28:1174–87. [PMID: 25175414]

Hladunewich MA, Hou S, Odutayo A, Cornelis T, Pierratos A, Goldstein M, et al. Intensive hemodialysis associates with improved pregnancy outcomes: a Canadian and United States cohort comparison. J Am Soc Nephrol. 2014;25:1103–9. [PMID: 24525032]

Kattah AG, Garovic VD. The management of hypertension in pregnancy. Adv Chronic Kidney Dis. 2013;20:229–39. [PMID: 23928387]

Nadeau-Fredette AC, Hladunewich M, Hui D, Keunen J, Chan CT. End-stage renal disease and pregnancy. Adv Chronic Kidney Dis. 2013;20:246–52. [PMID: 23928389]

Vellanki K. Pregnancy in chronic kidney disease. Adv Chronic Kidney Dis. 2013;20:223–8. [PMID: 23928386]

Zhang JJ, Ma XX, Hao L, Liu LJ, Lv JC, Zhang H. A systematic review and meta-analysis of outcomes of pregnancy in CKD and CKD outcomes in pregnancy. Clin J Am Soc Nephrol. 2015;10:1964–78. [PMID: 26487769]

Chronic Kidney Disease

Coresh J, Turin TC, Matsushita K, Sang Y, Ballew SH, Appel LJ, et al. Decline in estimated glomerular filtration rate and subsequent risk of end-stage renal disease and mortality. JAMA. 2014;311:2518–2531. [PMID: 24892770]

Dierickx D, Habermann TM. Post-transplantation lymphoproliferative disorders in adults. N Engl J Med. 2018;378:549–562. [PMID: 29414277]

Grubbs V, Moss AH, Cohen LM, Fischer MJ, Germain MJ, Jassal SV, et al; Dialysis Advisory Group of the American Society of Nephrology. A palliative approach to dialysis care: a patient-centered transition to the end of life. Clin J Am Soc Nephrol. 2014;9:2203–9. [PMID: 25104274]

Kidney Disease: Improving Global Outcomes (KDIGO) Anemia Work Group. KDIGO Clinical Practice Guideline for Anemia in Chronic Kidney Disease. Kidney Int Suppl. 2012;2:279–335. Available at www.kdigo.org.

Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int Suppl. 2013;3:1–150. Available at www.kdigo.org.

Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Update Work Group. KDIGO 2017 clinical practice guideline update for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease–mineral and bone disorder (CKD-MBD). Kidney Int Suppl. 2017;7:1–59. Available at www.kdigo.org.

Kidney Disease: Improving Global Outcomes (KDIGO) Transplant Work Group. KDIGO clinical practice guideline for the care of kidney transplant recipients. Am J Transplant. 2009;9 Suppl 3:S1–155. [PMID: 19845597]

McMahon EJ, Campbell KL, Bauer JD, Mudge DW. Altered dietary salt intake for people with chronic kidney disease. Cochrane Database Syst Rev. 2015:CD010070. [PMID: 25691262]

Mills KT, Chen J, Yang W, Appel LJ, Kusek JW, Alper A, et al; Chronic Renal Insufficiency Cohort (CRIC) Study Investigators. Sodium excretion and the risk of cardiovascular disease in patients with chronic kidney disease. JAMA. 2016;315:2200–10. [PMID: 27218629]

Murphy D, McCulloch CE, Lin F, Banerjee T, Bragg-Gresham JL, Eberhardt MS, et al; Centers for Disease Control and Prevention Chronic Kidney Disease Surveillance Team. Trends in prevalence of chronic kidney disease in the United States. Ann Intern Med. 2016;165:473–481. [PMID: 27479614]

Saunders MR, Cifu A, Vela M. Screening for chronic kidney disease. JAMA. 2015;314:615–6. [PMID: 26262800]

Tangri N, Grams ME, Levey AS, Coresh J, Appel LJ, Astor BC, et al; CKD Prognosis Consortium. Multinational assessment of accuracy of equations for predicting risk of kidney failure: a meta-analysis. JAMA. 2016;315:164–74. [PMID: 26757465]

Whelton PK, Carey RM, Aronow WS, Casey DE Jr, Collins KJ, Dennison Himmelfarb C, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. J Am Coll Cardiol. 2017. [PMID: 29146535]

Xie Y, Bowe B, Li T, Xian H, Balasubramanian S, Al-Aly Z. Proton pump inhibitors and risk of incident CKD and progression to ESRD. J Am Soc Nephrol. 2016;27:3153–3163. [PMID: 27080976]

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CME credits and MOC points are available from the publication date of December 31, 2018, until December 31, 2021. You may submit your answer sheet or enter your answers online at any time during this period.

Directions

*Each of the numbered items is followed by lettered answers. Select the **ONE** lettered answer that is **BEST** in each case.*

Item 1

A 72-year-old man is evaluated for near-syncope and a recent fall. History is significant for hypertension, hyperlipidemia, and coronary artery disease. Medications are hydrochlorothiazide, amlodipine, carvedilol, pravastatin, and aspirin. The hydrochlorothiazide dose was increased from 25 mg to 50 mg 1 month ago.

On physical examination, blood pressure is 164/88 mm Hg sitting and 140/76 mm Hg standing after 3 minutes, and pulse rate is 64/min sitting and 66/min standing; other vital signs are normal. Ecchymosis is noted over the left elbow. The remainder of the examination, including the neurologic examination, is unremarkable.

Laboratory studies:

Creatinine	1.4 mg/dL (123.8 µmol/L); 1 month ago: 1.0 mg/dL (88.4 µmol/L)
Bicarbonate	30 mEq/L (30 mmol/L); 1 month ago: 26 mEq/L (26 mmol/L)
Potassium	3.0 mEq/L (3.0 mmol/L); 1 month ago: 3.8 mEq/L (3.8 mmol/L)
Sodium	132 mEq/L (132 mmol/L); 1 month ago: 136 mEq/L (136 mmol/L)

A 12-lead electrocardiogram shows no changes from previous tracings.

Which of the following is the most appropriate management?

(A) Decrease hydrochlorothiazide dose and obtain ambulatory blood pressure monitoring
(B) Order telemetry and cardiac enzyme testing
(C) Schedule bilateral carotid ultrasonography
(D) Schedule head CT

Item 2

An 81-year-old man is hospitalized for an acute onset of edema in his legs and abdomen. History is significant for chronic back pain, for which he takes daily ibuprofen. He has no other symptoms.

On physical examination, vital signs are normal. There is no rash. Cardiac examination is without extra sounds or murmurs, and the estimated central venous pressure is normal. The lungs are clear on examination. Ascites is noted. There is 3-mm pitting edema of the extremities to the mid thigh.

Laboratory studies:

Albumin	2.1 g/dL (21 g/L)
Creatinine	2.9 mg/dL (256.4 µmol/L)
Electrolytes	Normal
Urinalysis	No blood; 4+ protein
Urine protein-creatinine ratio	7200 mg/g
24-Hour urine output	1.5 L

Doppler ultrasound of the kidneys is unremarkable.

Which of the following is the most appropriate next step in management?

(A) Initiate dialysis
(B) Schedule a kidney biopsy
(C) Start heparin
(D) Start intravenous glucocorticoids

Item 3

H

A 56-year-old man is seen during a routine evaluation for stage G4 chronic kidney disease (CKD). History is also significant for hypertension. Medications are losartan, labetalol, furosemide, and amlodipine. He has no symptoms and remains physically active.

On physical examination, blood pressure is 129/76 mm Hg, and pulse rate is 68/min; other vital signs are normal. The physical examination is otherwise unremarkable.

Laboratory studies:

Hemoglobin	11 g/dL (110 g/L)
Bicarbonate	19 mEq/L (19 mmol/L)
Creatinine	3.1 mg/dL (274 µmol/L)
Phosphorus	5.7 mg/dL (1.8 mmol/L)
Potassium	5.1 mEq/L (5.1 mmol/L)

The addition of which of the following will most likely slow progression of this patient's CKD?

(A) ACE inhibitor
(B) Erythropoiesis-stimulating agent
(C) Phosphate binder
(D) Sodium bicarbonate

Item 4

A 69-year-old woman is evaluated in the emergency department for new-onset dependent edema that began 3 weeks ago. She says it is difficult to walk, and she has gained 4.5 kg (10 lb) of fluid weight. History is significant for obesity and hypertension. Her only medication is lisinopril.

On physical examination, vital signs are normal. BMI is 32. There is no rash. There is 3-mm bilateral dependent edema stopping just below the abdomen; it is equal on both sides. The remainder of the examination is unremarkable.

Laboratory studies:

Albumin	2.1 g/dL (21 g/L)
Creatinine	1.3 mg/dL (114.9 µmol/L)
Urine protein-creatinine ratio	8700 mg/g

Kidney biopsy findings are consistent with a diagnosis of minimal change glomerulopathy with superimposed acute tubular necrosis.

In addition to initiating diuretic therapy, which of the following is the most appropriate treatment?

(A) Cyclosporine
(B) High-dose oral prednisone
(C) Rituximab
(D) No additional treatment

Item 5

A 67-year-old man is seen for an increase in serum creatinine level and an abnormal urinalysis found during the evaluation of monoclonal gammopathy of undetermined significance. His evaluation revealed an M-protein spike of 1.5 g/dL, <10% clonal plasma cells on bone marrow biopsy, and no evidence of anemia, hypercalcemia, or lytic bone lesions on skeletal survey. Immunofixation revealed IgG as the monoclonal type. He has no constitutional symptoms, no other medical problems, and takes no medications.

On physical examination, vital signs are normal. Trace lower extremity edema is noted. The remainder of the examination is unremarkable.

Laboratory studies:

Albumin	3.6 g/dL (36 g/L)
Creatinine	1.6 mg/dL (141.4 µmol/L)
Urinalysis	pH 5.5; 2+ blood; 3+ protein; 5-8 erythrocytes/hpf
Urine albumin-creatinine ratio	400 mg/g

Which of the following is the most appropriate next diagnostic test?

(A) ANCA testing
(B) β_2-Microglobulin levels
(C) Kidney biopsy
(D) Serum free light chains

Item 6

A 31-year old man is evaluated during a follow-up visit for IgA nephropathy found on kidney biopsy 3 months ago, at which time lisinopril was initiated. He is asymptomatic.

Physical examination and vital signs are unremarkable.

Laboratory studies:

	Current	3 Months Ago
Creatinine	1.1 mg/dL (97. 2 µmol/L)	1.0 mg/dL (88.4 µmol/L)
Potassium	4.8 mEq/L (4.8 mmol/L)	4.4 mEq/L (4.4 mmol/L)
Urinalysis	3+ blood; 2+ protein	3+ blood; 3+ protein
Urine protein-creatinine ratio	700 mg/g	1200 mg/g

Which of the following is the most appropriate next step in management?

(A) Add losartan
(B) Add oral glucocorticoid therapy
(C) Start alternating courses of intravenous and oral glucocorticoid therapy
(D) Make no changes to the current medication regimen

Item 7

A 48-year-old woman is evaluated in the emergency department for a 1-day history of hearing voices. History is significant for bipolar disorder. Medications are lithium carbonate and quetiapine.

On physical examination, the patient is disheveled and looks chronically ill. She is alert and oriented but appears anxious. Blood pressure is 138/78 mm Hg, and pulse rate is 80/min without orthostatic changes. There is no edema. The remainder of the examination is normal.

Laboratory studies:

Blood urea nitrogen	6 mg/dL (2.1 mmol/L)
Creatinine	0.9 mg/dL (79.6 µmol/L)
Electrolytes:	
Sodium	126 mEq/L (126 mmol/L)
Potassium	3.5 mEq/L (3.5 mmol/L)
Chloride	94 mEq/L (94 mmol/L)
Bicarbonate	26 mEq/L (26 mmol/L)
Glucose	156 mg/dL (8.7 mmol/L)
Urine sodium	12 mEq/L (12 mmol/L)
Urine osmolality	96 mOsm/kg H_2O

Which of the following is the most likely cause of this patient's hyponatremia?

(A) Hyperglycemia
(B) Nephrogenic diabetes insipidus
(C) Polydipsia
(D) Syndrome of inappropriate antidiuretic hormone secretion
(E) Volume depletion

Item 8

H

A 38-year-old man is evaluated after passing his second kidney stone. History is significant for chronic pancreatitis secondary to a past history of alcohol abuse. He has three to four loose bowel movements each day. He reports no fever, flank pain, or dysuria. There is no family history of kidney disease, hyperparathyroidism, or nephrolithiasis. Current medications are pancreatic enzymes and multivitamins.

Physical examination reveals a thin man. Vital signs and the remainder of the examination are unremarkable.

Laboratory studies:

Calcium	8.5 mg/dL (2.1 mmol/L)
Creatinine	0.7 mg/dL (61.9 µmol/L)
Electrolytes:	
Sodium	137 mEq/L (137 mmol/L)
Potassium	3.5 mEq/L (3.5 mmol/L)
Chloride	104 mEq/L (104 mmol/L)
Bicarbonate	21 mEq/L (21 mmol/L)
Urinalysis	Specific gravity; pH 5.0; negative dipstick; positive for calcium oxalate crystals

In addition to increasing fluid intake, which of the following is the most appropriate management?

(A) Add allopurinol
(B) Add potassium citrate
(C) Add vitamin C
(D) Decrease calcium intake
(E) Increase protein intake

Item 9

H

A 33-year-old man is hospitalized for headache, hypertension, and an elevated serum creatinine level. He has a 10-year

H CONT

history of poorly controlled type 2 diabetes mellitus and hypertension. Medications are insulin glargine, insulin lispro, atorvastatin, amlodipine, and low-dose aspirin.

On physical examination, blood pressure is 145/94 mm Hg; other vital signs are normal. Funduscopic examination reveals nonproliferative diabetic retinopathy. There is 1-mm pitting edema of the lower extremities to the ankles, equal on both sides. Dorsalis pedis and posterior tibial pulses are decreased bilaterally, and the feet are insensate.

Laboratory studies:

Complete blood count	Normal
Albumin	3.3 g/dL (33 g/L)
Creatinine	1.8 mg/dL (159.1 µmol/L)
Hemoglobin A_{1c}	8.1%
Antinuclear antibodies	Negative
Hepatitis B virus antibodies	Negative
Hepatitis C virus antibodies	Negative
HIV antibodies	Negative
Urinalysis	No blood; 3+ protein
Urine protein-creatinine ratio	6700 mg/g

Kidney ultrasound reveals mildly increased echogenicity bilaterally, and both kidneys are enlarged at 12 cm.

In addition to improved glycemic control, which of the following is the most appropriate management?

(A) Add an ACE inhibitor
(B) Obtain ANCA titers
(C) Obtain serum and urine protein electrophoresis
(D) Schedule a kidney biopsy

H

Item 10

A 32-year-old woman is brought to the emergency department by her boyfriend after she was found unresponsive and lying on the ground. She was last seen more than 24 hours ago. History is significant for substance use disorder. She has no other medical problems and takes no prescription drugs.

On physical examination, the patient is intubated and on mechanical ventilation. She is minimally responsive. Blood pressure is 120/75 mm Hg, and pulse rate is 110/min. The remainder of the vital signs and the cardiac, pulmonary, and abdominal examinations are unremarkable. The neurologic examination is nonfocal. Urine output has been <20 mL/h for the past 2 hours.

Laboratory studies:

Calcium	6.9 mg/dL (1.7 mmol/L)
Creatine kinase	40,000 U/L
Creatinine	2.8 mg/dL (247.5 µmol/L)
Electrolytes:	
Sodium	150 mEq/L (150 mmol/L)
Potassium	5.5 mEq/L (5.5 mmol/L)
Chloride	110 mEq/L (110 mmol/L)
Bicarbonate	16 mEq/L (16 mmol/L)
Phosphorous	5.9 mg/dL (1.9 mmol/L)
Fractional excretion of sodium	<1%
Urine myoglobin	300 mg/mL
Urinalysis	Reddish brown urine; pH 5.2; 4+ blood; 2+ protein; granular casts
Toxicology screen	Positive for cocaine and opiates

Which of the following is the most appropriate treatment?

(A) Hemodialysis
(B) Intravenous 0.9% saline
(C) Intravenous 5% dextrose
(D) Intravenous calcium gluconate infusion
(E) Intravenous isotonic sodium bicarbonate in 5% dextrose

Item 11

H

A 68-year-old woman is hospitalized for a non-ST-elevation myocardial infarction. History is significant for hypertension, hyperlipidemia, type 2 diabetes mellitus, and stage G3b chronic kidney disease. Medications on admission are furosemide, irbesartan, atorvastatin, basal and prandial insulin, and low-dose aspirin.

Vital signs and the physical examination are normal.

Transthoracic echocardiogram shows anterolateral hypokinesis with an estimated left ventricular ejection fraction of 35% to 40%.

Coronary angiography is scheduled.

In addition to stopping furosemide, which of the following is the most appropriate measure to prevent acute kidney injury?

(A) Begin intravenous 0.9% saline
(B) Begin oral N-acetylcysteine
(C) Discontinue atorvastatin
(D) Discontinue irbesartan

Item 12

H

A 75-year-old woman is hospitalized for a 1-week history of dizziness, nausea, vomiting, increased urination, and decreased appetite. History is significant for hypertension treated with hydrochlorothiazide. She also takes calcium carbonate for bone health.

On physical examination, blood pressure is 150/85 mm Hg supine and 122/70 mm Hg standing, pulse rate is 78/min supine and 100/min standing, and respiration rate is 18/min. There is no neck vein distention. Cardiac, pulmonary, and abdominal examinations are unremarkable. There is no lower extremity edema.

Laboratory studies:

Hematocrit	30%
Leukocyte count	3000/µL (3.0×10^9/L)
Platelet count	82,000/µL (82×10^9/L)
Calcium	12.8 mg/dL (3.2 mmol/L)
Creatinine	3.7 mg/dL (327.1 µmol/L)
Electrolytes:	
Sodium	132 mEq/L (132 mmol/L)
Potassium	4.9 mEq/L (4.9 mmol/L)
Chloride	115 mEq/L (115 mmol/L)
Bicarbonate	17 mEq/L (17 mmol/L)
Phosphorus	6.2 mg/dL (2.0 mmol/L)
Urine sodium	15 mEq/L (15 mmol/L)
Urinalysis	Specific gravity 1.018; trace protein; few erythrocytes/hpf; occasional leukocytes/hpf; few granular casts; numerous hyaline casts

H CONT.

Which of the following is the most likely cause of this patient's hypercalcemia and acute kidney injury?

(A) Hydrochlorothiazide therapy
(B) Milk alkali syndrome
(C) Multiple myeloma
(D) Primary hyperparathyroidism

Item 13

A 57-year-old man is evaluated during a routine visit. History is significant for hypertension. Medications are hydrochlorothiazide, 25 mg/d, and amlodipine, 5 mg/d.

On physical examination, blood pressure is 135/86 mm Hg, and pulse rate is 70/min; other vital signs are normal. There is 1+ bilateral ankle edema. The remainder of the examination is normal.

Laboratory studies show a serum creatinine level of 1.0 mg/dL (88.4 µmol/L), a serum potassium level of 3.6 mEq/L (3.6 mmol/L), and an estimated glomerular filtration rate >60 mL/min/1.73 m².

Which of the following is the most appropriate treatment?

(A) Add hydralazine
(B) Add losartan
(C) Double the amlodipine dose
(D) Double the hydrochlorothiazide dose

H

Item 14

A 25-year-old woman is evaluated in the emergency department after a suicide attempt. History is significant for major depression. She takes no medication.

On physical examination, temperature is normal, blood pressure is 142/92 mm Hg, pulse rate is 110/min, and respiration rate is 22/min. The patient is obtunded. The remainder of the examination is normal.

Laboratory studies:

Blood urea nitrogen	28 mg/dL (10 mmol/L)
Creatinine	2.2 mg/dL (194.5 µmol/L)
Electrolytes:	
Sodium	136 mEq/L (136 mmol/L)
Potassium	4.0 mEq/L (4.0 mmol/L)
Chloride	100 mEq/L (100 mmol/L)
Bicarbonate	12 mEq/L (12 mmol/L)
Ethanol	Undetected
Glucose	90 mg/dL (5.0 mmol/L)
Osmolality	314 mOsm/kg H_2O
Arterial blood gases:	
pH	7.25
P_{CO_2}	28 mm Hg (3.7 kPa)

Which of the following is the most appropriate management?

(A) Activated charcoal gastric decontamination
(B) Intravenous ethanol
(C) Intravenous hydration, fomepizole, and hemodialysis
(D) Intravenous sodium bicarbonate

Item 15

A 68-year-old woman is evaluated during a follow-up visit for a 3-week history of the nephrotic syndrome. She otherwise has been well and reports no additional symptoms. She has a 50-pack-year history of cigarette smoking with ongoing tobacco use.

On physical examination, vital signs are normal. Pitting edema to the ankles is present. The remainder of the examination is unremarkable.

Laboratory studies:

Albumin	2.9 g/dL (29 g/L)
C3	Normal
C4	Normal
Creatinine	Normal
Rapid plasma reagin	Normal
Antinuclear antibodies	Negative
Hepatitis B antibodies	Negative
Hepatitis C antibodies	Negative
24-Hour urine protein excretion	10,000 mg/24 h

Kidney ultrasound shows normal-appearing kidneys with no evidence of thrombus in the renal veins. Lower extremity Doppler ultrasound shows no evidence of deep venous thrombosis.

Kidney biopsy shows membranous glomerulopathy with negative staining for the phospholipase A2 receptor (PLA2R) on immunofluorescence.

Which of the following is the most appropriate management?

(A) Age- and sex-appropriate cancer screening
(B) Immunosuppression therapy
(C) Prophylactic anticoagulation
(D) Serologic testing for anti-PLA2R antibodies

Item 16

A 42-year-old man is evaluated for a 2-month history of painless gross hematuria. He was diagnosed with chronic kidney disease 4 years ago. His only medication is occasional ibuprofen. He is a recent immigrant from Bosnia.

On physical examination, blood pressure is 150/86 mm Hg. The remainder of the examination is unremarkable.

Laboratory studies:

Hemoglobin	10.5 g/dL (105 g/L)
Creatinine	4.0 mg/dL (353.6 µmol/L)
Urinalysis	1+ protein; numerous nondysmorphic erythrocytes; 5-8 leukocytes/hpf; occasional granular casts
Urine protein-creatinine ratio	900 mg/g

Kidney ultrasound shows echogenic kidneys measuring 8.0 cm and 8.5 cm in length; an irregular bladder wall is noted.

Which of the following is the most appropriate diagnostic test to perform next?

(A) CT urography
(B) Endoscopic urologic evaluation

(C) Kidney biopsy
(D) Urine cultures

H

Item 17

A 46-year-old man is evaluated for increased urination and thirst of 3 days' duration. History is significant for pulmonary sarcoidosis diagnosed 4 months ago; prednisone, 40 mg/d, was initiated and subsequently tapered to 10 mg/d. Initial symptoms were cough and dyspnea on exertion, which had improved with treatment. He is taking no other medications.

Physical examination and vital signs are normal.

Laboratory studies:

Blood urea nitrogen	16 mg/dL (5.7 mmol/L)
Calcium	9.9 mg/dL (2.5 mmol/L)
Creatinine	1.1 mg/dL (97.2 µmol/L)
Electrolytes:	
Sodium	146 mEq/L (146 mmol/L)
Chloride	110 mEq/L (110 mmol/L)
Potassium	3.8 mEq/L (3.8 mmol/L)
Bicarbonate	26 mEq/L (26 mmol/L)
Urine sodium	20 mEq/L (20 mmol/L)
Urine osmolality	115 mOsm/kg H_2O

In addition to increasing the prednisone, which of the following is the most appropriate treatment?

(A) Desmopressin acetate
(B) Hydrochlorothiazide
(C) Intravenous 5% dextrose
(D) Tolvaptan

H

Item 18

A 52-year-old woman was hospitalized 3 days ago for laparoscopic resection of the sigmoid colon secondary to recurrent diverticulitis. Diet has been advanced to a full diet. She has a 20-year history of hypertension, stage G3 chronic kidney disease, and migraine headaches. Medications are amlodipine, heparin, topiramate, and as-needed intravenous morphine.

On physical examination, vital signs are normal. Mild incisional tenderness is present. The remainder of the physical examination is unremarkable.

Laboratory studies:

	On Admission	Today
Creatinine	1.6 mg/dL (141.4 µmol/L)	1.9 mg/dL (168 µmol/L)
Electrolytes:		
Sodium	140 mEq/L (140 mmol/L)	138 mEq/L (138 mmol/L)
Potassium	4.9 mEq/L (4.9 mmol/L)	5.6 mEq/L (5.6 mmol/L)
Chloride	102 mEq/L (102 mmol/L)	110 mEq/L (110 mmol/L)
Bicarbonate	25 mEq/L (25 mmol/L)	20 mEq/L (20 mmol/L)
Glucose	116 mg/dL (6.4 mmol/L)	128 mg/dL (7.1 mmol/L)

Urine output during the past 24 hours is 1400 mL.

Which of the following is the most likely cause of this patient's elevated serum potassium?

(A) Acute kidney injury
(B) Heparin
(C) Hyperglycemia
(D) Metabolic acidosis
(E) Topiramate

Item 19

H

A 40-year-old man is evaluated for a 2-month history of fatigue, nausea, and poor appetite. History is significant for stage G5 chronic kidney disease and hypertension. He has no history of abdominal surgery. Medications are iron, sodium bicarbonate, sevelamer, furosemide, losartan, and amlodipine. He works full time as an on-site supervisor of a team of software engineers. He is on the kidney transplant waiting list.

On physical examination, vital signs are normal. BMI is 25. Conjunctival pallor is noted. There is no pericardial friction rub, jugular venous distention, lung crackles, or asterixis.

Laboratory studies are notable for a hemoglobin level of 8.7 g/dL (87 g/L) and an estimated glomerular filtration rate of 8 mL/min/1.73 m².

Which of the following considerations might favor the choice of peritoneal dialysis as the preferred pretransplant renal replacement therapy for this patient?

(A) Greater autonomy
(B) Improvement in anemia
(C) Improvement in mortality
(D) Lack of infectious complications

Item 20

A 44-year-old man is evaluated during a follow-up visit for treatment of persistently elevated blood pressure. He takes no medications.

Physical examination reveals a well-developed muscular man in no apparent distress. Blood pressure is 165/98 mm Hg, and pulse rate is 70/min; other vital signs are normal. BMI is 26. Jugular venous pressure is normal. Cardiac examination is unremarkable.

Laboratory studies:

Bicarbonate	27 mEq/L (27 mmol/L)
Creatinine	1.3 mg/dL (114.9 µmol/L)
Potassium	4.5 mEq/L (4.5 mmol/L)
Estimated glomerular filtration rate	>60 mL/min/1.73 m²
Urine toxicology screen	Negative

Electrocardiogram reveals normal sinus rhythm; voltage criteria for left ventricular hypertrophy are present.

Which of the following is the most appropriate treatment?

(A) Amlodipine/benazepril combination once daily
(B) Doxazosin and metoprolol, each once daily
(C) Hydralazine three times daily
(D) Telmisartan and ramipril, each once daily

Item 21

An 83-year-old man is evaluated for a 1-week history of poor appetite, myalgia, fatigue, arthralgia, and low-grade fever. He was previously healthy and active. His only medication is acetaminophen as needed.

On physical examination, the patient is afebrile. Blood pressure is 155/95 mm Hg, and pulse rate is 80/min; there are no orthostatic changes. There is trace lower extremity edema. A faint red-blue reticular rash is present over the lower extremities.

Laboratory studies:

Hemoglobin	12 g/dL (120 g/L)
Calcium	9.8 mg/dL (2.5 mmol/L)
Creatinine	Current: 3.1 mg/dL (274 µmol/L) Baseline 2 months ago: 0.9 mg/dL (79.6 µmol/L)
Urinalysis	3+ blood; 2+ protein; 20-30 dysmorphic erythrocytes/hpf; 5-10 leukocytes/hpf

Chest radiograph shows no acute infiltrates. Kidney ultrasound shows no masses or obstruction.

Which of the following is the most likely diagnosis?

(A) ANCA-associated glomerulonephritis
(B) Anti-glomerular basement membrane antibody disease
(C) Minimal change glomerulopathy
(D) Myeloma cast nephropathy
(E) Proliferative lupus nephritis

H

Item 22

A 79-year-old woman is evaluated in the emergency department for worsening confusion over the past 5 days. She also reports lower back pain for the past 3 months. History is significant for hypertension and coronary artery disease with stenting of the left anterior descending artery 2 years ago. Daily medications are metoprolol, hydrochlorothiazide, atorvastatin, low-dose aspirin, and acetaminophen. Her husband confirms that the patient takes all medications as directed.

On physical examination, temperature is normal, blood pressure is 128/76 mm Hg, pulse rate is 72/min, respiration rate is 20/min, and oxygen saturation is 95% on ambient air. BMI is 19. There is no abdominal pain. The patient is weak, confused to time and place, and sleepy but easily arousable. The remainder of the neurologic examination is normal.

Laboratory studies:

Blood urea nitrogen	35 mg/dL (12.5 mmol/L)
Creatinine	1.4 mg/dL (123.8 µmol/L)
Electrolytes:	
Sodium	138 mEq/L (138 mmol/L)
Potassium	4.8 mEq/L (4.8 mmol/L)
Chloride	102 mEq/L (102 mmol/L)
Bicarbonate	14 mEq/L (14 mmol/L)
Lactate	0.7 mEq/L (0.7 mmol/L)
Arterial blood gases:	
pH	7.31
P_{CO_2}	29 mm Hg (3.9 kPa)
Urinalysis	Specific gravity 1.025; no protein, ketones, cells, or crystals

Which of the following is the most likely diagnosis?

(A) D-Lactic acidosis
(B) Propylene glycol toxicity
(C) Pyroglutamic acidosis
(D) Salicylate toxicity

Item 23

An 18-year-old man is evaluated in the ICU for oliguric acute kidney injury. Eighteen hours ago he underwent hepatectomy for a giant fibrolamellar hepatic carcinoma. During the procedure he developed coagulopathy and hepatic bleeding and required resuscitation with eight units of packed red blood cells, multiple units of fresh frozen plasma, and several liters of crystalloid fluids. He is receiving cefepime, gentamicin, propofol, and fentanyl. Urine output has decreased to 10 mL/h since ICU admission 14 hours ago.

On physical examination, the patient is mechanically ventilated. Blood pressure is 120/70 mm Hg, pulse rate is 115/min, and respiration rate is 12/min. Breath sounds are decreased bilaterally. The abdomen is distended and tense with intact midline incision and wall edema. The remainder of the examination is noncontributory.

Laboratory studies:

Hemoglobin	10 g/dL (100 g/L)
Creatine kinase	1250 U/L
Creatinine	1.7 mg/dL (150.3 µmol/L); on admission: 0.9 mg/dL (79.6 µmol/L)
Potassium	5.2 mEq/L (5.2 mmol/L)
Urine sodium	<20 mEq/L (20 mmol/L)
Urinalysis	Specific gravity 1.030; pH 5.5; 4+ blood; trace protein; too numerous to count erythrocytes; few hyaline casts

Kidney ultrasound reveals normal-sized kidneys and no hydronephrosis; a large volume of ascites is noted.

Which of the following is the most appropriate diagnostic test to perform next?

(A) Fractional excretion of sodium
(B) Intra-abdominal pressure measurement
(C) Urine myoglobin levels
(D) Urine stain for eosinophils

Item 24

A 45-year-old man is evaluated for one episode of macroscopic hematuria. He currently does not see blood in his urine. He reports no flank pain and no associated trauma or exertion. He is a nonsmoker and takes no medications.

Physical examination and vital signs are normal.

Laboratory studies show a normal serum creatinine level; urinalysis shows 1+ blood, no protein, 10-15 isomorphic erythrocytes/hpf, 0-2 leukocytes/hpf, no nitrites, and no leukocyte esterase.

Contrast-enhanced CT urogram shows no kidney stones, masses, or cysts.

Which of the following is the most appropriate diagnostic test to perform next?

(A) Cystoscopy
(B) Kidney biopsy
(C) Kidney and renal vein Doppler ultrasonography
(D) Urine cytology

Item 25

A 27-year-old woman is evaluated for a 6-month history of fatigue, arthralgia, and myalgia. She has a history of urinary tract infections. Medications are an oral contraceptive pill and as-needed naproxen for pain.

On physical examination, temperature is 38.2 °C (100.8 °F), blood pressure is 142/90 mm Hg, and pulse rate is 90/min. Cardiac, lung, and abdominal examinations are normal.

Laboratory studies show a serum creatinine level of 1.4 mg/dL (123.8 µmol/L); urinalysis shows 2+ blood, 3+ protein, positive leukocyte esterase, no nitrites, 10-15 erythrocytes/hpf, 5-10 leukocytes/hpf, and no crystals.

Urine microscopy is shown.

Which of the following is the most likely diagnosis?

(A) Bladder cancer
(B) Glomerulonephritis
(C) Tubulointerstitial nephritis
(D) Urinary tract infection

Item 26

H

A 61-year old woman is evaluated in the ICU for acute kidney injury. She was discharged from the hospital 10 days ago following elective cholecystectomy. Seven days ago she was readmitted to the hospital with sepsis. A CT scan of the abdomen with intravenous contrast did not show any abdominal pathology but confirmed pneumonia. She was treated with intravenous fluids, norepinephrine infusion, vancomycin, and cefepime. The norepinephrine was stopped yesterday. History is significant for hypertension and stage G3a chronic kidney disease. Her baseline serum creatinine is 1.4 mg/dL (123.8 µmol/L). On admission the serum creatinine was 1.9 mg/dL (168 µmol/L) and returned to baseline by hospital day 2; it is 3.1 mg/dL (274 µmol/L) today. Outpatient medications are lisinopril and chlorthalidone.

On physical examination, temperature is 37.6 °C (99.7 °F), blood pressure is 140/82 mm Hg, pulse rate is 103/min, and respiration rate is 20/min. Examination of the lungs reveals bilateral crackles. There is 1+ pedal edema of the extremities. The remainder of the physical examination is noncontributory.

Current laboratory studies:

Serum creatinine	3.1 mg/dL (274 µmol/L)
Vancomycin trough	25 mg/L
Fractional excretion of sodium	2.5%
Urinalysis	Specific gravity 1.012; pH 5.5; no blood; 1+ protein; trace leukocyte esterase; no nitrites; no glucose; 2-4 leukocytes/hpf; 5-10 renal tubular epithelial cells/hpf; 5-10 coarse granular casts/hpf

Kidney ultrasound reveals normal-sized kidneys and no hydronephrosis.

Which of the following is the most likely cause of this patient's acute kidney injury?

(A) Cefepime
(B) Intravenous contrast
(C) Omeprazole
(D) Vancomycin

Item 27

H

An 18-year-old woman is brought to the emergency department by friends. She is confused and febrile. Her friends state that she took 3,4-methylenedioxymethamphetamine (ecstasy) at a party and was previously well. There is no other medical history.

On physical examination, the patient is confused and oriented to her name only. Temperature is 38.9 °C (102.0 °F), blood pressure is 148/94 mm Hg, pulse rate is 108/min, respiration rate is 20/min, and oxygen saturation is 96% breathing 2 L/min oxygen by nasal cannula. The remainder of the examination is unremarkable.

Laboratory studies:

Blood urea nitrogen	11 mg/dL (3.9 mmol/L)
Creatinine	0.8 mg/dL (70.7 µmol/L)
Electrolytes:	
Sodium	118 mEq/L (118 mmol/L)
Potassium	3.5 mEq/L (3.5 mmol/L)
Chloride	88 mEq/L (88 mmol/L)
Bicarbonate	21 mEq/L (21 mmol/L)
Glucose	88 mg/dL (4.9 mmol/L)
Urine osmolality	405 mOsm/kg H_2O

Self-Assessment Test

H CONT.

Which of the following is the most appropriate initial treatment?

(A) 0.9% sodium chloride, 100 mL/h
(B) 100-mL bolus of 3% saline
(C) Fluid restriction
(D) Oral urea
(E) Tolvaptan

H

Item 28

A 26-year-old woman is evaluated during a follow up visit for hypertension diagnosed 1 month ago. She is a marathon runner with previously normal blood pressure. Family history is significant for her mother who died of a ruptured cerebral aneurysm at the age of 50 years. Medications are lisinopril and an oral contraceptive.

On physical examination, blood pressure is 146/92 mm Hg, and pulse rate is 59/min. A systolic-diastolic abdominal bruit that lateralizes to the left side is heard. There is no lower extremity edema. The remainder of the examination is unremarkable.

Laboratory studies show a serum creatinine level of 1.4 mg/dL (123.8 µmol/L) (1 month ago: 0.8 mg/dL [70.7 µmol/L]). Urinalysis is normal with no blood, protein, or leukocyte esterase. A pregnancy test is negative.

A 12-lead electrocardiogram is normal.

Which of the following is the most appropriate diagnostic test to perform next?

(A) Plasma aldosterone concentration/plasma renin activity ratio
(B) Plasma fractionated metanephrines
(C) Renal artery imaging
(D) Transthoracic echocardiography

H

Item 29

A 75-year-old man is evaluated in the hospital for an acute anterior ST-elevation myocardial infarction. He was hospitalized for chest pain and shortness of breath 45 minutes ago. History is significant for stage G4 chronic kidney disease (estimated glomerular filtration rate, 24 mL/min/1.73 m^2), hypertension, and peripheral vascular disease. Medications are lisinopril, metoprolol, furosemide, sevelamer, sodium bicarbonate, aspirin, clopidogrel, and unfractionated heparin.

On physical examination, blood pressure is 145/88 mm Hg, pulse rate is 94/min, and respiration rate is 18/min. Cardiopulmonary examination reveals jugular venous distension, a grade 2/6 mitral regurgitation murmur, an S_4 gallop, and end-expiratory bilateral basilar crackles.

Which of the following is the most appropriate immediate management?

(A) Cardiac catheterization
(B) Cardiac magnetic resonance imaging
(C) Emergent dialysis followed by coronary catheterization
(D) Medical management

H

Item 30

A 36-year-old man is evaluated in the emergency department for renal colic. He is in otherwise good health and takes no medications.

Physical examination reveals left costovertebral angle tenderness. The remainder of the examination is normal.

Noncontrast helical CT scan shows an 11-mm stone at the left ureteral pelvic junction and mild left caliectasis.

Analgesics are initiated.

Which of the following is the most appropriate next step in management?

(A) Extracorporeal shock wave lithotripsy
(B) Forced diuresis with intravenous normal saline
(C) Nifedipine
(D) Tamsulosin

Item 31

A 41-year-old woman is evaluated for a 3-month history of increasing nonproductive cough, fatigue, anorexia, and malaise. History is significant for hypertension. Medications are hydrochlorothiazide, lisinopril, and self-prescribed vitamin D and calcium for bone health.

On physical examination, vital signs are normal. Bilateral crackles are heard on pulmonary auscultation. Trace pedal edema is present. The remainder of the examination is unremarkable.

Laboratory studies:

Calcium	11.3 mg/dL (2.8 mmol/L)
Creatinine	1.6 mg/dL (141.4 µmol/L); 1 year ago: 1.0 mg/dL (88.4 µmol/L)
Phosphorus	3.4 mg/dL (1.1 mmol/L)
Parathyroid hormone	12 pg/mL (12 ng/L)
25-Hydroxyvitamin D	43 ng/mL (107.3 nmol/L)
Urinalysis	Specific gravity 1.010; 1+ protein; 5-20 leukocytes/hpf; occasional granular casts
Urine protein-creatinine ratio	400 mg/g
24-Hour urine calcium	Elevated

Chest radiograph shows diffuse reticular opacities. Kidney ultrasound demonstrates nephrocalcinosis.

Which of the following is the most likely cause of this patient's findings?

(A) Hydrochlorothiazide
(B) Primary hyperparathyroidism
(C) Sarcoidosis
(D) Vitamin D intoxication

Item 32

A 25-year-old woman is evaluated in the emergency department for chest pain after a belted motor vehicle accident. She is pregnant at approximately 23 weeks' gestation. She reports no additional symptoms and is otherwise well. Her only medication is a prenatal vitamin.

On physical examination, the patient is afebrile, blood pressure is 102/62 mm Hg, and pulse rate is 80/min. Pain and bruising over the left chest wall are noted. Abdominal examination findings are consistent with changes of pregnancy.

Laboratory studies are significant for a serum sodium level of 132 mEq/L (132 mmol/L).

Which of the following is the most likely cause of this patient's low serum sodium level?

(A) Excessive water intake
(B) Hypotension-induced antidiuretic hormone release
(C) Normal physiologic change in pregnancy
(D) Syndrome of inappropriate antidiuretic hormone secretion

Item 33

A 51-year-old man is evaluated during a routine follow-up visit for stage G4 chronic kidney disease and hypertension. He is asymptomatic. Medications are valsartan, amlodipine, and furosemide.

On physical examination, blood pressure is 140/70 mm Hg, and pulse rate is 70/min. BMI is 32. The remainder of the physical examination is noncontributory.

Laboratory studies:

HDL cholesterol	32 mg/dL (0.83 mmol/L)
LDL cholesterol	119 mg/dL (3.08 mmol/L)
Total cholesterol	208 mg/dL (5.39 mmol/L)
Triglycerides	289 mg/dL (3.27 mmol/L)

Which of the following is the most appropriate management for this patient's dyslipidemia?

(A) Gemfibrozil
(B) Niacin
(C) Omega-3 fish oil
(D) Rosuvastatin

H

Item 34

A 28-year-old man is evaluated in the emergency department for acute right-sided flank pain and blood in the urine. He reports no prior episodes of hematuria or flank pain. He takes no medications.

On physical examination, vital signs are normal. Costovertebral angle tenderness is noted. The abdomen is soft and nontender.

Urinalysis shows 3+ blood, trace protein, and too numerous to count erythrocytes.

A kidney ultrasound shows normal-appearing kidneys, no hydronephrosis, and no nephrolithiasis.

Which of the following is the most appropriate test to perform next?

(A) Contrast MRI
(B) Contrast-enhanced helical abdominal CT
(C) Kidney, ureter, and bladder plain radiography
(D) Noncontrast helical abdominal CT

Item 35

A 26-year-old man is evaluated during a follow-up visit after presenting to an urgent care clinic for back pain 1 week ago. Laboratory studies at that time were significant for a serum creatinine level of 1.4 mg/dL (123.8 µmol/L); other laboratory studies, including urinalysis, were normal. A urine albumin-creatinine ratio obtained in preparation for this visit is 10 mg/g. He is a personal trainer, and his daily exercise regimen includes weightlifting. He states that his back pain has resolved. He occasionally takes ibuprofen; the last use was 1 week ago. He takes no over-the-counter supplements.

On physical examination today, vital signs are normal. BMI is 29. The patient is muscular, without signs of obesity. There is no muscle tenderness.

Which of the following is the most appropriate management?

(A) Avoid all NSAID medications
(B) Measure the serum creatine kinase level
(C) Measure the serum cystatin C level
(D) Schedule a kidney biopsy

Item 36

H

A 42-year-old man is evaluated during a follow-up visit for kidney stones. He had his first stone 4 years ago. Despite increasing his water intake, he has had two additional episodes. Stone analysis has revealed only calcium oxalate. He is in otherwise good health. He has no history of urinary tract infections. There is no family history of kidney disease, hyperparathyroidism, or nephrolithiasis.

The physical examination and vital signs are unremarkable. The patient weighs 80 kg (176 lb).

Laboratory studies:

Calcium	9.6 mg/dL (2.4 mmol/L)
Creatinine	0.9 mg/dL (79.6 µmol/L)
Electrolytes:	
Sodium	138 mEq/L (138 mmol/L)
Potassium	4.1 mEq/L (4.1 mmol/L)
Chloride	105 mEq/L (105 mmol/L)
Bicarbonate	25 mEq/L (25 mmol/L)
Urinalysis	Specific gravity 1.008; pH 5.5; no blood, protein, leukocyte esterase, or nitrites
24-Hour Urine Studies:	
Volume	2945 mL
pH	5.2
Calcium	320 mg/24 h (normal range, <320 mg/24 h)
Citrate	790 mg/24 h (normal range, 300-1100 mg/24 h)
Oxalate	32 mg/24 h (normal range, <40 mg/24 h)
Sodium	140 mEq/24 h (normal range, 40-220 mEq/24 h)
Uric acid	640 mg/24 h (normal range, <800 mg/24 h)

Noncontrast helical CT scan shows a 4-mm stone in the lower pole of the left kidney and a 3-mm stone in the mid pole of the right kidney.

H CONT.

Which of the following is the most appropriate next step to decrease this patient's stone recurrence?

(A) Add allopurinol
(B) Add hydrochlorothiazide
(C) Add potassium citrate
(D) Increase urine volume
(E) Recommend a low calcium diet

Item 37

A 25-year-old man is evaluated during a physical examination for a new job. He is adopted, with no knowledge of his biological parents' medical history. He takes no medications.

On physical examination, blood pressure is 100/60 mm Hg; other vital signs are normal. The remainder of the examination, including cardiac examination, is unremarkable.

Urinalysis shows 2+ blood and no protein.

Kidney ultrasound shows a 15-cm right kidney, a 16-cm left kidney, and multiple cysts bilaterally.

Screening for *PKD* mutations is performed, and the *PKD1* variant associated with autosomal dominant polycystic kidney disease is detected.

Which of the following is the most appropriate next step in management?

(A) Obtain echocardiography
(B) Obtain MR angiography of the brain
(C) Start amlodipine
(D) Start tolvaptan

Item 38

A 44-year-old man is evaluated during a follow-up visit for membranous glomerulopathy, which was diagnosed last week on kidney biopsy. He has no other pertinent personal or family history. His only medication is furosemide.

On physical examination, vital signs are normal. There is trace bilateral lower extremity edema to the ankles. The remainder of the examination is unremarkable.

Laboratory studies performed before kidney biopsy:

Albumin	3.0 g/dL (30 g/L)
Total cholesterol	310 mg/dL (8.0 mmol/L)
Creatinine	0.8 mg/dL (70.7 µmol/L)
Antinuclear antibodies	Negative
Anti-phospholipase A2 receptor antibodies	Titer: 1:80
Hepatitis B surface Ag and Ab antibodies	Negative
Hepatitis C Ab antibodies	Negative
HIV antibodies	Negative
24-Hour urine protein excretion	6500 mg/24 h

Ultrasound of the kidneys shows normal appearance with no evidence of thrombus in the renal veins.

An ACE inhibitor and a statin are initiated.

Which of the following is the most appropriate additional management?

(A) Alternating course of glucocorticoids and alkylating agents
(B) Anti-double-stranded DNA antibody measurement
(C) Cyclosporine
(D) Hepatitis B and hepatitis C viral polymerase chain reaction testing
(E) No additional management at this time

Item 39

A 65-year-old man is seen in the hospital for preoperative evaluation prior to an umbilical hernia repair. Medical history is significant for hypertension, hyperlipidemia, and chronic kidney disease. Medications are metoprolol, amlodipine, furosemide, hydralazine, simvastatin, and aspirin.

On physical examination, average blood pressure is 150/96 mm Hg, and pulse rate is 54/min; other vital signs are normal. BMI is 26. Cardiac examination reveals no murmurs, gallops, or rubs. The lungs are clear. The abdomen is nontender, with a bruit heard over the umbilical region. Lower extremity pulses are diminished. The remainder of the examination is unremarkable.

Laboratory studies:

Creatinine	1.7 mg/dL (150.3 µmol/L); 3 months ago: 1.8 mg/dL (159.1 µmol/L)
HDL cholesterol	46 mg/dL (1.2 mmol/L)
LDL cholesterol	100 mg/dL (2.6 mmol/L)
Total cholesterol	180 mg/dL (4.7 mmol/L)
Urine albumin-creatinine ratio	300 mg/g

Abdominal ultrasound with Doppler reveals 75% ostial right renal artery stenosis; there is no aortic aneurysm.

Which of the following is the most appropriate next step in management?

(A) Begin lisinopril
(B) Obtain renal intra-arterial angiography
(C) Perform percutaneous transluminal renal artery angioplasty and stenting
(D) Perform renal artery surgical revascularization

Item 40

A 68-year-old woman is hospitalized for chest pain. History is significant for stage G3 chronic kidney disease, hypertension, coronary artery disease, and type 2 diabetes mellitus. Medications are aspirin, losartan, basal and prandial insulin, metoprolol, nitroglycerin paste, and unfractionated heparin.

On physical examination, blood pressure is 130/80 mm Hg; other vital signs are normal. S_1 and S_2 are normal. There is no S_3, lung crackles, or leg edema.

Laboratory studies show a serum creatinine level of 1.8 mg/dL (159.1 µmol/L) and an elevated serum troponin level.

H Electrocardiogram shows a 2-mm ST-segment depression in leads I, aVL, and V_4 through V_6.

Cardiac catheterization is planned.

Which of the following is the most appropriate periprocedure management?

(A) Administer furosemide before cardiac catheterization
(B) Administer intravenous isotonic fluids before and after cardiac catheterization
(C) Administer oral sodium bicarbonate before catheterization
(D) Initiate hemodialysis following cardiac catheterization

H Item 41

A 40-year-old woman is evaluated for arthralgia, dry eyes, and dry mouth of several weeks' duration. She has been taking naproxen and acetaminophen daily for about 1 week. She has no pertinent personal or family history.

On physical examination, vital signs are normal. Mucous membranes and conjunctivae are dry. Bilateral parotid gland enlargement is present.

Laboratory studies:

Creatinine	0.9 mg/dL (79.6 µmol/L)
Electrolytes:	
Sodium	138 mEq/L (138 mmol/L)
Potassium	3.1 mEq/L (3.1 mmol/L)
Chloride	118 mEq/L (118 mmol/L)
Bicarbonate	12 mEq/L (12 mmol/L)
Glucose	74 mg/dL (4.1 mmol/L)
Urinalysis	pH 7.0; no blood, protein, glucose, erythrocytes, or leukocytes

Kidney ultrasound shows echogenic normal-sized kidneys.

Which of the following is the most likely cause of the patient's laboratory findings?

(A) Naproxen
(B) Type 1 (hypokalemic distal) renal tubular acidosis
(C) Type 2 (proximal) renal tubular acidosis
(D) Type 4 (hyperkalemic distal) renal tubular acidosis

H Item 42

A 49-year-old man is evaluated in the emergency department for abdominal pain, vomiting, and nausea after binge drinking. History is significant for alcohol abuse, with numerous hospitalizations for intoxications and withdrawal.

On physical examination, temperature is normal, blood pressure is 122/72 mm Hg sitting and 100/62 mm Hg standing, pulse rate is 100/min sitting and 118/min standing, respiration rate is 22/min, and oxygen saturation is 97% breathing ambient air. BMI is 18. Abdominal examination reveals diffuse abdominal tenderness to palpation; there is no rebound tenderness, ascites, or evidence of trauma. Neurologic examination is normal. There is no edema.

Laboratory studies:

Electrolytes:	
Sodium	137 mEq/L (137 mmol/L)
Potassium	3.7 mEq/L (3.7 mmol/L)
Chloride	96 mEq/L (96 mmol/L)
Bicarbonate	10 mEq/L (10 mmol/L)
Ethanol	10 mg/dL (2.2 mmol/L)
Glucose	94 mg/dL (5.2 mmol/L)
Lactate	0.8 mEq/L (0.8 mmol/L)
Arterial blood gases:	
pH	7.26
Pco_2	23 mm Hg (3.1 kPa)
Urinalysis	Specific gravity 1.020; pH 5.5; positive ketones; no blood or cells

Thiamine and B complex vitamin are administered.

Which of the following is the most appropriate treatment?

(A) 0.9% saline
(B) 5% dextrose in 0.9% saline
(C) 5% dextrose in water with 150 mEq (150 mmol) of sodium bicarbonate
(D) Insulin and 5% dextrose in 0.9% saline

Item 43

A 45-year-old man is evaluated during a follow-up visit for membranous glomerulopathy diagnosed 3 weeks ago. He reports persistent lower extremity edema and no weight loss despite adhering to a low-salt diet and taking maximal-dose furosemide. He does not have shortness of breath or abdominal discomfort. Other medications are enalapril and simvastatin.

On physical examination, vital signs are normal. The patient weighs 80 kg (176.4 lb), with a baseline weight of 75 kg (165.3 lb). There is no rash. Cardiac examination is normal, and there is no evidence of jugular venous distention. The lungs are clear on examination. There is pitting edema in the legs bilaterally to just below the patellae.

Laboratory studies:

Albumin	2.9 g/dL (29 g/L)
Blood urea nitrogen	Normal
Creatinine	1.0 mg/dL (88.4 µmol/L)
Electrolytes	Normal
Urinalysis	No blood; 4+ protein
Urine protein-creatinine ratio	6100 mg/g

Doppler ultrasound of the lower extremities performed 3 weeks ago showed no evidence of deep venous thrombosis.

Which of the following is the most appropriate management?

(A) Add metolazone
(B) Change furosemide to bumetanide
(C) Hospitalize for intravenous diuresis
(D) Repeat lower extremity Doppler ultrasonography

Item 44

A 27-year-old woman is evaluated for proteinuria identified on urinalysis performed for a life insurance examination. She

reports no symptoms. History is significant for premature birth, a 2-year history of hypertriglyceridemia and prediabetes, and a 5-year history of obesity. The remainder of her medical history is unremarkable. Her only medication is gemfibrozil.

On physical examination, vital signs are normal. BMI is 37. The remainder of the examination is unremarkable.

Laboratory studies:

Albumin	3.8 g/dL (38 g/L)
Creatinine	1.0 mg/dL (88.4 µmol/L)
Hemoglobin A_{1c}	6.4%
Urinalysis	No blood; 3+ protein
Urine protein-creatinine ratio	2100 mg/g

Kidney ultrasound shows normal-appearing kidneys with no masses or hydronephrosis.

Which of the following is the most likely diagnosis?

(A) Diabetic nephropathy
(B) Lipoprotein glomerulopathy
(C) Minimal change glomerulopathy
(D) Secondary focal segmental glomerulosclerosis

Item 45

A 38-year-old woman is evaluated during a follow-up visit for primary membranous glomerulopathy. Diagnosis was made by kidney biopsy 4 months ago, and she was found to be positive for anti-phospholipase A2 receptor (PLA2R) antibodies. Medications are furosemide, losartan, and simvastatin. Recent age- and sex-appropriate cancer screening tests were normal.

On physical examination, vital signs are normal. There is pitting lower extremity edema to the mid shins bilaterally.

Laboratory studies:

Albumin	2.1 g/dL (21 g/L)
Total cholesterol	288 mg/dL (7.5 mmol/L)
Creatinine	1.1 mg/dL (97.2 µmol/L)
Urine protein-creatinine ratio	9135 mg/g

Which of the following complications is this patient at greatest risk for developing?

(A) Gout
(B) Malignancy
(C) Renal cell carcinoma
(D) Venous thromboembolism

Item 46

A 50-year-old man is evaluated for elevated blood pressure measurements despite an increase in his hydrochlorothiazide dose 1 month ago. History is significant for hypertension and hyperlipidemia. Medications are hydrochlorothiazide and atorvastatin.

On physical examination, blood pressure is 150/92 mm Hg, and pulse rate is 69/min. BMI is 30. The remainder of the examination is normal.

Laboratory studies show a serum creatinine level of 1.0 mg/dL (88.4 µmol/L), a serum potassium level of 3.4 mEq/L (3.4 mmol/L), and a urine albumin-creatinine ratio of 550 mg/g.

In addition to weight loss, which of the following is the most appropriate management?

(A) Add amlodipine
(B) Add losartan
(C) Add spironolactone
(D) Schedule a follow-up visit for 3 months

Item 47

A 37-year-old woman is evaluated for a headache lasting 1 day. She is in the third trimester of her first pregnancy. Until now, the pregnancy has been unremarkable, including blood pressure and urine protein measurements. Her only medication is a prenatal vitamin.

On physical examination, blood pressure is 166/115 mm Hg; other vital signs are normal. There is no papilledema. Cardiac examination is normal. On abdominal examination, the patient has a gravid uterus consistent with her stage of pregnancy, and there is no abdominal tenderness.

Laboratory studies:

Hemoglobin	12.3 g/dL (123 g/L)
Platelet count	70,000/µL (70×10^9/L)
Alanine aminotransferase	72 U/L
Aspartate aminotransferase	80 U/L
Bilirubin	Normal
Creatinine	1.4 mg/dL (123.8 µmol/L)
Electrolytes	Normal
Peripheral blood smear	Normal
Urinalysis	2+ protein

Which of the following is the most likely diagnosis?

(A) Chronic hypertension
(B) Eclampsia
(C) Gestational hypertension
(D) HELLP syndrome
(E) Preeclampsia

Item 48

A 29-year-old man is evaluated in the emergency department for a 3-week history of headaches. He reports a painful burning sensation in his toes and feet for the past few years, particularly after he exercises at the gym, and states that he does not sweat as much after exercise compared with his peers. He takes no medications. Family history is notable for the following: His maternal grandfather and maternal granduncle had similar burning sensations in their feet for years and died from strokes in their early 40s; and his mother has occasional burning sensations in her feet as well as corneal dystrophy.

On physical examination, blood pressure is 160/95 mm Hg; other vital signs are normal. Numerous angiokeratomas over the sternal area are present. Reduced pain and temperature sensation in the lower extremities bilaterally is noted.

Laboratory studies show a blood urea nitrogen level of 60 mg/dL (21.4 mmol/L) and a serum creatinine level of 4.1 mg/dL (362.4 µmol/L); urinalysis shows 2+ blood and 3+ protein.

Kidney ultrasound shows increased echogenicity in bilateral kidneys.

Which of the following is the most likely diagnosis?

(A) Fabry disease
(B) Hereditary nephritis
(C) Medullary cystic kidney disease
(D) Tuberous sclerosis complex

H

Item 49

A 58-year-old woman is evaluated in the emergency department for fever and dysuria of 24 hours' duration. History is significant for frequent urinary tract infections. The patient takes no medications.

On physical examination, the patient appears ill. Temperature is 38.3 °C (101.0 °F), blood pressure is 148/84 mm Hg, pulse rate is 98/min, and respiration rate is 18/min. Abdominal examination reveals right costovertebral angle tenderness. The remainder of the examination is unremarkable.

Laboratory studies:

Creatinine	1.1 mg/dL (97.2 µmol/L)
Urinalysis	Specific gravity 1.010; pH 8.0; trace blood; trace protein; 2+ leukocyte esterase; 2+ nitrites; 3-4 erythrocytes/hpf; 10-12 leukocytes/hpf; positive for bacteria

Abdominal radiograph shows a staghorn calculus in the right kidney.

Empiric antibiotic therapy is initiated.

Which of the following is the most appropriate next step in management?

(A) Chronic antibiotic suppression
(B) Potassium citrate administration
(C) Stone removal
(D) Urease inhibitor administration
(E) Urinary acidification

H

Item 50

A 78-year-old woman is evaluated in the emergency department for severe pain in the left hip after a fall. History is significant for end-stage kidney disease as of 18 months ago, hypertension, and peripheral vascular disease. Medications are lisinopril, amlodipine, sevelamer, and epoetin alfa. She is also receiving morphine for the hip pain.

On physical examination, blood pressure is 132/70 mm Hg, and pulse rate is 72/min; other vital signs are normal. The left lower extremity is externally rotated at the hip. Peripheral pulses are diminished. The remainder of the physical examination is noncontributory.

Laboratory studies:

Alkaline phosphatase	78 U/L
Calcium	9.7 mg/dL (2.4 mmol/L)
Phosphorus	4.2 mg/dL (1.4 mmol/L)
Parathyroid hormone	62 pg/mL (62 ng/L)
25-Hydroxyvitamin D	32 ng/mL (80 nmol/L)

Radiographs of the hips show a left hip fracture and calcified arteries.

Which of the following is the most likely diagnosis for the underlying bone disease?

(A) Adynamic bone disease
(B) β_2-Microglobulin-associated amyloidosis
(C) Osteitis fibrosis cystica
(D) Osteomalacia

Item 51

H

A 72-year-old man is hospitalized for a 1-week history of worsening shortness of breath; he also has worsening lower extremity edema despite an increase in his furosemide dose 2 days ago. History is significant for hypertension, stage G3a chronic kidney disease, and heart failure with a preserved ejection fraction. Outpatient medications are amlodipine, lisinopril, furosemide, and low-dose aspirin.

On physical examination, blood pressure is 112/60 mm Hg, and pulse rate is 97/min. BMI is 28. Cardiac examination reveals an elevated jugular venous pressure and an S_4. Breath sounds are diminished at the lung bases. There is 2+ pitting edema of the lower legs.

Laboratory studies:

Blood urea nitrogen	64 mg/dL (22.8 mmol/L); 2 weeks ago, 40 mg/dL (14.3 mmol/L)
Creatinine	2.3 mg/dL (203.3 µmol/L); 2 weeks ago, 1.9 mg/dL (168 µmol/L)
Sodium	130 mEq/L (130 mmol/L); 2 weeks ago, 133 mEq/L (133 mmol/L)
Urinalysis	Specific gravity 1.009; 1+ protein; few hyaline casts

Chest radiograph shows bibasilar effusions and vascular congestion.

Which of the following is the most appropriate treatment?

(A) Add conivaptan
(B) Add dobutamine infusion
(C) Increase furosemide
(D) Start ultrafiltration

Item 52

H

A 62-year-old woman is evaluated for fatigue and weakness. History is significant for stage G4 chronic kidney disease and hypertension. Her only medication is amlodipine.

On physical examination, blood pressure is 135/85 mm Hg; other vital signs are normal. There is no jaundice. Conjunctival rim pallor is noted, and there is no scleral icterus.

Laboratory studies:

Hemoglobin	8.5 g/dL (85 g/L)
Leukocyte count	Normal
Mean corpuscular volume	80 fL
Platelet count	Normal
Reticulocyte count	1% of erythrocytes
Ferritin	30 ng/mL (30 µg/L)
Transferrin saturation	10%
Estimated glomerular filtration rate	18 mL/min/1.73 m²
Stool testing for occult blood	Negative

Colonoscopy performed at age 60 years was normal.

H CONT.

Which of the following is the most appropriate treatment?

(A) Blood transfusion
(B) Bone marrow biopsy
(C) Erythropoietin-stimulating agent
(D) Iron supplementation

H

Item 53

A 45-year-old woman is evaluated for the recent onset of resistant hypertension. During her last visit, chlorthalidone was added to her medication regimen. She reports no symptoms, and review of the systems is otherwise unremarkable. Current medications are metoprolol, amlodipine, hydralazine, and chlorthalidone.

On physical examination, blood pressure is 160/96 mm Hg, and pulse rate is 65/min; other vital signs are normal. BMI is 24. There is no proptosis. The thyroid gland is not enlarged. The remainder of the examination is unremarkable.

Laboratory studies:

Bicarbonate	34 mEq/L (34 mmol/L)
Creatinine	0.8 mg/dL (70.7 µmol/L)
Potassium	2.9 mEq/L (2.9 mmol/L)
Urine albumin-creatinine ratio	10 mg/g

Which of the following is the most appropriate diagnostic test to perform next?

(A) Kidney ultrasonography with Doppler
(B) Plasma aldosterone concentration/plasma renin activity ratio
(C) Plasma fractionated metanephrines
(D) Polysomnography

H

Item 54

A 28-year-old woman is evaluated in the emergency department for muscle cramps and weakness. She notes a weight loss of 15 kg (33 lb) over the past 3 months; baseline weight was 115 kg (254 lb). She reports no abdominal pain or diarrhea. She has a 1-year history of type 2 diabetes mellitus, for which she takes metformin.

On physical examination, temperature is normal, blood pressure is 122/72 mm Hg, pulse rate is 100/min, and respiration rate is 18/min. BMI is 36. Muscle strength of the lower and upper extremities is 4/5. Other than weakness, neurologic examination is normal.

Laboratory studies:

Electrolytes:	
Sodium	138 mEq/L (138 mmol/L)
Potassium	2.4 mEq/L (2.4 mmol/L)
Chloride	92 mEq/L (92 mmol/L)
Bicarbonate	34 mEq/L (34 mmol/L)
Arterial blood gases:	
pH	7.50
PCO_2	45 mm Hg (6.0 kPa)
Urine sodium	40 mEq/L (40 mmol/L)
Urine potassium	60 mEq/L (60 mmol/L)
Urine chloride	5 mEq/L (5 mmol/L)

Which of the following is the most likely diagnosis?

(A) Cushing syndrome
(B) Gitelman syndrome
(C) Primary hyperaldosteronism
(D) Surreptitious vomiting

Item 55

H

A 64-year-old man is evaluated for a 2-month history of increasing fatigue and bilateral swelling of the submandibular region. History is significant for autoimmune pancreatitis treated with prednisone 2 years ago, hypertension, and allergic rhinitis. Medications are losartan and fluticasone propionate.

On physical examination, blood pressure is 148/84 mm Hg, and pulse rate is 78/min. There is no rash. Head and neck examination reveals bilateral submandibular gland swelling. Trace edema of the ankles is present. The remainder of the examination is normal.

Laboratory studies:

Hemoglobin	12 g/dL (120 g/L)
Leukocyte count	10,000/µL (10×10^9/L); 33% eosinophils
Platelet count	180,000/µL (180×10^9/L)
C3	65 mg/dL (650 mg/L)
C4	7 mg/dL (70 mg/L)
Creatinine	3.1 mg/dL (274 µmol/L); 6 months ago: 1.8 mg/dL (159.1 µmol/L)
IgG	2600 mg/dL (26 g/L)
IgE	500 U/mL (500 kU/L)
Antinuclear antibodies	1:640
Urinalysis	Specific gravity 1.010; trace protein; 6-10 leukocytes/hpf

Kidney ultrasound demonstrates bilateral markedly enlarged kidneys measuring 15 cm in size with hyperechoic cortex and peripheral cortical nodules.

Which of the following is the most likely diagnosis?

(A) IgG4-related disease
(B) Lupus nephritis
(C) Sarcoidosis
(D) Sjögren syndrome

Item 56

H

A 70-year-old man is evaluated for new-onset swelling and fatigue for several weeks' duration, as well as right knee pain occurring during the same time period. History is significant for stage G3a chronic kidney disease and knee osteoarthritis. Medications are lisinopril and over-the-counter naproxen.

On physical examination, blood pressure is 150/80 mm Hg, and pulse rate is 70/min; other vital signs are normal. BMI is 30. There are no lung crackles or jugular venous distension. The bladder is not palpable. There is no abdominal bruit. Examination of the right knee reveals crepitus and

pain at extremes of flexion and extension. There is 1+ pedal edema.

Laboratory studies:

Bicarbonate	23 mEq/L (23 mmol/L)
Creatinine	2.4 mg/dL (212.2 µmol/L); baseline, 1.8 mg/dL (159.1 µmol/L)
Potassium	5.6 mEq/L (5.6 mmol/L)
Urinalysis	No blood; trace protein

Which of the following is the most appropriate management?

(A) Discontinue naproxen
(B) Obtain CT angiography of the renal arteries
(C) Obtain kidney biopsy
(D) Start furosemide

Item 57

A 40-year-old man is evaluated during a follow-up visit for a kidney transplant he received 2 years ago. History is also significant for hypertension. Medications are tacrolimus, mycophenolate mofetil, prednisone, and nifedipine.

On physical examination, blood pressure is 150/95 mm Hg; other vital signs are normal. BMI is 26. The cardiovascular and pulmonary examinations are normal. The abdomen and renal allograft are nontender to palpation. Trace pedal edema is noted.

Laboratory studies:

Potassium	5.6 mEq/L (5.6 mmol/L)
Sodium	Normal
Estimated glomerular filtration rate	90 mL/min/1.73 m^2

Duplex ultrasound of the kidneys shows no evidence of transplant renal artery stenosis.

Which of the following is the most appropriate treatment?

(A) Chlorthalidone
(B) Fludrocortisone
(C) Sodium polystyrene sulfonate
(D) Spironolactone

Item 58

A 48-year-old woman is evaluated in the emergency department for lower extremity weakness, nausea, and increased somnolence occurring during the past 24 hours. She had constipation for 3 days, for which she drank one bottle of milk of magnesia each night. History is significant for hypertension as well as stage G4 chronic kidney disease secondary to autosomal dominant polycystic kidney disease. Her only medication is lisinopril.

On physical examination, temperature is 36.6 °C (97.9 °F), blood pressure is 94/54 mm Hg, pulse rate is 58/min, respiration rate is 16/min, and oxygen saturation is 92% breathing ambient air. Bilateral flank fullness is present. Deep tendon reflexes are diminished diffusely. Strength in the lower extremities is 3/5.

Laboratory studies:

Calcium	8.0 mg/dL (2 mmol/L)
Creatinine	3.9 mg/dL (344.8 µmol/L)
Electrolytes:	
Sodium	138 mEq/L (138 mmol/L)
Potassium	3.7 mEq/L (3.7 mmol/L)
Chloride	104 mEq/L (104 mmol/L)
Bicarbonate	22 mEq/L (22 mmol/L)
Magnesium	8.1 mg/dL (3.3 mmol/L)
Phosphorous	4.4 mg/dL (1.4 mmol/L)

In addition to administration of 0.9% saline and furosemide, which of the following is the most appropriate treatment?

(A) Hemodialysis
(B) Intravenous calcium
(C) Intravenous potassium
(D) Intravenous sodium bicarbonate
(E) Oral sodium polystyrene sulfonate

Item 59

A 72-year-old man is evaluated in the hospital after developing acute kidney injury 2 days following coronary artery bypass grafting. He is currently on mechanical ventilation and requires vasopressors for hypotension. He underwent coronary angiography 12 hours prior to surgery. The serum creatinine has increased from 0.8 mg/dL (70.7 µmol/L) at baseline to 2.2 mg/dL (194.5 µmol/L), and urine output has decreased to 350 mL/24 h. History is significant for type 2 diabetes mellitus and coronary artery disease. Current medications are intravenous furosemide, insulin, propofol, fentanyl, and norepinephrine.

On physical examination, the patient is intubated and mechanically ventilated. A urinary catheter is in place. Temperature is 37.9 °C (100.2 °F), blood pressure is 98/60 mm Hg, pulse rate is 105/min, respiration rate is 28/min, and oxygen saturation is 96% on 30% FIO_2. There is no rash. Decreased breath sounds are heard in the lung bases. The remainder of the examination is noncontributory.

Which of the following is the most appropriate test to perform next?

(A) Examination of urine sediment
(B) Fractional excretion of sodium
(C) Kidney ultrasonography
(D) Measurement of central venous pressure

Item 60

A 42-year-old woman is evaluated during a routine visit. She recently had her blood pressure measured at her workplace; two measurements were taken, and both were elevated. The patient feels well, and review of systems is unremarkable. Family history is significant for hypertension in her father, mother, and two siblings; stroke in her father; and heart failure in her mother. She takes no medications.

On physical examination, the average of three blood pressure measurements is 128/78 mm Hg. BMI is 30. The remainder of the examination is normal.

Laboratory studies:

Bicarbonate	24 mEq/L (24 mmol/L)
Creatinine	0.9 mg/dL (79.6 µmol/L)
Potassium	4.0 mEq/L (4.0 mmol/L)
Urine albumin-creatinine ratio	10 mg/g

Electrocardiogram reveals normal sinus rhythm and positive voltage criteria for left ventricular hypertrophy.

Which of the following is the most appropriate test to perform next?

(A) 24-Hour ambulatory blood pressure monitoring
(B) Plasma aldosterone concentration/plasma renin activity ratio
(C) Polysomnography
(D) Thyroid-stimulating hormone measurement

Item 61

A 46-year-old man is evaluated during a follow-up visit for recently diagnosed hypertension. Hydrochlorothiazide, 25 mg/d, was initiated 1 month ago. He tries to adhere to a low-sodium, low-fat diet. The patient is black.

On physical examination, the average of three blood pressure measurements is 147/97 mm Hg, and pulse rate is 74/min. The remainder of the examination is normal.

Laboratory studies show a serum creatinine level of 1.2 mg/dL (106.1 µmol/L), a serum potassium level of 3.5 mEq/L (3.5 mmol/L), and a urine albumin-creatinine ratio of 15 mg/g.

Which of the following is the most appropriate next step in management?

(A) Add amlodipine
(B) Add lisinopril
(C) Increase hydrochlorothiazide
(D) Reassess blood pressure in 3 months

Item 62

A 28-year-old woman is evaluated during a follow-up visit for elevated blood pressure measurements during pregnancy. She is at 12 weeks' gestation of her first pregnancy. She feels well, and the pregnancy has been otherwise uncomplicated. She did not have routine medical care before her pregnancy. Family history is significant for hypertension in her father and sister. Her only medication is a prenatal vitamin.

On physical examination, blood pressure is 155/95 mm Hg; other vital signs are normal. Funduscopic, neurologic, and cardiac examinations are normal.

Laboratory studies are normal.

Which of the following is the most likely cause of this patient's elevated blood pressure?

(A) Chronic hypertension
(B) Gestational hypertension
(C) Normal physiologic changes in pregnancy
(D) Preeclampsia

Item 63

A 73-year-old woman is hospitalized for an elevated serum creatinine level that has been unresponsive to intravenous fluids. She was evaluated in the emergency department 2 days ago for weakness, myalgia, arthralgia, and cough and admitted to the hospital. She has no other medical history and takes no medications.

On physical examination, the patient is afebrile. Blood pressure is 155/95 mm Hg, pulse rate is 70/min, and oxygen saturation is 98% breathing 2 L of oxygen per minute by nasal cannula. Cardiac examination is normal, without evidence of jugular venous distention. Dullness to percussion and diminished breath sounds are present at the posterior lung bases bilaterally. There is pitting lower extremity edema.

Laboratory studies:

Hemoglobin	9.9 g/dL (99 g/L)
Creatinine	Baseline 6 months ago: 0.7 mg/dL (61.9 µmol/L) Emergency department: 4.1 mg/dL (362.4 µmol/L) Hospital day 1: 4.3 mg/dL (380.1 µmol/L)
Antinuclear antibodies	Negative
Antimyeloperoxidase antibodies	Positive
Antiproteinase 3 antibodies	Negative
Urinalysis	3+ blood; 2+ protein

Chest radiograph shows diffuse infiltrates at the lung bases bilaterally.

Kidney biopsy shows necrotizing and crescentic glomerulonephritis with linear staining for IgG on immunofluorescence.

Which of the following is the most appropriate diagnostic test to perform in this patient?

(A) Anti-double-stranded DNA antibodies
(B) Anti-glomerular basement membrane antibodies
(C) Anti-phospholipase A2 receptor antibodies
(D) Antihistone antibodies

Item 64

A 24-year-old woman is evaluated during a follow-up visit for elevated blood pressure measurements found on two separate occasions. The measurements were 144/94 mm Hg and 142/92 mm Hg. She states that going to the doctor makes her nervous, so she had her blood pressure measured at the local pharmacy, which was <130/80 mm Hg. Review of systems is otherwise unremarkable. She has no other pertinent personal or family history. She takes no medications.

On physical examination, the average of three blood pressure measurements is 143/93 mm Hg, and pulse rate is 80/min; other vital signs are normal. BMI is 21. The remainder of the examination is normal.

Laboratory studies show a serum creatinine level of 0.8 mg/dL (70.7 µmol/L), and a urine albumin-creatinine ratio is undetectable; pregnancy test results are negative.

Electrocardiogram is normal.

Which of the following is the most appropriate next step in management?

(A) Begin hydrochlorothiazide

(B) Obtain echocardiography

(C) Perform 24-hour ambulatory blood pressure monitoring

(D) Recheck blood pressure in 3 months

H

Item 65

A 79-year-old woman is evaluated for hyperkalemia. She was admitted to the surgical ICU after having an urgent partial colectomy for a ruptured diverticulum with peritonitis. She was treated with intravenous fluids, antibiotics, and vasopressor therapy. Today, postoperative day 1, she is oliguric with urine output <5 mL/h for the past 4 hours. She is now weaned off the vasopressor therapy. History is significant for hypertension and stage G4 chronic kidney disease. Outpatient medications are amlodipine, irbesartan, and furosemide. Current medications are morphine, propofol, cefotaxime, and metronidazole.

On physical examination, the patient is intubated and mechanically ventilated. A urinary catheter is in place. Temperature is 38.9 °C (102.0 °F), blood pressure is 108/70 mm Hg, and pulse rate is 101/min. There is generalized anasarca. The abdomen is distended and quiet.

Laboratory studies:

Creatinine	3.6 mg/dL (318.2 µmol/L); baseline, 2.0 mg/dL (176.8 µmol/L)
Electrolytes:	
Sodium	142 mEq/L (142 mmol/L)
Potassium	7.1 mEq/L (7.1 mmol/L)
Chloride	102 mEq/L (102 mmol/L)
Total bicarbonate	17 mEq/L (17 mmol/L)
Arterial pH	7.25
Urine sediment	Brown granular casts

Electrocardiogram shows peaked T waves with a QRS of 140 ms.

In addition to intravenous calcium, insulin, and dextrose, which of the following is the most appropriate treatment?

(A) Continuous renal replacement therapy

(B) Hemodialysis

(C) Intravenous furosemide

(D) Sodium bicarbonate

(E) Sodium polystyrene sulfonate enema

H

Item 66

A 55-year-old man is evaluated for a 4-month history of persistent hyperkalemia. He also has long-standing type 2 diabetes mellitus complicated by retinopathy and nephropathy. Medications are basal and prandial insulin, atorvastatin, and aspirin.

On physical examination, vital signs are normal. Nonproliferative retinopathy is noted on funduscopic examination. The remainder of the physical examination is noncontributory.

Laboratory studies:

Creatinine	1.9 mg/dL (168 µmol/L)
Electrolytes:	
Sodium	138 mEq/L (138 mmol/L)
Potassium	5.1 mEq/L (5.1 mmol/L)
Chloride	112 mEq/L (112 mmol/L)
Bicarbonate	18 mEq/L (18 mmol/L)
Estimated glomerular filtration rate	49 mL/min/1.73 m^2
Urinalysis	pH 5.0; no blood, protein, glucose, erythrocytes, or leukocytes
Calculated urine anion gap	Positive

Which of the following is the most likely cause of the patient's acid-base disorder?

(A) Chronic kidney disease

(B) Type 1 (hypokalemic distal) renal tubular acidosis

(C) Type 2 (proximal) renal tubular acidosis

(D) Type 4 (hyperkalemic distal) renal tubular acidosis

Item 67

A 21-year-old woman is evaluated during a follow-up visit for a 1-year history of systemic lupus erythematosus. At the time of diagnosis, she presented with a malar rash and arthritis, along with positive antinuclear and anti–double-stranded DNA antibodies. Medications are hydroxychloroquine, low-dose prednisone, calcium, and vitamin D. She currently feels well and is asymptomatic.

Vital signs are normal, and the physical examination is unremarkable.

Laboratory studies:

C3	40 mg/dL (400 mg/L)
C4	8 mg/dL (80 mg/L)
Anti–double-stranded DNA antibodies	Positive (titer: 1:320)
Urinalysis	2+ blood; 2+ protein; dysmorphic erythrocytes; no casts
Urine protein-creatinine ratio	600 mg/g

Kidney ultrasound shows kidneys of normal size and echogenicity.

Which of the following is the most appropriate next step in management?

(A) Begin pulse glucocorticoids followed by cyclophosphamide

(B) Begin pulse glucocorticoids followed by mycophenolate mofetil

(C) Increase oral prednisone dose and add mycophenolate mofetil

(D) Schedule a kidney biopsy

Item 68

H

A 45-year-old man is seen for a routine evaluation of his blood pressure. He has gained 1.5 kg (3.3 lb) since his last visit

Self-Assessment Test

H CONT.

3 weeks ago. History is significant for stage G4 chronic kidney disease, hypertension, type 2 diabetes mellitus, and coronary artery disease. Medications are amlodipine, lisinopril, carvedilol, chlorthalidone, basal and prandial insulin, atorvastatin, and low-dose aspirin.

On physical examination, blood pressure is 165/100 mm Hg, pulse rate is 58/min, and respiration rate is 16/min. There is 1+ bilateral leg edema. The remainder of the physical examination is noncontributory.

Laboratory studies:

Blood urea nitrogen	44 mg/dL (15.7 mmol/L)
Creatinine	2.8 mg/dL (247.5 µmol/L)
Potassium	5.4 mEq/L (5.4 mmol/L)
Estimated glomerular filtration rate	26 mL/min/1.73 m^2
Urinalysis	Normal

In addition to maintaining a low sodium diet, which of the following is the most appropriate treatment of this patient's blood pressure?

(A) Add hydralazine
(B) Add losartan
(C) Stop amlodipine; begin spironolactone
(D) Stop chlorthalidone; begin furosemide

H Item 69

A 52-year-old woman is hospitalized for a toe ulcer and foot pain occurring for 1 month. History is significant for stage G4 chronic kidney disease (estimated glomerular filtration rate, 22 mL/min/1.73 m^2) and type 2 diabetes mellitus. Medications are lisinopril, sevelamer, sodium bicarbonate, insulin glargine, and insulin aspart.

On physical examination, vital signs are normal. A foul-smelling toe ulcer is present. Probe-to-bone test is positive.

A plain radiograph shows changes compatible with osteomyelitis. The patient undergoes wound débridement and bone biopsy.

Bone cultures are pending, and empiric antibiotic therapy is to be administered.

Which of the following is the most appropriate venous access strategy?

(A) Arteriovenous graft creation followed by peripherally inserted central catheter placement in opposite arm
(B) Peripherally inserted central catheter in the dominant arm
(C) Peripherally inserted central catheter in the nondominant arm
(D) Tunneled internal jugular central venous catheter

Item 70

A 45-year-old woman is evaluated for elevated blood pressure found for the first time at her previous visit 1 month ago. She has a 7-year history of type 2 diabetes mellitus without retinopathy, as well as hyperlipidemia. Medications are metformin and atorvastatin.

On physical examination, blood pressure is 148/94 mm Hg (confirmed by home ambulatory blood pressure monitoring), and pulse rate is 74/min; other vital signs are normal. BMI is 32. The remainder of the physical examination is unremarkable.

Laboratory studies show a serum creatinine level of 0.9 mg/dL (79.6 µmol/L), a serum potassium level of 3.8 mEq/L (3.8 mmol/L), and a urine albumin-creatinine ratio of 50 mg/g.

The patient is instructed in appropriate lifestyle modifications.

Which of the following is the most appropriate treatment?

(A) Begin amlodipine
(B) Begin chlorthalidone
(C) Begin losartan
(D) Remeasure blood pressure in 2 months

Item 71

A 50-year-old man is evaluated during a routine follow-up visit. History is significant for chronic kidney disease, long-standing hypertension, and HIV infection. His antiretroviral regimen was recently adjusted to a once-a-day dosing, with the integrase inhibitor raltegravir discontinued and dolutegravir started 3 weeks ago. In addition to dolutegravir, current medications are abacavir, lamivudine, and lisinopril.

Physical examination and vital signs are normal.

Laboratory studies:

Serum creatinine	1.5 mg/dL (132.6 µmol/L); baseline, 1.3 mg/dL (114.9 µmol/L)
Urinalysis	No blood, protein, or erythrocytes
Urine albumin-creatinine ratio	100 mg/g (unchanged from baseline)

Which of the following is the most appropriate next step in management?

(A) Discontinue lisinopril
(B) Measure a 24-hour urine creatinine clearance
(C) Reassess the serum creatinine level in 1 week
(D) No further assessment

Item 72 H

A 42-year-old woman is evaluated in the emergency department for right flank pain of 3 hours' duration. History is significant for migraines. There is no family history of kidney stones. Medications are as-needed sumatriptan and daily topiramate.

On physical examination, right costovertebral angle tenderness is present.

Laboratory studies:

Creatinine	0.8 mg/dL (70.7 µmol/L)
Electrolytes:	
Sodium	138 mEq/L (138 mmol/L)
Potassium	3.5 mEq/L (3.5 mmol/L)
Chloride	104 mEq/L (104 mmol/L)
Bicarbonate	21 mEq/L (21 mmol/L)
Urinalysis	Specific gravity 1.005; pH 6.5; 1+ blood; negative leukocyte esterase; negative nitrites; 20-30 erythrocytes/hpf; 1-3 leukocytes/hpf; amorphous crystals

H CONT.

Noncontrast helical CT scan shows a 5-mm stone in the right proximal ureter.

Which of the following is the most likely composition of this patient's kidney stone?

(A) Calcium oxalate
(B) Calcium phosphate
(C) Cystine
(D) Struvite
(E) Uric acid

H

Item 73

A 77-year-old man is evaluated for a 2-month history of worsening fatigue, increasing frequency of urination, nocturia, and anorexia. History is significant for hypertension, hypertriglyceridemia, gastroesophageal reflux disease, and depression. He has been taking low-dose aspirin and valsartan for more than 10 years, omeprazole and St. John's wort for 8 months, and fenofibrate for 2 months.

On physical examination, blood pressure is 150/79 mm Hg, and pulse rate is 82/min. The remainder of the examination is unremarkable.

Laboratory studies:

Creatinine	2.8 mg/dL (247.5 µmol/L); 9 months ago: 1.2 mg/dL (106.1 µmol/L)
Urinalysis	Specific gravity 1.008; trace blood; 2+ protein; 3-5 erythrocytes/hpf; 5-7 leukocytes/hpf

Kidney ultrasound shows 9-cm kidneys without hydronephrosis or calculi bilaterally.

Which of the following is the most likely cause of the patient's kidney findings?

(A) Aspirin
(B) Fenofibrate
(C) Omeprazole
(D) St. John's wort

H

Item 74

A 54-year-old man is evaluated in the emergency department for a 5-day history of fever, fatigue, and bleeding gums. He was previously feeling well. He takes no medications.

On physical examination, the patient is pale and thin and appears chronically ill. Temperature is 39.0 °C (102.2 °F), blood pressure is 104/62 mm Hg, pulse rate is 108/min, respiration rate is 22/min, and oxygen saturation is 96% breathing ambient air. BMI is 22. Petechiae are present on the conjunctiva, forearms, and distal legs. Cardiac examination reveals tachycardia. There is no hepatosplenomegaly. There is no edema.

Laboratory studies:

Hemoglobin	8.8 g/dL (88 g/L)
Leukocyte count	111,000/µL (111×10^9/L), 98% blasts
Platelet count	28,000/µL (28×10^9/L)
Creatinine	1.2 mg/dL (106.1 µmol/L)
Electrolytes:	
Sodium	134 mEq/L (134 mmol/L)
Potassium	6.4 mEq/L (6.4 mmol/L)
Chloride	104 mEq/L (104 mmol/L)
Bicarbonate	21 mEq/L (21 mmol/L)

Electrocardiogram reveals sinus tachycardia but is otherwise normal.

Which of the following is the most appropriate next step in management?

(A) Administer intravenous 0.9% saline
(B) Administer intravenous calcium gluconate
(C) Order a plasma potassium measurement
(D) Start inhaled albuterol
(E) Start sodium bicarbonate

Item 75

H

A 65-year-old woman is evaluated for a 3-month history of increasing fatigue. History is significant for stage G4 chronic kidney disease and hypertension. Medications are sodium bicarbonate, sevelamer, furosemide, losartan, and amlodipine.

On physical examination, blood pressure is 120/60 mm Hg, and pulse rate is 75/min; other vital signs are normal. Conjunctival rim pallor is noted.

Laboratory studies:

Hemoglobin	8.5 g/dL (85 g/L)
Mean corpuscular volume	90 fL
Ferritin	600 ng/mL (600 µg/L)
Transferrin saturation	40%
Estimated glomerular filtration rate	25 mL/min/1.73 m²

Stool guaiac testing is negative.

Colonoscopy performed within the past 5 years was normal.

Which of the following is the most appropriate treatment?

(A) Discontinue losartan
(B) Schedule packed red blood cell transfusion
(C) Start an erythropoiesis-stimulating agent
(D) Start intravenous iron

Item 76

H

A 52-year-old woman is evaluated in the emergency department for a 2-day history of lower extremity weakness and nausea. She reports no diarrhea. History is significant for hypertension treated with amlodipine. She has a history of alcohol abuse.

On physical examination, vital signs are normal. On neurologic examination, lower extremity strength is 4/5. The remainder of the examination is unremarkable.

Laboratory studies:

Albumin	3.0 g/dL (30 g/L)
Calcium	8.4 mg/dL (2.1 mmol/L)
Creatinine	0.7 mg/dL (61.9 µmol/L)

H CONT

Electrolytes:	
Sodium	136 mEq/L (136 mmol/L)
Potassium	2.1 mEq/L (2.1 mmol/L)
Chloride	104 mEq/L (104 mmol/L)
Bicarbonate	26 mEq/L (26 mmol/L)
Magnesium	1.4 mg/dL (0.58 mmol/L)
Urine potassium	30 mEq/L (30 mmol/L)

Which of the following is the most likely cause of this patient's hypokalemia?

(A) Hypoalbuminemia
(B) Hypocalcemia
(C) Hypomagnesemia
(D) Poor nutrition

Item 77

A 71-year-old man is evaluated in the hospital for an elevated serum creatinine level. He was hospitalized 2 days ago for a 4-day history of progressive right lower leg cellulitis. History is also significant for type 2 diabetes mellitus with prior episodes of cellulitis. Medications are basal and prandial insulin.

On physical examination, temperature is 38.9 °C (102.0 °F), blood pressure is 150/100 mm Hg, pulse rate is 100/min, and respiration rate is 20/min. A well-defined area of tender erythema and edema is present over the right foot and leg to just below the knee. The remainder of the examination is unremarkable.

Laboratory studies:

Leukocyte count	13,500/µL (13.5×10^9/L)
C3	50 mg/dL (500 mg/L)
C4	12 mg/dL (120 mg/L)
Creatinine	On admission: 2.4 mg/dL (212.2 µmol/L); baseline: 1.1 mg/dL (97.2 µmol/L)
Urinalysis	3+ blood; 3+ protein
Urine protein-creatinine ratio	4100 mg/g

Kidney biopsy shows endocapillary proliferation on light microscopy, co-dominant granular staining for C3 and IgA on immunofluorescence microscopy, and subepithelial hump-like deposits on electron microscopy.

Which of the following is the most likely cause of this patient's kidney disease?

(A) *Staphylococcus aureus*
(B) *Streptococcus agalactiae*
(C) *Streptococcus pneumoniae*
(D) *Streptococcus pyogenes*

Item 78

A 72-year-old woman is evaluated during a routine visit. History is significant for hypertension treated with amlodipine and losartan. She has no other medical problems. She remains physically active and routinely plays tennis and golf.

On physical examination, blood pressure is 142/84 mm Hg, and pulse rate is 72/min; other vital signs are normal. BMI is 24. The remainder of the examination is unremarkable.

Laboratory studies show a serum creatinine level of 0.8 mg/dL (70.7 µmol/L) and a serum potassium level of 4.0 mEq/L (4.0 mmol/L).

According to the target blood pressure goals recommended by the American College of Physicians and the American Academy of Family Physicians, which of the following would be an appropriate management?

(A) Add chlorthalidone
(B) Increase the amlodipine dose
(C) Increase the losartan dose
(D) Make no changes to antihypertensive medications

Item 79

H

A 56-year-old man is evaluated during a follow-up visit for diabetic nephropathy. He has a 15-year history of type 2 diabetes mellitus. Medications are insulin detemir, insulin aspart, lisinopril, furosemide, and atorvastatin.

On physical examination, blood pressure is 129/76 mm Hg; other vital signs are normal. The remainder of the examination is unremarkable.

Laboratory studies:

Calcium	9.5 mg/dL (2.4 mmol/L)
Phosphorus	7.2 mg/dL (2.3 mmol/L)
Intact parathyroid hormone	385 pg/mL (385 ng/L)
25-Hydroxyvitamin D	32 ng/mL (80 nmol/L)
Estimated glomerular filtration rate	25 mL/min/1.73 m^2

Which of the following is the most appropriate treatment?

(A) Aluminum hydroxide
(B) Calcitriol
(C) Cinacalcet
(D) Sevelamer

Item 80

A 38-year-old man is evaluated during a follow-up visit for elevated blood pressure found for the first time during his last visit. He reports back pain of several weeks' duration after an episode of heavy lifting at work. History is also notable for seasonal allergies. He currently takes ibuprofen daily for the back pain and loratadine as needed for allergies.

On physical examination, the patient is well developed and muscular, and in no apparent distress. The average of three blood pressure measurements is 139/84 mm Hg, and pulse rate is 52/min; other vital signs are normal. BMI is 26. The remainder of the examination is normal.

Office electrocardiogram is normal.

In addition to follow-up in 1 month, which of the following is the most appropriate management?

(A) Begin amlodipine
(B) Begin hydrochlorothiazide
(C) Discontinue ibuprofen
(D) Discontinue loratadine

Item 81

A 29-year-old man is hospitalized for lower extremity edema and fatigue that has progressed over the past 6 months. Laboratory studies document kidney failure. History is notable for obesity. He has a remote history of intravenous drug use and a 5-year history of multiple sex partners (men and women). He takes no medications.

On physical examination, the patient is afebrile, and blood pressure is 148/94 mm Hg; other vital signs are normal. BMI is 38. There is no rash. There is pitting edema in the lower extremities to the ankles bilaterally. The remainder of the physical examination is unremarkable.

Laboratory studies:

C3	60 mg/dL (600 mg/L)
C4	7.0 mg/dL (70 mg/L)
Creatinine	2.8 mg/dL (247.5 µmol/L)
Urinalysis	3+ blood; 3+protein
Urine protein-creatinine ratio	2900 mg/g

Kidney biopsy shows membranoproliferative glomerulonephritis on light microscopy, with immunofluorescence microscopy showing 3+ staining for IgG, 1+ staining for IgM, 2+ staining for C1q, and 2+ staining for C3.

Results of which of the following tests will most likely explain this patient's findings?

(A) Genetic mutations in alternative complement pathway proteins
(B) Hepatitis B surface antigen and surface antibodies
(C) Hepatitis C antibodies
(D) HIV antibodies

Item 82

A 50-year-old man is evaluated for worsening right toe pain of 3 days' duration. He went to an urgent clinic 6 months ago for similar pain and was diagnosed with gout and hypertension. He has consumed illegally distilled alcohol (moonshine) for years. He is a native of Illinois, and his occupation history includes farming, tractor mechanic, and the postal service. His only medications are losartan and a 7-day course of ibuprofen for his previous gout attack. He reinitiated ibuprofen 2 days ago.

On physical examination, blood pressure is 148/84 mm Hg. The right great toe is red, swollen, warm, and tender to touch. There are no tophi. The remainder of the examination is unremarkable.

Kidney ultrasound shows echogenic but normal-sized kidneys bilaterally and no calculi.

Laboratory studies:

Creatinine	2.0 mg/dL (176.8 µmol/L)
Urate	9.0 mg/dL (0.53 mmol/L)
Urinalysis	Specific gravity 1.009; pH 5.0; 2+ protein; 3-5 leukocytes/hpf; occasional fine granular and waxy casts
Urine protein-creatinine ratio	1200 mg/g

Which of the following is the most likely diagnosis?

(A) Analgesic nephropathy
(B) Balkan nephropathy
(C) Cadmium nephropathy
(D) Lead nephropathy

Item 83

H

A 24-year-old woman is evaluated for progressive muscle weakness of several months' duration. She provides no pertinent personal or family history and takes no medications.

On physical examination, temperature is normal, blood pressure is 94/58 mm Hg, pulse rate is 98/min, and respiration rate is 16/min. BMI is 19. The remainder of the examination is normal.

Laboratory studies:

Serum electrolytes:	
Sodium	142 mEq/L (142 mmol/L)
Potassium	2.8 mEq/L (2.8 mmol/L)
Chloride	120 mEq/L (120 mmol/L)
Bicarbonate	15 mEq/L (15 mmol/L)
Urine electrolytes:	
Sodium	18 mEq/L (18 mmol/L)
Potassium	8.0 mEq/L (8.0 mmol/L)
Chloride	32 mEq/L (32 mmol/L)
Urinalysis	pH 5.0; no blood or protein

Which of the following is the most likely cause of this patient's metabolic acidosis?

(A) Laxative abuse
(B) Surreptitious vomiting
(C) Type 1 (hypokalemic distal) renal tubular acidosis
(D) Type 4 (hyperkalemic distal) renal tubular acidosis

Item 84

H

A 51-year-old man is evaluated in the hospital for acute kidney injury. He was admitted 14 days ago with sepsis and community-acquired pneumonia requiring mechanical ventilation. He was treated empirically with ceftriaxone and azithromycin; additional medications included omeprazole, insulin, and subcutaneous heparin. On hospital day 3, blood cultures were positive for *Streptococcus pneumoniae*, and ceftriaxone was continued. Hospital course was complicated by the ICU stay, with mechanical ventilation and pneumothorax requiring thoracostomy tube placement. On admission, his serum creatinine level was 1.0 mg/dL (88.4 µmol/L), increasing to 1.9 mg/dL (168 µmol/L) on hospital day 10; omeprazole and ceftriaxone were discontinued, and he was transferred to the floor. Today, hospital day 14, he is oliguric. History is significant for hypertension and diabetes mellitus. Outpatient medications are losartan and metformin.

On hospital day 14, the patient is on 4 L oxygen by nasal cannula. A right-sided thoracostomy tube is in place. Temperature is 36.1 °C (97.0 °F), blood pressure is 145/78 mm Hg, pulse rate is 92/min, and respiration rate is 12/min. There are coarse rhonchi in the left lower lung field. The remainder of the examination is normal.

H CONT.

Current (hospital day 14) laboratory studies:

Creatinine	2.7 mg/dL (238.7 µmol/L)
Fractional excretion of sodium	3%
Urinalysis	2+ blood; 2+ protein; 5-10 erythrocytes/hpf; 5-10 leukocytes/hpf; 3-5 granular casts/hpf
Urine protein-creatinine ratio	1100 mg/g

Kidney ultrasound is normal and without hydronephrosis.

Which of the following is the most appropriate next step in management?

(A) Empiric glucocorticoids
(B) Kidney biopsy
(C) Normal saline fluid bolus
(D) Urinary catheter placement

Item 85

A 30-year-old woman is evaluated because of her family history of kidney disease. Family history is notable for the following: older brother with end-stage kidney disease due to hereditary nephritis diagnosed by biopsy at age 18 years and now with a transplant at age 32 years; 50-year-old maternal uncle with end-stage kidney disease due to hereditary nephritis at age 31 years; mother and maternal grandmother with microscopic hematuria but normal kidney function; and younger brother and older sister without hematuria or proteinuria. The patient is planning for a pregnancy within the next year.

Physical examination and vital signs are normal.

Laboratory studies show a serum creatinine level of 0.7 mg/dL (61.9 µmol/L), and urinalysis shows 2+ blood and trace protein.

Kidney ultrasound shows bilateral kidneys of normal size and echogenicity with no masses or stones.

Which of the following is the most appropriate to perform next?

(A) Audiometry
(B) Genetic counseling
(C) Kidney biopsy
(D) Skin biopsy

H Item 86

A 46-year-old man is evaluated in the emergency department for right flank pain that began 3 hours ago. He describes the pain as sharp and severe with radiation to the right testicle. History is significant for chronic diarrhea from Crohn disease; he has two to three loose bowel movements each day. He reports no nausea, vomiting, or abdominal pain. He has no dysuria.

On physical examination, the patient appears uncomfortable. There is right costovertebral angle tenderness.

Laboratory studies:

Electrolytes:	
Sodium	138 mEq/L (138 mmol/L)
Potassium	3.9 mEq/L (3.9 mmol/L)
Chloride	106 mEq/L (106 mmol/L)
Bicarbonate	21 mEq/L (21 mmol/L)
Urinalysis	Specific gravity 1.025; pH 5.5; moderate blood; no protein, leukocyte esterase, or nitrites

Kidney ultrasound shows a 6-mm stone at the right ureteral pelvic junction.

Which of the following is the most likely composition of this patient's kidney stone?

(A) Calcium oxalate
(B) Calcium phosphate
(C) Cystine
(D) Struvite
(E) Uric acid

Item 87 H

A 54-year-old woman is evaluated in the emergency department for ataxia, confusion, and slurred speech occurring for several days. History is significant for antiphospholipid antibody syndrome with superior mesenteric artery embolus 1 year ago that required resection of a large segment of the small bowel. Her only medication is warfarin. There is no history of over-the-counter medication use.

On physical examination, blood pressure is 106/65 mm Hg, pulse rate is 95/min, and respiration rate is 20/min. The patient is confused, and her speech is slurred. She also has an unsteady, wide-based gait.

Laboratory studies:

Blood urea nitrogen	14 mg/dL (5.0 mmol/L)
Electrolytes:	
Sodium	141 mEq/L (141 mmol/L)
Potassium	3.8 mEq/L (3.8 mmol/L)
Chloride	105 mEq/L (105 mmol/L)
Bicarbonate	16 mEq/L (16 mmol/L)
Glucose	99 mg/dL (5.5 mmol/L)
Lactate	0.8 mEq/L (0.8 mmol/L)
Osmolality	298 mOsm/kg H_2O
Arterial blood gases:	
pH	7.31
P_{CO_2}	33 mm Hg (4.4 kPa)
Urinalysis	No protein, ketones, cells, or crystals

Noncontrast CT of the head is normal.

Which of the following is the most likely diagnosis?

(A) D-Lactic acidosis
(B) Ethylene glycol toxicity
(C) Methanol toxicity
(D) Pyroglutamic acidosis

Item 88

A 27-year-old woman seeks preconception counseling. She anticipates pregnancy within 3 to 6 months. She has a 10-year

history of type 1 diabetes mellitus and a 3-year history of hypertension. Medications are basal and prandial insulin, losartan, and hydrochlorothiazide.

Vital signs include a blood pressure of 110/70 mm Hg and a pulse rate of 70/min. Physical examination findings are normal.

Laboratory studies show a urine albumin-creatinine ratio of 25 mg/g.

Which of the following is the most appropriate next step in management?

(A) Discontinue hydrochlorothiazide
(B) Discontinue losartan
(C) Discontinue losartan; begin lisinopril
(D) No changes until patient is pregnant

H

Item 89

A 50-year-old man is evaluated during a follow-up visit for hypertension. Losartan was started 3 months ago. He is asymptomatic. Family history is notable for his father who was on chronic hemodialysis and died of a ruptured brain aneurysm at the age of 62 years.

On physical examination, blood pressure is 152/96 mm Hg, and pulse rate is 75/min; other vital signs are normal. BMI is 20. The thyroid gland is not enlarged. Abdominal examination reveals bilateral flank fullness and tenderness on deep palpation; the abdomen is otherwise soft and without bruits. The remainder of the examination is unremarkable.

Laboratory studies:

Bicarbonate	26 mEq/L (26 mmol/L)
Creatinine	1.0 mg/dL (88.4 µmol/L)
Potassium	4.7 mEq/L (4.7 mmol/L)
Urinalysis	Trace protein; 10-20 erythrocytes; 0-5 leukocytes

Which of the following is the most appropriate diagnostic test to perform next?

(A) Kidney ultrasonography
(B) Plasma aldosterone concentration/plasma renin activity ratio
(C) Plasma fractionated metanephrines
(D) Thyroid-stimulating hormone

H

Item 90

A 31-year-old woman seeks preconception counseling. She has end-stage kidney disease secondary to focal segmental glomerulosclerosis. She received a haploidentical kidney transplant from her brother 2 years ago. She had an acute rejection episode 18 months ago that was successfully treated with glucocorticoids, and kidney function has been stable since that time. She currently feels well and reports no symptoms. Current medications are mycophenolate mofetil, tacrolimus, and prednisone.

On physical examination, vital signs are normal. The allograft is palpable in the right lower quadrant and is nontender.

Laboratory studies show a serum creatinine level of 1.3 mg/dL (114.9 µmol/L).

Which of the following is the most appropriate management?

(A) Advise against pregnancy
(B) Discontinue mycophenolate mofetil; begin azathioprine
(C) Discontinue tacrolimus; begin cyclosporine
(D) Proceed with pregnancy without further intervention

Item 91

A 54-year-old woman is evaluated for a 4-week history of dyspnea on exertion, malaise, fatigue, and anorexia. History is significant for hypertension, gout, and osteoarthritis. Medications are losartan, hydrochlorothiazide, allopurinol, naproxen, and aspirin.

On physical examination, blood pressure is 148/84 mm Hg, and pulse rate is 98/min; other vital signs are normal. Conjunctivae are pale. There is 2+ edema of the ankles.

Laboratory studies:

Hemoglobin	8.0 g/dL (80 g/L)
Albumin	3.0 g/dL (30 g/L)
Calcium	9.8 mg/dL (2.5 mmol/L)
Creatinine	2.2 mg/dL (194.5 µmol/L); 3 weeks ago: 1.2 mg/dL (106.1 µmol/L)
Total protein	8.4 g/dL (84 g/L)
Urate	7.0 g/dL (0.41 mmol/L)
Urinalysis	1+ protein; 2-5 granular casts/hpf; 1-2 erythrocytes/hpf
Urine protein-creatinine ratio	6100 mg/g

Chest radiograph is normal.

Which of the following is the most likely diagnosis?

(A) Light chain cast nephropathy
(B) NSAID-induced acute tubular injury
(C) Renal sarcoidosis
(D) Uric acid nephropathy

Item 92

A 28-year-old woman is evaluated in the emergency department for hematuria of 12 hours' duration. She also reports upper respiratory infection symptoms for the past 2 days. She does not have dysuria or flank pain and is not currently menstruating. She reports a similar incident during college when she had the flu, but the urine cleared up after a few hours; she also had an episode of red urine after completing a half-marathon last year. She takes no medications.

Physical examination and vital signs are unremarkable.

Laboratory studies:

C3	Normal
C4	Normal
Creatinine	Normal
Urinalysis	4+ blood; 1+ protein; no leukocyte esterase; no nitrites
Pregnancy test	Negative

Noncontrast CT scan of the abdomen shows no renal masses, no evidence of nephrolithiasis, and no hydronephrosis.

Which of the following is the most likely diagnosis?

(A) Acute postinfectious glomerulonephritis
(B) IgA nephropathy
(C) IgA vasculitis
(D) Lupus nephritis

H

Item 93

A 76-year-old man is evaluated in the emergency department for confusion, an unsteady gait, tinnitus, nausea, and vomiting. His family has noticed progressive functional decline over the past 2 weeks. History is significant for osteoarthritis. His only medication is aspirin.

On physical examination, the patient is tachypneic and obtunded. Temperature is normal, blood pressure is 140/68 mm Hg, pulse rate is 96/min, respiration rate is 24/min, and oxygen saturation is 99% breathing ambient air. The neurologic examination is nonfocal.

Laboratory studies:

Electrolytes:	
Sodium	142 mEq/L (142 mmol/L)
Potassium	3.2 mEq/L (3.2 mmol/L)
Chloride	100 mEq/L (100 mmol/L)
Bicarbonate	20 mEq/L (20 mmol/L)
Arterial blood gases:	
pH	7.56
Pco_2	22 mm Hg (2.9 kPa)

Which of the following is the most likely acid-base diagnosis?

(A) Respiratory alkalosis with chronic compensation
(B) Respiratory alkalosis and increased anion gap metabolic acidosis
(C) Respiratory alkalosis and metabolic alkalosis
(D) Respiratory alkalosis, increased anion gap metabolic acidosis, and metabolic alkalosis

H

Item 94

A 65-year-old man is evaluated for a 2-month history of low back pain. The pain is worse with movement, but it does not radiate. He reports associated fatigue and a 4.5-kg (10-lb) weight loss. He has osteoarthritis and gastroesophageal reflux disease. He has been taking ibuprofen without any pain relief. His only other medication is omeprazole.

The physical examination, including vital signs and neurologic examination, is normal.

Laboratory studies:

Hemoglobin	9.2 g/dL (92 g/L)
Creatinine	3.0 mg/dL (265.2 µmol/L)
Urinalysis	Trace protein; no blood, erythrocytes, leukocytes, leukocyte esterase, or nitrites
Urine protein-creatinine ratio	2500 mg/g

Ultrasound reveals normal-sized kidneys with slightly increased echogenicity; no hydronephrosis or abnormalities of the collecting system are seen.

In addition to discontinuing ibuprofen, which of the following is the most appropriate next step in management?

(A) Discontinue omeprazole
(B) Obtain a 24-hour urine protein collection
(C) Obtain a noncontrast helical abdominal CT
(D) Obtain a urine protein electrophoresis

Item 95

A 60-year-old woman is evaluated for fatigue and weakness. She reports no nausea or vomiting. History is significant for hypertension, stage G4 chronic kidney disease, and type 2 diabetes mellitus. Medications are labetalol, amlodipine, insulin glargine, insulin lispro, and sodium bicarbonate.

On physical examination, blood pressure is 140/90 mm Hg; other vital signs are normal. A mature radiocephalic arteriovenous fistula (AVF) with a strong thrill and bruit is noted. There are no lung crackles. Trace pedal edema is present.

Laboratory studies show normal serum bicarbonate and potassium levels, a blood urea nitrogen level of 50 mg/dL (17.8 mmol/L), and an estimated glomerular filtration rate of 18 mL/min/1.73 m^2.

Which of the following is the most appropriate management?

(A) Clinical follow-up in 6 months
(B) Fistulography to evaluate patency of AVF
(C) Hemodialysis
(D) Kidney transplant evaluation

Item 96

H

A 55-year-old woman is evaluated for increasing serum creatinine and oliguria; she has cirrhosis. She was hospitalized 3 days ago for worsening ascites, confusion, and an elevated serum creatinine level of 1.5 mg/dL ([132.6 µmol/L]; baseline, 1.1 mg/dL [97.2 µmol/L]). Her diuretics were held, and lactulose was continued. An abdominal paracentesis was negative for spontaneous bacterial peritonitis. Intravenous albumin was administered at 1 g/kg/d for 2 days, and today her serum creatinine level is 3.0 mg/dL (265.2 µmol/L). Urine output for the previous 24 hours was 300 mL. History is significant for cirrhosis secondary to nonalcoholic steatohepatitis. Outpatient medications are lactulose, spironolactone, furosemide, and propranolol.

On physical examination, the patient is confused. She is afebrile, blood pressure is 100/70 mm Hg (stable since admission), pulse rate is 84/min, and respiration rate is 16/min. Asterixis is noted. The skin and sclera are icteric. The jugular venous pressure is normal. Ascites is present. There is 3+ lower extremity edema. The remainder of the examination is normal.

H
CONT.

Current laboratory studies:

Bicarbonate	18 mEq/L (18 mmol/L)
Creatinine	3.0 mg/dL (265.2 µmol/L)
Potassium	5 mEq/L (5 mmol/L)
Sodium	129 mEq/L (129 mmol/L)
Urine sodium	<10 mEq/L (10 mmol/L)
Urinalysis	Specific gravity 1.025; pH 5.0; trace protein; 2-4 erythrocytes/hpf; 1-3 pigmented granular casts/hpf

Abdominal ultrasound demonstrates ascites, and normal-sized kidneys with no hydronephrosis.

Which of the following is the most appropriate treatment?

(A) Hemodialysis
(B) Isotonic crystalloid
(C) Octreotide and oral midodrine
(D) Transjugular intrahepatic portosystemic shunt

H

Item 97

A 56-year-old woman is evaluated for hypernatremia. She was admitted to the ICU 6 days ago for pyelonephritis and septic shock requiring intubation, administration of fluids, norepinephrine, and cefepime. She developed nonoliguric acute kidney injury. She has been weaned off the norepinephrine, and she has been extubated. Her serum sodium level has increased from 142 mEq/L (142 mmol/L) to 148 mEq/L (148 mmol/L) over the past 72 hours.

Physical examination and vital signs are normal.

Urine output is 2.5 L over the past 24 hours.

Laboratory studies:

Blood urea nitrogen	74 mg/dL (26.4 mmol/L)
Creatinine	2.8 mg/dL (247.5 µmol/L)
Electrolytes:	
Sodium	148 mEq/L (148 mmol/L)
Potassium	3.7 mEq/L (3.7 mmol/L)
Chloride	112 mEq/L (112 mmol/L)
Bicarbonate	26 mEq/L (26 mmol/L)
Glucose	136 mg/dL (7.5 mmol/L)
Urine osmolality	420 mOsm/kg H_2O

Which of the following is the most likely cause of this patient's hypernatremia?

(A) Adrenal insufficiency
(B) Central diabetes insipidus
(C) Glycosuria
(D) Osmotic diuresis

Item 98

A 55-year-old man is evaluated for an increase in his serum creatinine level. History is significant for hypertension treated with lisinopril for 3 years. He reports no changes or additions to his medication regimen during the past year.

On physical examination, the patient is afebrile, blood pressure is 145/92 mm Hg, and pulse rate is 84/min. There is no rash, alopecia, or joint abnormalities. The remainder of the examination is unremarkable.

Laboratory studies:

Complete blood count	Normal
Creatinine	First specimen, 1.3 mg/dL (114.9 µmol/L); repeat specimen, 1.5 mg/dL (132.6 µmol/L); baseline 6 months ago, 0.9 mg/dL (79.6 µmol/L)
Estimated glomerular filtration rate (eGFR), using the Chronic Kidney Disease Epidemiology (CKD-EPI) Collaboration creatinine formula	>60 mL/min/1.73 m²
Urinalysis	Trace protein

Ultrasound reveals normal-sized kidneys with increased echogenicity, and no hydronephrosis or abnormalities of the collecting system are seen.

Which of the following is the most appropriate management?

(A) Discontinue lisinopril
(B) Obtain a 24-hour creatinine clearance
(C) Recalculate the eGFR using the CKD-EPI cystatin C formula
(D) Schedule a kidney biopsy

Item 99

H

An 82-year-old woman is evaluated during a follow-up visit for stage G5 chronic kidney disease. History is also significant for coronary artery bypass graft surgery 10 years ago, peripheral vascular disease, oxygen-dependent COPD, anemia, mild-moderate vascular dementia, and a transient ischemic attack 2 years ago. She has increasing difficulty with activities of daily living and mobility. She has an 80-pack-year history of smoking, having quit 10 years ago. Medications are albuterol, tiotropium, fluticasone-salmeterol inhalers, metoprolol, atorvastatin, iron, and low-dose aspirin. She currently lives in a nursing home.

On physical examination, the patient appears thin and frail. Vital signs include a blood pressure of 108/62 mm Hg, a respiration rate of 22/min, and an oxygen saturation of 92% on 2 L/min oxygen by nasal cannula. BMI is 19. Diminished breath sounds are present throughout the lungs. There is no edema or asterixis.

Laboratory studies:

Blood urea nitrogen	79 mg/dL (28.2 mmol/L)
Creatinine	4.6 mg/dL (406.6 µmol/L)
Potassium	4.6 mEq/L (4.6 mmol/L)
Estimated glomerular filtration rate	9.7 mL/min/1.73 m²

Which of the following is the most appropriate care strategy for this patient?

(A) Creation of an arteriovenous fistula for dialysis access
(B) Discussion of non-dialytic options
(C) Placement of a double-lumen catheter for long-term hemodialysis
(D) Placement of a peritoneal dialysis catheter

Item 100

A 62-year-old man is evaluated during a follow-up visit for difficult-to-control hypertension. He also has chronic kidney disease and hyperlipidemia. Medications are atorvastatin and carvedilol, as well as maximum doses of lisinopril, amlodipine, and hydralazine.

On physical examination, the average of three blood pressure measurements is 152/98 mm Hg, and pulse rate is 65/min. There is 1+ pitting pretibial lower extremity edema. The remainder of the examination is normal.

Laboratory studies:

Creatinine	2.5 mg/dL (221 µmol/L)
Potassium	4.8 mEq/L (4.8 mmol/L)
Estimated glomerular filtration rate	28 mL/min/1.73 m^2
Urine albumin-creatinine ratio	350 mg/g

Which of the following is the most appropriate additional treatment?

(A) Chlorthalidone
(B) Furosemide
(C) Hydrochlorothiazide
(D) Losartan

H

Item 101

A 64-year-old man is evaluated for a 5-day history of increased urination and weakness. He was recently diagnosed with non-small cell lung cancer and started on chemotherapy 10 days ago. Medications are cisplatin, gemcitabine, paclitaxel, bevacizumab, and ondansetron.

Physical examination reveals a chronically ill-appearing man. Blood pressure is 105/72 mm Hg, and pulse rate is 100/min; other vital signs are normal. The remainder of the examination is unremarkable.

Laboratory studies:

Complete blood count	Normal
Calcium	8 mg/dL (2 mmol/L)
Creatinine	2.1 mg/dL (185.6 µmol/L); baseline, 0.9 mg/dL (79.6 µmol/L)
Electrolytes:	
Sodium	132 mEq/L (132 mmol/L)
Potassium	2.8 mEq/L (2.8 mmol/L)
Chloride	105 mEq/L (105 mmol/L)
Bicarbonate	18 mEq/L (18 mmol/L)
Glucose	90 g/dL (5 mmol/L)
Magnesium	1.5 mg/dL (0.62 mmol/L)
Phosphorous	1.9 mg/dL (0.61 mmol/L)
Fractional excretion of sodium	2%
Urinalysis	Specific gravity 1.010; pH 6.0; 1+ protein; 1+ glucose; occasional granular casts

Which of the following is the most likely cause of this patient's acute kidney injury?

(A) Bevacizumab
(B) Cisplatin
(C) Gemcitabine
(D) Paclitaxel

Item 102

A 55-year-old man is evaluated during a routine visit. He was diagnosed with primary focal segmental glomerulosclerosis 2 months ago. History is also significant for hypertension. Medications are furosemide, amlodipine, losartan, and prednisone. He has been instructed on a low-sodium diet.

On physical examination, blood pressure is 136/86 mm Hg, and pulse rate is 70/min; other vital signs are normal. Jugular venous pressure is elevated to 14 cm H_2O. Cardiac examination reveals an S_3 gallop. The lungs are clear to auscultation. There is 1+ pitting pretibial edema bilaterally.

Laboratory studies:

Creatinine	1.6 mg/dL (141.4 µmol/L)
Potassium	4.5 mEq/L (4.5 mmol/L)
Estimated glomerular filtration rate	40 mL/min/1.73 m^2
Urine albumin-creatinine ratio	1000 mg/g

Which of the following is the most appropriate treatment?

(A) Increase the amlodipine dose
(B) Increase the furosemide dose
(C) Initiate treatment with lisinopril
(D) No changes to medication regimen

Item 103

A 55-year-old man is evaluated during a follow-up visit for newly diagnosed chronic kidney disease (CKD). He also has a 10-year history of hypertension treated with losartan.

On physical examination, blood pressure is 135/78 mm Hg. BMI is 32. The remainder of the vital signs and examination is unremarkable.

Laboratory studies:

Bicarbonate	22 mEq/L (22 mmol/L)
Blood urea nitrogen	27 mg/dL (9.6 mmol/L)
Creatinine	2.1 mg/dL (185.6 µmol/L)
Potassium	4.9 mEq/L (4.9 mmol/L)
Estimated glomerular filtration rate	34 mL/min/1.73 m^2
Urinalysis	No blood; 2+ protein

Which of the following additional measurement could best predict this patient's CKD progression?

(A) Serum albumin
(B) Serum calcium
(C) Serum phosphate
(D) Urine albumin-creatinine ratio

Item 104

A 48-year-old woman is evaluated for edema, dyspnea, and proteinuria. She has a 10-year history of rheumatoid arthritis. She was initially treated with NSAIDs, methotrexate, and prednisone. She stopped taking the NSAIDs 6 months ago because of gastritis. Three months ago she began noticing swelling of her legs, and two weeks ago she began experiencing dyspnea when walking. She has never received penicillamine, gold, or a biologic agent. Current medications are methotrexate, prednisone, and omeprazole.

On physical examination, the patient appears chronically ill. Temperature is 37.2 °C (99.0 °F), blood pressure is 158/90 mm Hg, pulse rate is 96/min, and respiration rate is 20/min. Jugular venous pressure is elevated. Cardiac examination reveals a summation gallop. The lungs are clear. Swelling and tenderness at the metacarpophalangeal joints and wrists are noted. There is 3+ lower extremity edema to the knees.

Laboratory studies:

Albumin	2.8 g/dL (28 g/L)
Creatinine	1.1 mg/dL (97.2 µmol/L)
Serum protein electrophoresis	Polyclonal gammopathy
Urinalysis	Specific gravity 1.0120; pH 5.5; no blood; 4+ protein
Urine protein-creatinine ratio	6000 mg/g

Electrocardiogram reveals low voltage, pronounced in the limb leads, but without acute changes.

Which of the following is the most likely cause of this patient's proteinuria?

(A) AA amyloidosis
(B) Focal segmental glomerulosclerosis
(C) Minimal change glomerulopathy
(D) NSAID-associated interstitial nephritis
(E) Proton pump-associated interstitial nephritis

Item 105

A 46-year-old man is evaluated during a follow-up visit for elevated blood pressure. His average blood pressure with home blood pressure monitoring is 126/77 mm Hg. He has no other pertinent medical history and takes no medications.

On physical examination, blood pressure is 128/78 mm Hg; other vital signs are normal. BMI is 28. The remainder of the examination is unremarkable.

Which of the following is the most appropriate next step in management?

(A) Initiate therapy with an angiotensin receptor blocker
(B) Initiate therapy with a thiazide diuretic
(C) Initiate a trial of lifestyle modification
(D) Remeasure blood pressure in 1 year

H Item 106

A 70-year-old man is evaluated for a recent onset of macroscopic hematuria. History is significant for end-stage kidney disease and hypertension. He has been on hemodialysis for 3 years. Urine output is approximately 250 mL/d. Medications are sevelamer, sodium bicarbonate, lisinopril, and amlodipine.

On physical examination, blood pressure is 150/90 mm Hg, and pulse rate is 70/min. Bilateral flank tenderness is noted. There is no abdominal mass.

Laboratory studies show a hemoglobin level of 15 g/dL (150 g/L).

Kidney ultrasound shows several complex cysts and two bilateral solid masses.

Which of the following is the most appropriate management?

(A) Bilateral partial nephrectomy
(B) Bilateral radical nephrectomy
(C) Percutaneous kidney biopsy
(D) Surveillance ultrasonography

Item 107

A 42-year-old man is evaluated for an elevated blood pressure measurement of 136/86 mm Hg found during a routine screening at his workplace. He exercises 5 days a week for 45 minutes and adheres to a low-fat, low-salt diet. Family history is significant for hypertension in his father and mother; his father died of a stroke at the age of 55 years. He takes no medications. The patient is black.

On physical examination, the patient is well developed and muscular. The average of three blood pressure measurements is 126/75 mm Hg, and pulse rate is 52/min. BMI is 24.5. The remainder of the examination is unremarkable.

Which of the following is the most appropriate management?

(A) Amlodipine
(B) Annual blood pressure screening
(C) Blood pressure screening in 3 months
(D) Hydrochlorothiazide

Item 108

A 62-year-old woman is evaluated during a follow-up visit for stage G5 chronic kidney disease. She is not a transplant candidate. She has opted for hemodialysis for her eventual dialysis modality; an arteriovenous fistula was created 6 months ago. She is active, has a fair appetite, and is sleeping well. She reports no nausea or vomiting. History is also significant for hypertension and secondary hyperparathyroidism. Medications are furosemide, amlodipine, epoetin alfa, sevelamer, calcitriol, and sodium bicarbonate.

On physical examination, blood pressure is 144/85 mm Hg; other vital signs are normal. The left upper extremity arteriovenous fistula appears functioning. There is no asterixis. There is 2+ lower extremity edema.

Laboratory studies:

Bicarbonate	21 mEq/L (21 mmol/L)
Blood urea nitrogen	89 mg/dL (31.7 mmol/L)
Creatinine	4.8 mg/dL (424.3 µmol/L)
Potassium	4.8 mEq/L (4.8 mmol/L)
Estimated glomerular filtration rate	9.7 mL/min/1.73 m²

Which of the following is the most appropriate management for this patient?

(A) Delay dialysis until uremic symptoms occur
(B) Discontinue diuretics
(C) Refer for palliative care
(D) Start dialysis now

Answers and Critiques

Item 1 Answer: A

Educational Objective: Use ambulatory blood pressure monitoring to evaluate antihypertensive treatment.

The most appropriate management is to decrease the hydrochlorothiazide dose and obtain ambulatory blood pressure monitoring (ABPM). The patient presents with orthostatic hypotension that likely resulted in his near-syncope and fall due to a recent increase in the dose of a thiazide diuretic. The maximal daily recommended dose for hydrochlorothiazide is 25 mg for the treatment of hypertension; side effects increase beyond this dose with little further antihypertensive effect. Increasing the daily dose to 50 mg likely resulted in an orthostatic drop in his blood pressure, and his pulse rate did not change because he is on a β-blocker. Additional evidence of overtreatment includes an increase in his serum creatinine level, hyponatremia, hypokalemia, and the development of metabolic alkalosis. The appropriate next step is to lower his hydrochlorothiazide dose and obtain ABPM, which is valuable in providing information supplementary to office blood pressure measurements in clinical situations such as hypotensive symptoms from antihypertensive medication treatment. ABPM may reveal that the patient has an element of white coat hypertension and that his blood pressures at home are well controlled on his previous lower dose of hydrochlorothiazide.

Bilateral carotid ultrasonography is not the appropriate next step for this patient. Although he has evidence of atherosclerotic vascular disease and may have carotid stenosis, it is an unlikely cause of near-syncope and falling. The dizziness and fall were most likely the result of orthostasis.

In a study of 1920 hospitalized patients with syncope, the most commonly ordered tests, in addition to electrocardiography, were telemetry (95%), cardiac enzymes (95%), and CT of the head (63%). These tests, along with echocardiography, carotid ultrasonography, and electroencephalography, aided diagnosis in <2% of patients and altered management decisions in <5% of patients. The most valuable diagnostic and management test was postural blood pressure. The American College of Physicians does not recommend brain imaging, with either CT or MRI, in the evaluation of a patient with simple syncope and a normal neurologic examination.

KEY POINT

- Ambulatory blood pressure monitoring provides valuable information supplementary to office blood pressure measurements in the evaluation of antihypertensive treatment.

Bibliography

Di Stefano C, Milazzo V, Totaro S, Sobrero G, Ravera A, Milan A, et al. Orthostatic hypotension in a cohort of hypertensive patients referring to a hypertension clinic. J Hum Hypertens. 2015;29:599-603. [PMID: 25631221]

Item 2 Answer: B

Educational Objective: Diagnose glomerulopathy with a kidney biopsy.

A kidney biopsy is the most appropriate next step for this patient who has the nephrotic syndrome most likely caused by minimal change glomerulopathy (MCG). MCG is the cause of the nephrotic syndrome in 10% to 15% of adults, with a significantly higher incidence in elderly patients (≥65 years of age) and very elderly patients (≥80 years of age). Most cases are idiopathic, but secondary causes must be considered in adults, including medications such as NSAIDs. Adults with MCG present with acute kidney injury (AKI) in up to 25% of cases. Factors associated with AKI include older age, male sex, hypertension, low serum albumin levels, and heavier proteinuria. The differential diagnosis for the nephrotic syndrome with AKI is limited to only a few entities: MCG with acute tubular necrosis or allergic interstitial nephritis, membranous glomerulopathy with bilateral renal vein thrombosis, amyloidosis with cast nephropathy, and collapsing focal segmental glomerulosclerosis. A kidney biopsy is therefore required to make the correct diagnosis.

Dialysis is used to control complications of severe AKI. Absolute indications for dialysis include hyperkalemia, metabolic acidosis, and pulmonary edema refractory to medical therapy; uremic symptoms; uremic pericarditis; and certain drug intoxications. This patient has no indication for dialysis.

The pathophysiology of hypercoagulability in the nephrotic syndrome is not well understood, nor has the mechanism underlying the higher propensity for thromboembolism in membranous glomerulopathy been well defined. There are no randomized clinical trials of prophylactic anticoagulation in patients with the nephrotic syndrome to guide clinical decision-making; in the absence of known risk and benefits, many experts recommend against prophylactic anticoagulation. Anticoagulation is typically recommended for patients with documented renal vein thrombosis to prevent further propagation of the thrombus and systemic embolization. The patient's ultrasound does not show evidence of renal vein thrombosis, and anticoagulation should be withheld.

Although this presentation is most suggestive of MCG given the patient's age, empiric glucocorticoids would not be indicated without a biopsy-confirmed diagnosis because glucocorticoids would not be efficacious in the treatment of membranous glomerulopathy or amyloidosis.

KEY POINT

- A kidney biopsy is required to make the diagnosis of glomerulopathy associated with the nephrotic syndrome in adult patients.

Bibliography

Waldman M, Crew RJ, Valeri A, Busch J, Stokes B, Markowitz G, et al. Adult minimal-change disease: clinical characteristics, treatment, and outcomes. Clin J Am Soc Nephrol. 2007;2:445-53. [PMID: 17699450]

H

Item 3 Answer: D

Educational Objective: Treat chronic metabolic acidosis in a patient with chronic kidney disease.

Sodium bicarbonate therapy is the most likely treatment to slow progression of this patient's chronic kidney disease (CKD). Metabolic acidosis frequently occurs in patients with CKD due to defective acid excretion (resulting in reduced bicarbonate generation), most commonly due to impaired ammoniagenesis. Untreated metabolic acidosis can lead to muscle loss and bone loss. In early CKD, metabolic acidosis is typically a normal anion gap hyperchloremic metabolic acidosis. As glomerular filtration rate (GFR) declines, organic and inorganic anions are retained, and an anion gap metabolic acidosis develops. Large observational studies have shown a strong association between lower serum bicarbonate levels and both increased progression of CKD and mortality. Alkali therapy, most commonly sodium bicarbonate or sodium citrate, can delay the progression of CKD. Therefore, the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines recommend starting alkali therapy when the serum bicarbonate is chronically <22 mEq/L (22 mmol/L). The alkali salt therapy dose should be titrated to achieve a serum bicarbonate level within the normal range; excessive alkali therapy in the setting of a reduced GFR may induce a metabolic alkalosis, which is associated with increased mortality. Patients with CKD who are treated with alkali should be monitored for symptoms of volume overload.

Blood pressure control, particularly with renin-angiotensin system agents, has been shown to slow progression of proteinuric renal diseases and especially diabetes mellitus. However, this patient is already taking an angiotensin receptor blocker (ARB), and dual therapy with an ACE inhibitor and an ARB may instead be detrimental because studies of dual blockade have shown increased risks of acute kidney disease and hyperkalemia.

As the estimated GFR declines below 30 mL/min/1.73 m^2 (stages G4-G5), anemia can become symptomatic. Erythropoiesis-stimulating agents (ESAs) are highly effective in raising hemoglobin concentrations and alleviating symptoms but have not been shown to slow progression of CKD. These agents are associated with risks and are expensive. Black box warnings for use of ESAs include the risk of increased mortality and/or tumor progression in patients with active malignancy, increased risk of thromboembolic events for postsurgical patients not on anticoagulant therapy, and increased risk of serious cardiovascular events when ESAs are administered to patients with hemoglobin values >11 g/dL (110 g/L).

Although poorly controlled hyperphosphatemia is associated with a greater risk of CKD progression, optimizing mineral metabolism parameters with a phosphate binder has not been shown to slow progression of CKD.

KEY POINT

- The Kidney Disease: Improving Global Outcomes (KDIGO) guidelines recommend treatment of metabolic acidosis with alkali therapy in patients with chronic kidney disease when the serum bicarbonate is chronically <22 mEq/L (22 mmol/L).

Bibliography

Kraut JA, Madias NE. Metabolic acidosis of CKD: an update. Am J Kidney Dis. 2016;67:307-17. [PMID: 26477665]

Item 4 Answer: B

Educational Objective: Treat minimal change glomerulopathy.

Diuretics plus high-dose prednisone is the most appropriate treatment for this patient with minimal change glomerulopathy (MCG; also known as minimal change disease). MCG is the most common cause of the nephrotic syndrome in children and accounts for approximately 10% to 15% of cases in adults. Immunosuppressive therapy is indicated for treatment of primary MCG, which invariably presents with the full nephrotic syndrome. The concomitant acute tubular necrosis makes treatment even more imperative in this case, because primary MCG with acute kidney injury has been shown to be a treatment-responsive lesion if treated in a timely manner. First-line therapy is prednisone at a dose of 1 mg/kg per day or 2 mg/kg every other day for 8 to 12 weeks, followed by a taper. Patients typically respond to glucocorticoids within 8 to 16 weeks. However, relapse is common, and in a substantial percentage of patients, the course of MCG is one of remission followed by relapse. For frequently relapsing or glucocorticoid-dependent disease, treatment options include cyclophosphamide, calcineurin inhibitors (tacrolimus or cyclosporine), mycophenolate mofetil, and rituximab. In addition to immunosuppression, patients should receive standard therapy for the nephrotic syndrome, including an ACE inhibitor or angiotensin receptor blocker (this patient is already taking lisinopril, with well-controlled blood pressure), diuretics for edema management, and cholesterol-lowering medication if total cholesterol >200 mg/dL (5.1 mmol/L). In rare cases of MCG secondary to malignancies (Hodgkin lymphoma, non-Hodgkin lymphoma, thymoma), medications (NSAIDs, lithium), infections (strongyloides, syphilis, mycoplasma, ehrlichiosis), and atopy (pollen, dairy products), treatment of the underlying condition without immunosuppression may be sufficient.

Cyclosporine and rituximab are generally reserved for glucocorticoid-resistant or glucocorticoid-dependent cases of MCG and, except for a clear contraindication to glucocorticoids, should not be used as first-line therapy.

Diuretics alone are not sufficient to manage this patient and prevent progressive kidney disease; immunosuppressive therapy is therefore indicated.

KEY POINT

- Glucocorticoids are first-line therapy for primary minimal change glomerulopathy; standard treatment of the nephrotic syndrome (ACE inhibitor or angiotensin receptor blocker, diuretics for edema, and cholesterol-lowering medication if total cholesterol >200 mg/dL [5.1 mmol/L]) is also indicated as needed.

Bibliography

Vivarelli M, Massella L, Ruggiero B, Emma F. Minimal change disease. Clin J Am Soc Nephrol. 2017;12:332-345. [PMID: 27940460]

Item 5 Answer: C

Educational Objective: Diagnose monoclonal gammopathy of renal significance with a kidney biopsy.

The most appropriate next diagnostic test is a kidney biopsy. This patient appears to have monoclonal gammopathy of renal significance (MGRS). This is a recently defined set of kidney disorders found in patients who would otherwise meet the criteria for monoclonal gammopathy of undetermined significance but have an abnormal urinalysis and kidney insufficiency. This patient who otherwise meets the diagnostic criteria for monoclonal gammopathy of undetermined significance has an active urine sediment and an increase in the serum creatinine level and thus has underlying kidney disease. MGRS is an increasingly recognized disorder, and a kidney biopsy is necessary to make the diagnosis by demonstrating the presence of monoclonal immunoglobulin deposition in the kidney. MGRS can affect the kidney in various ways, including amyloidosis, proliferative glomerulonephritis, immunoglobulin deposition disease, C3 glomerulopathy, and proximal tubulopathy. Kidney manifestations of MGRS are usually caused by deposition of monoclonal light chains. Patients can present with both nephrotic and subnephrotic proteinuria, hematuria, and elevated serum creatinine. Despite not meeting the definition of multiple myeloma, MGRS increases morbidity and, in most cases, should be treated with therapy designed to eliminate or suppress the immunoglobulin clone.

Pauci-immune glomerulonephritis is caused by microscopic vessel vasculitis affecting the kidney, resulting in necrotizing lesions in the glomeruli with few or no immune deposits. The renal lesion may occur with or without systemic vasculitis and is the most common cause of rapidly progressive glomerulonephritis. Most patients have circulating ANCA directed against neutrophils. Other than proteinuria, this patient has a bland urinalysis that is not consistent with a pauci-immune glomerulonephritis, and testing for ANCA in lieu of a kidney biopsy will not establish a diagnosis.

β_2-Microglobulin levels can be helpful as prognostic indicators in myeloma but cannot be used to make a diagnosis of a plasma cell disorder.

Serum free light chains can be used to diagnose myeloma and predict the risk of progression in patients with monoclonal gammopathy of undetermined significance; however, a kidney biopsy, not serum free light chain determination, will confirm the cause of this patient's kidney disease.

KEY POINT

- Monoclonal gammopathy of renal significance is diagnosed in patients who would otherwise meet the criteria for monoclonal gammopathy of undetermined significance but have an abnormal urinalysis and kidney insufficiency; kidney biopsy confirms the diagnosis.

Bibliography

Rosner MH, Edeani A, Yanagita M, Glezerman IG, Leung N; American Society of Nephrology Onco-Nephrology Forum. Paraprotein-related kidney disease: diagnosing and treating monoclonal gammopathy of renal significance. Clin J Am Soc Nephrol. 2016;11:2280-2287. [PMID: 27526705]

Item 6 Answer: D

Educational Objective: Treat IgA nephropathy with an ACE inhibitor or angiotensin receptor blocker.

No changes need to be made to this patient's current medication regimen. He was diagnosed with IgA nephropathy 3 months ago, at which time the ACE inhibitor lisinopril was initiated. Antiproteinuric therapy using an ACE inhibitor or angiotensin receptor blocker (ARB) is the hallmark for treating IgA nephropathy and remains the most proven therapy in slowing progression of the disease. This patient currently has preserved kidney function and proteinuria <1000 mg/24 h; therefore, continuing conservative therapy with the ACE inhibitor lisinopril is appropriate.

Combined use of any of the three renin-angiotensin system drug classes (ACE inhibitor, ARB, and direct renin inhibitors) is not recommended given the results of several clinical trials that revealed more adverse events with these combinations (hyperkalemia, hypotension, acute kidney injury), without additional cardiovascular or renal benefits. Therefore, adding the ARB losartan to this patient's medication regimen is not recommended.

The risk for disease progression appears to be significantly increased when patients have proteinuria >1000 mg/24 h, particularly in the setting of reduced kidney function. Studies on using immunosuppression (particularly glucocorticoids) have used this 1000 mg/24 h proteinuria threshold for enrollment and have demonstrated conflicting results. Although earlier small studies have shown a clear benefit in adding glucocorticoids (oral or a combination of intravenous and oral) to ACE inhibitors or ARBs when proteinuria is >1000 mg/24 h, more recent larger studies (STOP-IgAN and TESTING studies) have raised concerns about the toxicity of this treatment strategy outweighing any potential benefits. Therefore, the use of immunosuppression in IgA nephropathy remains controversial.

KEY POINT

- Antiproteinuric therapy with an ACE inhibitor or angiotensin receptor blocker is the hallmark and most validated treatment strategy for IgA nephropathy.

Bibliography

Feehally J. Immunosuppression in IgA nephropathy: guideline medicine versus personalized medicine. Semin Nephrol. 2017;37:464-477. [PMID: 28863793]

Item 7 Answer: C

Educational Objective: Identify polydipsia as the cause of isovolemic hypotonic hyponatremia.

This patient has isovolemic hypotonic hyponatremia secondary to polydipsia. Isovolemia is documented by the presence of normal vital signs and physical examination findings. Hypotonicity is documented by the low calculated serum osmolality of 156 mOsm/kg H_2O, using the following equation:

Serum Osmolality (mOsm/kg H_2O) = (2 × Serum Sodium [mEq/L]) + Plasma Glucose (mg/dL)/ 18 + Blood Urea Nitrogen (mg/dL)/2.8

Isovolemic hypotonic hyponatremia is secondary either to impaired dilution of urine or to water intake that exceeds the kidney's ability to excrete dilute urine. Urine osmolality distinguishes between these two entities. Urine osmolality <100 mOsm/kg H_2O indicates excessive water intake, as seen with psychogenic polydipsia or poor solute intake. Because the kidney cannot excrete pure water, a minimal solute concentration of 50 mOsm/kg H_2O is required. If solute intake is low while liquid intake remains high (as seen in beer potomania or chronic low food intake), water excretion is limited by available urinary solute.

Hyperglycemia causes the osmotic translocation of water from the intracellular to the extracellular fluid compartment, which results in a decrease in the serum sodium level by approximately 1.6 to 2.0 mEq/L (1.6-2.0 mmol/L) for every 100 mg/dL (5.6 mmol/L) increase in the plasma glucose above 100 mg/dL (5.6 mmol/L). Although the patient has mild hyperglycemia, her glucose is not elevated enough to lower her sodium to 126 mEq/L (126 mmol/L).

Diabetes insipidus, due to either a lack of antidiuretic hormone (ADH) secretion from the posterior pituitary gland or kidney resistance to ADH (nephrogenic diabetes insipidus), will result in low urine osmolality as seen in this patient. In the absence of ADH, excessive water is excreted by the kidneys. Serum sodium is typically normal but may be elevated in patients who do not have access to water. Although lithium can cause nephrogenic diabetes insipidus, the fact that she is hyponatremic rules out this diagnosis.

Hyponatremia most often results from an increase in circulating ADH in response to a true or sensed reduction in effective arterial blood volume with resulting fluid retention. Hyponatremia may also be caused by elevated ADH levels associated with the syndrome of inappropriate antidiuretic hormone secretion. Because she has dilute urine indicating a lack of ADH, neither the syndrome of inappropriate antidiuretic hormone secretion nor volume depletion is the cause of her hyponatremia. Volume depletion is also excluded by the normal blood pressure and pulse measurement and absence of orthostatic changes.

KEY POINT

- Isovolemic hypotonic hyponatremia associated with urine osmolality <100 mOsm/kg H_2O indicates excessive water intake, as seen with psychogenic polydipsia or poor solute intake.

Bibliography

Hoorn EJ, Zietse R. Diagnosis and treatment of hyponatremia: compilation of the guidelines. J Am Soc Nephrol. 2017;28:1340-1349. [PMID: 28174217]

Item 8 Answer: B

H

Educational Objective: Prevent calcium oxalate stones using potassium citrate in a patient who has malabsorption.

In addition to increasing fluid intake, potassium citrate is appropriate to prevent future calcium oxalate stones in this patient. Patients with chronic diarrhea and malabsorption are at increased risk for forming calcium oxalate stones for three reasons. First, because of the diarrhea and concomitant metabolic acidosis, urine citrate, an inhibitor of crystallization, is often reduced. In addition, volume depletion from the diarrhea decreases urine volume and thus increases the concentration of calcium and oxalate in the urine. Finally, in malabsorption, especially fat malabsorption as occurs in chronic pancreatitis, enteric calcium binds to fat as opposed to oxalate, leaving oxalate free to be absorbed and excreted in the urine. Although treatment should be based on the metabolic evaluation in this patient, his low urine pH and low serum bicarbonate level suggest that he has metabolic acidosis. Decreased systemic pH lowers urine citrate excretion. Supplementation with citrate as a base equivalent will help correct the acidosis and increase urine citrate, bind urinary calcium, and decrease the formation of calcium oxalate stones.

If the 24-hour urine metabolic evaluation showed elevated urine uric acid or if stone analysis revealed a uric acid nidus, allopurinol could be considered; however, in the absence of this information, allopurinol should not be prescribed.

Vitamin C increases urine oxalate excretion and would not have the desired effect of decreasing calcium oxalate stone formation.

Restricting dietary calcium intake in patients with hypercalciuria may paradoxically increase the risk of kidney stone formation by causing decreased binding of calcium with oxalate in the gut with increased absorption and urinary excretion of oxalate; therefore, dietary calcium should not be limited.

Increased protein intake increases glomerular filtration, and therefore the excretion of calcium, and would not

H

contribute to decreased kidney stone formation. In addition, high protein diets may exacerbate hypocitraturia.

KEY POINT

- Potassium citrate can be used to help prevent calcium oxalate stones in patients with chronic diarrhea and malabsorption.

Bibliography

Pfau A, Knauf F. Update on nephrolithiasis: core curriculum 2016. Am J Kidney Dis. 2016;68:973-985. [PMID: 27497526]

H

Item 9 Answer: A

Educational Objective: Treat diabetic nephropathy.

The addition of an ACE inhibitor or angiotensin receptor blocker (ARB) is the most appropriate management for this patient with diabetic nephropathy. The hallmark clinical features include a proteinuric form of chronic kidney disease in a patient with long-standing diabetes mellitus and evidence of other (microvascular and/or macrovascular) complications of disease. Diagnosis can be made clinically for this patient, and he can be treated with the cornerstone of treatment: improved glucose control, and blockade of the renin-angiotensin system (RAS) with an ACE inhibitor or ARB using the maximal tolerated dose. Combined use of any RAS drug class (ACE inhibitors, ARBs, and direct renin inhibitors) is not recommended; several clinical trials have revealed more adverse events with these combinations (hyperkalemia, hypotension, acute kidney injury), without additional cardiovascular or renal benefits.

ANCA-associated glomerulonephritis is associated with the nephritic syndrome. The nephritic syndrome is characterized by hematuria, proteinuria, and leukocytes in the urine sediment. The hallmark is the presence of dysmorphic erythrocytes, with or without erythrocyte casts. Systemic findings may include edema, hypertension, and kidney failure. This patient does not have hematuria, making ANCA testing unnecessary.

Serum and urine protein electrophoresis is used to evaluate for kidney failure secondary to dysproteinemia, which is more common in older patients (>65 years of age). Other potential clues to the presence of dysproteinemia-related kidney disease include anemia, hypercalcemia, and evidence of proximal tubular dysfunction such as hypokalemia, metabolic acidosis, hypophosphatemia, glycosuria (with normoglycemia), or hypouricemia.

The diagnosis of diabetic nephropathy usually does not require a kidney biopsy if the clinical presentation is consistent with its diagnosis. The best predictors of finding diabetic nephropathy are duration of diabetes for more than 8 years followed by presence of the nephrotic syndrome. Therefore, this patient with a 10-year history of poorly controlled diabetes, nephrotic-range proteinuria, and findings of microvascular and macrovascular complications does not require a kidney biopsy or other testing to confirm the diagnosis of diabetic nephropathy.

KEY POINT

- The best predictors for the presence of diabetic nephropathy are duration of diabetes mellitus for more than 8 years followed by the presence of the nephrotic syndrome.

Bibliography

Wylie EC, Satchell SC. Diabetic nephropathy. Clin Med (Lond). 2012;12:480-2; quiz 483-5. [PMID: 23101153]

Item 10 Answer: B

H

Educational Objective: Treat rhabdomyolysis-induced acute kidney injury.

Intravenous 0.9% saline is the most appropriate treatment for this patient who has severe rhabdomyolysis from cocaine and opiates. Major causes of rhabdomyolysis include trauma, drugs and toxins, seizures, metabolic and electrolyte disorders, endocrinopathies, and exercise. Rhabdomyolysis-induced acute kidney injury (AKI) is associated with elevated serum creatine kinase (usually >5000 U/L) and creatinine levels, hyperkalemia, hypocalcemia, hyperphosphatemia, hyperuricemia, and increased anion gap metabolic acidosis. Patients with rhabdomyolysis tend to be significantly volume depleted due to the sequestration of water in injured muscles. Therefore, initial management is early with aggressive repletion of fluids aimed at maintaining a urine output of 200 to 300 mL/h. Normal saline is the recommended initial fluid of choice, and patients can require 10 liters of fluid per day.

Hemodialysis is reserved for patients with severe AKI who remain oliguric with persistent hyperkalemia, persistent metabolic acidosis, and/or volume overload. This patient does not have an indication for hemodialysis at this time.

Although the patient has hypernatremia, intravenous 5% dextrose is not adequate to expand the extracellular fluid compartment. Due to the osmotic gradient, hypotonic fluids will leave the extracellular fluid compartment for the intracellular compartment.

Hypocalcemia is due to sequestration of calcium in damaged cells. Rebound hypercalcemia occurs during the recovery phase due to release of calcium from damaged muscles and is worsened by exogenous calcium treatment. Calcium should only be given in patients who are symptomatic or in patients at risk for arrhythmia due to severe hyperkalemia with electrocardiogram changes.

Although alkalinization of the urine to a pH >6.5 may prevent intratubular pigment cast formation, decrease the release of free iron from myoglobin, and decrease the risk for tubular precipitation of uric acid, clear benefit is lacking. Intravenous bicarbonate should only be used after diuresis is established with volume repletion. It should not be used if pH is >7.5, serum bicarbonate is >30 mEq/L (30 mmol/L), and/or severe hypocalcemia is present. Intravenous bicarbonate can cause symptomatic hypocalcemia and can promote deposition of calcium phosphate in the renal tubules.

KEY POINT

- Initial management of rhabdomyolysis-induced acute kidney injury includes aggressive fluid resuscitation with normal saline aimed at maintaining a urine output of 200 to 300 mL/h.

Bibliography

Cervellin G, Comelli I, Benatti M, Sanchis-Gomar F, Bassi A, Lippi G. Nontraumatic rhabdomyolysis: background, laboratory features, and acute clinical management. Clin Biochem. 2017;50:656-662. [PMID: 28235546]

H

Item 11 Answer: A

Educational Objective: Prevent contrast-induced nephropathy.

The administration of 0.9% saline is an appropriate measure to prevent contrast-induced nephropathy (CIN). CIN is a common cause of reversible acute kidney injury in the hospital. CIN is defined as an increase in serum creatinine within 24 to 48 hours following contrast exposure. Adequate intravenous volume expansion with isotonic crystalloids before the procedure and continued for 6 to 24 hours afterward has been shown to decrease the incidence of CIN in patients at risk. Intravenous hydration induces an increase of urine flow rate, reduces the concentration of contrast in the tubule, and increases the excretion of contrast. Because administration of intravenous crystalloid remains the primary strategy for reducing the risk of CIN, patients with compensated heart failure should still be given intravenous volume. Patients with uncompensated heart failure should undergo hemodynamic monitoring with continuation of diuretics. This patient has compensated heart failure noted on examination and should be given fluids.

A recent large randomized trial among patients at high risk for kidney complications compared three different strategies to prevent CIN: intravenous 1.26% sodium bicarbonate or intravenous 0.9% sodium chloride and 5 days of oral acetylcysteine or oral placebo. For fluid administration, this study used a protocol of 1 to 3 mL/kg/h before angiography, 1 to 1.5 mL/kg/h during angiography, and 1 to 3 mL/kg/h 2 to 12 hours after angiography. There was no benefit of intravenous sodium bicarbonate over intravenous sodium chloride or of oral acetylcysteine over placebo for the prevention of death, need for dialysis, or persistent decline in kidney function at 90 days or for the prevention of CIN.

Some but not all studies suggest that statins may reduce the risk of CIN. A 2016 meta-analysis suggested that statins given with N-acetylcysteine plus intravenous saline reduced the risk of CIN compared with N-acetylcysteine plus intravenous saline alone in relatively low-risk patients. Based on these results, there is no need to discontinue atorvastatin in this patient.

Discontinuation of ACE inhibitors or angiotensin receptor blockers such as irbesartan has not been clearly shown to decrease the risk of CIN.

KEY POINT

- Intravenous volume expansion with isotonic crystalloids has been shown to decrease the incidence of contrast-induced nephropathy in patients at risk.

Bibliography

Weisbord SD, Gallagher M, Jneid H, Garcia S, Cass A, Thwin SS, et al; PRESERVE Trial Group. Outcomes after angiography with sodium bicarbonate and acetylcysteine. N Engl J Med. 2018;378:603-614. [PMID: 29130810]

H

Item 12 Answer: C

Educational Objective: Diagnose multiple myeloma-associated hypercalcemia as a cause of acute kidney injury.

This patient's acute kidney injury (AKI) is due to hypercalcemia from multiple myeloma. Classic symptoms of polyuria, polydipsia, and nocturia sometimes occur with elevated serum calcium levels of 11 mg/dL (2.8 mmol/L) or less. Other symptoms such as anorexia, nausea, abdominal pain, constipation, increased serum creatinine levels, and mild mental status changes are more likely to occur with levels >11 mg/dL (2.8 mmol/L). Kidney dysfunction is found in about 30% of patients diagnosed with multiple myeloma, often due to cast nephropathy (also termed myeloma kidney), a condition in which excess monoclonal free light chains precipitate in the distal tubules and incite tubulointerstitial damage. Hypercalcemia and exposure to nephrotoxic agents are other frequent causes of kidney dysfunction. Hypercalcemia can decrease glomerular filtration rate through renal vasoconstriction, the natriuretic effects of high serum calcium levels, and impaired renal concentrating ability. This patient has orthostatic hypotension, a bland urinalysis with hyaline casts, and a fractional excretion of sodium <1%, consistent with a prerenal AKI from hypovolemia. The constellation of hypercalcemia, normal anion gap metabolic acidosis, pancytopenia, and AKI suggests multiple myeloma as the etiology.

Hydrochlorothiazide can cause volume depletion, decreased excretion of calcium and mild hypercalcemia, prerenal AKI, and metabolic alkalosis (due to hypovolemic stimulation of aldosterone release). However, the effect on serum calcium is usually minimal, and the patient has a metabolic acidosis, not metabolic alkalosis as might be seen with thiazide therapy.

Milk alkali syndrome occurs with the ingestion of large amounts of calcium and absorbable alkali (for example, calcium carbonate). It presents as hypercalcemia, metabolic alkalosis, and AKI. This patient has a metabolic acidosis, not a metabolic alkalosis, making this diagnosis unlikely.

Primary hyperparathyroidism is the most common cause of hypercalcemia in otherwise healthy outpatients and is diagnosed with a simultaneously elevated serum calcium level and an inappropriately normal or elevated intact parathyroid hormone level. Serum phosphorus levels are typically low or low-normal in these patients. This patient's phosphorus level is elevated, making the diagnosis of primary hyperparathyroidism unlikely.

KEY POINT

- A diagnosis of multiple myeloma is suggested by the constellation of anemia, hypercalcemia, normal anion gap metabolic acidosis, and acute kidney injury.

Bibliography

Rosner MH, Perazella MA. Acute kidney injury in patients with cancer. N Engl J Med. 2017;376:1770-1781. [PMID: 28467867]

Item 13 Answer: B

Educational Objective: Adjust an antihypertensive medication regimen to achieve a target blood pressure goal.

The addition of losartan is the most appropriate treatment. As antihypertensive agents are titrated or added when there is inadequate blood pressure control, it is important to recognize that there is a nonlinear and diminishing blood pressure-lowering effect when titrating from 50% maximal dose to 100% maximal dose of any agent. A general rule of thumb is that 75% of an agent's blood pressure-lowering effect may be achieved with 50% of its maximal dose. If blood pressure control requires an additional >5-mm Hg reduction, it is unlikely to be achieved by increasing the single agent from 50% to 100% maximal dose. The better strategy is to add a second drug or a third drug to a two-drug regimen, as seen in this patient.

Hydralazine is not the best option because it is a thrice-daily medication and may pose problems with adherence, considering that once-daily medication options have not been exhausted in this patient. In addition, hydralazine is a direct vasodilator and is associated with sodium and water retention and reflex tachycardia; use with a diuretic and a β-blocker is recommended. Hydralazine is typically reserved for patients with resistant hypertension or hypertensive urgencies.

Increasing the amlodipine or hydrochlorothiazide dose is not appropriate because there is diminishing return in blood pressure lowering if the dose is titrated up from 50% to 100% of maximum. Also, it is unlikely that increasing the dose from 50% to 100% of maximum will result in an additional >5-mm Hg reduction to bring this patient's blood pressure to a target of <130/80 mm Hg. In addition, titration to maximum doses may result in manifestation of undesirable side effects and decreased adherence. In this case, the patient already has dependent edema, which may increase with uptitration of the amlodipine dose. His serum potassium is borderline at 3.6 mEq/L (3.6 mmol/L), and increasing the dose of hydrochlorothiazide may further decrease his serum potassium and necessitate a potassium supplement, adding yet another medication to his drug regimen.

KEY POINT

- Three strategies can be used for antihypertensive dose adjustment in the treatment of hypertension: (1) maximize the medication dose before adding another; (2) add another class of medication before reaching the maximum dose of the first; and (3) start with two medication classes separately or as fixed-dose combinations.

Bibliography

Whelton PK, Carey RM, Aronow WS, Casey DE Jr, Collins KJ, Dennison Himmelfarb C, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Hypertension. 2017. [PMID: 29133356]

Item 14 Answer: C

H

Educational Objective: Treat ethylene glycol toxicity.

The most appropriate management is intravenous hydration, fomepizole, and hemodialysis. This patient has typical findings of ethylene glycol toxicity, including central nervous system depression, an increased anion gap metabolic acidosis, and an increased osmolal gap. In patients with an increased anion gap acidosis, calculation of the serum osmolal gap is helpful in assessing the presence of unmeasured solutes, such as ingestion of certain toxins (for example, methanol or ethylene glycol). The serum osmolal gap is the difference between the measured and calculated serum osmolality. Serum osmolality can be calculated using the following formula:

$$\text{Serum Osmolality (mOsm/kg } H_2O) = (2 \times \text{Serum Sodium [mEq/L]}) + \text{Plasma Glucose (mg/dL)}/18 + \text{Blood Urea Nitrogen (mg/dL)}/2.8$$

When the measured osmolality exceeds the calculated osmolality by >10 mOsm/kg H_2O, the osmolal gap is considered elevated. This patient has an osmolal gap of 27 mOsm/kg H_2O. Finally, this patient has kidney failure likely resulting from deposition of calcium oxalate crystals in the renal tubules. Because laboratory confirmation of ethylene glycol intoxication may take days, empiric therapy with fomepizole and aggressive fluid resuscitation with crystalloids (250-500 mL/h intravenous initially) should be instituted in all cases to increase kidney clearance of the toxin and to limit deposition of oxalate in the renal cortex. Hemodialysis to clear the alcohol and toxic metabolites should be instituted in the context of any organ-specific toxicity (central nervous system depression, acute kidney injury, systemic collapse), severe acidemia, or very large ingestions.

Activated charcoal gastric decontamination and nasogastric lavage have no role in toxic alcohol poisoning; both ethylene glycol and methanol are typically absorbed too rapidly for either of these modalities to be useful.

Intravenous ethanol was traditionally used as a competitive inhibitor of alcohol dehydrogenase. However, fomepizole has been found to be superior to alcohol with few side effects. Therefore, fomepizole is the preferred agent, and there is no additional benefit to coadministration of the two.

Adjunct therapy with intravenous sodium bicarbonate therapy in the context of pH <7.30 may reduce penetration of toxic metabolites of ethylene glycol (glycolate, glyoxylate, and oxalate) and methanol (formate) into the tissues and enhance renal excretion of glycolate and formate. However, the initiation of dialysis in this patient is more efficacious.

KEY POINT

- Management of ethylene glycol toxicity in the context of organ-specific toxicity, severe acidemia, or very large ingestions includes aggressive fluid resuscitation, fomepizole, and hemodialysis.

Bibliography

Kruse JA. Methanol and ethylene glycol intoxication. Crit Care Clin. 2012;28:661-711. [PMID: 22998995]

Item 15 Answer: A

Educational Objective: Evaluate for secondary causes of membranous glomerulopathy.

Age- and sex-appropriate cancer screening is the most appropriate management. The initial step in the management of newly diagnosed membranous glomerulopathy is to evaluate for secondary forms of the disease, which account for approximately 25% of cases. Some of this evaluation is often done in the prebiopsy screening laboratory tests (for example, screening for hepatitis B and C viruses, lupus, and syphilis). Secondary forms of membranous glomerulopathy correlate with age. Cancer screening is particularly important in evaluating for secondary forms of membranous glomerulopathy in patients over the age of 65 years. Up to 25% of such patients will have a malignancy discovered within 1 year of diagnosis, essentially accounting for all forms of secondary membranous glomerulopathy in this age group. This 68-year-old woman with newly diagnosed membranous glomerulopathy has a 50-pack-year history of smoking. She should be sent for age- and sex-appropriate cancer screening, which would include cervical cytology and human papillomavirus testing, mammography, colonoscopy, and low-dose chest CT.

Immunosuppression should not be offered in this case until a secondary form has definitively been ruled out and the patient has been carefully monitored for at least 3 to 6 months to allow for the possibility, if this is a primary form of membranous glomerulopathy, for spontaneous remission, which occurs in approximately one third of primary cases.

Membranous glomerulopathy is associated with a higher risk for clotting, particularly when serum albumin is <2.8 g/dL (28 g/L). However, there is no consensus on whether such patients should be offered prophylactic anticoagulation, and most experts in the United States opt for vigilant monitoring rather than prophylactic anticoagulation.

The M-type phospholipase A2 receptor (PLA2R) is the specific podocyte antigen responsible for eliciting immune complex formation with circulating autoantibodies in most cases of primary membranous glomerulopathy. Anti-PLA2R antibodies are detected in approximately 75% of primary cases and rarely found in secondary forms. A negative staining on biopsy for this antigen (which is a more specific test than serum antibody assays) raises suspicion for a secondary form of the disease and does not require serum testing for confirmation.

KEY POINT

- The initial step in the management of newly diagnosed membranous glomerulopathy is to evaluate for secondary forms of the disease, which account for approximately 25% of cases.

Bibliography

Leeaphorn N, Kue-A-Pai P, Thamcharoen N, Ungprasert P, Stokes MB, Knight EL. Prevalence of cancer in membranous nephropathy: a systematic review and meta-analysis of observational studies. Am J Nephrol. 2014;40:29-35. [PMID: 24993974]

Item 16 Answer: B

Educational Objective: Diagnose transitional cell (urothelial) cancer in a patient with Balkan endemic nephropathy.

The most appropriate next step for this patient is an endoscopic urologic evaluation with cystoscopy and upper tract imaging. The patient has Balkan endemic nephropathy (BEN), a slowly progressive tubulointerstitial disease that has been linked to aristolochic acid. Aristolochic acid is a nephrotoxic alkaloid from the plant *Aristolochia clematis*. BEN has a high prevalence rate in southeastern Europe (Serbia, Bulgaria, Romania, Bosnia and Herzegovina, and Croatia) and is the cause of kidney disease in up to 70% of patients receiving dialysis in some of the most heavily affected regions. Aristolochic acid is also sometimes found as a component of herbal therapies used for weight loss. Characteristics of BEN include chronic kidney disease due to tubulointerstitial injury, tubular dysfunction (polyuria and decreased concentrating ability, glucosuria without hyperglycemia, and tubular proteinuria), and anemia. Ultrasound demonstrates small echogenic kidneys. BEN has a familial but not inherited pattern of distribution. It is thought to be caused by exposure to aristolochic acid, and, because it is mutagenic, it is strongly associated with the development of upper tract transitional cell (urothelial) cancers. Therefore, urologic evaluation is indicated.

CT urography is the preferred test for patients with unexplained urologic/nonglomerular hematuria. However, CT urography involves the use of intravenous contrast, which would place this patient at a high risk of developing contrast-induced nephropathy given the severity of his kidney disease. Cystoscopy and retrograde ureteropyelography would be the preferred imaging techniques for this patient.

Kidney biopsy would not explain the nondysmorphic hematuria. Furthermore, kidney biopsy is not indicated in the setting of small echogenic kidneys <9 cm in size, which signifies chronic irreversible disease.

Pyuria, granular casts, and low-grade proteinuria are commonly found in patients with tubulointerstitial nephritis and contrasts with the isolated pyuria associated with most urinary tract infections. In addition, the small, echogenic kidneys, chronic hematuria, and irregular bladder wall are not consistent with a urinary tract infection and more strongly suggest the possibility of a malignancy. Therefore, urine cultures are not indicated.

KEY POINT

- Balkan endemic nephropathy is strongly associated with the development of upper tract transitional cell (urothelial) cancers, and urologic evaluation is necessary.

Bibliography

Stefanovic V, Toncheva D, Polenakovic M. Balkan nephropathy. Clin Nephrol. 2015;83:64-9. [PMID: 25725245]

H

Item 17 Answer: A

Educational Objective: Treat hypernatremia caused by central diabetes insipidus.

In addition to increasing the prednisone, the antidiuretic hormone (ADH) analogue desmopressin acetate is the most appropriate treatment. This patient most likely has central nervous system sarcoidosis and central diabetes insipidus (DI). Nearly half of hypothalamic-pituitary sarcoidosis cases occur in the course of previously treated sarcoidosis. Central DI results from inadequate production of ADH by the posterior pituitary gland. In the presence of ADH, aquaporin water channels are inserted in the collecting tubules and allow water to be reabsorbed. In the absence of ADH, excessive water is excreted by the kidneys. Frank hypernatremia is unusual because patients develop extreme thirst and polydipsia, and with free access to water, can maintain serum sodium in the high normal range. When patients do not drink enough to replace the water lost in the urine, due to poor or absent thirst drive or lack of free access to water, they develop hypernatremia. DI is diagnosed with simultaneous laboratory evidence of inability to concentrate urine (urine osmolality <300 mOsm/kg H_2O) in the face of elevated serum sodium and osmolality. If necessary, a water deprivation test can confirm the diagnosis. A response to exogenous ADH would support a diagnosis of central DI, whereas a lack of response is seen in nephrogenic DI.

Although volume depletion induced by hydrochlorothiazide will help decrease urine output and conserve water, this treatment is reserved for patients with nephrogenic DI and is not necessary in central DI.

The hypernatremia in this case is mild, without symptoms, and can be rapidly treated with the administration of desmopressin acetate; therefore, it is not necessary to administer intravenous 5% dextrose.

Tolvaptan is a vasopressin receptor antagonist sometimes used for the syndrome of inappropriate antidiuretic hormone secretion, which is characterized by normal volume status, hyponatremia, and inappropriately elevated urine osmolality (not present in this patient).

KEY POINT

- Diabetes insipidus (DI) is diagnosed with simultaneous laboratory evidence of inability to concentrate urine in the face of elevated serum sodium and osmolality; a water deprivation test can confirm the diagnosis, and response to exogenous antidiuretic hormone supports the diagnosis of central DI.

Bibliography

Langrand C, Bihan H, Raverot G, Varron L, Androdias G, Borson-Chazot F, et al. Hypothalamo-pituitary sarcoidosis: a multicenter study of 24 patients. QJM. 2012;105:981-95. [PMID: 22753675]

H

Item 18 Answer: B

Educational Objective: Identify heparin as a cause of hyperkalemia.

The most likely cause of this patient's elevated serum potassium level is heparin. Hypoaldosteronism caused by heparin, inhibitors of the renin-angiotensin system, type 4 renal tubular acidosis, or primary adrenal disease can cause hyperkalemia. Both unfractionated and low-molecular-weight heparin use is associated with a decrease in aldosterone synthesis. This occurs more frequently in patients with chronic kidney disease or diabetes mellitus, or in those taking an ACE inhibitor or angiotensin receptor blocker.

Major underlying causes of persistent hyperkalemia are disorders in which urine potassium excretion is impaired. This can be due to a marked decrease in glomerular filtration rate, decreased sodium delivery to the distal potassium secretory sites, and hypoaldosteronism. The most common cause is chronic kidney disease with a glomerular filtration rate <20 mL/min/1.73 m^2 or acute oliguric kidney injury. Except in these cases, the kidney is able to maintain potassium homeostasis. The patient is not oliguric, and the slight increase in serum creatinine postoperatively is not sufficient to cause hyperkalemia.

Extreme elevations in glucose by increasing serum osmolality can directly cause hyperkalemia by pulling water from the intracellular space into the extracellular space, dragging potassium with it. This patient's glucose is only mildly elevated and would have little effect on osmolality and hyperkalemia.

In patients with metabolic acidosis caused by mineral acids (such as hydrochloric acid), buffering of intracellular hydrogen ions leads to potassium movement into the extracellular fluid to maintain electroneutrality. This does not occur with organic acids such as lactate or ketoacids. In most cases of hyperchloremic metabolic acidosis, hyperkalemia typically does not develop because there is concomitant urinary and/or gastrointestinal potassium loss. This is the case in patients with hyperchloremic metabolic acidosis with losses of potassium in the stool as the result of diarrhea or in the urine in patients with renal tubular acidosis.

Topiramate is a carbonic anhydrase inhibitor. Carbonic anhydrase inhibition results in proximal bicarbonate, sodium, and chloride urinary loss. The increased sodium loss causes hypovolemia and triggers secondary hyperaldosteronism, promoting potassium loss and hypokalemia.

KEY POINT

- Hypoaldosteronism caused by heparin, inhibitors of the renin-angiotensin system, type 4 renal tubular acidosis, or primary adrenal disease can cause hyperkalemia, especially in patients with chronic kidney disease or diabetes mellitus, or in those taking an ACE inhibitor or angiotensin receptor blocker.

Bibliography

Kovesdy CP. Updates in hyperkalemia: outcomes and therapeutic strategies. Rev Endocr Metab Disord. 2017;18:41-47. [PMID: 27600582]

H

Item 19 Answer: A

Educational Objective: Select the most appropriate pretransplant renal replacement therapy.

Due to this patient's full-time occupation and requirement to be present on-site at the workplace, peritoneal dialysis might be the preferred management for his end-stage kidney disease (ESKD). Peritoneal dialysis is a renal replacement therapy (RRT) modality utilizing the peritoneal membrane for diffusion of solutes and osmosis of water against a concentration gradient provided by infused dialysate. Patients exchange the dialysate three to five times per day rather than go to a dialysis center for 4 hours three times per week for hemodialysis. Control over one's dialysis is conducive for patients with full-time obligations, such as school or employment. The peritoneal dialysis exchanges can be performed overnight while the individual is sleeping and allow for greater independence during the day. The patient is otherwise healthy and independent. He has never had abdominal surgery, and his BMI is normal. He is an ideal candidate for peritoneal dialysis, and this modality will also allow him to preserve his independence and more easily transition to a life with ESKD. Planning for the right dialysis modality that best fits the patient's daily routine and lifestyle is important for patient satisfaction and long-term success.

A recent meta-analysis analyzing the effect of peritoneal dialysis versus hemodialysis on renal anemia in patients with ESKD found no significant difference for levels of hemoglobin, ferritin, parathyroid hormone, and transferrin saturation index between the hemodialysis and peritoneal dialysis groups. Both of the two dialysis strategies have a similar effect on renal anemia in patients with ESKD.

Clinical outcomes are similar for patients receiving peritoneal dialysis compared with those receiving hemodialysis, although patients starting RRT with residual kidney function may have better outcomes with peritoneal dialysis. Furthermore, residual kidney function is preserved longer with peritoneal dialysis than with hemodialysis and, although small, helps maintain adequate solute clearance and euvolemia. Finally, patients treated with peritoneal dialysis are more satisfied with their treatment and indicate a more satisfying shared decision-making experience.

Peritonitis is one of the most important complications of peritoneal dialysis and can damage the peritoneum, reducing the efficacy of dialysis. Peritoneal dialysis-associated peritonitis is uncommon, with one episode of peritonitis every 2 to 3 years, usually caused by bacteria from skin introduced by poor sterile technique and often easily treated with antibiotics.

KEY POINT

- In properly selected individuals, peritoneal dialysis allows patients to preserve their independence and offers outcomes similar to those seen with hemodialysis.

Bibliography

Hansson JH, Watnick S. Update on peritoneal dialysis: core curriculum 2016. Am J Kidney Dis. 2016;67:151-64. [PMID: 26376606]

Item 20 Answer: A

Educational Objective: Initiate combination antihypertensive therapy for treatment of stage 2 hypertension.

Combination therapy with amlodipine/benazepril is appropriate treatment for this patient with stage 2 hypertension. The 2017 American College of Cardiology/American Heart Association blood pressure (BP) guideline recommends combination therapy with two first-line antihypertensive drugs of different classes (separately or as a single-dose pill) for adults with stage 2 hypertension and an average BP that is 20/10 mm Hg above their BP target. Stage 2 hypertension is defined as BP ≥140/90 mm Hg. This patient's target BP is <130/80 mm Hg. There are no definitive recommendations for best drug combinations, but some data suggest an ACE inhibitor/calcium channel blocker (CCB) combination may be more efficacious than an ACE inhibitor/thiazide diuretic combination. Using a thiazide diuretic/CCB combination is also an option. It is important to note that in black patients, ACE inhibitors are not as efficacious at reducing BP compared with thiazide diuretics or CCBs.

Specific non-recommended initial agents for the treatment of hypertension include β-blockers (due to higher rate of cardiovascular-related events and mortality compared with angiotensin receptor blockers) and α-blockers (due to higher rate of cardiovascular-related events and mortality compared with thiazides), although compelling clinical indications such as atrial fibrillation or benign prostatic hyperplasia may supersede these recommended restrictions.

Initiation of once daily dosing of a combination pill simplifies the medication regimen and is appropriate in this patient to ensure adherence. Therefore, initiation of hydralazine is not correct because two-drug therapy is recommended for this patient, and adherence to a thrice-daily medication will be problematic.

Combination therapy with an ACE inhibitor (ramipril) and an angiotensin receptor blocker (telmisartan) is not recommended. Several clinical trials (ONTARGET, NEPHRON-D, ALTITUDE) have revealed more adverse events with these combinations (hyperkalemia, hypotension, acute kidney injury), without additional cardiovascular or renal benefits.

KEY POINT

- The 2017 American College of Cardiology/American Heart Association blood pressure (BP) guideline recommends combination therapy with two first-line antihypertensive drugs of different classes (separately or as a single-dose pill) for adults with stage 2 hypertension and an average BP of 20/10 mm Hg above BP target.

Bibliography

Whelton PK, Carey RM, Aronow WS, Casey DE Jr, Collins KJ, Dennison Himmelfarb C, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Hypertension. 2017. [PMID: 29133356]

Item 21 Answer: A

Educational Objective: Diagnose ANCA-associated glomerulonephritis.

The most likely diagnosis is ANCA-associated glomerulonephritis (pauci-immune crescentic glomerulonephritis). This patient's clinical picture suggests a rapidly progressive glomerulonephritis (RPGN), with an acute and steep rise in serum creatinine accompanied by hematuria and proteinuria. The differential diagnosis for RPGN is classically accounted for by three immunofluorescence findings seen on diagnostic kidney biopsy: pauci-immune staining (for example, ANCA-associated glomerulonephritis), linear staining (for example, anti-glomerular basement membrane glomerulonephritis), and granular staining (for example, lupus nephritis). ANCA-associated glomerulonephritis accounts for more than half of all RPGN cases and has a particularly high prevalence in patients >65 years of age presenting with acute kidney injury and active urine sediment. The patient's clinical presentation of acute onset of flu-like symptoms is a classic presentation for vasculitis, and the lacy or reticular rash on examination is likely related to active ANCA-associated vasculitis. He should be tested for antiproteinase-3 and antimyeloperoxidase ANCA antibodies and undergo kidney biopsy to confirm the diagnosis.

Anti-glomerular basement membrane antibody disease is a far rarer form of RPGN, with peak incidences in young men and older women. More than half of patients present with concomitant alveolar hemorrhage that may progress to life-threatening respiratory failure. These findings are not present in this patient.

Minimal change glomerulopathy is characterized by sudden-onset nephrotic syndrome. It can be associated with acute kidney injury in elderly patients, and the presentation is one of severe nephrotic syndrome without significant hematuria. This is distinctly different from this patient's presentation of rash, hypertension, rapidly progressive kidney failure, and active urine sediment.

Kidney dysfunction is found in 29% of patients with multiple myeloma, often due to cast nephropathy (also termed myeloma kidney), a condition in which excess monoclonal free light chains precipitate in the distal tubules and incite tubulointerstitial damage. Patients will typically have concomitant anemia and hypercalcemia. These findings are absent in this patient.

Proliferative lupus nephritis is a cause of RPGN that is usually limited to the pediatric and young adult patient population.

KEY POINT

- ANCA-associated glomerulonephritis is typically characterized by a vasculitic prodrome of malaise, arthralgia, myalgia, and skin findings; hematuria, proteinuria, and acute kidney injury are present, and kidney biopsy will confirm diagnosis.

Bibliography

Bomback AS, Appel GB, Radhakrishnan J, Shirazian S, Herlitz LC, Stokes B, et al. ANCA-associated glomerulonephritis in the very elderly. Kidney Int. 2011;79:757-64. [PMID: 21160463]

Item 22 Answer: C

Educational Objective: Diagnose pyroglutamic acidosis.

The most likely diagnosis is pyroglutamic acidosis. Pyroglutamic acidosis, which presents with mental status changes and an increased anion gap, occurs in selected patients receiving therapeutic doses of acetaminophen on a chronic basis. Susceptible patients are those with critical illness, poor nutrition, liver disease, or chronic kidney disease, as well as those on a strict vegetarian diet. In this context, acetaminophen leads to depletion of glutathione, altering the γ glutamyl cycle to overproduce pyroglutamic acid (also known as 5-oxoproline). Diagnosis can be confirmed by measuring urine levels of pyroglutamic acid.

D-Lactic acidosis presents with an increased anion gap metabolic acidosis and characteristic neurologic findings of intermittent confusion, slurred speech, and ataxia in patients with short-bowel syndrome. Accumulation of the D-isomer of lactate can occur in patients with short-bowel syndrome following jejunoileal bypass or small-bowel resection. In these patients, excess carbohydrates that reach the colon are metabolized to D-lactate. Laboratory studies show increased anion gap metabolic acidosis with normal plasma lactate levels, because the D-isomer is not measured by conventional laboratory assays for lactate. Diagnosis is confirmed by specifically measuring D-lactate. This patient's lack of short-bowel syndrome rules out this diagnosis.

Propylene glycol, a solvent used to enhance the solubility of various intravenously administered medications, causes an increased anion gap metabolic acidosis through its acid metabolites, L-lactate and D-lactate. An increased osmolal gap accompanies the increased anion gap metabolic acidosis seen with propylene glycol. This patient's clinical history and lack of lactic acidosis are not consistent with propylene glycol toxicity.

Salicylate toxicity most commonly presents in adults as respiratory alkalosis or with features of both respiratory alkalosis and increased anion gap metabolic acidosis. This patient has appropriate respiratory compensation for the metabolic acidosis, not respiratory alkalosis, making salicylate toxicity unlikely.

KEY POINT

- Pyroglutamic acidosis occurs in patients receiving therapeutic doses of acetaminophen on a chronic basis in the setting of critical illness, poor nutrition, liver disease, chronic kidney disease, or a strict vegetarian diet; diagnosis can be confirmed by measuring urine levels of pyroglutamic acid.

Bibliography

Fenves AZ, Kirkpatrick HM 3rd, Patel VV, Sweetman L, Emmett M. Increased anion gap metabolic acidosis as a result of 5-oxoproline (pyroglutamic acid): a role for acetaminophen. Clin J Am Soc Nephrol. 2006;1:441-7. [PMID: 17699243]

Item 23 Answer: B

Educational Objective: Diagnose abdominal compartment syndrome.

The most appropriate diagnostic test to perform next is intra-abdominal pressure (IAP) measurement. This patient's findings are consistent with abdominal compartment syndrome, which occurs in the setting of abdominal surgery, large volume fluid resuscitation, and multiple transfusions. It can manifest as a distended abdomen, ascites, and sodium-avid acute kidney injury (AKI). The increased IAP causes direct compression of renal parenchyma and vasculature, resulting in oliguria and decreased glomerular filtration rate. The diagnosis of abdominal compartment syndrome is made by an IAP measurement >20 mm Hg and new organ dysfunction. Indirect measurement of IAP can be with intragastric, intracolonic, intravesical (bladder), or inferior vena cava catheters. Management includes supportive therapy, abdominal compartment decompression, and correction of positive fluid balance.

The increased specific gravity, low urine sodium, and presence of hyaline casts are consistent with a prerenal AKI. The fractional excretion of sodium would not provide any additional information to aid in the diagnosis.

Myoglobin is a heme pigment-containing protein that can cause AKI. The urine is reddish brown, pigmented casts are present, and the urine dipstick is positive for blood in the absence of erythrocytes. Abdominal compartment syndrome is a much more likely cause of this patient's AKI, and urine myoglobin levels do not need to be measured.

The patient is on a cephalosporin, which can cause acute interstitial nephritis (AIN). AIN is characterized by hematuria, pyuria, and/or leukocyte casts. However, the timing is too soon for AIN (unless the patient had been previously exposed), and the urine findings do not support it. Moreover, the urine eosinophil stain is neither sensitive nor specific for the diagnosis of AIN and does not need to be performed.

KEY POINT

- Abdominal compartment syndrome is defined as a sustained intra-abdominal pressure >20 mm Hg associated with at least one organ dysfunction; management includes supportive therapy, abdominal compartment decompression, and correction of positive fluid balance.

Bibliography

Patel DM, Connor MJ Jr. Intra-abdominal hypertension and abdominal compartment syndrome: an underappreciated cause of acute kidney injury. Adv Chronic Kidney Dis. 2016;23:160-6. [PMID: 27113692]

Item 24 Answer: A

Educational Objective: Identify the cause of nonglomerular hematuria.

Cystoscopy is the most appropriate diagnostic test to perform next in this patient. Hematuria is frequently encountered among adults in ambulatory care. For hematuria incidentally discovered on dipstick evaluation, clinicians should confirm the presence of hematuria with microscopic urinalysis that demonstrates ≥3 erythrocytes/hpf before initiating further evaluation in asymptomatic adults. Clinicians should also pursue evaluation of hematuria even if the patient is receiving antiplatelet or anticoagulant therapy. Macroscopic hematuria should prompt urology referral even if self-limited. Hematuria is most often of nonglomerular origin. If a nephrologic cause of hematuria is not suggested, hematuria may indicate a malignancy. Guidelines from the American Urological Association recommend that patients older than 35 years or with risk factors for lower urinary tract malignancy (such as irritative voiding symptoms, smoking, aniline dye exposure, or cyclophosphamide exposure) undergo evaluation for malignancy with imaging. If imaging is negative, cystoscopy should be performed. This male patient is 45 years old without evidence of glomerular disease (no proteinuria or increased serum creatinine) and negative imaging of the upper genitourinary tract. Therefore, it is appropriate to assess for bladder pathology using cystoscopy.

Kidney biopsy in a patient with hematuria is not indicated in the absence of evidence of glomerular disease or change in kidney function. This patient's lack of proteinuria rules out a significant glomerular process, and his normal serum creatinine and lack of systemic symptoms make other kidney disease unlikely.

Kidney ultrasonography will provide no additional information in this patient. Doppler is not indicated because the risk of renal vein thrombosis as a cause of hematuria in this patient is not suspected (normal kidney function, no flank pain, and no risk of thrombosis).

Routine cytologic evaluation of urine is no longer recommended in the initial evaluation of asymptomatic microscopic hematuria, and urine markers approved by the FDA for bladder cancer detection are specifically not recommended for patients with hematuria.

KEY POINT

- Patients with hematuria who are older than 35 years or with risk factors for lower urinary tract malignancy (such as irritative voiding symptoms, smoking, aniline dye exposure, or cyclophosphamide exposure) should undergo evaluation for malignancy with imaging; if imaging is negative, cystoscopy is appropriate to assess for bladder pathology.

Bibliography

Davis R, Jones JS, Barocas DA, Castle EP, Lang EK, Leveillee RJ, et al; American Urological Association. Diagnosis, evaluation and follow-up of asymptomatic microhematuria (AMH) in adults. Available at: http://www.auanet.org/guidelines/asymptomatic-microhematuria-(2012-reviewed-and-validity-confirmed-2016). Accessed December 15, 2017.

Item 25 Answer: B

Educational Objective: Diagnose glomerulonephritis.

This patient likely has glomerulonephritis. Glomerular hematuria typically features brown- or tea-colored urine with dysmorphic erythrocytes (or acanthocytes) and/or erythrocyte casts on urine sediment examination. Erythrocyte casts are recognized by their cylindrical or tubular structure and inclusion of small, agranular spherocytes and, when present, are specific for hematuria of glomerular origin.

Isomorphic erythrocytes are of the same size and shape and usually arise from an extraglomerular urologic process causing bleeding into the genitourinary tract, such as a tumor, stone, or infection. Dysmorphic erythrocytes have varying sizes and shapes. Acanthocytes, a specific form of dysmorphic erythrocytes, are characterized by vesicle-shaped protrusions and suggest a glomerular source of bleeding. Acanthocytes and erythrocyte casts are highly specific for glomerulonephritis and exclude an extraglomerular cause of bleeding such as bladder cancer.

Sterile pyuria and leukocyte casts are hallmarks of tubulointerstitial nephritis, which can present acutely or may progress indolently and present as chronic kidney disease of unclear duration. Mild subnephrotic proteinuria also can be seen with interstitial nephritis. The cells comprising a leukocyte cast are larger than erythrocytes and appear more granular. The presence of erythrocyte casts excludes the diagnosis of tubulointerstitial nephritis.

Although this febrile patient has leukocytes (granular cells larger than erythrocytes) on urinalysis and positive leukocyte esterase on dipstick analysis, the presence of erythrocyte casts is specific for glomerulonephritis. This patient has the nephritic syndrome, which is associated with glomerular inflammation resulting in hematuria, proteinuria, and leukocytes in the urine sediment.

KEY POINT

- Glomerular macroscopic hematuria typically features brown- or tea-colored urine with dysmorphic erythrocytes (or acanthocytes) and/or erythrocyte casts on urine sediment examination.

Bibliography

Simerville JA, Maxted WC, Pahira JJ. Urinalysis: a comprehensive review. Am Fam Physician. 2005;71:1153-62. [PMID: 15791892]

H

Item 26 Answer: D

Educational Objective: Diagnose vancomycin-induced acute tubular necrosis.

The most likely cause of this patient's acute kidney injury (AKI) is vancomycin. The most common cause of hospital-acquired AKI is acute tubular necrosis (ATN), which represents damage and destruction of the renal tubular epithelial cells and is most commonly caused by ischemia or toxins. A careful evaluation of hemodynamics, volume status, medications, and physical findings of associated illness can help determine the cause of ATN. Most reported cases of vancomycin toxicity are due to acute interstitial nephritis; however, ATN has been reported. ATN is supported by the rapid rise in serum creatinine, fractional excretion of sodium >2%, and urine microscopy with numerous renal tubular epithelial cells and granular casts. Risk factors associated with vancomycin nephrotoxicity include chronic kidney disease, prolonged therapy, vancomycin doses ≥4 g/d, vancomycin trough concentrations >15 mg/L, and concomitant use of loop diuretics. Early recognition and prompt discontinuation of the drug are essential for renal recovery.

Some antibiotics (such as cefepime) and proton pump inhibitors (such as omeprazole) can cause acute interstitial nephritis (AIN). AIN may be associated with drugs, infection, autoimmune diseases, and malignancy. Only 10% to 30% of patients with AIN have the classic triad of fever, rash, and eosinophilia. Urine chemistries will reveal a variable (and unhelpful) fractional excretion of sodium, and urinalysis is characterized by hematuria, pyuria, and/or leukocyte casts and possibly eosinophiluria. Drug-induced AIN is characterized by a slowly increasing serum creatinine 7 to 10 days after exposure; however, it can occur within 1 day of exposure if the patient has been exposed previously. Drug-induced AIN can also occur months after exposure, as seen with NSAIDs and proton pump inhibitors. The patient's urine findings do not support AIN.

Contrast-induced nephropathy (CIN) results in ATN with an increase in serum creatinine within 48 hours of exposure. This patient's serum creatinine was at baseline 48 hours after exposure, making CIN an unlikely diagnosis.

KEY POINT

- Risk factors associated with vancomycin nephrotoxicity include chronic kidney disease, prolonged therapy, doses ≥4 g/d, trough concentrations >15 mg/L, and concomitant use of loop diuretics.

Bibliography

Bamgbola O. Review of vancomycin-induced renal toxicity: an update. Ther Adv Endocrinol Metab. 2016;7:136-47. [PMID: 27293542]

Item 27 Answer: B

H

Educational Objective: Treat acute hyponatremia in a symptomatic patient with hypertonic saline.

The most appropriate initial treatment is a 100 mL bolus of 3% saline. The hyponatremia in this young woman who presents confused and febrile is most likely due to ingestion of 3,4-methylenedioxymethamphetamine (ecstasy). Ecstasy is associated with hyponatremia both because it stimulates the release of antidiuretic hormone and because users often drink large quantities of water. When treating hyponatremia,

H CONT.

the rate of correction of serum sodium concentration must be carefully considered to avoid the osmotic demyelination syndrome. Brain cells adapt to chronic hyponatremia by reducing intracellular concentration of organic osmolytes, such as myoinositol, to cope with hypotonicity. Acute hyponatremia is associated with an increase in brain water and cerebral edema and should be treated rapidly. Because the brain has not adapted to the hypotonic environment by the release of organic osmolytes, the risk of rapid correction and development of osmotic demyelination is absent. Treatment is with a bolus of 3% saline, and a 100-mL bolus should raise the serum sodium level by 2 to 3 mEq/L (2-3 mmol/L). If symptoms persist, this can be repeated one to two times.

In patients with neurologic symptoms, fluid restriction by itself is not an appropriate treatment. The immediate goal is to reduce brain swelling rapidly by the acutely raising the serum sodium level. Even in cases of chronic hyponatremia, the serum sodium can be increased acutely by 2 to 3 mEq/L (2-3 mmol/L) as long as the total change in the serum sodium is <10 mEq/L (10 mmol/L) in a 24-hour period. Except in cases of hypovolemic hyponatremia, the use of 0.9% sodium chloride is not recommended. In patients who are not volume depleted and have syndrome of inappropriate antidiuretic hormone secretion with a fixed urine osmolality, the infused saline can be excreted in the urine in a smaller volume, and thus the serum sodium can actually fall.

Both oral urea and tolvaptan are appropriate treatments for chronic hyponatremia, but they do not raise the serum sodium rapidly enough to reverse neurologic abnormalities and are therefore inappropriate for treatment of acute hyponatremia in this symptomatic patient.

KEY POINT

- Treatment of acute symptomatic hyponatremia includes a 100-mL bolus of 3% saline to increase the serum sodium level by 2 to 3 mEq/L (2-3 mmol/L).

Bibliography

Sterns RH. Disorders of plasma sodium–causes, consequences, and correction. N Engl J Med. 2015;372:55-65. [PMID: 25551526]

H

Item 28 Answer: C

Educational Objective: Diagnose fibromuscular dysplasia as the cause of secondary hypertension.

Renal artery imaging is the most appropriate diagnostic test to perform next to evaluate for fibromuscular dysplasia in this young woman with new-onset hypertension. Fibromuscular dysplasia is a nonatherosclerotic form of renovascular disease that usually affects the mid and distal portions of the renal artery. This disorder usually occurs in young persons, particularly young women, and abrupt onset of hypertension in a patient under the age of 35 years is suggestive. The elevation of serum creatinine more than 30% from baseline after the initiation of an ACE inhibitor is a clue that renovascular hypertension may be present. Fibromuscular dysplasia is associated with aneurysm and/or dissection in a variety of vascular territories (for example, renal artery, carotid artery, and intracranial arteries). This has resulted in a recommendation that patients with fibromuscular dysplasia undergo one-time, head-to-pelvic cross-sectional imaging.

The importance of primary aldosteronism as a cause of hypertension is being increasingly recognized. Testing for primary aldosteronism should be considered in all patients with difficult-to-control hypertension. It should also be performed in patients with hypertension and an incidentally noted adrenal mass, spontaneous hypokalemia, or diuretic-induced hypokalemia. In these cases, the plasma aldosterone concentration/plasma renin activity ratio is obtained. Primary aldosteronism cannot account for this patient's renal bruit or serum creatinine elevation after the initiation of an ACE inhibitor.

Plasma fractionated metanephrines are obtained to screen for a pheochromocytoma. The absence of episodic palpitations, headaches, and tachycardia as well as the presence of an abdominal bruit make pheochromocytoma a less likely diagnosis.

Transthoracic echocardiography can be used for patients with clinical suspicion for white coat hypertension and/or to evaluate for end-organ damage. There are no pertinent findings from the history, physical examination, or electrocardiogram results to raise clinical suspicion for end-organ damage. More importantly, echocardiography will not be helpful in diagnosing the cause of this patient's hypertension or directing its treatment.

KEY POINT

- Renal artery imaging is the most appropriate diagnostic test to evaluate for fibromuscular dysplasia in a young woman with new-onset hypertension.

Bibliography

Olin JW, Gornik HL, Bacharach JM, Biller J, Fine LJ, Gray BH, et al; American Heart Association Council on Peripheral Vascular Disease. Fibromuscular dysplasia: state of the science and critical unanswered questions: a scientific statement from the American Heart Association. Circulation. 2014;129:1048-78. [PMID: 24548843]

Item 29 Answer: A

Educational Objective: Treat acute coronary syndrome in a patient with chronic kidney disease.

The most appropriate management for this patient with stage G4 chronic kidney disease (CKD) and ST-elevation myocardial infarction is immediate cardiac catheterization. Cardiovascular disease is the leading cause of death among patients with CKD. The risk of cardiovascular-related death in patients with CKD stages G3 and G4 is four to five times higher than the risk of progression to end-stage kidney disease. Mortality risk increases with decreasing estimated glomerular filtration rate and increasing albuminuria. Unfortunately, many clinical trials that guide the prevention or treatment of cardiovascular disease have not included patients with advanced CKD, and the findings may not be generalizable to patients with CKD. However, the recommendation from experts is to

H CONT.

offer patients with CKD therapy for cardiovascular disease, including cardiac catheterization, percutaneous coronary intervention, and coronary bypass. The available data suggest that routine invasive management is associated with a statistically significant reduction in death, acute myocardial infarction, and rehospitalization, across most categories of CKD, at the predictable price of a significant increase in major and minor bleeding. Prognosis for patients following myocardial infarction, percutaneous intervention, and coronary artery bypass surgery is worse for patients with CKD than for those without CKD.

Suspected coronary anomalies, such as anomalous coronary origins, can be evaluated by cardiac magnetic resonance (CMR) imaging. CMR imaging is not a practical modality for patients with acute coronary syndrome because of the time necessary to generate the images and inability to provide revascularization therapy. In addition, CMR uses gadolinium contrast, which is associated with the development of nephrogenic systemic fibrosis in patients with CKD.

Studies have examined the potential efficacy of precatheterization dialysis to reduce the risk of contrast-induced nephropathy in patients with advanced CKD. The balance of the data suggests no benefit for this invasive maneuver, and it generally is not advocated.

This patient has acute coronary syndrome, and avoiding cardiac catheterization and potential intervention to treat this life-threatening condition in lieu of medical management will not be in the patient's best interest, regardless of the risk for contrast-induced nephropathy.

KEY POINT

- The available data suggest that routine invasive management of coronary artery disease is associated with a statistically significant reduction in death, acute myocardial infarction, and rehospitalization, across most categories of chronic kidney disease.

Bibliography

Lingel JM, Srivastava MC, Gupta A. Management of coronary artery disease and acute coronary syndrome in the chronic kidney disease population–a review of the current literature. Hemodial Int. 2017;21:472-482. [PMID: 28093874]

H

Item 30 Answer: A

Educational Objective: Manage large kidney stones with extracorporeal shock wave lithotripsy.

The most appropriate next step in management is extracorporeal shock wave lithotripsy. Acute management of symptomatic nephrolithiasis is aimed at pain management and facilitation of stone passage. Pain can be relieved by NSAIDs and opioids as needed. Combination NSAID and opioid therapy seems more effective than treatment with either one alone. Stone passage decreases with increasing size of the stone. Only 50% of stones >6 mm will pass spontaneously, whereas stones >10 mm are extremely unlikely to pass spontaneously. Urologic intervention is required in all patients with evidence of infection, acute kidney injury, intractable nausea or pain, and stones that fail to pass or are unlikely to pass. This patient has an 11-mm stone that is at the ureteral pelvic junction. There is associated dilation of the renal calyces suggesting obstruction to urine outflow. It is unlikely that a stone this size will pass. Appropriate management therefore is urology consultation. The patient will most likely require extracorporeal shock wave lithotripsy or percutaneous nephrolithotomy. Extracorporeal shock wave lithotripsy can be used for stones in the renal pelvis and proximal ureter, but it is less effective for stones located in the mid/distal ureter or the lower pole calyx, larger stones (>15 mm), and hard stones (calcium oxalate monohydrate or cystine). Potential complications of extracorporeal shock wave lithotripsy include incomplete stone fragmentation, kidney injury, and possibly increased blood pressure or new-onset hypertension.

Treatment of uncomplicated renal colic with analgesia and maintenance intravenous fluids is just as efficacious as with forced hydration with regard to patient pain perception and opioid use. Moreover, it appears the state of hydration has little impact on stone passage. This patient may require intravenous fluids to avoid dehydration if pain and nausea prevent adequate oral fluid intake, but not as a means to expel the kidney stone.

Stones up to 10 mm can be managed conservatively, although the likelihood of spontaneous passage decreases with increasing size. Medical expulsive therapy with α-blocker therapy (such as tamsulosin) or a calcium channel blocker (such as nifedipine) can aid the passage of small stones (≤10 mm in diameter). This large stone associated with probable obstruction is not a candidate for medical expulsive therapy with either tamsulosin or nifedipine.

KEY POINT

- Urologic intervention is required in all patients with evidence of infection, acute kidney injury, intractable nausea or pain, and stones that fail to pass or are unlikely to pass.

Bibliography

Lawler AC, Ghiraldi EM, Tong C, Friedlander JI. Extracorporeal shock wave therapy: current perspectives and future directions. Curr Urol Rep. 2017;18:25. [PMID: 28247327]

Item 31 Answer: C

Educational Objective: Diagnose sarcoidosis with kidney involvement.

The most likely diagnosis is sarcoidosis, a systemic inflammatory disease that can affect multiple organs. The most common presentations of sarcoidosis are hilar lymphadenopathy and parenchymal lung disease; common extrapulmonary organ involvement includes the skin, joints, and eyes. More than 90% of patients with kidney involvement have thoracic sarcoid identified on chest radiograph. Kidney manifestations in sarcoidosis are common and include nephrocalcinosis from hypercalcemia and hypercalciuria, nephrolithiasis, and chronic interstitial nephritis with

granuloma formation. Hypercalcemia occurs due to peripheral conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D by activated macrophages. Parathyroid hormone is typically suppressed in response to the hypercalcemia. The urinalysis is typical of other chronic tubulointerstitial diseases and can be normal or show only sterile pyuria or mild proteinuria, as in this patient's case. Kidney manifestations of hypercalcemia and interstitial nephritis are treated with glucocorticoids.

Thiazide diuretics can be associated with a mild hypercalcemia but not nephrocalcinosis. Furthermore, they decrease urinary calcium excretion. This patient's urinary calcium excretion is increased.

Primary hyperparathyroidism is characterized by hypercalcemia, hypophosphatemia, and inappropriately normal or elevated parathyroid hormone. This patient's parathyroid hormone is suppressed, making this an unlikely diagnosis.

Increased levels of calcium absorption from the gut can be from markedly high vitamin D levels. Vitamin D intoxication is usually defined as a value >150 ng/mL (374.4 nmol/L). Vitamin D intoxication is not consistent with the laboratory findings because the phosphorus and 25-hydroxyvitamin D levels are normal.

Finally, thiazide diuretic use, primary hyperparathyroidism, or vitamin D intoxication cannot account for the patient's pulmonary findings.

KEY POINT

- Kidney involvement in sarcoidosis can manifest as nephrocalcinosis from hypercalcemia and hypercalciuria, and as tubulointerstitial nephritis with granuloma formation.

Bibliography

Löffler C, Löffler U, Tuleweit A, Waldherr R, Uppenkamp M, Bergner R. Renal sarcoidosis: epidemiological and follow-up data in a cohort of 27 patients. Sarcoidosis Vasc Diffuse Lung Dis. 2015;31:306-15. [PMID: 25591142]

Item 32 Answer: C

Educational Objective: Identify normal physiologic changes in pregnancy as a cause of low serum sodium.

Normal physiologic change in pregnancy is the most likely cause of this patient's low serum sodium level. Mild hyponatremia is common in normal pregnancy due to plasma volume increases with water retention (mediated by an increase in antidiuretic hormone levels) greater than sodium retention. An associated drop in serum osmolality of 8 to 10 mOsm/kg H_2O and serum sodium concentration of 4 to 5 mEq/L (4-5 mmol/L) may occur. As the serum osmolality and sodium concentration decrease, a new set point is maintained, and thirst occurs in response to osmolality (reset osmostat). No treatment is necessary. Other conditions associated with reset osmostat include quadriplegia, tuberculosis, advanced age, psychiatric disorders, and chronic malnutrition.

Primary polydipsia should always be considered in the differential diagnosis of patients with mental illness and hyponatremia, particularly those with schizophrenia who are taking psychotropic drugs. Primary polydipsia presents with hyponatremia, decreased serum osmolality, and decreased urine osmolality, reflecting suppressed antidiuretic hormone (ADH) levels in response to water overload. Primary polydipsia is a rare cause of hyponatremia, and the volume of water intake would need to be very large to induce hyponatremia. This patient is not at risk for primary polydipsia.

Hypovolemia causes stimulation of the sympathetic nervous system, activation of the renin-angiotensin-aldosterone axis, and release of ADH. These adaptive responses allow volume maintenance at the expense of a low serum sodium with excessive water intake. Blood pressure in pregnant women begins to lower in the first trimester and reaches a nadir in the second. Furthermore, she is asymptomatic, and ADH release is therefore not likely to be induced by this level of blood pressure.

The syndrome of inappropriate antidiuretic hormone (SIADH) secretion may be associated with stress and pain; however, hyponatremia does not develop acutely. Although SIADH could have preceded the patient's car accident, she has no risk factors for SIADH (central nervous system disorders, pulmonary disorders, infection, drugs, postoperative status, tumors), and normal pregnancy is a more likely cause of her low serum sodium level.

KEY POINT

- Mild hyponatremia is common in normal pregnancy due to plasma volume increases with water retention greater than sodium retention; no treatment is necessary.

Bibliography

Cheung KL, Lafayette RA. Renal physiology of pregnancy. Adv Chronic Kidney Dis. 2013;20:209-14. [PMID: 23928384]

Item 33 Answer: D

Educational Objective: Treat dyslipidemia in a patient with stage G4 chronic kidney disease.

A statin is appropriate to treat dyslipidemia in this patient with stage G4 chronic kidney disease (CKD). Guidelines from the Kidney Disease: Improving Global Outcomes (KDIGO) group provide a grade 1A recommendation to treat adults aged ≥50 years with an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m², but not treated with chronic dialysis or kidney transplantation (GFR categories G3a-G5), with a statin or statin/ezetimibe combination. This recommendation largely emanates from results of the Study of Heart and Renal Protection (SHARP) trial, which included 9270 participants with CKD (mean eGFR, 27 mL/min/1.73 m²) who received simvastatin 20 mg plus ezetimibe 10 mg daily or placebo and were followed for 5 years. Statin plus ezetimibe therapy

led to a significant 17% reduction in the relative hazard of the primary outcome of major atherosclerotic events (coronary death, myocardial infarction, nonhemorrhagic stroke, or any revascularization) compared with placebo (HR, 0.83; 95% CI, 0.74-0.94), driven by significant reductions in nonhemorrhagic stroke and coronary revascularization. It should be noted that simvastatin plus ezetimibe did not reduce the risk of progression to end-stage kidney disease.

Hypertriglyceridemia is the primary lipid abnormality in patients with CKD. However, the 2013 KDIGO update states that the evidence supporting the safety and efficacy of fibrates (such as gemfibrozil) is extremely weak, especially in patients with CKD. Therefore, KDIGO does not recommend fibrates for the treatment of hypertriglyceridemia. Finally, in patients taking a statin for dyslipidemia, the addition of a fibrate increases the risk of myalgia, muscle injury, and rhabdomyolysis.

Although niacin raises HDL cholesterol, several trials involving patients with and without CKD have demonstrated no evidence of improvement in cardiovascular events.

Although randomized controlled trials of omega-3 fatty acids have demonstrated a reduction in cardiovascular disease end points in persons with atherosclerotic cardiovascular disease (ASCVD), little to no data demonstrate the role for the benefits of omega-3 fatty acids for the primary prevention of ASCVD in patients at high cardiovascular disease risk.

KEY POINT

- The Kidney Disease: Improving Global Outcomes (KDIGO) guidelines recommend treatment of dyslipidemia with a statin in patients aged ≥50 years with an estimated glomerular filtration rate <60 mL/min/1.73 m^2, but not treated with chronic dialysis or kidney transplantation.

Bibliography

Kidney Disease: Improving Global Outcomes (KDIGO) Lipid Work Group. KDIGO clinical practice guideline for lipid management in chronic kidney disease. Kidney inter., Suppl. 2013;3:259-305. Available at www.kdigo.org.

H

Item 34 Answer: D

Educational Objective: Diagnose nephrolithiasis with noncontrast helical abdominal CT.

Noncontrast helical abdominal CT is the most appropriate next test for this patient with nephrolithiasis suggested by unilateral flank pain and hematuria. Ultrasonography is an appropriate initial diagnostic test for suspected nephrolithiasis; it is easily available, safe, and relatively inexpensive, and it is the study of choice in pregnant women. Ultrasonography can demonstrate hydronephrosis, kidney size and cortical thickness, echogenicity, and the presence of cysts and tumors. It is useful for uncomplicated nephrolithiasis; a positive ultrasound may be adequate for initial diagnosis. Ultrasonography is less useful in evaluating diseases of the mid or distal ureter, including stones. Furthermore, the absence of hydronephrosis on ultrasound does not rule out kidney stones. Noncontrast helical CT is the gold standard for diagnosis of nephrolithiasis and is appropriate for evaluating renal colic. Most stones can be detected, including small stones and those in the distal ureter not detected on ultrasound. It may provide information regarding stone composition and, because the entire urinary tract and abdomen are visualized, alternative diagnoses may be suggested.

MRI with contrast is not as sensitive as CT in detecting suspected kidney stones. Due to lack of radiation, MRI may be useful in pregnant women with stone disease if ultrasound is nondiagnostic.

Contrast abdominal CT characterizes renal tumors and cysts, whereas CT urography is the preferred test for patients with unexplained urologic/nonglomerular hematuria. The decision to use contrast depends on the clinical scenario, the patient's risk factors for contrast-induced nephropathy, and the availability and utility of alternative imaging modalities. It is unnecessary in the evaluation of suspected nephrolithiasis and poses greater risk and cost in this situation compared with either ultrasonography or noncontrast helical abdominal CT.

Plain abdominal radiography has limited utility due to its inability to detect radiolucent uric acid stones and does not provide as much anatomic information as other modalities. However, it may be useful in assessing stone burden in patients with known radiopaque stones but is not the initial test of choice for acute nephrolithiasis.

KEY POINT

- Noncontrast helical CT is the gold standard for diagnosis of nephrolithiasis.

Bibliography

Brisbane W, Bailey MR, Sorensen MD. An overview of kidney stone imaging techniques. Nat Rev Urol. 2016;13:654-662. [PMID: 27578040]

Item 35 Answer: C

Educational Objective: Identify increased muscle mass as a cause of an increase in serum creatinine.

Measurement of the serum cystatin C level is appropriate for this patient. Cystatin C may be preferable to creatinine to assess kidney function in individuals with higher muscle mass. An increase in muscle mass would be expected to result in an increase in serum creatinine level in the absence of change in kidney function. This muscular man with a BMI of 29 has increase in muscle mass. Because serum creatinine is derived from the metabolism of creatinine produced by muscle, a significant increase in muscle mass would be expected to increase serum creatinine. An elevation in serum creatinine could also occur with creatine supplements, which he is not taking. This patient has a normal urinalysis and no proteinuria, all of which indicate no evidence of underlying kidney disease. Cystatin C, which is cleared by the kidney, is produced by all nucleated cells; therefore, levels are less dependent on muscle mass. Cystatin C can also be used for

more accurate glomerular filtration rate estimation in these patients as a component of the Chronic Kidney Disease Epidemiology Collaboration equation.

Although NSAIDs can cause acute kidney injury, the remote and infrequent use by this patient is unlikely to have any effect on serum creatinine. The hemodynamic effects of NSAIDs will disappear within 24 hours of stopping the medication, and interstitial nephritis from NSAIDs is unlikely to present with occasional dosing and is usually associated with proteinuria. The adverse effects of renal fibrosis associated with NSAIDs are only seen with extensive and long-term use.

Creatine kinase levels can be measured to evaluate for the presence of rhabdomyolysis. Rhabdomyolysis significant enough to cause kidney injury would be expected to result in myoglobinuria reflected by heme-positive urine in the absence of red cells. No blood was seen on urinalysis.

In the absence of other changes suggesting glomerular or interstitial disease, a kidney biopsy is not necessary.

KEY POINT

- Increased muscle mass can result in an increase in serum creatinine level in the absence of change in kidney function.

Bibliography

Baxmann AC, Ahmed MS, Marques NC, Menon VB, Pereira AB, Kirsztajn GM, et al. Influence of muscle mass and physical activity on serum and urinary creatinine and serum cystatin C. Clin J Am Soc Nephrol. 2008;3:348-54. [PMID: 18235143]

H Item 36 Answer: B

Educational Objective: Manage recurrent stone disease with hydrochlorothiazide.

The most appropriate next step to decrease this patient's stone recurrence is to add a thiazide diuretic such as hydrochlorothiazide. Hypercalciuria is the most common metabolic risk factor for calcium oxalate stones. In patients with hypercalcemia, increased filtered calcium results in hypercalciuria. However, hypercalciuria is often idiopathic and commonly familial, occurring without associated hypercalcemia. Hypercalciuria due to hypercalcemia is treated by addressing the cause of increased serum calcium. In patients with other forms of hypercalciuria, thiazide diuretics reduce calcium excretion in the urine by inducing mild hypovolemia, triggering increased proximal sodium reabsorption and passive calcium reabsorption. This effect can be enhanced by the addition of sodium restriction.

The patient's evaluation reveals a normal uric acid concentration. In calcium stones that form on a uric acid nidus, allopurinol has been associated with a decrease in stone formation. In this patient, however, stone analysis did not reveal a uric acid core and thus would not be the next step in management.

Urinary citrate inhibits stone formation by binding calcium in the tubular lumen, preventing it from precipitating with oxalate. Hypocitraturia is seen with diets high in animal protein and metabolic acidosis from chronic diarrhea, renal tubular acidosis, ureteral diversion, and carbonic anhydrase inhibitors (including seizure medications such as topiramate). The patient's urine citrate level is in the high-normal range, and the serum bicarbonate level is normal, thus increasing citrate in the urine would not be beneficial.

Although increasing urine volume will reduce the calcium saturation, the present urine volume is acceptable. Urine volume to prevent stone recurrence should be between 2500 and 3000 mL per day.

Recommending a low calcium diet is inappropriate for this patient because reducing calcium in the diet would provide less calcium in the gastrointestinal tract to bind oxalate and would increase oxalate absorption, and thus increase urine oxalate concentration and stone formation.

KEY POINT

- In patients with hypercalciuria and kidney stones, calcium excretion and stone formation can be decreased by the use of thiazide diuretics.

Bibliography

Qaseem A, Dallas P, Forciea MA, Starkey M, Denberg TD; Clinical Guidelines Committee of the American College of Physicians. Dietary and pharmacologic management to prevent recurrent nephrolithiasis in adults: a clinical practice guideline from the American College of Physicians. Ann Intern Med. 2014;161:659-67. [PMID: 25364887]

Item 37 Answer: B

Educational Objective: Screen for intracranial cerebral aneurysms in a patient with autosomal dominant polycystic kidney disease.

MR angiography of the brain is the most appropriate next step in management. This patient has autosomal dominant polycystic kidney disease (ADPKD), a genetic kidney disease characterized by enlarged kidneys with multiple cysts. Intracranial cerebral aneurysms are detected in 5% to 10% of patients with ADPKD and have a strong familial pattern. Guidelines for the Management of Patients with Unruptured Intracranial Aneurysms from the American Heart Association/American Stroke Association recommend that patients with a history of ADPKD, particularly those with a family history of intracranial aneurysm but even those without such history, should be offered screening by CT angiography or MR angiography. This is a class I recommendation (should be performed because benefit greatly exceeds risk) based on level B evidence (data derived from a single randomized trial or nonrandomized studies).

Mitral valve prolapse is an extrarenal manifestation seen in some patients with ADPKD, but screening with echocardiography should be limited to patients with findings of this valvular disorder, including chest pain, shortness of breath, edema, a systolic click(s) that is mobile (timing changes with squatting and standing), and a systolic murmur.

Blood pressure control is recommended to slow progression in ADPKD, but the utility of doing so in someone with low baseline blood pressures is unproven. The agent of choice when blood pressure medications are used in ADPKD is a blocker of the renin-angiotensin system and not a calcium channel blocker.

Vasopressin blockade with tolvaptan in patients with ADPKD has been shown in two randomized clinical trials to delay the need for dialysis from 6 to 9 years. Tolvaptan carries an FDA-mandated safety warning about the possibility of irreversible liver injury. Tolvaptan has not been approved for use in ADPKD in the United States.

KEY POINT

- Screening for intracranial cerebral aneurysms using CT or MR angiography is recommended for patients with autosomal dominant polycystic kidney disease.

Bibliography

Chapman AB, Devuyst O, Eckardt KU, Gansevoort RT, Harris T, Horie S, et al; Conference Participants. Autosomal-dominant polycystic kidney disease (ADPKD): executive summary from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. Kidney Int. 2015;88:17-27. [PMID: 25786098]

Item 38 Answer: E

Educational Objective: Manage primary membranous glomerulopathy.

An ACE inhibitor and statin are appropriate for this patient with recently diagnosed primary membranous glomerulopathy. His kidney biopsy findings are consistent with the diagnosis, and the presence of anti–phospholipase A2 receptor (PLA2R) antibodies has been shown to approach 100% specificity for the primary form of this disease. Approximately one third of patients with primary membranous glomerulopathy experience a spontaneous remission of disease over the first 6 to 24 months without immunosuppression. Therefore, within the first 6 months of diagnosis, barring signs of severe complications of the nephrotic syndrome (such as kidney failure, anasarca, or deep vein thrombosis), the recommended strategy is to treat patients with primary membranous glomerulopathy conservatively with renin-angiotensin system blockers, cholesterol-lowering medications (if cholesterol is above goal), and diuretics (for edema). The patient is then monitored with examinations and laboratory studies to gauge for spontaneous remission. If proteinuria increases in 6 to 12 months, a course of immunosuppression should be considered for those with persistent nephrotic-range proteinuria. With the advent of serologic testing for anti-PLA2R antibodies, these titers can now be followed during the observation period alongside traditional clinical parameters, such as proteinuria. Falling anti-PLA2R titers are associated with remission, whereas persistently high titers are associated with ongoing disease activity.

Alternating months of glucocorticoids and alkylating agents is first-line immunosuppressive therapy of choice for primary membranous glomerulopathy, and substituting with a calcineurin inhibitor such as cyclosporine is now considered a viable alternative for patients with contraindications to alkylating agents. However, utilization of such immunosuppressive therapies at this point is premature and runs the risk of treating a patient who may remit spontaneously.

Although hepatitis B and C virus infections, along with lupus, are well-known forms of secondary membranous glomerulopathy in adults, this patient's screening tests are negative and, with PLA2R antibody positivity, further testing is unnecessary.

KEY POINT

- Patients with newly diagnosed primary membranous glomerulopathy are usually observed for 6 to 12 months while on conservative therapy (renin-angiotensin blockade, cholesterol-lowering medication, and edema management) to allow time for possible spontaneous remission before initiating immunosuppression.

Bibliography

Couser WG. Primary membranous nephropathy. Clin J Am Soc Nephrol. 2017;12:983-997. [PMID: 28550082] doi:10.2215/CJN.11761116

Item 39 Answer: A

Educational Objective: Treat hypertension in a patient with atherosclerotic renovascular disease.

The most appropriate next step in management is to begin lisinopril. The patient most likely has atherosclerotic renovascular disease, given his age, diminished pulses, and resistant hypertension despite treatment with four antihypertensive medications, including a diuretic. Most patients with renovascular disease have atherosclerosis (>90%). In this patient, medical therapy should be optimized to include treatment of underlying cardiovascular risk factors such as hypercholesterolemia and addition of an ACE inhibitor or angiotensin receptor blocker (ARB) for blood pressure control. Kidney function should be checked 2 weeks after the addition of an ACE inhibitor or ARB to ensure that the serum creatinine does not increase, and the ACE inhibitor or ARB can be continued if there is not a >25% rise in the serum creatinine from baseline.

Although renal angiography is the gold standard for diagnosis of renovascular disease, it is not recommended as a routine test due to adverse risks such as contrast nephropathy and cholesterol emboli. It is undertaken only if an intervention to correct a discovered stenosis is planned. However, medical therapy is recommended for most adults with atherosclerotic renal artery stenosis.

Three randomized controlled trials (STAR, ASTRAL, and CORAL) failed to show that renal artery angioplasty confers additional benefit above optimal medical therapy for patients with atherosclerotic renovascular disease who have stable kidney function. Patients who may benefit from percutaneous angioplasty and stenting or surgical intervention include those who present with a short hypertension

duration; fail medical therapy; or have severe hypertension or recurrent flash pulmonary edema, refractory heart failure, acute kidney injury following treatment with an ACE inhibitor or ARB, or progressive impaired kidney function. In patients who have an indication for renal artery revascularization, surgery is preferred only for those with complex anatomic lesions such as aneurysm or aortoiliac occlusive disease.

KEY POINT

- In most patients with renal artery stenosis, the primary therapeutic intervention is medical management, including correction of modifiable cardiovascular risk factors.

Bibliography

Cooper CJ, Murphy TP, Cutlip DE, Jamerson K, Henrich W, Reid DM, et al; CORAL Investigators. Stenting and medical therapy for atherosclerotic renal-artery stenosis. N Engl J Med. 2014;370:13-22. [PMID: 24245566]

H

Item 40 Answer: B

Educational Objective: Prevent contrast-induced nephropathy in a patient with chronic kidney disease.

Intravenous isotonic fluid (0.9% sodium chloride or 1.26% sodium bicarbonate) administered before and after cardiac catheterization is the most appropriate preventive measure for this patient with chronic kidney disease (CKD) who is at risk for contrast-induced nephropathy (CIN). CIN is a common cause of acute kidney injury in the hospital. Patients can be exposed to iodinated intravenous contrast during cardiac catheterization, angiography, and CT. Contrast agents are thought to cause acute tubular necrosis through renal vasoconstriction and direct cytotoxicity; however, the mechanisms are not completely understood. Risk factors for CIN include advanced age, diabetic nephropathy, multiple myeloma, concomitant use of nephrotoxins (for example, aminoglycoside antibiotics, NSAIDs), severity of CKD, reduced renal perfusion (due to poor cardiac function or volume depletion), higher dose of contrast, high osmolar contrast (rarely used in industrialized contrast), repeated doses of contrast, and intra-arterial administration. Intravenous isotonic fluids (1-1.5 mL/kg/h 3 to 4 hours before the procedure and continued for 6 to 12 hours) are the mainstay in preventing CIN and perform better than hypotonic fluids. However, among isotonic fluids, evidence does not support the superiority of any one particular fluid when comparing normal saline with sodium bicarbonate. Intravenous fluids should not be given to prevent CIN in patients who are hypervolemic.

Furosemide before catheterization is incorrect because diuresis would induce volume contraction, activate the renal angiotensin-aldosterone system, and increase the risk for CIN.

Oral bicarbonate does not have a role in the prevention of CIN, as studies using alkali therapy looked at intravenous forms only. However, intravenous infusion of 1.26% sodium bicarbonate is as efficacious in preventing CIN as is 0.9% sodium chloride infusion.

This patient has no indications for renal replacement therapy. Hemodialysis does not improve CIN outcomes but rather may exacerbate kidney injury.

KEY POINT

- Intravenous isotonic fluids are the mainstay in preventing contrast-induced nephropathy.

Bibliography

Fähling M, Seeliger E, Patzak A, Persson PB. Understanding and preventing contrast-induced acute kidney injury. Nat Rev Nephrol. 2017;13:169-180. [PMID: 28138128]

H

Item 41 Answer: B

Educational Objective: Diagnose type 1 (hypokalemic distal) renal tubular acidosis.

The most likely cause of this patient's laboratory findings is type 1 (hypokalemic distal) renal tubular acidosis (RTA). It is due to a defect in urine acidification in the distal nephron and is most commonly caused by decreased activity of the proton pump in collecting duct intercalated-A cells. Because of the inability to excrete hydrogen ions, patients develop a metabolic acidosis with compensatory hyperchloremia, resulting in a normal anion gap, which is 8 mEq/L (8 mmol/L) in this patient, and the inability to acidify urine below a pH of 6.0, even in the context of an acidemia. The urine anion gap (using the equation: [Urine Sodium + Urine Potassium] − Urine Chloride) would be positive in this case, reflecting decreased acid excretion in the form of ammonium and chloride. The same defects also cause potassium wasting, and the increased proximal resorption of citrate that occurs with metabolic acidosis leads to hypocitraturia and increased risk of calcium phosphate kidney stones and nephrocalcinosis. This patient most likely has Sjögren syndrome (arthralgia, sicca, parotid gland enlargement) with concomitant interstitial nephritis (echogenicity seen on kidney ultrasound), one of the most common diseases associated with a distal RTA.

Naproxen, as well as other NSAIDs, can cause an interstitial nephritis usually accompanied by acute kidney injury and proteinuria, neither of which is seen in this case.

Type 2 (proximal) RTA involves a proximal tubular defect in reclaiming bicarbonate and is characterized by a normal anion gap metabolic acidosis, hypokalemia, glycosuria (without hyperglycemia), low-molecular-weight proteinuria, and renal phosphate wasting (known as Fanconi syndrome when all features are present). Because distal urine acidification remains intact, the urine pH is usually <5.5 without alkali therapy, and the urine anion gap should be negative, reflecting increased excretion of acid in the form of ammonium and chloride. This patient's high urine pH and absence of other characteristic features make type 2 (proximal) RTA unlikely.

Type 4 (hyperkalemic distal) RTA due to aldosterone deficiency or resistance is associated with hyperkalemia and a urine pH <5.5, neither of which is seen in this patient.

KEY POINT

- Type 1 (hypokalemic distal) renal tubular acidosis is due to a defect in urine acidification in the distal nephron and is characterized by a normal anion gap metabolic acidosis, positive urine anion gap, inability to acidify urine below a pH of 6.0, and potassium wasting.

Bibliography

Rastegar M, Nagami GT. Non-anion gap metabolic acidosis: a clinical approach to evaluation. Am J Kidney Dis. 2017;69:296-301. [PMID: 28029394]

H

Item 42 Answer: B

Educational Objective: Treat alcoholic ketoacidosis.

The most appropriate treatment is 5% dextrose in 0.9% saline for this patient who most likely has alcoholic ketoacidosis. Alcoholic ketoacidosis occurs in patients with chronic ethanol abuse, frequently with associated liver disease, and develops following an episode of acute intoxication. This patient has an increased anion gap metabolic acidosis (with an anion gap of 31), and ketoacidosis due to acute ethanol intoxication is the most likely cause. The ethanol level may be low or normal at the time of presentation because ingested ethanol may have already been extensively metabolized. Decreased insulin secretion (as a result of starvation) and increased counter-regulatory hormones cause lipolysis and generation of ketones, such as acetoacetate, which result in the anion gap. The urine in this case shows ketones, although ketone test results may be falsely negative in some cases because the nitroprusside reagent in the ketone assay detects only acetoacetate and the ketone β-hydroxybutyrate may predominate. Treatment with dextrose will increase insulin and decrease glucagon secretion, while saline will repair any volume deficit; the combination will correct ketoacidosis. In patients with alcoholism, thiamine should be administered before any glucose-containing solutions to decrease the risk of precipitating Wernicke encephalopathy.

Saline alone will correct the volume deficit, but glucose is needed to stimulate insulin secretion to correct the ketoacidosis.

Although dextrose with sodium bicarbonate may correct the underlying acidosis, there is no indication for additional bicarbonate in treating the ketoacidosis. In addition, alcoholic ketoacidosis may be associated with metabolic alkalosis due to concurrent vomiting. To determine if there is a concomitant metabolic alkalosis present, the corrected bicarbonate can be calculated. The corrected bicarbonate is the difference between the normal bicarbonate concentration and the delta anion gap. The delta anion gap is the difference between the measured anion gap and the normal anion gap. In this case the corrected bicarbonate concentration is 5 mEq/L (5 mmol/L) [24 − (31 − 12)]. Because the measured bicarbonate concentration (10 mEq/L [10 mmol/L]) is greater than the corrected, or expected, bicarbonate concentration, a concomitant metabolic alkalosis is present. Treatment with bicarbonate would be inappropriate.

Insulin treatment is not necessary because dextrose alone will increase insulin levels in patients who do not have diabetes mellitus.

KEY POINT

- For patients with alcoholic ketoacidosis, 5% dextrose in 0.9% saline is appropriate treatment.

Bibliography

Palmer BF, Clegg DJ. Electrolyte disturbances in patients with chronic alcohol-use disorder. N Engl J Med. 2017;377:1368-1377. [PMID: 28976856]

Item 43 Answer: A

Educational Objective: Treat edema associated with the nephrotic syndrome.

Addition of the thiazide diuretic metolazone is the most appropriate treatment. Edema management in a patient with newly diagnosed nephrotic syndrome generally starts with a salt-restricted diet and an oral loop diuretic, with a goal weight loss of 1 to 2 kg (2.2-4.4 lb) per week. Loop diuretics should be uptitrated toward this weight loss goal until a maximal dose is achieved, with close monitoring of electrolytes. It is appropriate for blood urea nitrogen, serum creatinine, and serum urate to rise slightly (≤10%) with effective diuresis. When oral loop diuretics have been maximally uptitrated, and weight loss and edema control are insufficient, it is often necessary to add a second oral diuretic (a thiazide diuretic and/or potassium-sparing diuretic) that works distal to the loop of Henle, which in this case can be accomplished via the addition of metolazone in this patient taking maximal-dose furosemide.

Loop diuretics are similarly effective when administered at equipotent doses. All loop diuretics have a similar dose-response curve characterized by an increased diuresis as more of the drug is renally excreted and flattening of the curve, at which further increases in dose are not associated with increased drug excretion and resultant diuresis.

Hospitalization for intravenous diuresis should be reserved for patients who have not responded to maximal doses of oral diuretics (that is, loop diuretic *and* thiazide diuretic) or for patients with severe symptoms of anasarca such as shortness of breath, swelling of genital regions, or gastrointestinal discomfort from ascites.

Repeating lower extremity Doppler ultrasonography is not indicated at this time given this patient's prior negative test results; serum albumin level >2.8 g/dL (28 g/L) (clotting risk in membranous glomerulopathy rises when albumin is ≤2.8 g/dL [28 g/L]); and the symmetric nature of his edema.

KEY POINT

- Edema management in a patient with newly diagnosed nephrotic syndrome starts with a salt-restricted diet and an oral loop diuretic; when loop diuretics have been maximally uptitrated and weight loss/edema control is insufficient, it is often necessary to add a thiazide and/or potassium-sparing diuretic.

Bibliography

Kodner C. Diagnosis and management of nephrotic syndrome in adults. Am Fam Physician. 2016;93:479-85. [PMID: 26977832]

Item 44 Answer: D

Educational Objective: Diagnose secondary focal segmental glomerulosclerosis.

Secondary focal segmental glomerulosclerosis (FSGS) is the most likely diagnosis. FSGS is the most common form of the nephrotic syndrome in black persons. In the United States, FSGS currently accounts for up to 40% of idiopathic (primary) nephrotic syndromes in adults. The pathogenesis of FSGS stems from podocyte injury due to immunologic, genetic, and/or hyperfiltration causes. A large and growing proportion of FSGS cases are considered secondary forms of FSGS due to hyperfiltration injury in the setting of relatively reduced renal mass. The overworking of the glomerulus in this setting leads to adaptive podocyte injury and segmental sclerosis. This hyperfiltration form of FSGS is classically seen in obese patients but also can manifest in patients with a history of premature birth or solitary kidney. This patient has two risk factors for the secondary form of FSGS: obesity and a history of premature birth. In addition, her presentation is more typical of a secondary FSGS lesion, with subnephrotic proteinuria and no associated clinical findings. Electron microscopy of her kidney biopsy would be expected to show only mild to moderate effacement of the podocyte's foot processes. An immunologic route to injury is considered the main pathogenic mechanism behind primary forms of FSGS, with leukocytes producing a soluble circulating factor that directly targets podocytes. In such cases, proteinuria tends to be heavy (nephrotic range) with associated hypoalbuminemia, and edema is usually present on physical examination. Electron microscopy of a kidney biopsy with primary FSGS will typically show extensive effacement of the podocyte's foot process.

Diabetic nephropathy is the sequelae of chronic glycemic-induced damage to the glomerulus. On average, it occurs 8 years after the diagnosis of overt diabetes mellitus and is typically associated with other microvascular or macrovascular complications of diabetes. This patient's short history of prediabetes and lack of other microvascular/macrovascular findings makes diabetic nephropathy an unlikely diagnosis.

Lipoprotein glomerulopathy is a rare kidney disease characterized by moderate to severe proteinuria, progressive kidney failure, and distinct histopathologic findings of glomerular capillary dilatation by lipoprotein thrombi. To date, less than 100 cases have been reported in the medical literature, nearly all of which are from East Asian countries (predominantly Japan and China). This patient does not fit the profile for lipoprotein glomerulopathy.

Minimal change glomerulopathy typically presents with the full nephrotic syndrome (proteinuria >3500 mg/24 h, serum albumin usually <3.0 g/dL [30 g/L], hypercholesterolemia, and edema on examination). These findings do not fit this patient's mild presentation.

KEY POINT

- Secondary focal segmental glomerulosclerosis is due to hyperfiltration injury in the setting of relatively reduced renal mass; it is classically seen in obese patients but also can manifest in those with a history of premature birth or solitary kidney.

Bibliography

D'Agati VD, Kaskel FJ, Falk RJ. Focal segmental glomerulosclerosis. N Engl J Med. 2011;365:2398-411. [PMID: 22187987] doi:10.1056/NEJMra1106556

Item 45 Answer: D

Educational Objective: Identify the risk of venous thromboembolism in the nephrotic syndrome.

The nephrotic syndrome can be complicated by clotting manifestations due to a secondary hypercoagulable state. Of all the nephrotic syndromes, membranous glomerulopathy carries the greatest risk for clotting abnormalities, with some series reporting thrombotic complications in up to 35% of the most severe membranous glomerulopathy cases. The etiology for the hypercoagulable state in membranous glomerulopathy and other forms of heavy nephrosis is multifactorial. In response to the hypoalbuminemia induced by nephrotic-range proteinuria, the liver overproduces proteins. This is most classically seen in the form of hyperlipidemia. In addition, hepatic overproduction of proteins in response to hypoalbuminemia can also lead to increased levels of procoagulant proteins such as factor V, factor VIII, and fibrinogen. Urinary loss of albumin in high volume is also accompanied by similar urinary losses of low-molecular-weight anticoagulants (notably, antithrombin III and protein S) and fibrinolytics (such as plasminogen). In a large retrospective cohort of clotting complications in membranous glomerulopathy, >70% of the clots occurred within 2 years of diagnosis, and the risk of clotting markedly increased once albumin levels dropped below 2.8 g/dL (28 g/L) (OR, 2.53; $P = 0.02$, compared with albumin ≥2.8 g/dL [28 g/L]).

Chronic kidney disease is a risk factor for hyperuricemia and acute gout due to underexcretion of urate by the kidneys. In these patients, hyperuricemia may be due to impaired glomerular filtration and/or defects of urate handling in the renal proximal tubule. This patient's current kidney function does not place her at increased risk for gout.

Patients with membranous glomerulopathy have an increased risk of malignancy. Most cancers are diagnosed in men ≥65 years of age and are often solid tumors of the prostate, lung, or gastrointestinal tract. The risk for malignancy seems to be reduced in patients with anti-phospholipase A2 receptor (PLA2R) antibody. Taking into account her negative age- and sex-appropriate cancer screening, young age, and anti-PLA2R antibody status, this patient's risk of malignancy is low.

Patients with end-stage kidney disease have a markedly increased risk for renal cell carcinoma. Although current guidelines do not support routine screening for renal cell carcinoma in all patients with chronic kidney disease, a high level of suspicion is warranted in patients with symptoms such as new-onset gross hematuria or unexplained flank pain. In the absence of end-stage kidney disease, this patient is not at increased risk for renal cell carcinoma.

KEY POINT

- The nephrotic syndrome can be complicated by clotting manifestations due to a secondary hypercoagulable state, and risk is related to the degree of hypoalbuminemia.

Bibliography

Gyamlani G, Molnar MZ, Lu JL, Sumida K, Kalantar-Zadeh K, Kovesdy CP. Association of serum albumin level and venous thromboembolic events in a large cohort of patients with nephrotic syndrome. Nephrol Dial Transplant. 2017;32:157-164. [PMID: 28391310]

Item 46 Answer: B

Educational Objective: Treat hypertension in a patient with chronic kidney disease using an ACE inhibitor or angiotensin receptor blocker.

The addition of losartan is the most appropriate management. This patient has chronic kidney disease (CKD), given the presence of albuminuria, as well as uncontrolled hypertension. His antihypertensive medication regimen needs to be modified to control his blood pressure to target, given that uncontrolled hypertension will lead to CKD progression. The best option for this patient is to add an angiotensin receptor blocker (ARB) (such as losartan) or an ACE inhibitor, which are antihypertensive agents of choice in patients with CKD. Several studies have shown that use of an ARB or ACE inhibitor can result in decreased progression of albuminuria and CKD. Addition of losartan will also likely increase his serum potassium back to within normal range.

Adding amlodipine, a calcium channel blocker, is not the most appropriate next step in hypertension management for this patient and should be reserved if treatment with a maximum-tolerated dose of an ACE inhibitor or ARB does not result in blood pressure control.

Adding a low-dose aldosterone antagonist (such as spironolactone or eplerenone) may improve blood pressure control in patients with resistant hypertension. Treatment-resistant hypertension is defined as blood pressure that remains above goal despite concurrent use of three antihypertensive agents of different classes, one of which is a diuretic. Spironolactone is typically the fourth drug added to a three-drug regimen. This patient does not meet the definition of resistant hypertension.

Failure to act on this patient's blood pressure and albuminuria and reevaluating in 3 months misses the opportunity to slow the progression of CKD and albuminuria. In addition, guidelines recommend that adults initiating a new or adjusted drug regimen for hypertension should have a follow-up evaluation of adherence and response to treatment at monthly intervals until control is achieved.

KEY POINT

- An ACE inhibitor or angiotensin receptor blocker is an agent of choice for treatment of hypertension in a patient with chronic kidney disease.

Bibliography

Whelton PK, Carey RM, Aronow WS, Casey DE Jr, Collins KJ, Dennison Himmelfarb C, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Hypertension. 2017. [PMID: 29133356]

Item 47 Answer: E

Educational Objective: Diagnose preeclampsia.

The most likely diagnosis is preeclampsia. Preeclampsia is defined by new-onset hypertension and proteinuria (≥300 mg/24 h from a timed collection or ≥300 mg/g by urine protein-creatinine ratio) that occurs after 20 weeks of pregnancy. New-onset hypertension with new-onset end-organ damage (such as liver or kidney injury, pulmonary edema, cerebral or visual symptoms, or thrombocytopenia) is also diagnostic of preeclampsia. Severe preeclampsia is identified by persistent systolic blood pressure >160 mm Hg or diastolic blood pressure >110 mm Hg and end-organ damage. Thrombocytopenia, liver enzyme elevation, and kidney involvement are all present in this pregnant patient with new-onset hypertension, making preeclampsia the most likely diagnosis.

Chronic hypertension is defined as a systolic blood pressure ≥140 mm Hg or diastolic pressure ≥90 mm Hg starting before pregnancy or before 20 weeks of gestation or persisting longer than 12 weeks' postpartum. In this case, the patient had normal blood pressures earlier in pregnancy.

Eclampsia is the presence of generalized tonic-clonic seizures in women with preeclampsia, which are not present in this patient.

Gestational hypertension first manifests after 20 weeks of pregnancy without proteinuria or other end-organ damage. Seen in 6% of pregnancies, gestational hypertension resolves within 12 weeks of delivery. Hypertension that persists beyond the 12 weeks is considered chronic hypertension. Of those who develop gestational hypertension, 15% to 25% progress to preeclampsia, and the rate increases to up to 50% in women who develop hypertension before 30 weeks. End-organ involvement in this case is inconsistent with gestational hypertension.

HELLP (hemolysis, elevated liver enzymes, and low platelets) syndrome is a life-threatening state that complicates 10% to 20% of cases of preeclampsia. The cause of HELLP syndrome is unknown, but it may be related to placental factors. However, it likely represents a separate disorder from preeclampsia. The diagnosis requires the presence

of microangiopathic hemolytic anemia, which is excluded by the normal bilirubin level and peripheral blood smear.

KEY POINT

- Preeclampsia is defined by new-onset hypertension and proteinuria that occurs after 20 weeks of pregnancy; new onset hypertension with new onset end-organ damage (such as liver or kidney injury, pulmonary edema, cerebral or visual symptoms, or thrombocytopenia) are also diagnostic.

Bibliography

American College of Obstetricians and Gynecologists. Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. Obstet Gynecol. 2013;122:1122-31. [PMID: 24150027]

Item 48 Answer: A

Educational Objective: Diagnose Fabry disease.

The most likely disease is Fabry disease, an X linked recessive inborn error of glycosphingolipid metabolism caused by deficiency of α-galactosidase A. The enzyme deficiency leads to defective storage of sphingolipid and progressive endothelial accumulation, causing abnormalities in the skin, eye, kidney, heart, brain, and peripheral nervous system. Typically, the disease begins in childhood with episodes of pain and burning sensations in the hands and feet. These painful episodes can be brought on by exercise, fever, fatigue, or other stressors. In addition, young patients often develop angiokeratomas (violaceous papules with overlying scale), decreased perspiration, and corneal and lens opacities of the eyes. The disease is progressive, and symptoms of kidney, heart, and/or neurologic involvement usually occur between the ages of 30 and 45 years. As an X-linked disorder, males who inherit a mutation in the gene responsible for α-galactosidase always display the disease phenotype. Females, on the other hand, who inherit only one copy of a disease-causing mutation, can show a wide range of clinical manifestations, ranging from asymptomatic carriers to severe heart and kidney failure no different from a hemizygous male's phenotype. This variability is likely due to varying degrees of random inactivation of one copy of the X chromosome in each cell (lyonization). The most common finding of Fabry disease seen in heterozygous females is corneal dystrophy, which occurs in more than half of females. Fabry disease should be considered as a cause of chronic kidney disease of unknown etiology in young adulthood, especially when there is a family history of early end-stage kidney disease or cardiovascular-related death (via myocardial infarction or cerebrovascular accident). Diagnosis can be made via kidney biopsy but also noninvasively with measurement of leukocyte enzymatic activity and subsequent genetic confirmation. Screening for the disease is recommended for family members of affected patients. Enzyme replacement therapy with recombinant human α-galactosidase A is available.

Hereditary nephritis (Alport syndrome), like Fabry disease, can present with kidney failure if diagnosed late but is not associated with abnormalities in the skin or peripheral nervous system.

Medullary cystic kidney disease is a familial form of kidney disease with no known extrarenal symptomatology and usually presents with bland urinary findings.

This degree of kidney failure in a patient with tuberous sclerosis complex would be associated with abnormal kidney imaging, such as angiomyolipomas and cysts, and the classic skin lesions in this condition are hamartoma formations, not angiokeratomas.

KEY POINT

- Fabry disease should be considered as a cause of chronic kidney disease of unknown etiology in young adulthood.

Bibliography

Pisani A, Visciano B, Imbriaco M, Di Nuzzi A, Mancini A, Marchetiello C, et al. The kidney in Fabry's disease. Clin Genet. 2014;86:301-9. [PMID: 24645664]

Item 49 Answer: C

H

Educational Objective: Manage a patient with a struvite stone.

In addition to starting antibiotics, stone removal should be considered to decrease future episodes of urinary tract infections in this patient who has a struvite stone. Struvite stones occur most frequently in older women with chronic urinary tract infections. These stones occur in the presence of urea-splitting bacteria such as *Proteus*, *Klebsiella*, or, less frequently, *Pseudomonas*. These bacteria split urea into ammonium, which markedly increases urine pH (>7.5) and results in the precipitation of magnesium ammonium phosphate (struvite). Struvite stones can form rapidly and commonly produce staghorn calculi (stones that bridge two or more renal calyces). Because bacteria can live within the interstices of the stone, limiting antibiotic access, the only intervention that will decrease recurrent infections is removal of the stone. Although this may be accomplished by means of shock wave lithotripsy, patients often require percutaneous nephrolithotomy and breakup of the stone. A percutaneous nephrostomy tube is often inserted to allow for irrigation and to ensure complete removal of all fragments.

Although antibiotics are needed to treat infection, chronic antibiotic suppression is rarely successful as a primary treatment. Continued use of antibiotics increases the risk of the development of antibiotic resistance.

Pure struvite stones often occur in women who have upper urinary tract infections, but oftentimes other components such as calcium oxalate serve as the initial nidus. Because this nidus may not be among the stone fragments submitted for analysis, it may be missed. It is therefore important that a metabolic evaluation be performed in all patients. If the evaluation reveals decreased levels of urine

citrate, potassium citrate can be added. Potassium citrate should not, however, be used empirically.

The urease inhibitor acetohydroxamic acid can decrease stone growth; however, it is associated with significant side effects (nausea, vomiting, diarrhea, headache, hallucinations, rash, abdominal discomfort, anemia) and is therefore not recommended as a primary treatment.

The use of acidifying agents such as ammonium chloride rarely is able to achieve acidic urine in patients with urea-splitting bacteria and therefore is not recommended.

KEY POINT

- Patients with struvite stones require stone removal.

Bibliography

Marien T, Miller NL. Treatment of the infected stone. Urol Clin North Am. 2015;42:459-72. [PMID: 26475943]

Item 50 Answer: A

Educational Objective: Diagnose adynamic bone disease in a patient with chronic kidney disease.

The most likely bone pathology is adynamic bone disease in this patient with end-stage kidney disease and normal serum calcium and phosphorus and relatively suppressed parathyroid hormone (PTH) and alkaline phosphatase levels. Adynamic bone disease can occur in patients with chronic kidney disease (CKD) or those on dialysis. It is typically associated with significant vascular calcifications. The gold standard for the diagnosis of adynamic bone disease is bone biopsy; however, this is rarely performed. Adynamic bone disease has no specific markers, but a constellation of findings may suggest this diagnosis. Patients with adynamic bone disease may present with fracture or bone pain. The latter has been attributed to the inability to repair microdamage because of low turnover. Serum calcium may be normal or elevated because the bone is unable to take up calcium. High PTH and alkaline phosphatase would exclude adynamic bone disease; in this disorder, both are typically normal. Treatment is targeted at factors that allow PTH secretion to rise. This includes avoiding calcium-based binders, conservative use of vitamin D, and decreasing the dialysate calcium concentration. It is important to note that, as with the general population, patients with CKD may also develop osteoporosis, particularly if they received glucocorticoid therapy for the primary kidney disorder or for immunosuppression in the setting of a kidney transplant.

β_2-Microglobulin-associated amyloidosis is usually seen in patients who have been on dialysis for at least 5 years. This disorder involves osteoarticular sites, and patients may present with carpal tunnel syndrome or shoulder pain. Bone cysts may be visible on radiograph.

Osteitis fibrosa cystica is the classic pathology associated with kidney disease. This disorder is associated with increased bone turnover and elevated PTH and alkaline phosphatase levels. Mixed uremic osteodystrophy has elements of both high and low bone turnover.

Osteomalacia refers to a defect with both low turnover and abnormal mineralization of bone. This disorder can be seen by vitamin D deficiency, but in the past, it was a common complication of aluminum toxicity. This patient's vitamin D level is in the "sufficient range," and there is no history of aluminum exposure.

KEY POINT

- Adynamic bone disease can occur in patients with chronic kidney disease or those on dialysis and is associated with fracture or bone pain; parathyroid hormone and alkaline phosphatase levels are typically normal.

Bibliography

Carvalho C, Alves CM, Frazão JM. The role of bone biopsy for the diagnosis of renal osteodystrophy: a short overview and future perspectives. J Nephrol. 2016;29:617-26. [PMID: 27473148]

Item 51 Answer: C

Educational Objective: Treat cardiorenal syndrome.

Increasing the furosemide dose is the most appropriate treatment in this patient with cardiorenal syndrome type 1 (CRS1). CRS is a disorder of the heart and kidneys in which acute or long-term dysfunction in one organ induces acute or long-term dysfunction in the other. CRS is characterized by the triad of concomitant decreased kidney function, diuretic-resistant heart failure with congestion, and worsening kidney function during heart failure therapy. CRS1 is defined as a worsening kidney function in patients with acute worsening of cardiac function (decompensated heart failure, acute coronary syndrome, cardiogenic shock). Management is challenging because treatment directed toward improving cardiac function can worsen kidney function. For this patient, an increase to his loop diuretic dose to a sufficient dose to induce a diuresis is appropriate. Among patients with decompensated heart failure, the best outcomes may occur with aggressive fluid removal even if associated with mild to moderate worsening of kidney function. An elevated blood urea nitrogen (BUN)-creatinine ratio should not discourage the use of diuretic therapy in patients with evidence of congestion. The decline in his kidney function with relative increase in BUN-creatinine ratio reflects the CRS1 physiology, rather than volume depletion due to diuresis.

Vasopressin receptor antagonists such as conivaptan can be used for the treatment of patients with hypervolemic or euvolemic hyponatremia. However, there is no evidence that treatment of hyponatremia improves clinical outcomes in patients with severe chronic heart failure.

Dobutamine, as well as milrinone, is used in the management of cardiogenic shock or decompensated acute heart failure with severe impaired left ventricular function and would not be indicated for a patient with preserved ejection fraction.

Ultrafiltration therapy is reserved for patients with severe volume overload refractory to medical management.

H CONT

In the Cardiorenal Rescue Study in Acute Decompensated Heart Failure (Caress HF) study, the use of a stepwise pharmacologic therapy algorithm was superior to ultrafiltration for the preservation of kidney function at 96 hours, with a similar weight loss between the two strategies.

KEY POINT

- In cardiorenal syndrome type 1, loop diuretics are first-line therapy for managing volume overload in patients with decompensated heart failure with evidence of peripheral and/or pulmonary edema.

Bibliography

Verbrugge FH, Grieten L, Mullens W. Management of the cardiorenal syndrome in decompensated heart failure. Cardiorenal Med. 2014;4:176-88. [PMID: 25737682]

H

Item 52 Answer: D

Educational Objective: Treat anemia associated with chronic kidney disease using iron supplementation.

Iron supplementation is the most appropriate treatment for this patient with anemia associated with stage G4 chronic kidney disease (CKD). The prevalence of anemia increases as CKD progresses due to several factors, including impaired erythropoietin production, erythropoietin resistance, and reduced erythrocyte life span. Initial evaluation for the cause of anemia in patients with CKD includes laboratory studies as would be appropriate for patients without CKD. All patients with CKD and anemia should have iron profiles assessed, including total transferrin saturation (serum iron ÷ total iron-binding capacity × 100) and serum ferritin levels. The Kidney Disease: Improving Global Outcomes (KDIGO) recommendations suggest maintaining transferrin saturation levels of >30% and serum ferritin levels of >500 ng/mL (500 µg/L) using either oral or intravenous iron supplementation. Patients with stage G3 or G4 CKD can be treated with oral iron supplements but may need parenteral administration if oral iron is not effective. Patients with stage G5 CKD generally do not respond well to oral iron due to impaired gastrointestinal absorption and therefore often need intravenous administration. This patient with stage G4 CKD has iron deficiency and should have iron repletion.

Although blood transfusions are effective at acutely raising the hemoglobin, they are associated with adverse side effects. Specific to the advanced CKD population, blood transfusions should be avoided if possible to prevent HLA sensitization to foreign antigens, which may increase waiting time for kidney transplantation.

A bone marrow biopsy is not indicated because there is no evidence to suggest bone marrow dysfunction. Platelet count and leukocyte count are normal. The low hemoglobin and erythrocyte reticulocyte count reflect the inadequate iron stores. A brisk reticulocytosis should be observed within days of starting iron therapy.

Although many patients with advanced CKD and end-stage kidney disease require an erythropoietin-stimulating agent (ESA), its use is indicated only when the patient has adequate iron stores. Iron deficiency is a common reason for ESA resistance. ESAs take several weeks to achieve full effect and are sometimes started at the same time as parenteral iron. Current KDIGO guidelines recommend consideration of ESAs for patients with CKD and hemoglobin concentrations <10 g/dL (100 g/L). However, it is premature to consider ESA in this patient for she may respond to supplemental iron administration alone with an increase in hemoglobin level.

KEY POINT

- All patients with chronic kidney disease and anemia should have iron profiles assessed, including transferrin saturation and ferritin levels; treatment target levels are a transferrin saturation level >30% and a serum ferritin level >500 ng/mL (500 µg/L) using either oral or intravenous iron supplementation.

Bibliography

Panwar B, Gutiérrez OM. Disorders of iron metabolism and anemia in chronic kidney disease. Semin Nephrol. 2016;36:252-61. [PMID: 27475656]

H

Item 53 Answer: B

Educational Objective: Evaluate for primary hyperaldosteronism as the underlying cause of hypokalemia and resistant hypertension.

The most appropriate diagnostic test to perform next is plasma aldosterone concentration (PAC)/plasma renin activity (PRA) ratio. The patient presents with a triad of resistant hypertension, metabolic alkalosis, and hypokalemia following the addition of a thiazide diuretic, which raises suspicion for primary hyperaldosteronism. Primary hyperaldosteronism, in which aldosterone production cannot be suppressed with sodium loading, is the most common cause of secondary hypertension in middle-aged adults and an important cause of resistant hypertension. Testing for primary hyperaldosteronism is recommended if any of the following are present: resistant hypertension, hypokalemia (spontaneous or substantial, if diuretic induced), incidentally discovered adrenal mass, family history of early-onset hypertension, or stroke at age <40 years. Diuretics should be discontinued prior to testing to assure euvolemia. Calculation of the PAC/PRA ratio is used for screening, with a very high ratio of PAC/PRA suggestive of diagnosis. A positive screening test would reveal a reduced or undetectable PRA or concentration and an inappropriately high (usually >15 ng/dL) PAC, which results in a high PAC/PRA ratio of >20. Confirmatory testing is performed except when initial testing is diagnostic, as in cases of spontaneous hypokalemia with undetectable PRA and PAC (>30 ng/dL [828 pmol/L]). Confirmatory tests include oral and intravenous salt loading and the fludrocortisone suppression and captopril challenge tests.

Kidney ultrasonography with Doppler is performed to diagnose renovascular disease, which can be a secondary cause of hypertension. However, no clinical trials have

H CONT.

demonstrated that percutaneous intervention results in improvement of hypertension or lessens kidney deterioration; therefore, diagnostic testing is reserved for patients with otherwise strong indications for this study, such as a young woman with possible fibromuscular dysplasia, but not this patient.

Plasma fractionated metanephrines are obtained to screen for a pheochromocytoma, which could result in hypertension; however, this is a relatively rare diagnosis that cannot explain the patient's current findings, and there are no symptoms or signs (episodic headaches, palpitations) in this patient to indicate pheochromocytoma.

Polysomnography is used to diagnose obstructive sleep apnea, another secondary cause of hypertension. However, clinical suspicion for this diagnosis is low given that it cannot explain the patient's metabolic findings, and the patient is not obese and does not present with snoring and daytime sleepiness.

KEY POINT

- Calculation of the plasma aldosterone concentration/plasma renin activity ratio is used to diagnose primary hyperaldosteronism.

Bibliography

Braam B, Taler SJ, Rahman M, Fillaus JA, Greco BA, Forman JP, et al. Recognition and management of resistant hypertension. Clin J Am Soc Nephrol. 2017;12:524-535. [PMID: 27895136]

H

Item 54 Answer: D

Educational Objective: Diagnose surreptitious vomiting as a cause of metabolic alkalosis.

The most likely cause of this patient's metabolic alkalosis is surreptitious vomiting. Metabolic alkalosis is diagnosed by an elevation in serum bicarbonate concentration. This disorder is caused either by a loss of acid or administration or retention of bicarbonate. Conditions that contribute to the maintenance of metabolic alkalosis include volume contraction, ineffective arterial blood volume, hypokalemia, chloride depletion, and decreased glomerular filtration. Laboratory evaluation of metabolic alkalosis is based on urine chloride concentration. Metabolic alkalosis is considered saline responsive when associated with true hypovolemia and responds to correction of the volume deficit with isotonic saline. Saline-responsive metabolic alkalosis presents with a low urine chloride of <15 mEq/L (15 mmol/L); the most common causes are vomiting, nasogastric suction, and diuretic use. Hypokalemia occurs secondarily due to aldosterone elevation and cation loss as the kidney attempts to lose bicarbonate. Although these patients are usually hypovolemic or normovolemic (with normal or low blood pressures), patients with preexisting chronic hypertension may present with high to normal blood pressures.

For those who have a high urine chloride (>15 mEq/L [15 mmol/L]) with elevated blood pressure and hypokalemia and do not appear to be overtly volume overloaded, a mineralocorticoid excess disorder must be considered (saline-resistant metabolic alkalosis). Examples include Cushing syndrome and primary aldosteronism. Neither is a likely diagnosis based on the low urine chloride and absence of hypertension. Rarely, patients with metabolic alkalosis may appear to have clinical features consistent with saline-responsive metabolic alkalosis (normal/low extracellular fluid status, normal/low blood pressure) but have a urine chloride of >15 mEq/L (15 mmol/L). Diuretic use and inherited kidney disorders of sodium and chloride handling, such as Bartter and Gitelman syndromes, can mimic this presentation. These two autosomal recessive genetic disorders of renal sodium and chloride transporters clinically mimic loop diuretic and thiazide diuretic use, respectively. These diagnoses should be considered only after urine diuretic screening.

KEY POINT

- Saline-responsive metabolic alkalosis typically presents with hypovolemia and a low urine chloride of <15 mEq/L (15 mmol/L); the most common causes are vomiting, nasogastric suction, and diuretic use.

Bibliography

Soifer JT, Kim HT. Approach to metabolic alkalosis. Emerg Med Clin North Am. 2014;32:453-63. [PMID: 24766943]

Item 55 Answer: A

H

Educational Objective: Diagnose IgG4-related disease.

The patient's decline in kidney function is most likely due to IgG4-related disease, a syndrome that mostly affects middle-aged or older men. Plasma cell–rich tubulointerstitial nephritis (TIN) is the most common kidney manifestation. Other manifestations can include autoimmune pancreatitis, allergic rhinitis, submandibular gland swelling, an elevated antinuclear antibody (ANA) titer, low serum complement levels, elevated serum IgG, elevated serum IgE, and peripheral eosinophilia. Kidney imaging may show enlarged kidneys or renal masses that may present as small peripheral cortical nodules. This patient's urinalysis findings of trace protein and pyuria with progressive decline of kidney function are consistent with TIN. Definitive diagnosis of IgG4-related disease requires a tissue biopsy to demonstrate an infiltrate with IgG4-positive plasma cells. IgG4-related disease is readily treatable with glucocorticoids.

Although elevated ANA titers and hypocomplementemia are seen in lupus, lupus nephritis is usually characterized by proteinuria and a more active urine sediment (dysmorphic erythrocytes and cellular casts). Furthermore, lupus is more common in women and usually manifests at a much earlier age than in this patient.

Sarcoidosis can affect multiple organs and cause TIN. However, sarcoidosis is not associated with autoimmune pancreatitis, hypocomplementemia, elevated serum immunoglobulin levels, or cortical nodules on kidney ultrasound.

H CONT.

Although Sjögren syndrome can affect lacrimal and salivary glands and cause TIN, this patient's constellation of symptoms is more consistent with IgG4-related disease. Dryness of the eyes and mouth is extremely common in Sjögren but not in IgG4-related disease. Allergy symptoms, such as asthma or allergic rhinitis, are rarely seen in Sjögren but are common in IgG4-related disease. Hypocomplementemia and the presence of cortical nodules on kidney ultrasound also favor the diagnosis of IgG4-related disease.

KEY POINT

- Tubulointerstitial nephritis is the most common kidney manifestation of IgG4-related disease and typically presents with pyuria, proteinuria, and elevated serum IgG and IgE levels; kidney imaging may show enlarged kidneys or renal masses.

Bibliography

Zhang P, Cornell LD. IgG4-related tubulointerstitial nephritis. Adv Chronic Kidney Dis. 2017;24:94-100. [PMID: 28284385]

H

Item 56 Answer: A

Educational Objective: Identify NSAIDs as a cause of acute kidney injury in a patient with chronic kidney disease.

Discontinuation of naproxen is the most appropriate management for this patient with chronic kidney disease (CKD) who has developed acute kidney injury. NSAIDs are one of the most frequently used over-the-counter medications and a mainstay in many pain and inflammatory conditions. However, NSAIDs inhibit cyclooxygenase-1 and cyclooxygenase-2, which decrease vasodilatory prostaglandin production. In patients who are prostaglandin dependent (volume depleted, heart failure, CKD), this decreases renal blood flow and leads to decreased glomerular filtration rate. Patients with CKD are sensitive to the nephrotoxic effects of NSAIDs; therefore, these medications are a frequent cause of acute kidney injury in this patient population. The nephrotoxic effect of NSAIDs is augmented by concomitant use of renin-angiotensin system inhibitors due to concomitant effects on afferent and efferent vascular tone. Discontinuation of naproxen is the best treatment for this patient's acute kidney injury. The American Society of Nephrology recommends the avoidance of NSAIDs, including cyclooxygenase-2 inhibitors, in patients with CKD due to the risk of worsening kidney function. There are safer treatment alternatives for osteoarthritis (OA). Exercise is among the most important nonpharmacologic treatments for most patients with OA, and evidence for its efficacy is most convincing for knee OA. Because excessive weight contributes to both knee OA risk and symptomatology, measures to promote weight loss are appropriate for overweight patients with knee OA. Topical NSAIDs may be a safer, effective alternative to oral NSAIDs in this patient population.

CT angiography of the renal arteries with iodinated contrast is contraindicated in the setting of acute kidney injury. There is no evidence to suggest that renal artery stenosis is contributing to this patient's acute kidney injury.

Kidney biopsy can be performed to diagnosis glomerulonephritis. Although NSAIDs can cause glomerulonephritis, there are no signs to suggest acute glomerulonephritis because the patient's urinalysis does not show blood or significant protein.

Starting furosemide would help with the new peripheral edema that has developed but would not reverse the acute kidney injury; in fact, it may worsen the acute kidney injury by decreasing intravascular volume and further decreasing renal blood flow.

KEY POINT

- In patients with chronic kidney disease, NSAIDs are potentially nephrotoxic and a frequent cause of acute kidney injury and should be avoided.

Bibliography

Zhang X, Donnan PT, Bell S, Guthrie B. Non-steroidal anti-inflammatory drug induced acute kidney injury in the community dwelling general population and people with chronic kidney disease: systematic review and meta-analysis. BMC Nephrol. 2017;18:256. [PMID: 28764659]

Item 57 Answer: A

Educational Objective: Treat calcineurin inhibitor–induced hypertension and hyperkalemia in a kidney transplant recipient.

The most appropriate treatment for calcineurin inhibitor–induced hypertension and hyperkalemia in this kidney transplant recipient is a thiazide or thiazide-like diuretic such as chlorthalidone. Patients with kidney transplants must receive immunosuppressive medications to prevent their immune system from rejecting the kidney allograft. Doses are typically highest immediately after transplant and are tapered gradually over several months to minimize toxicities associated with these medications while maintaining adequate immunosuppression. The most commonly used immunosuppressants in the immediate posttransplant period for immunosuppression induction are anti-T-cell and interleukin-2 receptor–blocking antibodies. The most commonly prescribed medications for chronic maintenance immunosuppression include calcineurin inhibitors (tacrolimus or cyclosporine), antimetabolites (mycophenolate mofetil or azathioprine), and glucocorticoids. Although these medications are usually well tolerated, they can have significant side effects. Calcineurin inhibitors activate the sodium chloride cotransporter in the distal convoluted tubule, which reabsorbs sodium and chloride to cause hypertension. Decreased distal tubular flow impairs potassium secretion in the connecting tubule and collecting duct, leading to hyperkalemia. Calcineurin inhibitor–induced hypertension and hyperkalemia share the same phenotype as Gordon syndrome (familial hyperkalemic hypertension), which is due to a dysregulation of the WNK kinases in the distal convoluted tubule. Thiazide and thiazide-like diuretics such as chlorthalidone address the underlying mechanism of

calcineurin inhibitor-induced hypertension and hyperkalemia by inhibiting the sodium chloride cotransporter.

Although fludrocortisone, a synthetic mineralocorticoid, would treat the hyperkalemia, this medication would exacerbate sodium retention and raise blood pressure in this patient with already uncontrolled hypertension. Sodium polystyrene sulfonate would also treat the hyperkalemia but provides a significant sodium load with each dose and may also raise the blood pressure. These medications do not address the underlying mechanism and are therefore not indicated.

Spironolactone may lower the blood pressure but would raise serum potassium and is therefore contraindicated in this patient who is already hyperkalemic.

KEY POINT

- Treatment using thiazide diuretics is appropriate for calcineurin inhibitor-induced hypertension and hyperkalemia in kidney transplant recipients.

Bibliography

Moes AD, Hesselink DA, Zietse R, van Schaik RH, van Gelder T, Hoorn EJ. Calcineurin inhibitors and hypertension: a role for pharmacogenetics? Pharmacogenomics. 2014;15:1243-51. [PMID: 25141899]

H

Item 58 Answer: B

Educational Objective: Treat hypermagnesemia using intravenous calcium.

In addition to administration of 0.9% saline and furosemide, intravenous calcium is appropriate treatment for this patient with hypermagnesemia. Because the kidney can efficiently eliminate magnesium, hypermagnesemia occurs infrequently and most commonly results from excessive intake in the setting of decreased kidney function. Numerous medications such as antacids and laxatives contain magnesium, and magnesium sulfate is the treatment of choice for prevention of eclampsia. Hypermagnesemia is usually not associated with significant symptoms until the level is >7.2 mg/dL (2.9 mmol/L). Symptoms include somnolence, headache, loss of deep tendon reflexes, bradycardia, hypotension, and hypocalcemia. At levels >12 mg/dL (4.9 mmol/L), flaccid paralysis, respiratory failure, and complete heart block can occur. Hypermagnesemia is usually self-limited. Magnesium-containing medications should be discontinued, and magnesium excretion can be enhanced with saline diuresis. In patients with hypotension and significant neuromuscular deficits, treatment is aimed at direct antagonism of the effects of hypermagnesemia, which is accomplished by intravenous administration of calcium. After this, efforts to lower the serum level should be instituted. If kidney function is adequate, a trial of 0.9% saline and furosemide will increase kidney excretion. Magnesium-containing agents should be limited or avoided in individuals with kidney disease.

If kidney failure is advanced, hemodialysis will effectively lower magnesium levels. However, this would require access to the central venous system and mobilization of the dialysis team, which can take several hours, and in the interim patients with symptomatic hypermagnesemia should be given intravenous calcium.

There is no role for either intravenous potassium or sodium bicarbonate other than correcting preexisting metabolic abnormalities.

Although sodium polystyrene sulfonate will bind a small amount of magnesium, this effect is minimal and not advocated as a treatment.

KEY POINT

- Management of hypermagnesemia includes discontinuation of magnesium-containing medications, administration of saline diuresis to enhance magnesium excretion, and administration of intravenous calcium to treat severe symptoms.

Bibliography

Van Hook JW. Endocrine crises. Hypermagnesemia. Crit Care Clin. 1991;7:215-23. [PMID: 2007216]

Item 59 Answer: A

H

Educational Objective: Diagnose the cause of acute kidney injury.

The most appropriate next step is examination of the urine sediment for cells and casts. This patient has developed oliguric acute kidney injury (AKI). He has multiple risk factors for AKI, including type 2 diabetes mellitus, recent coronary arteriography, hypotension, and cardiac surgery. The main consideration is whether the AKI is due to renal hypoperfusion (prerenal AKI) or whether the AKI is due to acute tubular necrosis (ATN). In the setting of diuretics, the fractional excretion of urea (FE_{Urea}) is more accurate than the fractional excretion of sodium because urea excretion is not promoted by diuretics and is still retained in volume-depleted states. FE_{Urea} is calculated using the equation:

$$FE_{Urea} = (U_{Urea} \times P_{Creatinine})/(U_{Creatinine} \times P_{Urea}) \times 100\%$$

FE_{Urea} <35% is suggestive of a prerenal state. The presence of granular casts and/or renal epithelial cells has strong predictive value for ATN. Urine microscopy can also help differentiate other causes of AKI, such as acute interstitial nephritis and glomerulonephritis.

The fractional excretion of sodium (FE_{Na}) is calculated as follows:

$$FE_{Na} = (U_{Sodium} \times P_{Creatinine})/(U_{Creatinine} \times P_{Sodium}) \times 100\%$$

FE_{Na} <1% indicates prerenal AKI but can also be seen in contrast-induced nephropathy, acute interstitial nephritis, rhabdomyolysis, glomerulonephritis, and early obstruction because the tubular handling of sodium is intact in these conditions. FE_{Na} >2% indicates ATN but is also seen in patients who are prerenal and are on diuretics or who have adrenal insufficiency, bicarbonaturia, or chronic kidney disease due to the increased distal tubular delivery of sodium in these conditions.

H CONT.

Kidney ultrasonography should be performed to rule out obstructive uropathy as the cause of AKI. However, the patient already has a urinary catheter, so the likelihood of obstruction as the cause of AKI is low.

Central venous pressure is not a reliable indicator of organ perfusion and would not be able to differentiate prerenal AKI from ATN or other causes of AKI.

KEY POINT

- The presence of granular casts and/or renal epithelial cells on urine microscopy has strong predictive value for acute tubular necrosis.

Bibliography

Perazella MA, Coca SG, Kanbay M, Brewster UC, Parikh CR. Diagnostic value of urine microscopy for differential diagnosis of acute kidney injury in hospitalized patients. Clin J Am Soc Nephrol. 2008;3:1615-9. [PMID: 18784207]

Item 60 Answer: A

Educational Objective: Diagnose masked hypertension using ambulatory blood pressure monitoring.

The most appropriate test to perform next is 24-hour ambulatory blood pressure monitoring (ABPM) in this patient who has a strong family history of hypertension with cardiovascular complications. According to the American College of Cardiology/American Heart Association (ACC/AHA) blood pressure guideline, the patient has elevated blood pressure (BP), defined as systolic BP between 120-129 mm Hg and diastolic BP <80 mm Hg, and is at risk for development of hypertension (defined as systolic BP ≥130 mm Hg or diastolic BP ≥80 mm Hg). In addition, she has left ventricular hypertrophy on electrocardiogram, which raises concern for underlying long-standing hypertension. Therefore, masked hypertension, defined as BP that is normal in the office but elevated in the ambulatory setting, should be ruled out. Masked hypertension is associated with an increased risk of sustained hypertension and cardiovascular disease. The diagnostic test of choice is 24-hour ABPM; home blood pressure monitoring is an alternative strategy. Up to 10% to 40% of patients who are normotensive by clinic measurement may be hypertensive by ABPM or home blood pressure monitoring, which should be performed in patients referred for hypertension but with normal office BP and in those with end-organ damage such as left ventricular hypertrophy. Finally, the ACC/AHA notes that it is reasonable to evaluate for masked hypertension in patients with elevated BP, even in the absence of a strong family history of cardiovascular disease or evidence of sustained hypertension (for example, left ventricular hypertrophy on electrocardiogram).

A plasma aldosterone concentration/plasma renin activity ratio is often obtained in the evaluation of hyperaldosteronism. Such patients present with hypertension and often hypokalemia and metabolic alkalosis. It is premature to evaluate the patient for secondary causes of hypertension without first establishing the diagnosis of hypertension with ABPM or home blood pressure monitoring.

Disordered breathing events such as obstructive sleep apnea are associated with autonomic instability, increased vascular tone, hypertension, and alterations in heart rate. However, this patient has no symptoms to suggest obstructive sleep apnea (frequent awakenings, dry mouth, snorting, daytime sleepiness, nonrestorative sleep), and testing with polysomnography is not indicated at this time.

Measurement of thyroid-stimulating hormone levels is not the next best diagnostic test because the patient does not manifest any symptoms or signs concerning for hyperthyroidism, such as tachycardia, heat intolerance, palpitations, dyspnea, tremulousness, weight loss, fatigue, insomnia, and mood disturbances.

KEY POINT

- Suspected masked hypertension (defined as blood pressure that is normal in the office but elevated in the ambulatory setting) should be confirmed with ambulatory blood pressure monitoring or home blood pressure monitoring.

Bibliography

Whelton PK, Carey RM, Aronow WS, Casey DE Jr, Collins KJ, Dennison Himmelfarb C, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Hypertension. 2017. [PMID: 29133356]

Item 61 Answer: A

Educational Objective: Treat hypertension in a black patient using a thiazide diuretic and a calcium channel blocker.

Addition of the calcium channel blocker (CCB) amlodipine is the most appropriate next step in management. A landmark trial (ALLHAT) revealed that in black patients, a thiazide diuretic was more effective in improving cardiovascular outcomes compared with an ACE inhibitor, and there was a higher risk of stroke with use of an ACE inhibitor as initial therapy compared with a CCB. For these reasons, initial antihypertensive treatment in black patients, including those with diabetes mellitus, should include a thiazide diuretic or CCB, or combination of the two. However, if chronic kidney disease (CKD) is present, initial or add-on therapy should include an ACE inhibitor or angiotensin receptor blocker, especially in those with proteinuria, as illustrated by the AASK study. There is no evidence of CKD in this patient, given the normal serum creatinine and absence of an elevated urine albumin-creatinine ratio. Although hydrochlorothiazide was initiated 1 month ago, his blood pressure is still not at the target. Addition of the CCB amlodipine is therefore appropriate.

This patient is already on an adequate dose of hydrochlorothiazide, and his serum potassium level is borderline low at 3.5 mEq/L (3.5 mmol/L). Increasing the hydrochlorothiazide dose may further decrease his serum potassium

and may be associated with adverse side effects, such as orthostasis and erectile dysfunction.

According to the American College of Cardiology/American Heart Association (ACC/AHA) blood pressure guideline, target blood pressure for most patients with hypertension, with or without coronary artery disease, diabetes, or CKD is <130/80 mm Hg. This patient is substantially above target, and reassessing in 3 months' time would not be adequate management. In addition, the ACC/AHA guideline recommends that adults initiating a new or adjusted drug regimen for hypertension should have a follow-up evaluation of adherence and response to treatment at monthly intervals until control is achieved. Waiting 3 months to reevaluate the patient is too long.

KEY POINT

- Initial antihypertensive treatment in black patients without chronic kidney disease should include a thiazide diuretic or calcium channel blocker, or combination of the two.

Bibliography

ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. The Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). JAMA. 2002;288:2981-97. [PMID: 12479763]

Item 62 Answer: A

Educational Objective: Diagnose chronic hypertension in a pregnant patient.

The most likely diagnosis in this pregnant patient is chronic hypertension. Hypertension first recognized during pregnancy at <20 weeks' gestation usually indicates chronic hypertension. The American College of Obstetricians and Gynecologists (ACOG) defines chronic hypertension as a systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg starting before pregnancy or before 20 weeks of gestation or persists longer than 12 weeks' postpartum. In normal pregnancy, the blood pressure declines during the first trimester, reaches its lowest level in the second trimester, and rises slowly thereafter. A patient with hypertension in the first trimester suggests that the hypertension predates the pregnancy. To avoid overtreatment of hypertension and associated fetal risk, the 2013 ACOG guidelines recommend treating persistent systolic blood pressure ≥160 mm Hg or diastolic blood pressure ≥105 mm Hg in women with chronic hypertension. Blood pressure goals with medications are 120 to 160/80 to 105 mm Hg. Antihypertensive treatment reduces the risk of progression to severe hypertension by 50% compared with placebo but has not been shown to prevent preeclampsia, preterm birth, small size for gestational age, or infant mortality.

Gestational hypertension first manifests after 20 weeks of pregnancy without proteinuria or other end-organ damage and resolves within 12 weeks of delivery. This patient's early presentation is not consistent with gestational hypertension.

Normal physiologic changes in pregnancy are usually associated with decreased blood pressure in the first trimester with a nadir blood pressure in the second. In this patient, the high blood pressure is inconsistent with normal pregnancy changes.

Preeclampsia is defined clinically by new-onset hypertension and proteinuria that occur after 20 weeks of pregnancy. In addition to blood pressure criteria, there must be proteinuria or new-onset end-organ damage, including liver or kidney injury, pulmonary edema, cerebral or visual symptoms, or thrombocytopenia. This patient's early presentation in the first trimester and lack of end-organ involvement is not consistent with preeclampsia.

KEY POINT

- The American College of Obstetricians and Gynecologists defines chronic hypertension as a systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg starting before pregnancy or before 20 weeks of gestation or persists longer than 12 weeks' postpartum.

Bibliography

American College of Obstetricians and Gynecologists. Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. Obstet Gynecol. 2013;122:1122-31. [PMID: 24150027]

Item 63 Answer: B

Educational Objective: Diagnose anti–glomerular basement membrane antibody disease.

The most appropriate diagnostic test to perform next is anti-glomerular basement membrane (GBM) antibodies. This patient presents with a rapidly progressive glomerulonephritis (RPGN), an acute and steep rise in serum creatinine accompanied by hematuria and proteinuria. The differential diagnosis for RPGN is divided histologically into three patterns on immunofluorescence microscopy of the kidney biopsy: pauci-immune staining (for example, ANCA-associated glomerulonephritis), linear staining (for example, anti-GBM antibody disease), and granular staining (for example, lupus nephritis). The patient's positive antimyeloperoxidase (MPO) antibodies predict that she will have pauci-immune staining on the biopsy, but the linear staining on her biopsy is more consistent with anti-GBM antibody disease. Therefore, testing for anti-GBM antibodies is required to confirm this diagnosis, although treatment for her condition should not be delayed while awaiting results. One in three patients with anti-GBM antibody disease will have positive ANCA serologies, usually MPO antibodies (or p-ANCA in older assays). This combined seropositivity is most commonly seen in the subset of anti-GBM patients who are older women, as in this case. Diagnosing anti-GBM antibody disease could affect treatment decisions in this

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case, particularly whether to pursue plasmapheresis, which is indicated for all cases of anti-GBM antibody disease. For ANCA-associated glomerulonephritis, plasmapheresis is reserved for those with alveolar hemorrhage and/or severe kidney failure (defined as requiring dialysis or a serum creatinine >5.8 mg/dL [512.7 µmol/L]).

This patient has negative antinuclear antibody testing and a biopsy not consistent with lupus nephritis, making testing for anti-double-stranded DNA antibodies unnecessary.

Anti-phospholipase A2 receptor (PLA2R) antibodies can be checked in patients suspected of having primary membranous glomerulopathy, which typically presents with the nephrotic syndrome and preserved kidney function, not RPGN.

Antihistone antibodies are measured if drug-induced vasculitis or drug-induced lupus erythematosus is suspected. This patient was not taking any medications, making this test unnecessary.

KEY POINT

- Serologic testing for anti–glomerular basement membrane antibodies and kidney biopsy can confirm the diagnosis of anti-glomerular basement membrane antibody disease as the cause of rapidly progressive glomerulonephritis.

Bibliography

Sethi S, Haas M, Markowitz GS, D'Agati VD, Rennke HG, Jennette JC, et al. Mayo Clinic/Renal Pathology Society consensus report on pathologic classification, diagnosis, and reporting of GN. J Am Soc Nephrol. 2016;27:1278-87. [PMID: 26567243]

Item 64 Answer: C

Educational Objective: Diagnose white coat hypertension using ambulatory blood pressure monitoring.

The most appropriate next step is to evaluate for white coat hypertension using 24-hour ambulatory blood pressure monitoring (ABPM). ABPM uses a continuously worn device that can be programmed to measure blood pressure every 15 to 20 minutes during the day and every 30 to 60 minutes at night. White coat hypertension refers to elevated blood pressure measured in the office, but normal out-of-office blood pressure averages. According to the American College of Cardiology/American Heart Association blood pressure guideline, in adults with untreated systolic blood pressure >130 mm Hg but <160 mm Hg or diastolic blood pressure >80 mm Hg but <100 mm Hg, it is reasonable to screen for white coat hypertension using either ABPM (the gold standard) or home blood pressure monitoring. Before white coat hypertension is diagnosed, it needs to be confirmed that the out-of-office measurements are reliable; for example, the patient's home blood pressure monitor should be calibrated against the office sphygmomanometer or, preferably, blood pressure should be measured by ABPM. If white coat hypertension is confirmed, lifestyle modification and careful monitoring are indicated because there is risk for future development of hypertension.

Before initiating hydrochlorothiazide, 24-hour ABPM or home blood pressure monitoring should be performed to rule out white coat hypertension.

Screening echocardiography is not the correct next step in diagnosis, although it may be considered if the diagnosis of hypertension remains in doubt in order to evaluate for left ventricular hypertrophy. The presence of confirmed left ventricular hypertrophy will necessitate treatment with antihypertensive medication.

The patient's blood pressure has been elevated in the office on three different occasions, and it is unlikely that another measurement in 3 months' time will produce a different result. The issue at hand is the diagnosis of white coat hypertension, which will require out-of-office blood pressure measurements.

KEY POINT

- White coat hypertension refers to elevated blood pressure measured in the office, but normal out-of-office blood pressure averages; diagnosis requires confirmation using 24-hour ambulatory blood pressure monitoring (gold standard) or home blood pressure monitoring.

Bibliography

Pierdomenico SD, Cuccurullo F. Prognostic value of white-coat and masked hypertension diagnosed by ambulatory monitoring in initially untreated subjects: an updated meta analysis. Am J Hypertens. 2011;24:52-8. [PMID: 20847724]

Item 65 Answer: B

H

Educational Objective: Treat hyperkalemia in a patient with acute kidney injury using hemodialysis.

Intermittent hemodialysis (IHD) is the most efficient way to correct this patient's hyperkalemia in the setting of anuric-oliguric acute kidney injury (AKI). IHD, typically delivered 3 to 6 times a week for 3 to 5 hours per session, allows for rapid correction of electrolyte disturbances and rapid removal of drugs or toxins. This patient has severe hyperkalemia with electrocardiographic changes, which should be corrected urgently to prevent lethal cardiac arrhythmias. Calcium, insulin, and dextrose are only temporizing measures and will not result in potassium removal from the body. Only dialysis will result in potassium removal from the body.

Continuous renal replacement therapy (CRRT) is a type of dialysis that is performed in critically ill patients who are hemodynamically unstable. CRRT provides hemodynamic stability by removing fluid and solutes at a much slower rate than IHD. As a result, CRRT would not be able to clear potassium rapidly but may be considered if the patient cannot tolerate IHD.

Furosemide can induce urinary potassium loss by increasing urine flow and delivery of sodium to the distal nephron for exchange with potassium. However, this patient

is nearly anuric with acute tubular necrosis based on urine microscopy and unlikely to respond to furosemide.

Sodium bicarbonate causes a shift of hydrogen ion from the intracellular fluid compartment to the extracellular compartment, causing an opposing net intracellular potassium shift to maintain electroneutrality. The effect of bicarbonate is transient and ineffective in end-stage kidney disease or severe AKI.

Sodium polystyrene sulfonate is a cation exchange resin that removes potassium through the gastrointestinal tract. The onset of action is hours to days, and its effectiveness is disputed. It is contraindicated in patients with recent bowel surgery because of an increased risk for intestinal necrosis.

KEY POINT

- In the setting of anuric-oliguric acute kidney injury, intermittent hemodialysis allows for rapid correction of electrolyte disturbances and rapid removal of drugs or toxins.

Bibliography

Rossignol P, Legrand M, Kosiborod M, Hollenberg SM, Peacock WF, Emmett M, et al. Emergency management of severe hyperkalemia: guideline for best practice and opportunities for the future. Pharmacol Res. 2016;113:585-591. [PMID: 27693804]

Item 66 Answer: D

Educational Objective: Diagnose type 4 (hyperkalemic distal) renal tubular acidosis.

The most likely diagnosis is type 4 (hyperkalemic distal) renal tubular acidosis (RTA), which is caused by aldosterone deficiency or resistance. Primary adrenal insufficiency (Addison disease) may cause aldosterone deficiency, although hyporeninemic hypoaldosteronism is a more common cause and may occur in the presence of various kidney diseases, most often diabetes mellitus. Aldosterone resistance is seen in patients with tubulointerstitial disease, including urinary obstruction, sickle cell disease, medullary cystic kidney disease, and kidney transplant rejection. Drug-induced type 4 (hyperkalemic distal) RTA can be caused by numerous drugs that reduce aldosterone production, including ACE inhibitors, angiotensin receptor blockers, heparin, and NSAIDs. Patients with type 4 (hyperkalemic distal) RTA have a positive urine anion gap (using the equation: [Urine Sodium + Urine Potassium] − Urine Chloride), indicating a reduced excretion of acid in the form of ammonium and chloride, but a urine pH <5.5. Hyperkalemia decreases ammonia production with consequent lower ammonium excretion and therefore results in the positive urine anion gap. Due to the inadequate amount of ammonia available to buffer protons, the few protons that are secreted distally will result in the low urine pH (<5.5). Treatment is focused on correcting the underlying cause if possible. Fludrocortisone is used to replace mineralocorticoids in adrenal insufficiency and should be considered in hyporeninemic hypoaldosteronism in those without hypertension or heart failure.

Although chronic kidney disease may result in hyperkalemia and metabolic acidosis, the acidosis does not usually develop until later progression (glomerular filtration rate <40-45 mL/min/1.73 m²), and hyperkalemia is usually not present until the glomerular filtration rate is at even lower levels (usually stage 4 or worse).

The normal anion gap of type 1 (hypokalemic distal) RTA results from a distal tubular defect and associated impaired excretion of hydrogen ions by the distal nephron. It is usually associated with hypokalemia and a negative urine anion gap, which are not present in this patient.

Type 2 (proximal) RTA results from failure of the proximal tubule to adequately reclaim filtered bicarbonate, driving the development of a normal anion gap metabolic acidosis and a positive urine anion gap. Type 2 (proximal) RTA is usually accompanied by other evidence of proximal tubular dysfunction (hypokalemia, glycosuria, and hypophosphatemia), none of which is present in this patient.

KEY POINT

- Type 4 (hyperkalemic distal) renal tubular acidosis is characterized by hyperkalemia, a normal anion gap metabolic acidosis, impaired urine acidification (positive urine anion gap), and a urine pH <5.5.

Bibliography

Yaxley J, Pirrone C. Review of the diagnostic evaluation of renal tubular acidosis. Ochsner J. 2016;16:525-530. [PMID: 27999512]

Item 67 Answer: D

Educational Objective: Diagnose lupus nephritis.

The most appropriate next step is a kidney biopsy. The presence of hematuria, dysmorphic erythrocytes, and proteinuria in a patient with known systemic lupus erythematosus (SLE) is highly suggestive of lupus nephritis; when serologies are positive and serum complement levels are low, this diagnosis is even more likely. Commonly cited indications for kidney biopsy include increasing serum creatinine without explanation, proteinuria >500 mg/24 h, or active urine sediment (dysmorphic erythrocytes, erythrocyte casts). Patients meeting these criteria are more likely to have focal or diffuse proliferative lupus nephritis or lupus membranous nephropathy requiring immunosuppressive therapy. Patients with proteinuria <500 mg/24 h and inactive urine sediment are more likely to have milder kidney involvement and may be followed with urinalysis, urine protein-creatinine ratio, and serum creatinine every 3 to 6 months.

Unless absolutely contraindicated (for example, bleeding diathesis or inability to stop anticoagulation), both rheumatology and nephrology guidelines support performing a kidney biopsy in patients with SLE who develop evidence of significant kidney involvement to establish the diagnosis and, of equal importance with regard to treatment decisions, to identify the International Society of Nephrology/Renal Pathology Society (ISN/RPS) class of lupus nephritis.

This patient's kidney biopsy could show a proliferative lupus nephritis (class III or IV), in which case treatment with glucocorticoids and mycophenolate mofetil or cyclophosphamide would be indicated (mycophenolate mofetil would likely be preferred given this patient's age). However, her biopsy could also conceivably show a milder, mesangial proliferative lupus nephritis (class II) or membranous lupus nephritis (class V), neither of which would require immunosuppression at this stage. Therefore, empiric therapy in this setting is substandard to biopsy-guided therapy according to ISN/RPS class of nephritis.

KEY POINT

- A kidney biopsy should be performed in patients with known systemic lupus erythematosus with suspected significant kidney involvement to establish the diagnosis and to identify the class, which will guide treatment decisions.

Bibliography

Hahn BH, McMahon MA, Wilkinson A, Wallace WD, Daikh DI, Fitzgerald JD, et al; American College of Rheumatology. American College of Rheumatology guidelines for screening, treatment, and management of lupus nephritis. Arthritis Care Res (Hoboken). 2012;64:797-808. [PMID: 22556106]

H

Item 68 Answer: D

Educational Objective: Treat hypertension associated with volume expansion in chronic kidney disease.

Stopping chlorthalidone and beginning furosemide is the most appropriate treatment for this patient's hypertension. Hypertension is a risk factor for cardiovascular morbidity and mortality. The most common cause of death in patients with chronic kidney disease (CKD) is cardiovascular disease. Therefore, blood pressure control is critical for preventing disease and death. Diuretics are central to the management of hypertension. Although thiazide diuretics (such as chlorthalidone) are recommended first-line agents for hypertension, efficacy decreases with advanced stages of CKD. Therefore, loop diuretics (furosemide, bumetanide, torsemide) are a cornerstone of blood pressure management in patients with advanced CKD. Sodium retention and impaired natriuresis lead to volume expansion and an increase in blood pressure. Loop diuretics are effective natriuretics and retain their activity even at low glomerular filtration rate (GFR); however, doses need to be increased as GFR declines to maintain appropriate urine output and negative fluid balance. Loop diuretics are equally effective if given in equipotent doses. The loop diuretic furosemide would effectively treat this patient's volume expansion and therefore reduce blood pressure. Additional benefit would include increased urine potassium and acid excretion to treat the mild hyperkalemia and metabolic acidosis associated with CKD. The most common side effects of loop diuretics are electrolyte and fluid abnormalities, hypersensitivity, and ototoxicity.

Hydralazine is not indicated for this patient who has volume expansion and needs diuresis; this drug is also relatively contraindicated in coronary artery disease.

Losartan is an angiotensin receptor blocker, which should not be combined with an ACE inhibitor due to the risk of hyperkalemia and acute kidney injury.

Although spironolactone can help reduce blood pressure and edema through its anti-aldosterone effects and blockade of sodium reabsorption in the cortical collecting duct, it would be contraindicated in this patient with advanced CKD and hyperkalemia.

KEY POINT

- Loop diuretics are a cornerstone of blood pressure management in patients with advanced chronic kidney disease.

Bibliography

Valika A, Peixoto AJ. Hypertension management in transition: from CKD to ESRD. Adv Chronic Kidney Dis. 2016;23:255-61. [PMID: 27324679]

Item 69 Answer: D

H

Educational Objective: Select the most appropriate venous access for a patient with advanced chronic kidney disease.

A tunneled internal jugular central venous catheter is the most appropriate venous access strategy for this patient. In patients with osteomyelitis, 6 weeks of antimicrobial therapy after surgical débridement is the preferred treatment course, and for most patients this requires long-term reliable venous access. However, this patient's advanced degree of kidney disease, relatively young age, and type 2 diabetes mellitus put her at high risk for progressing to end-stage kidney disease, and the upper extremity veins should be protected for future hemodialysis access creation. The American Society of Nephrology recommends nephrology consultation first before placing peripherally inserted central catheter (PICC) lines in patients with stage G3 to G5 CKD. PICCs are long catheters that are inserted peripherally and terminate in the central veins. PICCs are popular because of their ease of insertion and use. However, a national, population-based analysis revealed that PICCs placed before or after hemodialysis initiation were independently associated with lower likelihoods of transition to any working fistula or graft. PICC lines can lead to significant vein trauma and venous stenosis in the veins that may be used for arteriovenous fistula creation. This could impair blood flow through the fistula, impair maturation, and even lead to primary nonfunctioning of the hemodialysis access. Although central lines are associated with central venous stenosis, a central line is a better alternative than a PICC for long-term parenteral antibiotics because central lines are not inserted into a peripheral vein, which would be used for the creation of a hemodialysis site.

Arteriovenous fistula or graft creation is inappropriate due to the presence of active infection. Additionally, inserting a PICC line in the arm next to the fistula may also

H CONT.

still cause damage to the access itself or damage one of the branching veins, which could impair the maturation of the access.

KEY POINT

- Peripherally inserted central catheter placement before or after hemodialysis initiation is associated with adverse vascular access outcomes in patients with chronic kidney disease.

Bibliography

McGill RL, Ruthazer R, Meyer KB, Miskulin DC, Weiner DE. Peripherally inserted central catheters and hemodialysis outcomes. Clin J Am Soc Nephrol. 2016;11:1434-40. [PMID: 27340280]

Item 70 Answer: C

Educational Objective: Treat hypertension in a patient with diabetes mellitus and albuminuria using an ACE inhibitor or angiotensin receptor blocker.

In addition to lifestyle modifications, initiation of the angiotensin receptor blocker (ARB) losartan is the most appropriate treatment for this patient with newly diagnosed hypertension. She has a normal serum creatinine level but has moderately increased albuminuria. Her blood pressure has been elevated at two office visits and confirmed with home blood pressure monitoring, and she needs to be treated to target, given that uncontrolled hypertension will lead to progression of albuminuria and chronic kidney disease (CKD). A reasonable target blood pressure for this patient is <130/80 mm Hg. The 2017 high blood pressure guideline from the American College of Cardiology (ACC), American Heart Association (AHA), and nine other organizations recommends a treatment goal of <130/80 mm Hg. The ACC/AHA guideline notes that ACE inhibitors or ARBs may be considered as initial treatment choices in the presence of albuminuria. The American Diabetes Association (ADA) Standards of Medical Care in Diabetes 2018 recommends that most patients with diabetes mellitus and hypertension should be treated to a systolic blood pressure goal of <140 mm Hg and a diastolic blood pressure goal of <90 mm Hg. Lower systolic and diastolic blood pressure targets, such as 130/80 mm Hg, may be appropriate for individuals at high risk of cardiovascular disease if they can be achieved without undue treatment burden. In nonpregnant patients with diabetes and hypertension, the ADA recommends either an ACE inhibitor or an ARB for those with albuminuria. Several large randomized controlled trials and systematic reviews have shown that use of an ARB or ACE inhibitor can result in decreased progression of albuminuria and CKD in patients with diabetes.

The ACC/AHA blood pressure guideline recommends the following lifestyle modifications for individuals with elevated blood pressure or hypertension: weight loss in adults who are overweight or obese; a heart-healthy diet, such as DASH (Dietary Approaches to Stop Hypertension), that facilitates achieving a desirable weight; sodium reduction; potassium supplementation, preferably in dietary modification, unless contraindicated by the presence of CKD or use of drugs that reduce potassium excretion; increased physical activity with a structured exercise program; and limiting alcohol consumption of standard drinks to two (men) and one (women) per day. Although these recommendations are appropriate for this patient, it is not the only recommended intervention to control hypertension in this patient with diabetes and albuminuria. Therefore, simply asking the patient to return in 2 months for a blood pressure measurement after initiating lifestyle changes is not sufficient.

Calcium channel blockers (such as amlodipine) and thiazide diuretics (such as chlorthalidone) are not initial choices for treating hypertension in patients with diabetes and albuminuria. If this patient's blood pressure is still not controlled to target after maximizing the dose of the ARB, then one of these agents can be added.

KEY POINT

- An ACE inhibitor or angiotensin receptor blocker is the initial treatment of choice for hypertension in patients with diabetes mellitus and albuminuria.

Bibliography

Palmer SC, Mavridis D, Navarese E, Craig JC, Tonelli M, Salanti G, et al. Comparative efficacy and safety of blood pressure lowering agents in adults with diabetes and kidney disease: a network meta-analysis. Lancet. 2015;385:2047-56. [PMID: 26009228]

Item 71 Answer: C

Educational Objective: Identify medication as a cause of an increase in serum creatinine.

Reassessing this patient's serum creatinine level in 1 week is the most appropriate next step in management. Some medications (such as cimetidine, trimethoprim, cobicistat, dolutegravir, bictegravir, and rilpivirine) reduce proximal tubule secretion of creatinine, resulting in increases in serum creatinine that are nonprogressive. This patient has chronic kidney disease (CKD), long-standing hypertension, and HIV infection. His antiretroviral medication regimen was recently adjusted to a once-a-day dosing, with the integrase inhibitor raltegravir discontinued and dolutegravir started 3 weeks ago. Dolutegravir is known to interfere with creatinine secretion without affecting glomerular filtration rate. Slight increases in serum creatinine of 0.2 to 0.3 mg/dL (17.7-26.5 µmol/L) may occur. This is more pronounced in those with preexisting CKD, in which creatinine secretion may contribute proportionately more to creatinine clearance. In patients with HIV taking the integrase inhibitors dolutegravir or bictegravir, the non-nucleoside reverse transcriptase inhibitor rilpivirine, or the pharmacokinetic enhancer (CYP3A inhibitor) cobicistat, serum creatinine elevations are nonprogressive and will remain unchanged within 1 to 2 weeks of initiation. Therefore, in the absence of other signs of kidney disease (hematuria, pyuria, or increasing proteinuria), reassessment of the serum creatinine level in 1 week will confirm the drug's effect in this patient.

Further increases in serum creatinine levels will require additional evaluation.

Discontinuation of the ACE inhibitor lisinopril is not necessary. This patient has long-standing hypertension and is likely benefiting from the lisinopril for his CKD and moderate albuminuria. It is unlikely to have caused this acute increase in serum creatinine because the hemodynamic effects of ACE inhibitors on glomerular filtration occur within days of initiating the medication and then stabilize.

A 24-hour urine creatinine clearance will be decreased in this case (due to drug-related lower creatinine secretion) and will not provide additional diagnostic information.

Should a repeat serum creatinine level be stable, no further evaluation will be necessary.

KEY POINT

- Some medications (such as cimetidine, trimethoprim, cobicistat, dolutegravir, bictegravir, and rilpivirine) reduce proximal tubule secretion of creatinine, resulting in increases in serum creatinine that are nonprogressive; repeat serum creatinine measurement is required to confirm stable levels.

Bibliography

Milburn J, Jones R, Levy JB. Renal effects of novel antiretroviral drugs. Nephrol Dial Transplant. 2017;32:434-439. [PMID: 27190354]

H

Item 72 Answer: B

Educational Objective: Identify calcium phosphate as the composition of a kidney stone in a patient taking topiramate.

The most likely composition of this patient's kidney stone is calcium phospate. Approximately 80% of kidney stones contain calcium oxalate, calcium phosphate, or both. Calcium stones are radiopaque on plain radiograph. Hypercalciuria, hyperoxaluria, and hypocitraturia are risk factors for calcium stones. Calcium phosphate stones occur when there is persistently elevated urine pH. These stones are therefore commonly associated with distal renal tubular acidosis and hyperparathyroidism. This patient is taking topiramate for migraine prophylaxis, a carbonic anhydrase inhibitor that is associated with calcium phosphate stones. Carbonic anhydrase promotes proximal tubule sodium, bicarbonate, and chloride reabsorption. Inhibitors of carbonic anhydrase produce both sodium chloride and bicarbonate urinary loss. The resultant mild metabolic acidosis causes decreased citrate excretion, and the persistent alkaline urine favors the precipitation of calcium phosphate.

Although calcium oxalate is the most common cause of kidney stones, there are no calcium oxalate crystals noted on this patient's urinalysis. The most common crystal formations of calcium oxalate in the urine are the dumbbell-shaped calcium oxalate monohydrate crystals and envelope-shaped calcium oxalate dihydrate crystals. She has amorphous crystals in alkaline urine, which are usually calcium phosphate crystals.

Cystine stones occur with cystinuria, which is a genetic disease. This patient has no family history of kidney stones, and the characteristic hexagonal-shaped crystals are not seen on urine microscopy.

Struvite stones occur in the presence of urea-splitting bacteria (*Proteus*, *Klebsiella*, or, less frequently, *Pseudomonas*). These bacteria split urea into ammonium, which markedly increases urine pH and results in the precipitation of magnesium ammonium phosphate (struvite). The pH of the urine will be >7.5. Struvite stones commonly produce staghorn calculi (stones that bridge two or more renal calyces) and occur most frequently in older women with chronic urinary infections. Coffin lid-shaped crystals may be seen in the urine. This patient does not demonstrate these findings.

Uric acid stones are uncommon (10% of stones), but the incidence increases in hotter, arid climates due to low urine volumes. The main risk factor is low urine pH, which decreases the solubility of uric acid. Hyperuricosuria is not a consistent finding. Comorbid risk factors for uric acid stones include gout, diabetes mellitus, the metabolic syndrome, and chronic diarrhea. Because uric acid stones occur in persistently acidic urine, this is an unlikely diagnosis for this patient.

KEY POINT

- Topiramate, a carbonic anhydrase inhibitor, causes a decrease in urinary citrate excretion and formation of alkaline urine that favor the creation of calcium phosphate stones.

Bibliography

Dell'Orto VG, Belotti EA, Goeggel-Simonetti B, Simonetti GD, Ramelli GP, Bianchetti MG, et al. Metabolic disturbances and renal stone promotion on treatment with topiramate: a systematic review. Br J Clin Pharmacol. 2014;77:958-64. [PMID: 24219102]

Item 73 Answer: C

H

Educational Objective: Diagnose proton pump inhibitor-induced tubulointerstitial nephritis.

The proton pump inhibitor omeprazole is the most likely cause of this patient's kidney findings. Nonspecific symptoms of tubulointerstitial disease include polyuria, malaise, and anorexia, as well as progressive kidney dysfunction. Urinary findings can range from minimal findings to the presence of sterile pyuria, proteinuria, and hematuria. Chronic tubulointerstitial diseases most commonly result from previous injury due to acute interstitial nephritis. Therefore, the history and physical examination should focus on conditions associated with acute tubulointerstitial disease and other potential treatable causes with a careful review of medications. Proton pump inhibitors are the most commonly prescribed drugs worldwide. The occurrence of interstitial nephritis is not dose related, and disease can recur with reexposure. The median time from drug initiation to interstitial nephritis diagnosis is variable but can exceed 6 months to 9 months, with 10 to 11 weeks the most common interval. There is also emerging

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literature that proton pump inhibitors may contribute to the development and progression of chronic kidney disease.

Although large amounts of aspirin and NSAIDs can cause tubulointerstitial nephritis, a daily dose of low-dose aspirin (81 mg) is unlikely to cause interstitial nephritis. It is unlikely that therapeutic doses of aspirin alone cause chronic kidney disease in patients with normal underlying kidney function.

Fenofibrate nephrotoxicity is characterized by a rise in serum creatinine typically occurring ≥6 months after initiation of therapy. The sediment is bland, and there is usually no significant proteinuria. The mechanism of increase in creatinine is unknown. This patient has been taking fenofibrate for only 2 months, making this drug an unlikely cause of his interstitial nephritis.

St. John's wort (*Hypericum perforatum*) is most commonly used to treat depression. Adverse effects are uncommon but the following have been reported: gastrointestinal symptoms, dizziness, confusion, tiredness, sedation, photosensitivity, dry mouth, urinary frequency, anorgasmia, and swelling. St. John's wort has not been associated with tubulointerstitial nephritis.

KEY POINT

- Chronic tubulointerstitial nephritis can be caused by proton pump inhibitors, and the median time from drug initiation to diagnosis may exceed 6 to 9 months.

Bibliography

Moledina DG, Perazella MA. PPIs and kidney disease: from AIN to CKD. J Nephrol. 2016;29:611-6. [PMID: 27072818]

H

Item 74 Answer: C

Educational Objective: Diagnose pseudohyperkalemia.

The most appropriate next step in management is a repeat plasma potassium measurement. This patient has an elevated serum potassium level of 6.4 mEq/L (6.4 mmol/L) in the setting of leukocytosis likely due to acute leukemia. Hyperkalemia is defined as a serum potassium level >5.0 mEq/L (5.0 mmol/L). Any level >6.0 mEq/L (6.0 mmol/L) can be life-threatening. Because of the potential cardiac effects of hyperkalemia, immediate electrocardiography (ECG) is indicated. The earliest ECG changes of hyperkalemia are peaking of the T waves and shortening of the QT interval. As hyperkalemia progresses, there is prolongation of the PR interval, loss of P waves, and eventual widening of the QRS complexes with a "sine-wave" pattern that can precede asystole. This patient has no ECG evidence of hyperkalemia. Pseudohyperkalemia is therefore the most likely cause of his elevated serum potassium level. Pseudohyperkalemia occurs with a false rise in potassium values from cellular release of potassium during venipuncture due to hemolysis or prolonged tourniquet use. It also occurs with significant leukocytosis or thrombocytosis. During the clotting process, these cells are disrupted with the release of intracellular potassium, and pseudohyperkalemia may occur in serum specimens when there are extreme elevations of leukocytes or platelets. The next step is to obtain a plasma specimen and rapidly separate the plasma from the cells. Normally, the serum potassium is 0.3 to 0.4 mEq/L (0.3-0.4 mmol/L) greater than a plasma specimen obtained at the same time. In extreme cases of leukocytosis or thrombocytosis, the serum potassium can be more than 1.0 mEq/L (1.0 mmol/L) higher. In cases of pseudohyperkalemia, a rapidly processed plasma specimen will be normal.

In patients with normal kidney function, intravenous saline, usually with the concomitant administration of a loop diuretic, can increase potassium excretion. Intravenous calcium should be reserved for cases of hyperkalemia exhibiting ECG changes. The effect of calcium on stabilizing the cardiac membrane is a transient event that lasts only 30 minutes. Inhaled albuterol lowers potassium by shifting it into cells. However, this patient has no indication to rapidly reduce potassium levels or stabilize the cardiac membrane because his ECG is normal.

The use of sodium bicarbonate in hyperkalemia has fallen out of favor. It has minimal effects on potassium levels and is usually reserved for patients with metabolic acidosis.

KEY POINT

- Pseudohyperkalemia may occur in serum specimens when there are extreme elevations of leukocytes or platelets; repeat plasma potassium measurements can confirm a normal potassium level.

Bibliography

Meng QH, Wagar EA. Pseudohyperkalemia: a new twist on an old phenomenon. Crit Rev Clin Lab Sci. 2015;52:45-55. [PMID: 25319088]

Item 75 Answer: C

H

Educational Objective: Treat anemia associated with chronic kidney disease using an erythropoiesis-stimulating agent.

An erythropoiesis-stimulating agent (ESA) is appropriate to treat anemia in this patient with stage G4 chronic kidney disease (CKD). The prevalence of anemia increases as CKD progresses due to several factors, including impaired erythropoietin production, erythropoietin resistance, and reduced erythrocyte life span. Iron deficiency may contribute to erythropoietin resistance. The Kidney Disease: Improving Global Outcomes (KDIGO) recommendations suggest maintaining transferrin saturation levels of >30% and serum ferritin levels of >500 ng/mL (500 µg/L). The patient's iron stores are adequate based on the patient's transferrin saturation and ferritin levels, and the next step in treatment is to start an ESA. ESAs are highly effective in raising hemoglobin concentrations and alleviating symptoms, and can avoid the need for transfusion. ESAs should not be used in patients with active malignancy, history of malignancy, or history of stroke. ESAs should be started in symptomatic patients with CKD who have a hemoglobin concentration <10 g/dL (100 g/L), and the dose should be titrated to avoid hemoglobin concentrations increasing above 11.5 g/dL (115 g/L).

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ACE inhibitors and angiotensin receptor blockers (ARBs) inhibit erythropoiesis, and patients on maintenance dialysis taking either ACE inhibitors or ARBs may have increased erythropoietin requirements. However, the mechanisms by which this occurs are poorly defined. Discontinuing losartan is incorrect because renin-angiotensin system blockade in CKD is beneficial in delaying the progression of CKD to end-stage kidney disease, which outweighs any potential interaction with anemia. However, discontinuing the medication could be considered if the patient demonstrated signs of erythropoietin resistance or refractory anemia.

Packed red blood cell transfusion is not indicated at this time and would expose the patient to transfusion-related risks and side effects. Additionally, blood transfusions can cause allosensitization, which can lead to antibody formation, and may prolong transplant waiting times.

Starting iron is incorrect because the patient is iron replete. Iron repletion is recommended if the transferrin saturation is ≤30% and the ferritin is ≤500 ng/mL (500 µg/L).

KEY POINT

- The Kidney Disease: Improving Global Outcomes (KDIGO) guidelines recommend consideration of erythropoiesis-stimulating agents to treat anemia in patients with chronic kidney disease and adequate iron stores who have hemoglobin concentrations <10 g/dL (100 g/L); the dose should be titrated to avoid hemoglobin concentrations increasing above 11.5 g/dL (115 g/L).

Bibliography

Kidney Disease: Improving Global Outcomes (KDIGO) Anemia Work Group. KDIGO clinical practice guideline for anemia in chronic kidney disease. Kidney inter., Suppl. 2012;2:279-335. Available at www.kdigo.org.

H

Item 76 Answer: C

Educational Objective: Identify hypomagnesemia as a cause of hypokalemia.

The most likely cause of this patient's hypokalemia is hypomagnesemia. Symptoms of hypokalemia include weakness or paralysis; decreased gastrointestinal motility or ileus with nausea; and cardiac arrhythmias. This patient has symptomatic hypokalemia, presenting with lower extremity weakness and nausea. Hypokalemia can be caused by renal losses or nonrenal losses. In this case, the urine potassium is inappropriately high, pointing toward renal potassium wasting. Renal losses of potassium can occur with renal tubular acidosis; renal excretion of non-reabsorbable anions such as bicarbonate, hippurate, and ketones; drugs such as aminoglycosides or cisplatinum; Gitelman and Bartter syndromes; or hypomagnesemia. Hypomagnesemia is common, occurring in up to 12% of hospitalized patients. Chronic alcohol abuse results in excessive urinary excretion of magnesium and appears to reflect a reversible alcohol-induced tubular dysfunction. Intracellular magnesium is necessary to modulate the excretion of potassium through the potassium channel in the cortical collecting tubule. Hypomagnesemia results in loss of potassium through this channel. Importantly, the hypokalemia will be refractory to therapy until magnesium is repleted. Target levels for magnesium replacement are at least 2 mg/dL (0.83 mmol/L).

Unlike calcium and magnesium, which have substantial binding to albumin, potassium levels are not affected by the concentration of albumin.

Low levels of magnesium (due to alcohol abuse or malnutrition) activate G-proteins that stimulate calcium-sensing receptors and decrease parathyroid hormone (PTH) secretion and are a cause of hypocalcemia. Low magnesium levels are also associated with resistance to PTH activity at the level of bone, further contributing to hypocalcemia. Hypocalcemia and hypokalemia in this patient are a direct result of chronic magnesium loss due to the patient's alcoholism. Hypocalcemia has no significant effect on potassium concentration.

Because the kidneys can reduce urine potassium excretion to <20 mEq/24 h (20 mmol/24 h), hypokalemia from inadequate intake is uncommon. Urinary or gastrointestinal losses of potassium are most common. Assessment of urine potassium excretion is critical to establish renal potassium wasting. Urine potassium loss >20 mEq/24 h (20 mmol/24 h), a spot urine potassium >20 mEq/L (20 mmol/L), or a spot urine potassium-creatinine ratio >13 mEq/g (1.5 mEq/mmol) suggests excessive urinary losses. Conversely, urine potassium loss <20 mEq/24 h (20 mmol/24 h) suggests cellular shift, decreased intake, or extrarenal losses of potassium. This patient's high urinary potassium suggests urinary loss rather than poor nutrition as the cause of hypokalemia.

KEY POINT

- Hypomagnesemia can cause symptomatic hypokalemia via renal losses of potassium; importantly, the hypokalemia will be refractory to therapy until magnesium is repleted.

Bibliography

Rodan AR, Cheng CJ, Huang CL. Recent advances in distal tubular potassium handling. Am J Physiol Renal Physiol. 2011;300:F821-7. [PMID: 21270092]

Item 77 Answer: A

Educational Objective: Identify *Staphylococcus aureus* as a cause of infection-related glomerulonephritis.

Staphylococcus aureus is the most likely cause of this patient's infection-related glomerulonephritis (IRGN). This patient has acute kidney injury in the setting of cellulitis, with active urine sediment and low serum complement levels. The biopsy shows a proliferative glomerulonephritis on light microscopy with immunofluorescence of C3 and IgA and subepithelial hump-like deposits on electron microscopy, confirming a diagnosis of IRGN. In the developed world, the epidemiology of IRGN has drastically shifted over the past few decades, moving away from streptococcal-associated glomerulonephritides to infections

caused primarily by *S. aureus* and, at a significantly lower rate, gram-negative bacteria. In this patient with cellulitis and IRGN occurring at the time of infection, *S. aureus* is the most likely culprit pathogen.

In patients with poststreptococcal glomerulonephritis (group A *Streptococcus*, or *Streptococcus pyogenes*), there is a latent period between the resolution of the streptococcal infection and the acute onset of the nephritic syndrome, usually 7 to 10 days after oropharyngeal infections and 2 to 4 weeks after skin infections. In adults with non-poststreptococcal IRGN, the glomerulonephritis often coexists with the triggering infection. Sites of infection can include the upper and lower respiratory tract, skin/soft tissue, bone, teeth/oral mucosa, heart, deep abscesses, shunts, and indwelling catheters. Notably, this patient's kidney failure has occurred at the same time as the cellulitis, consistent with a staphylococcal-mediated form of IRGN.

Streptococcus pneumoniae is an uncommon cause of cellulitis, and *Streptococcus agalactiae* (group B *Streptococcus*) is capable of causing cellulitis in nonpregnant adults in special circumstances (lymphedema, vascular insufficiency, chronic dermatitis, or radiation-induced cutaneous injury). *S. pyogenes* and *S. aureus* are much more common causes of cellulitis, and the co-occurrence of the infection and IRGN points to *S. aureus* as the most likely culprit.

KEY POINT

- In adults, most cases of infection-related glomerulonephritis are no longer poststreptococcal, and the glomerulonephritis often coexists with the triggering infection.

Bibliography

Glassock RJ, Alvarado A, Prosek J, Hebert C, Parikh S, Satoskar A, et al. Staphylococcus-related glomerulonephritis and poststreptococcal glomerulonephritis: why defining "post" is important in understanding and treating infection-related glomerulonephritis. Am J Kidney Dis. 2015; 65:826-32. [PMID: 25890425]

Item 78 Answer: D

Educational Objective: Recognize differing guideline recommendations for blood pressure targets in older patients.

According to target blood pressure goals recommended by the American College of Physicians and the American Academy of Family Physicians, this 72-year-old woman's blood pressure is at target, and no changes are necessary. This guideline recommends that antihypertensive drugs be initiated in patients ≥60 years old if blood pressure is >150/90 mm Hg, with a goal of reducing systolic blood pressure to <150 mm Hg to reduce the risk for mortality, stroke, and cardiac events. The guideline further recommends that physicians consider initiating or intensifying pharmacologic treatment in patients ≥60 years of age with a history of stroke or transient ischemic attack to achieve a target systolic blood pressure <140 mm Hg to reduce the risk for recurrent stroke. The guideline also recommends considering the initiation or intensification of pharmacologic treatment in some patients ≥60 years of age at high cardiovascular risk, based on individualized assessment, to achieve a target systolic blood pressure <140 mm Hg to reduce the risk for stroke or cardiac events. These recommendations are based on evidence that demonstrates the greatest absolute benefit of antihypertensive therapy is seen in patients with the highest blood pressure and cardiovascular risk.

On the other hand, the 2017 American College of Cardiology/American Heart Association blood pressure guideline recommends a target systolic blood pressure goal of <130 mm Hg for noninstitutionalized, ambulatory community-dwelling patients ≥65 years of age. In those with a high burden of comorbidity and limited life expectancy, clinical judgment, patient preference, and an assessment of risk-benefit ratio should be considered for decisions about the intensity of blood pressure control and antihypertensive medication choice. This recommendation is based upon randomized controlled trials of antihypertensive therapy that have included large numbers of older persons, which demonstrated that more intensive treatment safely reduced the risk of cardiovascular disease for those ≥65 years of age.

KEY POINT

- Based on evidence that the greatest absolute benefit of antihypertensive therapy is seen in patients with the highest blood pressure and cardiovascular risk, the American College of Physicians and American Academy of Family Physicians recommend that antihypertensive drugs be initiated in patients ≥60 years old if blood pressure is >150/90 mm Hg, with a goal of reducing systolic blood pressure to <150 mm Hg; the American College of Cardiology/American Heart Association recommends a systolic blood pressure target of <130 mm Hg in patients ≥65 years old.

Bibliography

Kansagara D, Wilt TJ, Frost J, Qaseem A. Pharmacologic treatment of hypertension in adults aged 60 years or older. Ann Intern Med. 2017;167:291-292. [PMID: 28806807]

Item 79 Answer: D

H

Educational Objective: Treat hyperphosphatemia in a patient with stage G4 chronic kidney disease.

Sevelamer is the most appropriate treatment for this patient with secondary hyperparathyroidism and hyperphosphatemia associated with stage G4 chronic kidney disease (CKD). Increased plasma parathyroid hormone (PTH) occurring as a result of CKD is referred to as secondary hyperparathyroidism. Increased PTH levels result in reduced calcium excretion and increased phosphorus excretion by the kidneys. Early in CKD, the PTH-induced increase in renal phosphorus excretion enables normal serum phosphorus levels despite reduced renal excretory capacity. However, as CKD progresses, the kidney is unable to compensate for the increased phosphorus, and

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phosphorus levels rise. This results in a vicious cycle as phosphorus stimulates PTH production. Initial treatment of secondary hyperparathyroidism in CKD stages G3 through G5 is correction of serum calcium, phosphorus, and vitamin D levels. Current Kidney Disease: Improving Global Outcomes (KDIGO) guidelines recommend that elevated phosphorus levels should be lowered *toward* the normal range, not into the normal range, because there is an absence of data showing that efforts to maintain phosphorus in the normal range are of benefit to CKD stage G3a to G4. Thus, treatment should be aimed at overt hyperphosphatemia, and decisions to start phosphate-lowering treatment should be based solely on progressively or persistently elevated serum phosphorus levels. KDIGO guidelines also recommend avoiding hypercalcemia. In this patient, treatment of hyperphosphatemia with a phosphate binder and a low phosphorus diet is indicated. Sevelamer is a non-calcium-containing binder that might improve bone turnover, limit vascular calcification, and reduce all-cause mortality, compared with calcium-containing binders, although these potential benefits have not been consistently proven.

Aluminum hydroxide is an effective phosphate binder and is still used for very short-term treatment of severe secondary hyperparathyroidism. However, it would not be recommended in the chronic setting due to the toxic effects of aluminum (myalgia, weakness, osteomalacia, iron-resistant microcytic anemia, dementia), particularly because non-calcium-containing binders are now available.

This patient's 25-hydroxyvitamin D level is in the "sufficient" range. However, calcitriol may be warranted if hyperparathyroidism persists after normalization of serum calcium and phosphorus levels even in the setting of normal 25-hydroxyvitamin D levels, as impaired hydroxylation at the 1 position by the kidney can lead to functional deficiency.

Cinacalcet, a calcimimetic that decreases PTH levels, is currently FDA approved only for use in patients who are undergoing dialysis, although it has been used off-label for secondary hyperparathyroidism associated with hypercalcemia in cases in which use of vitamin D analogues has led to hypercalcemia.

KEY POINT

- Initial treatment of secondary hyperparathyroidism in chronic kidney disease stages G3 through G5 is correction of serum calcium, phosphorus, and vitamin D levels.

Bibliography

Patel L, Bernard LM, Elder GJ. Sevelamer versus calcium-based binders for treatment of hyperphosphatemia in CKD: a meta-analysis of randomized controlled trials. Clin J Am Soc Nephrol. 2016;11:232-44. [PMID: 26668024]

Item 80 Answer: C

Educational Objective: Discontinue NSAIDs in a patient with elevated blood pressure.

The most appropriate management is to discontinue ibuprofen and measure the blood pressure (BP) in 1 month. The American College of Cardiology/American Heart Association BP guideline defines stage 1 hypertension as a systolic BP of 130 to 139 mm Hg or diastolic BP of 80 to 89 mm Hg. This change is based on epidemiologic studies that indicate systolic BP >115 mm Hg and diastolic BP >75 mm Hg are associated in a linear fashion with cardiovascular events. In the initial assessment of a patient with elevated BP, before a diagnosis of hypertension is made, it is imperative that a complete history with a list of prescription, nonprescription (including complementary and alternative medications such as herbals), and illicit drugs is elicited. NSAIDs are one of the medication classes that can result in reversible elevations in BP, the mechanism for which is increased sodium retention. Therefore, ibuprofen, an NSAID, should be discontinued and BP remeasured. If the patient has ongoing pain, an alternative pain management strategy that does not result in BP elevation, such as nondrug interventions, topical analgesics (if appropriate), or acetaminophen, should be prescribed because pain can also result in BP elevation.

This patient's elevated BP would need to be confirmed 1 month after discontinuation of ibuprofen before antihypertensive medications such as amlodipine or hydrochlorothiazide are started in this otherwise healthy young individual.

Antihistamines such as loratadine generally do not result in BP elevation; therefore, loratadine does not need to be discontinued in this patient.

KEY POINT

- Many medications, such as NSAIDS, can result in reversible elevations in blood pressure; discontinuation of the drug and a reassessment of blood pressure 1 month later are necessary to confirm a return to normal blood pressure measurement.

Bibliography

Weir MR. In the clinic: hypertension. Ann Intern Med. 2014;161:ITC1-15; quiz ITC16. [PMID: 25437425]

Item 81 Answer: C

Educational Objective: Identify hepatitis C virus infection as the cause of membranoproliferative glomerulonephritis.

The most appropriate test to perform next is measurement of hepatitis C antibodies. This patient presents with glomerulonephritis (elevated serum creatinine level, hematuria, and subnephrotic proteinuria), which shows a membranoproliferative (MPGN) pattern on kidney biopsy. The new approach to MPGN lesions is a bifurcation based on the pattern of staining on immunofluorescence microscopy. The more common pattern, as seen in this patient, is immune-complex deposition with the presence of both immunoglobulin (IgG, IgM, and/or IgA) and complement (C1q and/or C3) on immunofluorescence, which infers that the classical pathway has been activated by an inciting cause or event that generally falls into one of three major categories: infectious, autoimmune,

or malignancy associated. The most common is infectious, specifically infection with hepatitis C virus (HCV).

When an MPGN lesion on immunofluorescence microscopy shows only C3 staining (that is, without immunoglobulin or C1q staining), this extremely rare finding is suggestive of an antibody-independent means of complement activation and points to hyperactivity of the alternative complement pathway. In these C3 glomerulopathies, named based on the isolated C3 staining pattern seen on immunofluorescence, screening for genetic abnormalities in alternative complement pathway proteins is an appropriate part of the diagnostic evaluation.

Hepatitis B virus infection and HIV infection have been linked to glomerular diseases, but these are classically associated with the nephrotic syndrome, specifically membranous glomerulopathy with hepatitis B virus infection and focal segmental glomerulosclerosis with HIV infection.

KEY POINT

- An immune-complex membranoproliferative glomerulonephritis is the classic form of kidney involvement seen in patients with hepatitis C virus infection.

Bibliography

Sethi S, Fervenza FC. Membranoproliferative glomerulonephritis–a new look at an old entity. N Engl J Med. 2012;366:1119-31. [PMID: 22435371]

Item 82 Answer: D

Educational Objective: Diagnose lead nephropathy.

The most likely diagnosis is lead nephropathy, which causes a chronic tubulointerstitial disease after years of continuous or intermittent lead exposure. Lead nephropathy can occur in patients with occupational exposure to lead or exposure to lead in water, soil, paint, or food products. Chronic lead nephropathy is frequently associated with hyperuricemia, hypertension, and recurrent gouty attacks. This patient's lead exposure is likely due to lead-contaminated moonshine. Contamination occurs when lead-containing car radiators are used to condense the alcohol during the distilling process. The initial diagnostic test is measurement of blood lead levels, although lead levels may have normalized if exposure has been reduced or stopped.

Analgesic nephropathy occurs in patients with long-term excessive ingestion of analgesics such as aspirin, acetaminophen, and phenacetin, usually in combination. Patients frequently present with nocturia, sterile pyuria, hypertension, anemia, and chronic tubulointerstitial disease. This patient has no history of prolonged analgesic exposure.

Balkan nephropathy is a form of chronic tubulointerstitial disease that progresses to end-stage kidney disease in patients from southeastern Europe (Serbia, Bulgaria, Romania, Bosnia and Herzegovina, and Croatia). This patient is not from this region.

Cadmium nephropathy occurs in patients with prolonged exposure to plastic, metal, alloys, and electrical equipment manufacturing industries. Early manifestations are those of tubular dysfunction, including low-molecular-weight tubular proteinuria (for example, β_2-microglobulin), aminoaciduria, renal glucosuria, and hypercalciuria. Patients can develop osteomalacia and nephrolithiasis. Clinically, patients present with hypertension, bone pain, and chronic kidney disease. This patient does not give any history of an occupation that would result in cadmium exposure.

KEY POINT

- Lead nephropathy can occur in patients with occupational exposure to lead or exposure to lead in water, soil, paint, or food products; it is frequently associated with hyperuricemia, hypertension, and recurrent gouty attacks.

Bibliography

Lin JL, Lin-Tan DT, Li YJ, Chen KH, Huang YL. Low level environmental exposure to lead and progressive chronic kidney diseases. Am J Med. 2006;119:707.e1-9. [PMID: 16887418]

Item 83 Answer: A

Educational Objective: Identify laxative abuse as a cause of a normal anion gap metabolic acidosis.

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Laxative abuse is the most likely cause of this patient's normal anion gap metabolic acidosis. Normal anion gap metabolic acidosis can be caused by gastrointestinal bicarbonate loss, renal loss of bicarbonate, or the inability of the kidney to excrete acid. The normal physiologic response to systemic acidosis is an increase in urine acid excretion. Therefore, an initial diagnostic step in normal anion gap metabolic acidosis is to determine whether the kidney is appropriately excreting acid or whether impaired kidney acid excretion is the cause of the metabolic acidosis. Increased acid excretion by the kidney is reflected as a marked increase in urine ammonium. However, urine ammonium is difficult to measure directly. Because ammonium carries a positive charge, chloride is excreted into the urine in equal amounts with ammonium to maintain electrical neutrality. Therefore, the amount of chloride in the urine reflects the amount of ammonium present, and the urine anion gap can be used as an indicator of the ability of the kidney to excrete acid. The urine anion gap is calculated as follows:

$$\text{Urine Anion Gap} = (\text{Urine Sodium} + \text{Urine Potassium}) - \text{Urine Chloride}$$

In the context of increased urinary ammonium excretion, therefore, the urine anion gap will be negative. The negative urine anion gap in this patient (−6 mEq/L [−6 mmol/L]) suggests a gastrointestinal cause of the normal anion gap metabolic acidosis, and laxative abuse is a possible, even likely explanation. In addition, the low urine potassium indicates appropriate renal compensation in context of laxative-induced hypokalemia.

Vomiting and gastric acid loss result in metabolic alkalosis, not metabolic acidosis.

H CONT.

Renal causes of normal anion gap metabolic acidosis are due to specific defects in renal handling of bicarbonate reclamation (type 2/proximal RTA) or in hydrogen ion secretion (type 1/hypokalemic distal RTA). Type 1 (hypokalemic distal) RTA is caused by a defect in hydrogen secretion and a consequent decrease in ammonium excretion, and is therefore associated with a positive urine anion gap; it is also characterized by high urine potassium secretion and hypokalemia. Type 4 (hyperkalemic distal) RTA is usually caused by aldosterone deficiency or resistance and is characterized by a high serum potassium and positive urine anion gap.

KEY POINT

- Normal anion gap metabolic acidosis can be caused by gastrointestinal bicarbonate loss, renal loss of bicarbonate, or the inability of the kidney to excrete acid.

Bibliography

Rastegar M, Nagami GT. Non-anion gap metabolic acidosis: a clinical approach to evaluation. Am J Kidney Dis. 2017;69:296-301. [PMID: 28029394]

H

Item 84 Answer: B

Educational Objective: Diagnose the cause of acute kidney injury with a kidney biopsy.

The most appropriate next step in the evaluation of this patient's acute kidney injury (AKI) is a kidney biopsy. This patient with sepsis has developed AKI that has continued to worsen despite discontinuation of antibiotics 4 days ago. His urinalysis is notable for hematuria, pyuria, and proteinuria. The differential diagnosis includes ischemic or toxic acute tubular necrosis in the setting of hypotension, acute interstitial nephritis (AIN) from antibiotics or a proton pump inhibitor, and infection-associated glomerulonephritis. Given multiple potential contributing factors, a kidney biopsy is necessary to differentiate.

Glucocorticoids would be indicated if AIN is identified on biopsy, but empiric therapy is not justified because other causes may be contributing to his AKI. Moreover, glucocorticoids can cause significant adverse side effects, including worsening glycemic control in a patient with diabetes mellitus. If AIN is confirmed on kidney biopsy, a trial of glucocorticoids can be considered.

Prerenal AKI results from decreased renal perfusion and will typically respond to restoration of effective arterial circulation. However, the patient has no findings of hypoperfusion, and the elevated fractional excretion of sodium argues against this diagnosis (typically <1%) and the need for a fluid challenge. Such an intervention may be deleterious in a patient with oliguric AKI.

Postrenal AKI results from urinary tract obstruction. Bladder outlet obstruction should be suspected in patients with prostate enlargement or in the setting of diabetes mellitus (neurogenic bladder), pain medications, or anticholinergic medications. This patient's kidney ultrasound does not show obstruction; therefore, placement of a urinary catheter is not appropriate and would increase his risk of catheter-associated urinary tract infection.

KEY POINT

- Kidney biopsy should be considered in patients with acute kidney injury from no apparent or unclear cause, suspected glomerulonephritis, or unexplained systemic disease.

Bibliography

Levey AS, James MT. Acute kidney injury. Ann Intern Med. 2017;167:ITC66-ITC80. [PMID: 29114754]

Item 85 Answer: B

Educational Objective: Recognize the role of genetic counseling in the diagnosis and management of hereditary nephritis.

Genetic counseling potentially followed by genetic testing for hereditary nephritis (Alport syndrome) is appropriate for this patient. Hereditary nephritis is a familial form of glomerulonephritis that affects approximately 0.4% of U.S. adults. The earliest presentation is microscopic hematuria, with or without proteinuria. Heavier proteinuria, hypertension, and chronic kidney disease usually develop over time, with end-stage kidney disease occurring between the late teenage years and the fourth decade of life. There are three genetic variants: X-linked (80%), autosomal recessive (15%), and autosomal dominant (5%). This patient's family history fits the X-linked version of disease. Her mother and maternal grandmother are asymptomatic carriers; each has a 50% chance of passing the affected gene to male offspring (in this family, the maternal uncle and the patient's older brother), and their daughters likewise have a 50% chance of carrying the gene. Almost all female heterozygotes have some degree of hematuria. Females with the X-linked variant can develop kidney disease depending on activity of the X chromosome in somatic renal cells (lyonization), but that does not appear to be the case in this family. Given widespread access to genetic testing, in patients with a clearly documented family history and abnormal urinary findings, the diagnosis of hereditary nephritis is now increasingly being made by the noninvasive route using genetic testing. Genetic testing is the only way to diagnose a female with a family history of X-linked hereditary nephritis, such as this patient.

Hereditary nephritis is accompanied by sensorineural hearing loss that can be subtle and only picked up by audiometry, but this complication would not be expected in an asymptomatic carrier, such as this patient.

The diagnosis of hereditary nephritis for affected patients has traditionally been made by the more invasive route of kidney biopsy, with electron microscopy required for the hallmark finding of prominent thickening and lamellation of the glomerular basement membrane (a basket-weave appearance). Other than the expected

microscopic hematuria, this patient has normal kidney function and does not require a kidney biopsy.

A diagnostic skin biopsy can be performed when X-linked hereditary nephritis is suspected. Type IV collagen alpha 5 chain (COL4A5) is normally present in the skin, and approximately 60% to 80% of patients with X-linked hereditary nephritis will show abnormal staining for COL4A5 in the skin biopsy, although these findings would not be expected in an asymptomatic carrier.

KEY POINT

- The diagnosis of hereditary nephritis is confirmed with kidney biopsy, skin biopsy, or molecular genetic analysis.

Bibliography

Gross O, Kashtan CE, Rheault MN, Flinter F, Savige J, Miner JH, et al. Advances and unmet needs in genetic, basic and clinical science in Alport syndrome: report from the 2015 International Workshop on Alport Syndrome. Nephrol Dial Transplant. 2017;32:916-924. [PMID: 27190345]

H

Item 86 Answer: A

Educational Objective: Identify the composition of a kidney stone in a patient with Crohn disease.

The most likely composition of this patient's kidney stone is calcium oxalate. This patient has classic symptoms of renal colic, including flank pain that radiates to the groin. Stone movement may result in pain migration to the genitalia. Nausea, vomiting, and dysuria may also be present. Microscopic hematuria is usually noted, although its absence does not exclude a stone. Patients with diarrhea who are volume depleted and have a metabolic acidosis are at increased risk for developing a kidney stone, particularly stones composed of calcium oxalate and uric acid. In this patient with Crohn disease and chronic diarrhea, the most likely composition of the stone is calcium oxalate because the chronic metabolic acidosis (suggested by the low serum bicarbonate concentration and relatively low urine pH) increases calcium loss from bone and decreases citrate excretion. Citrate is the major inhibitor of calcium crystallization in the urine. In addition, if there is concomitant fat malabsorption, a common occurrence in inflammatory bowel disease, calcium will bind to fat in the gut, allowing increased absorption of oxalate.

Struvite stones are composed of magnesium ammonium phosphate (struvite) and calcium carbonate apatite and occur in the presence of urea-splitting bacteria, such as *Proteus* or *Klebsiella*, in the upper urinary tract. These organisms convert urea to ammonium, which alkalinizes the urine, decreases the solubility of phosphate, and leads to struvite precipitation. Struvite stones can rapidly enlarge to fill the entire renal pelvis within weeks to months, taking on a characteristic "staghorn" shape. Calcium phosphate stones also form in alkaline urine. The low urine pH and absence of signs of infection on urinalysis make these diagnoses unlikely.

Cystine stones are caused by cystinuria, a rare autosomal recessive disorder of proximal tubular transport of dibasic amino acids such as cystine that presents at a young age.

The main risk factor for uric acid stones is low urine pH, usually <5.0, which decreases the solubility of uric acid. Hyperuricosuria is not a consistent finding. Comorbid risk factors for uric acid stones include gout, diabetes mellitus, the metabolic syndrome, and chronic diarrhea.

KEY POINT

- Patients with diarrhea who are volume depleted and have a metabolic acidosis are at increased risk for developing kidney stones, particularly calcium oxalate stones and, less commonly, uric acid stones.

Bibliography

Worcester EM, Coe FL. Clinical practice. Calcium kidney stones. N Engl J Med. 2010;363:954-63. [PMID: 20818905]

Item 87 Answer: A

H

Educational Objective: Diagnose D-lactic acidosis.

The most likely diagnosis is D-lactic acidosis. D-lactic acidosis is an unusual cause of lactic acidosis that presents with an increased anion gap metabolic acidosis in patients with short-bowel syndrome, mostly in the context of small-bowel resection or jejunoileal bypass. D-lactate may accumulate when excess carbohydrates reach the colon and are metabolized to D-lactate by bacteria. Therefore, it is sometimes manifested after a large carbohydrate load. D-lactate is the stereoisomer of L-lactate, the isomer usually responsible for lactic acidosis. The conventional lactate assay measures the L-lactate isomer, and therefore lactic acid levels in this case are normal. Characteristic symptoms include intermittent confusion, slurred speech, and ataxia. The diagnosis should therefore be considered in a patient with characteristic neurologic findings who presents with an increased anion gap metabolic acidosis, normal lactate level, negative ketones, and short-bowel syndrome or other forms of malabsorption; it is confirmed by measuring a D-lactate level.

Ethylene glycol or methanol intoxication also presents with an increased anion gap metabolic acidosis and neurologic symptoms. However, they are usually accompanied by a serum osmolal gap >10 mOsm/kg H_2O (6 mOsm/kg H_2O in this case) and a serum bicarbonate level <10 mEq/L (10 mmol/L). The serum osmolal gap is calculated as the difference between the measured osmolality and calculated osmolality, which is determined as follows:

$$\text{Serum Osmolality (mOsm/kg } H_2O) = (2 \times \text{Serum Sodium [mEq/L]}) + \text{Plasma Glucose (mg/dL)}/18 + \text{Blood Urea Nitrogen (mg/dL)}/2.8$$

Pyroglutamic acidosis also manifests as mental status changes in the context of an increased anion gap. This acidosis occurs in patients chronically receiving therapeutic doses of acetaminophen. Susceptible patients are those with critical illness, poor nutrition, liver disease, and chronic kidney

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disease, as well as those on a strict vegetarian diet. Diagnosis can be confirmed by measuring urine levels of pyroglutamic acid. This patient's history does not include acetaminophen ingestion and is more consistent with a D-lactic acidosis.

KEY POINT

- D-lactic acidosis is characterized by an increased anion gap metabolic acidosis in patients with short-bowel syndrome or other forms of malabsorption; diagnosis is confirmed by measuring the D-lactate level rather than the conventional L-lactate level.

Bibliography

Scheult J, Fitzpatrick G, Boran G. Lactic acidosis: an update. Clin Chem Lab Med. 2017;55:322-333. [PMID: 27522622]

Item 88 Answer: B

Educational Objective: Manage chronic hypertension prior to conception.

Discontinuation of the angiotensin receptor blocker (ARB) losartan is necessary for this patient who anticipates pregnancy. The renin-angiotensin system agents (ACE inhibitors, ARBs, and direct renin inhibitors) are contraindicated in pregnancy and should be stopped prior to conception. Exposure during the second and third trimesters of pregnancy has been associated with neonatal kidney failure and death. Although the level of risk for first trimester exposure is controversial, studies have suggested an association with cardiac abnormalities, and consensus is to stop these drugs prior to pregnancy. In patients with chronic hypertension, the 2013 American College of Obstetricians and Gynecologists guidelines recommend a goal blood pressure during pregnancy of 120-160/80-105 mm Hg. Antihypertensive treatment reduces the risk of progression to severe hypertension by 50% compared with placebo but has not been shown to prevent preeclampsia, preterm birth, small size for gestational age, or infant mortality. This patient's blood pressure is well below this goal of therapy, and her blood pressure would be expected to decline during pregnancy. Therefore, monitoring her blood pressure after discontinuation of losartan is a reasonable approach. If her blood pressure rises, initiation of a drug that is safe during pregnancy is recommended. Candidate drugs include methyldopa, nifedipine, and/or labetalol. No specific agent is first choice because no data support one over another. Therapeutic classes are not recommended because potential toxicity differs among agents within classes.

Diuretics may be continued in pregnancy, particularly if the woman is already taking them prior to pregnancy. If blood pressure remains low through the first trimester of pregnancy, the dose of the diuretic may be lowered. Although one could consider discontinuation of the diuretic if the patient's blood pressure remains within at or below target, there is no contraindication to its use.

Because ARBs and ACE inhibitors are contraindicated in pregnancy and carry similar risk, switching to the ACE inhibitor lisinopril is not recommended.

Although risks are less during the first trimester, recent data regarding first trimester risk of exposure suggest that the safest approach is to discontinue a renin-angiotensin system agent prior to conception. Waiting until the patient is pregnant is not recommended.

KEY POINT

- The renin-angiotensin system agents (ACE inhibitors, angiotensin receptor blockers, and direct renin inhibitors) are contraindicated in pregnancy and should be stopped prior to conception.

Bibliography

Whelton PK, Carey RM, Aronow WS, Casey DE Jr, Collins KJ, Dennison Himmelfarb C, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Hypertension. 2017. [PMID: 29133356]

Item 89 Answer: A

H

Educational Objective: Diagnose autosomal dominant polycystic kidney disease as a secondary cause of hypertension.

Kidney ultrasonography is the most appropriate diagnostic test to perform in this patient. The presence of hypertension, microhematuria, and a positive family history of chronic kidney disease requiring dialysis, as well as a brain aneurysm, raises clinical suspicion for autosomal dominant polycystic kidney disease (ADPKD). Clinical manifestations of ADPKD include gradual kidney enlargement, which may cause persistent abdominal pain and/or early satiety. Hypertension is common in patients with ADPKD, often preceding chronic kidney disease. Kidney cyst enlargement leads to stimulation of the intrarenal and circulating renin-angiotensin-aldosterone system. More than 50% of patients with ADPKD develop recurrent flank or back pain; causes include kidney stones, cyst rupture or hemorrhage, or infection. Nephrolithiasis occurs in approximately 20% of patients. A ruptured intracranial cerebral aneurysm resulting in a subarachnoid or intracerebral hemorrhage is the most serious extrarenal complication of ADPKD. Kidney ultrasonography is the most common and least costly screening and diagnostic method for ADPKD; it would reveal bilaterally enlarged kidneys with multiple cysts.

Calculation of the plasma aldosterone concentration/plasma renin activity ratio is used to screen for primary hyperaldosteronism, characterized by a triad of resistant hypertension, metabolic alkalosis, and hypokalemia. Although <50% of patients with primary hyperaldosteronism manifest hypokalemia, this diagnosis cannot account for the patient's flank fullness on palpation and hematuria or his family history of kidney failure.

Plasma fractionated metanephrines are obtained to screen for a pheochromocytoma, which could result in hypertension, but this patient has no symptoms or signs (for example, resistant hypertension, headaches, sweating) to indicate the presence of this tumor, and this diagnosis cannot account for the patient's flank fullness and hematuria.

H CONT.

Although hyperthyroidism can be a secondary cause of hypertension, the patient does not manifest any symptoms or signs (heat intolerance, resting tachycardia, thyromegaly) to suggest this, making measurement of thyroid-stimulating hormone unnecessary.

KEY POINT

- Hypertension is common in patients with autosomal dominant polycystic kidney disease (ADPKD), often preceding chronic kidney disease; kidney ultrasonography is the most common and least costly screening and diagnostic method for ADPKD.

Bibliography

Krishnappa V, Vinod P, Deverakonda D, Raina R. Autosomal dominant polycystic kidney disease and the heart and brain. Cleve Clin J Med. 2017;84:471-481. [PMID: 28628430]

H

Item 90 Answer: B

Educational Objective: Discontinue mycophenolate mofetil in a woman who is planning pregnancy.

The most appropriate management for this kidney transplant recipient who is planning pregnancy is to discontinue mycophenolate mofetil and begin azathioprine. Fertility increases after kidney transplantation, although fertility rates remain lower and pregnancy complications are higher compared with the general population. Pregnancy planning for a kidney transplant recipient is essential to improve outcomes and includes adjusting medications and optimizing clinical status. Kidney transplant recipients should wait 1 to 2 years with a stable allograft before attempting conception. Other comorbid conditions (such as systemic lupus erythematosus) should also be stable prior to conception. Outcomes are improved with better allograft function (serum creatinine <1.5 mg/dL [132.6 µmol/L]) and stable immunosuppression. Mycophenolate mofetil (as well as sirolimus and everolimus) is teratogenic and needs to be replaced 3 to 6 months prior to conception with azathioprine, which is generally safer and well tolerated in pregnancy.

Calcineurin inhibitors (both tacrolimus and cyclosporine) have been used safely in pregnancy. Therefore, tacrolimus does not need to be discontinued and replaced with cyclosporine in this patient.

Although this would constitute a high-risk pregnancy, the success rate of pregnancies in patients with kidney transplants is high; with stable allograft function, a normotensive patient and her fetus have favorable prognoses, and therefore the patient could proceed with pregnancy following modification of her maintenance immunosuppression regimen.

KEY POINT

- In kidney transplant recipients who are planning pregnancy, mycophenolate mofetil, sirolimus, and everolimus must be discontinued 3 to 6 months prior to conception and replaced with azathioprine, which is generally safer and well tolerated in pregnancy.

Bibliography

Hou S. Pregnancy in renal transplant recipients. Adv Chronic Kidney Dis. 2013;20:253-9. [PMID: 23928390]

Item 91 Answer: A

Educational Objective: Diagnose light chain cast nephropathy in a patient with multiple myeloma.

The most likely diagnosis is light chain cast nephropathy in this patient with multiple myeloma. In multiple myeloma, acute kidney injury from light chain cast nephropathy is the most common type of kidney disease. Cast nephropathy is characterized by intratubular obstruction with light chain casts that can result in acute tubular injury. A clinical clue to the diagnosis is the presence of an elevated urine protein-creatinine ratio, with minimal proteinuria detected by dipstick urinalysis (dipstick urinalysis detects albumin but not light chains). Other supporting findings are the presence of anemia and hypercalcemia (when calcium measurement is corrected for albumin).

Exposure to NSAIDs can cause tubular injury. However, NSAIDs do not cause a discrepancy in proteinuria between urinalysis and urine protein-creatinine ratio.

Renal sarcoidosis can result in tubulointerstitial dysfunction. Other kidney manifestations include direct ureteral involvement, retroperitoneal fibrosis, and, more commonly, hypercalcemia, hypercalciuria, nephrolithiasis, and nephrocalcinosis via excessive production of 1,25-dihydroxyvitamin D in granulomas. However, renal sarcoidosis is rare in patients without thoracic sarcoidosis and cannot account for the discrepancy in proteinuria between urinalysis and urine protein-creatinine ratio.

Uric acid nephropathy is unlikely given the modest elevation in the serum urate level. Furthermore, an elevated urine protein-creatinine ratio is not consistent with uric acid nephropathy.

KEY POINT

- Clinical clues to the diagnosis of light chain cast nephropathy from multiple myeloma include an elevated urine protein-creatinine ratio with minimal proteinuria by urine dipstick, anemia, and hypercalcemia.

Bibliography

Heher EC, Rennke HG, Laubach JP, Richardson PG. Kidney disease and multiple myeloma. Clin J Am Soc Nephrol. 2013;8:2007-17. [PMID: 23868898]

Item 92 Answer: B

Educational Objective: Diagnose IgA nephropathy.

IgA nephropathy is the most likely diagnosis. Recurrent gross hematuria, in which macroscopic hematuria occurs concomitantly or within days after an upper respiratory infection (synpharyngitic nephritis) or physical exertion, is a classic presentation of IgA nephropathy, particularly in younger patients.

This nephritic presentation usually follows a benign clinical course without associated kidney insufficiency, although in a minority of cases intraluminal obstructive erythrocyte casts can be a cause of moderate to severe acute kidney injury that typically responds to supportive care measures. The diagnosis of IgA nephropathy can only be made by kidney biopsy, but some clinicians will make an empiric diagnosis for young patients with a classic history of recurrent gross hematuria, negative imaging for masses/stones, and normal kidney function with little to no proteinuria.

IgA vasculitis (Henoch-Schönlein purpura) is the most common childhood vasculitis and tends to appear after upper respiratory infections. IgA vasculitis is rarer among adults. Characteristic symptoms are abdominal pain and palpable purpura. Gastrointestinal ischemia may be severe enough to cause intestinal bleeding. Arthritis is common, other organ systems may be involved, and patients may present with glomerulonephritis. The patient's recurrent symptoms, lack of additional findings, benign clinical course, and urine findings are not compatible with a diagnosis of IgA vasculitis.

Lupus nephritis and postinfectious glomerulonephritis can present with macroscopic glomerular hematuria, but these disease states usually induce low complement levels (low C3 with or without low C4). Postinfectious glomerulonephritis, when associated with upper respiratory infections caused by streptococcal organisms, usually occurs 2 to 3 weeks after the resolution of the streptococcal infection. In the developed world, it is more common to see peri-infectious glomerulonephritis associated with staphylococcal infections (usually skin infections), with onset at the time of infection, but these are not usually associated with gross hematuria or a recurrent history of such episodes.

KEY POINT

- A classic presentation of IgA nephropathy is recurrent gross hematuria that occurs concomitantly or within days after an upper respiratory infection or physical exertion and usually follows a benign course.

Bibliography

Lai KN, Tang SC, Schena FP, Novak J, Tomino Y, Fogo AB, et al. IgA nephropathy. Nat Rev Dis Primers. 2016;2:16001. [PMID: 27189177]

H

Item 93 Answer: D

Educational Objective: **Diagnose a complex mixed acid-base disorder.**

The most likely diagnosis is a complex mixed acid-base disorder consisting of respiratory alkalosis, increased anion gap metabolic acidosis, and metabolic alkalosis. Interpretation of acid-base disorders requires the identification of the likely dominant acid-base disorder, followed by an assessment of the compensatory response. When measured values fall outside the expected compensatory range, a mixed acid-base disorder is considered present. Multiple acid-base disturbances may coexist, as seen in this patient.

Because the blood pH is 7.56, the patient's dominant acid-base disorder is an alkalosis. The low P_{CO_2} indicates a respiratory component to the alkalosis. The expected metabolic compensation for chronic respiratory alkalosis is a reduction in the serum bicarbonate of 4 to 5 mEq/L (4-5 mmol/L) for each 10 mm Hg (1.3 kPa) decrease in the P_{CO_2} (in this case, the decrease in P_{CO_2} is 20 mm Hg [2.7 kPa]). The expected serum bicarbonate concentration in this patient is calculated as follows:

Normal Bicarbonate − Expected Compensation
24 − (8-10) mEq/L (mmol/L) = 14-16 mEq/L (14-16 mmol/L)

Because the measured bicarbonate of 20 mEq/L (20 mmol/L) is higher than expected, this suggests coexistence of a metabolic alkalosis.

An elevated anion gap is also present, indicating the presence of an increased anion gap metabolic acidosis. Assessing the ratio of the change in the anion gap (Δ anion gap) to the change in bicarbonate level (Δ bicarbonate), or the "delta-delta (Δ-Δ) ratio," may indicate the presence of a coexistent acid-base disturbance. A ratio of <0.5 to 1 may reflect the presence of concurrent normal anion gap metabolic acidosis, whereas a ratio >2 may indicate the presence of metabolic alkalosis. This patient's Δ-Δ ratio is 2.5 [Δ anion gap/Δ bicarbonate = (22 − 12)/(24 − 20) = 2.5], confirming the coexistence of the metabolic alkalosis.

The clinical situation most likely to present with this acid-base disorder is salicylate toxicity. Central hyperventilation from salicylate will cause the respiratory alkalosis; salicylate itself will cause the anion gap metabolic acidosis; and vomiting will cause the metabolic alkalosis.

KEY POINT

- Interpretation of acid-base disorders requires the identification of the likely dominant acid-base disorder, followed by an assessment of the compensatory response; when measured values fall outside the range of the predicted compensatory response, a mixed acid-base disorder is considered present.

Bibliography

Seifter JL, Chang HY. Disorders of acid-base balance: new perspectives. Kidney Dis (Basel). 2017;2:170-186. [PMID: 28232934]

Item 94 Answer: D

H

Educational Objective: **Evaluate proteinuria in the absence of albuminuria.**

The most appropriate next step in management is to obtain a urine protein electrophoresis. Albumin is the predominant protein detected on urine dipstick, which detects albumin excretion graded as trace (10-30 mg/dL), 1+ (30 mg/dL), 2+ (100 mg/dL), 3+ (300 mg/dL), and 4+ (>1000 mg/dL). Highly alkaline urine specimens can produce false-positive results on dipstick testing for protein. The sulfosalicylic acid (SSA) test can be used to detect the presence of not only albumin

H CONT.

but also other proteins that are not detected with the urine dipstick, such as urine light chains or immunoglobulins. The possibility of cast nephropathy should be raised in patients with acute kidney injury and anemia when the urine dipstick reads negative or trace for protein, but the urine shows increased positivity for protein by the SSA test or by measuring the urine protein-creatinine ratio. Although these findings are most concerning for myeloma cast nephropathy, light chains are associated with other renal findings such as proximal tubulopathy. Proximal tubule involvement may be associated with hypophosphatemia and glucosuria (Fanconi syndrome).

Omeprazole and other proton pump inhibitors are well-described causes of acute interstitial nephritis. Although this is possible, this patient's proteinuria patterns are far more consistent with multiple myeloma.

Although a 24-hour urine collection is likely to provide a more accurate assessment of the total urine protein, the urine protein-creatinine ratio is sufficiently accurate to determine the presence of proteinuria.

Noncontrast helical abdominal CT may be helpful if the presence of a stone or mass in the kidney is suspected; however, in the absence of flank pain or hematuria, this imaging study is unlikely to provide additional diagnostic information.

KEY POINT

- The presence of significant measured proteinuria in the context of minimal proteinuria on urine dipstick suggests the presence of Bence-Jones (light chain) proteinuria, which can be confirmed by a urine protein electrophoresis.

Bibliography

Simerville JA, Maxted WC, Pahira JJ. Urinalysis: a comprehensive review. Am Fam Physician. 2005;71:1153-62. [PMID: 15791892]

Item 95 Answer: D

Educational Objective: Refer a patient with chronic kidney disease for kidney transplant evaluation.

Kidney transplant evaluation is the most appropriate management for this patient with stage G4 chronic kidney disease (CKD). Referral to a kidney transplant center is indicated when the estimated glomerular filtration rate (eGFR) is <20 mL/min/1.73 m². Kidney transplantation is the preferred treatment for patients with end-stage kidney disease, because it improves life expectancy and quality of life. It also provides a significant cost savings to the health care system compared with maintaining a patient on dialysis. Early referral allows adequate time to identify suitable living donors. If no living donor is available, early listing is essential to begin the waiting process for a deceased-donor kidney. Patients undergo an extensive health screening to identify potential issues that may affect the safety and/or outcome of the transplant. In the potential recipient, these include active malignancy, coronary ischemia, or active infections. An adequate social support system and financial resources also are important to ensure medication adherence and long-term survival of the transplanted allograft.

Patients with stage G4 chronic kidney disease should be seen at least every 3 months, not 6 months. More importantly, clinical follow-up alone does not address the immediate problem of planning for renal replacement therapy, ideally with kidney transplantation.

Fistulography is not indicated because physical examination findings suggest that the fistula is mature and may be ready to use for hemodialysis. Invasive imaging is not required to confirm patency unless physical examination findings suggest a problem. Additionally, fistulography exposes the patient to nephrotoxic iodinated contrast and may reduce residual kidney function.

Although this patient has an arteriovenous fistula, hemodialysis is not indicated at this time because she has normal serum potassium and bicarbonate levels, does not have significant volume overload, and does not have uremic symptoms. Several recent studies have demonstrated no benefit in starting dialysis in asymptomatic patients early based upon an arbitrary eGFR cutoff compared with waiting until patients develop very low eGFR (<8-10 mL/min/1.73 m²) or clinical indications for dialysis are present.

KEY POINT

- Referral for kidney transplant evaluation is indicated when the estimated glomerular filtration rate is <20 mL/min/1.73 m² to allow for adequate time to identify suitable living donors or to be put on an early listing if no living donor is available.

Bibliography

Educational Guidance on Patient Referral to Kidney Transplantation-Organ Procurement and Transplantation Network. US Department of Health and Human Services. Available at: https://optn.transplant.hrsa.gov/resources/guidance/educational-guidance-on-patient-referral-to-kidney-transplantation/. Accessed October 30, 2017.

Item 96 Answer: C

H

Educational Objective: Treat type 1 hepatorenal syndrome.

Vasoconstrictor therapy with octreotide and oral midodrine is appropriate for this patient with type 1 hepatorenal syndrome (HRS). Type 1 HRS is a clinical diagnosis made after exclusion of other causes of kidney dysfunction. It is characterized by a rise in serum creatinine of at least 0.3 mg/dL (26.5 µmol/L) and/or ≥50% from baseline within 48 hours, bland urinalysis, and normal findings on kidney ultrasound. It is also supported by a lack of improvement in kidney function after withdrawal of diuretics and 2 days of volume expansion with intravenous albumin. Often, patients also have low urine sodium, low fractional excretion of sodium, and oliguria. Type 2 HRS is defined as a more gradual decline in kidney function associated with refractory ascites. General management of type 1 HRS includes discontinuing diuretics, restricting sodium, restricting water in hyponatremic patients, and searching for precipitating factors. Initial therapeutic interventions include

H CONT.

treatment with vasoconstrictors in conjunction with intravenous albumin.

Dialysis should be initiated only if the patient does not respond to HRS medical therapy with midodrine and octreotide and/or if indications for dialysis develop. Absolute indications for dialysis include hyperkalemia, metabolic acidosis, and pulmonary edema refractory to medical therapy; uremic symptoms; uremic pericarditis; and certain drug intoxications. Currently, this patient has no acute indications for dialysis.

The patient was volume expanded with intravenous albumin, which should have corrected hypovolemia. Furthermore, she is not volume depleted on physical examination, has edema and ascites, and has stable blood pressure without tachycardia. Therefore, intravenous fluids are not indicated.

The transjugular intrahepatic portosystemic shunt is primarily used to treat variceal hemorrhage and ascites. It has been used as a last resort in the treatment of refractory ascites in highly selected patients with HRS who do not respond to medical therapy and who are awaiting liver transplantation. Complications include an increase in the rate of hepatic encephalopathy and risk of kidney injury associated with intravenous contrast. This procedure is not indicated at this time.

KEY POINT

- General management of type 1 hepatorenal syndrome includes discontinuing diuretics, volume replacement with albumin, and use of vasoconstrictors.

Bibliography

Colle I, Laterre PF. Hepatorenal syndrome: the clinical impact of vasoactive therapy. Expert Rev Gastroenterol Hepatol. 2018;12:173-188. [PMID: 29258378]

H

Item 97 Answer: D

Educational Objective: Identify urea osmotic diuresis as a cause of hypernatremia.

Urea osmotic diuresis is the most likely cause of this patient's hypernatremia. This patient is recovering from acute kidney injury and is having a urea diuresis, with an elevated urine osmolality of 420 mOsm/kg H_2O. In osmotic diuresis, urine osmolality is usually between 300 and 600 mOsm/kg H_2O. The majority of the osmolality of the urine is made up of nonelectrolytes. This loss of electrolyte-free water is causing her serum sodium level to increase. The two major nonelectrolytes found in urine are urea and glucose. Her glucose is only 136 mg/dL (7.5 mmol/L), below the threshold for glucose appearing in the urine; therefore, the likely cause is excretion of urea. This can be confirmed by measuring urea in the urine.

Hyponatremia is found in 70% to 80% of patients with adrenal insufficiency and is a consequence of sodium loss and volume depletion caused by mineralocorticoid deficiency and increased vasopressin secretion caused by cortisol deficiency. In addition, hyperkalemia and hyperchloremic acidosis is found in approximately 50% of patients with adrenal insufficiency. Hypernatremia and hypokalemia would be unusual manifestations of adrenal insufficiency.

In the absence of antidiuretic hormone, excessive water is excreted by the kidneys, and the urine osmolality is low. The patient's urine osmolality is 420 mOsm/kg H_2O, making diabetes insipidus unlikely. In addition, there is no reason to suspect diabetes insipidus in this woman. Nevertheless, it would not be possible to rule out partial nephrogenic diabetes insipidus until her urea normalized.

Glycosuria is not the cause of this patient's hypernatremia because her glucose level is below the tubular threshold for reabsorption, approximately 180 mg/dL (10 mmol/L). A urine dipstick would verify the lack of glycosuria.

KEY POINT

- Hypernatremia may be caused by osmotic diuresis, in which the urine osmolality is usually between 300 and 600 mOsm/kg H_2O.

Bibliography

Lindner G, Schwarz C, Funk GC. Osmotic diuresis due to urea as the cause of hypernatraemia in critically ill patients. Nephrol Dial Transplant. 2012;27:962-7. [PMID: 21810766]

Item 98 Answer: D

Educational Objective: Perform a kidney biopsy to evaluate a decline in kidney function.

A kidney biopsy is appropriate for this patient with a decline in kidney function. Clinical and laboratory features are often insufficient for definitive diagnosis of kidney disease. Kidney biopsy may therefore be essential for diagnosis and management. Indications include glomerular hematuria, severely increased albuminuria, acute or chronic kidney disease of unclear cause, and kidney transplant dysfunction or monitoring. In this case, the patient has an elevated serum creatinine without clear cause. Although further serologic testing may be done to guide diagnosis, a kidney biopsy will provide definitive diagnosis.

Due to preferential dilation of the efferent arteriole, the ACE inhibitor lisinopril may reduce glomerular filtration rate (GFR) and hence increase serum creatinine; however, this change in serum creatinine will occur within days of drug initiation and then stabilize. In this case, the serum creatinine increased without a change in dose, suggesting an unrelated cause.

A 24-hour creatinine clearance may be helpful in estimating kidney function but will not change the evaluation at this time. Most studies show that the Chronic Kidney Disease Epidemiology (CKD-EPI) Collaboration equation or the Modification of Diet in Renal Disease (MDRD) study equation provides a more accurate estimated GFR (eGFR) compared with creatinine clearance.

Although this patient's CKD-EPI eGFR is reported as >60 mL/min/1.73 m², his increasing serum creatinine is consistent with a significantly declining eGFR. Although cystatin C will potentially add to the accuracy of the

CKD-EPI formula, it will not change the evaluation, as GFR is declining as documented by the serum creatinine elevation (and no baseline cystatin C is available to show otherwise).

KEY POINT

- Indications for kidney biopsy include glomerular hematuria, severely increased albuminuria, acute or chronic kidney disease of unclear cause, and kidney transplant dysfunction or monitoring.

Bibliography

Hogan JJ, Mocanu M, Berns JS. The native kidney biopsy: update and evidence for best practice. Clin J Am Soc Nephrol. 2016;11:354-62. [PMID: 26339068]

H

Item 99 Answer: B

Educational Objective: Manage end-stage kidney disease in an elderly patient with multiple comorbidities and poor prognosis.

Discussion of conservative management and non-dialytic options is appropriate for this 82-year-old patient with end-stage kidney disease (ESKD) who has multiple comorbidities and poor prognosis. The life expectancy of some patients with ESKD with advanced age and severe comorbidities can be extremely short and may not be improved by dialysis. In elderly persons with progressing or advanced chronic kidney disease, decisions need to be made about the desires and plans to initiate renal replacement therapy and/or referral for evaluation for kidney transplantation. Several factors, including comorbid medical conditions, functional status, expected outcomes, and patient preferences regarding goals of care, should be considered. There is growing recognition that clinicians need to ensure maximal involvement of patients and their families in treatment decisions. This shared decision-making is a process whereby patients and providers can discuss the benefits and burdens of potential treatment strategies in the context of each patient's priorities and needs.

Patients with low comorbidity levels and a predicted survival of >3 years should be considered for all kidney disease treatment modalities, including kidney transplantation. In contrast, patients with a high 3- and 6-month expected mortality may choose to delay initiation and may be candidates for non-dialytic conservative management. Patients who choose conservative therapy have relatively preserved functional status until the last months of life. Conservative management may be a reasonable choice for patients whose primary goal is to maintain their independence and to avoid the time, pain, and discomfort related to dialysis, as well as for patients with poor functional status and a predicted post-dialysis initiation projected survival of <3 months.

KEY POINT

- Non-dialytic therapy is a reasonable treatment option for elderly patients with end-stage kidney disease and multiple comorbidities; treatment focuses on symptom management.

Bibliography

Verberne WR, Geers AB, Jellema WT, Vincent HH, van Delden JJ, Bos WJ. Comparative survival among older adults with advanced kidney disease managed conservatively versus with dialysis. Clin J Am Soc Nephrol. 2016;11:633-40. [PMID: 26988748]

Item 100 Answer: B

Educational Objective: Manage difficult-to-control hypertension with the addition of a loop diuretic.

The addition of a loop diuretic such as furosemide is the most appropriate treatment. This patient has difficult-to-control hypertension in the setting of stage G4 chronic kidney disease (CKD), and his blood pressure is not at target. The American College of Cardiology/American Heart Association blood pressure guideline recommends a target blood pressure of <130/80 mm Hg for all patients, including those with CKD. The most appropriate treatment is the addition of a loop diuretic. Suboptimal blood pressure therapy in patients with difficult-to-control hypertension is frequently the result of not including a diuretic, which prevents or corrects extracellular volume expansion. Persistent volume expansion, even if not sufficient to produce clinically evident edema, contributes significantly to hypertension. This is particularly important in sodium-retentive, edematous conditions such as heart failure, liver cirrhosis, or CKD.

Although thiazide diuretics are frequently used as initial diuretic therapy, they are generally less effective in patients with lower glomerular filtration rates. At estimated glomerular filtration rates <30 mL/min/1.73 m², loop diuretics tend to be more effective at controlling extracellular volume expansion and should be used instead of (or added to) thiazide diuretics. The dosage of loop diuretics depends on the sodium intake and the severity of CKD. Generally, furosemide doses of 40 to 80 mg twice daily is initiated with a salt-restricted diet and adjusted according to the response. When it is appropriate to add a thiazide diuretic to a blood pressure regimen, chlorthalidone is often preferred because of its longer duration of action.

The patient is already on a maximum dose of the ACE inhibitor lisinopril, which is appropriate for the treatment of hypertension in patients with CKD. Although he still has albuminuria, addition of the angiotensin receptor blocker (ARB) losartan is inappropriate because several trials have shown that combination therapy with an ACE inhibitor and ARB may result in adverse events, such as acute kidney injury and hyperkalemia, and does not improve cardiovascular outcomes compared with treatment with an ACE inhibitor or ARB alone.

KEY POINT

- Patients with difficult-to-control hypertension typically require the addition of a diuretic, which prevents or corrects extracellular volume expansion in sodium-retentive, edematous conditions (heart failure, liver cirrhosis, chronic kidney disease).

Bibliography

Braam B, Taler SJ, Rahman M, Fillaus JA, Greco BA, Forman JP, et al. Recognition and management of resistant hypertension. Clin J Am Soc Nephrol. 2017;12:524-535. [PMID: 27895136]

H

Item 101 Answer: B

Educational Objective: Diagnose cisplatin-induced acute kidney injury.

The patient has cisplatin-induced acute kidney injury (AKI). AKI due to renal tubular dysfunction can occur following administration of cisplatin and ifosfamide. High-dose methotrexate can also cause renal tubular injury, which can be avoided with aggressive intravenous hydration, forced diuresis, urine alkalization, and administration of leucovorin. Cisplatin induces direct cellular toxicity as a result of their transport through tubular cells, induction of mitochondrial injury, oxidative stress, and activation of apoptotic signaling pathways. Cisplatin-induced AKI develops 7 to 10 days after administration and is characterized by polyuria, tubular injury, hypomagnesemia, and proximal renal tubular acidosis (RTA) with Fanconi syndrome. Cisplatin nephrotoxicity results in volume depletion from urinary excretion of sodium and hypomagnesemia from urinary magnesium loss with ensuing hypokalemia and hypocalcemia. Fanconi syndrome in this patient is supported by the normal anion gap metabolic acidosis, hypophosphatemia, and urinary findings of glycosuria (in the setting of normal blood glucose) and proteinuria. In patients receiving cisplatin, serum electrolyte levels and kidney function must be carefully monitored because early recognition and prompt discontinuation of the drug are essential for renal recovery.

Bevacizumab and gemcitabine can cause hypertension and AKI due to thrombotic microangiopathy, which manifests as thrombocytopenia with hemolytic anemia, elevated lactate dehydrogenase, decreased haptoglobin, and schistocytes on peripheral smear. Urinary findings usually demonstrate significant proteinuria and hematuria. No laboratory findings in this patient support this diagnosis, and these drugs do not cause renal tubular injury.

Paclitaxel has been associated with subacute diffuse interstitial lung disease and peripheral neuropathy. Paclitaxel does not cause AKI or the electrolyte abnormalities as seen in this patient.

KEY POINT

- Cisplatin-induced acute kidney injury is characterized by polyuria, tubular injury, hypomagnesemia, and proximal renal tubular acidosis with Fanconi syndrome.

Bibliography

Rosner MH, Perazella MA. Acute kidney injury in patients with cancer. N Engl J Med. 2017;376:1770-1781. [PMID: 28467867]

Item 102 Answer: B

Educational Objective: Treat hypertension to a blood pressure target of <130/80 mm Hg in a patient with chronic kidney disease and hypervolemia.

The most appropriate management is to increase the furosemide dose. The patient has chronic kidney disease and proteinuria of 1000 mg/g, and he is taking prednisone for his primary focal segmental glomerulosclerosis. The pathophysiology of hypertension in kidney disease is complex, but sodium retention is the predominant mechanism and is related to a reduction in glomerular filtration rate (GFR), resistance to natriuretic peptides, and increased activity of the renin-angiotensin-aldosterone system. Control of sodium balance is an essential component of blood pressure management in patients with kidney disease. Dietary sodium restriction to <2000 mg/d combined with appropriate use of diuretics is advised. As the GFR declines, thiazide diuretics become less effective. Loop diuretics should be employed in such patients, with doses titrated to clinical response. Because this patient is hypervolemic (elevated jugular venous pressure, S_3, lower extremity edema), the dose of the loop diuretic needs to be increased.

Increasing the amlodipine dose is not the best option because it will not treat the underlying hypervolemia, and increasing the dose of amlodipine may worsen the lower extremity edema.

Adding an ACE inhibitor (such as lisinopril) is inappropriate because the patient is already on an angiotensin receptor blocker (losartan), and combination therapy with these agents and other renin-angiotensin system agents may result in adverse events such as hyperkalemia and acute kidney injury.

The 2017 American College of Cardiology/American Heart Association high blood pressure guideline recommends a target blood pressure of <130/80 mm Hg in patients with hypertension and chronic kidney disease. Therefore, maintaining this patient's current medication regimen would be inappropriate.

KEY POINT

- Control of sodium balance is an essential component of blood pressure management in patients with kidney disease; dietary sodium restriction to <2000 mg/d combined with appropriate use of diuretics is recommended.

Bibliography

Gargiulo R, Suhail F, Lerma EV. Hypertension and chronic kidney disease. Dis Mon. 2015;61:387-95. [PMID: 26328515]

Item 103 Answer: D

Educational Objective: Predict chronic kidney disease progression using the four-variable kidney failure risk equation.

A urine albumin-creatinine ratio is needed to complete the four-variable kidney failure risk equation (KFRE) for this patient with newly diagnosed chronic kidney disease (CKD). Not all patients with CKD will progress to end-stage kidney disease. In 2011, Tangri and colleagues developed and validated a set of risk prediction models for progression to kidney failure among Canadian patients with moderate to severe CKD. They demonstrated that using laboratory data that are routinely obtained in patients with CKD provided

excellent discrimination for prediction of progression of CKD to kidney failure over a 2- to 5-year period. Several models and variables were tested. Ultimately, the highest-performing models were the four-variable KFRE (age, sex, estimated glomerular filtration rate, and urine albumin-creatinine ratio) and the eight-variable KFRE (previous four variables, plus serum calcium, phosphate, bicarbonate, and albumin). The addition of diabetes mellitus, hypertension, blood pressure, and body weight did not improve the ability to discriminate risk for kidney failure.

In 2016, the KFRE was validated in 31 international cohorts comprised of 721,357 patients with stage G3 to G5 CKD. Calculation of the area under the receiver operating characteristic (ROC) curve quantifies the performance of a diagnostic test and allows comparison of different tests. A perfect test has an area under the curve (AUC) equal to 1; the closer the AUC is to 1, the better the test. The pooled AUC for the four-variable KFRE was 0.90 (95% CI, 0.89-0.92) to predict kidney failure at 2 years and 0.88 (95% CI, 0.86-0.90) at 5 years. Use of the eight-variable KFRE did not add to the predictive accuracy (AUC for 2 years, 0.89 [95% CI, 0.88-0.91]; AUC for 5 years, 0.86 [95% CI, 0.84-0.87]). Thus, the four-variable original risk equation appears generalizable and highly accurate in most cohorts and can be easily implemented across multiple health care systems. The KFRE performs well across age, sex, race, and the presence or absence of diabetes. The use of this equation is consistent with the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines, which recommend integration of risk prediction in the evaluation and management of CKD.

KEY POINT

- The kidney failure risk equation uses four variables (age, sex, estimated glomerular filtration rate, and albuminuria) to predict 2-year and 5-year risk of end-stage kidney disease in patients with stages G3 to G5 chronic kidney disease.

Bibliography

Tangri N, Grams ME, Levey AS, Coresh J, Appel LJ, Astor BC, et al; CKD Prognosis Consortium. Multinational Assessment of Accuracy of Equations for Predicting Risk of Kidney Failure: A Meta-analysis. JAMA. 2016;315:164-74. [PMID: 26757465]

Item 104 Answer: A

Educational Objective: Diagnose AA amyloidosis in a patient with rheumatoid arthritis.

AA amyloidosis is the most likely cause of this patient's proteinuria. Chronic inflammatory states, particularly rheumatoid arthritis, are associated with production of amyloid protein A. This acute phase reactant deposits in numerous tissues, most commonly the kidney (80%-90%) and heart, forming β-pleated sheets. In the kidney, amyloidosis presents with a bland urinary sediment and nephrotic-range proteinuria. Progression to end-stage kidney disease is frequent. Cardiac manifestations may include systolic or diastolic dysfunction and heart failure; low voltage on electrocardiogram can be seen. Although serum amyloid P component scintigraphy can diagnose amyloid, it is not available in the United States. Confirmation would therefore require a kidney biopsy in this case. Current treatment strategies are aimed at the underlying disease. Tocilizumab, an anti-interleukin-6 antibody, has been used successfully in patients with AA amyloidosis from rheumatoid arthritis.

Both focal segmental glomerulosclerosis (FSGS) and minimal change glomerulopathy (MCG) are associated with the nephrotic syndrome. However, FSGS more frequently affects black persons, and MCG is the most common cause of the nephrotic syndrome in children. Finally, this patient's history of a chronic inflammatory disease and findings of heart failure and an abnormal electrocardiogram more strongly suggest the possibility of amyloidosis.

NSAIDs are associated with interstitial nephritis and the nephrotic syndrome due to MCG or membranous glomerulopathy; typical findings include hematuria, pyuria, leukocyte casts, proteinuria, and an acute rise in the plasma creatinine concentration. However, this patient has not been using NSAIDs for the past 6 months and her urinalysis is bland, making this diagnosis unlikely.

Proton pump inhibitors can cause acute interstitial nephritis but are not associated with nephrotic-range proteinuria.

KEY POINT

- AA amyloid is formed by serum amyloid A protein, an acute phase reactant produced in various inflammatory diseases such as rheumatoid arthritis; confirmation of AA renal amyloidosis requires a kidney biopsy.

Bibliography

Obici L, Raimondi S, Lavatelli F, Bellotti V, Merlini G. Susceptibility to AA amyloidosis in rheumatic diseases: a critical overview. Arthritis Rheum. 2009;61:1435-40. [PMID: 19790131]

Item 105 Answer: C

Educational Objective: Treat elevated blood pressure with lifestyle modification.

The most appropriate next step in management is lifestyle modification. According to the American College of Cardiology/American Heart Association (ACC/AHA) blood pressure guideline, this patient has elevated blood pressure (BP), defined as systolic BP between 120-129 mm Hg and diastolic BP <80 mm Hg. Meta-analysis of observational studies has demonstrated that elevated BP and hypertension (systolic BP >130 mm Hg or diastolic BP >80 mm Hg) are associated with an increased risk of cardiovascular disease, end-stage kidney disease, subclinical atherosclerosis, and all-cause death. Nonpharmacologic therapy alone is especially useful for prevention of hypertension, including in adults with elevated BP, and for management of high BP in adults with milder forms of hypertension. Recommended lifestyle modifications include weight loss in adults who are overweight or obese; a

heart healthy diet that facilitates achieving a desirable weight; reduced sodium intake; high potassium intake (unless contraindicated by the presence of chronic kidney disease or use of drugs that reduce potassium excretion); increase in physical activity; and limiting alcohol consumption of standard drinks to no more than two (men) or one (women) per day.

According to the ACC/AHA BP guideline, the use of antihypertensive medications is recommended for secondary prevention of recurrent coronary events in patients with clinical coronary vascular disease and an average systolic BP of ≥130 mm Hg or an average diastolic BP of ≥80 mm Hg. Drug therapy is also recommended for primary prevention in adults with an estimated 10-year atherosclerotic cardiovascular disease risk ≥10% and an average systolic BP ≥130 mm Hg or average diastolic BP ≥80 mm Hg. For initiation of antihypertensive drug therapy, first-line agents include thiazide diuretics, calcium channel blockers, and ACE inhibitors or angiotensin receptor blockers. Because this patient has elevated BP (not hypertension), initiation of drug therapy is not indicated at this time.

The ACC/AHA recommends that adults with an elevated BP, such as this patient, should be managed with nonpharmacologic therapy and have a repeat BP evaluation within 3 to 6 months. Patients with normal BP (systolic BP <120 mm Hg and diastolic BP <80 mm Hg) can be reevaluated in 1 year.

KEY POINT

- Nonpharmacologic therapy alone is especially useful for prevention of hypertension, including in adults with elevated blood pressure, and for management of high blood pressure in adults with milder forms of hypertension.

Bibliography

Whelton PK, Carey RM, Aronow WS, Casey DE Jr, Collins KJ, Dennison Himmelfarb C, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Hypertension. 2017. [PMID: 29133356]

H Item 106 Answer: B

Educational Objective: Manage acquired cystic kidney disease with suspected renal cell carcinoma in a patient with end-stage kidney disease.

Bilateral radical nephrectomy is the most appropriate management for this patient with end-stage chronic kidney disease (ESKD) and bilateral kidney solid masses. Acquired kidney cysts often develop in patients with severe chronic kidney disease (CKD) and are frequently detected during routine kidney ultrasound or incidentally noted on abdominal CT or MRI scan. Acquired cystic kidney disease becomes more common and progresses during the course of ESKD, and some studies suggest that it may affect >50% of patients who have had ESKD for >3 years. The epithelial cells lining these cysts may undergo malignant transformation by poorly understood mechanisms. Patients with ESKD have a markedly increased risk for renal cell carcinoma. Although current guidelines do not support routine screening for renal cell carcinoma in all patients with CKD, a high level of suspicion is warranted in patients with symptoms such as new-onset gross hematuria or unexplained flank pain.

Partial nephrectomy and nephron-sparing approaches would be indicated for less severe stages of CKD. However, this patient has ESKD, and maintaining residual kidney function is no longer a concern; therefore, radical nephrectomy would be the most appropriate option.

Kidney biopsy should be considered in patients with glomerular hematuria, severely increased albuminuria, acute or chronic kidney disease of unclear etiology, and kidney transplant dysfunction or monitoring. The role of kidney biopsy for a suspicious mass is more limited. It may be useful in the evaluation of a small mass if there is suspicion of a renal metastasis or lymphoma and is likely useful to confirm the diagnosis of renal cell carcinoma in patients who cannot tolerate surgery prior to initiating medical therapy. The best approach for this patient with a high likelihood of renal cell carcinoma is bilateral nephrectomy. The excised tissue will provide histological confirmation of the diagnosis and thus guide further therapy.

Surveillance ultrasonography would not be the best management of this patient with bilateral solid kidney masses. The new-onset hematuria and kidney masses in the context of advanced CKD are highly suspicious for renal cell carcinoma.

KEY POINT

- Patients with end-stage kidney disease have a markedly increased risk for renal cell carcinoma, and a high level of suspicion is warranted in patients with symptoms such as new-onset gross hematuria or unexplained flank pain.

Bibliography

Hu SL, Chang A, Perazella MA, Okusa MD, Jaimes EA, Weiss RH; American Society of Nephrology Onco-Nephrology Forum. The nephrologist's tumor: basic biology and management of renal cell carcinoma. J Am Soc Nephrol. 2016;27:2227-37. [PMID: 26961346]

Item 107 Answer: B

Educational Objective: Provide appropriate blood pressure screening for a patient at increased risk for cardiovascular disease.

Annual blood pressure screening is the most appropriate management. This patient is healthy, physically active, not overweight, and does not meet criteria for hypertension based on these office blood pressure (BP) readings measured during one visit. However, he is at risk for future hypertension given his age (>40 years), black race, and a positive family history of hypertension. In addition, according to the American College of Cardiology/American Heart Association (ACC/AHA) guideline, the patient has elevated BP, defined as systolic BP between 120-129 mm Hg and diastolic BP <80 mm Hg. Although no

interventions are needed during this visit, the patient does need to be screened for high BP at least annually or more frequently. The U.S. Preventive Services Task Force (USPSTF) recommendations have not been updated since the release of the ACC/AHA guideline, with borderline and normal BP defined by older guidelines; however, the USPSTF recommends screening for hypertension in adults ≥18 years of age to identify those at increased risk for cardiovascular disease from hypertension and to begin early interventions to decrease this risk. Adults aged 18 to 39 years with normal BP and without cardiovascular risk factors should be rescreened every 3 to 5 years. Those who are ≥40 years of age and persons at increased risk for hypertension should be screened annually.

Beginning antihypertensive therapy with medications such as amlodipine or hydrochlorothiazide is inappropriate for this patient who does not meet the criteria for hypertension (defined by the ACC/AHA as a systolic BP ≥130 mm Hg and/or a diastolic BP ≥80 mm Hg). According to this guideline, patients with clinical cardiovascular disease and an average systolic BP ≥130 mm Hg or an average diastolic BP ≥80 mm Hg should be treated with lifestyle changes and medications for secondary prevention of cardiovascular events. Adults without clinical cardiovascular disease but an estimated 10-year atherosclerotic cardiovascular disease risk ≥10% and an average systolic BP ≥130 mm Hg or an average diastolic BP ≥80 mm Hg should also be treated with lifestyle interventions and pharmacologic therapy for primary prevention of cardiovascular disease.

KEY POINT

- Annual blood pressure screening is appropriate for patients who are ≥40 years of age and persons at increased risk for hypertension.

Bibliography

Siu AL; U.S. Preventive Services Task Force. Screening for high blood pressure in adults: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2015;163:778-86. [PMID: 26458123]

Item 108 Answer: A

Educational Objective: Manage stage G5 chronic kidney disease in a patient who will imminently require renal replacement therapy.

The most appropriate management for this patient with stage G5 chronic kidney disease (CKD) is to delay dialysis until she has uremic symptoms. She is not a candidate for transplant and has opted for hemodialysis for her renal replacement therapy (RRT). The decision of when to start RRT for CKD is complicated and requires frank discussion between providers and the patient and their families. For many years, consensus guidelines suggested that dialysis be initiated on the basis of estimated glomerular filtration rate (eGFR) cutoffs, ranging between 10 and 15 mL/min/1.73 m². In 2010, results were published from the IDEAL (Initiating Dialysis Early and Late) trial, which demonstrated no significant difference between the early dialysis group (eGFR, 10-15 mL/min/1.73 m²) and late dialysis group (eGFR, 5-7 mL/min/1.73 m²) in the frequency of adverse events (cardiovascular events, infections, or complications of dialysis). Although 76% of the late-start group ultimately initiated dialysis with eGFR >7.0 mL/min/1.73 m², the median delay in onset of dialysis was 5.6 months compared with the early start group. Thus, this study demonstrated that with careful clinical management, dialysis may be delayed until either the GFR drops below 7.0 mL/min/1.73 m² or more traditional clinical indicators (such as uremic symptoms or metabolic abnormalities) for the initiation of dialysis are present.

Discontinuation of diuretics is inappropriate because the patient does have some evidence of total body sodium and water overload (2+ edema) and thus needs continued diuretic therapy to avoid frank volume overload.

Referral for palliative care is not indicated because the patient is functioning well and is without signs of terminal illness or symptoms that require palliation; moreover, she has already chosen hemodialysis for future RRT. However, if her condition worsens over time, it is strongly encouraged to practice "kidney supportive care" or "patient-centered dialysis," in which treatment goals are closely aligned with patient preferences in a shared decision-making process.

KEY POINT

- There is no benefit in starting renal replacement therapy (RRT) in asymptomatic patients or at an arbitrary estimated glomerular filtration rate cutoff compared with careful clinical management and initiating RRT for symptoms or metabolic abnormalities that are refractory to medical treatment.

Bibliography

Cooper BA, Branley P, Bulfone L, Collins JF, Craig JC, Fraenkel MB, et al; IDEAL Study. A randomized, controlled trial of early versus late initiation of dialysis. N Engl J Med. 2010;363:609-19. [PMID: 20581422]

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Medical Knowledge Self-Assessment Program®

Pulmonary and Critical Care Medicine

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Welcome to the Pulmonary and Critical Care Medicine Section of MKSAP 18!

In these pages, you will find updated information on pulmonary diagnostic testing; airways disease; diffuse parenchymal lung disease; occupational lung disease; pleural disease; pulmonary vascular disease; lung tumors; sleep medicine; high-altitude–related illnesses; principles of ventilation in critical care; common ICU conditions such as upper airway emergencies, respiratory failure, sepsis, anaphylaxis, and toxicologic emergencies; and other clinical challenges. All of these topics are uniquely focused on the needs of generalists and subspecialists *outside* of pulmonary and critical care medicine.

The core content of MKSAP 18 has been developed as in previous editions—all essential information that is newly researched and written in 11 topic areas of internal medicine—created by dozens of leading generalists and subspecialists and guided by certification and recertification requirements, emerging knowledge in the field, and user feedback. MKSAP 18 also contains 1200 all-new peer-reviewed, psychometrically validated, multiple-choice questions (MCQs) for self-assessment and study, including 103 in Pulmonary and Critical Care Medicine. MKSAP 18 continues to include *High Value Care* (HVC) recommendations, based on the concept of balancing clinical benefit with costs and harms, with associated MCQs illustrating these principles and HVC Key Points called out in the text. Internists practicing in the hospital setting can easily find comprehensive *Hospitalist*-focused content and MCQs, specially designated in blue and with the H symbol.

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The learning objectives of MKSAP 18 are to:

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- Diagnose disease states that are less common and sometimes overlooked and confusing
- Improve management of comorbid conditions that can complicate patient care
- Determine when to refer patients for surgery or care by subspecialists
- Pass the ABIM Certification Examination
- Pass the ABIM Maintenance of Certification Examination

Target Audience

- General internists and primary care physicians
- Subspecialists who need to remain up to date in internal medicine
- Residents preparing for the certifying examination in internal medicine
- Physicians preparing for maintenance of certification in internal medicine (recertification)

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Key Points in the text that relate to High Value Care concepts (that is, concepts that discuss balancing clinical benefit with costs and harms) are designated by the HVC icon [HVC].

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Errata for MKSAP 18 will be available through the MKSAP Resource Site at mksap.acponline.org as new information becomes known to the editors.

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Pulmonary and Critical Care Medicine High Value Care Recommendations

The American College of Physicians, in collaboration with multiple other organizations, is engaged in a worldwide initiative to promote the practice of High Value Care (HVC). The goals of the HVC initiative are to improve health care outcomes by providing care of proven benefit and reducing costs by avoiding unnecessary and even harmful interventions. The initiative comprises several programs that integrate the important concept of health care value (balancing clinical benefit with costs and harms) for a given intervention into a broad range of educational materials to address the needs of trainees, practicing physicians, and patients.

HVC content has been integrated into MKSAP 18 in several important ways. MKSAP 18 includes HVC-identified key points in the text, HVC-focused multiple choice questions, and, for subscribers to MKSAP Digital, an HVC custom quiz. From the text and questions, we have generated the following list of HVC recommendations that meet the definition below of high value care and bring us closer to our goal of improving patient outcomes while conserving finite resources.

High Value Care Recommendation: A recommendation to choose diagnostic and management strategies for patients in specific clinical situations that balance clinical benefit with cost and harms with the goal of improving patient outcomes.

Below are the High Value Care Recommendations for the Pulmonary and Critical Care Medicine section of MKSAP 18.

- Spirometry before and after workplace exposures is a cost-effective way to confirm a suspected diagnosis of occupational asthma.
- A sputum culture is not routinely used to assess COPD exacerbations as it rarely affects management.
- The diagnosis of diffuse parenchymal lung disease can often be made based on high-resolution CT without a lung biopsy.
- Avoid mechanical ventilation for patients with idiopathic pulmonary fibrosis if lung transplantation is not an option.
- Uvulopalatopharyngoplasty and similar procedures are ineffective for treatment of obstructive sleep apnea.
- Do not routinely use haloperidol or atypical antipsychotics for the prevention of delirium.
- Do not routinely measure gastric residuals in critically ill malnourished patients because it delays achievement of feeding goals and may increase the risk of aspiration.
- Do not order diagnostic tests at regular intervals but rather in response to specific clinical questions.
- Do not use parenteral nutrition in adequately nourished critically ill patients within the first 7 days of an ICU stay.
- Adjunctive therapies for severe asthma exacerbation, including anesthetics with bronchodilator properties, inhalation of a helium-oxygen mixture, mucolytics, and leukotriene receptor antagonists lack evidence of clear efficacy.
- Pulmonary artery catheters have no benefit, and in some cases increase risk to patients when used to guide therapy for shock.
- Given the relative expense of colloids, crystalloid administration for distributive shock is generally preferred.
- There is no role for procalcitonin measurement in sepsis that is likely due to infection.
- There is no role for glucocorticoids in sepsis without shock.
- Home sleep testing is preferred in a patient with a high probability of obstructive sleep apnea without underlying cardiopulmonary or neuromuscular disease (see Item 4).

Pulmonary and Critical Care Medicine

Pulmonary Diagnostic Tests

Pulmonary Function Testing

Pulmonary function testing is an essential tool to diagnose obstructive and restrictive pathophysiology and to quantify the severity of the abnormality. Pulmonary function testing can include spirometry, bronchial challenge testing, lung volume testing, and measurement of diffusion capacity of the lung for carbon monoxide (DLCO). These findings are compared to age, sex, height, and race-adjusted population norms and expressed as a percent of the predicted value (**Table 1**). Values below 80% of the predicted value are considered reduced. Recent American Thoracic Society guidelines alternatively use the lower limit of normal (below the fifth percentile of healthy never-smokers) as a cutoff, but in most cases this is very similar to 80% of the predicted value.

KEY POINT

- Pulmonary function test results below 80% of predicted or below the lower limit of normal are indicative of pulmonary impairment.

H Spirometry

Measurement of expiratory airflow and volume is an essential diagnostic and management test for patients with lung diseases. Spirometry measures the maximal volume and flow of air during a best-effort, forced exhalation; reported values include the FEV_1, the FVC, and the FEV_1/FVC ratio. Measurement of maximal expiratory flow by peak flow meter is commonly used at home and in office settings to follow and manage patients with asthma, but is not considered a valid diagnostic tool for airways disease. Spirometry correlates with hand-held peak expiratory flow-meter measurements, but is more reliable, provides more data, and is used in both diagnosis and management of airways disease. Although spirometry is easily performed in the outpatient setting, technical test validation and patient factors—including poor effort, coughing, and failure to exhale for a minimum of 6 seconds—may result in suboptimal test performance and misinterpretation. H

TABLE 1. Characterization of Impairment Severity in Pulmonary Function Tests

Severity of Impairment	% of Predicted
FEV_1	
Mild	79-70
Moderate	60-69
Moderately severe	50-59
Severe	35-49
Very severe	<35
DLCO	
Mild	<LLN but >60
Moderate	40-60
Severe	<40

LLN = lower limit of normal; below the fifth percentile of healthy never-smokers.

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Bronchial Challenge Testing

Bronchial challenge testing is used to identify bronchial hyperresponsiveness, a diagnostic feature of asthma. This is particularly helpful in patients whose symptoms are suggestive of asthma but for whom other pulmonary function test results are normal. Patients inhale increasing doses of a substance known to induce bronchospasm, such as methacholine or histamine, in a stepwise fashion. This is followed by repeated measurements of FEV_1; if FEV_1 falls by 20% or more from the baseline value, the test is considered positive. Bronchial challenge testing has a high negative predictive value for diagnosing asthma; however, a positive test can be caused by other conditions including COPD, smoking, upper respiratory infections, allergic rhinitis, bronchiectasis, and cystic fibrosis.

KEY POINT

- Bronchial challenge testing is a helpful diagnostic tool in patients whose symptoms are suggestive of asthma but for whom other pulmonary function test results are normal.

Lung Volumes and DLCO

Measures of lung volume include total lung capacity (TLC), vital capacity (VC), and residual volume (RV). DLCO measurement estimates the amount of gas transfer through the alveolar/capillary unit and is proportional to the surface area of functional lung. DLCO is measured by inhalation of a gas mixture containing carbon monoxide and helium; the resulting value is corrected for hemoglobin level.

Pulmonary Function Testing Interpretation H

The purpose of pulmonary function testing interpretation is to classify abnormal results as an obstructive, a restrictive, or a mixed obstructive/restrictive pattern and to assess the severity of

H CONT.

impairment (**Figure 1**). The initial step is to review the results of spirometry. An FEV_1/FVC ratio below 0.70 is consistent with obstruction, and the severity is determined based on the measured FEV_1 as a percent of the predicted value (see Table 1). Reversibility of obstruction is determined by the response to a short-acting inhaled bronchodilator. An increase from baseline in FEV_1, FVC, or both of at least 12% and at least 200 mL indicates a positive bronchodilator response (reversibility). The TLC is normal or even increased in pure obstructive disease. Elevation of TLC and residual volume (120% or greater of predicted) can be observed in obstruction and generally is indicative of hyperinflation and air trapping, a common pattern in severe COPD or asthma.

If FEV_1 or FVC is reduced and the FEV_1/FVC ratio is 0.70 or greater, then the pattern may be interpreted as restrictive, but measurement of TLC is needed to confirm this. If the TLC is below 80% of predicted (or the lower limit of normal) a restrictive pattern is present.

Some patients may present with coexisting obstructive and restrictive pulmonary disorders, such as a COPD patient who develops an interstitial lung disease. In these cases, a low FEV_1/FVC ratio (obstructive pattern) and a low TLC (restrictive pattern) are both present.

DLCO is reduced in conditions where functioning alveolar capillary units are destroyed (COPD), infiltrated (interstitial lung diseases), removed (lung resection), or their function is compromised (pulmonary parenchymal and vascular disorders). Conditions that increase pulmonary capillary blood volume, such as pulmonary alveolar hemorrhage, left-to-right shunt, or asthma, can cause an elevation in DLCO.

The flow-volume loop is a graphic representation of maximally forced inspiratory and expiratory flow (on the Y axis) against volume (on the X axis). The shape of the spirometric flow-volume loop is also useful in differentiating obstructive from restrictive patterns (**Figure 2**). H

KEY POINTS

- The purpose of pulmonary function testing interpretation is to classify abnormal results as either an obstructive or restrictive pattern and to assess the severity of impairment.
- The FEV_1/FVC ratio is the primary measurement that defines obstructive disease, and total lung capacity is the primary measurement to confirm restrictive disease.

6-Minute Walk Test

The 6-minute walk test provides a valid and reliable measurement of exercise capacity in patients with lung disease. Patients walk at their own pace along a course for 6 minutes,

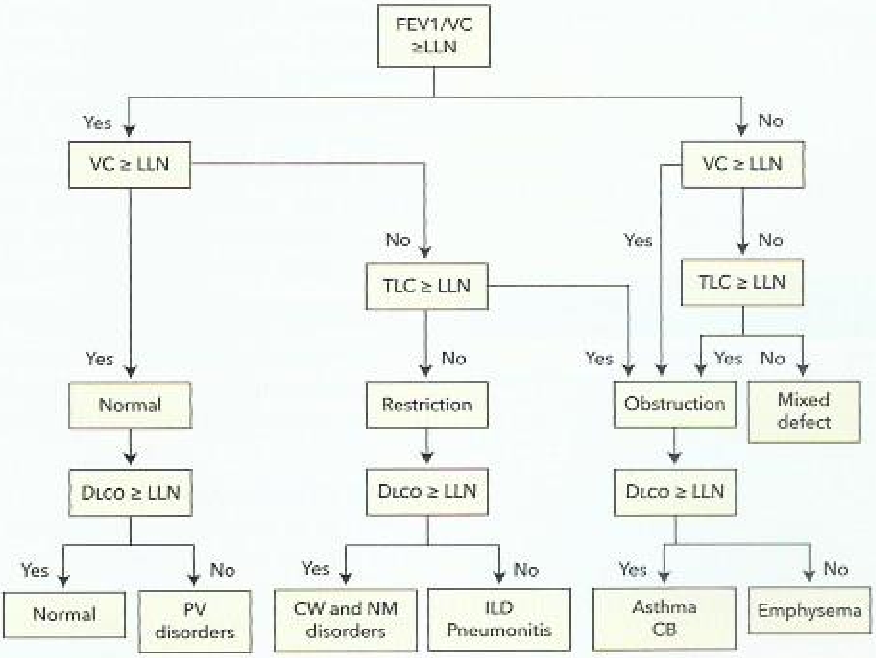

FIGURE 1. A simplified algorithm such as this may be used to assess lung function in clinical practice. It presents classic patterns for various pulmonary disorders. As in any such diagram, patients may or may not present with the classic patterns, depending on their illnesses, severity, and lung function prior to the disease onset (for example, did they start with a vital capacity [VC] close to the upper or lower limit of normal [LLN]?). The decisions about how far to follow this diagram are clinical, and will vary depending on the questions being asked and the clinical information available at the time of testing. The FEV_1/VC ratio and VC should be considered first. Total lung capacity (TLC) is necessary to confirm or exclude the presence of a restrictive defect when VC is below the LLN. The algorithm also includes DLCO measurement with the predicted value adjusted for hemoglobin. In the mixed defect group, the DLCO patterns are the same as those for restriction and obstruction. This flow chart is not suitable for assessing the severity of upper airway obstruction. CB = chronic bronchitis; CW = chest wall; ILD = interstitial lung diseases; NM = neuromuscular; PV = pulmonary vascular.

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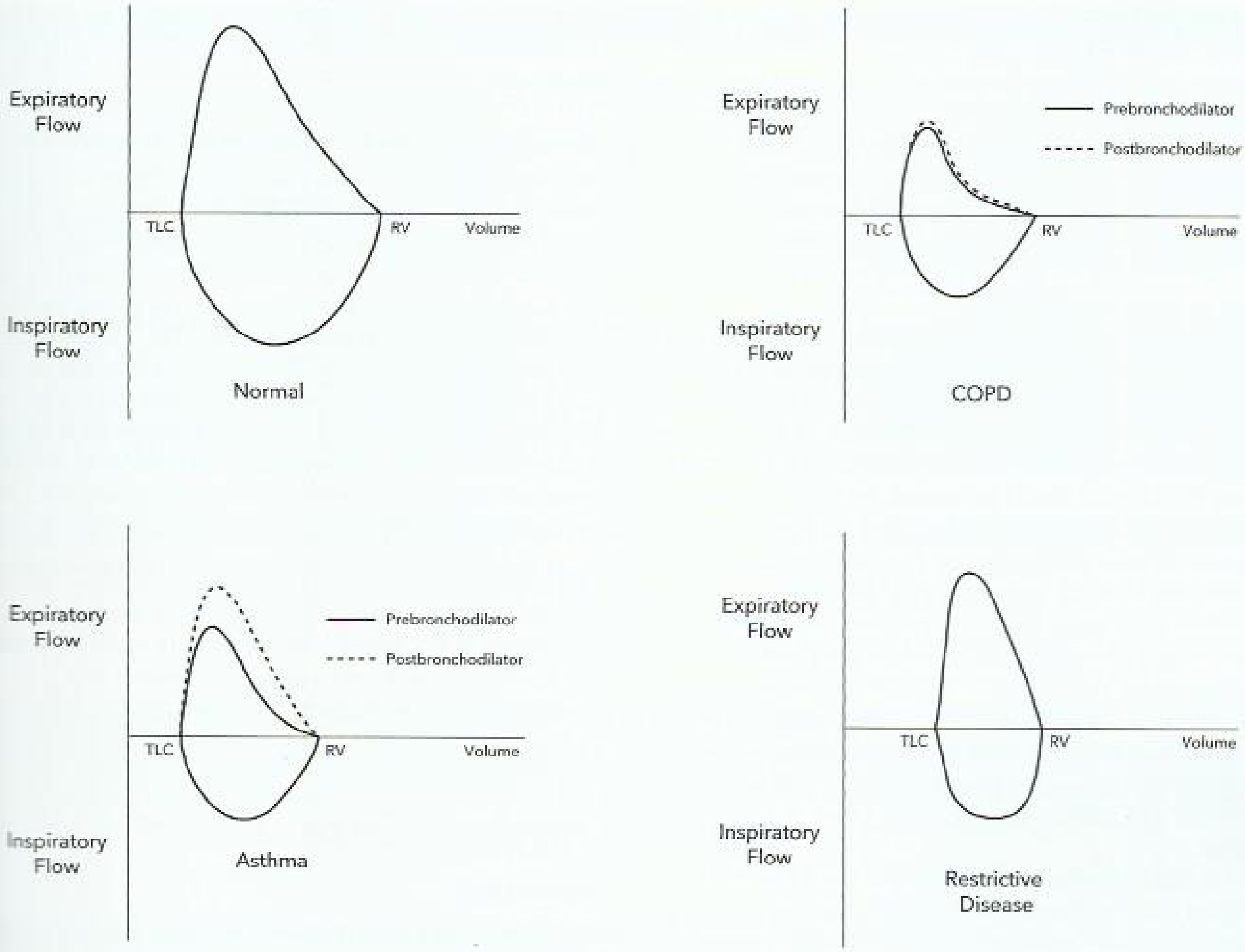

FIGURE 2. Pulmonary function test flow-volume patterns. RV = residual volume; TLC = total lung capacity.

and the total distance walked is recorded. Lower 6 minute walk test distances correlate with increased mortality in several lung diseases, including COPD, interstitial lung disease, and pulmonary arterial hypertension. Serial 6-minute walk testing may be used to assess response to therapy in patients with chronic respiratory disorders, especially pulmonary arterial hypertension.

Pulse Oximetry

Pulse oximetry provides a readily available noninvasive measurement of oxygen-bound hemoglobin in the circulation. Oximeters work by calculating the differential between absorption of infrared light by oxygenated and deoxygenated blood. A normal hemoglobin saturation measured by pulse oximetry is 95% to 100% and values below 90% indicate hypoxemia. Substances in the blood that absorb infrared light may cause erroneous readings, including carboxyhemoglobin (present in carbon monoxide poisoning), methemoglobin (caused by nitrates), methylene blue, and some topical anesthetics. More commonly, patient factors such as cool extremities, poor circulation, and motion artifact result in erroneous readings. In these cases, alternative methods of measuring oxygenation are needed.

Imaging and Bronchoscopy

Imaging

Chest Radiography

Conventional chest radiographs are indicated as the initial imaging procedure for most patients with significant respiratory symptoms. Posteroanterior and lateral views should be obtained. Advantages are the availability of testing and low dose of radiation exposure for the patient. Limitations of chest radiographs include patient factors such as the need to take a deep inspiration, breath holding, image resolution, and the 2-dimensional nature of the images.

Computed Tomography

CT of the thorax allows detailed, high-resolution imaging of the lungs and options for both static and dynamic imaging techniques. Helical scanners allow rapid scanning, but may require patients to hold their breath at full inspiration for 30 or

H CONT. more seconds. Reconstruction can include sagittal and coronal images, which result in 3 dimensional representation of the extent and distribution of disease. More specialized techniques reformat the data to highlight imaging of specific structures, such as maximum intensity projection (MIP), which focuses on the vasculature, and minimum intensity projection (MINIP), which focuses on the airways. Additional variables in CT imaging including slice thickness and interval; contrast enhancement may be used to augment the value of imaging based on the underlying disease.

The choice of examination will depend on the clinical context and information sought. For most patients, a routine (slice thickness of 2 or 2.5 mm) noncontrast CT is sufficient to provide the needed information. For patients suspected of having interstitial lung disease, a high resolution (slice thickness of 1 mm) study should be ordered. Addition of expiratory views can evaluate for air trapping and further inform the diagnosis of small airways disease. However, because the slice interval (the distance between individual slices) with high-resolution CT is larger than with conventional CT, this technique "skips" interval sections of the lung and should not be used to evaluate lung nodules. Use of intravenous contrast dye helps delineate mediastinal structures and is particularly useful in patients with suspected lymphadenopathy or vascular pathology. CT angiography is used for detection of pulmonary embolism and utilizes a rapid, timed bolus of intravenous contrast.

CT scanning exposes the patient to a much higher dose of radiation than traditional chest radiographs, and CT is currently the primary source of imaging radiation exposure for patients. Efforts to reduce radiation doses are ongoing, and low-dose CT scanning of the chest is now the recommended choice for lung cancer screening in the United States (see Lung Tumors). H

KEY POINT

- High-resolution CT techniques are preferred for evaluation of interstitial lung disease, conventional noncontrast CT is used to evaluate lung nodules, and CT angiography is used for detection of pulmonary embolism.

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Positron Emission Tomography Scanning

PET scans utilize the radionuclide 18-fluoro-2-deoxyglucose, which accumulates within highly metabolically active cells such as cancer cells, and can be visualized as discrete areas of uptake. Integrated PET/CT scanning allows improved localization of the metabolic activity. PET scans are widely used to evaluate risk of malignancy in lung nodules, to stage known thoracic tumors, and to evaluate for metastatic disease from other non-thoracic malignancies. False positive PET scans can occur in other hypermetabolic conditions where cells accumulate fluorodeoxyglucose, such as infection or inflammation. False negatives can occur when tumors have low rates of metabolic activity, such as carcinoid, adenocarcinoma in situ, and, rarely, metastatic kidney, prostate, or testicular cancer. PET scanning is not useful for determination of malignant potential in lung nodules less than 8 mm in size.

Bronchoscopy and Endobronchial Ultrasound

Bronchoscopy is a diagnostic and therapeutic tool for patients with lung disorders (**Table 2**). It is used for the diagnosis of localized and diffuse pulmonary diseases. It is important in the diagnostic evaluation for pulmonary infections, particularly in the immunocompromised host, and also has various therapeutic uses (**Table 3**). The addition of endobronchial ultrasound (EBUS) to visualize mediastinal and hilar lymph nodes for needle aspiration has made EBUS bronchoscopy the initial procedure of choice for obtaining tissue from mediastinal and hilar lymph nodes in the diagnosis and staging of patients with known or suspected thoracic malignancy. H

KEY POINT

- Endobronchial ultrasound (EBUS) is the initial procedure of choice for obtaining tissue from mediastinal and hilar lymph nodes in the staging of patients with known or suspected thoracic malignancy.

Airways Disease

Asthma

Epidemiology and Natural History

Asthma is an inflammatory disorder of the airways characterized by cough, wheezing, chest tightness, dyspnea, and variable airflow obstruction. Asthma is a major health burden throughout the world, and approximately 7.4% of the U.S. population has been diagnosed with asthma, accounting for more than 10 million office visits per year. Prevalence is increased among patients older than 65 years, women, blacks, and persons below the poverty level. Mortality in asthma is significant, causing 10.3 deaths per million Americans in 2015, with significantly higher mortality among patients who are black or are older than 65 years.

The onset of asthma can occur at any age, and the natural history varies with the duration and severity of symptoms, sex, and response to therapy. Children often have a family history of atopy, or exposure to sensitizing allergens such as dust mites or cockroaches. Childhood asthma may improve or resolve during teen and adult years, particularly in males. New-onset asthma in adults may have occupational exposures known to induce bronchial hyperreactivity. Those with severe symptoms generally have a more persistent course, lower pulmonary function, and increased risks of developing fixed airway obstruction. Diagnosis and treatment of asthma in older adults is often challenged by symptom overlap with other conditions (COPD, heart failure) and the normal effects of aging on pulmonary physiology.

TABLE 2. Bronchoscopic Diagnostic Procedures

Technique	Description	Examples of Indications
Airway inspection	Visualization of the tracheobronchial tree to the level of segmental airways	Hemoptysis Localized wheeze Persistent atelectasis Diagnosis of tracheobronchomalacia Inhalational injury
Bronchial washings	Samples from large airways	Diagnosis of infections
Bronchoalveolar lavage	Samples from small bronchi and alveoli	Diagnosis of infections Cell counts in diagnosis of parenchymal lung disease Alveolar hemorrhage Cytology for malignancy
Bronchial brushings	Brushings of the endobronchial mucosa for cells	Endobronchial lesions
Endobronchial biopsy	Biopsy within the airway lumen	Endobronchial mass or lesion
Transbronchial lung biopsy	Biopsy of the lung parenchyma or lung nodules/masses using small forceps; often aided by guidance technology including electromagnetic navigation and radial ultrasound	Diffuse lung disease Persistent infiltrates Lung nodules/masses Posttransplant rejection
Transbronchial needle aspiration	Aspiration of a lymph node or mass adjacent to the airway	Lymphadenopathy Pulmonary mass Mediastinal mass
Endobronchial ultrasound	Use of an ultrasound probe at the distal end of the bronchoscope to guide transbronchial needle aspiration	Lymphadenopathy Pulmonary mass Mediastinal mass
Electromagnetic navigation	Images from a recent CT are "linked" with the bronchoscope. An electromagnetic guidance system at the bronchoscope creates a map of the airways and guides the physician to the area of interest.	Pulmonary mass or nodule

TABLE 3. Bronchoscopic Therapeutic Procedures

Technique	Description	Examples of Indications
Flexible bronchoscopy	Large airway suctioning Basket and forceps Balloon tamponade of airway	Lobar atelectasis from mucus plugs Foreign body Bleeding
Bronchial thermoplasty	Radiofrequency energy ablation of proximal airway smooth muscle	Severe asthma
Endobronchial stent placement	Bronchoscopic placement of silicon and metal prostheses to expand and support the airways	Malignant obstruction Benign strictures Tracheomalacia or bronchomalacia Anastomotic dehiscence
Airway ablative therapies	Laser therapy Electrocautery Argon plasma coagulation Cryotherapy Brachytherapy	Malignant airway obstruction Benign airway obstruction Airway tumor ablation
Endobronchial valve placement	Airway placement of one-way valves	Bronchopleural fistula Emphysema
Balloon dilation	Targeted endobronchial balloon inflation	Benign or malignant airway stricture

KEY POINT

- Approximately 7.4% of the U.S. population has been diagnosed with asthma, and prevalence is increased among patients older than 65 years, women, blacks, and persons below the poverty level.

Pathogenesis

The pathophysiologic mechanisms of asthma include chronic airway inflammation, airway narrowing due to edema, subepithelial fibrosis, smooth muscle hypertrophy, and mucus hypersecretion, in addition to airway smooth muscle constriction causing bronchial hyperreactivity in response to various stimuli. The airway cellular inflammatory profile is variable; persists even during the absence of symptoms; and includes eosinophils, T lymphocytes, mast cells, and neutrophils. Eosinophilic inflammation is commonly recognized in allergic asthma, but patients may have other cellular profiles, with neutrophilic inflammation increasingly recognized in older patients. Bronchial hyperreactivity that causes airway obstruction is typically episodic and triggered by stimuli that would not induce symptoms in healthy people. Common triggers include allergens, dusts, fumes, exercise, extremes of temperature, and viral respiratory infections.

Risk Factors

Risk factors for asthma include both host and environmental factors. Genes predisposing to atopy, bronchial hyperreactivity, and airway inflammation have been identified, but genetic predisposition is thought to interact with additional factors, including exposure to indoor allergens (mites, furred animals, cockroaches, molds) and outdoor allergens (pollens, molds), tobacco smoke, occupational sensitizers and allergens, viral respiratory infections, and air pollution. In addition, obesity is an important risk factor for asthma.

Asthma is heterogeneous, but distinct phenotypes are recognized and have implications for underlying mechanisms, treatment, and outcomes. Although specific phenotypes are not yet broadly accepted, many are commonly described. Clinically recognizable groups include allergic, nonallergic, late-onset, adult onset eosinophilic, and obesity-associated asthma. These subsets tend to have different cellular compositions of airway inflammation and may respond variably to anti-inflammatory therapies.

KEY POINT

- Genetic predisposition to asthma is thought to interact with additional factors, including exposure to indoor allergens (mites, furred animals, cockroaches, molds) and outdoor allergens (pollens, molds), tobacco smoke, occupational sensitizers and allergens, viral respiratory infections, and air pollution.

Symptoms and Clinical Evaluation

Common symptoms of asthma are cough, wheezing, chest tightness, and shortness of breath that are intermittent and occur in response to various potential stimuli, including allergens, infections, dusts, fumes, and exercise. Symptoms often have a diurnal variation, worsening in the evening and early morning. Viral respiratory infections are a particularly robust trigger for most patients. Variability of symptoms (both improvement and worsening of symptoms over time) is a key diagnostic feature of asthma.

History taking should establish whether the patient has ever smoked tobacco or other products, has pets, or has had environmental exposures (either recreationally or in the work place) to dust, fumes, or particulate matter known to cause bronchial hyperreactivity. A personal or family history of atopy or allergic sinus disease may be present. In particular, the presence of nasal polyps, sensitivity to aspirin, and wheezing is known as the "asthmatic triad." The physical examination may demonstrate wheezing, reduced airflow, or a prolonged expiratory phase. However, patients may also have a completely normal respiratory exam, particularly when they are symptom free.

Confirmation of reversible airflow obstruction is a cornerstone of asthma diagnosis and can be assessed by spirometry, with measurement of forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), and the FEV_1/FVC ratio, or by serial measurement of peak expiratory flow rates. Airway obstruction that improves with bronchodilators, on subsequent measurements, or after 4 weeks of anti-inflammatory treatment supports a diagnosis of asthma. For adults, a significant change in FEV_1 is an increase from baseline of at least 12% and at least 200 mL. For some patients, airflow obstruction is not present during the initial evaluation, and demonstration of bronchial hyperreactivity with bronchial challenge testing is indicated. This is usually performed with inhaled methacholine, although other stimuli (exercise, mannitol) have been validated. If a bronchial challenge test is negative, it is unlikely that a patient has asthma. A positive challenge test confirms bronchial hyperreactivity, but is not sufficient to confirm asthma because other disorders may demonstrate this finding. Therefore, clinical correlation of this finding with symptoms and other testing is needed.

A chest radiograph is helpful in many patients to rule out other diagnoses, such as COPD, heart failure, parenchymal lung disorders, central airway obstruction, and bronchiectasis. This is especially important in older adults, in whom asthma is often underrecognized and undertreated.

KEY POINTS

- Common symptoms of asthma are cough, wheezing, chest tightness, and shortness of breath that are intermittent and occur in response to various potential stimuli, including allergens, infections, dusts, fumes, and exercise.
- Confirmation of reversible airflow obstruction with bronchodilators is a cornerstone of asthma diagnosis and can be assessed by spirometry, with measurement of FEV_1, FVC, and the FEV_1/FVC ratio showing an increase from baseline of ≥12% and ≥200 mL.

(Continued)

KEY POINTS *(continued)*

- In patients with clinical symptoms suggestive of asthma but with normal spirometry, bronchial challenge testing (such as with methacholine) may be helpful to evaluate for asthma. A negative test excludes asthma, whereas a positive test requires clinical correlation and may require additional testing.

Asthma Syndromes

Allergic Asthma

Identifying the presence of atopy can identify an allergic asthma phenotype in a patient with respiratory symptoms. The most common tests are allergy skin prick tests, which may be administered in the outpatient setting by qualified personnel, or laboratory measurement of allergen-specific IgE in serum. Results of each method are generally concordant. Skin testing is more sensitive but subject to errors related to administration, whereas serum tests are more specific but have higher costs. Measurement of total serum IgE is not useful because a normal level does not preclude clinical allergies. However, IgE is a therapeutic target for advanced treatments such as omalizumab (monoclonal antibody targeting IgE in severe atopic asthma), so measurement of IgE can help guide the use of these agents.

Identifying eosinophilic airway inflammation through either elevated serum or sputum eosinophil counts, or measurement of exhaled nitric oxide levels, may help phenotype patients. A phenotype of severe adult onset asthma with significant eosinophilia has been recognized, often without a significant component of allergies or atopy. These patients often require treatment with systemic glucocorticoids and may be appropriate for advanced anti-interleukin therapies such as mepolizumab.

Cough-Variant Asthma

Patients with asthma whose primary symptom manifestation is chronic cough without other symptoms are considered to have cough-variant asthma. Diagnosis requires documentation of bronchial hyperreactivity, as most patients will have normal baseline spirometry. Recommended therapies are the same as those for other types of asthma. Other causes of chronic cough should be investigated, including gastroesophageal reflux and upper airway cough syndrome due to rhinitis. Frequently, these etiologies coexist and require concomitant therapy (see MKSAP 18 General Internal Medicine).

Exercise-Induced Bronchospasm

Exercise-induced bronchospasm (EIB) refers to acute, measurable airway obstruction that occurs in response to exercise. EIB is one of the most common triggers of symptoms in patients with known asthma, and also occurs in patients without asthma, typically elite athletes, during periods of high-intensity exercise. Environmental factors play a key role in precipitating symptoms. Exercise in cold, dry air, such as during winter or in indoor ice rinks; exposure to high levels of trichloramines in swimming pools; and inhalation of airborne particulates and ozone have all been implicated.

Other disorders, such vocal cord dysfunction and cardiac disorders, can mimic EIB; therefore, establishing the presence of bronchial hyperreactivity is crucial to make an accurate diagnosis. For most patients this entails bronchial challenge testing with inhaled agents or, ideally, exercise. Initial pharmacologic therapy should consist of administration of an inhaled short-acting β2-agonist (SABA) 15 minutes before exercise. If patients require use of a SABA every day, or have inadequate symptom control, a second controller agent (inhaled glucocorticoid or a leukotriene receptor antagonist) should be added. Nonpharmacologic measures including preexercise warm-up and warming cold air before inhalation (such as a mask or scarf) are also recommended.

KEY POINT

- Initial pharmacologic therapy for exercise-induced bronchospasm should consist of administration of a short-acting β2-agonist 15 minutes before exercise.

Occupational Asthma

A careful occupational history is an essential part of asthma evaluation, as it is estimated that 15% of adult asthma is work-related. Occupational asthma includes asthma directly caused by exposure to sensitizing or irritant substances in the workplace, as well as preexisting asthma that is exacerbated by these same factors. Typical sensitizing agents are high molecular weight substances, such as proteins, that induce an IgE-mediated immunologic response. Examples include animal and plant allergens, latex, grains, and diisocyanates. Once sensitized, patients may subsequently react to very low levels of exposure. Those at risk include farmers and animal workers, health care workers, latex glove users, bakers, and manufacturers of polyurethane products. A key clinical indicator is the relationship of symptoms to work exposures; patients often improve during weekends and time away from work. Spirometry before and after workplace exposures is a cost-effective way to confirm a suspected diagnosis of occupational asthma. Alternatively, demonstration of bronchial hyperreactivity through bronchial challenge testing or serial peak flow measurements can be used. Treatment consists of reducing exposure to the offending agent through workplace modifications or removing patients from the workplace entirely, in addition to pharmacologic therapy. The overriding principle of treatment should be prevention, which includes workplace interventions to avoid exposures and monitoring for early identification of disease.

KEY POINT

- A key clinical indicator of occupational asthma is symptom improvement during weekends and time away from work; spirometry before and after workplace exposures is a cost-effective way to confirm a suspected diagnosis. HVC

Reactive Airways Dysfunction Syndrome

Reactive airways dysfunction syndrome is a well-described subset of irritant-induced occupational asthma. This syndrome occurs in patients without preexisting asthma following a single, high-level exposure to fumes, gases, or vapors; usually the exposure is severe enough to prompt immediate medical evaluation. The diagnosis requires evidence of asthmatic symptoms for at least 3 months following the exposure and is confirmed by airway obstruction or bronchial hyperreactivity.

Aspirin-Exacerbated Respiratory Disease

Aspirin-exacerbated respiratory disease describes asthma and rhinosinusitis that are precipitated by exposure to aspirin or other NSAIDs that inhibit cyclooxygenase-1. Clinical characteristics include an onset in adulthood; airway and peripheral eosinophilia; inflammatory sinusitis with polyposis; and persistent, often severe asthma. Ingestion of triggering substances can cause life-threatening bronchospasm within minutes to hours, sometimes accompanied by rhinorrhea, conjunctival injection, and flushing. Chronic management, in addition to the usual stepped asthma care includes discontinuing all NSAIDs and use of leukotriene-receptor antagonists that target the increased leukotriene production implicated in the mechanism of this particular asthma. Aspirin desensitization can improve control in a significant percentage of patients but requires specialized expertise.

Allergic Bronchopulmonary Aspergillosis

Allergic bronchopulmonary aspergillosis is an ongoing immunologic response to inhaled *Aspergillus* species that leads to persistent eosinophilic airway inflammation, increased IgE levels (both total and *Aspergillus* specific), and eventually tissue damage with airway remodeling. Patients present with difficult-to-control asthma, productive cough, and expectoration of brownish mucus plugs. Radiographs may demonstrate pulmonary infiltrates and bronchiectasis. The diagnostic criteria are debated but include the presence of asthma, elevated IgE levels, positive skin tests to *Aspergillus* antigens, increased pulmonary *Aspergillus*-specific IgE and IgG levels, and either central bronchiectasis or infiltrates. Management is aimed at suppressing the enhanced immunologic response with systemic glucocorticoids and reducing the fungal antigenic burden with antifungal agents.

Common Comorbidities

Comorbidities in asthma are common and should be considered and actively managed to reduce symptoms and potentially improve asthma control.

Gastroesophageal Reflux Disease

Gastroesophageal reflux disease frequently coexists in asthma patients, and may be an independent cause of respiratory symptoms such as cough and chest pain. In patients with active gastroesophageal reflux disease symptoms, an empiric trial of a proton pump inhibitor for 2 months is indicated. Patients whose reflux symptoms do not improve should be considered for further testing such as endoscopy and 24-hour esophageal pH monitoring (see MKSAP 18 Gastroenterology and Hepatology).

Sinus Disease

Disease of the upper airway, including rhinitis and sinusitis, is extremely common in patients with asthma and is associated with more severe asthma symptoms. Allergic rhinitis is an IgE-driven inflammatory response to sensitizing allergens, and is characterized by rhinorrhea, nasal obstruction, itching, and sneezing. Symptoms can be seasonal, intermittent, or perennial (usually caused by persistent exposure to indoor allergens such as dust mites). Patients with chronic rhinosinusitis have endogenous, ongoing inflammation of both the nose and paranasal sinuses, with additional symptoms of facial pain, sinus pressure, and sometimes anosmia. Those that develop nasal polyposis have more-difficult-to-control asthma. Guidelines suggest treating with intranasal glucocorticoids; more severe cases may require combined use of intranasal glucocorticoid and intranasal H1-antihistamines, oral antileukotrienes, oral glucocorticoids, biologics targeting IgE, and immunotherapy.

Obstructive Sleep Apnea

Symptomatic obstructive sleep apnea (OSA) and polysomnographic evidence of OSA are more common in patients with asthma compared to those without asthma. The association becomes stronger with increasing severity of asthma. The presence of OSA also worsens asthma control, increases asthma-related health care utilization, and reduces quality of life. Although nocturnal worsening of asthma symptoms is common, patients should also be asked about snoring, excessive daytime sleepiness, and witnessed apneas, which are typical symptoms of OSA. If present, diagnostic testing to confirm the presence of OSA is indicated because treatment of OSA improves asthma outcomes, including symptoms, quality of life, bronchodilator use, and peak flow rates.

Vocal Cord Dysfunction

Vocal cord dysfunction refers to paradoxical adduction of the vocal cords during inspiration, leading to functional upper airway obstruction. This entity is important as its symptoms mimic those of asthma. Vocal cord dysfunction should be considered in the differential diagnosis of asthma, particularly if patients complain of prominent inspiratory breathlessness, with throat tightness or voice dysfunction during attacks. Symptoms are often triggered by exercise, exposure to fumes or irritants, and stress. Patients with vocal cord dysfunction do not respond to standard asthma therapy. Vocal cord dysfunction also can coexist with asthma. The gold standard diagnosis is demonstration of the paradoxical vocal cord adduction using direct laryngoscopy during a symptomatic episode. However, patients are generally asymptomatic when evaluated or unable to tolerate the maneuver during an acute episode. Therefore, in patients with suggestive symptoms, a trial of treatment is often indicated. Management includes addressing

factors known to worsen vocal cord dysfunction (gastroesophageal reflux disease, postnasal drip), but the mainstay of treatment is speech therapy, which employs cognitive-behavioral techniques to self-identify triggers and symptoms and to reduce the functional obstruction.

KEY POINT

- Vocal cord dysfunction should be considered in the differential diagnosis of asthma, particularly if patients complain of prominent inspiratory breathlessness, with throat tightness or voice dysfunction during attacks.

Obesity

Obese patients have a higher prevalence of asthma and poorer control of symptoms. Increased BMI appears to influence asthma through mechanisms related to both systemic inflammation and respiratory mechanics. Obese patients with asthma do not respond as well to standard controller therapies as nonobese patients, possibly because of an alternate inflammatory profile or the presence of comorbidities associated with obesity, such as gastroesophageal reflux disease and OSA. Asthma may be overdiagnosed and underdiagnosed in obese patients because of the overlap of symptoms of breathlessness and exertional wheezing. Therefore, it is important to measure BMI in all patients undergoing asthma evaluation and to objectively document reversible airway obstruction through pulmonary function testing. In patients with obesity-related asthma, weight loss has been demonstrated to improve asthma control and lung function and should be considered an essential part of the treatment plan. In some patients, bariatric surgery may be indicated because greater amounts of weight loss correlate with better outcomes, including reduction in asthma exacerbations, improved quality of life, improved lung function, and decreased systemic and bronchial inflammation (see MKSAP 18 General Internal Medicine).

Management of Chronic Asthma

The goals of longitudinal asthma management are to control chronic asthma symptoms, prevent acute exacerbations, and minimize risks of developing fixed airway obstruction. This should be accomplished by assessing asthma severity, controlling symptoms on an ongoing basis, and then modifying therapies appropriately using a stepwise approach (**Figure 3**). There are three essential components to the management of asthma:

1. Assessment of symptom control and risk—Standardized, validated questionnaires that can discriminate between well-controlled and inadequately controlled asthma based on patient symptoms include the Asthma Control Test and the Asthma Control Questionnaire. Patients with daytime symptoms less than twice weekly and nocturnal symptoms less than twice monthly during the preceding 4 weeks are considered well controlled. Risk is based on measured lung function and the potential for future exacerbations, which is related to the presence of comorbidities and historical features known to predict future exacerbations.
2. Treatment—Once symptoms and risk are established, therapy should be initiated. All patients with asthma should be provided with rescue medication to use as needed for symptoms. Controller medications are used as a maintenance therapy to control symptoms and prevent exacerbations. A critical component of this therapy is teaching and assessing proper inhaler technique, as patients require skill and training to effectively use these devices. Use of a spacer can be helpful with compatible inhaler devices.
3. Review response and adjust therapy—After initiation of asthma therapies, patients should be reassessed after several months for their level of control and tolerance of medications. Controller medications can be stepped up or down with the goal to maintain symptom control and minimize medication exposure.

KEY POINTS

- Control of asthma should be assessed with the use of validated questionnaires.
- Inhaler skills training and adherence are essential for successful treatment.

Quick Relief Medications

All patients with asthma should be provided with quick relief, or rescue, therapy. Short-acting β_2 agonists (SABAs) are the preferred medications to quickly reverse bronchospasm and relieve acute asthma symptoms (**Table 4**). These inhaled agents have a rapid onset of action and deliver medications directly through the airways, reducing systemic side effects; SABAs are generally well tolerated. Their main mechanism of action is induction of airway smooth muscle relaxation using stimulation of β_2-agonist receptors. SABAs should be used as needed for symptoms and are generally not administered on a scheduled basis. They may also be used before exercise to prevent EIB. Albuterol is the most commonly used SABA in the United States. Use of SABAs as single-agent asthma therapy is only indicated for patients with symptoms occurring not more than twice weekly, normal lung function between exacerbations, and nocturnal symptoms not more than twice monthly. For all others, rescue therapy is used in conjunction with controller therapy.

H Short-acting inhaled anticholinergics are less effective than SABAs at relieving acute bronchospasm; however, they may be used as adjunctive therapy to SABA treatment in the management of acute exacerbations in the emergency department; this combination has been shown to reduce hospital admission rates. H

KEY POINTS

- All patients with asthma should be provided with quick relief, or rescue, therapy.
- Short-acting β_2-agonists are the preferred medications to quickly reverse bronchospasm and relieve acute asthma symptoms.

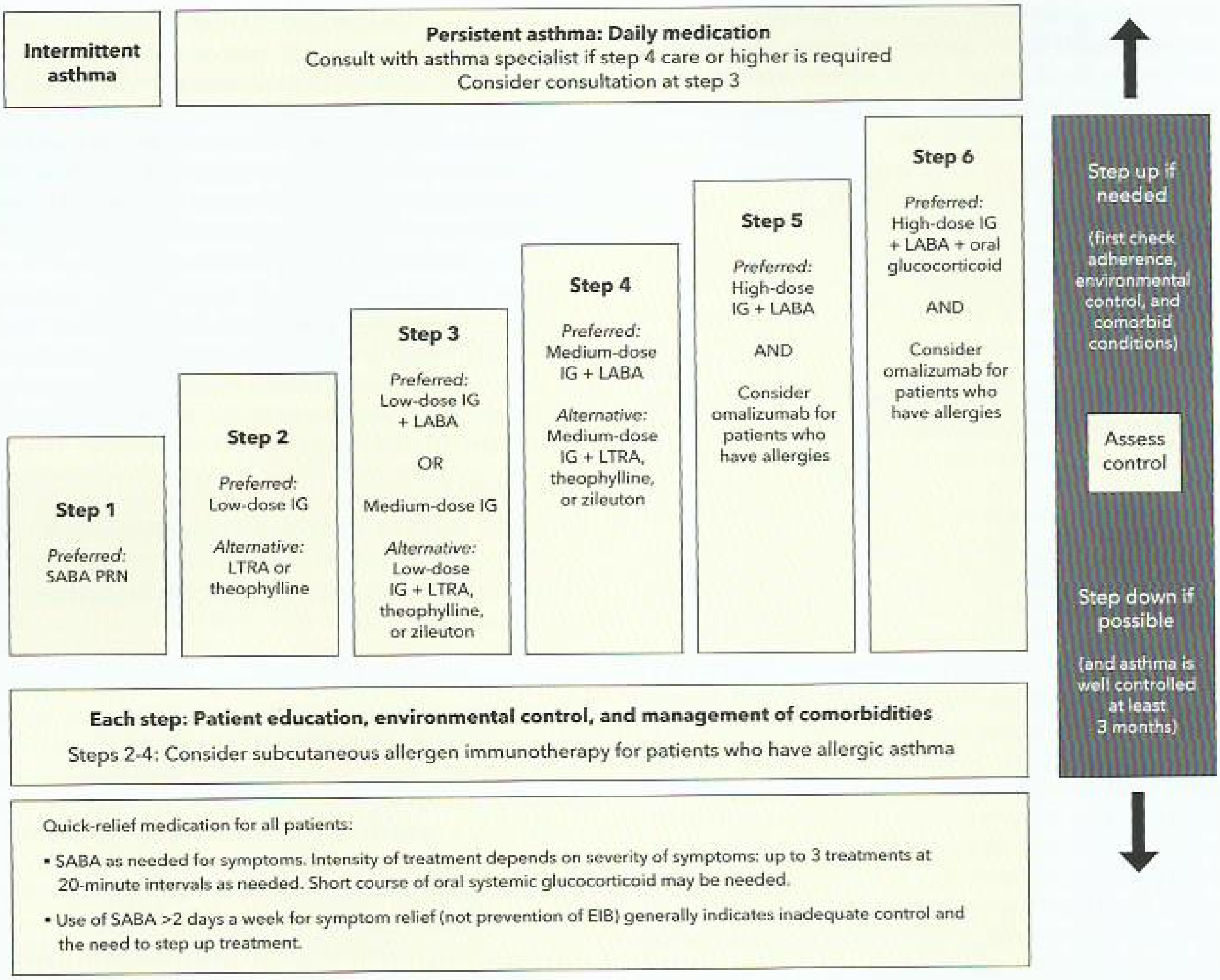

FIGURE 3. Stepwise approach to asthma therapy. EIB = exercise-induced bronchospasm; IG = inhaled glucocorticoid; LABA = long-acting β_2-agonist; LTRA = leukotriene receptor antagonist; PRN = as needed; SABA = short-acting β_2-agonist.

Source: National Heart, Lung, and Blood Institute; National Institutes of Health; U.S. Department of Health and Human Services. National Asthma Education and Prevention Program. Expert Panel Report 3 (EPR-3): Guidelines for the Diagnosis and Management of Asthma. www.nhlbi.nih.gov/files/docs/guidelines/asthsumm.pdf. Published 2007. Accessed May 9, 2018.

Controller Medications

Controller medications are used to provide ongoing symptom relief and to prevent asthma exacerbations. Several different classes of controllers exist that target different mechanisms of the asthmatic profile; therefore, medications can be effectively combined to achieve good control. The choice of therapy generally depends on the assessment of risk as described in **Management of Chronic Asthma**, and adjusted based on symptom response and patient tolerance (see Figure 3 and Table 4).

Inhaled glucocorticoids are the most effective class of asthma controller medications. These agents alleviate several pathologic processes that comprise the asthmatic response, including airway mucosal edema, mucus hypersecretion, and airway inflammation. Many strengths and formulations are available, and because individual patient response can vary, it is reasonable to try an alternate brand if the therapeutic response is not adequate. Side effects are dose-related and vary with the steroid formulation. Side effects relate to local deposition (oral candidiasis, dysphonia) and can sometimes be generalized due to some degree of systemic absorption. Systemic adverse effects such as adrenocortical suppression, reduced bone mineral density, and cataracts do not generally occur at doses below 400 µg of inhaled budesonide daily or equivalent doses of other inhaled glucocorticoid formulations. An increased rate of pneumonia is found with high dose and high potency formulations. Despite these risks, use of inhaled glucocorticoids to prevent the need for oral glucocorticoids should outweigh these potential adverse effects. In active smokers, the effectiveness of these medications is diminished, and higher dosing may be required.

Inhaled long-acting β_2 agonists (LABAs) that provide sustained airway dilation with just once- or twice daily dosing are an important tool for asthma treatment. When added to inhaled glucocorticoids, they provide improved control and

TABLE 4. Asthma Medications

Drug	Formulations	Side Effects
Short-Acting β_2-Agonists		
Albuterol	HFA-MDI, nebulizer solution	Tachycardia and hypokalemia
Levalbuterol	HFA-MDI, nebulizer solution	
Short-Acting Anticholinergics (Muscarinic Antagonists)		
Ipratropium bromide	HFA-MDI, nebulizer solution	Dry mouth, tachycardia, acute narrow angle glaucoma (rare)
Albuterol/ipratropium bromide	HFA-MDI, nebulizer solution	Same and combined effects of both drug classes
Long-Acting β_2-Agonists		
Formoterol	DPI	Tremor, tachycardia; black box warning for use in asthma
Salmeterol	DPI	
Arformoterol	Nebulizer solution	
Formoterol fumarate	Nebulizer solution	
Olodaterol	SMI	
Indacaterol maleate	DPI	
Long-Acting Muscarinic Antagonists (Anticholinergics)		
Tiotropium	DPI, SMI	Dry mouth, tachycardia, urinary retention, acute narrow angle glaucoma (rare)
Aclidinium bromide	DPI	
Umeclidinium	DPI	
Glycopyrrolate	DPI	
Inhaled Glucocorticoids		
Beclomethasone	HFA-MDI	Dysphonia, oral candidiasis, skin bruising, pneumonia, side effects of oral glucocorticoids (rare)
Budesonide	DPI, nebulizer solution	
Fluticasone propionate	HFA, DPI	
Fluticasone furoate	DPI	
Mometasone	DPI	
Ciclesonide	HFA-MDI	
Flunisolide	HFA-MDI	
Inhaled Glucocorticoid and Long-Acting β_2-Agonist		
Budesonide and formoterol	HFA	Same as combined effects of both drug classes
Fluticasone and salmeterol	HFA, DPI	
Mometasone furoate and formoterol fumarate	HFA	
Fluticasone furoate and vilanterol	DPI	
Oral Glucocorticoids		
Prednisone	Tablet, liquid	Bruising, adrenal suppression, osteoporosis, glaucoma, diabetes mellitus, opportunistic infection, insomnia, cataracts, hypertension
Prednisolone	IV infusion, tablet	
Long-Acting Muscarinic Antagonist and Long-Acting β_2-Agonist		
Tiotropium and olodaterol	SMI	Same as combined effects of both drug classes
Umeclidinium and vilanterol	DPI	
Glycopyrrolate and formoterol	MDI	
Indacaterol and glycopyrrolate	DPI	

(Continued on the next page)

TABLE 4. Asthma Medications (*Continued*)

Drug	Formulations	Side Effects
Leukotriene-Receptor Antagonists		
Montelukast	Tablet	Headache, liver disease (rare)
Zafirlukast	Tablet	
Zileuton (5-lipoxygenase inhibitor)	Tablet	
Biologic Agents		
Omalizumab (Anti-IgE)	Subcutaneous injection	Anaphylaxis, increased risk of malignancy
Mepolizumab (Anti-IL5)	Subcutaneous injection	
Reslizumab (Anti-IL5)	IV infusion	
Other		
Theophylline	Tablet, capsule, liquid	Tachycardia, nausea, overdose can be fatal

DPI = dry powder inhaler; HFA = hydrofluoroalkane; IV = intravenous; MDI = metered dose inhaler; SMI = soft mist inhaler.

decrease risk of exacerbation. For patients whose asthma is not adequately controlled by moderate-strength inhaled glucocorticoids, addition of a LABA as combined therapy with inhaled glucocorticoids in a single inhaler device is the recommended next step. Administration in a single inhaler is preferred because of greater adherence and reduced cost compared with administration of each drug in a separate inhaler. Single-agent use of LABAs is not recommended because of the demonstrated increased risk of asthma-related death when used without a simultaneous controller medication, which led the FDA to place a black box warning on all medications containing these agents. However, the FDA recently removed the black box warning from combination inhaled glucocorticoids and LABA inhalers because five large clinical trials have shown that LABAs, when used with inhaled glucocorticoids, do not significantly increase the risk of asthma-related hospitalization, intubation, or death compared to inhaled glucocorticoids alone and result in significantly fewer asthma exacerbations.

Leukotriene-receptor antagonists have a modest bronchodilation effect and treat upper airway conditions such as allergic rhinitis. Patients with aspirin-exacerbated respiratory disease often respond well to these agents.

Oral glucocorticoids are a cornerstone of therapy for treatment of acute asthma exacerbations, but long-term use exposes patients to the well-known side effects of these agents (see Table 4).

Long-acting muscarinic antagonists (LAMAs) provide sustained airway dilation, and when added to therapy in patients not controlled with inhaled glucocorticoid/LABA combination therapy, tiotropium has been shown to improve lung function and reduce exacerbations. For patients with excessive side effects from LABAs, a LAMA can reasonably be substituted. However, there is not substantial evidence that LAMAs should be the first choice for long-acting airway dilation instead of LABAs.

Newer but expensive antibody therapies directed against specific mediators of the asthmatic response can be used in patients with severe asthma not adequately controlled on standard therapy. Currently, two types of biologic therapies are available: those targeting IgE and those targeting eosinophils through the interleukin-5 pathway. Anti-IgE therapy (such as omalizumab) is indicated for use in patients with elevated levels of IgE and sensitivity to allergens, as documented by skin testing or elevated serum allergen-specific IgE. Mepolizumab and reslizumab are anti-interleukin-5 monoclonal antibodies that act to reduce eosinophil levels in airway and sputum by blocking the action of interleukin-5, a cytokine that plays a significant role in eosinophil recruitment and maturation. These agents are effective in patients with eosinophil levels above 150 cells/µL (0.15×10^9/L), regardless of IgE level. Both anti-IgE and anti-interleukin-5 therapies reduce symptoms, need for oral glucocorticoids, and exacerbations in eligible patients with moderate or severe persistent asthma.

Although expensive, omalizumab reduces emergency department visits and may be cost-effective in eligible patients with moderate to severe atopic asthma not well controlled with other therapies.

KEY POINTS

- Inhaled glucocorticoids are the most effective class of asthma controller medications.
- For patients whose asthma is not adequately controlled by moderate-strength inhaled glucocorticoids, addition of a long-acting β_2-agonist as combined therapy with an inhaled glucocorticoid in a single inhaler device is the recommended next step.
- Single-agent use of long-acting β_2-agonists is not recommended because of the demonstrated increased risk of asthma-related death when used without another controller medication.
- Targeting elevated IgE or eosinophil levels with antibody therapies in eligible patients with severe persistent allergic asthma despite standard therapy reduces symptoms, need for oral glucocorticoids, and exacerbations.

Nonpharmacologic Therapy

Comprehensive asthma-care strategies include avoidance of triggers with allergen management (mold abatement, pest control, air filters), reduced exposure to environmental tobacco smoke, and a healthy diet and exercise program to promote weight loss.

Bronchial thermoplasty is a radiofrequency airway treatment administered using bronchoscopy that can reduce exacerbations and improve quality of life. Candidates are patients with an FEV_1 above 60% and severe asthma that is poorly controlled despite high-dose inhaled glucocorticoid/LABA combination therapy.

Management of Asthma Exacerbations

Asthma exacerbation refers to an acute worsening in symptoms or lung function from baseline that necessitates a step-up in therapy (see Figure 3). Prompt recognition and treatment of asthma exacerbations are needed to relieve symptoms and prevent hospitalizations. All asthma patients should have a written asthma management plan that helps them to recognize the symptoms of an exacerbation and begin self-treatment. Clinicians should screen for patient factors that contribute to an increased risk of death from asthma and counsel patients appropriately (**Table 5**). Self-treatment of an exacerbation consists of frequent use of reliever medications; increasing the dose, frequency, or both of controller medications; and adding a short course of oral glucocorticoids (typically 5 to 7 days of prednisone 40-50 mg/day). Patients who do not improve with self-care or who have signs that indicate a severe attack should be evaluated in an acute care facility. Management there should include close monitoring of dyspnea, work of breathing, and vital signs; treatment should include frequent inhaled SABA administration, prompt glucocorticoid therapy, and administration of supplemental oxygen to maintain oxygen saturation above 93%. For further discussion of severe asthma exacerbations, see Common ICU Conditions.

TABLE 5. Severe Asthma Exacerbation Risk Factors and Signs

Risk Factors
History of near-fatal asthma attack or intubation
Emergency department or hospital visit in the last 12 months
Poor asthma medication adherence
Recent treatment with oral glucocorticoid
Psychosocial stressors or psychiatric disease
Signs
Unable to speak in full sentences
Use of accessory muscles of respiration
Respiration rate >30/min, heart rate >120/min
SpO_2 <90% on ambient air
Agitation, confusion, or drowsiness

SpO_2 = oxygen saturation as measured by pulse oximetry.

Data from Prasad Kerlin M. In the clinic. Asthma. Ann Intern Med. 2014;160:ITC3 2-15; quiz ITC3 16-9. [PMID: 24737276] doi:10.7326/0003-4819-160-5-201403040-01003 and Most Recent Asthma Data. Centers for Disease Control and Prevention Web site. www.cdc.gov/asthma/most_recent_data.htm. Updated February 27, 2017. Accessed May 9, 2018.

KEY POINT

- All asthma patients should have a written asthma management plan that helps them recognize the symptoms of an exacerbation and begin self-treatment.

Severe Refractory Asthma

Severe refractory asthma is present in patients who require high doses of inhaled glucocorticoids plus a second controller and/or oral steroids to prevent worsening, or who experience 2 or more exacerbations within one year that require emergency department visits or hospitalization. This group of patients consumes most asthma-related health care resources. It is important to verify the diagnosis in these patients, document medication compliance, and correct inhaler technique before considering additional therapies. Additionally, comorbidities should be aggressively managed, and the possibility of coexisting vocal cord dysfunction should be considered. Treatment guided by specific phenotypes can be helpful in this group, such as biologic agents for patients with high IgE or high eosinophil levels, and leukotriene-receptor antagonists for patients with aspirin sensitivity. Referral to a team of subspecialists is often indicated.

Asthma in Pregnancy

Pregnant patients should be advised that the advantages of treatment are significantly greater than the potential risk to the fetus from asthma therapies or exacerbations. Pregnancy can affect asthma control, leading to either worsening or improvement, and patients should be closely monitored for signs of exacerbation, which occurs most frequently during the second trimester. Inhaled glucocorticoids, oral glucocorticoids, SABAs, leukotriene-receptor antagonists (montelukast, zafirlukast), and LABAs have all been used extensively during pregnancy without data to suggest fetal harm.

Chronic Obstructive Pulmonary Disease

Definition

Chronic obstructive pulmonary disease (COPD) is a chronic lung disease defined by persistent respiratory symptoms and airflow limitation or obstruction that is not fully reversible.

Epidemiology

COPD is a common disorder that currently affects 5% of the U.S. population. The worldwide prevalence continues to rise, and the World Health Organization predicts that by 2020 COPD will become the fifth most prevalent disorder and the third leading cause of death. COPD is associated with a high

morbidity and mortality, and is the third leading cause of death in the United States.

Pathophysiology

COPD is an inflammatory condition. Cigarette smoke and other irritants activate both macrophages and epithelial cells within the respiratory tract. The epithelial cells then release several neutrophil chemotactic factors. Macrophages and neutrophils release proteases that cause destruction of lung parenchyma. Proteases are typically inactivated by antiproteases, such as α_1 antitrypsin, which may also be reduced in COPD. Oxidative stress from irritants and inflammatory cells may lead to additional inflammation and tissue destruction. Ultimately, patients develop fibrosis of the small airways and reduced elastic recoil of the lungs leading to static hyperinflation. As the degree of inflammation increases, airflow obstruction worsens and the ability to fully exhale decreases. Inhalation is initiated before exhalation is completed, resulting in dynamic hyperinflation, termed air trapping, which is seen as increased anteroposterior diameter of the chest and flattening of the diaphragm on chest radiographs. The diaphragmatic flattening limits the ability to increase breath volume during exertion. Compensatory use of accessory muscles, which increases tidal volume, and increased respiration rate augment minute ventilation. These changes increase the work of breathing and contribute to the sensation of dyspnea in patients with COPD.

Risk Factors

Exposure to cigarette smoke (both first- and second hand exposure) is the most important risk factor for COPD. Genetic predisposition seems to explain some of the variation in susceptibility to developing COPD when exposed to cigarette smoke. Long-term exposure to other irritants can also result in COPD. This includes exposure to air pollution (both indoor and outdoor) and occupational chemicals and dusts. An important example of indoor air pollution is the use of biomass fuel for cooking inside the home. Although it is uncommon in the United States, use of biomass fuel indoors is a common risk factor for COPD in the developing world. A family history of COPD is also considered a risk factor for the disease, as is a genetic condition that results in a deficiency of α_1-antitrypsin.

KEY POINT

- Exposure to cigarette smoke is the most important risk factor for COPD.

Heterogeneity of COPD

COPD is a heterogeneous condition. Some patients present predominately with a chronic productive cough due to mucus hypersecretion, whereas others present predominately with progressive dyspnea secondary to hyperinflation. The heterogeneity extends beyond clinical symptoms. Phenotypic heterogeneity has been characterized on the basis of clinical, physiologic, molecular, and radiographic variables. For example, eosinophilia has been associated with increased responsiveness to glucocorticoids. There also appears to be a subgroup of patients who are more prone to developing acute exacerbations. Understanding such variables could potentially improve the accurate assessment of prognosis and individualize patient care. Because of the heterogeneity of the disease and its presentation, tools have been developed to aid in determining prognosis and best treatment strategies. Several staging assessments exist. For example, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) system combines the degree of airflow obstruction obtained from spirometry with the number of previous exacerbations as well as symptoms to help determine treatment. The BODE index uses the variables of body mass index (B), airflow obstruction (O), dyspnea (D), and exercise capacity (E) to predict outcomes and response to therapy. Airflow obstruction is determined using the post-bronchodilator FEV_1 percent of predicted for age, gender, height, and race. The index uses the Modified British Medical Research Council (mMRC) questionnaire to grade perceived dyspnea ranging from dyspnea only with strenuous exercise to dyspnea even when getting dressed. The exercise capacity is determined by the walking distance on a 6-minute walk test. This index provides better prognostic information than the FEV_1 alone and has been used to approximate 4-year survival and risk of hospitalization for COPD.

Comorbid Conditions

Patients with COPD often suffer from comorbid conditions that further increase morbidity and mortality. Some conditions, like cardiovascular disease, share common risk factors, but others seem to be independently associated with COPD or a consequence of treatment of COPD. These include muscle loss with associated weakness and weight loss, osteoporosis, and depression.

KEY POINT

- COPD is a heterogeneous condition, and patients present with variable symptoms including cough, sputum production, and dyspnea.

Diagnosis

H

The possibility of COPD should be considered and spirometry should be performed in patients 40 years of age or older with progressive dyspnea, chronic cough, or chronic sputum production, particularly in the presence of known risk factors for the disease, especially smoking. The role of screening spirometry in asymptomatic individuals with risk factors is controversial. The USPSTF guideline and the joint guideline developed by ACP/ATS/ACCP/ERS recommend against screening for COPD in asymptomatic adults, whereas GOLD advocates performing screening spirometry in individuals with risk factors for COPD. The diagnosis of COPD is made using spirometric measurement to document airflow obstruction. COPD is confirmed by a post-bronchodilator FEV_1/FVC ratio of less than 0.70. This

differs from the finding in asthmatic patients, whose airflow obstruction is fully reversible with bronchodilator therapy.

Some patients have bronchial inflammation with features of both asthma and COPD, referred to as asthma-COPD overlap syndrome. A GOLD and the Global Initiative for Asthma (GINA) consensus statement characterizes asthma-COPD overlap syndrome as persistent airflow limitation with several features usually associated with asthma and several features usually associated with COPD. Measuring lung volumes and diffusing capacity is not required to diagnose COPD but may help in determining the severity of disease. Clinicians should rule out other causes of chronic respiratory symptoms including heart failure, bronchiectasis, obliterative bronchiolitis, tuberculosis, and diffuse panbronchiolitis.

KEY POINTS

HVC
- There is no role for spirometric screening for COPD in asymptomatic individuals.
- COPD is defined as a post-bronchodilator FEV_1/FVC ratio of less than 0.70.

Disease Assessment

After a diagnosis of COPD has been established, the initial assessment focuses on disease severity, which is determined using a combination of symptoms, degree of airflow obstruction on spirometry, history of acute exacerbations, and presence of comorbid conditions. Several validated tools are available to assess patients' symptoms, including the COPD Assessment Test (CAT), the Clinical COPD Questionnaire (CCQ), and the mMRC scale (**Table 6**). The GOLD criteria use the CAT or mMRC scale to determine symptom severity, whereas the BODE index requires the use of the mMRC scale. The CCQ is often used to screen patients for symptoms of COPD. Symptoms are then combined with the results from spirometry (**Table 7**) to determine disease severity (**Table 8**).

Patients who have had two or more acute exacerbations within the last year, who have an FEV_1 of less than 50% of predicted, or who have ever been hospitalized for an acute exacerbation are considered to be at high risk for recurrent acute exacerbations. Clinicians should determine if the patient suffers from any of the common comorbid conditions associated with COPD that indicate a higher morbidity and mortality and treat appropriately.

Pulse oximetry at rest and at exertion should be used to determine the need of supplemental oxygen. Arterial blood gases should be measured to assess for underlying hypercapnia in patients with a low FEV_1, change in mental status, an acute exacerbation, an elevated level of serum bicarbonate, or oxygen saturation of less than 92% on pulse oximetry.

An α_1 antitrypsin level should be obtained in patients with COPD under the age of 45 who have a strong family history of COPD or who are without identifiable COPD risk factors. A pattern of basilar emphysema, associated liver disease

TABLE 6. Modified Medical Research Council Dyspnea Scale

Score	Description of Dyspnea	Severity
0	I get breathless only with strenuous exercise.	None
1	I get short of breath when hurrying on level ground or walking up a slight hill.	Mild
2	On level ground, I walk slower than other people my age because of breathlessness, or I have to stop for breath when walking at my own pace.	Moderate
3	I stop for breath after walking approximately 100 yards or after a few minutes on level ground.	Severe
4	I am too breathless to leave the house or breathless when dressing.	Very severe

Used with the permission of the Medical Research Council.

TABLE 7. Classification of COPD Severity by Spirometry[a]

Category	Severity	Spirometry
GOLD 1	Mild	$FEV_1 \geq 80\%$ of predicted
GOLD 2	Moderate	$50\% \leq FEV_1 < 80\%$ of predicted
GOLD 3	Severe	$30\% \leq FEV_1 < 50\%$ of predicted
GOLD 4	Very severe	$FEV_1 < 30\%$ of predicted

[a]In Patients with FEV_1/FVC less than 70%.

Reprinted from Vogelmeier CF, Criner GJ, Martinez FJ, Anzueto A, Barnes PJ, Bourbeau J, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease 2017 report. GOLD executive summary. Am J Respir Crit Care Med. 2017;195:557-582. [PMID: 28128970] doi:10.1164/rccm.201701-0218PP

TABLE 8. GOLD Model for Classifying Severity of Disease in COPD[a]

Patient Category	Characteristics	Exacerbations Per Year	CAT Score	mMRC Score
A	Low risk, fewer symptoms	≤1	<10	0-1
B	Low risk, more symptoms	≤1	≥10	≥2
C	High risk, fewer symptoms	≥2	<10	0-1
D	High risk, more symptoms	≥2/≥1 with hospital admission	≥10	≥2

CAT = COPD Assessment Test; mMRC = Modified Medical Research Council.

[a]See Table 7 for definitions of spirometric classifications.

Data from Vogelmeier CF, Criner GJ, Martinez FJ, Anzueto A, Barnes PJ, Bourbeau J, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease 2017 report. GOLD executive summary. Am J Respir Crit Care Med. 2017;195:557-582. [PMID: 28128970] doi:10.1164/rccm.201701-0218PP

or panniculitis, or a strong family history of emphysema in patients with COPD should also prompt consideration of α_1-antitrypsin deficiency in middle-aged and older patients. Some guidelines even recommend that all patients with COPD regardless of age be tested for α1-antitrypsin deficiency after weighing the risks and benefits of testing.

KEY POINTS

- After a diagnosis of COPD has been established, the initial assessment focuses on disease severity, which is determined using a combination of symptoms, degree of airflow obstruction on spirometry, history of acute exacerbations, and presence of comorbid conditions.
- Patients who have had two or more acute exacerbations within the last year, who have an FEV_1 of less than 50% of predicted, or who have ever been hospitalized for an acute exacerbation are considered to be at high risk for recurrent acute exacerbations.

Management of COPD

A management plan for COPD should include the identification and reversal of risk factors, especially ongoing exposure to cigarette smoke. The severity of a patient's COPD should guide the choice of therapy (**Table 9**). No currently available treatments can prevent long-term decline in lung function, so patients should be monitored for evidence of disease progression that may guide additional therapy. The goals of therapy are to reduce symptoms, improve exercise tolerance and quality of life, as well as prevent and treat exacerbations, prevent disease progression, and decrease mortality.

Smoking Cessation

H

Smoking cessation is essential in the management of COPD, as it can slow the decline of FEV_1. Providers should encourage patients to quit smoking and be aware that the success rates for smoking cessation increase when counseling is combined with medication therapy. Effective medications for cessation

TABLE 9. Pharmacologic Management of COPD

Patient Group	Recommended Therapy	Alternative Therapy	Other Considerations
A	Short-acting bronchodilator *or* Long-acting bronchodilator	Evaluate effect of therapy and continue, stop, or try alternative bronchodilator as appropriate	All patients in Group A should receive bronchodilator therapy based on its effect on dyspnea; therapy should be continued if symptomatic benefit is documented.
B	Long-acting bronchodilator (LABA or LAMA) *or* Combination therapy with two bronchodilators may be considered for patients with severe dyspnea.	If symptoms persist after one long-acting bronchodilator, try combined therapy with LABA and LAMA	Long-acting inhaled bronchodilators are superior to short-acting bronchodilators taken as needed. There is no evidence to support use of one class of long-acting bronchodilators over another for initial relief of symptoms for patients in Group B. In the individual patient, the choice should depend on the patient's perception of symptom relief. Patients in Group B are likely to have comorbidities that affect symptoms and prognosis, and these should be investigated.
C	LAMA; if further exacerbations, LAMA and LABA	LABA and inhaled glucocorticoids	LABA and LAMA is preferred to LABA and inhaled glucocorticoids because inhaled glucocorticoids increase the risk of developing pneumonia in some patients.
D	LABA and LAMA; if further exacerbations, add inhaled glucocorticoids	If exacerbations continue, consider: roflumilast (patients with an FEV_1 <50% of predicted and chronic bronchitis, particularly if they have experienced at least one hospitalization for an exacerbation in the previous year); *or* macrolide therapy (the best available evidence exists for the use of azithromycin)	Initial therapy with LABA and inhaled glucocorticoids may be appropriate in some patients, including those with a history or findings suggestive of asthma-COPD overlap.

LABA = long-acting β_2-agonist; LAMA = long-acting muscarinic agent.

Data from Vogelmeier CF, Criner GJ, Martinez FJ, Anzueto A, Barnes PJ, Bourbeau J, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease 2017 report. GOLD executive summary. Am J Respir Crit Care Med. 2017;195:557-582. [PMID: 28128970] doi:10.1164/rccm.201701-0218PP

include nicotine replacement, varenicline, and bupropion (see MKSAP 18 General Internal Medicine).

KEY POINT

- Smoking cessation is essential in the management of COPD, as it can slow the decline of FEV_1.

Pharmacologic Therapy

Pharmacologic therapies in COPD are used to reduce symptoms, improve quality of life, and reduce the frequency and severity of exacerbations (**Table 10**). Bronchodilators are mainstays of therapy in COPD irrespective of the severity of the disease. Any time bronchodilators or other inhalers are prescribed, the clinician should ensure that the patient receives education on proper inhaler technique. Initial management is outlined in Table 9.

Bronchodilators

Inhaled bronchodilators include β_2-agonists and anticholinergics/antimuscarinic agents. Both are available as short-acting and long-acting inhalers and improve symptoms and expiratory airflow. Short-acting β_2-agonists and muscarinic antagonists result in similar bronchodilation, and either can be used as monotherapy. However, dual treatment results in a greater degree of bronchodilation and expiratory airflow, which may lead to symptom benefit in select patients.

If short-acting bronchodilators are insufficient to control symptoms in patients with more severe disease, a long-acting bronchodilator, either a LABA or a LAMA, can be added. Choosing the appropriate long-acting bronchodilator inhaler requires consideration of patient and physician preference, potential side effects, and cost. If symptoms persist on monotherapy, addition of a second long-acting bronchodilator from the alternate bronchodilator class may result in clinical improvement. Long-acting bronchodilators alone should not be used in patients with an asthma component to their COPD (asthma-COPD overlap syndrome) unless an inhaled glucocorticoid is also prescribed because of the potential for increased risk of mortality in this patient population when a LABA is used without an inhaled glucocorticoid.

Inhaled Glucocorticoids

Inhaled glucocorticoids are typically used only in combination with a long-acting bronchodilator for treatment of COPD (see Table 9). Inhaled glucocorticoids are not used alone unless a patient is not able to use long-acting bronchodilators (see Table 10). Inhaled glucocorticoids, used alone and in combination with long-acting bronchodilators, improve lung function and reduce symptoms and exacerbations in patients with moderate to severe COPD, but are associated with an increased risk of pneumonia. In patients with severe COPD, triple inhaler therapy with a LABA, a LAMA, and an inhaled glucocorticoid may provide additional symptom benefit.

KEY POINT

- Bronchodilators are mainstays of therapy in COPD irrespective of the severity of the COPD; any time bronchodilators or other inhalers are prescribed, the clinician should ensure that the patient receives education on proper inhaler technique.

Systemic Glucocorticoids

Systemic glucocorticoids are recommended for short-duration treatment of acute exacerbations of COPD. (See Acute Exacerbations: Goals and Therapeutic Management section.) However, long-term use of systemic glucocorticoids should be avoided due to the risk of significant side effects, including diabetes and osteoporosis.

Methylxanthines

The methylxanthines (aminophylline and theophylline) are now rarely used to treat COPD. Theophylline has been shown to improve functional capacity and reduce the number of exacerbations. However, it has a narrow window between therapeutic and toxic dosages and is therefore only used for patients with advanced COPD who have refractory symptoms not controlled by standard therapy. Studies of the use of either aminophylline or theophylline during acute exacerbations have shown no benefit.

Roflumilast

Roflumilast is a selective phosphodiesterase-4 inhibitor that is used to reduce chronic symptoms and the frequency of exacerbations in patients with severe COPD who have either primarily symptoms of chronic bronchitis or frequent exacerbations.

α_1-Antitrypsin Augmentation Therapy

Antiproteases, including α_1-antitrypsin, typically inactivate proteases that may lead to permanent lung injury. In patients with α_1-antitrypsin deficiency, replacing this enzyme with augmentation therapy may slow the progression of related emphysema. However, it is costly, has not been shown to decrease exacerbations or the rate of FEV_1 decline, and is not effective for treatment of patients whose COPD is not caused by α_1-antitrypsin deficiency.

Other Agents

Macrolide antibiotics have inflammatory and antimicrobial effects. Long-term macrolide therapy may reduce the frequency of exacerbations when prescribed to patients with severe COPD and a history of frequent exacerbations. Mucolytics and antitussives are not routinely used in the management of COPD but may provide some symptomatic relief in patients with significant sputum production.

Immunization

Immunizations can prevent infections in patients with COPD. Because infections are the most common trigger of

TABLE 10. Drug Treatment for COPD

Agent	Side Effects	Notes
Bronchodilators		
Inhaled short-acting β_2-agonists (albuterol, fenoterol, levalbuterol, metaproterenol, pirbuterol, terbutaline)	Tachycardia and hypokalemia (usually dose dependent), but generally well tolerated by most patients	Generally used as needed for mild disease with few symptoms
Inhaled short-acting anticholinergic agents (ipratropium)	Dry mouth, mydriasis on contact with eye, tachycardia, tremors, rarely acute narrow angle glaucoma; this drug class has been shown to be safe in a wide range of doses and clinical settings	Generally used as needed for mild disease with few symptoms; avoid using both short- and long-acting anticholinergics
Inhaled long-acting anticholinergic agents (tiotropium, aclidinium, umeclidinium, glycopyrronium)	Dry mouth, mydriasis on contact with eye, tachycardia, tremors, rarely acute narrow angle glaucoma	Not to be used with ipratropium; use when short-acting bronchodilators provide insufficient control of symptoms for patients with an FEV_1 <60% of predicted
Inhaled long-acting β_2-agonists (salmeterol, formoterol, arformoterol, indacaterol, olodaterol)	Sympathomimetic symptoms such as tremor and tachycardia; overdose can be fatal	Use as maintenance therapy when short-acting bronchodilators provide insufficient control of symptoms for patients with an FEV_1 <60% of predicted; not intended to be used for treatment of exacerbations of COPD or acute bronchospasm
Methylxanthines (theophylline, aminophylline; sustained and short-acting)	Tachycardia, nausea, vomiting, and disturbed sleep; narrow therapeutic index; overdose can be fatal with seizures and arrhythmias	Used as maintenance therapy; generally use only after long-acting bronchodilator treatment to provide additional symptomatic relief of exacerbations; may also improve respiratory muscle function
Oral β_2-agonists (albuterol, metaproterenol, terbutaline)	Sympathomimetic symptoms such as tremor and tachycardia	Used as maintenance therapy; rarely used because of side effects but may be beneficial for patients who cannot use inhalers
Oral Phosophodiesterase-4 Inhibitor		
Roflumilast	Diarrhea, nausea, backache, decreased appetite, dizziness	Used to reduce risk for exacerbations in patients with severe COPD (blood levels not required) with chronic bronchitis and history of exacerbations; roflumilast should not be used with methylxanthines owing to potential toxicity; very expensive and should be used only in select patients
Anti-Inflammatory Agents		
Inhaled glucocorticoids (fluticasone, budesonide, mometasone, ciclesonide, beclomethasone)	Dysphonia, skin bruising, oral candidiasis, rarely side effects of oral glucocorticoids (see below)	Most effective in patients with a history of frequent exacerbations and when used in conjunction with long-acting bronchodilators
Oral glucocorticoids (prednisone, prednisolone)	Skin bruising, adrenal suppression, glaucoma, osteoporosis, diabetes mellitus, systemic hypertension, pneumonia, cataracts, opportunistic infection, insomnia, mood disturbance	Use for significant exacerbations of COPD; avoid, if possible, in stable COPD to limit glucocorticoid toxicity; consider inhaled glucocorticoids to facilitate weaning of systemic glucocorticoids
Combination Agents		
Combined inhaled long-acting β_2-agonist and inhaled glucocorticoid in a single inhaler (fluticasone/salmeterol, budesonide/formoterol)	Same/combined effects of both drug classes	Fluticasone/salmeterol is approved by the FDA as maintenance therapy and for prevention of exacerbations; budesonide/formoterol metered-dose inhaler is approved by the FDA as maintenance therapy; combinations are not to be used for treatment of acute bronchospasm
Combined short-acting β_2-agonist plus short-acting anticholinergic in a single inhaler (fenoterol/ipratropium, salbutamol/ipratropium)	Same/combined effects of both drug classes	Generally used as needed for mild disease with few symptoms; avoid using both short- and long-acting anticholinergics; this combination therapy may be used for maintenance therapy only if patients have well-controlled disease on this combination treatment and do not require rescue therapy if/when expense is a determining factor
Combined inhaled glucocorticoid and ultra-long-acting β_2-agonist in a single inhaler (fluticasone/vilanterol)	Same/combined effects of both drug classes	Not to be used for treatment of acute bronchospasm
Combined long-acting anticholinergic plus ultra-long-acting β_2-agonist in a single inhaler (umeclidinium/vilanterol)	Same/combined effects of both drug classes	Not to be used for treatment of acute bronchospasm. Avoid using both short- and long-acting anticholinergics.

acute exacerbations, routine immunizations are recommended for all patients with COPD. Patients should receive annual influenza immunization and the pneumococcal polysaccharide vaccine (PPSV23). Those above the age of 65 should also receive the pneumococcal conjugate vaccine (PCV13).

KEY POINTS

- Systemic glucocorticoids are recommended for short-duration treatment of acute exacerbations of COPD; long-term use of systemic glucocorticoids should be avoided.
- All COPD patients should have annual influenza immunization and the pneumococcal polysaccharide vaccine; those above the age of 65 should also receive the pneumococcal conjugate vaccine.

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Nonpharmacologic Therapy

Pulmonary Rehabilitation

Pulmonary rehabilitation is a comprehensive program that combines exercise training, nutritional support, education, and social support for patients with chronic lung conditions. It has been shown to relieve symptoms, improve quality of life, and decrease frequency of hospitalizations in patients with COPD. Clinicians should consider adding this to appropriate medical therapy in symptomatic patients with an FEV_1 of less than 50% of predicted and to patients recovering from COPD exacerbation; particularly those recently hospitalized or treated with systemic steroids would benefit from pulmonary rehabilitation.

Oxygen Therapy

The use of supplemental oxygen has been shown to improve quality of life and decrease mortality in patients with COPD and resting hypoxemia with an arterial Po_2 of 55 mm Hg or less, or oxygen saturation as measured by pulse oximetry of 88% or less. Patients with cor pulmonale, heart failure, or erythrocytosis should be offered the use of supplemental oxygen if the Po_2 is 59 mm Hg or less or the oxygen saturation is 89% or less. Some patients may not qualify for oxygen at rest but may desaturate during sleep, exertion, or air travel. Supplemental oxygen is typically prescribed if the oxygen saturation as measured by pulse oximetry falls below 89% in these situations, but the benefits are less defined.

Noninvasive Mechanical Ventilation

Noninvasive mechanical ventilation (NIV), also termed noninvasive positive pressure ventilation (NIPPV), can be used for acute and chronic respiratory failure. For patients with a COPD exacerbation and acute hypercapnic respiratory failure with acidosis, NIV improves symptoms and reduces intubation rates, length of hospital stay, and mortality. It may also be beneficial in COPD patients with pneumonia, to help with discontinuing mechanical ventilation, and for palliative care. It does not replace intubation and mechanical ventilation in critically ill patients, comatose patients, or patients who have sustained a cardiac arrest. NIV is generally well tolerated, and improvement of the pH and Pco_2 within 1 to 2 hours predicts success. The benefit of using NIV in the treatment of chronic respiratory failure or in the outpatient setting is less clear. It may, especially if used at night, provide additional symptomatic relief when added to medical therapy in patients with severe COPD. H

Prognosis and Goals of Care

The current GOLD initiative recommends combining the degree of airflow limitation using the post-bronchodilator FEV_1 with the number of exacerbations and the patient's symptoms to classify the severity of disease. This will allow the clinician to guide escalation or de-escalation of medical therapies as appropriate.

The BODE index can be used as a prognostic indicator for patients with COPD. Using the BMI, the post-bronchodilator FEV_1 percent of predicted, dyspnea as defined using the mMRC scale (see Table 6), and the distance walked on a 6-minute walk test, it is possible to approximate the patient's 4-year survival. In patients with severe disease with an overall poor prognosis, referral for hospice and palliative care can provide significant improvements in symptom burden.

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Palliative care can significantly aid in symptom management in patients with COPD at any stage of disease. Patients experience not only dyspnea, but also anxiety and depression, which may also be addressed. Opioids are commonly used to treat dyspnea that persists despite medical therapy. Current guidelines suggest a patient with severe COPD—defined by disabling symptoms despite medical therapy, progression of disease as evidenced by increasing emergency department evaluations or hospitalizations, and hypoxemia or hypercapnia—should be considered for hospice care. H

KEY POINT

- Current guidelines suggest a patient with severe COPD (defined by disabling symptoms despite medical therapy, progression of disease as evidenced by increasing emergency department evaluations or hospitalizations, and hypoxemia or hypercapnia), should be considered for hospice care.

Lung Volume Reduction Therapy

The National Emphysema Treatment Trial (NETT) demonstrated that patients with upper lobe–predominant and significant exercise limitations even after participation in a pulmonary rehabilitation program had improved quality of life, exercise tolerance, pulmonary function, and survival with lung volume reduction surgery. A key finding from NETT was that patient selection was critical to success and that patients with an FEV_1 of less than 20% of predicted, a diffusing capacity of less than 20% of predicted, or non–upper lobe predominant disease had a high operative mortality and should not be offered lung volume reduction surgery. The procedure should be considered in patients with upper lobe–predominant who have low exercise tolerance despite

maximal medical therapy and completion of a pulmonary rehabilitation program. Nonsurgical lung volume reduction procedures, including bronchoscopic placement of endobronchial one way valves, plugs, or coils; administration of biologic sealants; and thermal ablation of the airway are being studied for treatment of emphysematous changes in patients with COPD. Early results suggest patients with severe air trapping and hyperinflation may get the most benefit from these new techniques.

Lung Transplantation

Referral for lung transplantation can be considered in patients with severe COPD. The decision to refer should depend on the patient's life expectancy, quality of life, and patient preferences. In general, patients at high risk of dying in less than 2 years who have a high probability of 90 day postoperative survival are candidates. Patients with an elevated BODE index (5 or 6), resting hypoxemia, hypercapnia, an FEV_1 of less than 25% of predicted, or significant exercise limitation despite medical therapy, smoking cessation, and participation in a pulmonary rehabilitation program may be referred for evaluation for lung transplantation. Transplantation improves quality of life, and the median life expectancy is 5.7 years.

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Acute Exacerbations

Definition

An acute exacerbation of COPD is a change in a patient's typical symptoms that leads to a change in medical therapy or requires hospitalization. Most commonly, exacerbations are manifested by an increase in the severity or frequency of cough, worsening dyspnea, and an increase in the amount or change in the character of sputum produced. Most exacerbations are triggered by a respiratory infection (either viral or bacterial), smoking, and environmental exposures. An exacerbation can be triggered by other causes, but in some cases no trigger is ever identified. Studies suggest that exacerbations are underreported by patients and result in adverse outcomes. H

KEY POINT

- An acute exacerbation of COPD is a change in a patient's typical symptoms that leads to a change in medical therapy or hospitalization; the most common exacerbations are manifested by an increase in the severity or frequency of cough, worsening dyspnea, and an increase in the amount or change in the character of sputum produced.

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Prevention

Acute exacerbations of COPD can have substantial effects on quality of life and health care costs, and may accelerate the decline in lung function and increase mortality. It is therefore important to prevent exacerbations whenever possible. Strategies to prevent exacerbations include smoking cessation, participating in pulmonary rehabilitation programs when appropriate, receiving recommended immunizations, and ensuring proper inhaler technique and use of medications. Long term use of azithromycin or roflumilast has also been shown to prevent future exacerbations in patients who have a history of frequent exacerbations. H

KEY POINT

- Strategies to prevent COPD exacerbations include smoking cessation, participating in pulmonary rehabilitation programs when appropriate, receiving recommended immunizations, and ensuring proper inhaler technique and use of medications.

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Initial Assessment and Setting of Care

The first steps in managing a patient with a presumed COPD exacerbation are to confirm the diagnosis and determine the severity of the exacerbation for accurate triaging. A mild exacerbation is one that can be managed solely by increasing the dose of the regular medications the patient is already on. A moderate exacerbation requires treatment with antibiotics, steroids, or both; a severe exacerbation is defined by the need for an evaluation in the emergency department or hospitalization. Patients with respiratory distress or who are at risk of developing respiratory distress should be hospitalized; additional testing, including a chest radiograph, electrocardiogram, complete blood count, and basic metabolic panel, should be obtained to rule out other causes or comorbidities contributing to the acute presentation. Oxygen saturation should be measured by pulse oximetry. Arterial blood gas measurement is recommended for patients with a severe exacerbation to determine the presence of hypercapnia or hypoxemia. A sputum culture is not routinely used to assess COPD exacerbations as it rarely affects management. Patients with mild symptoms may not require any additional testing. H

KEY POINTS

- Patients who have COPD and respiratory distress or who are at risk of developing respiratory distress should be hospitalized and evaluated with a chest radiograph, electrocardiogram, complete blood count, basic metabolic panel, and oxygen saturation; arterial blood gas measurements can determine the presence of hypercapnia or hypoxemia.
- A sputum culture is not routinely used to assess COPD exacerbations as it rarely affects management. HVC

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Goals and Therapeutic Management

The management goals during an acute exacerbation are to relieve acute symptoms and to prevent future exacerbations. Supplemental oxygen should be used to maintain oxygen saturation between 89% and 92%. Noninvasive mechanical ventilation may be required if oxygenation or ventilation

cannot be maintained. Patients may require mechanical intubation if they cannot tolerate noninvasive mechanical ventilation, have an altered mental status, or have worsening hypercapnic or hypoxemic respiratory failure despite the use of noninvasive mechanical ventilation. Short acting β_2 agonists with or without anticholinergic agents should be used to relieve acute symptoms. The use of oral glucocorticoids during acute exacerbations has been shown to decrease the frequency of treatment failures, length of stay, and the time to subsequent exacerbations while improving FEV_1 and hypoxemia. Glucocorticoids have also been shown to decrease the need for hospitalization if used early. Recent randomized trials have demonstrated that short courses of lower-dose oral glucocorticoids, 40 mg for 5 days, are usually equivalent to longer courses, higher doses, and intravenous administration.

Antibiotics should be prescribed in cases of moderate or severe exacerbations or for patients with mild exacerbations who have noted an increase or change in sputum production. The most common infectious triggers are viruses, but bacterial causes include *Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis,* and *Mycoplasma pneumoniae.* If the patient is still smoking, treatment should also focus on smoking cessation because this can prevent future exacerbations. Because the prevalence of pulmonary embolism is higher in patients with COPD, a thromboembolic event should be considered as a potential trigger if patients do not improve with typical therapies for a COPD exacerbation, and appropriate testing should be performed.

Bronchiectasis

Definition

Bronchiectasis is a chronic suppurative lung disease associated with irreversible enlargement of the airways due to destruction of airway architecture. An injury to the lung typically results in prolonged airway inflammation, which leads to localized injury with subsequent mucus stasis, which can lead to further airway obstruction, chronic infection, and inflammation with worsening bronchiectasis.

Causes

In many cases of bronchiectasis, an underlying cause is not identified. The most common causes of bronchiectasis include cystic fibrosis, aspiration, immunodeficiencies, and connective tissue diseases (**Table 11**).

TABLE 11. Common Causes of Bronchiectasis
Airway obstruction
Tumor
Foreign body
Aspiration
COPD
Congenital
Mounier-Kuhn syndrome
Young syndrome
Connective tissue diseases
Rheumatoid arthritis
Sjögren's syndrome
Cystic fibrosis
Hypersensitivity
Allergic bronchopulmonary aspergillosis
Immunodeficiency
Common variable immunodeficiency
HIV
Mucociliary dysfunction
Primary ciliary dyskinesia
Postinfection
Tuberculosis
Pneumonia, especially recurrent

Presentation

Bronchiectasis should be considered in the differential diagnosis of any patient with a chronic cough, especially if the patient has a history of frequent respiratory infections or if the cough is productive. Other possible symptoms include hemoptysis, wheezing, and chest pain. Features that should alert the clinician to consider bronchiectasis include previous sputum cultures growing uncommon pathogens such as *Pseudomonas aeruginosa, Aspergillus,* or nontuberculous mycobacteria; clubbing; and minimal or no smoking history.

Patients with bronchiectasis may also present with extrapulmonary symptoms, especially fatigue.

Diagnosis

Initial evaluation should include a comprehensive medical history, including childhood diseases, family history, and careful evaluation to exclude known causes of bronchiectasis. Bronchiectasis is diagnosed by high resolution chest CT. Diagnostic criteria include airway diameter that is greater than that of its accompanying vessel and lack of distal airway tapering (**Figure 4**). Bronchial wall thickening or cysts are often present. For every diagnosed patient, it should be determined whether there is an underlying cause that can be treated. This may involve testing for chronic bacterial or mycobacterial infections. These tests can identify causes of disease progression and help determine targeted antimicrobial therapy for exacerbations. Patients should also be evaluated for the presence of connective tissue disease and immune function. In selected patients, testing for cystic fibrosis, ciliary dysfunction, or α_1 antitrypsin deficiency may be appropriate if suspected. However, even with rigorous evaluation, more than half of all cases are still considered idiopathic.

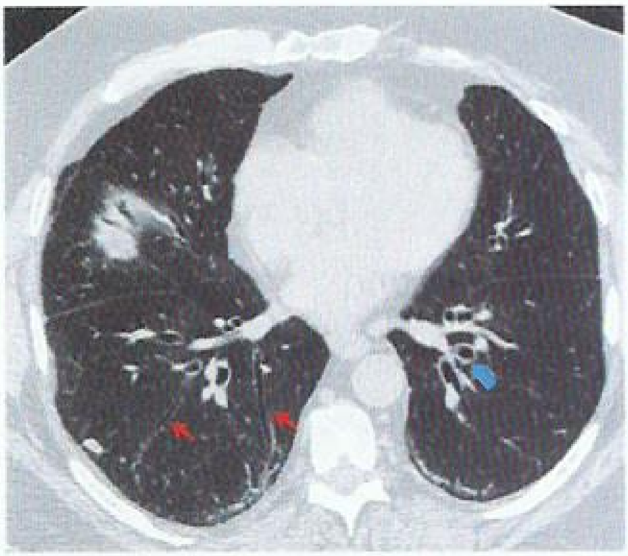

FIGURE 4. Bronchiectasis on chest CT. The airway is larger than its accompanying blood vessel (*thick arrow*), and the airway fails to taper distally (*thin arrows*).

KEY POINTS

- Bronchiectasis is diagnosed by high-resolution chest CT; diagnostic criteria include airway diameter greater than that of its accompanying vessel, and lack of distal airway tapering.
- For every patient diagnosed with bronchiectasis, it should be determined whether there is an underlying cause that can be treated.

Treatment

The presence of chronic symptoms of cough and sputum production typically indicates irreversible airway dilation. Therefore, treatment of the underlying cause may not lead to improvement in current symptoms but could prevent further progression. Otherwise, treatment of bronchiectasis focuses on airway clearance, treating infections, and preventing exacerbations. The goal of airway clearance is to improve mucous clearance and thereby prevent chronic or recurrent infections. Bronchodilators, inhaled glucocorticoids, and combination inhalers have been shown to decrease symptoms but have no effect on the decline of lung function or frequency of exacerbations. Studies suggest that long-term use of macrolide antibiotics may prevent future exacerbations due to their anti-inflammatory effects. When deciding whether to use macrolide antibiotics, the risk of future exacerbations should be weighed against the possibility of developing macrolide resistance. Antibiotics may also be used in the management of chronic non–cystic fibrosis bronchiectasis to eradicate organisms such as *Pseudomonas aeruginosa* or methicillin-resistant *Staphylococcus aureus*. If eradication of bacterial colonization is not successful, there may be some symptomatic benefit from suppressive therapy with inhaled antibiotics. Patients should also be encouraged to exercise, which can improve airway clearance and symptoms. Surgical resection should be considered in patients who have localized disease with persistent symptoms despite therapy.

KEY POINTS

- Identification and treatment of underlying causes of bronchiectasis should be initiated if possible.
- Treatment of bronchiectasis focuses on airway clearance, treating infections, and preventing exacerbations.

Treatment of Exacerbations

Exacerbations of bronchiectasis may be difficult to differentiate from baseline symptoms. However, changes in sputum volume, viscosity, or purulence; increased cough; wheezing; shortness of breath; hemoptysis; or declines in lung function are considered evidence of an exacerbation. Therapy for an exacerbation is ideally guided by routine sputum and acid-fast bacilli culture results to identify a possible predominant organism for treatment. Empiric antibiotic therapy is recommended and may be based on previous culture data until the results of the current sputum culture become available. If previous data are not available, a fluoroquinolone can be started to ensure *Pseudomonas* coverage until sputum culture results are available.

Cystic Fibrosis

Cystic fibrosis (CF) is an autosomal recessive disease affecting the CF transmembrane conductance regulator (*CFTR*) gene. It is diagnosed in approximately 1 of 2000-3000 live births with a predilection for disease in those of European descent. The most common genetic variant resulting in disease is ΔF508, but there are at least 1500 other genetic mutations. The pathogenesis for clinical manifestations of CF remains incompletely understood; however, the abnormal homozygous *CFTR* genotype results in abnormally thick secretions that are difficult to clear. There is an increased concentration of chloride in sweat gland secretions, and sweat chloride testing is a primary diagnostic tool for CF. The changes in respiratory secretions lead to bacterial colonization of airways and chronic bacterial infection, resulting in chronic inflammation and, ultimately, bronchiectasis. Further tissue destruction results from insufficient lung antiproteases to counteract the effect of elastase released from neutrophils. This ongoing inflammatory process also results in large amounts of free DNA and matrix protein deposition within areas of tissue destruction, which further drives increased viscosity of lung secretions.

Thickened secretions in the gastrointestinal tract impair flow of bile and pancreatic secretions, leading to pancreatic exocrine and endocrine deficiency, liver disease, and the development of malabsorption and maldigestion. The secretions increase the risk for bowel obstruction (distal ileal obstructive syndrome, intussusception, and rectal prolapse). Consequently, individuals with CF often present with malnutrition and weight loss.

Diagnosis

Few patients with CF are diagnosed as adults. Adults diagnosed with CF most often present with pulmonary or gastrointestinal symptoms. Pulmonary manifestations often include chronic productive cough, recurrent sinusitis, and recurrent pulmonary infections requiring several courses of antibiotics. For those with gastrointestinal symptoms, loose and frequent stools with abdominal pain are the most common. Pancreatic insufficiency (either endocrine or exocrine) may occur but is less common. Chronic, persistent pulmonary or gastrointestinal symptoms requiring repetitive treatment should raise suspicion for CF. Radiographic findings of upper lobe-predominant with mucoid impaction may be present.

Often the greatest challenge to making the diagnosis is failing to include CF in the differential diagnosis. A family history of CF can be quite helpful in this regard. Sweat chloride testing is the initial test for CF, although it is less sensitive in adults. Abnormal results on repeat testing are diagnostic of CF. DNA testing confirms the diagnosis and helps with prognosis. A negative sweat chloride test in an adult patient does not rule out disease. Therefore, if the clinical suspicion remains high after negative repeat sweat chloride testing, consideration for referral to a center with expertise in CF or genetic testing is appropriate.

KEY POINTS

- Adults diagnosed with cystic fibrosis most often present with pulmonary or gastrointestinal symptoms; pulmonary manifestations often include chronic productive cough, recurrent sinusitis, and recurrent pulmonary infections requiring several courses of antibiotics.
- A negative sweat chloride test in a patient who presents as an adult should not rule out cystic fibrosis.

Treatment

The pillars of CF management are airway clearance, antibiotic therapy, nutritional support, and psychosocial support. The primary objectives of CF treatment are maintaining lung health and controlling/minimizing the impact of CF-affected organ disease. The Cystic Fibrosis Foundation practice guidelines recommend use of chronic medications to improve lung function and reduce exacerbations. These medications include mucolytics, hydrating agents, inhaled antibiotics, oral macrolide antibiotics, and *CFTR* potentiators. The treatment of CF lung disease is experiencing a period of rapid evolution, and management is suboptimal unless it involves a multidisciplinary approach best provided at a CF care center.

Diffuse Parenchymal Lung Disease

Diffuse parenchymal lung diseases (DPLDs) are a group of disorders based on similar clinical, radiographic, physiologic, and pathologic changes that affect the alveolar walls and often the related small airways and distal pulmonary vasculature. Like other lung diseases, these disorders present primarily with shortness of breath. Imaging studies will typically demonstrate bilateral rather than unilateral lung disease. Although COPD and pulmonary hypertension affect the distal airways and vasculature, these are excluded from the category of DPLD.

Classification and Epidemiology

Although there are hundreds of disorders that can present with diffuse parenchymal lung disease, they are typically divided into those with a known cause or those which are idiopathic (**Table 12**). The updated classification of idiopathic interstitial pneumonia will be discussed below. A thorough history that defines the time course is a critical first step in making the diagnosis.

DPLD is uncommon, compared to other pulmonary diseases such as asthma or COPD. The true prevalence of DPLDs is unknown; however, the literature estimates the prevalence at approximately 70 per 100,000 persons, with idiopathic cause accounting for 30% to 40% of disease in these patients.

Diagnostic Approach and Evaluation

Nonproductive cough and dyspnea are the most common presenting symptoms of a DPLD. Dyspnea that comes on suddenly and is of short duration is more likely due to respiratory infection, asthma, pulmonary embolism, or heart failure than DPLD. In contrast, patients presenting with subacute or chronic dyspnea lasting weeks to months without response to treatment should be evaluated for DPLD. As opposed to the typical nonproductive cough of DPLD, a long history of cough with sputum production can suggest an underlying chronic infection, airways inflammation such as chronic bronchitis, or bronchiectasis.

When DPLD is suspected, questions should focus on determining the onset of symptoms, the disease course (improving or worsening), medications, and exposures. The most common identifiable etiologies of DPLDs are those associated with exposures, and the history should include a thorough review of occupations, home environment, hobbies, and other activities. Medication review should include current medications as well as those taken before the onset of symptoms.

Connective tissue diseases can lead to the development of DPLD; therefore, the review of systems should assess for symptoms of arthralgia, myalgia, arthritis, tenosynovitis, dry eyes, dry mouth, dysphagia, gastroesophageal reflux, and unexplained rash. A family history of DPLD due to connective tissue disease should substantially increase clinical suspicion.

Physical examination findings differ depending on the underlying cause of DPLD. In patients with connective tissue disorders, findings may include Raynaud phenomenon, skin

TABLE 12. Classification and Distinguishing Features of Select Forms of Diffuse Parenchymal Lung Disease	
Known Causes	
Drug-induced	Examples: amiodarone, methotrexate, nitrofurantoin, chemotherapeutic agents (see www.pneumotox.com for a complete listing).
Smoking-related	"Smokers'" respiratory bronchiolitis characterized by gradual onset of persistent cough and dyspnea. Radiograph shows ground-glass opacities and thickened interstitium. Smoking cessation improves prognosis. Desquamative interstitial pneumonitis and pulmonary Langerhans cell histiocytosis are other histopathologic patterns associated with smoking and DPLD.
Radiation	May occur 6 weeks to months following radiation therapy.
Chronic aspiration	Aspiration is often subclinical and may exacerbate other forms of DPLD.
Pneumoconioses	Asbestosis, silicosis, berylliosis.
Connective tissue diseases	
Rheumatoid arthritis	May affect the pleura (pleuritis and pleural effusion), parenchyma, airways (bronchitis, bronchiectasis), and vasculature. The parenchymal disease can range from nodules to organizing pneumonia to usual interstitial pneumonia.
Systemic sclerosis	Nonspecific interstitial pneumonia pathology is most common; may be exacerbated by aspiration due to esophageal involvement; antibody to Scl-70 or pulmonary hypertension portends a poor prognosis. Monitoring of diffusing capacity for early detection is warranted.
Polymyositis/dermatomyositis	Many different types of histology; poor prognosis.
Other connective tissue diseases	Varying degrees of lung involvement and pathology can be seen in other forms of connective tissue disease.
Hypersensitivity pneumonitis	Immune reaction to an inhaled antigen; may be acute, subacute, or chronic. Noncaseating granulomas are seen.
Unknown Causes	
Idiopathic interstitial pneumonias	
Idiopathic pulmonary fibrosis	Chronic, insidious onset of cough and dyspnea, usually in a patient aged >50 years. Usual interstitial pneumonia pathology (honeycombing, bibasilar infiltrates with fibrosis). Diagnosis of exclusion.
Acute interstitial pneumonia	Dense bilateral acute lung injury similar to acute respiratory distress syndrome; 50% mortality rate.
Cryptogenic organizing pneumonia	May be preceded by flu-like illness. Radiograph shows focal areas of consolidation that may mimic infectious pneumonia or may migrate from one location to another.
Sarcoidosis	Variable clinical presentation, ranging from asymptomatic to multiorgan involvement. Stage 1: hilar lymphadenopathy. Stage 2: hilar lymphadenopathy plus interstitial lung disease. Stage 3: interstitial lung disease. Stage 4: fibrosis. Noncaseating granulomas are hallmark.
Rare DPLD with Well-Defined Features	
Lymphangioleiomyomatosis	Affects women in their 30s and 40s. Associated with spontaneous pneumothorax and chylous effusions. Chest CT shows cystic disease.
Chronic eosinophilic pneumonia	Chest radiograph shows "radiographic negative" heart failure, with peripheral alveolar infiltrates predominating. Other findings may include peripheral blood eosinophilia and eosinophilia on bronchoalveolar lavage.
Pulmonary alveolar proteinosis	Median age of 39 years, and males predominate among smokers but not in nonsmokers. Diagnosed using bronchoalveolar lavage, which shows proteinaceous material in and around alveolar macrophages. Chest CT shows "crazy paving" pattern.

DPLD = diffuse parenchymal lung disease.

thickening, sclerodactyly, malar rash, inflammatory arthritis, or tenosynovitis. Lung examination findings are variable and may be normal. This is more likely early in disease or in those with imaging findings of ground-glass opacity or micronodules. Decreased breath sounds and dullness to percussion may suggest a pleural effusion, which is atypical for many DPLDs. Wheezes may suggest small airways disease, while inspiratory dry "Velcro" crackles are more suggestive of fibrosis. In more severe disease there may be right heart strain on electrocardiography or evidence of right-sided heart failure with findings of jugular venous distention, peripheral edema, a pronounced pulmonic second sound, and an S_3. These findings are also suggestive of more long-standing disease.

The physical examination should include resting and exertional pulse oximetry. It is common for patients with DPLD to have normal resting pulse oximetry. However, because of reductions in the functional pulmonary capillary bed, individuals with DPLD will often demonstrate desaturation when ambulating. The desaturation may not require supplemental oxygen; however, desaturation of greater than 4% while ambulating is consistent with a diffusion limitation, which is a hallmark of interstitial lung disease.

Patients with a clinical suspicion of DPLD should undergo full pulmonary function testing, including lung volumes and DLCO. The vast majority of DPLDs have restrictive physiology. However, there are a few diseases that have obstruction or exhibit a combined obstructive and restrictive deficit. Simple spirometry has a limited role because it can only identify obstruction and may be normal in the setting of restriction or reduced DLCO.

Plain chest radiography is an appropriate initial test for the evaluation of dyspnea and cough in patients suspected of having DPLD. Chest radiography may show various findings in patients with DPLD, including diffuse reticular and reticulonodular patterns, increased septal line thickening, consolidation, pleural effusions with or without pleural calcification, bronchiectasis, and hilar or mediastinal lymphadenopathy. The chest radiograph can be normal in patients with minimal disease, and a normal chest radiograph does not rule out DPLD.

KEY POINTS

- Patients presenting with subacute or chronic symptoms of dyspnea lasting weeks to months without response to treatments should be evaluated for diffuse parenchymal lung disease.
- Patients with a clinical suspicion of diffuse parenchymal lung disease should undergo full pulmonary function testing, including lung volumes and DLCO.
- A normal chest radiograph does not rule out diffuse parenchymal lung disease.

High-Resolution CT Scanning

High-resolution CT (HRCT) scan of the chest (slice thickness 1-2 mm) is the best imaging study to identify abnormalities that can help diagnose the underlying disease (**Table 13**). When disease of the small airways is suspected, HRCT imaging should be obtained both on inspiration and on expiration to accentuate air trapping. Prone images may be helpful if there is subtle septal thickening posteriorly that can be difficult to

TABLE 13. Patterns of Disease Associated with a Diagnosis of Diffuse Parenchymal Lung Disease

Lung Disease	Imaging	Comments
Acute interstitial pneumonia	Diffuse ground glass with consolidation	Indistinguishable from ARDS but without a risk factor for ARDS
Organizing pneumonia	Patchy ground glass, alveolar consolidation, peripheral and basal predominance	Connective tissue diseases, infections, drug-related, or idiopathic
Idiopathic pulmonary fibrosis/usual interstitial pneumonia	Basal-predominant and peripheral-predominant septal line thickening with traction bronchiectasis and honeycomb changes	The usual interstitial pneumonia pattern can be seen in connective tissue disease, asbestosis, and chronic hypersensitivity pneumonitis; idiopathic pulmonary fibrosis is a diagnosis of exclusion
Nonspecific interstitial pneumonia	Ground glass, basal predominance	Idiopathic and common finding in connective tissue disease
Respiratory bronchiolitis	Centrilobular nodules and ground-glass opacity in an upper-lung predominant distribution	May be an asymptomatic finding in an active smoker
Desquamative interstitial pneumonia	Basal-predominant and peripheral-predominant ground-glass opacity with occasional cysts	
Hypersensitivity pneumonitis	Acute: ground-glass opacification; centrilobular micronodules that are upper- and mid-lung predominant Chronic: mid- and upper-lung predominant septal lung thickening with traction bronchiectasis; usual interstitial pneumonia pattern may be seen	Acute: associated with flulike illness Chronic: often cannot identify a causative antigen
Sarcoidosis	Upper lobe-predominant; mediastinal and hilar lymphadenopathy; cystic changes including development of aspergilloma; small nodules oriented along bronchovascular bundles	Findings for sarcoidosis are often not specific; DPLD with diffuse mediastinal and hilar lymphadenopathy greater than 2 cm in size should raise suspicion

ARDS = acute respiratory distress syndrome; DPLD = diffuse parenchymal lung disease.

distinguish from dependent atelectasis. The findings on HRCT highly correlate with the histopathology identified on open lung biopsy. In fact, most of the time the diagnosis of idiopathic pulmonary fibrosis can be made without lung biopsy based on the results of HRCT.

Serologic Testing

Although the American Thoracic Society guidelines recommend screening all patients with DPLD with an antinuclear antibody (ANA), rheumatoid factor, and anti-cyclic citrullinated peptide antibodies, it is most appropriate in younger patients, in particular those younger than 40 years of age, patients with symptoms of an underlying rheumatologic disorder, and patients with a family history of autoimmune or rheumatologic disease. Standard serological testing for individuals who have no clinical evidence of autoimmune disease remains controversial. Additional serologic tests for connective tissue and vascular diseases should be based on history and physical examination. See MKSAP 18 Rheumatology for further discussion of testing for connective tissue disease.

Lung Biopsy

When pulmonary function tests and HRCT are insufficient for making the diagnosis, the physician must consider the risks and benefits of either a bronchoscopic or surgical lung biopsy, including the patient's general health and risk of intervention. Careful assessment of risk factors, alternate diagnostic strategies, and impact of the results of lung biopsy on treatment should be discussed within a multi-disciplinary team, including a thoracic radiologist, thoracic surgeon, and pulmonary specialist with expertise in DPLD. Although a bronchoscopic biopsy provides much less tissue than a surgical lung biopsy, it has a high yield for making a diagnosis of sarcoidosis and is typically performed as an outpatient procedure. Overall in-hospital mortality associated with a surgical lung biopsy (either thoracoscopic or open biopsy) for DPLD remains low for scheduled cases (1.7%), but is much higher for emergency cases (16%).

KEY POINTS

HVC
- The diagnosis of diffuse parenchymal lung disease can often be made based on high-resolution CT without a lung biopsy.
- Serologic testing for diffuse parenchymal lung disease is most appropriate in young patients, those with symptoms of rheumatologic disease, or those with a family history of rheumatologic conditions.

Diffuse Parenchymal Lung Diseases with a Known Cause

Smoking-Related Diffuse Parenchymal Lung Disease

There are several DPLDs that occur almost exclusively in individuals who are current smokers. Examples include respiratory bronchiolitis associated interstitial lung disease (RB-ILD), desquamative interstitial pneumonia (DIP), and pulmonary Langerhans cell histiocytosis (PLCH). A history of smoking is also believed to be a risk factor for the development of idiopathic pulmonary fibrosis.

RB-ILD is the histopathologic diagnosis associated with the HRCT finding of centrilobular micronodular disease in current smokers. This diagnosis may incidentally be made in asymptomatic smokers undergoing low-dose CT lung cancer screening. DIP is characterized by alveolar filling with macrophages and is associated with ground-glass opacities on CT imaging, although this imaging finding is not specific for DIP. Patients with DIP typically are symptomatic with a dry cough and dyspnea.

PLCH, on the other hand, has diffuse thin walled cysts and several pulmonary nodules that are mid- and upper-lung zone predominant on HRCT. PLCH can also be associated with the development of pulmonary hypertension. Demonstrating the presence of Langerhans cells with S100 or CD1a staining of tissue obtained by either transbronchial or open lung biopsy confirms the diagnosis.

On physiologic testing, RB-ILD may have combined restriction and obstruction, whereas DIP typically is associated with pure restrictive disease. PLCH often produces restrictive disease, but may have preserved total lung capacity and evidence of obstruction when significant cystic disease is present. D_{LCO} is reduced in all of these conditions.

For all smoking-related DPLDs, the primary management is smoking cessation. The use of glucocorticoids for those with more severe smoking-related DPLD or who have quit smoking and have persistent symptoms is often attempted, but has uncertain treatment effect.

KEY POINTS

- Respiratory bronchiolitis-associated interstitial lung disease may be diagnosed in asymptomatic smokers based on high-resolution CT findings and pulmonary function testing.
- The primary management of all smoking-related diffuse parenchymal lung diseases is smoking cessation.

Connective Tissue Diseases

Individuals younger than 40 years of age who present with DPLD have a high prevalence of connective tissue disease (CTD). The review of systems should include a thorough review of rheumatologic symptoms. Signs and symptoms of CTD warrant serologic evaluation based on the most likely disorder. Ruling out this potential cause for DPLD is very important even in the older population, despite the lower prevalence of CTD, because of the implications for treatment with immunomodulating agents. Pulmonary abnormalities are extremely common in patients with rheumatoid arthritis and include bronchiolitis, organizing pneumonia, rheumatoid nodules, nonspecific interstitial

pneumonia (NSIP), and usual interstitial pneumonia (the same pathology that is seen with idiopathic pulmonary fibrosis). Furthermore, patients with rheumatoid arthritis treated with methotrexate are also at risk for possible drug-induced DPLD.

Patients with systemic sclerosis are at high risk for the development of lung disease, which is the leading cause of death in these patients. NSIP is the most common histopathologic diagnosis on lung biopsy, and HRCT imaging typically demonstrates findings of bilateral lower lobe ground-glass opacities with or without septal line thickening and traction bronchiectasis. The pathologic pattern of NSIP can occasionally be diagnosed in a patient before the development of systemic disease. Although cyclophosphamide has been shown to be of modest benefit, it has high toxicity and has been replaced by mycophenolate mofetil, which has similar efficacy and is better tolerated with decreased side effects. As a result, mycophenolate mofetil is considered first-line therapy for those with progressive DPLD and systemic sclerosis. For patients thought to have idiopathic NSIP, rheumatology consultation and evaluation for immunosuppressive treatment is appropriate.

KEY POINTS

- Pulmonary abnormalities are extremely common in patients with rheumatoid arthritis and can include bronchiolitis, organizing pneumonia, rheumatoid nodules, nonspecific interstitial pneumonia, and usual interstitial pneumonia.
- Patients with systemic sclerosis are at high risk for the development of lung disease, which is the leading cause of death in these patients.

Hypersensitivity Pneumonitis

Repetitive inhalation of antigens in a sensitized patient can result in hypersensitivity pneumonitis (HP), an immunologic response that results in noncaseating granulomas and peribronchial mononuclear cell infiltration with giant cells. The antigens are typically complex proteins, which can come from several sources including agricultural dusts, thermophilic fungi, and bacteria, but can also be some small-molecular weight chemical compounds. There are three forms of HP, and they each present differently. The acute form, which is most easily identified, results after a large exposure to an inciting antigen. The patient will develop fevers, cough, and fatigue, typically within 12 hours of exposure. Chest radiography can demonstrate diffuse micronodular disease but may be normal. Physical examination will reveal inspiratory crackles. If a HRCT scan is performed, it will demonstrate diffuse centrilobular micronodules and ground-glass opacities (**Figure 5**). After removal from the offending antigen, symptoms will resolve within approximately 48 hours. The recurrence of symptoms if the patient is rechallenged is the hallmark of the disease.

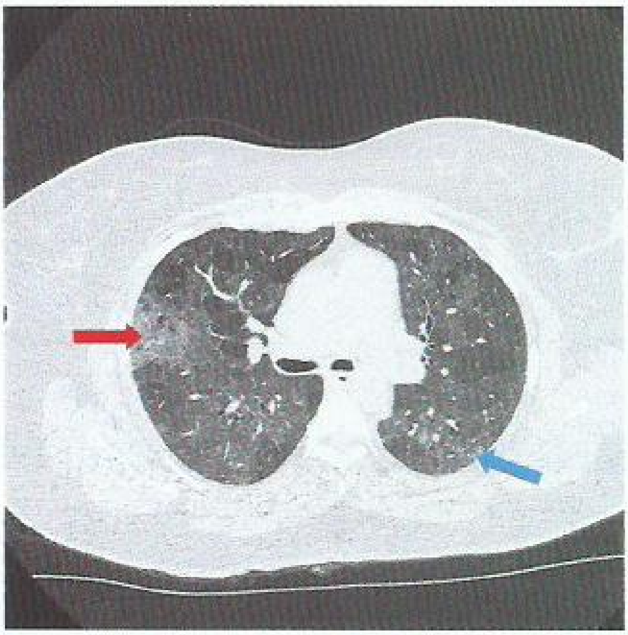

FIGURE 5. Chest CT scan demonstrating hypersensitivity pneumonitis with patchy, bilateral ground-glass opacities (*red arrow*) and centrilobular micronodules (*blue arrow*) in the mid-lung section.

Subacute and chronic forms of HP likely occur after more prolonged lower-level antigen exposure. Bird fanciers disease is an example of a chronic disorder. These patients have a chronic low-level exposure to avian antigens within the home and will ultimately experience cough, fatigue, weight loss, and shortness of breath. Similar to the acute form, the HRCT will show micronodules and ground-glass opacities, but there is also evidence of septal line thickening and fibrosis. In its most severe and chronic form, significant traction bronchiectasis and honeycomb changes will be evident. Evidence of severe fibrosis on CT imaging significantly increases the risk for progression of disease and death.

Removal of exposure to the offending antigen is essential in the treatment of HP. To identify potential antigens, careful history is vital, as serologic testing is often limited and may not include antibodies to the responsible antigen. Glucocorticoids are often used for those with more severe symptoms. Response to this therapy is variable. Prolonged glucocorticoid use is associated with significant side effects, and should be avoided without clear objective evidence of improved pulmonary function.

KEY POINTS

- The acute form of hypersensitivity pneumonitis is characterized by fever, cough, and fatigue within 12 hours of a major exposure to an inciting antigen; recurrence of symptoms with rechallenge is the hallmark of acute hypersensitivity pneumonitis.
- Removal of exposure to the offending antigen is essential in treatment of hypersensitivity pneumonitis.

Drug-Induced Diffuse Parenchymal Lung Disease

Many medications have been implicated in the development of DPLD (**Table 14**). A review of medications should include those that are new and those taken for prolonged periods because the duration of exposure to the development of disease can vary, even for the same agent. For instance, amiodarone lung toxicity has an acute form consistent with acute lung injury/acute respiratory distress syndrome, and a chronic indolent form with reticular abnormalities and subpleural nodules. Prompt treatment by removal of the offending agent is important for resolution of symptoms. For those with more severe symptoms, glucocorticoids may have some benefit, although data are anecdotal.

Radiation Pneumonitis

Radiation pneumonitis typically occurs 4 to 12 weeks after initial radiation exposure. Patients present with cough, shortness of breath, and a new radiographic infiltrate. Fever, pleuritic chest pain, fatigue, and weight loss are accompanying nonspecific symptoms. Differential diagnosis often includes infection and drug-induced lung injury. HRCT will demonstrate ground-glass opacities, usually within the field of

TABLE 14. Select Drug-Induced Parenchymal Lung Diseases

Drug	Clinical Points	Radiographic Findings and Treatment
Amiodarone	More common in: Older patients Increased dosage and higher cumulative dose First year of therapy (but can occur late)	Multiple radiographic presentations possible, including ground-glass opacities, subpleural nodules, and reticular abnormalities Very long half-life prevents clearance from the pulmonary parenchyma: Rare improvement with discontinuation of the drug alone High risk of recurrence with tapering of glucocorticoids
Methotrexate	Occurs in less than 5% of treated patients Unpredictable time to presentation No clear correlation between dose and disease severity	Diffuse reticular and ground-glass attenuation Patients generally do well after stopping medication. Glucocorticoids are often given and duration is based on response.
Nitrofurantoin	Acute (more common): Fevers, chills, cough, shortness of breath, chest pain; rash can occur in 10%-20% of patients. Peripheral eosinophilia common Chronic: Distinct from the acute form Onset months to years after prolonged exposure	Acute: Faint bilateral lower lobe septal lines; moderate pleural effusions may be present. Treatment: Often will resolve with discontinuation but will recur with repeat exposure. Chronic: Reticular opacities with subpleural lines and thickened peri-bronchovascular areas. Treatment: Possible benefit of glucocorticoids from anecdotal reports.
Busulfan	Occurs in less than 8% of treated patients. Currently used solely as a conditioning regimen for HSCT; often combined with other agents associated with pulmonary toxicity. Injury typically occurs 30 days to 1 year after exposure.	Multiple patterns including: ground glass opacities, reticulation, bibasilar septal lines, asymmetric peripheral and peribronchial consolidation, centrilobular nodules, and dependent consolidation Optimal treatment unknown and is often supportive. Glucocorticoids may be used for more progressive disease.
Bleomycin	Risk significantly increases with cumulative dose. Increased age, renal insufficiency, concomitant chemotherapy and/or radiation also increases risk of toxicity. Typically subacute presentation 1-6 months after exposure; may resemble hypersensitivity pneumonitis but with more rapid onset and progressive course.	Imaging patterns suggest the multiple possible pathologic findings seen: Consolidation with ground glass (diffuse alveolar damage) Septal line thickening, traction bronchiectasis, and honeycomb change (end-stage fibrosis) Patchy ground glass with subpleural consolidation or peribronchial consolidation (organizing pneumonia) Diffuse ground glass with centrilobular micronodules (hypersensitivity pneumonitis) Glucocorticoids are used for more severe disease and disease may recur with tapering of steroids.

HSCT = hematopoietic stem cell transplantation.

radiation exposure. A well-defined nonanatomic demarcation between normal and abnormal lung consistent with the radiation field is pathognomonic but not always present. Radiographic abnormalities, such as organizing pneumonia, may also be seen outside the field of exposure and can be nodular or alveolar. Treatment of radiation pneumonitis is typically glucocorticoids for severe disease with more extensive abnormalities on imaging, respiratory symptoms, or with hypoxemia. Observation may be appropriate for those with mild disease. From 6 to 12 months after radiation exposure, additional findings on HRCT may develop, including septal line thickening, traction bronchiectasis, and volume loss more consistent with chronic fibrosis. In addition, individuals exposed to radiation are at risk for the development of radiation-recall pneumonitis, which can occur when exposed to select chemotherapy agents including adriamycin, etoposide, gemcitabine, paclitaxel, and pemetrexed.

KEY POINTS

- Radiation pneumonitis typically presents 4 to 12 weeks after initial radiation exposure, with cough, shortness of breath, and a new radiographic infiltrate.
- Treatment of severe forms of radiation pneumonitis typically is glucocorticoids, whereas observation may be appropriate for those with mild disease.

Diffuse Parenchymal Lung Diseases with an Unknown Cause

Idiopathic Pulmonary Fibrosis

H

Idiopathic pulmonary fibrosis (IPF), which is associated with the histopathologic appearance of usual interstitial pneumonia (UIP), is the most common idiopathic form of DPLD. It typically presents in patients between 50 and 70 years of age who have a greater than 6-month duration of a dry cough and dyspnea on exertion. History will reveal no potential cause for the development of fibrosis, and lung examination is notable for Velcro inspiratory crackles that are predominant at the bases and may be subtle in early disease. Clubbing is present in up to 50% of patients and should raise suspicion for IPF. The diagnosis of IPF is challenging because it is uncommon and indolent. Because smoking is a risk factor, patients are often treated for COPD without significant improvement. Similarly, crackles on examination may lead to management for presumed heart failure. Chest radiographs may demonstrate bibasilar septal line thickening with reticular changes, and volume loss and bronchiectasis when the disease is more severe. The best diagnostic test is HRCT, which may show abnormalities, such as bilateral, peripheral, and basal predominant septal line thickening with honeycomb changes, when the chest radiograph is normal (**Figure 6**). When HRCT is consistent with UIP, lung biopsy may not be necessary for diagnosis.

IPF is progressive, with a median survival of 3 to 5 years after diagnosis. The progression of disease, however, is variable and may be associated with periods of stability with intermittent periods of acute decline. A subset of patients develop an acute exacerbation with a worsening of symptoms, typically of less than 1 month's duration, and associated new findings on chest CT of bilateral ground glass opacities after having relatively stable disease over time. These events can be "triggered" by an inciting event such as an infection or may be "idiopathic." Heart failure and volume overload should be excluded as causes of the radiographic changes or clinical decompensation.

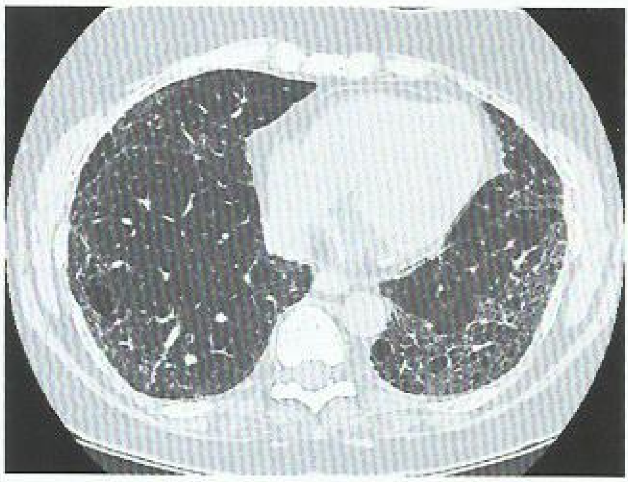

FIGURE 6. High-resolution chest CT demonstrating the typical findings in idiopathic pulmonary fibrosis, including increased reticular changes that are predominantly peripheral and basilar in distribution, honeycombing (at the left base), and absence of significant ground-glass opacification.

An important aspect of treatment of IPF includes optimum management of comorbidities such as obesity, heart failure, and deconditioning. Sleep-disordered breathing is common in this population due to nocturnal hypoxemia and increased prevalence of obstructive sleep apnea. Treatment of hypoxemia includes supplemental oxygen with exertion and at rest as needed based on pulse oximetry testing. For those with deconditioning, pulmonary rehabilitation has demonstrated benefits in exercise tolerance and quality of life in several small studies. In progressive and severe disease, pulmonary hypertension and right-sided heart failure are commonly observed. One preliminary study suggesting improvement in quality of life with sildenafil needs further study before recommending its use in this population.

In 2014, two FDA-approved therapies, nintedanib and pirfenidone, became available. Both therapies target the fibroblast, which is considered central in the progression of fibrosis. Although the mechanisms of these two medications differ, clinical response is quite similar, with both demonstrating a decline in the rate of progression of disease. Although these medications delay IPF progression, they are not curative. Referral to a pulmonologist or interstitial lung disease (ILD) center may be appropriate before initiating treatment with these medications.

H CONT.

Lung transplantation is a life prolonging therapy for those without comorbidities that may otherwise limit life expectancy. Typically, transplant centers exclude those with untreatable end-organ damage outside the lungs. Early referral of eligible patients to a transplant center is appropriate given the unpredictability of disease progression.

The most common cause of death in patients with IPF is respiratory failure. In patients with respiratory failure, the need for mechanical ventilation portends an extremely poor prognosis. As a result, consensus-based guidelines recommend against mechanical ventilation for IPF patients if lung transplantation is not an option. Palliative care consultation to establish advanced care plans should be considered for patients with IPF who are not candidates for lung transplantation and who have a severe exacerbation and poor performance status. Ideally, advance care planning, including end-of-life goals of care and palliative strategies, should be decided before urgently facing the decision of whether to begin mechanical ventilation in the setting of respiratory failure. H

KEY POINTS

- FDA-approved therapy with nintedanib and pirfenidone decreases the rate of progression of idiopathic pulmonary fibrosis but is not curative.
- HVC Consensus-based guidelines recommend against mechanical ventilation for patients with idiopathic pulmonary fibrosis if lung transplantation is not an option.

Nonspecific Interstitial Pneumonia

Nonspecific interstitial pneumonia (NSIP) is the most common DLPD associated with autoimmune disorders, but it can occasionally be idiopathic and not associated with an underlying connective tissue disease. There are two forms of NSIP: cellular and fibrotic. The fibrotic form has a worse prognosis and is poorly responsive to treatment. The cellular form has a better prognosis and will typically respond to immunosuppressive treatments. Although the overall prognosis is better than for IPF, the 5-year mortality of idiopathic NSIP remains approximately 15% to 25%. Individuals with progressive decline in pulmonary function are at increased risk of death regardless of the underlying pathology. Similar to IPF, select patients may benefit from lung transplantation. NSIP affects a younger population than IPF. HRCT will demonstrate bilateral lower-lobe reticular changes and an absence of honeycombing, but can also demonstrate areas of ground-glass opacification. These findings on HRCT have been associated with systemic sclerosis, systemic lupus erythematosus, Sjögren's syndrome, dermatomyositis, and polymyositis, as well as undifferentiated connective tissue disease. Because idiopathic NSIP is rare, a thorough investigation for an underlying autoimmune disorder is essential. NSIP was common in patients with AIDS in the pre-antiretroviral therapy era; however, it is much less common since the advent of antiretroviral therapy.

KEY POINTS

- Nonspecific interstitial pneumonia is the most common diffuse parenchymal lung disease associated with autoimmune disorders.
- Bilateral lower-lobe reticular changes and an absence of honeycombing on high-resolution CT scan, often accompanied by areas of ground-glass opacification, have been associated with systemic sclerosis, systemic lupus erythematosus, Sjögren's syndrome, dermatomyositis, and polymyositis, as well as undifferentiated connective tissue disease.

Cryptogenic Organizing Pneumonia

Organizing pneumonia is defined by histopathologic findings of patchy proliferation of granulation tissue that affects the terminal bronchiole, and alveolar ducts and spaces, and is associated with surrounding inflammation. This pattern often follows or is associated with various types of injury to the lung, including acute infection, radiation exposure, drug-induced pneumonitis, and autoimmune diseases. In patients in whom no cause is identified, the diagnosis is termed cryptogenic organizing pneumonia (COP).

H Patients with COP typically present with cough, fever, and malaise for 6 to 8 weeks. Initial chest radiographs will demonstrate patchy opacities that mimic pneumonia and, as a result, patients are often initially misdiagnosed with community-acquired pneumonia and treated with standard antibiotics (**Figure 7**). However, nonresolving symptoms and failure to respond to antibiotics should raise suspicion for organizing pneumonia or COP. HRCT imaging will demonstrate ground-glass opacities or areas of alveolar consolidation resembling an infectious pneumonia, but findings can include peripheral nodules and nodules along the bronchovascular bundle. The diagnosis may not require lung biopsy if the clinical presentation and HRCT findings are consistent with COP. For cases with atypical presentation, lung biopsy may be necessary to make the diagnosis. H

Patients with COP typically respond to glucocorticoid therapy. In organizing pneumonia associated with an autoimmune disorder, treatment should focus on the autoimmune condition. Relapses of COP with tapering of glucocorticoids are common, and therefore a long taper of glucocorticoids or transition to alternate immunosuppressive therapy should be considered.

KEY POINT

- Patients with cryptogenic organizing pneumonia typically present with complaints of cough, fever, and malaise for 6 to 8 weeks, which may mimic community-acquired pneumonia.

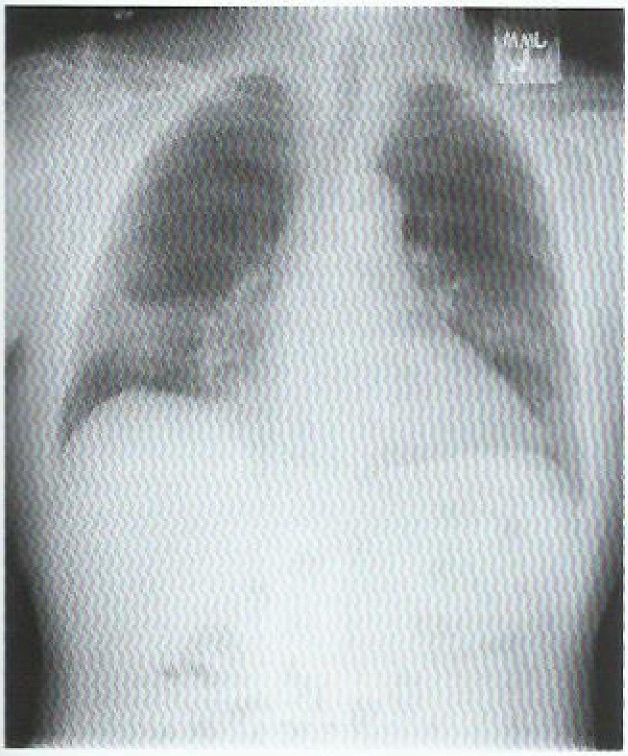

FIGURE 7. Chest radiograph showing cryptogenic organizing pneumonia, demonstrating multiple patchy bilateral alveolar opacities that are nonspecific and may be difficult to distinguish from more typical infectious pneumonia. Infiltrates may be migratory, with resolution of established opacities as new areas appear on serial imaging. Imaging may also be nonspecific, showing interstitial infiltrates and alveolar opacification or one or more rounded nodules that may be interpreted as malignancy.

Acute Interstitial Pneumonia

Acute interstitial pneumonia develops rapidly during days to weeks, resulting in acute respiratory failure with bilateral alveolar opacities on HRCT of the chest consistent with pulmonary edema. The pathologic findings on open lung biopsy are those of diffuse alveolar damage. This process is clinically, radiographically, and pathologically indistinguishable from acute respiratory distress syndrome. The differentiating factor is the lack of risk factors for the development of acute respiratory distress syndrome. The history should carefully assess any history of aspiration, sepsis, or inhalational exposure that could result in acute lung injury.

Management includes supportive care, as for other patients with acute lung injury or acute respiratory distress syndrome. This includes low tidal volume ventilation if required and critical care management to avoid complications of illness. Although glucocorticoids are often used, there is little evidence other than case reports of improvement with their use. Mortality remains high (approximately 50%), and those who recover from the initial illness often have complications, are at risk for the development of chronic lung disease, and may have a relapse. Long-term management of these patients includes consideration of immunosuppression; however, there are limited data to guide therapy.

KEY POINT

- Acute interstitial pneumonia is clinically, radiographically, and pathologically indistinguishable from acute respiratory distress syndrome; the differentiating point is the lack of risk factors for the development of acute respiratory distress syndrome.

Sarcoidosis

Sarcoidosis is a granulomatous disease of unknown cause that can affect several organ systems. Greater than 90% of patients with sarcoidosis have lung involvement. The prevalence of sarcoidosis is approximately 10 to 20 per 100,000 individuals. Sarcoidosis affects blacks more frequently than whites and typically occurs in younger patients. Many patients are asymptomatic, and lung involvement is incidentally found on chest radiography done for other reasons (**Figure 8**). Findings from chest radiography can help predict the probability of spontaneous resolution (**Table 15**). CT scanning can show pulmonary parenchymal disease or intrathoracic lymphadenopathy, either alone or in combination. Although there are various appearances of sarcoidosis on chest CT scanning, a particularly characteristic finding is the presence of small nodules alongside bronchovascular bundles.

Pulmonary function testing is typically abnormal and findings can be obstructive, restrictive, or both. Sarcoidosis is a diagnosis of exclusion. Diagnosis, with a few exceptions (**Table 16**), typically requires bronchoscopic biopsy, with tissue obtained from a lymph node or from the pulmonary

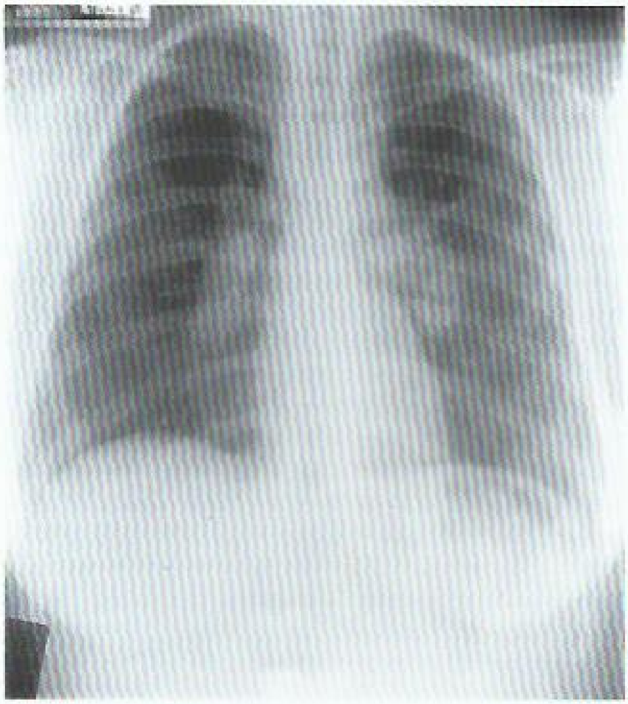

FIGURE 8. Chest radiograph showing stage I pulmonary sarcoidosis with hilar lymphadenopathy and normal lung parenchyma.

TABLE 15. Chest Radiograph Staging of Pulmonary Sarcoidosis

Stage	Radiographic Pattern	Clinical Course and Comments
0	Normal	
I	Hilar lymphadenopathy with normal lung parenchyma	>90% will have spontaneous resolution without treatment
II	Hilar lymphadenopathy with abnormal lung parenchyma	Approximately 50% rate of spontaneous improvement without treatment
III	No lymphadenopathy with abnormal lung parenchyma	Approximately 20% rate of spontaneous improvement without treatment
IV	Parenchymal changes with fibrosis and architectural distortion	

TABLE 16. Clinical Presentations of Sarcoidosis that Do Not Require a Biopsy

Syndrome	Additional Findings/Symptoms
Asymptomatic bilateral hilar lymphadenopathy	No evidence of fevers, malaise, or night sweats to suggest a malignancy
Löfgren syndrome	Bilateral hilar lymphadenopathy, migratory polyarthralgia, erythema nodosum, and fever
Heerfordt syndrome	Anterior uveitis, parotiditis, fever (uveoparotid fever), and facial nerve palsy

H CONT.

parenchyma. The diagnosis is made by the finding of noncaseating granulomas with exclusion of potential mimicking infections (mycobacteria, fungi), exclusion of other systemic granulomatous diseases, and ideally with involvement of more than one organ system.

Pulmonary hypertension may develop through several different mechanisms, including chronic hypoxemia, destruction of the capillary bed resulting in severely reduced capillary surface area, granulomatous inflammation of the pulmonary arteries, compression of pulmonary arteries secondary to contiguous lymphadenopathy, pulmonary veno-occlusion from granulomatous inflammation, and left ventricular dysfunction from cardiac involvement. Development of pulmonary arterial hypertension is a poor prognostic indicator, with a median survival of approximately 3 years.

The primary treatment of sarcoidosis is glucocorticoids, although many patients do not need to be treated. In addition, spontaneous resolution without treatment is common and related to the radiographic stage of disease (see Table 15). The decision to treat and assessment of response should be based on symptoms and organ dysfunction, not radiographic findings. For those without symptoms or organ dysfunction, observation is appropriate. If treatment is required, low- to medium-dose glucocorticoid therapy, often on alternate days, is appropriate. Short-term symptomatic benefit is clear from retrospective study data; however, long-term benefits remain less clear. For patients with more severe or prolonged symptoms, side effects from chronic glucocorticoids should be considered. In this setting, adjunctive glucocorticoid-sparing therapies are often used. Pulmonary consultation should be considered for management of persistent disease. For patients with pulmonary hypertension or severe disease with significant activity limitation due to lung disease, evaluation for lung transplantation is appropriate. H

KEY POINTS

- Greater than 90% of patients with sarcoidosis have lung involvement; radiographic staging can predict the probability of spontaneous resolution.
- The primary treatment of symptomatic sarcoidosis is glucocorticoids.

Occupational Lung Disease

When to Suspect an Occupational Lung Disease

Occupational lung disease can affect any part of the respiratory tract, including sinuses, airways, the lung parenchyma, and the surrounding pleura. As a result, signs and symptoms associated with occupational exposure include rhinitis, reactive airways disease, COPD, pleural disease, diffuse parenchymal lung disease, and malignancy. Occupational lung diseases can present acutely, subacutely, or slowly after many years of exposure. As a result, these diseases require that clinicians maintain suspicion for and obtain a careful history of occupational exposures. Clinical presentations related to silica and asbestos exposures are well characterized and recognized. However, new agents that may lead to respiratory diseases are frequently introduced in industry. Factors suggesting an underlying occupational lung disease include patient concerns about an exposure, a temporal association with an exposure, unexplained signs or symptoms, and evidence of coworkers with similar symptoms (**Table 17**). In addition, patients may experience relief of symptoms when away from the work environment and recurrence of symptoms upon their return. For the patient with occupational lung disease, similar to diffuse parenchymal lung disease, cough and dyspnea on exertion are common.

TABLE 17. Occupational Lung Disease Screening Questionnaire

Occupation
What do you do every day at your job?
Have you always done these tasks at work?
Have you had other duties?
How long have you been working in this job? Have you had a similar job elsewhere?
What other types of work have you done?*
Type and Extent of Exposure
Describe your work area. Is there adequate ventilation? Is there visible dust in the air? Is visibility across the work area limited due to the extent of dust in the air?
Are you exposed to vapors, gases, dust, or fumes in your work?
Does your employer require you to wear personal protective equipment? If so, do you wear it for the full extent of your exposure?
Do you know the amount and type of chemicals used?
Do you have Material Safety Data Sheets (MSDSs) from your workplace?
Temporal Relationship of Symptoms to the Work Environment
Before symptoms began, were there any changes in the processes at work or new exposures?
When you are off work, do your symptoms improve?
Are there others at work who have developed similar symptoms?
Has a process change at work resulted in improved symptoms?
Other Relevant Exposures
Do you perform activities at home that may expose you to organic or inorganic dust (for example, refurbishing old cars or wood working)?
Do you have any pet birds at home? Do you have any pets?
Have you always lived in the area?
Have you traveled recently?

*Obtain a full accounting of other jobs as well.

Key Elements of the Exposure History

The time course from exposure to the development of signs and symptoms of occupational lung disease is highly variable. Therefore, it is essential to obtain a complete history, including employment history. Exposures within the same industry can vary based on use of best practices and on the type of workplace. For example, coal worker's pneumoconiosis in the United States has substantially decreased since the institution of federal safety standards. However, rates of coal worker's pneumoconiosis are higher for individuals who work for companies with fewer than 50 employees, and for those who work in thin-seam mines. Thin-seam mines appear to have higher crystalline silica exposure and pose greater risk. More than 95% of these mines are located in Kentucky, West Virginia, and Virginia. Adequate determination of exposure requires a clear description of job duties and determination of the extent of dust exposure. Clinicians should also obtain a history of additional exposures from hobbies or the home environment (see Table 17).

When an occupational lung disease is suspected, clinicians should request Material Safety Data Sheets (MSDSs) from the employer, which detail chemical properties and known health risks associated with substances within the workplace. The U.S. Occupational Safety and Health Administration (OSHA) requires that this information is available upon request for employees who work with potentially harmful materials.

For individuals who have undiagnosed disorders, persistent unexplained symptoms, or permanent impairment possibly due to an occupational lung disease, referral to an occupational and environmental lung disease specialist is appropriate.

KEY POINTS

- Presentations of occupational lung disease include rhinitis, reactive airways disease, COPD, pleural disease, diffuse parenchymal lung disease, or malignancy.
- When an occupational lung disease is suspected, it is essential to obtain a complete history, including occupation, type and extent of exposure, temporal relationship of exposure to symptoms and disease, and other exposures at home and from hobbies.

Management

The key to management of occupational lung disease is removal of the offending agent from the workplace or the worker from the offending agent. Because workers typically have colleagues in a similar environment, further investigation of the workplace to ensure identification of all affected individuals is essential. Beyond one specific patient, prevention through mitigation of further exposures in the workplace is best practice.

Workers' compensation often becomes an issue during medical management. It may be difficult to define the degree of impairment resulting from the exposure, and the determination of disability related to the impairment may require referral to a specialist with expertise in occupational lung disease.

KEY POINT

- The key to management of occupational lung disease is removal of the offending agent from the workplace or the worker from the offending agent; further investigation of the workplace to ensure identification of all affected individuals is essential.

Surveillance

For individuals at high risk for the development of pulmonary disease, the use of health questionnaires and pulmonary function screening is appropriate; such screening can also identify

a new exposure and any associated risk of disease development. Surveillance systems that catalogue sentinel cases of disease can help identify clustering of cases. However, one major limitation of these databases is the failure of physicians to report events.

Asbestos-Related Lung Disease

Asbestos includes a group of minerals that, when crushed, will break into fibers. These fibers are chemically heterogeneous hydrated silicates that are used in industry because of their high tensile strength, heat resistance, and acid resistance. In the past, asbestos fibers were widely used in insulation, brake linings, flooring, cement paint, and textiles. Because of the known toxicities associated with asbestos, these compounds are used far less frequently today.

Asbestos-associated diseases have a prolonged latency period (15 to 35 years), resulting in continued identification of new cases despite the decreased use of asbestos in the United States. Continued exposures within the United States and the developed world occur through updating, demolition, and abatement of older construction. Asbestos exposure remains an occupational hazard for workers in developing nations.

Risk Factors

Duration and extent of exposure are key risk factors for the development of disease. Asbestos-related lung diseases are common in mine workers who procure the asbestos and in industries that make use of the products. In the United States, workers in construction, naval shipyards, and the automotive service industries are particularly at risk. Exposure is also possible in areas where manufacturing of asbestos leads to environmental contamination. Similarly, there are reports of people who develop asbestos-related lung diseases after exposure to asbestos dust from family members working in an asbestos-related industry.

KEY POINT

- Asbestos-related lung diseases are common in mine workers who procure the asbestos and in industries that make use of products containing asbestos; in the United States, workers in construction, naval shipyards, and the automotive service industries are particularly at risk.

Pathophysiology

Inhaled asbestos fibers deposit deep within the lung, reaching airway bifurcations; respiratory bronchioles; and the alveolus, where they promote alveolitis. Type I alveolar epithelial cells take up the fibers, which migrate to the interstitium. Lymphatic channels transport asbestos fibers to the pleural surface. Although activated macrophages phagocytose and remove fibers, remaining fibers stimulate the macrophage to produce inflammatory mediators. These and other cell mediators stimulate fibroblast proliferation and chemotaxis, resulting in collagen deposition and development of fibrosis.

Asbestos exposure increases the risk for development of lung cancer regardless of smoking status, but the risks are substantially higher in smokers. This risk of cancer is apparent when any form of asbestos-related lung disease is present; however, for those with a history of asbestosis (that is, diffuse parenchymal lung disease secondary to asbestos), the risk of lung cancer is 36 times higher than in those with no history of smoking. Smoking cessation is essential. Findings of parietal pleural calcifications or plaques on chest radiograph should alert the clinician to the possibility of asbestos exposure. Although most patients with pleural plaques are asymptomatic, the most common symptom is exertional dyspnea. Additional evaluation including evaluation for lung cancer or mesothelioma should be considered.

Silicosis

Silicosis is a fibrotic lung disease caused by the inhalation of silica dust. Silica exposure typically occurs in industries that grind, cut, or drill silica-containing materials such as concrete, tile, and masonry. Pottery making, foundry work, and sand blasting can also result in exposure. Sandblasting of denim jeans (stone washing) recently resulted in an outbreak of disease in Turkey. Hydraulic fracturing for natural gas and oil may expose workers to hazards, as this process involves fine sand and a wide variety of chemicals.

There are four main types of silicosis (**Table 18**), and they are associated with altered cell immunity and macrophage function. Patients with silicosis are at increased risk for the development of mycobacterial infection and connective tissue disease. Chronic silicosis is associated with the development of infection, including tuberculosis, and clinicians should have a high index of suspicion for this complication. Once fibrosis develops in silicosis, there is little evidence that any therapies alter disease course. If individuals have continued exposure, removal from the environment will prevent further lung injury. Silica exposure is associated with increased risk of lung cancer, particularly for smokers. As a result, smoking cessation remains an essential intervention.

KEY POINTS

- Silica exposure can occur in individuals who work with hydraulic fracturing, concrete, tile, masonry, pottery, sand blasting, or in those who do foundry work.
- Once fibrosis develops in patients with silicosis, no therapies alter the course of the disease.

Pleural Disease

The two main abnormalities affecting the pleura result from the presence of fluid (pleural effusion) or air (pneumothorax) in the pleural space.

TABLE 18. Key Features of Silica-Related Lung Diseases

Type	Latency	Exposure Level[a]	Imaging Findings	Clinical
Acute silicoproteinosis (acute silicosis)	A few weeks to 3 years	High level	Crazy-paving pattern (extensive ground-glass opacity and interlobular septal thickening)	Rapidly progressive dyspnea with constitutional symptoms. Typically fatal. BAL yields a thick, milky effluent
Chronic simple silicosis	10-20 years	Low to moderate	Upper-zone predominant with centrilobular or peri-lymphatic nodules 1-9 mm in diameter Hilar lymph nodes may have eggshell calcification.	Often asymptomatic Rarely will progress to PMF
Chronic complicated silicosis (PMF)[b]	10-20 years	Low to moderate for those who progress from simple silicosis	Coalescent fibrosis >1 cm in diameter, typically in the periphery, enlarging over time and progressing towards the hilum. May contain air bronchograms and calcifications	Debilitating disease marked by progressive dyspnea and functional impairment
Accelerated silicosis	3-10 years	Accelerated disease may occur with very high exposure for a shorter period of time	Similar to chronic disease other than more rapid development	As for chronic disease

BAL = bronchoalveolar lavage; PMF = progressive massive fibrosis.

[a]Exposure refers to both quantity of dust exposure and duration.

[b]A form of chronic silicosis that may progress from simple silicosis.

Pleural Effusion

Each year more than 1.5 million new cases of pleural effusion are diagnosed in the United States. Most effusions are benign; however, approximately 16% of them are secondary to malignancy. Heart failure, pneumonia, and malignancy are the most common etiologies in the United States. The pleurae are thin membranes that cover the surface of the lung (visceral pleura) and the chest wall (parietal pleura). Normally the pleural space contains only a small amount of fluid (less than 15 mL). Pleural effusions result from conditions that affect the rate of fluid entry from pleural capillaries and the ability of lymphatics to absorb the fluid.

KEY POINT

- Heart failure, pneumonia, and malignancy are the most common causes of pleural effusion in the United States.

H

Evaluation

History and Physical Examination

The cause of a pleural effusion is often suggested by patient history and physical exam. Symptoms typically include dyspnea, cough, and pleuritic chest pain. Key questions include severity and duration of symptoms; constitutional symptoms such as fevers, night sweats, and weight loss; occupation; recent illness, injury, or travel; exposures (for example, asbestos); and medical history such as heart failure, previous surgeries, and medications. The chest examination may reveal dullness to percussion and diminished or absent fremitus and breath sounds if the effusion is larger than 300 mL. There are several other key physical examination findings that may suggest the cause of the effusion (**Table 19**).

Diagnostic Imaging

A chest radiograph should be performed as the first test in an evaluation of a possible pleural effusion. The radiographic findings are variable, but abnormalities may be seen with as little as 200 mL on the posterior-anterior (PA) chest radiograph or 50 mL on the lateral view (**Figure 9**).

TABLE 19. Key Physical Examination Findings in the Evaluation of a Pleural Effusion

Finding	Possible Cause of Pleural Effusion
Distended neck veins, S_3 gallop, pulmonary crackles	Heart failure
Bilateral peripheral edema	Heart failure, nephrotic syndrome, cirrhosis
Calf or thigh swelling, erythema, edema, tenderness, palpable cord	Pulmonary embolus
Accentuated cardiac pulmonic sound, right ventricular heave	Pulmonary embolus
Lymphadenopathy	Malignancy
Ascites	Cirrhosis

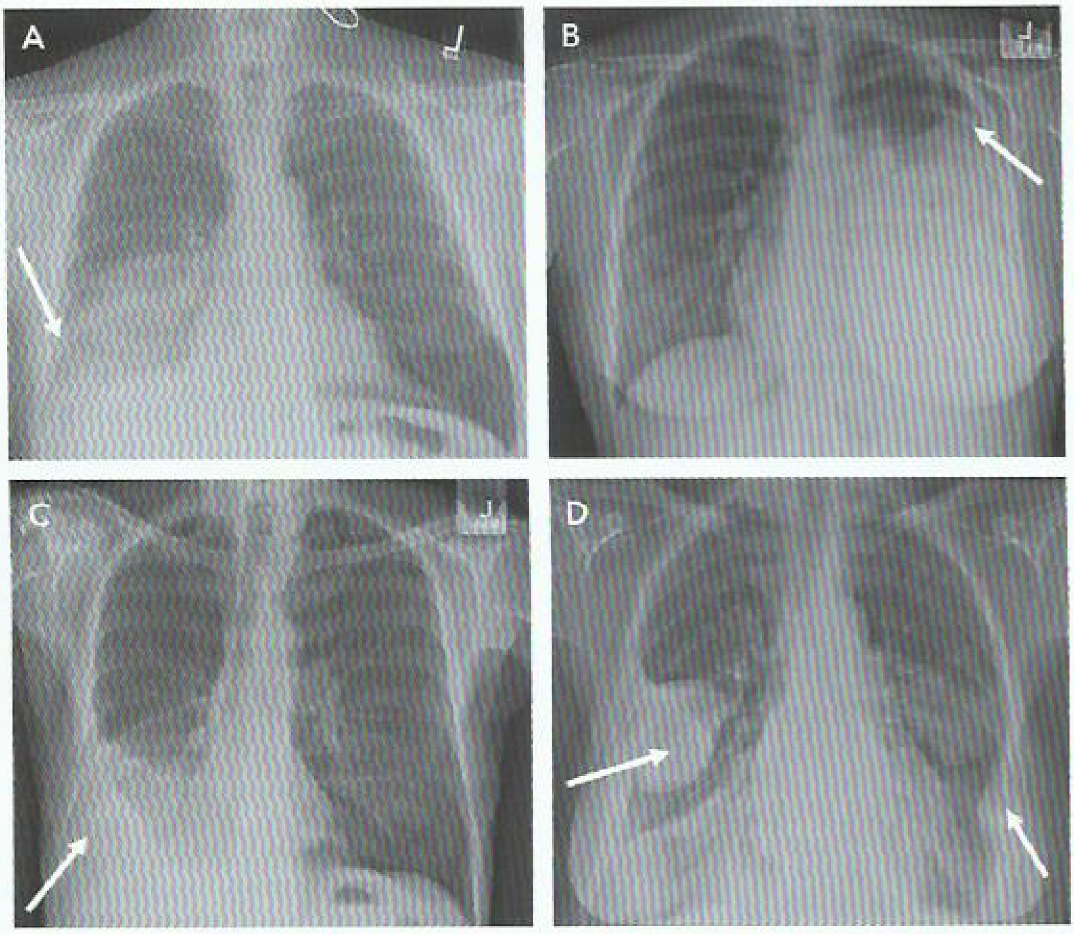

FIGURE 9. *A:* Moderate right pleural effusion which layers over the lower hemithorax; *B:* Large left pleural effusion with meniscus sign (a rim of fluid ascending the lateral chest wall); *C:* Loculated pleural effusion along the right lateral chest wall (presence of septations and separate compartments within the effusion); *D:* Bilateral multi-loculated pleural effusions.

H CONT.

Thoracic ultrasound is a helpful addition to chest radiography for identification of small effusions, particularly in patients who are semirecumbent, such as those who are critically ill. This imaging allows estimation of the quantity of the fluid and determination of whether it is free-flowing or loculated (that is, with septations) (**Figure 10**). In addition, there is no radiation exposure with ultrasound.

Advantages of CT imaging include the ability to detect small amounts of pleural fluid; assessment of coexisting intrathoracic abnormalities, such as pulmonary masses and malignant pleural disease; and identification of an empyema, as enhancement of the pleura around the fluid creates a lenticular-shaped opacity (**Figure 11**). H

KEY POINTS

- A chest radiograph should be performed in the initial evaluation of possible pleural effusion.
- In supine patients and in those with small effusions, thoracic ultrasound is more sensitive than chest radiography for diagnosis of pleural effusion.

Indications for Thoracentesis

H

Once a pleural effusion is identified, the next diagnostic test to consider is thoracentesis.

Indications include pleural effusion of unknown cause and greater than 1 cm of fluid thickness on ultrasound or lateral decubitus film. Fluid less than 1 cm thick is technically difficult to sample and less likely to be clinically meaningful, but still may be appropriate for thoracentesis based on clinical judgment. Thoracentesis should be done with ultrasound guidance, as it allows for both a greater success rate and a reduced risk of solid organ puncture and iatrogenic pneumothorax.

Pleural Fluid Analysis

The first step in pleural fluid evaluation is assessing the appearance of the pleural fluid (**Table 20**). The next step is to determine whether it is a transudate or exudate. Transudates are due to an imbalance between hydrostatic and oncotic pressures, as occurs with heart failure and cirrhosis. Exudates are due to inflammation causing increased capillary permeability, impaired drainage by lymphatics, or both.

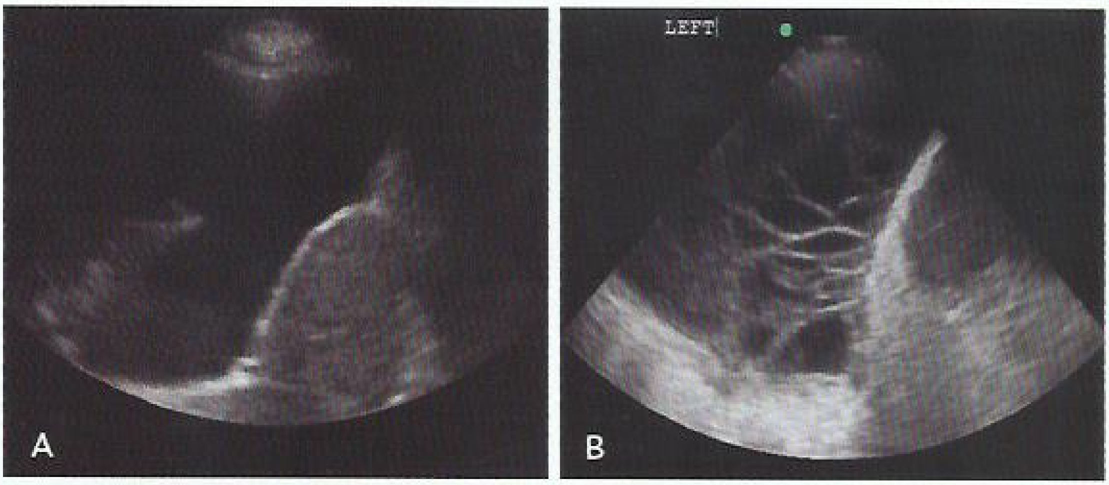

FIGURE 10. Comparison of a simple (*A*) and complicated (*B*) pleural effusion on thoracic ultrasound. A hypoechoic effusion (*A*) may be transudate or exudate. A multi-septated (loculated) effusion (*B*) is exudate.

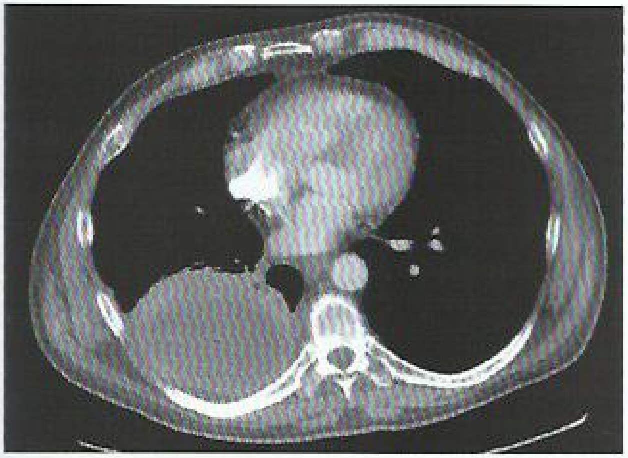

FIGURE 11. CT imaging reveals an empyema, as enhancement of the pleura around the fluid creates a lenticular-shaped opacity.

H CONT.

There are many causes of exudative effusions but the most common are infection and malignancy. Differentiation is commonly made using Light's criteria, based on the levels of lactate dehydrogenase and total protein in both serum and pleural fluid (**Table 21**). However, a recent review also found that checking pleural fluid cholesterol was an accurate method for classifying the effusion as an exudate. Exudative and transudative effusions have a wide range of causes (**Table 22**).

In addition to characterizing a pleural effusion as a transudate or exudate, other tests are often performed depending on clinical suspicion. If infection is suspected then pH, glucose, cell count, Gram stain, and aerobic and anaerobic cultures should also be performed. If malignancy is suspected, then cytological analysis of fluid should be performed.

TABLE 20. Pleural Fluid Characteristics and Diagnostic Considerations

Appearance	Possible Cause	Additional Tests to Perform
Bloody	Malignancy, pulmonary embolus, trauma, pneumonia, benign asbestos pleural effusion	Hematocrit If >50% of the serum, it is a hemothorax; consider aortic rupture, myocardial rupture, and injuries to hilar structures, lung parenchyma, and intercostal vessels
Milky	Chylothorax or cholesterol effusion	Triglyceride level
Yellow-green	Rheumatoid pleurisy	Serum rheumatoid factor Pleural fluid glucose <60 mg/dL (3.33 mmol/L)
Dark green	Bilothorax	Bilirubin
Dark brown/black	Long-standing hemothorax, fungal infection, malignancy	Hematocrit, cytology, fungal cultures
Purulent	Empyema	Aerobic and anaerobic cultures

TABLE 21. Criteria for Exudative Pleural Effusion

Test	Sensitivity (%)	Specificity (%)
Combined Light's criteria (1 or more of the following 3):	97	85
Ratio of pleural-fluid protein to serum protein level >0.5	90	90
Ratio of pleural-fluid LDH level to serum LDH level >0.6	88	91
Pleural-fluid LDH level >2/3 the upper limit of normal for serum LDH	88-89	93-100
Pleural fluid cholesterol level >55 mg/dL	85-94	95-99
Ratio of pleural-fluid cholesterol to serum cholesterol >0.3	93	94

LDH = lactate dehydrogenase.

Data from Wilcox MF, Chong CA, Stanbrook MB, Tricco AC, Wong C, Straus SE. Does this patient have an exudative pleural effusion? The Rational Clinical Examination systematic review. JAMA. 2014;311:2422-31. [PMID: 24938565] doi:10.1001/jama.2014.5552

TABLE 22. Causes of Transudates and Exudates

Transudates	Exudates
Very Common	**Very Common**
Heart failure	Parapneumonic
Cirrhosis	Malignancy
Less Common	**Less Common**
Nephrotic syndrome	Pulmonary embolism
Hypoalbuminemia	Tuberculosis
Unexpandable (trapped) lung	Autoimmune diseases (RA, SLE)
Peritoneal dialysis	Benign asbestos effusion
Atelectasis	Post-coronary artery bypass
Urinothorax	Pancreatitis
Constrictive pericarditis	Post-myocardial infarction
Meigs syndrome (ovarian fibroma with ascites)	Yellow nail syndrome (lymphatic disorders)
	Drugs

RA = rheumatoid arthritis; SLE = systemic lupus erythematosus.

H CONT.

Cell Counts and Differential

Cell counts are useful for determining the cause of a pleural effusion; however, they are not disease-specific. Neutrophil-predominant effusions are secondary to an acute process such as pneumonia (parapneumonic effusion) or pulmonary embolus. Lymphocyte predominance (more than 50%) is common in chronic effusions. The most common causes worldwide of lymphocyte-predominant effusions are tuberculosis and cancer. An eosinophilic effusion of greater than 10% is most commonly due to current or recent air or blood in the pleural space and is a nonspecific finding (**Table 23**).

Chemical Analysis

Pleural fluid acidosis (pH less than 7.3) is nonspecific and occurs in malignant effusions, complicated parapneumonic effusions, esophageal rupture, and inflammatory conditions such as rheumatoid and lupus pleuritis. Clinically, pH is most useful if an infection is suspected. A pH less than 7.2 in a parapneumonic effusion indicates a complicated pleural effusion is present and tube thoracostomy drainage is needed. Glucose normally diffuses freely across the pleural membrane. A pleural glucose concentration of less than 60 mg/dL (3.33 mmol/L) narrows the differential significantly and suggests that the effusion is secondary to malignancy, empyema or complicated parapneumonic effusion, tuberculosis, esophageal rupture, or rheumatoid or lupus pleuritis.

Pleural fluid amylase concentration should be checked if there is concern that the effusion may be due to pancreatitis or esophageal rupture. Pleural fluid amylase greater than the upper limit of normal for serum amylase, or a pleural fluid to serum amylase ratio greater than 1.0, is indicative of pancreatitis or esophageal rupture.

Pleural fluid triglycerides elevated above 110 mg/dL (1.24 mmol/L) support the diagnosis of chylothorax. If the triglyceride level is between 50 and 110 mg/dL (0.56 and 1.24 mmol/L), chylomicrons should be checked. A true chylothorax results from a disruption of the thoracic duct and is usually the result of thoracic surgery or trauma. Other causes include malignancy (lymphoma), tuberculosis, and lymphatic malformations.

Tests for Tuberculous Effusions

The diagnosis of tuberculosis should be considered in a patient with a lymphocyte-predominant exudative effusion of unclear cause; however, confirming the diagnosis may be challenging. An acid-fast smear of pleural fluid has a sensitivity of less than 5%, and mycobacterial culture has a sensitivity of only 10% to 20% due to the low mycobacterial load. Adenosine deaminase (ADA) is an enzyme present in lymphocytes that is elevated in most tuberculous pleural effusions (sensitivity 90%). In countries with a low incidence of tuberculosis, testing for ADA can be useful, as a negative test helps exclude tuberculosis. Pleural biopsy is useful for histology and is also the most likely source to yield a positive mycobacterial culture (greater than 70%).

TABLE 23. Pleural Cell Counts and Clinical Conditions

Cell Type	Cell Count	Clinical Conditions
Erythrocyte	5000-10,000/µL (5-10 × 10^9/L)	Hemothorax if pleural fluid hematocrit >50% peripheral hematocrit
Nucleated cells	>50,000/µL (50 × 10^9/L)	Complicated parapneumonic effusions and empyema
	>10,000/µL (10 × 10^9/L)	Simple parapneumonic effusion, acute pancreatitis and lupus pleuritis
	<5000/µL (5 × 10^9/L)	Chronic exudates (TB pleuritis and malignancy)
Lymphocytes	>80%	TB, lymphoma, malignancy, RA pleuritis, sarcoidosis, late post-CABG effusions
Eosinophils	>10%	Air or blood in the pleural space. Also parapneumonic effusions, drug-induced pleuritis, eosinophilic granulomatosis with polyangiitis, benign asbestos effusions, malignancy (lymphoma), pulmonary infarction, parasitic disease

CABG = coronary artery bypass graft; RA = rheumatoid arthritis; TB = tuberculosis.

Tests for Pleural Malignancy

Cytologic examination of pleural fluid has an average sensitivity of 60%. This is slightly higher in adenocarcinoma and lower in mesothelioma, squamous cell carcinoma, and lymphoma. There is minimal benefit for obtaining and sending more than two fluid samples. If cytology is negative and malignancy is still suspected, thoracoscopy may be the next step in evaluation. This procedure allows for the direct visualization and biopsy of the pleural surface and has a diagnostic sensitivity for malignant disease of greater than 90%. Closed pleural biopsy provides only a random sample of pleural tissue without visualization of pleural abnormalities. It is less sensitive than fluid cytology and has been replaced by thoracoscopy in the diagnostic evaluation of pleural malignancy.

Management

Parapneumonic Effusions and Empyema

A pleural effusion associated with a bacterial pneumonia is called a parapneumonic effusion. It can be uncomplicated (sterile and free-flowing) or complicated (either infected or loculated). Uncomplicated effusions are typically small and resolve on their own with treatment of the pneumonia. Complicated parapneumonic effusions occur with significant inflammation or when bacteria invade the pleural space. An empyema is defined as a bacterial infection of the pleural space, which results in purulent fluid or a positive Gram stain. Pleural fluid cultures identify pathogens in only 60% of cases. If infection is suspected, culture bottles should be inoculated at the bedside to increase yield. Any pleural effusion greater than 10 mm in depth on lateral decubitus radiograph and associated with a pneumonic illness should be sampled with a diagnostic thoracentesis. Drainage is required if there is a positive Gram stain or culture, or when the pH is less than 7.2. The bacteriology of pleural space infection differs depending on if it is community-acquired or hospital-acquired. In the community, *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Staphylococcus aureus*, and *Streptococcus anginosus* group are the organisms typically associated with pleural infection. Methicillin-resistant *Staphylococcus aureus* and *Enterobacteriaceae* are more prevalent in nosocomial empyema. Anaerobic bacteria are cultured in greater than 20% of pleural-space infections and may be due to the common association with aspiration or the anaerobic environment of the pleural space. Polymicrobial infections are common, and empiric antibiotic regimens before obtaining culture results should include coverage for anaerobes.

Complicated parapneumonic effusions and empyema require drainage. The combined use of intrapleural fibrinolytics (streptokinase, urokinase, tissue plasminogen activator) and a mucolytic agent (deoxyribonuclease, or DNase) has demonstrated utility in decreasing the size of the effusion and lowering the rate of surgical referral for definitive treatment. The size of drainage tube needed to best manage pleural-space infection remains controversial, but several studies have demonstrated equal efficacy and improved patient comfort with the use of smaller (10 to 14 Fr) thoracostomy tubes. Effusions due to infection refractory to antibiotics and drainage require surgical debridement.

Malignant Pleural Effusion

The diagnosis of a malignant pleural effusion signifies advanced disease and overall poor prognosis. As a result the goal of management is the relief of symptoms. Several therapeutic options exist, and treatment decisions should be based on symptoms, prognosis, degree of anticipated lung re-expansion, and patient performance status. Repeat therapeutic thoracentesis is appropriate for patients with poor prognosis (less than 3 months) and slow re-accumulation of fluid. Patients with rapid re-accumulation of fluid and dyspnea should be offered more definitive management. Indwelling pleural catheters with intermittent outpatient drainage provide significant symptom relief, and 50% to 70% of patients achieve spontaneous pleurodesis after 2 to 6 weeks. Chemical pleurodesis refers to obliteration of the pleural space with a sclerosing agent (typically talc). Talc can be introduced through a thoracostomy tube (talc slurry) or during a thoracoscopy (talc poudrage). Talc pleurodesis is very effective, with a success rate of 60% to 90% depending on the degree of lung re-expansion. Pleurectomy and pleuroperitoneal shunt are other management options but are rarely performed.

Pneumothorax

Evaluation

Air in the pleural space is defined as a pneumothorax, which can occur spontaneously or as a result of trauma or a procedural complication. A primary spontaneous pneumothorax (PSP) occurs in someone without known underlying lung disease. A secondary spontaneous pneumothorax (SSP) occurs in someone with known underlying lung disease, such as COPD. Risk of recurrence for PSP is 23% to 50% over 1 to 5 years, and greater than 50% over 1 to 3 years in those with SSP. Risk factors for pneumothorax are listed in **Table 24**.

Symptoms include the sudden onset of dyspnea and sharp pleuritic chest pain. The symptoms are typically more severe with SSP, as patients have less respiratory reserve. Physical examination findings can be subtle but usually reveal reduced lung expansion, hyperresonance to percussion, and diminished breath sounds on the side of the pneumothorax. Tension pneumothorax should be suspected in patients presenting with significant cardiorespiratory distress (worsening dyspnea, hypotension, absent breath sounds on one side, tracheal deviation, and distended neck veins).

A chest radiograph is an appropriate initial test and can confirm the diagnosis and determine the size of the pneumothorax. If the lung margin is greater than 2 cm away from the chest wall at the level of the hilum, it is considered a large pneumothorax. A CT scan is the most sensitive imaging modality for small pneumothoraces and is particularly useful in patients with bullous emphysema.

Management

Management of pneumothorax is driven by clinical symptoms. A tension pneumothorax (large and hemodynamically significant) should be managed by emergent needle thoracostomy followed by thoracostomy tube placement and hospitalization. Observation alone has been shown to be safe for small pneumothoraces in patients with minimal symptoms (**Table 25**).

Recurrence prevention is recommended after the second episode of pneumothorax on the ipsilateral side in PSP and after the first occurrence in SSP. Patients should be encouraged to stop smoking, as the lifetime incidence rates for PSP are much higher in men who are lifelong heavy smokers than men who have never smoked (12% vs 0.1%). Intervention to prevent recurrence includes both chemical and mechanical pleurodesis. Air travel should be avoided until complete resolution of the pneumothorax, and scuba diving is not recommended unless definitive therapy, such as surgical pleurectomy, has been applied.

TABLE 24. Risk Factors for Pneumothorax

Risk Factors for PSP
Smoking
Family history
Thoracic endometriosis
Tall stature
Risk Factors for SSP
COPD
Interstitial lung disease
Tuberculosis
Cystic fibrosis
Malignancy
Necrotizing pneumonia
Marfan syndrome

PSP = primary spontaneous pneumothorax; SSP = secondary spontaneous pneumothorax.

Pulmonary Vascular Disease

Pulmonary Hypertension

Pulmonary hypertension (PH) is defined as a resting mean pulmonary artery pressure of 25 mm Hg or greater measured during right heart catheterization. The normal mean pulmonary artery pressure is less than 20 mm Hg. Untreated PH eventually leads to right ventricular failure and may directly contribute to death; however, the rate of progression is highly variable and dependent upon the origin of disease and comorbidities.

The current classification system subdivides PH into five groups, which are based on similarities in mechanisms, hemodynamics, clinical presentation, and approach to treatment (**Table 26**).

TABLE 25. Management of Pneumothorax

Size[a] and Clinical Symptoms	Management
<2 cm on chest radiograph, minimal symptoms	Admit to hospital for observation and supplemental oxygen (PSP may be managed as an outpatient if good access to medical care)
>2 cm on chest radiograph, breathlessness, and chest pain	Insertion of a small-bore (<14 Fr) thoracostomy tube with connection to a high-volume low-pressure suction system
Cardiovascular compromise (hypotension, increasing breathlessness) regardless of size	Emergent needle decompression followed by thoracostomy tube insertion
	Note: If persistent air leak (>48 hours) refer to a thoracic surgeon

[a]Measured between lung and chest wall

PSP = primary spontaneous pneumothorax.

TABLE 26. Classification of Pulmonary Hypertension

1	Pulmonary arterial hypertension (includes idiopathic and heritable, and disease related to drugs and toxins, connective tissue diseases, HIV infection, schistosomiasis, and portal hypertension)
2	Pulmonary hypertension due to left-sided heart disease
3	Pulmonary hypertension due to lung diseases and/or hypoxia
4	Chronic thromboembolic pulmonary hypertension and other pulmonary artery obstructions
5	Pulmonary hypertension with unclear or multifactorial causes

Data from Simonneau G, Gatzoulis MA, Adatia I, Celermajer D, Denton C, Ghofrani A, et al. Updated clinical classification of pulmonary hypertension. J Am Coll Cardiol. 2013;62:D34-41. [PMID: 24355639] doi:10.1016/j.jacc.2013.10.029

KEY POINT

- Pulmonary hypertension is defined as a resting mean pulmonary artery pressure of 25 mm Hg or greater measured during right heart catheterization.

Pathophysiology

Most cases of PH are caused by left-sided heart disease (group 2) and hypoxic respiratory disorders (group 3). Left-sided heart disease (heart failure with reduced or preserved ejection fraction, valvular disease) results in elevations in left atrial and pulmonary venous pressures. Chronic hypoxia is probably the primary contributor to PH in advanced respiratory disorders such as COPD, interstitial lung disease, and sleep hypoventilation syndromes; obliteration of the vascular bed in emphysema also contributes. Regardless of the underlying causes or disease associations, untreated PH is usually progressive, eventually leading to vascular remodeling and right ventricular hypertrophy and dilatation. PH is often a risk factor for death in patients with group 2 and 3 disease, and may be directly contributory in death due to right ventricular ischemia, arrhythmias, or heart failure.

KEY POINT

- Most cases of pulmonary hypertension are secondary and caused by left-sided heart disease and hypoxic respiratory disorders.

Diagnosis

Because early symptoms of PH (exertional dyspnea and fatigue) are nonspecific and may be attributed to an underlying disorder such as heart failure or lung disease, a high index of suspicion can help identify PH in its earlier stages. Progressive disease, eventually resulting in right ventricular impairment, is associated with symptoms of exertional chest pain, syncope, and edema. Findings on physical examination depend on the severity of disease. An early sign is a prominent S_2; an audible split eventually widens. A prominent jugular venous *a* wave and a parasternal heave reflect right ventricular hypertrophy. As the right ventricle dilates, a holosystolic tricuspid regurgitant murmur may be detected. Right ventricular failure leads to jugular venous distention, hepatomegaly, ascites, and peripheral edema. Pulmonary findings reflect underlying lung disease.

Enlarged central pulmonary arteries with peripheral pruning, along with a prominent right ventricle detectable on the lateral view on chest radiograph, are suggestive of PH (**Figure 12**). If PH is suspected, transthoracic echocardiography should be performed, as it allows an estimation of pulmonary arterial systolic pressure and assessment of both right and left heart size and function. However, echocardiography does not confirm the diagnosis because the estimation of true pulmonary artery pressure may be inaccurate. Right heart catheterization confirms the diagnosis of PH and is typically an essential component of the diagnostic evaluation, although it may be deferred in certain situations, such as in patients whose PH is attributable to advanced lung disease such as COPD.

Once PH is confirmed, further testing, guided by clinical history, helps determine underlying causes and important comorbid conditions. Left heart catheterization can assess the coronary arteries if ischemic cardiomyopathy is suspected. Additional diagnostics may include pulmonary function tests, high-resolution CT if interstitial lung disease is a consideration, and tests for nocturnal hypoxemia. Abnormal overnight pulse oximetry to detect nocturnal hypoxemia followed by polysomnography to characterize the cause can identify sleep-related breathing disorders as a cause of PH. Assessment of functional status with the 6-minute walk test should be performed to provide prognostic information and to determine a baseline for assessment of therapeutic response.

KEY POINTS

- If pulmonary hypertension is suspected, echocardiography should be performed, as it allows an estimation of pulmonary arterial systolic pressure and assessment of both right and left heart size and function.
- Right heart catheterization confirms the diagnosis of pulmonary hypertension and is an essential component of the diagnostic evaluation.

Treatment of Pulmonary Hypertension

Therapy for patients with groups 2, 3, and 5 PH is directed at the underlying condition. Optimization of treatment of underlying left ventricular systolic and diastolic function and valvular disease is appropriate. COPD should be managed in a stepwise fashion. For a discussion of treatment of COPD, see Airways Disease. Supplemental oxygen for hypoxemia due to underlying lung disease causing PH may provide mortality benefit. Positive airway pressure therapy may be indicated for sleep-disordered breathing and hypoventilation syndromes. The use of advanced vasodilator therapy in groups 2 through 5 PH can be considered on a patient-by-patient basis. Treatment with such pulmonary vasodilators, however, may be harmful in patients with PH due to left ventricular dysfunction (group 2)

FIGURE 12. Posteroanterior chest radiograph (*left*) of a woman with pulmonary arterial hypertension showing right atrial dilatation (straightening of the right heart border), pulmonary artery enlargement, attenuation ("pruning") of the peripheral vessels, and oligemic lung fields. The lateral chest radiograph (*right*) demonstrates diminished retrosternal airspace, a sign of right ventricular hypertrophy.

or lung disease (group 3) because of the potential to overload a compromised left ventricle and to worsen ventilation perfusion (V/Q) mismatching, respectively.

KEY POINTS

- Therapy for patients with pulmonary hypertension caused by left-sided heart disease, lung diseases, or hypoxia, is typically directed at the underlying condition.
- Treatment with pulmonary vasodilators may be harmful in patients with pulmonary hypertension due to left ventricular dysfunction or lung disease because of the potential to overload a compromised left ventricle and to worsen ventilation-perfusion mismatching, respectively.

Chronic Thromboembolic Pulmonary Hypertension (Group 4)

Progressive exertional dyspnea is the most common symptom of chronic thromboembolic pulmonary hypertension (CTEPH). Less than 5% of patients who experience an acute pulmonary embolism (PE) develop CTEPH. Greater than 25% of patients diagnosed with CTEPH do not have a documented history of PE. For further discussion of pulmonary embolism, see MKSAP 18 Hematology and Oncology. In patients with CTEPH, the organized thrombus is incorporated into the pulmonary arterial endothelium, increasing pulmonary vascular resistance and pressures, eventually leading to right-sided heart failure. Such patients are only occasionally diagnosed with an underlying hypercoagulable state.

Diagnosis

Because PE (acute or previous) isn't always evident, CTEPH remains an underrecognized cause of PH and requires a high index of suspicion. The diagnosis is made in the setting of PH in the absence of left heart pressure overload accompanied by imaging evidence of chronic thromboembolism.

Ventilation/perfusion scanning is the most sensitive indicator of CTEPH and should be performed in all patients in whom the diagnosis is suspected. CT pulmonary angiography (CT-PA), which is often performed in the evaluation of a dyspneic patient, may demonstrate proximally located vascular abnormalities such as webs, intimal irregularities, and luminal narrowing, but may be less sensitive for more distal lesions. Conventional pulmonary angiography is used to best characterize the extent and distribution of organized thrombus to determine suitability for surgical intervention.

KEY POINTS

- The diagnosis of chronic thromboembolic pulmonary hypertension is made in the setting of pulmonary hypertension in the absence of left heart pressure overload accompanied by imaging evidence of chronic thromboembolism.

(Continued)

KEY POINTS *(continued)*

- Ventilation/perfusion scanning is the most sensitive indicator of chronic thromboembolic pulmonary hypertension and should be performed in all patients in whom the diagnosis is suspected.

Management

Anticoagulation and consideration of thromboendarterectomy are indicated for CTEPH. Lifelong anticoagulant therapy is indicated in all patients to help prevent further thromboembolism. The only potentially curative therapy for CTEPH is pulmonary thromboendarterectomy. Because the disease usually irreversibly progresses, surgical evaluation at an experienced center is warranted in all patients with CTEPH regardless of disease severity. About half of patients with CTEPH will be eligible for surgery; a proportion will opt for the operation. Pulmonary thromboendarterectomy can result in normalization of pulmonary hemodynamics in about one-third of patients who undergo surgery. Riociguat, an advanced therapy vasodilator, may be used in those who are not candidates for surgery or have persistent PH following surgery. The role of inferior vena cava filters in patients with a coexisting clot in the lower extremities is controversial, and its effect on long-term outcomes is not known.

KEY POINT

- Lifelong anticoagulation and consideration of thromboendarterectomy are indicated for chronic thromboembolic pulmonary hypertension.

H Pulmonary Arterial Hypertension

Pulmonary arterial hypertension (PAH) is caused by changes in the small pulmonary arterioles resulting in high pulmonary vascular resistance. PAH is defined by a proliferative vasculopathy originating in the pulmonary arteriolar bed, with pathophysiologic contributions from endothelial cell proliferation, vasoconstriction, and in situ thrombosis. Imbalances in nitric oxide, prostacyclin, and endothelin that affect vascular tone and endothelial and smooth muscle cellular growth drive the process and are targets for currently available therapy. PAH is classified as idiopathic (previously referred to as primary pulmonary hypertension), heritable, or associated with drugs, toxins, or other conditions.

Idiopathic PAH is typically seen in younger adults, particularly women. Heritable forms account for less than 10% of cases of PAH, with the majority due to mutations in bone morphogenetic protein receptor type 2 (*BMPR2*). Mutations in *BMPR2*, a gene related to the apoptotic process, might explain the propensity for cellular proliferation in PAH. Although otherwise clinically indistinguishable from sporadic disease, those with heritable PAH may have a worse prognosis.

PAH is most commonly associated with connective tissue diseases, portal hypertension, HIV infection, drug use, and toxin exposure.

In connective tissue disease, PAH is classically seen in systemic sclerosis, where it is a leading cause of death. Patients with limited cutaneous disease in association with CREST syndrome (calcinosis cutis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia) may be at highest risk. PAH can also be seen in rheumatoid arthritis and systemic lupus erythematosus.

Portopulmonary hypertension affects some patients who have chronic liver disease (see MKSAP 18 Gastroenterology and Hepatology). The mechanism may relate to the diseased liver's inability to clear vasoactive substances.

PAH in patients with HIV infection is not common, but HIV-infected patients have an approximately 10-fold higher risk of PAH compared with patients without HIV infection. Both viral and host factors have been implicated, and disease can occur in the absence of AIDS-related complications.

The drugs most strongly associated with PAH are the anorectics, including fenfluramine, phentermine, and dexfenfluramine. The tyrosine kinase inhibitors dasatinib and imatinib have been implicated, as well as interferon alfa. There is an increasing association between PAH and illicit drugs such as methamphetamine and cocaine. H

KEY POINT

- Pulmonary arterial hypertension is most commonly associated with connective tissue diseases, portal hypertension, HIV infection, drug use, and toxin exposure.

Diagnosis

H

The diagnosis of PAH requires confirmation of high pulmonary vascular resistance as well as a normal pulmonary capillary wedge pressure to exclude left-sided heart disease. During right heart catheterization, vasoreactivity testing can help guide subsequent therapy (see below). Lung biopsy poses a significant risk in PAH and is not indicated in the diagnostic evaluation. The role of genetic testing is yet to be defined. Laboratory studies to investigate underlying cause of PAH depend on the clinical situation and may include HIV serologies, tests of liver function, and autoantibody titers. H

KEY POINT

- The diagnosis of pulmonary arterial hypertension requires confirmation of high pulmonary vascular resistance as well as a normal pulmonary capillary wedge pressure to exclude left-sided heart disease.

Treatment

Therapy for PAH is directed at PH itself, referred to as "advanced therapy." These vascular-targeted treatments are directed at reducing vasoconstriction and interrupting the pathways mediating cellular proliferation. Use of advanced agents may be guided by disease severity (**Table 27**). Before administering advanced therapy for patients with PAH, vasoreactivity testing with nitric oxide is performed to identify those who may respond to calcium channel blockers. Calcium channel

TABLE 27. Pharmacologic Therapy for Pulmonary Arterial Hypertension

Class	Comments
Calcium channel blockers	Only for patients with acute vasodilator response at catheterization; acute response does not assure chronic response; side effects such as hypotension can occur.
Prostanoids (epoprostenol, treprostinil, iloprost)	Parenteral prostacyclin analogues such as epoprostenol, administered by a continuous central venous infusion, are first-line therapy for severe disease and for those in whom disease progresses despite oral therapy; inhaled iloprost requires frequent administration; prostanoids supplement endogenous levels of prostacyclin (PGI_2), a vasodilator with antismooth muscle proliferative properties.
Endothelin-1 receptor antagonists (bosentan, ambrisentan)	Reasonable initial oral therapies for mild to moderate disease. Blocks action of endogenous vasoconstrictor and smooth muscle mitogen endothelin; class-wide risk of liver injury and teratogenicity; liver chemistry testing and pregnancy testing for reproductive-aged women are required[a].
Phosphodiesterase-5 inhibitors (sildenafil, tadalafil)	Reasonable initial oral therapies for mild to moderate disease. Prolongs effect of intrinsic vasodilator cyclic GMP by inhibiting hydrolysis by phosphodiesterase-5.

GMP = guanosine monophosphate.

[a]Although not required for ambrisentan, some experts suggest that it is prudent to perform liver chemistry tests at the outset of treatment for pulmonary arterial hypertension and at periodic intervals thereafter at the discretion of the managing physician.

blockers are desirable therapy because they are less expensive and have fewer side effects than other forms of advanced therapy. Failure to achieve a favorable hemodynamic response with nitric oxide predicts unresponsiveness to calcium channel blockers and the need for other advanced therapy. Given the complexity of management, the increasing number of drugs available to treat PAH, and cost, these patients are best managed by specialists at a center experienced with PAH management.

Additional treatments include diuretic therapy to combat volume overload and supplemental oxygen for hypoxemia at rest or with exercise. Women of reproductive age who have PAH should be counseled on the risks of pregnancy; most specialists would advise against pregnancy. Because PAH predisposes patients to in-situ pulmonary vascular thrombosis and embolism, anticoagulation is often prescribed. Experience with direct oral anticoagulants in this setting is limited; therefore, warfarin remains the agent of choice. Digoxin might be used to improve right ventricular function or as a rate-control adjunct for supraventricular dysrhythmias or atrial fibrillation. Supervised exercise training has been shown to improve functional capacity. Lung or heart-lung transplantation should be considered for patients in whom drug treatment is unsuccessful.

KEY POINTS

- Therapy for pulmonary arterial hypertension is directed at pulmonary hypertension itself, referred to as *advanced therapy*, and is best managed by specialists at a center experienced with pulmonary arterial hypertension management.
- Before administering advanced therapy for patients with pulmonary arterial hypertension, vasoreactivity testing with nitric oxide is performed to identify those who may respond to calcium channel blockers.

Lung Tumors

Pulmonary Nodule Evaluation

Pulmonary nodules are small rounded radiographic opacities that are less than 3 cm in size. A solitary pulmonary nodule is a nodule completely surrounded by aerated lung and not associated with atelectasis, hilar enlargement, or pleural effusion. These nodules are usually asymptomatic and found either incidentally or on screening. In contrast, a focal pulmonary opacity larger than 3 cm is considered a lung mass and is presumed malignant until proved otherwise.

The finding of a pulmonary nodule is increasingly common because of the frequency of CT scans done for other reasons, as well as lung cancer screening programs. Management of these lesions can be complicated and often requires subspecialty referral. Principles of pulmonary nodule evaluation include the review of imaging history, estimating the probability of malignancy, performing functional imaging tests (PET scan) to further characterize the nodule, and discussing management preferences with the patient. Guidelines recommend management based on nodule size and characteristics. When more than one nodule is present, follow-up is dictated by the size and characteristics of the largest lesion. Shared decision making is an integral part of the evaluation and management of pulmonary nodules.

KEY POINTS

- Principles of pulmonary nodule evaluation include the review of imaging history, estimating the probability of malignancy, performing functional imaging tests to further characterize the nodule, and discussing management preferences with the patient.
- A focal pulmonary opacity larger than 3 cm are presumed malignant until proved otherwise.

Solid Indeterminate Nodule Larger Than 8 mm

The first step in evaluating a solid nodule that is larger than 8 mm in size is to estimate the probability of malignancy. Criteria included in the calculation include age, smoking

history, nodule size, location within the lung, and presence of spiculated or lobular border (https://brocku.ca/lung-cancer-screening-and-risk-prediction/risk-calculators/). Solid nodules with low to moderate probability of malignancy should be characterized further with a PET scan. If the PET scan is negative for metabolic activity, continued surveillance is warranted (**Table 28**). A nodule with moderate or intense uptake is suggestive of malignancy and requires further evaluation, including complete staging followed by surgical resection or chemotherapy and radiation, for definitive management.

If the probability of malignancy is initially high, the next step is staging with a PET scan followed by definitive management with surgical resection or chemotherapy and radiation.

TABLE 28. Fleischner Society Recommendations for Single Pulmonary Nodule Follow-Up

Risk Factors for Lung Cancer?	Size	Recommended Follow-Up
No (Low-risk patient)	<6 mm	No follow-up
	6-8 mm	CT at 6-12 months then consider CT at 18-24 months
	>8 mm	Consider CT at 3 months, PET/CT, or tissue sampling
Yes (High-risk patient)	<6 mm	Optional CT at 12 months
	6-8 mm	CT at 6-12 months then CT at 18-24 months
	>8 mm	Consider CT at 3 months, PET/CT, or tissue sampling

Data from MacMahon H, Naidich DP, Goo JM, Lee KS, Leung ANC, Mayo JR, et al. Guidelines for management of incidental pulmonary nodules detected on CT images: From the Fleischner Society 2017. Radiology. 2017;284:228-243. [PMID: 28240562] doi:10.1148/radiol.2017161659

KEY POINT

- The first step in evaluating a solid pulmonary nodule larger than 8 mm in size is to estimate the probability of malignancy.

Solid Indeterminate Nodule of 8 mm or Smaller

Solid indeterminate nodules of 8 mm or smaller are usually detected incidentally. The first step as with larger nodules is an estimation of the likelihood of malignancy (https://brocku.ca/lung-cancer-screening-and-risk-prediction/risk-calculators/). Nodules of 8 mm or smaller have a lower probability of being malignant, are difficult to biopsy, and are not reliably characterized by PET scan. As a result, these small nodules are usually followed by serial CT scans. The frequency and duration of follow-up is based on the recommendations of the Fleischner Society and endorsed by other professional societies (see Table 28).

Subsolid Nodule

A subsolid nodule is a focal rounded opacity that is either pure ground glass in appearance (focal density with underlying lung architecture still preserved) or has a solid component (part solid) but is still more than 50% ground glass (**Figure 13**). These nodules often represent premalignant disease, such as adenocarcinoma in situ, and can be very slow growing. Observed growth rates for subsolid nodules can range between 400 to 800 days. This has implications for both the frequency and duration of follow-up. Subsolid nodules are not reliably characterized by PET scans and nonsurgical biopsies also have limited sensitivity. Development of a solid component in a pure ground-glass nodule or enlargement of the solid component suggests malignancy (see Figure 13). Recommendations for nonsolid and part-solid nodule follow-up are in **Table 29**.

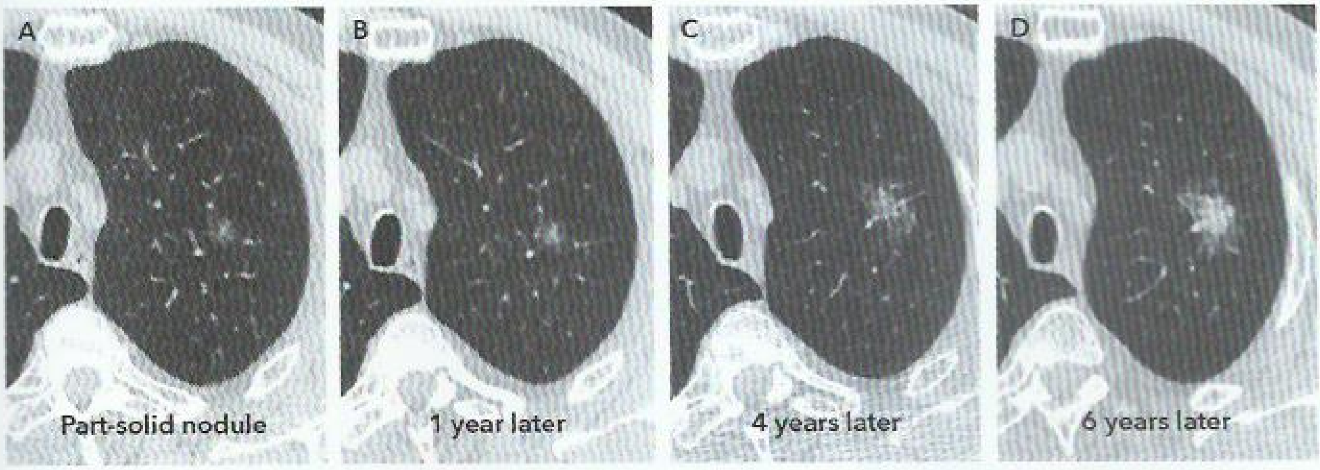

FIGURE 13. Radiographs show the evolution of a part-solid nodule from adenocarcinoma in situ to invasive adenocarcinoma: part-solid, part-ground-glass nodule in the left upper lobe (*A*); growth in the solid component of the nodule 1 year after initial imaging (*B*); an increase in size in the ground-glass component 4 years after initial imaging (*C*); and further increase in the solid component of the nodule 6 years after initial imaging (*D*). This growth rate is characteristic of a part-solid, part-ground-glass nodule and demonstrates why patients with this finding must be followed for at least 5 years.

TABLE 29. Fleischner Society Recommendations for Follow-Up of Solitary Subsolid Lung Nodule

Imaging Findings	Size	Recommended Follow-Up
Pure ground glass	<6 mm	No follow-up
	≥6 mm	CT at 6-12 months to confirm persistence, then CT every 2 years until 5 years
Part solid nodule	<6 mm	No follow-up
	≥6 mm	CT at 3-6 months to confirm persistence. If unchanged and solid component remains <6 mm, annual CT should be performed for 5 years

Data from MacMahon H, Naidich DP, Goo JM, Lee KS, Leung ANC, Mayo JR, et al. Guidelines for Management of Incidental Pulmonary Nodules Detected on CT Images: From the Fleischner Society 2017. Radiology. 2017;284:228-243. [PMID: 28240562] doi:10.1148/radiol.2017161659

Lung Cancer

Lung cancer is the leading cause of cancer death worldwide. In the United States, it is estimated that 225,000 new cases will be diagnosed and more than 160,000 deaths occur each year. The overall 5-year survival rate remains low at 17.7%. However, much progress has been made recently regarding screening, diagnosis, and treatment.

KEY POINT

- Lung cancer is the leading cause of cancer death world wide, with an estimated 225,000 new cases and more than 160,000 deaths each year.

H Lung Cancer Types

There are two major classes of lung cancer: non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). NSCLC accounts for most lung cancer cases (80%) and is divided into adenocarcinoma, squamous cell carcinoma, and large cell carcinoma. Adenocarcinoma is the most common NSCLC and accounts for almost all lung cancer diagnoses in nonsmokers. The most frequent location of adenocarcinoma is in the peripheral aspects of the lung parenchyma as a solitary nodule or mass. Squamous cell carcinoma is the second most common subtype of NSCLC. It correlates highly with smoking history and usually originates in the central airways (trachea, main stem bronchi, lobar and segmental bronchi) (**Figure 14**). Individuals with squamous cell carcinoma often have symptoms of cough and hemoptysis due to central airway involvement. Radiographically, squamous cell carcinoma may present with postobstructive pneumonia or lobar collapse. Large cell carcinoma is an undifferentiated carcinoma and characteristically presents as a peripheral mass with prominent necrosis (**Figure 15**).

In the past decade the development of targeted therapy for specific gene mutations has revolutionized the treatment of lung cancer. The separation of adenocarcinoma and squamous cell carcinoma is important for determining the optimal therapy. Testing for epidermal growth factor receptor (*EGFR*) mutation, anaplastic lymphoma kinase receptor tyrosine kinase (*ALK*) translocation, and ROS proto-oncogene 1 receptor tyrosine kinase (*ROS1*) translocation is recommended in advanced-stage adenocarcinoma or mixed cancers. Targeted treatment has resulted in better responses than standard chemotherapy.

SCLC accounts for about 15% of all lung cancers. It is the most strongly associated with cigarette smoking and typically occurs adjacent to the central airways with extensive lymphadenopathy and distant metastasis at diagnosis. Imaging commonly shows a large mediastinal mass that encompasses lymph nodes with an uncertain primary site of origin (**Figure 16**). Paraneoplastic syndromes are most commonly associated with SCLC, including hyponatremia due to the syndrome of inappropriate antidiuretic hormone secretion (rare in other lung tumors), hypertrophic pulmonary osteoarthropathy, inflammatory myopathies, Cushing syndrome caused by ectopic adrenocorticotropic hormone secretion, and other hematologic and neurologic syndromes. H

KEY POINTS

- There are two major classes of lung cancer: non-small cell lung cancer and small cell lung cancer; non-small cell lung cancer accounts for 80% of lung cancers and is divided into adenocarcinoma, squamous cell carcinoma, and large cell carcinoma.

(Continued)

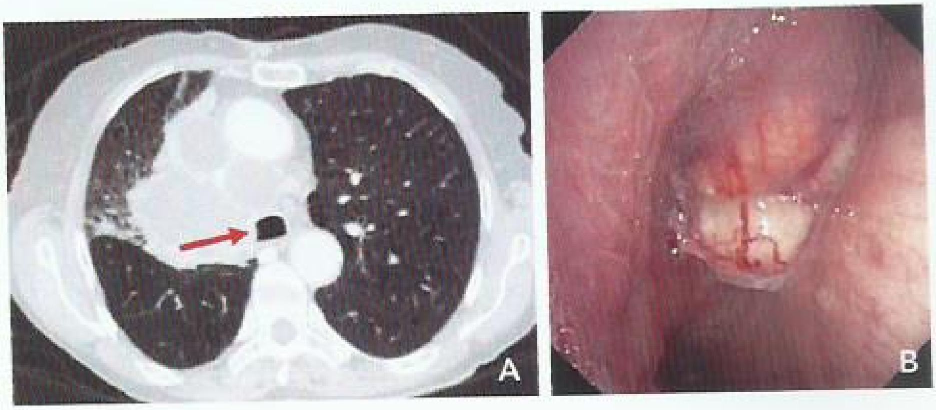

FIGURE 14. Metastatic squamous cell carcinoma can be seen as an 8-cm right hilar mass with invasion into the trachea on CT scan (*A*), and as tumor invasion into the distal trachea and occlusion of the right main stem on bronchoscopy (*B*).

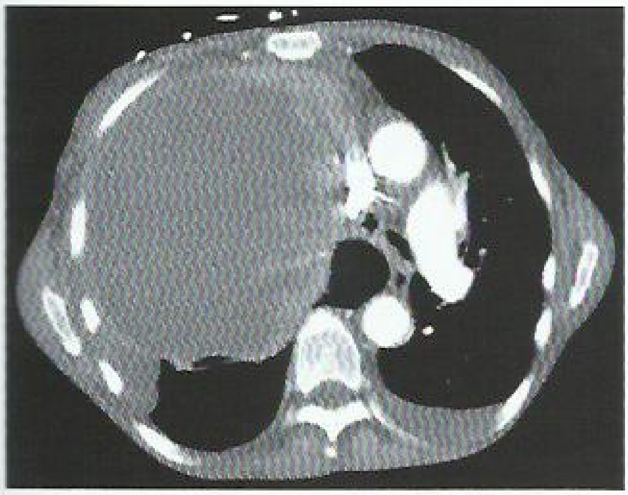

FIGURE 15. Large cell carcinoma with predominant necrosis can be seen on CT scan as a large necrotic tumor that has completely replaced the right upper and middle lobes, with deviation of the central airway structures to the left. Necrosis is noted by the mixed attenuation of the mass as noted on CT.

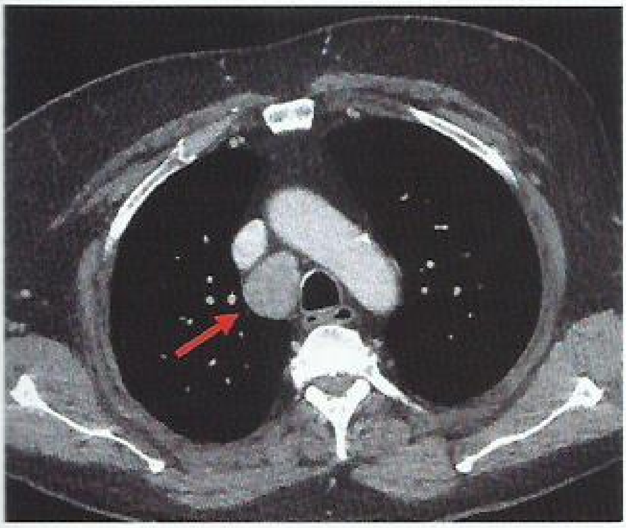

FIGURE 16. Small cell lung cancer can be seen on chest CT with a right paratracheal mass (*arrow*). This patient initially presented with encephalitis (paraneoplastic syndrome).

KEY POINTS ***(continued)***

- Testing for epidermal growth factor receptor (*EGFR*) mutation, anaplastic lymphoma kinase receptor tyrosine kinase (*ALK*) translocation, and ROS proto-oncogene 1 receptor tyrosine kinase (*ROS1*) translocation is recommended in advanced-stage adenocarcinoma or mixed cancers.

Risk Factors

The main risk factor for lung cancer is smoking tobacco (voluntary or secondhand). This risk increases based on the number of pack-years of smoking and other carcinogenic exposures. Any reduction in lung cancer mortality will be linked to an overall reduction of cigarette smoking. Other risk factors that have been associated with lung cancer include previous radiation therapy, exposure to environmental toxins (asbestos, radon, metals, and diesel fumes), pulmonary fibrosis, HIV infection, family history of lung cancer, and alcohol abuse.

Screening

Until recently, screening for lung cancer was not widely done, as previous studies had not shown early detection resulted in any mortality benefit for lung cancer. The National Lung Screening Trial (NLST) was a randomized trial comparing CT screening to chest radiograph for detecting lung cancer in current or heavy smokers. The trial demonstrated a 20% reduction in lung cancer mortality in heavy smokers who were screened annually for 3 years. As a result, the U.S. Preventive Services Task Force has recommended annual lung cancer screening using low-dose CT scan for high-risk current and former smokers. The criteria for screening are based on the inclusion criteria for the NLST and include those who are age 55 to 80 years (other guidelines offer different ages to discontinue screening, ranging from 74 to 77 years), have at least a 30-pack-year smoking history, and are current smokers or have quit within the last 15 years. Cessation of screening should be considered in those with limited life expectancy or those who would not be candidates for or willing to undergo surgery.

KEY POINT

- The U.S. Preventive Services Task Force recommends annual lung cancer screening using low-dose CT scan for those who are age 55 to 80 years, have at least a 30-pack-year smoking history, and are either current smokers or have quit smoking within the last 15 years.

Diagnosis and Staging

H

When evaluating a patient who has a lung nodule or mass for possible lung cancer, two questions must be answered: first, what is the cell type?; and second, what is the stage? The radiographic abnormality should first be compared to any previous chest imaging studies the patient has undergone in order to determine the age and growth pattern of the lesion. A solid lung nodule that has been stable for 2 years or longer is unlikely to represent malignancy. However, ground-glass or part-solid lesions usually grow at a much slower rate (400 to 800 days) and need a longer period of time (5 years) to exclude cancer based on radiographic stability.

Initial evaluation should start with a full history, physical exam, complete blood count, serum chemistries, and CT scan of the chest. Most lung cancers present at a late stage. Symptoms result from the local effects of the tumor, metastatic spread involving other organs, or paraneoplastic syndromes. The most common symptoms at presentation include cough, dyspnea, chest pain, weight loss, and hemoptysis. NSCLC and SCLC present with similar symptoms. Similarly, the presence of findings on physical examination (consolidation, effusion, bone tenderness, neurological findings) will indicate advanced disease. CT

H CONT.

scan findings that are suggestive of malignancy are listed in **Table 30**. A CT scan provides an accurate assessment of the location and size of the tumor within the chest and helps to direct tissue biopsy for diagnosis and staging. PET scans can be very helpful in the initial evaluation of potential lung cancer, as several studies have demonstrated that PET identifies unsuspected mediastinal involvement, distant disease, or both, which informs staging biopsies and reduces futile (noncurative) surgery. The sensitivity of a PET scan to detect lung cancer is affected by the mass of the nodule and its metabolic rate, with increased potential for false negative results for cancers smaller than 1 cm and slow-growing cancers, such as carcinoid tumors.

The definitive diagnosis of lung cancer requires tissue histopathology. If the nodule has a high probability for malignancy and the PET scan shows uptake only in the lesion, it is reasonable to offer surgical resection to diagnose and treat in a single procedure. In patients with radiographic evidence of advanced stage disease, diagnosis and staging are best accomplished with a single invasive test at a location that will establish both the diagnosis and the stage. Because there are many techniques available for tissue diagnosis, the strategy will depend on size and location of the tumor, patient characteristics, and surgical expertise. In general, mediastinal and central lesions are best approached with bronchoscopy, and smaller peripheral lesions are best approached with a transthoracic needle aspiration.

Definitive staging of lung cancer is essential, allows for accurate prognostication, and serves as a guide for treatment decision making. NSCLC is staged based on the TNM staging system, taking into account the characteristics of the primary tumor (T), regional lymph node involvement (N), and metastatic disease (M).

SCLC is generally staged as either "limited" or "extensive" disease. Limited disease is defined as disease limited to one hemithorax and ipsilateral supraclavicular lymph nodes. The presence of disease outside these locations defines extensive stage disease.

Treatment of lung cancer is discussed in MKSAP 18 Hematology and Oncology. H

KEY POINTS

- The definitive diagnosis of lung cancer requires tissue histopathology.
- In patients with radiographic evidence of advanced-stage lung cancer, diagnosis and staging are best accomplished with a single invasive test at a location that will establish both the diagnosis and the stage of disease.

TABLE 30. CT Findings Suggestive of Lung Malignancy

Irregular or Spiculated Borders
Upper-lobe location
Thick-walled cavitation
Solid component within a ground-glass lesion
Detection of growth on follow-up imaging

Other Pulmonary Neoplasms

Carcinoid tumors are low-grade neoplasms comprised of neuroendocrine cells and are uncommon, accounting for 1% to 2% of all lung cancers. Unlike the case for NSCLC and SCLC, smoking is not a risk factor. Most lung carcinoid tumors arise in the proximal airways, and the predominant symptoms or signs are those of an obstructing tumor mass (cough, dyspnea, monophonic wheezing) or bleeding. Bronchial obstruction may be responsible for lobar atelectasis and recurrent episodes of pneumonia in the same pulmonary segment, but may be asymptomatic (**Figure 17**). Misdiagnosing carcinoid tumors as asthma or pneumonia is responsible for delayed diagnosis. It is rare for lung carcinoid tumors to produce and release serotonin and other vasoactive substances into the systemic circulation and be associated with carcinoid syndrome. Surgical resection is often curative, and 10-year survival rates are higher than 90%.

Adenoid cystic carcinoma is a salivary gland tumor that occurs in the lower respiratory tract and accounts for less than 1% of all lung cancers. Surgical resection is the preferred treatment. Hamartomas are the most common benign lung neoplasm. These rare lesions are a combination of cartilage, connective tissue, smooth muscle, fat, and respiratory epithelium. On imaging they tend to be smooth bordered nodules, which may contain fat. Additionally, they may be recognized by their classic appearance on CT of "popcorn" calcification; however, this only occurs 25% of the time.

The lung is a frequent site for metastatic disease from primary malignancies, which include head and neck, colon, kidney, breast, thyroid, and melanoma. Metastatic disease can present as solitary or multiple nodules; lymphangitic spread; and endobronchial, pleural, or embolic lesions. Surgical resection may be appropriate when a solitary pulmonary metastasis is identified without evidence of other metastatic disease.

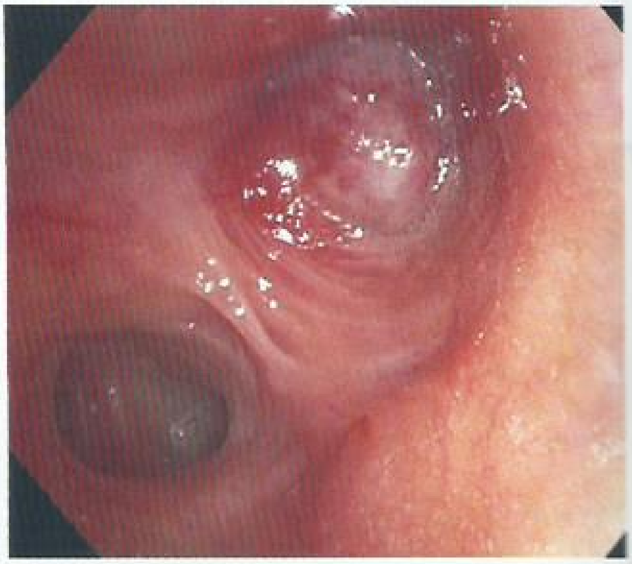

FIGURE 17. Endobronchial carcinoid can be seen on bronchoscopy as a smooth, polypoid, vascular-appearing mass that completely occludes a subsegmental airway of the right lower lobe.

KEY POINT

- Surgical resection of carcinoid tumors is often curative, and 10-year survival rates are higher than 90%.

Mesothelioma

Malignant pleural mesothelioma is a rare neoplasm that originates from the cells that line the pleural cavity (mesothelium). It can present as small nodules, plaque-like masses, or confluent sheets that can encase the lung. It is associated with inhalational exposure to asbestos fibers and has a latency of 20 to 40 years. Asbestos is a naturally occurring silicate mineral that is found in soil and rock as long fibers. It is valued for its resistance to heat and combustion and has been used in cement, ceiling tiles, pool tiles, automobile brake linings, and shipbuilding. In addition to malignant pleural mesothelioma and lung cancer, asbestos exposure has been linked to a spectrum of nonmalignant pleuropulmonary diseases (**Table 31**); for further discussion of asbestos-related disease, see Occupational Lung Disease. Because of environmental control of asbestos, the rate of mesothelioma in the United States has been declining since 2000.

Patients with malignant pleural mesothelioma usually present with advanced disease. Symptoms include chest pain, dyspnea, cough, hoarseness, night sweats, or dysphagia. Clinical suspicion for malignant pleural mesothelioma should arise in the setting of pleural thickening or exudative pleural effusion and a history of asbestos exposure. Pleural fluid cytology is typically negative in this scenario and the diagnosis requires a pleural biopsy. Medical or surgical thoracoscopy allows for direct visualization of the pleural surface and has a greater than 90% sensitivity for malignancy. Treatment options depend on the extent of disease and patient factors and preferences, and may include surgery, radiation therapy, and systemic chemotherapy. The overall prognosis of malignant pleural mesothelioma remains poor, with a median survival of 6 to 8 months.

KEY POINTS

- Mesothelioma is associated with inhalational exposure to asbestos fibers and has a latency of 20 to 40 years.
- Clinical suspicion for malignant pleural mesothelioma should arise in the setting of pleural thickening or exudative pleural effusion and a history of asbestos exposure.

TABLE 31. Nonmalignant Asbestos-Related Pleural and Pulmonary Diseases

Disease	Characteristics
Asbestosis	Slowly progressive diffuse pulmonary fibrosis caused by inhalation of asbestos fibers
Benign asbestos pleural effusion	Small unilateral pleural effusion, may be associated with concomitant pleural plaques
Pleural plaques	Benign circumscribed areas of pleural thickening with linear or nodular appearance

Mediastinal Masses

H

The mediastinum is anatomically near the center of the thoracic cavity and is bound by the sternum anteriorly, the lungs and pleura laterally, and the vertebral column posteriorly. Tumors in the mediastinum can be either benign or malignant, and symptoms vary depending on size (mass effect) and systemic effects of the tumor. Dividing the mediastinum into compartments can be useful in developing a differential diagnosis when a mediastinal mass is discovered (**Figure 18**).

Anterior Mediastinum

The anterior mediastinal compartment lies between the posterior sternum and the great vessels and heart. It is the most common mediastinal location where malignant tumors occur. Masses in this location are usually remembered as the "terrible T's": thymoma, teratoma/germ cell tumor, "terrible" lymphoma, and thyroid. Thymic lesions are the most common and are associated with various paraneoplastic syndromes, such as myasthenia gravis. Myasthenia gravis is an autoimmune disorder of the neuromuscular junction that commonly presents with muscular weakness, fatigability, ptosis, diplopia, and bulbar symptoms. Diagnosis can be confirmed with an acetylcholine receptor antibody test. H

KEY POINT

- Thymic lesions are the most common tumor in the anterior mediastinum and are associated with various paraneoplastic syndromes, such as myasthenia gravis.

Middle Mediastinum

H

Masses in the middle mediastinum are common and are attributed to lymphadenopathy, cysts, esophageal disorders, or vascular lesions (aneurysm). Lymphadenopathy is most common and can be secondary to lymphoma, sarcoid, or metastatic disease. H

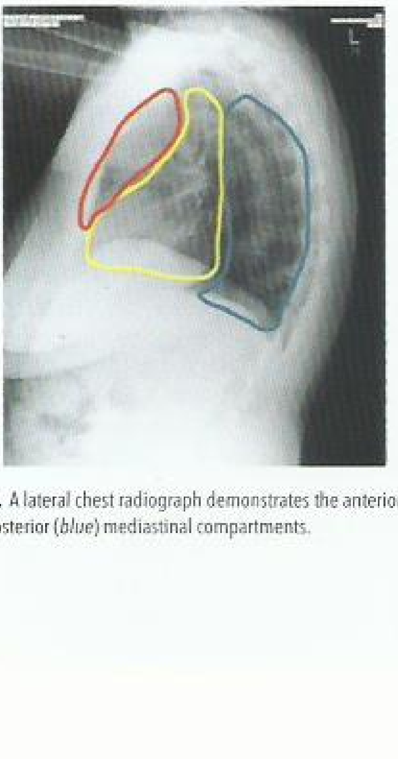

FIGURE 18. A lateral chest radiograph demonstrates the anterior (*red*), middle (*yellow*), and posterior (*blue*) mediastinal compartments.

KEY POINT

- Lymphadenopathy is the most common mass in the middle mediastinum and can be secondary to lymphoma, sarcoid, or metastatic disease.

Posterior Mediastinum

Masses in the posterior mediastinum include neurogenic tumors, meningoceles, and spine lesions. Neurogenic neoplasms are most common and are classified based on their neural origin.

KEY POINT

- Neurogenic neoplasms are the most common tumors in the posterior mediastinum and are classified based on their neural origin.

Sleep Medicine

Classification of Sleep Disorders

Sleep disorders are broadly grouped into six classifications: insomnia, sleep-related breathing disorders, central disorders of hypersomnolence, circadian rhythm sleep-wake disorders, parasomnias, and sleep-related movement disorders (which includes restless leg syndrome).

Excessive Daytime Sleepiness

Excessive daytime sleepiness refers to difficulty staying awake and alert during daytime hours. Sleepiness is most prominent during passive situations such as reading or watching television. Lack of self-recognition is common and can pose a safety hazard if sleepiness occurs while driving or operating machinery. When obtaining a history from the patient, it is important to distinguish sleepiness, a cardinal symptom of many sleep disorders, from fatigue, which refers to a lack of energy or sense of exhaustion that prevents mental or physical activity at the intensity or pace desired. Fatigue is unlikely to be explained solely by a sleep disorder, and is more likely to occur in the setting of certain medical conditions (malignancies, autoimmune disorders, anemia, endocrinopathies, infections), neurologic disorders (myasthenia gravis, multiple sclerosis, Parkinson disease), psychiatric conditions (mood disorders), and chronic fatigue syndrome.

Causes of excessive daytime sleepiness can be categorized as extrinsic (circumstantial) or intrinsic (disease-related) processes (**Table 32**).

TABLE 32. Extrinsic and Intrinsic Causes of Excessive Daytime Sleepiness

Extrinsic Causes
Insufficient sleep duration (or inadequate opportunity for sleep)
Circadian rhythm disturbance (shift work sleep disorder, jet lag)
Drug-, substance-, or medical condition-related hypersomnia
Environmental sleep disorder (ambient noise, pets)
Intrinsic Causes
Sleep-disordered breathing syndromes, such as obstructive sleep apnea and central sleep apnea
Narcolepsy
Idiopathic hypersomnia
Restless leg syndrome and periodic limb movement disorder
Circadian rhythm sleep disorders (misalignment of the intrinsic circadian timing with the desired sleep schedule; for example, dementia and blindness)

Sleepiness can occur acutely when a person is deprived of the 7 to 8 hours of sleep most adults require. Functional impairment resulting from chronic sleep debt due to inadequate amount of sleep is termed insufficient sleep syndrome. It likely is the most common cause of excessive daytime sleepiness and has been associated with cardiovascular disease and metabolic disorders such as glucose intolerance and obesity.

The initial evaluation of excessive daytime sleepiness should include a thorough history to assess the time available for and spent sleeping before pursuing additional testing. A 1- or 2-week diary of the sleep-wake schedule is a simple tool that promotes self-realization of suboptimal sleep habits. A more objective assessment of sleep and wakefulness can be obtained with a wrist actigraph, a device that measures movement and ambient light during a period of 1 or 2 weeks. Wrist-worn consumer fitness products using similar technology may provide useful feedback. Questionnaires such as the Epworth Sleepiness Scale can quantify sleepiness and help gauge the response to treatment.

Objective sleep testing, either in-lab or at-home multichannel recordings, is often indicated when a primary sleep disorder (such as obstructive sleep apnea) is suggested by the history and physical examination. In certain cases a multiple sleep latency test, a sleep laboratory–based study that measures the time to sleep during a series of daytime nap opportunities following a normal night of sleep, provides an objective measure of sleepiness and is key to establishing the diagnoses of narcolepsy and idiopathic hypersomnia. A mean sleep latency of more than 15 minutes is considered normal and less than 5 minutes is indicative of pathologic sleepiness.

All patients with excessive daytime sleepiness should be counseled about the dangers of drowsy driving and the need to maintain a routine sleep-wake schedule that allows for 7 to 8 hours of sleep per night. Specific treatment depends on the underlying condition (positive airway pressure for obstructive sleep apnea or stimulant medications for narcolepsy). Short-term management of the occasional bout of acute sleepiness may include strategically timed naps or caffeinated beverages.

KEY POINTS

- The initial evaluation of excessive daytime sleepiness should include a thorough history to assess the time available for and spent sleeping before pursuing additional testing.
- All patients with excessive daytime sleepiness should be counseled about the dangers of drowsy driving and the need to maintain a routine sleep-wake schedule that allows for 7 to 8 hours of sleep per night.
- Functional impairment resulting from chronic sleep debt due to inadequate amount of sleep is termed insufficient sleep syndrome; it likely is the most common cause of excessive daytime sleepiness and has been associated with cardiovascular disease and metabolic disorders such as glucose intolerance and obesity.
- When obtaining a history from the patient, it is important to distinguish sleepiness, a cardinal symptom of many sleep disorders, from fatigue, which refers to a lack of energy or sense of exhaustion that prevents mental or physical activity at the intensity or pace desired.

Conditions that Disrupt Circadian Rhythm

Jet Lag

Jet lag results when the internal circadian clock is out of phase with the local time following air travel across multiple (typically more than five) time zones. Symptoms occur within one to two days following travel and may include insomnia, daytime sleepiness, and neuropsychiatric impairment. For short trips (one to two days), remaining on origin time might be preferable, if feasible. For longer trips, adjusting to the destination time may alleviate jet lag. Ways to promote adjustment include pretravel measures (avoidance of sleep deprivation and dehydration and, for the highly motivated, bright light therapy starting up to 3 days before travel with the intention to advance the circadian phase). In flight hypnotic medications are popular, though they pose a risk of parasomnias, particularly if alcohol is consumed. Postarrival measures include timed bright light exposure and melatonin, depending upon the direction traveled, caffeine intake, and naps.

Shift Work Sleep Disorder

As much as one fifth of the American work force maintains a job schedule outside the usual day shift hours. Although some people acclimate well to this schedule (and may even prefer it), many do not and suffer daytime symptoms such as excessive sleepiness, mood perturbations, and neurocognitive dysfunction. Such symptoms can render the next-morning drive home from work dangerous. Symptoms persisting at least 3 months meet criteria for shift work sleep disorder. Management should first include consideration of eliminating shift work by a change in work schedule. If this isn't feasible, interventions to improve daytime sleep may include bright light avoidance in the morning (wearing sunglasses if necessary), maintaining a structured sleep wake pattern, and melatonin, which is of modest benefit in shifting the physiologic sleep cycle. Hypnotic medications have been used to promote daytime sleep but are of varying effectiveness and pose the risk of carryover effects into the nighttime work period. Interventions to promote nighttime wakefulness include bright light treatment in the evening before the night shift, caffeinated beverages or wake promoting stimulants (such as modafinil) during work hours, and planned napping during work breaks.

Obstructive Sleep Apnea H

Obstructive sleep apnea (OSA) is an increasingly common disorder defined by sleep interruption due to repetitive upper airway narrowing or collapse. These disordered breathing events, captured during sleep testing, are classified as *apneas* (complete cessation of airflow) or *hypopneas* (reductions in airflow), and when these events are divided by total sleep time (in hours) collectively comprise the apnea-hypopnea index (AHI). Although, this frequency-based measure doesn't incorporate every important OSA outcome (for example, it does not capture the degree of oxyhemoglobin desaturations), the AHI is probably the best composite metric of disease severity. An AHI of 5/hour to 15/hour indicates mild OSA, 15/hour to 30/hour indicates moderate OSA, and more than 30/hour indicates severe OSA. H

KEY POINTS

- Obstructive sleep apnea is an increasingly common disorder defined by sleep interruption due to repetitive upper airway narrowing or collapse.
- The apnea-hypopnea index (AHI) is the total number of apnea and hypopnea events divided by total sleep time (in hours) and can classify obstructive sleep apnea as mild (5/hour to 15/hour), moderate (15/hour to 30/hour), or severe (more than 30/hour).

Pathophysiology

With sleep onset, pharyngeal muscles acting to maintain upper airway patency relax, resulting in redundancy of the soft tissues that line the airway. Snoring is often (though not universally) a result of this process, as inspired air collides with these tissues. In OSA, airflow is further compromised by forces (see Risk Factors) that overwhelm the neuromuscular mechanisms promoting upper airway patency. Posture and sleep stage are also important factors. The supine position promotes posterior displacement of the tongue, further narrowing the airway lumen. Disordered breathing events are most prominent during rapid eye movement (REM), a stage of sleep characterized by atonia of nearly all muscles, with the exception of the extraocular muscles and respiratory diaphragm. Efforts to breathe persist against the airway

occlusion, resulting in intrathoracic pressure swings. The process is terminated with a brief awakening from sleep (called a microarousal), during which upper airway patency is restored and ventilation resumes, typically followed by resumption of sleep and continual repetition of the process.

Repetitive arousals and disruption of sleep architecture contribute to the development of excessive daytime sleepiness and neurocognitive symptoms of OSA. Oxyhemoglobin desaturations can be profound, particularly in those with underlying cardiopulmonary disease. This hypoxic stress, along with a host of other intermediary mechanisms including inflammation and high adrenergic tone, raise the question of whether OSA may directly contribute to commonly comorbid systemic disorders such as metabolic and cardiovascular disease. Current evidence, based in part on results of randomized controlled trials of positive airway pressure therapy, suggest a causal link between OSA and systemic hypertension. However, relationships with other disorders such as heart failure, cardiac arrhythmias, diabetes mellitus, and mortality are merely associative; causation remains unproven.

Risk Factors

The most important risk factor for OSA is obesity, particularly in those with prominence of adipose tissue in the trunk and neck. Partially on account of gender-specific distribution of fat tissue, men are at higher risk than women, though rates equalize following menopause. The prevalence of OSA increases with age. Blacks and Asians are at higher risk. Alcohol and sedative drugs can exacerbate OSA. Tonsillar hypertrophy, macroglossia, retrognathia/micrognathia, and upper airway mass lesions can contribute to upper airway narrowing.

KEY POINT

- The most important risk factor for obstructive sleep apnea is obesity, particularly in those with prominence of adipose tissue in the trunk and neck.

H Clinical Features and Diagnosis

Patients are commonly brought to medical attention by the concerns of a bed partner who observes loud snoring, gasping, and breathing pauses. Nocturnal choking or gasping is probably the most sensitive pretest indicator of OSA. Other symptoms include overnight awakenings, nocturia, and feeling unrested after a night of sleep.

The most important established consequence of OSA is excessive daytime sleepiness. Although it is not a universal symptom, the lack of self-report may not reflect the true degree of impairment. Collateral history from a family member as well as questionnaires such as the Epworth Sleepiness Scale can help identify excessive daytime sleepiness. Neuropsychiatric symptoms are common, including mood alterations, difficulty in concentrating, and problems completing tasks at school or the workplace.

With increasing use of screening tools such as the STOP-BANG questionnaire and perioperative care pathways, unexpected patient events due to undiagnosed OSA following a surgical procedure involving general anesthesia or narcotic analgesics are less common than in the past.

Objective testing is required for a diagnosis of OSA. Physical examination findings (crowded oropharynx) and questionnaires might enhance pretest probability and guide decision-making about whether to pursue testing, but alone are insufficiently sensitive or specific. Overnight pulse oximetry is also poorly discriminative to diagnose OSA, but in those who are asymptomatic with a low pretest probability, normal overnight oximetry might be reassuring and support the decision to avoid further testing. The historic gold standard—in-laboratory polysomnography—which is costly and resource-intensive, is being replaced in many regions by home sleep testing. Home sleep testing doesn't measure electroencephalographic sleep like polysomnography. Yet, it is diagnostically similar in otherwise uncomplicated patients (without underlying cardiopulmonary or neuromuscular disease) who are felt to have at least moderate to severe OSA (to minimize false negatives that may occur in milder disease). H

KEY POINTS

- Normal overnight pulse oximetry in those who are asymptomatic with a low pretest probability can be reassuring and supports the decision to avoid further testing for obstructive sleep apnea.
- Home sleep testing may be most appropriate in patients without underlying cardiopulmonary or neuromuscular disease who are felt to have at least moderate to severe obstructive sleep apnea.

Treatment

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There are several treatment options for OSA, the efficacy of which are generally based upon the ability to reduce, if not abolish, apneas and hypopneas. Positive airway pressure therapy, which typically reduces the AHI toward zero, is the most reliable means to accomplish this, though because the AHI doesn't always correlate with important outcomes in OSA, other treatments may adequately manage OSA for a given patient, even in the face of residual sleep apnea.

Based upon clinical trial results, the strongest indication for treatment of OSA is excessive daytime sleepiness, which generally improves with effective therapy. Although they are not as easily measured as excessive daytime sleepiness, other associated symptoms such as choking or gasping would also be expected to respond to treatment. Neurocognitive and mood symptoms are probably indications for treatment. In patients who perform mission-critical work (truck drivers, pilots), the threshold for treatment may be lower than for others. The role of treatment in otherwise healthy or asymptomatic individuals is a matter of debate. Device therapy (positive airway pressure and oral appliances) has been shown to modestly reduce blood pressure in hypertensive patients with

OSA, but the effect of treatment to manage comorbid cardiovascular disease or to prevent major cardiovascular events is unproven.

Weight Loss, Behavioral Modifications

OSA severity improves with weight loss, so all overweight or obese patients with OSA should be counseled accordingly. In minimally symptomatic patients with mild OSA, weight loss might be preferred therapy. Weight loss associated with dieting programs or bariatric surgery generally improves but may not eradicate OSA, so close follow-up is required. Additional measures that may help manage mild OSA include reducing alcohol intake before bedtime and avoiding a supine posture if OSA is position dependent. H

KEY POINT

- Obstructive sleep apnea severity improves with weight loss, so all overweight or obese patients with obstructive sleep apnea should be counseled accordingly.

H

Positive Airway Pressure

Positive airway pressure remains the most effective therapy for preventing disordered breathing events and alleviating symptoms in patients who have OSA. It acts by pressurizing the upper airway to maintain lumenal patency, thereby eliminating snoring and airflow limitation.

As home sleep testing becomes more widespread in uncomplicated OSA, the traditional paradigm of in-lab polysomnography titration performed by a sleep technologist to arrive at an optimal fixed and constant value referred to as continuous positive airway pressure will be less common. The diagnosis by home sleep testing is coupled to treatment with auto-adjusting positive airway pressure, which uses a computer algorithm to detect and overcome upper airway resistance in real time. Auto-adjusting positive airway pressure and continuous positive airway pressure are considered therapeutic equivalents in terms of reducing the AHI and adherence to treatment. Bilevel positive airway pressure, which delivers separate inspiratory and expiratory pressures (the gradient is referred to as pressure support) to augment alveolar ventilation, has no proved role in OSA without a hypoventilation syndrome (see below).

The effectiveness of positive airway pressure therapy hinges upon patient adherence. Symptom burden probably drives adherence but for those who lack motivation, educational programs can help, as can direct-to-patient reports wirelessly transmitted from the device directly to smartphones or computers. Side effects such as xerostomia and nasal dryness and congestion can be ameliorated by in-line humidification. Intranasal glucocorticoids or anticholinergics may be useful for recalcitrant nasal congestion or rhinitis. Modified pressure profiles that slightly reduce pressure on exhalation may enhance comfort. Proper mask fit enhances comfort and mitigates air leak. Positive airway pressure interfaces, ranging from nasal pillows that sit at the nasal openings to nasal masks that cover the nose to oronasal (full face) masks that cover the nose and mouth, are frequently updated and improved. H

KEY POINTS

- Positive airway pressure remains the most effective therapy for preventing disordered breathing events and alleviating symptoms in patients who have obstructive sleep apnea.
- Auto-adjusting positive airway pressure and continuous positive airway pressure are considered therapeutic equivalents for reducing the apnea-hypopnea index and increasing adherence to treatment.

Oral Appliances

Oral appliances increase upper airway caliber primarily by exerting traction to advance the mandible. They do not reduce the AHI or increase oxygen levels as reliably as positive airway pressure, and are, therefore, generally avoided in more severe cases of OSA. Oral appliances have some potential advantages over positive airway pressure, however, including a reduced incidence of side effects and a potentially higher rate of adherence. The most common side effects are morning occlusal changes, which are generally reversible, and sialorrhea.

Upper Airway Surgery

Although surgical procedures are generally not first-line therapy for OSA, maxillomandibular advancement (MMA) significantly improves the AHI, even in severe disease, and can be considered for patients who do not benefit from or refuse positive airway pressure therapy. Factors that predict surgical success are not fully known, though younger patients who are less obese probably fare better. Traditional soft palatal procedures such as uvulopalatopharyngoplasty (UPPP) are ineffective; tonsillectomy in adults may or may not be effective. Tracheotomy, which bypasses the entire upper airway, is an effective though uncommonly used treatment of OSA, limited by patient acceptance and aesthetics.

If surgery is performed, reassessment by objective testing should be performed within 3 to 6 months to assess effect.

KEY POINT

- Traditional soft palatal procedures such as uvulopalatopharyngoplasty are ineffective for treatment of obstructive sleep apnea. HVC

Other Devices

A hypoglossal nerve stimulator approved for use in OSA has been shown to improve the AHI in some patients. Implanted in the chest wall, it synchronizes with the respiratory cycle to contract the tongue muscles during inspiration. It is expensive, and those patients most likely to benefit from this treatment are yet to be determined.

A nasal end-expiratory positive airway pressure device applied to the nasal openings by way of an adhesive has also been shown to reduce the AHI in some but not all patients. No

drug therapy is effective for OSA. Supplemental oxygen is not recommended as primary therapy for OSA. A direct comparison of supplemental oxygen versus positive airway pressure therapy found that blood pressure was reduced in the positive airway pressure group but not in the supplemental oxygen group.

Central Sleep Apnea Syndromes

Classification and Pathophysiology

Central sleep apnea (CSA) syndromes are defined by pauses in airflow due to loss of output from the central respiratory generators in the brainstem, resulting in lack of respiratory effort. Ventilation during sleep is primarily determined by the arterial Pco_2, particularly during non-REM sleep, which comprises about 75% of total sleep time. Under normal circumstances, a steady state exists where ventilation maintains the arterial Pco_2 in the normal range (approximately 40 mm Hg [5.3 kPa]). In CSA, the response to arterial Pco_2 is exaggerated, resulting in ventilatory overshoot, hyperventilation, and reduction of the arterial Pco_2 to a level near the apneic threshold, the level at which respiratory efforts cease. This central apnea further destabilizes ventilation and perpetuates the process. On polysomnography, a central apnea is identified by the absence of respiratory effort associated with loss of airflow for at least 10 seconds.

KEY POINT

- Central sleep apnea syndromes are defined by pauses in airflow due to loss of output from the central respiratory generators in the brainstem, resulting in lack of respiratory effort.

Risk Factors

Comorbid illnesses that predispose to instability of the ventilatory control system are the most common risk factors for CSA. The most important and prevalent association is between CSA and heart failure, which classically manifests as Cheyne-Stokes breathing, characterized by a crescendo decrescendo pattern of ventilation. Atrial fibrillation, both in the setting of heart failure and also in those with normal left ventricular systolic function, is a risk factor for CSA.

Known for their respiratory depressant effects in high doses, opioid analgesics are also associated with CSA. Opioids have destabilizing effects on ventilation, resulting in CSA and a chaotic breathing rhythm.

Approximately 10% percent of OSA patients treated with positive airway pressure exhibit "treatment-emergent CSA," the significance of which is a matter of debate. In many, the central apneas dissipate as patients acclimate to positive airway pressure therapy.

Other risk factors for CSA include stroke, brainstem lesions, and possibly kidney failure. Men may be at higher risk than woman. High-altitude periodic breathing is a form of CSA. Primary or idiopathic CSA, in which no risk factors are identified, is uncommon.

Symptoms and Diagnosis

It can be difficult to determine which symptoms are specific to CSA and which are associated with the comorbid condition(s). Some symptoms may be indistinguishable from OSA, such as frequent awakenings from sleep and nocturnal dyspnea, although daytime sleepiness is uncommon in those with CSA and heart failure. In-lab polysomnography is required to accurately diagnose CSA, though the Cheyne Stokes breathing pattern is sometimes recognizable on home sleep testing. It should also be noted that although the AHI is traditionally used to describe the severity of CSA, it hasn't been validated as a predictor of important clinical outcomes as it has been in OSA. Finally, abnormal oximetry does not reliably discriminate between OSA and CSA.

Treatment

There are few clinical trials proving a role for specific treatment of CSA, so initial management should target modifiable risk factors. For example, reduction or elimination of opioids improves CSA. Medical optimization of heart failure (with drugs or devices, optimizing fluid balance in the setting of volume overload, or surgery such as valve repair or cardiac transplantation) has been shown to improve CSA and Cheyne Stokes breathing, though it remains controversial as to whether CSA is an independent risk factor for worsened prognosis in those with heart failure.

Sleep related symptoms probably represent an indication for treatment. Continuous positive airway pressure may occasionally be useful, especially in patients with overlapping OSA, though "treatment-emergent CSA" may persist. Adaptive servo ventilation is a form of positive airway pressure therapy that effectively suppresses CSA. Its role in treatment, however, was called into question by the results of a recent large trial showing an unexpected increase in mortality in patients with CSA and heart failure with reduced ejection fraction.

KEY POINT

- Initial management of central sleep apnea should target modifiable risk factors such as heart failure and elimination of opioids.

Sleep-Related Hypoventilation Syndromes

Sleep-related hypoventilation syndromes are associated with advanced COPD, obesity hypoventilation syndrome, and restrictive lung diseases related to kyphoscoliosis or neuromuscular disorders and others diseases (**Table 33**). These conditions are defined by impaired gas exchange during wakefulness that is further compromised with sleep, especially during the muscle atonia of REM. Capnometry (measurement of either transcutaneous or end-tidal carbon dioxide levels) are increasingly used to confirm hypoventilation during sleep, although oxygenation criteria are also used to diagnose

TABLE 33. Causes of Sleep-Related Hypoventilation Syndromes
COPD
Obesity hypoventilation syndrome
Myxedema
Neuromuscular disease
Muscular dystrophy
Amyotrophic lateral sclerosis
Myasthenia gravis
Guillain-Barré syndrome
Phrenic nerve injury
Poliomyelitis, post-polio syndrome
Cervical spine injury
Kyphoscoliosis

sleep-related hypoventilation syndromes. Sustained reductions in oxyhemoglobin saturation (less than 90% for at least 5 minutes or more than 30% total sleep time by oximetry or polysomnography) in the setting of a compatible medical condition signify a hypoventilation syndrome. Obstructive sleep apnea may or may not be an associated feature.

KEY POINT

- Sleep-related hypoventilation syndromes are defined by impaired gas exchange during wakefulness that is further compromised with sleep; common associated conditions include advanced COPD, obesity hypoventilation syndrome, and restrictive lung diseases related to kyphoscoliosis or neuromuscular disorders.

Chronic Obstructive Pulmonary Disease

Patients with severe airflow obstruction due to COPD often exhibit sleep-related hypoventilation. In addition to optimization of COPD therapy, supplemental oxygen is often used. The noninvasive pressure support of bilevel positive airway pressure can be used if hypercapnia is confirmed. In the overlap syndrome where OSA is superimposed on COPD, continuous positive airway pressure therapy has been shown to decrease mortality rates.

Obesity Hypoventilation Syndrome

The obesity hypoventilation syndrome (OHS) results from a combination of the mechanical load on the respiratory pump and blunting of the chemoreflex (ventilatory response to carbon dioxide) in those with marked obesity. The hallmark of OHS is daytime hypercapnia, defined as a P_{CO_2} greater than 45 mm Hg (5.9 kPa). OSA is usually but not always superimposed. Biventricular heart failure, pulmonary hypertension, and volume overload are common.

Weight loss is essential and consideration can be given to bariatric surgery. Positive airway pressure therapy is indicated. Although comparative trials are lacking, most would consider bilevel positive airway pressure the mode of choice to augment ventilation. Supplemental oxygen may need to be added and its continued need reassessed at a later date. See Principles of Critical Care for a discussion of acute respiratory failure associated with OHS.

KEY POINT

- The hallmark of obesity hypoventilation syndrome is daytime hypercapnia, defined as an arterial P_{CO_2} greater than 45 mm Hg (5.9 kPa).

Neuromuscular Diseases

Noninvasive positive pressure ventilation devices are often prescribed to alleviate sleep-related symptoms and support blood oxygen levels in patients with neuromuscular disorders (**Table 34**). Bilevel positive airway pressure or volume-assured devices (average volume-assured pressure support, or AVAPS), with or without supplemental oxygen, are indicated once there is evidence of daytime hypercapnia indicative of chronic respiratory failure. Polysomnography may aid in optimizing machine and oxygen settings and in assessing concomitant sleep disorders, but is not always needed. Tracheostomy and home mechanical ventilation are effective and may be appropriate for some patients. Supplemental oxygen may further depress ventilation in patients with respiratory muscle weakness and should generally not be prescribed without

TABLE 34. Positive Airway Pressure Modes

Mode	Description	Indication
CPAP	Fixed pressure derived from an in-lab titration attended by a technician	OSA Occasionally CSA
APAP	Range of pressure delivered to maintain upper airway patency, determined by a proprietary computer algorithm	OSA
BPAP	Inspiratory pressure support delivered over and above a minimum expiratory pressure, derived from an in-lab titration	Hypoventilation syndromes OSA when CPAP fails (including patient intolerance)
Auto-BPAP	Range of bilevel pressures determined by a proprietary computer algorithm	Same as BPAP
ASV	Breath-by-breath adjustment of inspiratory pressure support and back-up rate determined by a proprietary computer algorithm; expiratory pressure set by a technician	CSA (including mixed CSA and OSA)
Auto-ASV	Inspiratory and expiratory pressures determined by a proprietary algorithm	Same as ASV

APAP = auto-adjusting positive airway pressure; ASV = adaptive servo ventilation; BPAP = bilevel positive airway pressure; CPAP = continuous positive airway pressure; CSA = central sleep apnea; OSA = obstructive sleep apnea.

adjunctive ventilatory support, either by noninvasive means or by tracheostomy.

KEY POINT

- Noninvasive positive pressure ventilation devices are often prescribed to alleviate sleep-related symptoms and support blood oxygen levels in patients with neuromuscular disorders.

High-Altitude–Related Illnesses

Sleep Disturbances and Periodic Breathing

Diminishing barometric pressure associated with an ascent to altitude reduces the amount of ambient oxygen available for gas exchange, a condition known as hypobaric hypoxia. Physiologic responses to hypobaric hypoxia mechanistically underlie many disorders collectively referred to as high-altitude illness. In general, high-altitude illnesses occur at elevations of 2500 meters (approximately 8200 feet) and higher but have been reported below this elevation. Susceptibility to high-altitude illness is individualized and difficult to predict. Although high-altitude illnesses can occur at all ages and in the fittest of sojourners, patients who have a history of high-altitude–related illness are at risk for recurrence. Higher altitudes and a rapid rate of ascent are two key risk factors. Prevention is the best method of management. Because high-altitude illnesses are likely to recur, prophylactic measures are indicated on subsequent trips to elevation.

With the onset of hypoxic stress associated with hypobaric hypoxia, there is stimulation of peripheral chemoreceptors that are sensitive to hypoxia, leading to an attendant increase in ventilation, which is a key pathophysiologic mechanism in the sleep disorder termed high-altitude periodic breathing. In high-altitude periodic breathing, arterial P_{CO_2} is driven toward the apneic threshold, which, when crossed, results in a pause in breathing (central apnea). With this pause, arterial P_{CO_2} eventually rises sufficiently to again stimulate breathing. The cycle of ventilatory overshoot, hypocapnia, and central apneas repeats, at night and at high altitude. Patients complain of interrupted sleep and insomnia and may experience paroxysms of dyspnea that awaken them. Alcohol ingestion, which promotes dehydration, can intensify the sequelae of high-altitude periodic breathing.

Gradual ascent of less than 1000 feet per day, especially at higher altitudes, is suggested to prevent high-altitude periodic breathing and other high-altitude illnesses. Spending one night at an intermediate altitude to allow acclimatization often suffices. Acetazolamide, a carbonic anhydrase inhibitor and weak diuretic, induces a slight metabolic acidosis, is used to stabilize ventilation and enhance gas exchange, and can be used prophylactically in patients who have previously suffered high-altitude illness. Supplemental oxygen can relieve symptoms of disrupted sleep and paroxysmal nocturnal dyspnea, but because most cases of high-altitude periodic breathing are self-limited after a few nights, this is generally not indicated in otherwise healthy individuals.

KEY POINTS

- Gradual ascent of less than 1000 feet per day, especially at higher altitudes, is suggested to prevent high-altitude periodic breathing and other high-altitude illnesses.
- Acetazolamide is used to stabilize ventilation and enhance gas exchange at high altitude, and can be used prophylactically in patients who have previously suffered high-altitude illness.

Acute Mountain Sickness

Cerebral blood flow and oxygen delivery to the brain are altered by the hypoxia and hypocapnia associated with the ascent to altitude. Cerebral autoregulatory mechanisms can dampen the stress on blood flow, and symptoms can be mild in acute mountain sickness (AMS), but when the compensatory pathways are overwhelmed, severe, life-threatening cerebral edema can ensue. In AMS, the most common high-altitude illness, symptoms are nonspecific and include headache, fatigue, nausea, and vomiting; disturbed sleep related to high-altitude periodic breathing is also common. AMS is probably more common than what comes to medical attention, with estimates of as many as 25% of visitors to an altitude of 2000 meters (approximately 6500 feet), the elevation at most major U.S. ski areas. Heavy exertion and dehydration tend to amplify symptoms, which, provided there is no further ascent, typically resolve within 24 to 48 hours. As in high-altitude periodic breathing, slow ascent helps prevent the syndrome. For mild symptoms, conservative treatment may include rest, fluid replacement, aspirin, NSAIDs, or antiemetics. Acetazolamide is best used as a prophylactic but has been used as a treatment as it is believed to accelerate acclimatization. Dexamethasone is equally effective to reduce symptoms of AMS and can be used as an alternative to acetazolamide, which is a sulfonamide, for either prophylaxis or treatment in patients with sulfonamide allergy. Supplemental oxygen or portable hyperbaric therapies to simulate descent, when available, are also used to treat more symptomatic cases of AMS. Descent should also be considered when feasible.

KEY POINT

- Symptoms of acute mountain sickness are nonspecific and include headache, fatigue, nausea, and vomiting; disturbed sleep related to high-altitude periodic breathing is common.

High-Altitude Cerebral Edema

High-altitude cerebral edema is a feared manifestation of acute mountain sickness that tends to occur at higher elevations

(above 3000 to 4000 meters, or approximately 9800 to 13,000 feet). Vascular leak leads to brain swelling, resulting in a range of manifestations from confusion and irritability, to ataxic gait, to coma and death. Prophylactic acetazolamide should be considered in individuals planning to ascend to these elevations. Recognition of cerebral edema mandates immediate intervention. Definitive treatment is immediate descent from altitude, particularly when the patient is still ambulatory, because incapacitation at high altitude exponentially complicates evacuation. Dexamethasone, supplemental oxygen, and hyperbaric therapy may be used in addition to descent in altitude.

KEY POINT

- Definitive treatment of high-altitude cerebral edema is immediate descent from altitude, particularly when the patient is still ambulatory, because incapacitation at high altitude exponentially complicates evacuation.

High-Altitude Pulmonary Edema

Vascular leak resulting from hypoxia-induced high pulmonary vascular pressures is felt to be mechanistically important in the development of high-altitude pulmonary edema. Within 2 to 4 days of ascent (typically to at least 2500 meters, approximately 8200 feet), pulmonary artery pressures begin to rise in response to hypoxic stress. Cough, dyspnea, and exertional intolerance are usually insidious but may occur abruptly and awaken a patient from sleep. Other features of acute mountain sickness may or may not be present. A key feature of high-altitude pulmonary edema is dyspnea at rest. Patients are often tachypneic and tachycardic; crackles or wheezing can be heard on chest examination. Pink, frothy sputum or frank hemoptysis may occur, which heralds worsening gas exchange and respiratory failure. The treatment of choice is supplemental oxygen along with rest, both of which will acutely reduce pulmonary artery pressures. Descent from altitude should be considered. Salvage therapies in the absence of supplemental oxygen and descent include vasodilators such as nifedipine or phosphodiesterase-5 inhibitors (sildenafil or tadalafil). Conventional treatments for pulmonary edema in the setting of heart failure, such as diuretics and nitrates, are not recommended in this setting. Rarely, climbers may require assisted ventilation, including intubation.

Air Travel in Pulmonary Disease

The principles of hypobaric hypoxia also apply to commercial airline travel. Cabins are pressurized to the equivalent of 1500 to 2500 meters (approximately 5000 to 8000 feet) in altitude, resulting in an inspired oxygen tension between 110 and 120 mm Hg (about 70% of the levels encountered at sea level). The resultant arterial Po_2 of approximately 60 mm Hg (8.0 kPa) is adequate for healthy individuals, but those with underlying pulmonary disease are at risk for significant hypoxemia during flight. Patients most at risk include those with advanced COPD complicated by chronic hypercapnic respiratory failure, patients with pulmonary hypertension, and those with restrictive lung disease. Patients with a recent exacerbation of their chronic lung condition should be fully compensated back to baseline before air travel. Patients who have had previous in-flight symptoms are likely to have recurrent issues and warrant closer assessment. Pulse oximetry is a useful screening tool, where an oxyhemoglobin saturation less than 92% at sea level indicates a likely need for in-flight supplemental oxygen. In most cases, 2 to 3 liters per minute of supplemental oxygen by nasal cannula is adequate. In those with sea level oxygen saturation between 92% and 95%, hypoxia altitude simulation testing, available at some centers, can be used to determine the need for oxygen supplementation. In patients who are already on long-term supplemental oxygen, doubling of the flow rate during flight is typically adequate.

Patients with advanced lung disease over time may develop air-filled bullae, blebs, or cysts. These noncommunicating cavities will expand under hypobaric conditions; however, because airline cabins are pressurized, the risk of in-flight rupture and subsequent pneumothorax is believed to be low. The risk of pneumothorax is probably higher in those who have had a recent exacerbation of obstructive airways disease (asthma or COPD), during which air trapping can be pronounced, and such patients should delay air travel until the acute phase resolves. Signs or symptoms indicative of a pneumothorax (acute chest pain, dyspnea) should prompt the in-flight administration of supplemental oxygen, which promotes resorption of pleural air.

Following cardiothoracic surgery, a delay of 3 to 4 weeks before air travel is reasonable. An existing pneumothorax has traditionally been considered a contraindication to flight owing to the potential risk of expansion and tension physiology. Air travel may be safe in the presence of a small postoperative pneumothorax that has been radiographically stable.

KEY POINTS

- Pulse oximetry is a useful screening tool for patients who have had previous in-flight symptoms of pulmonary disease, where an oxyhemoglobin saturation of less than 92% at sea level indicates a likely need for in-flight supplemental oxygen.
- In patients who are already on long-term supplemental oxygen, doubling of the flow rate during flight is typically adequate.

Critical Care Medicine: ICU Utilization H

Recognizing the Critically Ill Patient

There are no commonly accepted criteria for admission to an ICU. Signs and symptoms of clinical instability including

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hypotension, hypoxemia, arrhythmias, and mental status changes may be useful to identify patients who require intense resources or may be at risk of deterioration. Several scoring systems (APACHE, SOFA, SAP) have been designed to help classify the severity of disease of patients admitted to the ICU. These scoring systems use vital signs and risk factors such as chronic disease, emergent surgery, and immunosuppression to calculate risk of mortality. Although they are rarely, if ever, used as ICU admission criteria, they are used to objectively compare severity and progression of disease and expected and observed mortality. Disease-specific scoring systems can also be used to triage patients based on risk of deterioration or death. Examples are the simplified Pulmonary Embolism Severity Index (sPESI), the Pneumonia Severity Index (PSI), or CURB-65 for predicting mortality in community-acquired pneumonia. Electronic early warning systems based on vital signs, age, and current or trending clinical information have also been developed to identify at-risk patients. These systems, which utilize telemedicine, have been available for some time, but data supporting their effectiveness are lacking.

Organization of Critical Care

To improve early management and resuscitation of patients at risk or deteriorating, many health care systems have developed rapid response teams (RRT) or medical emergency response teams, with the aim of recognizing patients promptly, triggering early evaluation and management, and moving the patient to a higher level of care. A key element of this system is the ability for any member of the health care team to trigger the RRT. Systematic reviews and meta-analyses of the effectiveness of these teams have demonstrated a decrease in cardiac and respiratory arrests and unexpected deterioration but not decreased mortality in adults.

Determining the admission to a critical care bed is more complicated than simply assessing the level of patient illness. This is determined in a significant way by hospital and unit policies and resources unique to each institution. No standard admission model exists, although international societies have published guidelines. Hospitals have developed institution-specific protocols to better manage patients who require life support technology.

An ICU is equipped with technology that allows continuous monitoring and delivery of life-sustaining interventions, such as mechanical ventilation or extracorporeal circulation. Hospital units designated as ICUs typically have the sickest patients and require nurse-to-patient ratios of 1:1 or 1:2, whereas a progressive care unit (also called intermediate, transitional, or step-down unit) may have a nurse-to-patient ratio as high as 1:5, reflecting patients with less acuity.

Critical care is generally defined as open-unit versus closed-unit, and low-intensity versus high intensity. In an open unit, patients are managed by their primary team, which may include, but does not require a critical care consultant. Patients in a closed unit are managed primarily by the critical care team. Low-intensity units are open units. Although high-intensity units can be open or closed units, the critical care team is present throughout the day providing consultation. High-intensity and closed models with continuous staffing of ICUs by intensivists have been controversial; recent systematic reviews and meta-analyses show no differences in mortality between the staffing models, and minimal differences in length of stay. H

KEY POINTS

- Rapid response teams have been shown to decrease the incidence of cardiac and respiratory arrests but not change hospital mortality in adults.
- Recent evidence shows no differences in mortality between open and closed ICUs, and minimal differences in length of stay.
- HVC High-intensity and closed models of critical care with continuous staffing of ICUs by intensivists have been controversial; recent systematic reviews and meta-analyses show no differences in mortality between the staffing models, and minimal differences in length of stay.

Principles of Critical Care

H

Comprehensive Management of Critically Ill Patients

The care of patients in an ICU must be multidisciplinary and team-based. Critical care teams often include pharmacists, respiratory therapists, physical therapists, occupational therapists, case managers, and social workers in addition to nurses and physicians. The goal of care is to restore health and allow the patient to return home while minimizing time in the hospital, medical complications, and long-term effects of critical illness.

Patients in the ICU are at risk for developing many hospital-acquired conditions. The most common are health care-associated infections (central line-associated bloodstream infection, ventilator-associated pneumonia, catheter-associated urinary tract infection, *Clostridium difficile* colitis), skin and soft tissue pressure injury (including ulceration), malnutrition, gastrointestinal bleeding, delirium, and neuromuscular weakness (see MKSAP 18 Infectious Disease). Protocolized care can improve safety and decrease the incidence of these conditions. Hospital-acquired infections are considered avoidable and unacceptable events. Infections have become quality metrics and the focus of protocols standardizing care, for example to reduce central line infections. Other interventions include the use of a checklist during rounding on patients to improve compliance with ICU prophylaxis measures.

Protocols used in the ICU should be evidence-based and periodically reviewed to ensure accuracy. For instance, although stress ulcer prophylaxis with acid suppression has been standard practice, recent recognition of its association

with increased risk of ventilator-associated pneumonia, *C. difficile* colitis, respiratory failure, and coagulopathy has raised concerns about the risk versus benefit for acid suppression. Coupled with data suggesting that the incidence of stress ulcers is decreasing, which may be due to early low-volume enteral feeding in critically ill patients, this emphasizes the importance of critical review of protocols as new evidence becomes available.

Skin and soft tissue pressure injuries are a key quality metric in the performance of an ICU. Scoring systems such as the Braden scale use clinical criteria to define risk of pressure injury in an objective manner. This helps establish specific care to prevent development of such injuries. Essential nursing care includes skin integrity monitoring and avoidance of high-risk situations, such as ongoing contact on pressure points and excessive skin moisture (see MKSAP 18 General Internal Medicine).

The complexity of disease and interventions in a critically ill patient requires a methodical approach to daily care. Many ICUs use an organ system–based approach, which allows caregivers to review the main disease process, its effects on organs and systems, and prophylactic and maintenance interventions that are essential to patient well-being.

Mechanical Ventilatory Support: General Ventilator Principles

Admission to the ICU for respiratory insufficiency is prompted by three basic conditions: (1) hypoxemic respiratory failure; (2) ventilatory (hypercapnic) respiratory failure; and (3) upper airway impairment. Acute hypoxemic respiratory failure is caused by ongoing perfusion of lung units that are no longer ventilating because of alveolar collapse or flooding with pus, edema fluid, or blood. Hypoxemia is reversed by application of positive end-expiratory pressure to the lung, which opens up flooded or collapsed alveoli. Adequate ventilation requires the generation of sufficient pressure by the respiratory muscles to create a pressure gradient that moves air from the mouth to the alveoli. The pressure generated has to overcome both elastic (chest wall and lung) and resistive (airway) forces. Ventilatory failure can result from elastic and resistive forces that are too high or respiratory muscles that are too weak to generate the necessary pressure gradient. Mechanical ventilator support for ventilatory failure can be accomplished by one of two methods: noninvasive, using a nasal or full face mask; or invasive, with an endotracheal tube or tracheostomy. Selection of noninvasive or invasive ventilation is dependent on the clinical situation and the goals of treatment. Initiation of any form of mechanical ventilatory support should be done in a monitored unit (for example, emergency department, ICU).

Noninvasive Mechanical Ventilation

Fundamental Concepts

Noninvasive positive pressure ventilation is administered through a facial or nasal mask. Higher pressures usually require a full face mask to achieve the desired level of positive pressure.

There are two types of noninvasive mechanical ventilation (NIV): continuous positive airway pressure (CPAP) and bilevel positive airway pressure (BPAP). CPAP delivers a constant airway pressure during inspiration and expiration. BPAP delivers a higher level of positive airway pressure during inspiration than during expiration, thus providing additional inspiratory support. This additional inspiratory support with BPAP increases tidal volume and maintains an appropriate level of gas exchange while requiring less respiratory effort by the patient. **Table 35** highlights the physiological effects and indications for these different modes of ventilatory support.

TABLE 35. Modes of Noninvasive Ventilation

Mode	Function	Physiologic Effects	Indications
CPAP	Applies and maintains a constant airway pressure throughout the respiratory cycle	Maintains patent airway in setting of obstructive sleep apnea, increases functional residual capacity, increases mean airway pressure	Obstructive sleep apnea Pulmonary edema Excessive dynamic airway collapse Pre-intubation Post-extubation
BPAP	Applies two different levels of airway pressure: inspiratory (IPAP) and expiratory (EPAP) positive airway pressure	Same as CPAP, but also decreases work of breathing and augments tidal volume	COPD exacerbation Obesity hypoventilation syndrome Neuromuscular diseases Time-limited trial in selected "do not intubate" patients with clear goals of care
BPAP with S/T mode	BPAP with a minimum set respiration rate	In case of apnea it will continue to deliver breaths	Hypoventilation, central apneas

BPAP = bilevel positive airway pressure; CPAP = continuous positive airway pressure; EPAP = expiratory positive airway pressure; IPAP = inspiratory positive airway pressure; S/T = spontaneous/timed.

H CONT.

Indications and Patient Selection

Evidence favors the use of NIV in the critical care setting in patients with COPD exacerbations, cardiogenic pulmonary edema, neuromuscular disease, obesity hypoventilation syndrome, and in patients who have been extubated, which places them at high risk of morbidity. However, NIV also increases the risk of mortality in some patients, such as those with COPD who require subsequent intubation. All patients placed on NIV need to be monitored and reevaluated within 2 hours to determine if the therapy is effective or if adjustments or more invasive therapy is needed.

The use of NIV has not been shown to benefit patients with asthma exacerbations, although the data are limited because of small numbers of patients and methodological design flaws. NIV is often used for patients who are not candidates for invasive mechanical ventilation, in part to decrease or palliate respiratory distress. NIV was thought to be beneficial for immunosuppressed patients, but recent trials have cast doubt about its effectiveness. Finally, the use of NIV in patients with hypoxemic respiratory failure remains controversial. Studies have not demonstrated benefit, and there is some evidence of harm.

Contraindications to the use of NIV include altered mental status, increased airway secretions, emesis, gastric distention, airway obstruction, recent esophageal surgery, cardiac arrest, inability to protect the airway, facial trauma/surgery (including oral, nasal, or sinus), and patient intolerance of the mask.

Application

NIV can be delivered with a critical care ventilator, a portable ventilator, or a home device. Initiation of NIV for patients with acute respiratory failure should always be done in a monitored unit by trained providers. Proper mask sizing and patient adaptation to the device are essential; these require time and coaching of the patient. The timing of instituting NIV is essential, as late application (impending respiratory failure) is related to the need for subsequent intubation and to worse outcomes. After initiation, patients should be closely monitored for tolerance and adverse effects (patient comfort, skin integrity, gastric distention, and eye irritation), effectiveness of the ventilatory settings (measured using tidal volumes and respiration rate), and clinical improvement (blood pH, respiration rate, oxygen saturation as measured by pulse oximetry, and mental status). Failure to improve on NIV is associated with increased mortality.

High-Flow Humidified Nasal Cannula Devices

High-flow humidified nasal cannula has surged as a new modality for oxygenation support in the critically ill. It consists of a device that mixes and humidifies high-flow air and oxygen (30 L/min or more) to deliver a reliable FIO_2 (0.21 to 1.0) through a nasal cannula. The high flow creates positive airway pressure; the amount of pressure depends on the flow rate and cannot be measured or monitored consistently. Delivery of inspired gas through high-flow humidified nasal cannula decreases the work of breathing, provides heated and humidified gas at a reliable FIO_2, and decreases dead space. High-flow humidified nasal cannula is effective for preoxygenating critically ill patients before intubation, as support for postoperative hypoxemic respiratory failure, and as support for acute hypoxemic respiratory failure. Its initial application should occur in the critical care setting with close monitoring for tolerance and effectiveness.

Invasive Mechanical Ventilation

Fundamental Concepts

Invasive mechanical ventilation involves the use of an endotracheal tube or tracheostomy to deliver positive pressure ventilation. Invasive mechanical ventilation allows the use of higher inspiratory pressures and addresses limitations of NIV, such as the ability to protect the airway. The indications for invasive mechanical ventilation are hypoxemic and ventilatory respiratory failure, contraindication to NIV, and inability to protect the airway. The timing, the ventilation mode, and the settings depend on the disease and the patient (**Table 36**).

The appropriate mode of invasive mechanical ventilation is chosen based on its ability to achieve safety, comfort, and ultimate liberation from the ventilator, as well as on the patient's disease and physiological status. Safe mechanical ventilation requires adequate minute ventilation and oxygenation while maintaining an appropriate tidal volume to prevent ventilator-induced lung injury (see Common ICU Conditions). Ventilator-induced lung injury can occur early or late in the course of inappropriate ventilation. Appropriate tidal volume is especially important for patients who cannot independently sustain minute ventilation because of paralysis or sedation, as well as for patients who require limited tidal volume, such as those with early acute respiratory distress syndrome.

When patients are awake and the risk of lung injury has decreased, patient-ventilator interaction should be optimized to provide comfort through adequate breath support. Important considerations include the patient's level of respiratory muscle weakness or fatigue, the presence of acidosis, and the patient's level of anesthesia.

Weaning

Patients should be liberated from mechanical ventilation as soon as possible. The concurrent use of daily awakening or targeted light sedation protocols and spontaneous breathing trials reduces mechanical ventilation time and mortality (**Table 37**). Weaning strategies have shifted from gradual reduction of support to intermittent testing for readiness to breathe, with trials of minimal or no ventilator assistance. Spontaneous breathing trials of 30 minutes to 2 hours using low levels of pressure support (8 cm H_2O or less) or T-piece can identify patients who will be successfully extubated. Recent guidelines suggest pressure support is the preferred method.

TABLE 36. Most Frequently Used Ventilator Modes

Common Name	Mode Classification	Breath Control Variable	Breath Sequence	Targeting Scheme
Volume control and assist/control	VC-CMVs	VC: The ventilator controls the flow (volume) during the mandatory breath. If the patient's effort, lung compliance, or resistance changes, the ventilator will still deliver the set tidal volume (but the pressure will change).	CMV: All breaths are mandatory. The patient may or may not trigger the breath, but the ventilator always ends the breath when the tidal volume is delivered. The name "assist/control" is a misnomer from the past.	Set-point, s: The operator sets all the parameters of the breath (flow waveform, flow rate, and volume). The ventilator only delivers the breath and does not adjust to the patient's effort or change in lung characteristics.
Pressure control and assist/control	PC-CMVs	PC: The ventilator controls the pressure during the mandatory breath. If the patient's effort, lung compliance, or resistance changes, the ventilator will still deliver the set inspiratory pressure (but the tidal volume delivered will change).	CMV: All breaths are mandatory. The patient may or may not trigger the breath, but the ventilator always ends the breath when the preset inspiratory time elapses.	Set-point, s: The operator sets all the parameters of the breath (inspiratory pressure and inspiratory time). The ventilator only delivers the breath and does not adjust to the patient's effort or change in lung characteristics.
Pressure support, continuous positive airway pressure	PC-CSVs	PC: The ventilator controls the pressure during the breath.	CSV: All breaths are spontaneous. The patient triggers and cycles the breath.	Set-point, s: The operator sets all the parameters of the breath (inspiratory pressure). The ventilator delivers the breath and does not adjust to the patient's effort or change in lung characteristics.
Synchronized intermittent mandatory ventilation	PC-IMVs,s or VC-IMVs,s	PC or VC: The mandatory breaths can be set to be volume or pressure controlled, not both.	IMV: Preset mandatory breaths are delivered by the ventilator at a minimum set rate. Spontaneous breaths are permitted in between mandatory breaths. The triggering of the mandatory breath will be coordinated with the patient if the inspiratory effort occurs close to the scheduled time trigger (determined by the set frequency).	Set-point, s: One "s" refers to the mandatory breath and the other to the spontaneous breath. Generally, all spontaneous breaths in IMV are pressure supported (PC-CSVs).

CMV = continuous mandatory ventilation; CSV = continuous spontaneous ventilation; IMV = intermittent mandatory ventilation; PC = pressure controlled; s = set point; VC = volume controlled.

Synchronized intermittent mechanical ventilation is a mode of ventilation that combines mandatory and spontaneous breaths. Some newer technologies are being marketed that use intermittent mandatory ventilation (IMV) sequences and different targeting algorithms, but evidence regarding their performance is scant, and synchronized IMV should not be used to wean patients from mechanical ventilation.

The use of NIV immediately (preemptive) after extubation prevents extubation failure in patients at high risk, such as those with heart failure, COPD, or hypercapnia. The delayed use of noninvasive ventilation after extubation, that is, when the patient develops features of respiratory failure, should be avoided as it is associated with increased mortality.

Ventilator-Associated Pneumonia

Ventilator-associated pneumonia develops 48 hours or more after endotracheal intubation. Preventive strategies include minimizing sedation, early mobilization, minimizing pooling of supraglottic secretions, scheduled oral care with chlorhexidine, head of bed elevation, minimization of changes of the ventilator circuit, and proper hand hygiene. For further discussion of pneumonia see MKSAP 18 Infectious Disease.

KEY POINTS

- Spontaneous breathing trials of 30 minutes to 2 hours using low levels of pressure support (8 cm H_2O or less) can identify patients who will be successfully extubated.
- The use of noninvasive mechanical ventilation immediately after extubation prevents extubation failure in patients at high risk, such as those with heart failure, COPD, or hypercapnia.

Invasive Monitoring

Patients in the ICU often require intensive monitoring of vital signs or vascular pressures, which necessitates the use of invasive methods. Monitoring devices increase the risk of adverse

TABLE 37. Common Criteria for Spontaneous Breathing Trials (SBT) and Extubation[a]
Criteria to Perform SBT
Cause of respiratory failure improved
FIO_2 ≤40% and PEEP ≤5-8 cm H_2O
pH >7.25
Hemodynamic stability
Able to spontaneously breathe
Criteria to Pass SBT: At Least 30 Minutes Without
Clinical evidence of respiratory distress
SpO_2 <90%
Respiration rate >35/min
New arrhythmias
Tachycardia
Hypotension or hypertension
Additional Considerations Before Extubation
Quantity of secretions
Adequacy of cough
Altered mental status

[a]These criteria may differ between institutions.

PEEP = positive end-expiratory pressure; SpO_2 = peripheral arterial oxygen saturation.

H CONT.

effects, so they should be used only when required to obtain information that cannot be obtained with noninvasive methods. For example, the routine use of pulmonary artery catheters does not lead to improved outcomes, is associated with increased side effects, and may increase mortality.

Intravenous Access

There are different types of devices for central intravenous (IV) access. The determination of the type of access depends on many factors including urgency of access, expected duration, and reason for access (**Table 38**). Removal of intraosseus devices must be done as soon as IV access is obtained. Peripheral venous access with a short, wide-bore catheter is the route of choice for rapid volume resuscitation. In general, all IV access should be removed as soon as possible to decrease the risk of complications, mainly infection and thrombosis. Procedure related complications, such as arterial injury, nerve injury, or pneumothorax can be minimized with the use of ultrasound-guided placement. Devices with lower risk of complications (for example, peripheral IV access) should be used whenever possible. H

KEY POINTS

- All intravenous access should be removed as soon as possible to decrease the risk for complications.
- Peripheral intravenous access with a short, wide-bore catheter is the route of choice for volume resuscitation.

Blood Pressure Support

H

Systemic arterial pressure is determined by cardiac output and systemic vascular resistance. Maintenance of arterial blood pressure requires compensatory adjustments when there is either a decrease in cardiac output or inappropriate reduction in systemic vascular resistance (vasodilation). A mean arterial pressure of 65 mm Hg is considered to be the threshold at which there is sufficient pressure for organ perfusion. A study comparing a lower (65-70 mm Hg) vs a higher (80-85 mm Hg) mean arterial pressures strategy in patients

TABLE 38. Types of Central Venous Access

Type	Indications	Duration	Potential Complications	Contraindications
Peripherally inserted central venous catheter	Delivery of potentially caustic medications such as vasoactive agents, sedatives or antibiotics; central venous access	Few days up to 1 year	Low risk overall, avoiding pneumothorax and reducing infectious risk; clot formation or occlusion due to smaller vessel diameter	Current or pending dialysis
Temporary non-tunneled	Same as peripherally inserted central venous catheter; short-term dialysis; central venous pressure monitoring	Usually not more than 6 weeks	Infection; site-specific complications such as pneumothorax for subclavian or low intrajugular approach	
Long-term tunneled (valved tip and nonvalved tip)	Long-term TPN; chemotherapy; long-term antibiotics; dialysis	More than 6 weeks	Infection; valves prevent back bleeding but have an increased risk of catheter malfunction	
Ports or totally implanted	Long-term intermittent access such as chemotherapy	More than 6 weeks	Lowest risk of infection but more difficult to implant with more costs; hidden extravasation beneath skin	
Intraosseous (tibia or humeral head [adults])	When IV access otherwise not obtained but need emergency fluids and/or medications	About 24 hours	Low risk of infection; flow rates may be slower; if pain with infusion can use 2% preservative-free lidocaine injected slowly to control it	Do not place in a bone with a fracture, diagnosis of osteoporosis, or recent (24-48 h) intraosseous access attempt

IV = intravenous; TPN = total parenteral nutrition.

with septic shock demonstrated no difference in mortality. Blood pressure is usually monitored noninvasively with a blood pressure cuff. An arterial line for continuous monitoring is useful when the systolic blood pressure is less than 90 mm Hg, when frequent measurements are needed (particularly for patients requiring IV medication for blood pressure management), or when the cuff readings are unreliable. Assessment of tissue perfusion includes physical examination (skin temperature, mottling, jugular venous distention), ultrasound assessment of inferior vena cava diameter and other dynamic indices, and cardiac examination (echocardiogram, invasive and noninvasive cardiac output monitors). However, in a patient with several physical examination findings suggestive of decreased intravascular volume, the physical examination, including basic vital signs, is sufficient. Management should focus on the underlying cause of blood pressure derangement. For instance, hypotension due to deceased preload should be initially treated with volume resuscitation. Support of blood pressure may require the use of vasopressors (**Table 39**). Norepinephrine is the most commonly used agent and has been shown to reduce mortality. However, other agents are available and may be used in specific situations.

KEY POINT

HVC
- A study comparing a lower (65-70 mm Hg) vs a higher (80-85 mm Hg) mean arterial pressures strategy in patients with septic shock demonstrated no difference in mortality.

Sedation and Analgesia

ICU patients often require sedation and analgesia. The need for analgesia should be monitored frequently, at least every 4 hours, and assessed using an objective scale such as the Behavioral Pain Scale or Critical Care Pain observation tool. Analgesics should be titrated to a goal and the patient should be monitored for side effects. Analgesia should include nonpharmacologic methods, such as relaxation techniques, non narcotic and narcotic medication for general pain, and gabapentin or carbamazepine for neuropathic pain. Intravenous opioids are the drug of choice for treating nonneuropathic pain in critically ill patients, and all have similar efficacy and clinical outcomes when titrated to similar pain intensity endpoints. Additional analgesia should be given before painful procedures, such as thoracostomy tube placement. Most if not all patients requiring invasive mechanical ventilation will need some level of sedation. Sedation in the ICU requires monitoring and should be objectively assessed using a scale such as the Richmond Agitation Sedation Scale (RASS). Agents such as propofol or dexmedetomidine are preferred rather than benzodiazepines. If oversedation occurs, the drug should be stopped until the appropriate level of sedation is achieved, then restarted at half the previous dose.

Interruption of Sedation and Analgesia

Daily interruption of sedation and analgesia is appropriate in critically ill patients and is associated with decreased length of mechanical ventilation, length of ICU stay, and incidence of

TABLE 39. Selection of Vasopressors

Medication	Type of Shock	Receptor Target	Primary Impact	Comments
Dobutamine	Cardiogenic Distributive	β_1, β_2	↑ Inotropy	First choice for cardiogenic shock without hypotension Add-on therapy for distributive shock with depressed cardiac function
Dopamine (high-dose)	Cardiogenic	D, α_1, β_1	↑ SVR, ↑ inotropy	Alternative to norepinephrine in (distributive) shock associated with absolute or relative bradycardia
Dopamine (low-dose)	Cardiogenic Distributive	D, β_1	↑ Inotropy, ↑ HR	Not recommended to augment renal blood flow
Epinephrine	Cardiogenic Distributive Hypovolemic	α_1, α_2, β_1, β_2	↑ SVR, ↑ inotropy	First choice anaphylactic (distributive) shock May be added to norepinephrine in distributive shock
Norepinephrine	Cardiogenic Distributive Hypovolemic	α_1, α_2, β_1	↑ SVR, ↑ inotropy	First choice in cardiogenic, distributive, and hypovolemic shock
Phenylephrine	Distributive	α_1	↑ SVR	May be used when norepinephrine contraindicated (tachyarrhythmias) or failure of first-line drugs
Vasopressin	Distributive Hypovolemic	V	↑ SVR	May be added to norepinephrine in septic shock

HR = heart rate; SVR = systemic vascular resistance.

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delirium. Protocolized light sedation has shown similar patient outcomes to daily sedation interruption.

Delirium

Delirium is characterized by an acute change in cognitive functioning occurring over hours to days, with fluctuations during the course of the day. Features of delirium include inattention, disorganized thinking, executive dysfunction, altered level of consciousness (lethargy or hypervigilance), perceptual disturbances (such as hallucinations or delusions), altered psychomotor activity (hyperactivity, hypoactivity, or alternating periods of hyperactivity and hypoactivity), sleep-wake disturbances, and labile mood. It is extremely common in ICU patients and is associated with increased length of ICU stay, morbidity, mortality, and post-intensive care cognitive impairment. Risk factors for delirium include preexisting dementia, hypertension, alcoholism, and high severity of illness on ICU admission. Patients should be monitored regularly and assessed using scales such as the Confusion Assessment Method-ICU (CAM-ICU) or Intensive Care Delirium Screening Checklist (ICDSC). Measures to decrease the risk of delirium include early mobilization, preservation of nocturnal sleep, adequate pain management, orientation of the patient, provision of visual and hearing aids, and minimization of nonessential medications. Early mobilization, consisting of interruption of sedation and physical and occupational therapy in the earliest days of critical illness, can be effective for treating and preventing delirium. In general, benzodiazepines should not be used for treating delirium in the ICU, unless needed in patients with alcohol withdrawal or seizures. Data do not support the routine use of haloperidol or atypical antipsychotics for the prevention of delirium. Treatment involves identification and correction of the underlying cause, maintaining adequate nutrition and hydration, and preventing complications. For further discussion of delirium see MKSAP 18 Neurology. H

KEY POINTS

- Sedation and analgesia should be monitored using objective standardized scales.
- HVC In general, benzodiazepines should not be used for treating delirium in the ICU, unless needed in patients with alcohol withdrawal or seizures; data do not support the routine use of haloperidol or atypical antipsychotics for the prevention of delirium.

H

Nutrition

Malnutrition in critically ill patients leads to increased morbidity and mortality, and all patients admitted to the ICU should have a nutritional evaluation. Enteral nutrition is preferred unless a contraindication is present (perforation, hemorrhage, or surgery). Guidelines recommend that enteral nutrition should be started within 24 to 48 hours of admission in critically ill patients. There is evidence that early enteral nutrition is associated with decreases in mortality and infections, yet the level of evidence remains low. Critically ill patients who cannot maintain volitional nutritional intake may be fed using a gastric tube, large-bore tube, small-bore tube, or post-pyloric tube; there is no evidence of increased incidence of ventilator-associated pneumonia or aspiration among these methods. Routine measurement of gastric residuals is discouraged because it delays achievement of feeding goals, increases the risk of clogging the enteral access, and may increase the risk of aspiration.

Guidelines recommend that in patients at either low or high risk of problems with nutrition, use of supplemental parenteral nutrition should be considered only after 7 to 10 days of not meeting more than 60% of energy and protein requirements by the enteral route alone. Administration of parenteral nutrition to supplement enteral nutrition may lead to harm and should be avoided. In contrast, parenteral nutrition should be started as soon as possible for severely malnourished patients, those at high risk of malnutrition, and those for whom enteral nutrition is not possible. H

KEY POINTS

- Enteral nutrition is preferred unless a contraindication is present and should be started within 24 to 48 hours of admission in patients anticipated to have prolonged critical illness.
- Parenteral nutrition should be started as soon as possible for severely malnourished patients, those at high risk of malnutrition, and those for whom enteral nutrition is not possible.
- Routine measurement of gastric residuals is discouraged in malnourished patients who are critically ill because it delays achievement of feeding goals, increases the risk of clogging the enteral access, and may increase the risk of aspiration. HVC
- Administration of parenteral nutrition to supplement enteral nutrition may lead to harm and should be avoided. HVC

Early Mobilization

H

Many factors contribute to neuromuscular weakness in critically ill patients, including immobility, disease, medications, and medical interventions in the ICU. Immobility may result in muscular weakness, joint stiffness, ankylosis, pressure ulcers, osteoporosis, gastrointestinal dysmotility, and dysautonomia. Even a few days of immobility can have a prolonged effect on muscular strength; long-term follow-up of patients with critical illness demonstrates persistent muscular weakness at 1 and 5 years. The use of early mobilization strategies consisting of interruption of sedation and physical and occupational therapy in the earliest days of critical illness decreases length of time in the ICU and hospital stay, improves functional status, and decreases mortality. Despite the evidence favoring early mobilization and physical therapy, implementation remains low overall. H

KEY POINT

- The use of early mobilization strategies decreases length of time in the ICU and hospital stay, improves functional status, and decreases mortality.

H

ICU Care Bundles

An ICU care bundle is a series of evidenced-based interventions that have been shown to improve patient outcomes when used together. Bundles can help clinicians monitor patients and guide appropriate interventions. The Institute for Healthcare Improvement has defined three bundles that apply to critical care (**Table 40**).

High Value Care in the ICU

The cost of health care in the United States is the highest per capita in the world. Critical care is responsible for a large proportion of health care costs. However, the survival and quality-of-life outcomes are not that different from those in other top-economy countries. Societal, organizational, and payment pressures have encouraged a focus on providing high value care, which is defined as care that maximizes benefit relative to harms and cost. The ICU is an environment in which high value care can have major effects, as the resources are expensive and the culture favors aggressive resource use. Internal medicine and critical care medical societies have joined the American Board of Internal Medicine (ABIM) Foundation's *Choosing Wisely*® campaign to promote cost-effective strategies that improve patient care (**Table 41**). The focus on resource utilization and cost will remain a central point of health care for the foreseeable future. H

KEY POINTS

- Don't order diagnostic tests at regular intervals (such as every day), but rather in response to specific clinical questions. HVC
- Don't transfuse erythrocytes in hemodynamically stable, nonbleeding patients in the ICU who have a hemoglobin concentration greater than 7 g/dL (70 g/L). HVC
- Don't use parenteral nutrition in adequately nourished critically ill patients within the first 7 days of an ICU stay. HVC
- Don't deeply sedate mechanically ventilated patients without a specific indication and without daily attempts to lighten sedation. HVC
- Don't continue life support for patients at high risk for death or severely impaired functional recovery without offering patients and their families the alternative of care focused entirely on comfort. HVC

ICU Complications

H

Critical care illness is no longer viewed as an acute event that ends at the time of discharge from the ICU. ICU complications may be classified as early, which occur during the hospitalization, or late, which persist after the critical care illness. During the last decade, there has been increased recognition of

TABLE 40. ICU Care Bundles

Prevention of Ventilator-Associated Pneumonia
Head of bed elevation at least 30 degrees
Daily sedation interruption and assessment of readiness to extubate
Stress ulcer prophylaxis
Deep vein thrombosis prophylaxis
Daily oral care with chlorhexidine
Central Line-Associated Bloodstream Infections
Hand hygiene
Maximal barrier precautions
Chlorhexidine skin antisepsis
Avoid femoral access
Daily review of line necessity
Sepsis
3-hour bundle
Measure lactate level
Obtain blood cultures before antibiotics
Administer broad-spectrum antibiotics
Administer 30 mL/kg crystalloids for hypotension or lactate ≥4 mEq/L (4 mmol/L)
6-hour bundle
Use vasopressors if no response to fluids; keep MAP above 65 mm Hg
Repeat volume status and tissue perfusion assessment

MAP = mean arterial blood pressure, calculated as [(2 × diastolic) + systolic]/3.

TABLE 41. ICU *Choosing Wisely*® Top Five

Don't order diagnostic tests at regular intervals (such as every day), but rather in response to specific clinical questions.
Don't transfuse erythrocytes in hemodynamically stable, nonbleeding patients in the ICU who have a hemoglobin concentration greater than 7 g/dL (70 g/L).
Don't use parenteral nutrition in adequately nourished critically ill patients within the first 7 days of an ICU stay.
Don't deeply sedate mechanically ventilated patients without a specific indication and without daily attempts to lighten sedation.
Don't continue life support for patients at high risk for death or severely impaired functional recovery without offering patients and their families the alternative of care focused entirely on comfort.

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persistent disability and a focus on treatment to prevent late consequences of critical illness.

ICU-Acquired Weakness

Between 50% and 100% of critically ill patients develop muscle weakness. Muscle weakness may result from complications involving the nervous system (critical illness polyneuropathy), the muscles themselves (critical illness myopathy), or some combination thereof, or may be nonspecific (ICU-acquired weakness). It may also be related to prolonged neuromuscular blockade (**Table 42**). Identified risk factors include sepsis, multisystem organ failure, severe illness, prolonged immobility, and hyperglycemia. Evaluation for ICU-acquired weakness can initially be done at the bedside using the Medical Research Council muscle scale. ICU-acquired weakness generally improves over weeks to months, but may persist in a small percentage of patients for up to 2 years. Strategies to minimize ICU-acquired weakness include aggressive management of critical illness, early mobilization, and management of hyperglycemia. H

TABLE 42. Definitions and Characteristics of ICU-Acquired Weakness

ICU-Acquired Weakness
Clinically detected weakness with no other explanation other than the critical illness
Proximal and distal symmetrical flaccid weakness with sparing of cranial nerves
Often failure to wean from mechanical ventilation is first indication of weakness
Diagnosis of exclusion
Critical Illness Polyneuropathy
ICU-acquired weakness with electrophysiological evidence of axonal polyneuropathy
Quadriparesis or quadriplegia, decreased muscle tone, sparing of facial muscles. Deep tendon reflexes decreased
Critical Illness Myopathy
ICU-acquired weakness with electrophysiological and/or histological evidence of myopathy
Examination is similar to critical illness polyneuropathy. New sensory loss is suggestive, CK may be elevated
Critical Illness Neuromyopathy
Coexistence of critical illness polyneuropathy and critical illness myopathy
Mixed features, perhaps most prevalent form
Prolonged Neuromuscular Blockade
Prolonged effects in patients with renal failure, liver failure, hypermagnesemia
Flaccid areflexic quadriplegia with cranial nerve involvement
Repetitive nerve stimulation shows decremental response

CK = creatine kinase.

KEY POINT

- Strategies to minimize ICU-acquired weakness include aggressive management of critical illness, early mobilization, and management of hyperglycemia.

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Long-Term Cognitive Impairment

As many as 30% to 80% of patients with critical care illness develop long-term impairment in cognition, which manifests clinically as cognitive impairment with similarities to acquired dementia. Observations have demonstrated that the level of impairment 1 year after critical illness is similar to mild Alzheimer disease. Although the specific risk factors and interventions related to developing cognitive impairment are not well defined, the development and duration of delirium during the ICU stay appear to be major predictors.

Post-Intensive Care Syndrome

Post-intensive care syndrome describes a group of symptoms that present in patients after an episode of critical care. The symptoms have been grouped according to the area that they affect (physical impairment, mental health, and cognitive impairments). Patients with post-intensive care syndrome have increased health care use, increased morbidity and mortality, and impaired quality of life. Post-intensive care syndrome also affects the caregivers and family of the critically ill patient; it has been reported that family members experience anxiety, depression, and post-traumatic stress disorder. Current research and interventions are focusing on how to improve recognition, prevention, diagnosis, and management. H

Common ICU Conditions

Acute Respiratory Failure

Acute respiratory failure occurs when a patient cannot adequately oxygenate blood (hypoxemia) or remove carbon dioxide (hypercarbia or hypercapnia) from the blood. It is essential to quickly stabilize the patient and identify the cause of respiratory failure. History and physical examination are essential, but tests such as chest radiograph (**Table 43**), CT scan, arterial blood gas, and pulse oximetry are also useful. A structured approach allows clinicians to both identify and treat factors leading to respiratory failure. This approach includes evaluation for airway compromise, inadequate oxygenation, and inadequate ventilation. (**Figure 19**)

Acute Upper Airway Management

In patients who cannot maintain a patent airway or protect their airway against aspiration, a secure airway should be established by inserting a cuffed endotracheal or tracheostomy tube. High-flow oxygen; bag-valve mask ventilation; or oropharyngeal, nasopharyngeal, or laryngeal mask airway can aid oxygenation and ventilation when immediate intubation is not feasible and should be used until the airway can be secured. H

TABLE 43. Radiographic Findings and Differential Diagnosis in Acute Respiratory Failure

Finding	Differential Diagnosis
No infiltrate	Asthma/COPD exacerbation
	Drug overdose
	Intracardiac shunt
	Neuromuscular weakness
	Pulmonary embolus
Diffuse infiltrates	Acute respiratory distress syndrome
	Cardiogenic pulmonary edema
	Acute exacerbation of idiopathic pulmonary fibrosis
	Pneumonia
	Other (for example, acute hypersensitivity pneumonitis, acute eosinophilic pneumonia)
Focal infiltrate	Airway obstruction
	Atelectasis
	Pneumonia
	Pulmonary infarction

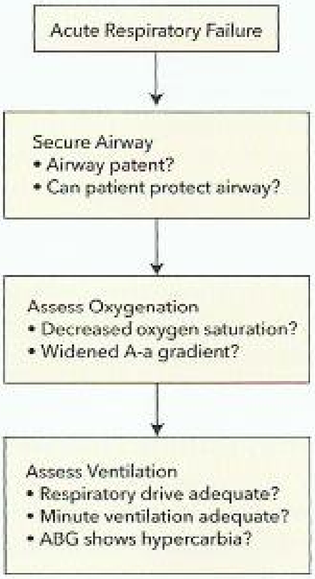

FIGURE 19. Key components to the assessment of acute respiratory failure. A-a = alveolar-arterial; ABG = arterial blood gas.

KEY POINT

- In patients who cannot maintain a patent airway or protect their airway against aspiration, a secure airway should be established by inserting a cuffed endotracheal or tracheostomy tube.

Airway Obstruction

Respiratory failure can result from intraluminal obstruction or extraluminal compression of the upper airways. Patients with partial airway obstruction may have tachypnea, increased respiratory effort, or an upright (tripod) posture with use of accessory muscles. Absent air movement, inability to talk, or cyanosis suggests complete obstruction and signifies a medical emergency. Inspiratory stridor suggests an obstruction above the level of the vocal cords, whereas expiratory stridor and wheezing suggest an intrathoracic process. Pulse oximetry in the setting of partial upper airway obstruction and stridor is usually normal. Patients with potential upper airway obstruction should be cautiously examined to prevent exacerbation of the condition. In patients with respiratory distress or for whom the risk of respiratory deterioration is high, early intubation is indicated.

Acute Inhalational Injuries

Smoke Inhalation

Pulmonary complications are a leading cause of morbidity and mortality in patients who have been burned or experienced significant smoke exposure from fires. Direct thermal injury due to smoke inhalation is usually limited to the upper airways. However, steam inhalation causes direct thermal injury throughout the tracheobronchial tree due to its ability to carry heat more efficiently than dry, hot gas. Following smoke inhalation, one-third of patients develop airway edema or mucosal sloughing from epithelial necrosis. Chest physiotherapy and serial bronchoscopic suctioning are frequently necessary to facilitate continued airway clearance. Injury to the distal tracheobronchial tree and lung parenchyma is caused by chemicals in smoke that generate a complex cascade of bronchoconstriction, pulmonary edema, ventilation perfusion ($\dot{V}/\dot{Q}$) mismatch, and bronchial cast formation. Treatment is largely supportive.

Secondary respiratory infections are common and are a major cause of morbidity and mortality. Pneumonia is the most common complication following smoke inhalation injury, especially from *Staphylococcus* and *Pseudomonas* specie. Systemic toxicity from substances like carbon monoxide (CO) and hydrogen cyanide (HCN) are common following smoke inhalation. Clinicians should suspect CO and HCN poisoning in all patients with smoke exposure. Both can cause a reduction in the oxygen-carrying capacity of hemoglobin. Unfortunately this may not be apparent, as CO and HCN are not detected by standard pulse oximetry, and oxygen saturation measurement may be falsely normal. Additional details of CO and HCN poisoning are reviewed in Toxicology.

Other Forms of Inhalational Injury

Inhalational injuries related to chemical vapors are uncommon. War, industrial, or farming operations and exposure to home cleaning or pesticide agents constitute most chemical inhalational injuries. Water-soluble agents usually affect mucosal structures of the upper airway and have rapid onset of symptoms. Water insoluble agents affect deeper structures including lung parenchyma and distal airways, and symptoms are often delayed. Edema, bronchospasm, asphyxiation, and direct systemic toxicity are common. Key features of

H CONT.

inhalational agents are listed in **Table 44**. Treatment is supportive, with a specific antidote, atropine, indicated only in cholinesterase inhibitor exposure.

Hypoxemic Respiratory Failure

Hypoxemic respiratory failure is caused by inadequate oxygenation of hemoglobin. The most common causes of hypoxemic respiratory failure in the ICU are $\dot{V}/\dot{Q}$ mismatch and shunt ($\dot{V}/\dot{Q}$ = 0), which occur when perfused areas of the lung are not ventilated, whether because of alveolar collapse (atelectasis) or filling of alveoli with blood, pus, protein, or water. An increased alveolar-arterial oxygen difference (gradient) is the key feature of $\dot{V}/\dot{Q}$ mismatch and shunt. The gradient is derived by subtracting the measured arterial Po_2 from the calculated alveolar Po_2.

The alveolar Po_2 is calculated using the alveolar gas equation:

$$\text{Alveolar } Po_2 = (Fio_2 \times [P_{atm} - 47]) - (1.25 \times Pco_2)$$

Fio_2 is the fraction of inspired oxygen (0.21 in ambient air), P_{atm} is the atmospheric pressure (760 mm Hg at sea level), and 47 represents the partial pressure of water in mm Hg at 37°C (98.6°F). The alveolar-arterial gradient increases with age, and normal gradients in individuals breathing ambient air (but not applicable in patients on supplemental oxygen) can be estimated with the equation:

$$\text{Expected alveolar-arterial oxygen gradient} = 2.5 + 0.21 \times \text{age in years}$$

TABLE 44. Key Features of Inhaled Agents

Agent	Characteristics	Clinical Features Following Exposure
Ammonia	Colorless, ammonia odor	Cough, upper airway burns, pulmonary edema, asphyxiation in poorly vented areas
Chlorine	Yellow-green, chlorine odor	Upper airway irritation and burns, bronchospasm, pulmonary edema
Phosgene	Colorless, musty odor like fresh cut grass	Systemic toxicity including elevated methemoglobin level, cyanosis and metabolic acidosis. Pulmonary edema
Mustard gas	Yellow-brown vapor, odor like garlic or onions	Upper airways burns and obstruction can occur
Organophosphates and other cholinesterase inhibitors	Colorless, fruity odor	Systemic toxicity causing acetylcholine toxicity (rhinorrhea, bronchorrhea, diarrhea, bronchospasm, flaccid paralysis, apnea)

Scenarios of acute and chronic hypoxemia are difficult to distinguish using arterial blood gases alone. A helpful distinguishing feature is the time course of development of symptoms; in addition, the presence of polycythemia suggests chronic hypoxemia. Findings on chest imaging studies may be helpful, as diffuse alveolar filling is more suggestive of acute hypoxemic respiratory failure, whereas interstitial lung disease is more suggestive of a chronic process.

Signs of acute hypoxemic respiratory failure include recent onset of increased work of breathing, tachypnea, and anxiety. Cyanosis of the lips or fingers may be present when oxygenation of hemoglobin is severely compromised, often below 80%. Findings on auscultation such as crackles, wheezing, egophony, or rhonchi may suggest an underlying cause.

Management of hypoxemic respiratory failure centers on administration of supplemental oxygen and measures to open alveoli that are fluid-filled or collapsed, such as mechanical ventilation with administration of both positive inspiratory and positive end-expiratory pressure (PEEP). In extreme cases where the technology and expertise are available, extracorporeal membrane oxygenation (ECMO) can be used to provide external oxygenation of, and removal of carbon dioxide from, the blood. Disease-specific management is discussed below. H

KEY POINTS

- The most common causes of hypoxemic respiratory failure in the ICU are ventilation-perfusion mismatch and shunt, which occurs when perfused areas of the lung are not ventilated, whether because of alveolar collapse (atelectasis) or filling of alveoli with blood, pus, protein, or water.
- Management of hypoxemic respiratory failure centers on administration of supplemental oxygen and measures to open alveoli that are fluid-filled or collapsed.

Acute Respiratory Distress Syndrome

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Acute respiratory distress syndrome (ARDS) is characterized by a dysregulated inflammatory response within the lungs. The most common overall cause of ARDS is sepsis, but there are various other common causes of ARDS, including both direct and indirect pulmonary insults (**Table 45**).

In ARDS, disruption of surfactant production, vascular endothelial injury, and alveolar epithelial cell injury occur, leading to excess fluid and protein extravasation into interstitial and alveolar spaces. This results in interstitial and alveolar filling, microatelectasis, increased $\dot{V}/\dot{Q}$ mismatch, decreased lung compliance, and increases in both shunt and dead-space ventilation. Histology shows diffuse alveolar damage.

ARDS is a clinical diagnosis. The most recent guidelines defining ARDS were updated in the 2012 Berlin Definition of ARDS (**Table 46**). The Berlin definition emphasizes that ARDS occurs rapidly after an inciting event and is

TABLE 45. Common Causes of Acute Respiratory Distress Syndrome

Direct Pulmonary Injury	Indirect Pulmonary Injury
Aspiration of gastric contents	Disseminated intravascular coagulation
Fat embolism	Non-thoracic trauma
Near drowning	Pancreatitis
Pneumonia	Pulmonary reperfusion injury (following lung transplantation)
Smoke or chemical inhalation	Sepsis/septic shock
Thoracic trauma/thoracic contusion	Transfusion of blood products

TABLE 46. 2012 Berlin Definition of Acute Respiratory Distress Syndrome

The following criteria must be met:
Onset within 1 week of known ARDS insult (most cases occur within 72 hours)
Bilateral opacities on chest imaging consistent with pulmonary edema
Respiratory failure not related to cardiac failure or volume overload
Arterial PO_2/FIO_2 <300 on at least 5 cm H_2O PEEP from noninvasive or invasive mechanical ventilator
Once criteria for diagnosis are met, severity of ARDS is based on the following criteria:
Mild = Arterial PO_2/FIO_2 >200 to <300
Moderate = Arterial PO_2/FIO_2 100 to 200
Severe = Arterial PO_2/FIO_2 <100

ARDS = acute respiratory distress syndrome; PEEP = positive end-expiratory pressure.

Data from Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, Fan E, et al; ARDS Definition Task Force. Acute respiratory distress syndrome: the Berlin definition. JAMA. 2012;307:2526-33. [PMID: 22797452] doi:10.1001/jama.2012.5669

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characterized by diffuse, bilateral, noncardiogenic pulmonary edema. Patients with ARDS are at high risk of mortality, which increases with ARDS severity. However, mortality is usually the result of the underlying disease that triggered ARDS, secondary infection, or multi-organ dysfunction rather than refractory hypoxemia.

Ventilatory Management

Most patients with ARDS are managed with invasive mechanical ventilation. PEEP and low tidal volume ventilation (LTVV) are the cornerstones of ARDS management, as they are associated with prevention of ventilator-associated lung injury. Because lungs affected by ARDS are frequently characterized by areas of noncompliant, diseased lung adjacent to lung with more normal compliance, high tidal volumes can lead to regional areas of lung overdistention and injury (volutrauma). In 2000, the ARMA trial evaluated the benefits of LTVV (tidal volumes of 4 to 8 mL/kg) compared with higher tidal ventilation conventionally used at the time. The trial showed a significant, 11% absolute reduction in mortality with the use of LTVV. This trial also sought to prevent two other causes of ventilator induced lung injury. Barotrauma, or lung injury due to high transpulmonary pressures, was prevented in the LTVV arm by avoiding plateau pressures greater than 30 cm H_2O. Current ARDS goals include both a tidal volume of ~6 mL/kg of predicted body weight and maintenance of the lowest possible plateau pressure. The ARMA trial also affirmed the utility of PEEP as having three benefits. First, it prevents lung injury associated with repeated opening and closing of distal airways and alveoli (atelectrauma). Second, it improves homogeneity of the lung parenchyma by reducing gross differences in regional lung compliance. Third, it improves $\dot{V}/\dot{Q}$ mismatch and shunt by maintaining alveolar recruitment. Although PEEP is now a standard part of lung protective ventilation, no definitive level of optimal PEEP has been designated for ventilation of patients with ARDS.

Despite the clear benefits of LTVV, adherence remains poor. Barriers to improved adherence include underrecognition of patients with ARDS, improper sedation of patients who do not initially tolerate LTVV, and a propensity for patients to develop respiratory acidosis from hypercapnia when using LTVV.

Ventilating patients in the prone position may reduce compression of portions of the lung behind the cardiac and mediastinal structures and improve $\dot{V}/\dot{Q}$ matching in ARDS patients. A recent large, randomized trial (PROSEVA) demonstrated improved mortality in patients with an arterial PO_2/FIO_2 ratio less than 150 who were treated with early prone positioning and LTVV. Early prone positioning for at least 12 hours a day should be considered in patients with severe ARDS.

The use of ECMO has been increasing, largely due to a single, prospective randomized controlled trial performed during the 2009 H1N1 influenza pandemic (CESAR trial). Although this trial suggested improved mortality in ARDS patients referred to a center capable of administering ECMO, many referred patients never received ECMO. This suggests that improved mortality may have simply been the result of referral to a center with improved expertise in ARDS management, not due to treatment with ECMO itself. In patients with severe, refractory hypoxemia, both prone positioning and ECMO may be considered; however, the effectiveness of prone positioning is better supported by data.

In patients with refractory hypoxemia, a recruitment maneuver—applying a high level of CPAP to open collapsed alveoli (for example, continuous pressure to 35 cm H_2O for 40 seconds)—may be considered. Although controversial, the 2017 ATS/ESICM/SCCM Guideline on Mechanical Ventilation in Adults with Acute Respiratory Distress Syndrome provides

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a conditional recommendation for recruitment maneuvers. The guideline cautions that recruitment maneuvers should not be used in patients with preexisting hypovolemia or shock due to a high propensity for hemodynamic deterioration during the maneuver.

Other methods to optimize ventilator management in ARDS have been suggested, including inverse ratio ventilation, esophageal pressure and driving pressure-guided titration of PEEP, and high-frequency oscillator ventilation (HFOV). None of these have demonstrated mortality benefit in ARDS. H

KEY POINT

- Treating patients with severe acute respiratory distress syndrome using early prone positioning and low tidal volume ventilation has demonstrated clinically important mortality benefit.

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Nonventilatory Management

Although mortality in ARDS has decreased, most of this is attributed to improved mechanical ventilation strategies. Mechanically ventilated patients often require sedation to improve patient-ventilator interactions and achieve LTVV goals. Data support minimizing sedation to intermittent, bolus administration when possible and daily awakening of patients who require continuous sedation. Use of nursing-led sedation protocols can decrease the overall sedation required and improve patient outcomes. Excessive sedation increases risk of delirium and nosocomial infection, increases length of ICU stays, and is a likely contributor to many long-term psychological and physical effects now associated with ARDS.

ICU patients receive volume resuscitation for a host of reasons. In ARDS, the FACCT trial suggested excessive fluid resuscitation is harmful to ARDS patients. This trial compared conservative to liberal fluid strategies based on central venous pressure and pulmonary artery occlusion pressure (a surrogate for left atrial pressure) in patients with ARDS. Although mortality did not differ between groups, patients who were treated with conservative fluid management showed improved oxygenation and decreased time on the ventilator and in the ICU. In patients who are hemodynamically stable and do not have end-organ hypoperfusion, minimizing fluid administration is warranted.

The use of paralytic agents in ARDS to improve oxygenation and decrease ventilator-induced lung injury is controversial, as there have been concerns about the potential association of paralytics with critical illness myopathy. However, a recent study in patients with ARDS who were paralyzed within 48 hours of starting mechanical ventilation found no difference in critical illness myopathy and a lower mortality. Although further study is warranted, this practice has been recommended as an early intervention strategy in patients with severe ARDS.

Other therapies, including nutritional modifications, glucocorticoid administration, macrolide antibiotics, inhaled nitric oxide, prostacyclin analogues, and stem cells or granulocyte-macrophage colony-stimulating factor have conflicting or limited evidence and are not recommended in the management of ARDS.

Heart Failure

Clinically, both acute cardiogenic pulmonary edema and ARDS present with pulmonary edema and hypoxemic respiratory failure. But unlike ARDS, cardiogenic pulmonary edema responds to aggressive diuresis and optimization of cardiac function. In patients who present with acute respiratory failure and features of ARDS, but no clear trigger, it is important to evaluate for cardiogenic causes, which include heart failure, mitral and aortic valve disease, myocardial ischemia, and arrhythmias (particularly atrial fibrillation with rapid ventricular rate). Evaluation for a cardiac cause of pulmonary edema should include an assessment for fluid overload (jugular venous distention, S_3, peripheral edema), an electrocardiogram, B-type natriuretic peptide, serial serum troponins, and an echocardiogram. H

KEY POINT

- Evaluation for a cardiac cause of pulmonary edema should include an assessment for fluid overload, an electrocardiogram, B-type natriuretic peptide, serial serum troponins, and an echocardiogram.

Atelectasis

Atelectasis is a common postoperative complication. Inadequate postoperative analgesia or impaired respiratory mechanics following thoracic and abdominal surgeries can lead patients to adopt shallow breathing patterns or avoid airway clearance and cough. Presentation is often delayed following liberation from a ventilator and patients may be asymptomatic or present with diminished breath sounds at the lung bases, rhonchi, and labored breathing. Management of secretions with aggressive chest physiotherapy, suctioning, and incentive spirometry is recommended postoperatively. Bronchoscopy for airway mucous clearance offers no clear benefit compared to other methods of chest physiotherapy. If secretions are minimal, CPAP therapy to recruit collapsed alveoli may be considered. Use of mucolytics such as N-acetylcysteine have not been adequately studied and are not indicated for treatment of atelectasis. H

KEY POINT

- Management of secretions with aggressive chest physiotherapy, suctioning, and incentive spirometry is recommended postoperatively to prevent atelectasis; bronchoscopy for airway mucous clearance offers no clear benefit compared to other methods of chest physiotherapy.

Pneumonia

Pneumonia is a common cause of respiratory failure in the ICU and is the most common cause of ARDS that develops outside the hospital. In patients with an appropriate history, chest

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radiograph is the standard for diagnosis. However, a negative clinical examination or chest radiograph does not necessarily rule out community-acquired pneumonia in symptomatic patients, especially in elderly individuals. Therefore, absence of typical features or focal infiltrates on chest radiograph should not preclude early antibiotic administration to individuals with an otherwise high probability of pneumonia. For further discussion of pneumonia see MKSAP 18 Infectious Disease. In patients who do not respond appropriately to antibiotics, repeat sputum cultures should be obtained, and both nonbacterial causes of infection and noninfectious causes should be considered. In addition, further evaluation with chest CT scan, bronchoscopy, or both should be considered to evaluate for complicating factors such as pleural effusion, abscess, or airway obstruction stemming from malignancy or foreign body aspiration. H

KEY POINT

- A negative clinical examination or chest radiograph does not necessarily rule out community-acquired pneumonia in symptomatic patients, especially in elderly individuals.

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Diffuse Parenchymal Lung Disease

Acute exacerbations of diffuse parenchymal lung disease (DPLD), particularly idiopathic pulmonary fibrosis (IPF) can occur either as a complication of an inciting event, or in many cases, for unknown reason. See the Diffuse Parenchymal Lung Disease section earlier for a detailed discussion of diagnosis and management. The mortality in patients with hypoxemic respiratory failure due to an exacerbation of IPF exceeds 50%. Most patients with hypoxemic respiratory failure due to IPF are treated empirically with high dose glucocorticoids, but the data are insufficient to support dose, duration, or certainty of benefit. Outcomes following intubation and mechanical ventilation are very poor, as mortality can approach 100%. Therefore, many clinicians recommend that goals of care discussion and palliative care be involved early and other therapies, such as ECMO, only be offered as a bridge for patients eligible for lung transplantation.

Patients in the ICU with an exacerbation of IPF are frequently given broad spectrum antibiotics if infection has not been ruled out. Although the cause of most IPF exacerbations is unclear, new data suggest that aspiration and infection may play a significant role. H

KEY POINT

- Because outcomes following intubation and mechanical ventilation are very poor for patients with acute exacerbations of idiopathic pulmonary fibrosis, goals of care and palliative care should be discussed early, and other therapies, such as extracorporeal membrane oxygenation, should only be offered as a bridge for patients eligible for lung transplantation.

Pulmonary Embolism

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Pulmonary embolism (PE) causes respiratory failure primarily through $\dot{V}/\dot{Q}$ mismatch, and to a less common extent through shunting or low mixed venous oxygen saturation. Following an acute PE, resistance to pulmonary blood flow increases, due to both thrombosis and to vasospasm of adjacent pulmonary blood vessels from activated inflammatory mediators. Subsequently, blood flow is directed to unembolized areas of normal lung, which become overperfused. If ventilation of the normal lung is insufficient to fully oxygenate blood in the overperfused vessels, hypoxemia ensues. In addition, regional atelectasis is common following PE and lung infarction. Chest radiograph or chest CT scan may demonstrate peripheral, ground-glass, wedge-shaped opacities (Hampton hump sign) signifying the presence of infarcted lung and surrounding atelectasis. Blood flow through atelectatic lung can result in shunt and hypoxemia.

Pulmonary emboli can also cause strain on the right ventricle (RV) if the PE is sufficiently large. In these cases, cardiac output may be impaired. Low cardiac output leads to reduced mixed venous oxygen saturations, especially when metabolic demands exceed cardiac capacity. If this occurs in conjunction with $\dot{V}/\dot{Q}$ mismatch and shunt, blood cannot fully saturate with oxygen before leaving the alveolar capillaries. This adds to hypoxemia and subsequent respiratory failure.

Although most patients with hypoxemia following PE can be managed with supplemental oxygen alone, some patients require intubation and positive pressure ventilation.

Mechanical ventilation produces several physiologic effects that need to be considered in the patient with PE and RV dysfunction. Increased pleural pressure from mechanical ventilation can cause decreased venous return and result in low RV preload. Additionally, overdistention of alveoli increases RV afterload. These effects can lead to further RV dysfunction and hemodynamic instability. Although there is no absolute contraindication to mechanical ventilation in patients with underlying PE, the risks and benefits should be weighed carefully. In patients with hemodynamic collapse, treatment with thrombolytics is associated with decreased mortality, and the vast majority of patients demonstrate improvement in clinical and echocardiographic parameters following thrombolytic administration.

Thrombolytics carry a significant side effect profile, including an up to 2% risk of intracranial hemorrhage, but this should be considered relative to the life-threatening risk of massive PE leading to hemodynamic collapse. In patients with contraindications to thrombolysis, and in those in whom thrombolysis has failed to improve the hemodynamic status, surgical embolectomy is recommended if resources are available. For further discussion of PE, see MKSAP 18 Hematology and Oncology.

Hypercapnic (Ventilatory) Respiratory Failure

CONT.

Hypercapnic, or ventilatory, respiratory failure occurs when alveolar ventilation is inadequate to clear the CO_2 produced by cellular metabolism, and the level of CO_2 increases in the blood. Most commonly, hypercapnia reflects alveolar hypoventilation, but can also result from increased metabolic load (fever, increased work of breathing) that is not matched by an increase in alveolar ventilation. Alveolar hypoventilation occurs when the patient is unable to ventilate because of decreased respiratory drive, decreased tidal volume (V_T), or increased volume of dead space (V_D) relative to the overall tidal volume (V_D/V_T) (**Table 47**).

Clinical features of acute hypercapnic respiratory failure are variable and nonspecific. Symptoms may include somnolence and myoclonic jerks in the setting of CO_2 narcosis. In some cases, increased work of breathing may precede the development of acute hypercapnic respiratory failure. Underlying chest wall deformity, neurologic weakness, or polycythemia should also prompt evaluation for hypercapnia in the setting of respiratory failure.

Patients presenting with acute hypercapnic respiratory failure frequently have coexisting hypoxemia. Administration of supplemental oxygen may improve the hypoxemia, but will not necessarily improve hypercapnia. All patients who are suspected of acute hypercapnic respiratory failure should have arterial blood gas analysis even if hypoxemia resolves with oxygen administration (**Table 48**). The pH helps to determine the acuity and severity of respiratory failure. In chronic hypercapnia, pH changes are less marked due to metabolic compensation resulting in increased serum bicarbonate levels. Management of an elevated arterial P_{CO_2} depends on the clinical situation and the resultant pH. For instance, a moderately elevated arterial P_{CO_2} may represent the baseline in patients with COPD; however, in an asthmatic, the development of elevated arterial P_{CO_2} may indicate imminent respiratory failure requiring emergent intubation.

TABLE 47. Causes of Acute Hypercapnic Respiratory Failure

Decreased Respiratory Drive	Decreased V_T or Increased V_D/V_T
Anesthesia	Amyotrophic lateral sclerosis
Central apnea	Ankylosing spondylitis
Obesity hypoventilation syndrome	Asthma exacerbation
Drugs (such as opioids, benzodiazepines, ethanol)	Botulism
Encephalitis	Bronchiectasis flare (including cystic fibrosis)
Hypothermia	COPD exacerbation
Hypothyroidism	Critical illness myopathy
Meningitis	Electrolyte disorder (low magnesium, low phosphate)
Stroke	Guillain-Barré syndrome
	Multiple rib fractures (flail chest)
	Myasthenia gravis
	Myositis (such as polymyositis, dermatomyositis)
	Polio
	Spinal or phrenic nerve injury
	Thoracic cage deformity (kyphoscoliosis)

V_T = tidal volume; V_D = volume of dead space.

KEY POINT

- All patients who are suspected of acute hypercapnic respiratory failure should have arterial blood gas analysis even if hypoxemia resolves with oxygen administration.

Management of Hypercapnic Respiratory Failure

Decreased Respiratory Drive

Decreased respiratory drive leads to diminished alveolar CO_2 clearance and hypercapnia. Patients often present with somnolence and difficulty protecting their airway. Noninvasive positive pressure ventilation (NIPPV) should be considered if the patient can protect his or her airway. This improves minute ventilation and gas exchange. If airway protection is compromised, or if there is either significant respiratory acidosis (generally pH less than 7.25) or hemodynamic instability, intubation and mechanical ventilation are indicated. See MKSAP 18 Nephrology for further discussion of respiratory acidosis.

Drug Overdose

Sedating drugs (illicit or prescribed), anesthetics, and severe alcohol intoxication can lead to depressed central respiratory drive. In cases of pharmacologic overdose, contact with a local poison control center is helpful to determine the most appropriate care of the patient. If opiate overdose is suspected, rapid reversal with naloxone is safe, effective, and may prevent the need for intubation. The benefits of flumazenil for patients with benzodiazepine overdose are less certain. Flumazenil carries the risk of precipitating withdrawal seizures in chronic users and is a short-acting agent, so several administrations

TABLE 48. Features of Acute and Chronic Hypercapnia

	Acute Hypercapnia	Chronic Hypercapnia
pH	<7.35	~7.35-7.40
Arterial P_{CO_2}	>45 mm Hg (6.0 kPa)	>45 mm Hg (6.0 kPa)
Bicarbonate concentration [HCO_3]	22-26 mEq/L (22-26 mmol/L)	>26 mEq/L (26 mmol/L)
Expected metabolic compensation	1.0 mEq/L ↑ [HCO_3] for each 10 mm Hg (1.3 kPa) ↑ in arterial P_{CO_2}	3.5 mEq/L ↑ [HCO_3] for each 10 mm Hg (1.3 kPa) ↑ arterial P_{CO_2}

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may be required to keep respiratory failure from recurring, especially if long acting benzodiazepines were ingested.

Obesity Hypoventilation Syndrome

Obesity hypoventilation syndrome (OHS) is characterized by the presence of obesity, sleep-disordered breathing, and persistent daytime hypercapnia (arterial Pco_2 greater than 45 mm Hg [5.9 kPa]). Hypercapnia stems from low tidal volumes and from inappropriate central respiratory response to hypoxemia and elevated Pco_2 levels. Acute hypercapnic respiratory failure due to OHS should be a diagnosis of exclusion. Positive pressure ventilation is the key to improving hypercapnia in patients with OHS.

NIPPV is reasonable in patients who can protect their airway, but high levels of positive pressure are often needed because of poor chest wall compliance from obesity, diminished lung compliance from atelectasis, and cephalad displacement of the diaphragm from central adiposity. If NIPPV is used, arterial blood gases should be monitored to ensure clinical improvement. If patients are not improving, early intubation is warranted. Respiratory stimulants, such as acetazolamide, a progestin, and theophylline offer a compelling theoretical benefit to patients with chronic hypercapnia or depressed respiratory drive, but have limited data supporting their use in this setting. H

KEY POINT

- Acute hypercapnic respiratory failure due to obesity hyperventilation syndrome is a diagnosis of exclusion; if airway protection is compromised, or there is significant respiratory acidosis or hemodynamic instability, intubation and mechanical ventilation are indicated.

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Decreased Tidal Volume and Increased Dead Space

Neuromuscular Weakness

The diaphragm is the main muscle responsible for inspiration and accounts for more than two-thirds of the ventilatory work in humans. The C3-C5 cervical nerve roots form the phrenic nerves, which directly innervate the diaphragm. Patients with diaphragmatic weakness develop orthopnea, shallow breathing, and often paradoxical movement of the chest wall and abdomen. Although exhalation is generally a passive process, intercostal and abdominal wall muscles are required for coughing. Lower cervical and upper thoracic nerve roots supply the intercostal and abdominal wall muscles. Weak cough, difficulty managing secretions, or a change in voice, which can become softer or more "breathy," may point to weakness in these areas.

Assessment of cranial nerves and respiratory muscle function is important in a patient with suspected neurologic disease. Specific components of pulmonary function testing can be helpful (**Table 49**) but are effort-dependent, and facial or postural weakness can complicate accurate measurement.

Guillain-Barré syndrome and myasthenic crisis are the most common causes of acute neurologic respiratory failure in the ICU. Infection can precipitate myasthenic crisis or Guillain-Barré syndrome. Myasthenic crisis can occur following medication changes or significant stressors.

TABLE 49. Pulmonary Function Value Suggestive of Neuromuscular Weakness

Function	Value
FVC	>20% decrement in supine position compared with upright position
Maximal inspiratory pressure (MIP)	Unable to achieve −30 cm H_2O
Maximal expiratory pressure (MEP)	Unable to achieve +40 cm H_2O

Patients with Guillain-Barré syndrome generally present with rapid onset of ascending, symmetric paralysis and areflexia occurring over the course of 2 to 4 weeks. Dysautonomia is common and can cause hemodynamic instability or cardiac arrhythmias. In myasthenic crisis, the hallmark feature is muscle fatigability. Diplopia, ptosis, dysarthria, limb weakness, and weak cough are common. See MKSAP 18 Neurology for further discussion of Guillain-Barré syndrome and myasthenic crisis.

In the 25% of patients with Guillain-Barré syndrome who develop respiratory failure, intubation is necessary because respiratory function can take days to weeks to recover. In myasthenic crisis, early NIPPV may prevent the need for intubation. Therapy for both diseases includes plasma exchange or intravenous immune globulin. Glucocorticoids have no benefit in Guillain-Barré syndrome, but are indicated in addition to cholinesterase inhibitors in myasthenic crisis.

Acute spinal cord injuries at or above the C5 level invariably require mechanical ventilation. In some cases (complete spinal cord injury below C3 or incomplete injury above C3), recovery of independent respiratory function can occur. However, atelectasis, aspiration pneumonia, and pulmonary emboli are common and can lead to recurrent acute hypercapnic respiratory failure. Aggressive chest physiotherapy and use of mechanical cough assist devices are helpful and may lower the risk of these events. H

KEY POINTS

- Guillain-Barré syndrome and myasthenic crisis are the most common causes of acute neurologic respiratory failure in the ICU.
- Evaluation of maximum inspiratory and expiratory pressures and positional changes in vital capacity are helpful in assessing neuromuscular weakness as a cause of hypercapnic respiratory failure.

Restrictive Chest Wall Disease

H

Restrictive disease from disorders affecting the pulmonary parenchyma (such as the various causes of diffuse parenchymal lung disease primarily leads to hypoxemia without

H CONT.

hypercapnia. Acute hypercapnic respiratory failure is more common in patients with extrapulmonary chest wall restriction (pectus deformity, scoliosis, kyphosis), which causes compromised respiratory mechanics. Ascites and severe bowel distention can also compromise respiratory mechanics by exerting a significant cephalad force on the diaphragm. Commonly, extrapulmonary chest wall restriction causes poor ventilatory reserve without overt respiratory failure. However, acute insults such as infection or sedating medications can upset this delicate balance and precipitate hypercapnic respiratory failure. NIPPV and invasive positive pressure mechanical ventilation are both appropriate while the precipitating condition is managed. In patients with thoracic cage deformity, NIPPV in the outpatient setting is frequently beneficial. Improved V_T, especially during sleep when respiratory drive and minute ventilation decrease, can reduce the incidence of acute hypercapnic respiratory failure and improve patient function and quality of life.

Obstructive Lung Diseases (Asthma and COPD)

Abnormal mechanical properties of the airways and the lung parenchyma cause both static and dynamic hyperinflation. A decrease in the lung's elastic recoil (as seen in emphysema) results in increased total lung capacity and is one of the factors leading to an increase in functional residual capacity (lung volume after a normal, not forced, exhalation). In addition, the ability to exhale is dependent on the elastic recoil of the lung, the degree of airflow obstruction (associated with structural changes, inflammation, increases in cholinergic tone, and mucous plugging), and the rate of breathing.

The degree of airflow obstruction and the respiration rate can each vary and cause greater air trapping during periods of exertion and exacerbation of disease, leading to increased lung volumes at the end of exhalation. This complication of airflow obstruction and insufficient time for exhalation is called dynamic hyperinflation and can result in intrathoracic pressure remaining positive at the end of exhalation, a phenomenon called auto-PEEP. Dynamic hyperinflation, auto-PEEP, and decreased elastic recoil of the lung all contribute to disordered lung mechanics, increased work of breathing, and respiratory muscle fatigue. Auto-PEEP may also decrease venous return and contribute to hemodynamic instability in patients receiving mechanical ventilation who are not given sufficient time for exhalation.

At the time of a COPD exacerbation, patients may present with signs of increased respiratory work. They may also have findings related to the presence of hypercapnia, such as altered sensorium or somnolence. See Airways Disease for more detailed information about management of COPD exacerbations.

In patients with COPD, excessive oxygen can increase $\dot{V}/\dot{Q}$ mismatch by disrupting compensatory vasoconstriction in poorly ventilated regions of lung, potentially leading to further elevation in P_{CO_2}. Therefore, in patients with COPD exacerbation, oxygen therapy should be titrated to 88% to 92% oxyhemoglobin saturation. In patients with hypercapnic respiratory failure due to COPD exacerbation, NIPPV is preferred as the initial means to reduce P_{CO_2}. If patients cannot protect their airway, are hemodynamically unstable, or do not improve on NIPPV, intubation and mechanical ventilation are necessary. Strategies for mechanical ventilation in COPD include assuring sufficient expiratory time during the respiratory cycle to minimize auto-PEEP.

In patients with asthma, upright posture, inability to speak in full sentences, flaring of the nares, and contraction of the sternocleidomastoid muscles during inspiration, are signs of increased respiratory work and may herald respiratory failure. Blood gases usually demonstrate respiratory alkalosis due to rapid, shallow breathing patterns. Therefore, the presence of a normal or elevated arterial P_{CO_2} may signal impending respiratory failure. Oxygen should be given to maintain a hemoglobin saturation of 90% to 95%. Hypoxemia can result from $\dot{V}/\dot{Q}$ mismatch, but should correct with oxygen. If oxygen saturation does not readily correct, other factors should be considered, including pneumonia, pneumothorax, or pulmonary embolism.

In cases of severe asthma exacerbation, magnesium sulfate may be used in addition to standard therapies to promote further bronchodilation. Adjunctive therapies, including anesthetics with bronchodilator properties (ketamine, isoflurane, sevoflurane), inhalation of a helium-oxygen mixture, mucolytics, and leukotriene receptor antagonists are not recommended because of lack of clear efficacy.

There is little objective evidence to support use of NIPPV in management of asthma exacerbations. Therefore, in asthmatic patients with respiratory failure, intubation is recommended. In these patients, efforts should be directed at maximizing expiratory time, as this improves dynamic hyperinflation and reduces auto-PEEP. The most effective way to do this is to minimize the patient's respiration rate. Doing so often requires sedation or paralytics and can lower a patient's overall minute ventilation. Because this may increase arterial P_{CO_2}, arterial blood gas analysis should be performed frequently in these patients. H

KEY POINTS

- Patients with hypercapnic respiratory failure and COPD exacerbation benefit from NIPPV provided they can protect their airway and are hemodynamically stable.
- In asthmatic patients with respiratory failure, intubation and mechanical evaluation are recommended rather than NIPPV.
- Adjunctive therapies for severe asthma exacerbation, including anesthetics with bronchodilator properties (ketamine, isoflurane, sevoflurane), inhalation of a helium-oxygen mixture, mucolytics, and leukotriene receptor antagonists are not recommended because of lack of clear efficacy.

HVC

H Shock

Shock occurs when systemic tissue perfusion is inadequate. In early states of tissue hypoperfusion, aerobic metabolism is supplanted by anaerobic metabolism and tissue injury is reversible. As compensatory mechanisms fail, sustained organ hypoperfusion can lead to cellular dysfunction and death. There are three primary mechanisms of shock: decreased circulating volume (hypovolemic), decreased cardiac output (cardiogenic), and inappropriate vasodilation (distributive).

Low blood pressure alone should not be considered diagnostic of end organ hypoperfusion. Instead, blood pressure should be considered in the context of other physical examination findings that may suggest end organ hypoperfusion (**Table 50**), as well as other general considerations for early shock assessment (**Figure 20**).

Treatment of a patient in shock is predicated on distinguishing the type of shock present and directing treatment toward correcting the root cause of the shock state (**Table 51**). Although many tools are available to aid in shock assessment and management, the use of bedside echocardiography has increased significantly during the last 10 years. Echocardiography can provide useful data regarding cardiac function and cardiac response to treatment. Other tools such as pulmonary artery catheters or those that predict response to volume replacement such as pulse pressure or stroke volume variation can also be considered; however, these technologies often carry higher risk due to their invasive nature, and the assessment of pulse pressure and stroke volume have procedural limitations (mechanical ventilation, receiving 8 mL/kg or greater of tidal volume, need for sinus rhythm, not triggering the ventilator) that may make them impractical. Pulmonary artery catheters have lost favorability in recent years because several large studies and meta analyses that suggest no benefit, and in some cases increased risk to patients when used to guide therapy. Technologies that employ pulse contour, pulse pressure, or stroke volume variation assessment should be used with caution as well, given a broad array of clinical scenarios that can skew results and limited data to support their benefit in guiding therapy. H

TABLE 50. Common Clinical Findings in Patients with Shock

Altered mentation
Hypotension (SBP < 90 mm Hg) or 30 mm Hg drop in SBP from baseline
Mottled skin
Tachycardia (heart rate >100/min)
Tachypnea (respiration rate >25/min)
Urine output <0.5 mL/kg/h
Weak or absent peripheral pulses
Elevated serum lactate (>3 mEq/L [3 mmol/L])

SBP = systolic blood pressure.

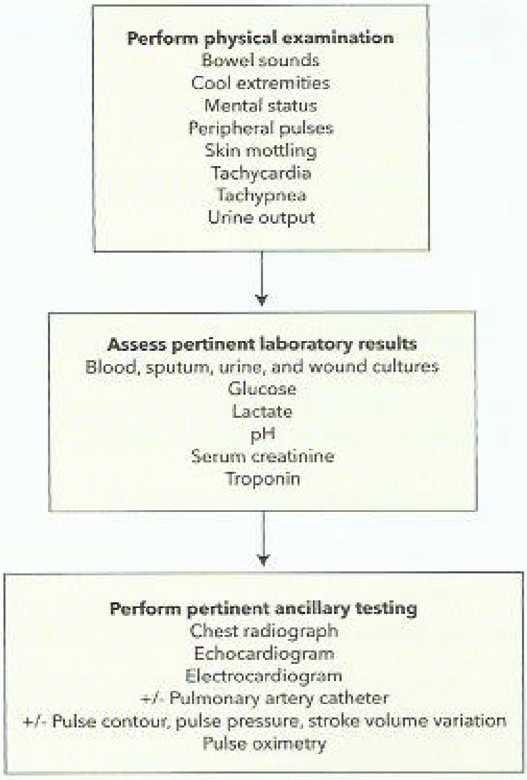

FIGURE 20. Early assessment of suspected shock.

KEY POINTS

- Treatment of a patient in shock is predicated on distinguishing the type of shock present and directed toward the root cause of the shock state.
- Pulmonary artery catheters have lost favorability in recent years because several large studies and meta-analyses that suggest no benefit, and in some cases increased risk to patients when used to guide therapy. HVC

Distributive Shock H

In distributive shock, the blood volume is generally normal, but a state of "relative" hypovolemia occurs from excessive vasodilation and microvascular dysfunction. This causes blood to bypass vital capillary beds, leading to tissue hypoxia. Cardiac output is often increased, but still cannot maintain a pressure sufficient for normal tissue perfusion. Initial treatment of distributive shock should focus on fluid resuscitation. Several studies have compared the effectiveness of crystalloid versus colloid administration, with no clear evidence that one is better than the other. Given the relative expense of colloids, crystalloid administration is generally preferred and recommended by guidelines. Vasopressor support is warranted if fluid administration alone is insufficient to support tissue perfusion. The selection of a vasopressor should be based on the patient's comorbidities and underlying cause of shock (see Table 39). H

TABLE 51. Selected Causes of Shock

Distributive
Anaphylaxis
Sepsis
Spinal injury (usually above T4 level)
Drugs (peripheral vasodilators, nitrates)
Hypovolemic
Acute blood loss (trauma, GI bleeding, surgery, uterine bleeding, obstetrical, retroperitoneal bleeding, aortic rupture)
Crush injury, metabolic rhabdomyolysis
Cutaneous losses (burns, toxic epidermal necrolysis, erythroderma, excessive sweating)
Drugs (diuretics, laxatives)
GI losses (vomiting/diarrhea)
Kidney losses (diabetic ketoacidosis, hyperglycemic hyperosmolar syndrome, adrenal insufficiency, post-ATN osmotic diuresis)
Cardiogenic (Including Noncardiac Causes of Decreased Cardiac Output)
Abdominal compartment syndrome
Arrhythmia (tachycardia, bradycardia)
Atrial myxoma
Heart failure
Left ventricular infarction, right ventricular infarction
Pericardial tamponade, constrictive pericarditis
Pulmonary embolism
Tension pneumothorax, severe dynamic hyperinflation (for example, excessive PEEP)
Valvular heart disease (severe insufficiency, valve or chordae rupture, critical stenosis)
Ventricular septal rupture, free ventricular wall rupture

ATN = acute tubular necrosis; GI = gastrointestinal; PEEP = positive end-expiratory pressure; T4 = fourth thoracic vertebra.

KEY POINT

HVC
- Several studies have compared the effectiveness of crystalloid versus colloid administration for treatment of distributive shock, with no clear evidence that one is better than the other; given the relative expense of colloids, crystalloid administration is generally preferred and recommended by guidelines.

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Hypovolemic Shock

Hypovolemic shock occurs when decreased intravascular blood volume causes decreased preload, decreased ventricular filling, and diminished stroke volume. Initially, tachycardia and peripheral vasoconstriction help to preserve perfusion of vital organs but cannot compensate in the setting of severe hypovolemia. Treatment of hypovolemic shock includes aggressive volume or blood product replacement and, if possible, control of bleeding. Patients with hemorrhage may initially receive intravenous fluids to maintain hemodynamic stability, but ultimately need erythrocyte transfusion to prevent tissue ischemia. In stable ICU patients, hemoglobin levels should be maintained at about 7 g/dL (70 g/L); however, different thresholds and hemoglobin levels may trigger transfusion in actively bleeding patients who are in shock. Higher values may be necessary in patients with underlying cardiovascular disease. In patients with severe trauma, massive blood replacement requirements, and coagulopathy, evidence supports early resuscitation with a 1:1:1 ratio of erythrocytes, platelets, and fresh frozen plasma.

Cardiogenic Shock

Cardiogenic shock occurs when a primary cardiac insult causes decreased cardiac output. This can result from any combination of obstructed filling or emptying of the ventricles, high or low heart rates, and decreased ejection fraction. It is essential to promptly identify the cause of cardiogenic shock to ensure appropriate medical therapy, surgical therapy, or both. In addition to a physical examination, evaluation should include laboratory testing for myocardial ischemia and heart failure, chest radiograph, electrocardiogram, and echocardiogram. In patients presenting with severe cardiogenic shock, additional supportive measures may include short-term mechanical support to allow a bridge toward definitive therapy. These include ECMO, intraaortic balloon pump, temporary pacemaker, and left or right ventricular assist device. However, recent technological advances have allowed many of these devices to be used for longer durations and even as destination therapy.

Sepsis

Definition, Pathophysiology, and Clinical Presentation of Sepsis

The Third International Definitions for Sepsis and Septic Shock (Sepsis-3) were published in 2016 and reflect evolving understanding of sepsis. Sepsis-3 defines sepsis as life-threatening organ dysfunction caused by a dysregulated host response to infection. Septic shock is defined as a subset of sepsis in which profound circulatory, cellular, and metabolic abnormalities are associated with a greater risk of mortality than with sepsis alone. The previous definition, combining known or suspected infection and systemic inflammatory response syndrome criteria, which can be appropriate (not necessarily dysregulated) responses to infection, is neither sensitive nor specific enough to diagnose sepsis. The terms *severe sepsis* and *septicemia* should no longer be used.

Infections giving rise to sepsis can include any agent and involve any organ, and need not be disseminated. The pathophysiology of sepsis is complex and involves dysfunction at many levels, from subcellular mitochondrial dysfunction to failure of entire organ systems. Loss of regulation of the body's finely balanced proinflammatory and antiinflammatory

mediators and unregulated coagulation in the microvasculature are characteristic of the syndrome, although these features are difficult to assess clinically.

Operationally, sepsis can be identified whenever infection is known or suspected and clinical criteria defining organ dysfunction are met. The recommended criteria to assess organ dysfunction are included in the Sequential Organ Failure Assessment (SOFA) score, which assigns a value of 0-4 for each of six organ systems assessed: respiratory, coagulation, hepatic, cardiovascular, central nervous, and kidney, with increasing scores for more severe dysfunction (online SOFA score calculators are available: http://clincalc.com/IcuMortality/SOFA.aspx; https://www.mdcalc.com/sequential-organ-failure-assessment-sofa-score). An initial SOFA score of 2 or greater or an increase in SOFA score of 2 or more correlates with acute organ dysfunction and predicts hospital mortality of greater than 10%. The SOFA score should be used to assess patients in the ICU.

In the pre-ICU arena, Sepsis-3 guidelines recommend the use of the quick SOFA (qSOFA) score, a simplified clinical scoring system that includes only three criteria: respiration rate of 22/min or greater, altered mentation, and systolic blood pressure 100 mm Hg or less (**Table 52**). A qSOFA score of 2 or greater in the setting of known or suspected infection predicts increased mortality and should prompt evaluation for resuscitation and consideration of ICU admission. Failure to meet two or more qSOFA criteria should not be construed as ruling out sepsis, and investigation or treatment of infection should be pursued as deemed necessary by the responsible physicians. Although there is no definitive test for sepsis, the qSOFA score (specific but not sensitive) and the systemic inflammatory response syndrome (SIRS) criteria (sensitive but not specific) are complementary and can be used together to inform clinical judgment when diagnosing sepsis.

The criteria for diagnosing septic shock include hypotension requiring pressors to maintain a mean arterial pressure of greater than 65 mm Hg and serum lactate level of greater than 2 mEq/L (2 mmol/L) after adequate volume resuscitation. Patients who meet these criteria have a 40% or greater risk of in-hospital mortality. H

TABLE 52. qSOFA Score

Criterion	Value	qSOFA Points
Respiration rate	>22/min	1
Systolic blood pressure	<100 mm Hg	1
Mental status	Altered from baseline	1
qSOFA score	**Predicted mortality**	
0	<1%	
1	2-3%	
≥2	≥10%	

qSOFA = quick sequential organ failure assessment.

KEY POINTS

- Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection.
- Septic shock is defined as a subset of sepsis in which profound circulatory, cellular, and metabolic abnormalities are associated with a greater risk of mortality than with sepsis alone.

Epidemiology of Sepsis

H

The epidemiology of sepsis is difficult to judge accurately because of its evolving definition, challenges with clinical recognition of the syndrome, and lack of standardized reporting. However, it is possible to estimate its incidence and clinical and economic effects. There are disparities in sepsis rates among different demographic groups. For example, sepsis is more common among black men than other racial groups or women. Sepsis is also more common among elderly patients, with incidence increasing with each year after the age of 65. Mortality from sepsis is high. A patient who is septic has a mortality rate 4 or more times greater for the same underlying condition and comorbidities without sepsis. Mortality increases by roughly 15% for each sepsis-related organ system failure.

Management of Sepsis

Early diagnosis and timely treatment of sepsis are important to improve survival. In settings where sepsis is suspected, cultures and other investigations to identify infection, as well as the use of diagnostic instruments like the SOFA and qSOFA scoring tools to identify organ dysfunction, are helpful. Once sepsis is diagnosed, the two main pillars of management are: 1) supporting organ perfusion and function; and 2) controlling the infection. Various other adjunctive therapies may also affect survival. H

KEY POINT

- The two main pillars of sepsis management are: 1) supporting organ perfusion and function; and 2) controlling the infection.

Initial Resuscitation

H

Sepsis can have serious hemodynamics effects, with decreased preload (due to capillary leak), impaired cardiac contractility, and decreased vascular tone. Patients may present in shock, sometimes with profound hypotension requiring large volume resuscitation with intravenous fluids and often vasopressor therapy.

The fourth iteration of the Surviving Sepsis Guidelines, published in 2016, recommends early and aggressive fluid resuscitation for patients with hypoperfusion due to sepsis, with an initial bolus of 30 mL/kg of body weight. Additional fluids may be needed, and physiologic markers such as mean arterial pressure, pulse pressure variation, change in serum lactate level, bedside echocardiographic assessment of inferior

vena cava filling, or other techniques are used as indicators of adequate fluid resuscitation. Although experts agree that aggressive fluid resuscitation is essential, the adequacy of fluid resuscitation requires clinical judgment in conjunction with the available data.

Fluid resuscitation should be with crystalloid, using normal saline or a balanced crystalloid solution. A balanced crystalloid solution has an electrolyte composition similar to plasma with the addition of a buffer, such as lactate (for example, Ringer's lactate solution). Data are emerging that suggest a balanced crystalloid solution may be associated with improved outcomes compared to normal saline, particularly in patients receiving a large volume of fluid, but current guidelines recommend either. There is weak evidence suggesting benefit from the use of albumin in patients requiring large volume resuscitation; however, sepsis guidelines offer this as a consideration rather than a recommendation.

KEY POINT

- Early and aggressive fluid resuscitation for patients with hypoperfusion due to sepsis begins with an initial bolus of 30 mL/kg body weight of normal saline or a balanced crystalloid solution.

Antibiotic Therapy

Early administration of antibiotic therapy is crucial in treating sepsis. Broad spectrum antibiotics should be given within the first hour of suspected sepsis, and the regimen adjusted based on culture results. A delay in the first dose of antibiotic therapy increases sepsis mortality. The Surviving Sepsis Guidelines recommend empiric combination therapy for the initial management of septic shock, or when broad empiric coverage is needed for initial management of sepsis, bacteremia, or both. However, they recommend against combination therapy for the routine or ongoing treatment of sepsis and bacteremia without shock, even in the setting of neutropenia. The guidelines define combination therapy as the use of two different classes of antibiotics for a single putative pathogen expected to be sensitive to both, for purposes of accelerating pathogen clearance. The term is not used when the purpose of a multidrug strategy is to strictly broaden the range of antimicrobial activity. Antibiotic therapy should usually be continued for 7 to 10 days, depending on the clinical situation, and continually reassessed for efficacy and possible deescalation.

Procalcitonin, a serum marker for bacterial infection, should be measured when the probability of infection is estimated to be low. If the procalcitonin level is low, bacterial infection is unlikely and antibiotic therapy may not be warranted. There is no role for procalcitonin measurement in sepsis likely due to infection.

Prompt identification and control of any potential source of infection is essential in the management of sepsis. Examples include drainage of abscesses and removal of possibly infected intravenous catheters (once alternative intravenous access has been established). One exception is necrotizing pancreatitis, for which definitive resection should be delayed until the extent of necrosis is clear.

KEY POINTS

- Antibiotic therapy for patients with sepsis should usually be continued for 7 to 10 days, depending on the clinical situation, and continually reassessed for efficacy and for possible deescalation.
- Procalcitonin, a serum marker for infection, should be measured when the probability of infection is estimated to be low.
- There is no role for procalcitonin measurement in sepsis likely due to infection. HVC
- Prompt identification and control of any potential source of infection is essential in the management of sepsis.

Adjunctive Therapies

Norepinephrine is the vasopressor of choice for shock due to sepsis. Vasopressin at a fixed dose of 0.03 or 0.04 units per minute can be added to norepinephrine to further raise blood pressure or reduce the dose of norepinephrine. Vasopressin should generally not be used in cardiogenic or hypovolemic shock and is not recommended as a first pressor agent in septic shock (see Table 39). If possible, all patients receiving vasopressor therapy should have an arterial catheter for continuous blood pressure monitoring.

The use of glucocorticoids in the setting of sepsis is suggested to achieve hemodynamic stability when not achieved using intravenous fluids and vasopressor therapies. They have no role in sepsis without shock. If used, glucocorticoids can be added at a dose of not more than 200 mg daily of hydrocortisone (usually 50 mg intravenously every 6 hours). An adrenocorticotropic hormone stimulation test is not recommended.

KEY POINTS

- Norepinephrine is the vasopressor of choice in treatment of shock due to sepsis; vasopressin can be added to further raise the blood pressure or reduce the dose of norepinephrine.
- The use of glucocorticoids in the setting of sepsis is suggested if adequate fluid resuscitation and vasopressor therapy are unable to restore hemodynamic stability; there is no role for glucocorticoids in sepsis without shock. HVC

Specific Critical Care Topics

Anaphylaxis

Anaphylaxis is a severe reaction caused by acute mediator release into the circulation, usually triggered by IgE-linked

immunological responses to specific foods, medications, insect venom, latex, or other antigens, but sometimes occurring without an allergic trigger. The mediator release results in various clinical manifestations including pruritus, hypotension, and tissue swelling (known as angioedema) caused by capillary leak from widespread inflammatory mediator release (**Table 53**). Onset of symptoms may be immediate after antigen exposure or delayed, sometimes for hours or even days, although more rapid onset usually signals a more severe reaction. This capillary leak can result in distributive shock with many of the same features as septic shock. Angioedema can be life-threatening when it compromises the airway.

Initial treatment is with epinephrine, which may be administered intramuscularly or intravenously. Adjunctive therapy with antihistamine medications may be used to relieve symptoms of pruritus and rash. Although commonly administered, evidence that glucocorticoids are useful in the treatment of anaphylaxis is sparse. Sometimes epinephrine must be given many times or continuously to achieve clinical stability. Patients should be given supplemental oxygen and watched closely for signs of airway compromise, which may require intubation to maintain airway patency. Patients often require fluid resuscitation, with or without vasopressor therapy. Removal of the precipitating antigen is also important if exposure is ongoing. Fortunately, anaphylaxis is rarely fatal but successful management requires early recognition and prompt attention to supportive and disease-reversing therapies, especially when shock or airway compromise is present.

Angioedema can occur without allergic stimulus (bradykinin-mediated), sometimes in response to medications (notably ACE inhibitors, even after long-term use), and sometimes for no identifiable reason. Nonallergic angioedema usually has slower onset and is not associated with urticaria, pruritus, or hypotension, but the tissue swelling can be clinically significant, especially in the airway, and may require intubation. Recurrent angioedema can be hereditary or acquired, as in C1 inhibitor deficiency. As in other forms of angioedema, treatment is supportive, sometimes with additional measures to control abnormal bradykinin, complement activation, or both. For more detail on angioedema see MKSAP 18 Dermatology.

KEY POINT

- Initial treatment of anaphylaxis is with epinephrine, which may be administered intramuscularly or intravenously.

Hypertensive Emergencies

Hypertensive emergency refers to elevated blood pressure significantly above the normal range causing acute organ damage or dysfunction. The end-organ damage is the defining characteristic, particularly clinical dysfunction of the central nervous system (ischemic or hemorrhagic stroke, encephalopathy), the renal system (acute kidney injury), or the cardiovascular system (acute myocardial infarction, aortic dissection, acute heart failure). These effects often occur at blood pressures above 180/120 mm Hg, but there is no specific pressure threshold above which the syndrome is defined. When blood pressure is significantly elevated without evidence of end-organ damage, this is often labeled hypertensive urgency.

Hypertensive emergency should be treated by rapidly lowering the blood pressure, usually using intravenous short-acting agents in the ICU setting (**Table 54** and **Table 55**). The 2017 blood pressure guidelines from the American College of Cardiology/American Heart Association and nine other organizations recommend that for adults with a compelling condition (such as aortic dissection, severe preeclampsia or eclampsia, or pheochromocytoma crisis), systolic blood pressure (SBP) should be reduced to less than 140 mm Hg during the first hour and to less than 120 mm Hg in aortic dissection. For adults without a compelling condition, SBP should be reduced by no more than 25% within the first hour; then, if stable, to 160/100 mm Hg within the next 2 to 6 hours; and then cautiously to normal during the following 24 to 48 hours. See MKSAP 18 Neurology for further discussion of the treatment of hypertension associated with ischemic stroke and intracerebral hemorrhage.

TABLE 53. Organ System Involvement in Anaphylaxis

Organ System	Symptoms	Signs	Patients with Organ Involved
Skin and mucosa	Pruritus of skin, oropharynx, genitals, palms, soles	Flushing, urticaria, morbilliform rash, angioedema	85%
Respiratory	Dyspnea, chest and throat tightness, stridor, cough, hoarseness, sneezing, rhinorrhea	Wheeze, stridor, respiratory distress	70%
Cardiovascular	Lightheadedness, chest pain, palpitations	Hypotension, tachycardia > bradycardia	45%
Gastrointestinal	Pain, nausea, vomiting, diarrhea		45%
Neurologic	Anxiety, headache	Encephalopathy	15%

TABLE 54. Intravenous Antihypertensive Drugs for Treatment of Hypertensive Emergencies without a Compelling Comorbidity

Class	Examples	Comments
Dihydropyridine calcium channel blockers	Nicardipine	Nicardipine: Contraindicated in patients with severe aortic stenosis
	Clevidipine	Clevidipine: Contraindicated in patients with soy allergy, egg allergy, hyperlipidemia, lipoid nephrosis, and acute pancreatitis
Vasodilator-nitric oxide dependent	Sodium nitroprusside	Sodium nitroprusside: Intraarterial blood pressure monitoring recommended. Tachyphylaxis common with prolonged use. Irreversible cyanide toxicity possible with prolonged use
	Nitroglycerin	Nitroglycerin: Use only for patients with acute coronary syndrome or acute pulmonary edema; avoid in patients with right ventricular infarction and those taking PDE-5 inhibitors
Vasodilator-direct	Hydralazine	Not first-line drug due to unpredictable response and long duration of action
Adrenergic blocker-β_1 selective	Esmolol	Contraindicated with concurrent β-blocker therapy, bradycardia, pulmonary edema, severe HF
Adrenergic blocker-combined α_1 and nonselective β blocker	Labetalol	Useful in hyperadrenergic syndromes. Contraindicated in patients with asthma, COPD, heart block. May worsen heart failure
Adrenergic blocker-nonselective α-blocker	Phentolamine	Useful in patients with pheochromocytoma, cocaine toxicity, amphetamine overdose, clonidine withdrawal
Dopamine$_1$-agonist	Fenoldopam	Contraindicated in patients with glaucoma or increased intracerebral pressure
ACE inhibitor	Enalaprilat	Useful in situations associated with high plasma renin activity (scleroderma renal crisis). Contraindicated in pregnancy, acute MI, bilateral renal artery stenosis

HF = heart failure; MI = myocardial infarction; PDE = phosphodiesterase.

Data from Whelton PK, Carey RM, Aronow WS, Casey DE Jr, Collins KJ, Dennison Himmelfarb C, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: executive summary: A report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. Hypertension. 2018;71:1269-1324. [PMID: 29133354] doi:10.1161/HYP.0000000000000066

TABLE 55. Intravenous Antihypertensive Drugs for Treatment of Hypertensive Emergencies in Patients with a Compelling Comorbidity

Comorbidity	Preferred Drugs[a]	Comments
Acute aortic dissection	Esmolol, labetalol	Rapid SBP lowering to ≤120 mm Hg. β-Blockade should precede vasodilator (such as with nicardipine or nitroprusside) administration.
Acute pulmonary edema	Nitroglycerin, nitroprusside, clevidipine	β-Blockers contraindicated
Acute coronary syndromes	Esmolol, labetalol, nicardipine, nitroglycerin	Esmolol and nitroglycerin are first-line drugs.
Acute kidney injury	Clevidipine, fenoldopam, nicardipine	
Eclampsia or preeclampsia	Hydralazine, labetalol, nicardipine	ACE inhibitors, ARBs, renin inhibitors, nitroprusside contraindicated

[a]See Table 54 for specific drug contraindications.

ARB = angiotensin receptor blocker; SBP = systolic blood pressure.

Data from Whelton PK, Carey RM, Aronow WS, Casey DE Jr, Collins KJ, Dennison Himmelfarb C, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: executive summary: A report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. Hypertension. 2018;71:1269-1324. [PMID: 29133354] doi:10.1161/HYP.0000000000000066

KEY POINTS

- For adults with a hypertensive emergency and a compelling condition (such as aortic dissection, severe preeclampsia or eclampsia, or pheochromocytoma crisis), systolic blood pressure should be reduced to less than 140 mm Hg during the first hour and to less than 120 mm Hg in aortic dissection.
- For adults with a hypertensive emergency but without a compelling condition, systolic blood pressure should be reduced by no more than 25% within the first hour; then, if stable, to 160/100 mm Hg within the next 2 to 6 hours; and then cautiously to normal during the following 24 to 48 hours.

Hyperthermic Emergencies

Hyperthermic emergency is defined as elevation of core body temperature, usually above 40°C (104°F), causing end-organ dysfunction or damage, which may include alteration in mental status, seizures, kidney injury, muscle rigidity, rhabdomyolysis, acute respiratory distress syndrome, and disseminated intravascular coagulation. Common causes of hyperthermia include heat stroke, malignant hyperthermia, and neuroleptic malignant syndrome, all of which can be fatal if not recognized and treated appropriately (Table 56).

Heat Stroke

Heat stroke is a failure of the body's thermal regulatory system caused by dysfunction, as in elderly patients taking

TABLE 56. Causes of Severe Hyperthermia

Diagnosis	Suggestive History	Key Examination Findings	Treatment	Notes
Heat stroke	Environmental exposure	Encephalopathy and fever	Evaporative cooling Ice water immersion	Avoid ice water immersion if nonexertional
Malignant hyperthermia	Exposure to volatile anesthetic or succinylcholine	Masseter muscle rigidity; ↑ arterial P_{CO_2}	Stop inciting drug Dantrolene	Monitor and treat ↑ K^+ and ↑ arterial P_{CO_2}
Neuroleptic malignant syndrome	Typical > atypical antipsychotic agent; onset over days to weeks	Altered mentation, severe rigidity, ↑ HR, ↑ BP, hyporeflexia, no clonus	Stop the inciting drug Dantrolene Bromocriptine	Resolves over days to weeks Mentation change first
Severe serotonin syndrome[a]	Onset within 24 hours of initiation or increasing dose, gastrointestinal prodrome	Agitation, clonus, ↑ reflexes, rigidity	Stop inciting drug Benzodiazepines Cyproheptadine	Resolves in 24 hours

[a]Not routinely considered a cause of severe hyperthermia but commonly confused with neuroleptic malignant syndrome.

BP = blood pressure; HR = heart rate; K^+ = potassium.

H CONT.

anticholinergic medications; volume depletion (diuretics, insensible water loss); or because the system is overwhelmed, as in athletes or military recruits who train strenuously in hot, humid weather. When the core temperature rises above 40°C patients develop encephalopathy. They may also experience hypotension, nausea, and muscle weakness.

If untreated, mortality in heat stroke can be up to 60%. Centrally acting antipyretics such as NSAIDs or acetaminophen are not effective. For patients with nonexertional heat stroke, evaporative cooling with or without ice packs can be used to lower the core temperature to a safe target level, usually 38.5°C (101°F). For exertional heat stroke, evaporative cooling may be effective, but patients who remain severely symptomatic despite evaporative cooling efforts sometimes require immersion in ice water to bring the core temperature down rapidly. Because immersion therapy may be complicated by hypothermia, it is not recommended as first-line treatment. H

KEY POINT

- For patients with nonexertional heat stroke, evaporative cooling with or without ice packs can be used to lower the core temperature to a safe target level; for exertional heat stroke, immersion in ice water is sometimes required for severe cases.

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Malignant Hyperthermia

Malignant hyperthermia is a rare cause of severe hyperthermia in response to inhaled anesthetic agents (such as halothane and isoflurane) or depolarizing paralytic agents (such as succinylcholine). When a patient with inherited susceptibility is exposed to one of these agents, he or she may develop muscle rigidity, rhabdomyolysis, cardiac arrhythmias, and core body temperature elevation to 45°C (113°F) or more. Mortality can reach 10%. Treatment consists of discontinuing the triggering agent, active cooling, and administration of the muscle relaxant dantrolene every 5 to 10 minutes until muscle rigidity and hyperthermia resolve.

Neuroleptic Malignant Syndrome and Serotonin Syndrome

Neuroleptic malignant syndrome is an idiosyncratic response to neuroleptic agents such as haloperidol. It can occur with any neuroleptic medication, even after prolonged use, although it is more common at times of initiation or dose escalation. It can also occur with rapid withdrawal of dopaminergic medications for Parkinson disease. Dehydration may increase the risk of the syndrome, which includes fever, mental status changes, and rigidity. Mortality may exceed 10%. Treatment includes stopping the triggering agent (or reinstating the withdrawn dopaminergic agent), active cooling, and rehydration. Evidence for using dantrolene is weak. Neuroleptic medications can be reintroduced after a waiting period of at least 2 weeks, usually at lower dose, with care to avoid dehydration and concomitant administration with lithium.

Serotonin syndrome is a less severe hyperthermic reaction triggered by simultaneous use of two or more medications that affect release or reuptake of serotonin. Unlike neuroleptic malignant syndrome, serotonin syndrome usually includes hyperreflexia and myoclonus, and generally resolves after 24 hours. H

KEY POINT

- Treatment of neuroleptic malignant syndrome includes stopping the triggering agent, active cooling, and rehydration.

H Accidental Hypothermia

Accidental hypothermia results from heat loss significant enough to overwhelm the body's ability to maintain its core temperature. Shivering is the body's usual mechanism for raising a low core temperature and is quite effective. In the mild stage of hypothermia, shivering occurs, and patients may develop tachycardia, hyperventilation, poor judgment, loss of coordination, and diuresis. Clinical findings may progress to include hypotension, bradycardia, and further depression of mental status. As hypothermia worsens, victims stop shivering, lose consciousness, and can develop life-threatening complications, including pulmonary edema and ventricular arrhythmias (**Table 57**). In moderate to severe hypothermia Osborne waves may be present on electrocardiogram tracings (**Figure 21**).

If a severely hypothermic patient becomes pulseless and requires resuscitation, it is reasonable to continue cardiopulmonary resuscitation for a prolonged period of time until the patient can be rewarmed. There are reports of cardiopulmonary resuscitation lasting hours and resulting in full recovery when a severely hypothermic patient has a cardiac arrest.

Hypothermic patients who are shivering will passively rewarm themselves if they are removed from the cold environment and given adequate insulation to prevent heat loss, but as hypothermia progresses, shivering stops, usually when the core temperature drops below 32°C (89.6°F). At this point, a patient must be actively rewarmed to prevent complications. Active rewarming techniques include surface methods, such as heating pads and forced-air warming systems, as well as invasive methods such as rewarming by peritoneal or pleural space irrigation using peritoneal catheters or thoracostomy tubes. Extracorporeal support, including cardiopulmonary bypass, is recommended for patients in cardiac arrest because it maximizes the rewarming rate and can provide hemodynamic support. During active rewarming, core temperature should be monitored with an esophageal temperature probe, as rectal and bladder temperatures will lag behind the rising core temperature during the rewarming process.

TABLE 57. Symptoms and Signs of Hypothermia

Severity	Temperature	Findings
Mild	32.0-35.0 °C (89.6-95.0 °F)	↑ HR, ↑ BP, ↑ RR, shivering, alert, poor judgment
Moderate	28.0-32.0 °C (82.4-89.6 °F)	↓ HR, ↓ BP, ↓ RR, ↓ CO, ↓O_2 consumption, ↓ kidney function, somnolence, no shivering, supraventricular arrhythmia
Severe	<28.0 °C (82.4 °F)	Coma, absent reflexes, ventricular arrhythmia, asystole, apnea

BP = blood pressure; CO = cardiac output; HR = heart rate; RR = respiration rate.

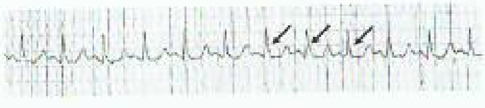

FIGURE 21. Electrocardiogram showing Osborne waves associated with hypothermia. They are best seen in the inferior and lateral chest leads. Osborne waves are defined by the shoulder or "hump" between QRS and ST segments.

Toxicology

Alcohol Poisoning

Ethanol and other ingested alcohols activate the γ-aminobutyric acid receptor, which is the primary central nervous system (CNS) inhibitor, thus leading to CNS depression, including loss of consciousness and suppression of respiratory drive at high doses. In addition to this acute toxicity, which can lead to life-threatening apnea or aspiration events, alcohol withdrawal can also be fatal, and patients should be monitored for signs of withdrawal, including seizures. Ethanol is the most commonly ingested alcohol and the most often encountered toxicity (**Table 58**). For further discussion of alcohol withdrawal see MKSAP 18 General Internal Medicine.

Other alcohols ingested include ethylene glycol (antifreeze), methanol (wood alcohol), and isopropyl alcohol (rubbing alcohol). These all have similar CNS depressant effects to those of ethanol. However, after ingestion, ethylene glycol is metabolized by alcohol dehydrogenase to oxalic acid, which crystalizes in the renal tubules and can lead to permanent kidney damage. Methanol is metabolized to formic acid, which is toxic to the retina and leads to blindness. When either of these alcohols has been ingested, there is an elevated anion gap metabolic acidosis as well as an osmolal gap (see MKSAP 18 Nephrology: Increased Anion Gap Metabolic Acidosis). Therapy includes elimination but also prevention of metabolism by alcohol dehydrogenase to toxic metabolites. The enzymatic process can be competitively inhibited by administering fomepizole.

Isopropyl alcohol has no toxic metabolites and does not elevate the anion gap, although it does increase the osmolal gap. Treatment is supportive. Dialysis removes all alcohols effectively, but is not necessary for patients who are inebriated but otherwise stable.

Carbon Monoxide Poisoning

Carbon monoxide (CO) is a colorless, odorless product of hydrocarbon combustion that is readily absorbed into the circulation when inhaled, and binds avidly to hemoglobin to form carboxyhemoglobin, displacing oxygen and causing clinical tissue hypoxia and ischemia. CO toxicity occurs almost exclusively in enclosed areas where combustion is occurring and is often accidental, but may be intentional in suicide attempts. Exposed patients present with headache, nausea,

TABLE 58. Presentation and Treatment of Alcohol Poisoning

Alcohol	Common Sources	Major Findings	Anion Gap	Osmolar Gap	Antidote
Ethanol	Alcoholic beverages	CNS depression Nausea, emesis	Possible	Yes	Supportive care
Isopropyl alcohol	Rubbing alcohol Disinfectants Antifreeze	CNS depression Ketone elevation	No	Yes	Supportive care
Methanol	Windshield wiper fluid De-icing solutions Solvents "Moonshine"	CNS depression Vision loss Hypotension	Yes	Yes	Fomepizole HD for severe acidemia, very large ingestions, severe CNS depression, and any visual impairment
Ethylene glycol	Antifreeze De-icing solutions Solvents	CNS depression AKI Hypocalcemia Hypotension	Yes	Yes	Fomepizole HD for severe acidemia, very large ingestions, severe CNS depression, AKI, and systemic collapse

AKI = acute kidney injury; CNS = central nervous system; HD = hemodialysis.

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malaise, confusion, syncope, seizures, or coma. Patients with coronary artery disease may develop signs and symptoms of cardiac ischemia.

Pulse oximetry is not helpful, as current transcutaneous oximetry technology does not differentiate between oxyhemoglobin and carboxyhemoglobin. Blood gas analysis, including cooximetry, will provide the carboxyhemoglobin level, which is less than 3% in normal individuals. Smokers may have up to 10% to 15% carboxyhemoglobin, and anything higher is consistent with CO poisoning.

The primary treatment is displacement of CO on the hemoglobin molecule with oxygen, which depends on the alveolar concentration of oxygen and the minute ventilation. Once the CO exposure has been stopped, the half-life of carboxyhemoglobin is 300 minutes if patients are breathing ambient air, 90 minutes if breathing 100% oxygen, and 30 minutes if given hyperbaric oxygen in a chamber where the pressure is gradually increased to 2 to 3 times the normal atmospheric pressure. Patients with high levels of carboxyhemoglobin (25% and greater) and evidence of organ ischemia should be treated with hyperbaric oxygen if possible.

Besides the immediate complications resulting from tissue hypoxia in the setting of CO toxicity, there are also delayed neurologic sequelae in approximately 40% of severe cases of CO poisoning. The mechanism is poorly understood, but probably relates to ischemic damage sustained in specific, oxygen-sensitive areas of the brain. These delayed neurocognitive and personality defects usually appear within 20 days of the exposure, but can appear later. They can last for a year or longer. There is weak evidence that hyperbaric oxygen therapy reduces the risk and severity of these delayed neurologic sequelae. H

KEY POINTS

- Pulse oximetry is not helpful in diagnosing carbon monoxide poisoning, as it does not differentiate between oxyhemoglobin and carboxyhemoglobin. HVC
- Patients with high levels of carboxyhemoglobin (25% or higher) and evidence of organ dysfunction should be treated with hyperbaric oxygen if possible.

Cyanide Poisoning

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Cyanide is one of the most lethal poisons known. It inhibits cellular respiration by binding to cytochrome oxidase a_3 in the mitochondria, blocking the cells' ability to use oxygen for aerobic metabolism. This results in clinical signs of hypoxia, despite normal oxyhemoglobin saturation. Symptoms often include headache, anxiety, nausea, and either a metallic or bitter almond odor and taste. More severe or prolonged exposure can lead to coma, seizures, liver or kidney injury, vomiting, ischemic pain, rhabdomyolysis, and death. Serum lactate elevation is a sensitive but nonspecific marker for cyanide toxicity. A normal lactate concentration effectively rules out significant cyanide exposure.

Cyanide can be ingested or inhaled and is absorbed readily and acts quickly to inhibit cellular metabolism. Inhalation exposure is common in house fires where cyanide is produced and aerosolized when vinyl burns. Cyanide is a common coexposure with carbon monoxide.

Successful treatment depends on early recognition of cyanide toxicity, elimination of ongoing exposure (for example, removal of contaminated clothing), and either neutralization or competitive binding of the cyanide to remove it from the mitochondrial respiration system. Hydroxocobalamin avidly binds to cyanide to produce

H CONT. cyanocobalamin, which is soluble, nontoxic, and readily excreted. The usual dose is 5 g for an adult. Other antidotes include nitrites (amyl nitrite and sodium nitrite) to induce methemoglobin, which in turn binds cyanide, as well as sodium thiosulfate, which donates sulfur to combine with cyanide, producing harmless thiocyanate. Inducing methemoglobinemia in inhalation injury victims who may also have high levels of carboxyhemoglobin is not safe, so nitrite therapy should be avoided. Of these potential treatment strategies, hydroxocobalamin is the most commonly recommended due to ease and safety of administration. H

KEY POINT

- Successful treatment of cyanide poisoning depends on early recognition of cyanide toxicity, elimination of ongoing exposure, and administration of hydroxocobalamin to remove the cyanide from the mitochondrial respiration system.

H Toxicity of Drugs of Abuse

Drugs of abuse may be taken singly or in combination, and an accurate history may be impossible to obtain due to alteration of mental status, reluctance on the part of the patient or others to admit what was taken, and insufficient or incorrect knowledge about the composition of illicit drugs. Clinical toxic syndromes, or constellations of symptoms and signs indicative of certain classes of drugs, can be recognized and provide clues as to what should be done for effective medical management of overdose (**Table 59** and **Table 60**).

In addition to seeking to identify the specific agent(s) or class(es) of drugs taken, care of overdose patients is primarily supportive; critically important is maintenance of airway patency and ventilation in patients with decreased mental status. Patients are often intubated to prevent aspiration and allow for mechanical ventilation in cases where respiratory drive is impaired by drugs.

An early empiric trial of the opioid antagonist naloxone is warranted when opioid overdose is suspected to reverse respiratory depression and depressed mental status. It is important to remember that naloxone has a very short half-life, and its antidote effects will usually wear off before the opioid effects are gone; patients should be observed for signs of opioid withdrawal (which is not fatal and requires only supportive care) and for continued or recurrent signs of respiratory distress, which may require repeated dosing of naloxone.

Administration of flumazenil for suspected benzodiazepine overdose is more problematic, as reversing the effect of benzodiazepines can lead to life-threatening CNS activation, including seizures, which are most likely in patients taking benzodiazepines chronically. It is usually best to manage patients with ventilator support and allow elimination of the agent over time.

In patients who have taken sympathomimetic agents, such as cocaine or amphetamines, benzodiazepines are the cornerstone of therapy for agitation. Beta blocker medications should be avoided, as they will block the beta-adrenergic receptors and theoretically leave the activated alpha receptors unopposed, thus leading to severe hypertension.

Hallucinogenic agents have no antidote, so care is supportive, including maintaining the airway, ventilation, and hemodynamic support. These patients may be extremely agitated and combative, requiring physical restraints or sedation to prevent them from harming themselves and others.

TABLE 59. Toxic Syndromes and Their Manifestations

Syndrome	Manifestations	Representative Drugs
Sympathomimetic	Tachycardia Hypertension Diaphoresis Agitation Seizures Mydriasis	Cocaine Amphetamines Ephedrine Caffeine
Cholinergic	"SLUDGE" (Salivation, Lacrimation, increased Urination and Defecation, Gastrointestinal upset, and Emesis) Confusion Bronchorrhea Bradycardia Miosis	Organophosphates (insecticides, sarin) Carbamates Physostigmine Edrophonium Nicotine
Anticholinergic	Hyperthermia Dry skin and mucous membranes Agitation, delirium Tachycardia, tachypnea Hypertension Mydriasis	Antihistamines Tricyclic antidepressants Anti-Parkinson agents Atropine Scopolamine
Opioids	Miosis Respiratory depression Lethargy, confusion Hypothermia Bradycardia Hypotension	Morphine, fentanyl, oxycodone and related drugs Heroin

Overdose of Therapeutic Drugs

Patients may overdose on prescribed medications either inadvertently or intentionally, and often many medications

TABLE 60. Presentation and Toxicity of Some Drugs of Abuse

Drug Class	Examples	Examination Findings	Antidote
Opioids	Heroin, oxycodone, fentanyl analogs	↓HR, ↓temp, ↓BP, ↓RR, miosis	Naloxone
Benzodiazepines	Lorazepam	CNS depression, usually normal vital signs and eye examination	Flumazenil (may be complicated by seizure)
Sympathomimetics		*Shared findings: ↑HR, ↑BP, ↑temp, diaphoresis, mydriasis, agitation, seizure,* ↑CK, ↑liver chemistry studies, ↑Cr	*Benzodiazepines are first line for agitation* Avoid β-blockers for hypertension Haloperidol may worsen hyperthermia
	Cocaine	30-minute duration, myocardial infarction prominent	
	Methamphetamine	Violent agitation prominent, ↓Na, duration 20 hours	
	MDMA ("ecstasy")	↓Na, serotonin syndrome	
	Bath salts ("plant food")	Hallucinations, violent agitation common, duration up to 48 hours, negative urine drug screen	
Hallucinogens	Dextromethorphan	↑HR, ↑BP, agitation, coma	Benzodiazepines are first line for agitation Haloperidol is second line
	Lysergic acid diethylamide (LSD)	Mild ↑HR, ↑BP; rare ↑temp and hemodynamic instability	
	Phencyclidine (PCP)	Variable mental status: ↑agitation, CNS depression, nystagmus	
	Synthetic cannabinoids ("Spice," "K-2")	↑HR, agitation > marijuana, ↑Cr, negative urine drug screen	

BP = blood pressure; CK = creatine kinase; CNS = central nervous system; Cr = creatinine; ECG = electrocardiogram; HR = heart rate; MDMA = 3-4 methylenedioxymethamphetamine; Na = sodium; RR = respiration rate; temp = temperature.

are taken together, sometimes with alcohol. Information about suicidal ideation or intent, what medications a patient and family members have been prescribed, what prescriptions were filled, events reported by the patient or bystanders, and clinical signs and symptoms are all important in determining the nature of an overdose. If patients are alert and cooperative enough to protect their airway, administration of activated charcoal may be beneficial if it can be given within 1 to 2 hours of ingestion (**Table 61**). Acetaminophen overdose is discussed in MKSAP 18 Gastroenterology and Hepatology, and salicylate overdose in MKSAP 18 Nephrology.

Acute Abdominal Surgical Emergencies

A large number of conditions can cause abdominal pain, distention, and rigidity. Although many of them can and should be managed medically, some require surgery, and timely diagnosis followed by surgical intervention is needed to improve survival. Imaging decisions should be based on history and examination findings, and should not delay intervention (**Table 62**). For further discussion of abdominal compartment syndrome see MKSAP 18 Nephrology.

Encephalopathy

Alterations in mental status are common in the ICU because of both critical illness and the ICU environment, which can provide sick patients few contextual clues to reorient themselves to time, place, and events. There are many situations that involve mental status change, but three are most important in the context of critical care medicine: delirium (addressed earlier in Principles of Critical Care), coma, and anoxic brain injury.

Coma

Coma describes a condition of absent cortical function of the CNS, with intact brainstem function, whether due to illness, trauma, or medication. Patients in a coma do not respond to external stimuli. The Glasgow Coma Scale (GCS) is an instrument for assessing the severity of deficit based on three categories of stimulus response: eye response, verbal response, and motor response (**Table 63**). A GCS score of 15 means a normal,

TABLE 61. Presentation and Treatment of Therapeutic Drug Toxicities

Medication	Key Clinical Findings	Treatment	Notes
Nonopioid analgesics			
Acetaminophen	↑ liver chemistry studies, ↑Cr, ↑ INR, encephalopathy, cerebral edema, vomiting	*N*-acetylcysteine	Transfer to liver transplant center if severe
Salicylates	Mixed respiratory alkalosis/anion gap metabolic acidosis, tinnitus, agitation, confusion, hyperthermia	Bicarbonate infusion, dextrose	Target urine pH 7.5 to 8.0; hemodialysis if acute kidney injury or severe toxicity
Cardiovascular			
β-Blocker, calcium channel blocker	↓ HR, ↓ BP, heart block, altered mental status if β-blocker	Atropine 1 mg IV up to 3 doses, glucagon, calcium chloride, vasopressors, cardiac pacemaker (if indicated), high-dose insulin and glucose, IV lipid emulsion	Treatments may be added sequentially or initiated simultaneously depending on severity of case and response to treatment
Digoxin	↓ HR, arrhythmia, nausea, emesis, abdominal pain, confusion, weakness	Digoxin-specific antibody	Use of antibody lowers K^+; hemodialysis not effective
Anticholinergics			
Tricyclic antidepressants	↓ BP, sedation, seizure, anticholinergic signs, arrhythmia	Bicarbonate infusion titrated to QRS duration; benzodiazepines for seizure	Physostigmine contraindicated
Antihistamines	Anticholinergic signs including agitation and seizures	Benzodiazepines; physostigmine if isolated anticholinergic overdose	Physostigmine use requires continuous cardiac monitor and bedside atropine
Hypoglycemic			
Sulfonylurea	↓ glucose, confusion, seizure, anxiety, diaphoresis, tremor	Dextrose + octreotide, glucagon IM = temporizing	Monitor for ↓ glucose for 48 hours if large ingestion
Metformin	↑ lactate, abdominal pain	Hemodialysis for severe ↓ pH or acute kidney injury	Glucose usually normal if isolated metformin ingestion
Others			
Lithium	GI distress, confusion, ataxia, tremor, myoclonic jerks, diabetes insipidus	Hemodialysis if lithium level >4 mEq/L or severe symptoms	Serum level can guide need for hemodialysis, confirm diagnosis
SSRI/SNRI	Agitation, clonus, ↑ reflexes, rigidity, fever, ↑ HR	Benzodiazepines, cyproheptadine if severe	Venlafaxine has ↑ cardiac toxicity

BP = blood pressure; Cr = creatinine; GI = gastrointestinal; HR = heart rate; IM = intramuscular; IV = intravenous; K^+ = potassium; SNRI = serotonin norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor.

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alert (or fully arousable) patient, and a score of 3 means no response at all. Comatose patients are often hyperreflexic. In addition to a clinical examination, lumbar puncture and CNS imaging with MRI or CT scan are useful in diagnosing the cause of coma. Treatment is supportive with efforts to reverse the specific cause of the coma if possible.

Anoxic Brain Injury

Anoxic brain injury refers to damage to the CNS caused by prolonged, profound tissue hypoxia. There are many possible causes of such hypoxia, including near drowning, seizures, obstructed airway, lung disease, cardiac arrest, asphyxiation, and other inhalational injury. Brain imaging shows edema and loss of grey-white matter demarcation. Electroencephalographic monitoring shows various patterns, from diffuse slowing (typical of many types of encephalopathy) to burst suppression or seizure activity (indicative of more severe injury) to absence of brain electrical activity (which can indicate brain death). Prognosis is often not immediately apparent, and patients with anoxic brain injury require supportive care for 3 to 5 days or longer before the extent of injury can be understood well enough to be declared irreversible. H

KEY POINT

- Prognosis for patients with anoxic brain injury is often not immediately apparent, and patients require supportive care for 3 to 5 days or longer before the extent of injury can be understood well enough to be declared irreversible.

TABLE 62. Acute Abdominal Emergencies

Diagnosis	Presentation	Diagnostic Imaging	Notes
Acute cholecystitis and cholangitis	Persistent peritoneal RUQ or epigastric pain, fever, emesis, positive Murphy sign	Ultrasound EUS and ERCP for diagnosis and treatment of cholangitis	↑ alkaline phosphatase, ↑ bilirubin suggests cholangitis but typically not cholecystitis
Bowel obstruction	Cramping pain, emesis, distention, obstipation, dehydration	Radiograph: dilated loops of bowel with air-fluid levels CT scan: identifies cause, complications	Top causes: incarcerated hernia, adhesions, volvulus, intussusception
Acute appendicitis	Classic: periumbilical then RLQ pain, emesis, ↑ leukocyte count	Often unnecessary CT or ultrasound if unclear	Pain quality and location vary with appendix location
Peptic ulcer perforation	Abrupt peritoneal pain, later distention and hypovolemia	Radiograph: free air CT scan if unclear	Surgery necessary in majority of cases
Acute mesenteric ischemia	Pain > examination findings, vomiting, hypotension, risk factors for clotting, embolism	CT angiography or conventional arteriography	↑ amylase, ↑ phosphate common Regular CT and lactate can be normal early in course
Toxic megacolon	Pain, diarrhea, fever, ↑ HR, ↓ BP, confusion	Radiograph: dilated colon, air-fluid levels in colon CT scan if unclear	Causes: inflammatory bowel disease, *Clostridium difficile* infection
Ruptured abdominal aortic aneurysm	↓ BP, abdominal and/or flank pain, pulsatile mass	Unnecessary if high suspicion and unstable CT or ultrasound if unclear	Risk factors: older age, male, smoking, hypertension, family history of aneurysm
Ectopic pregnancy with tubal rupture	↓ BP, ↓ Hb, ↑ hCG, abdominal pain, vaginal bleeding	Transvaginal ultrasound	High mortality without early surgery

BP = blood pressure; ERCP = endoscopic retrograde cholangiopancreatography; EUS = endoscopic ultrasound; Hb = hemoglobin; hCG = human chorionic gonadotropin; HR = heart rate; RLQ = right lower quadrant; RUQ = right upper quadrant; temp = temperature.

TABLE 63. Glasgow Coma Scale

Eyes	Score
Does not open eyes	1
Opens eyes in response to painful stimuli (when given pain)	2
Opens eyes in response to voice	3
Opens eyes spontaneously	4
Verbal	
Makes no sound	1
Incomprehensible sounds (mumbles)	2
Utters inappropriate words	3
Confused, disorientated	4
Oriented, chats normally	5
Motor (physical reflexes)	
Makes no movements	1
Extension (straightens limb when given painful stimulus)	2
Abnormal flexion (flexes limbs indiscriminately when given painful stimulus)	3
Flexion/withdrawal to painful stimuli (moves away when given painful stimulus)	4
Localizes painful stimuli (can pinpoint where pain is)	5
Obeys commands	6
Brain Injury as Classified in the Glasgow Coma Scale (Eyes + Verbal + Motor)	
Coma	3 to 8
Moderate brain injury	9 to 12
Mild brain injury	13 to 15

Bibliography

Pulmonary Diagnostic Tests

Berrizbeitia LD. The lower limit of normal in the evaluation of pulmonary function [Editorial]. Heart Lung. 2014;43:267-8. [PMID: 24856225] doi:10.1016/j.hrtlng.2014.04.011

Johnson JD, Theurer WM. A stepwise approach to the interpretation of pulmonary function tests. Am Fam Physician. 2014;89:359-66. [PMID: 24695507]

Little BP. Approach to chest computed tomography. Clin Chest Med. 2015;36:127-45, vii. [PMID: 26024596] doi:10.1016/j.ccm.2015.02.001

Murgu SD. Diagnosing and staging lung cancer involving the mediastinum. Chest. 2015;147:1401-12. [PMID: 25940251] doi:10.1378/chest.14-1355

Parreira VF, Janaudis-Ferreira T, Evans RA, Mathur S, Goldstein RS, Brooks D. Measurement properties of the incremental shuttle walk test. a systematic review. Chest. 2014;145:1357-69. [PMID: 24384555]

Pellegrino R, Viegi G, Brusasco V, Crapo RO, Burgos F, Casaburi R, et al. Interpretative strategies for lung function tests. Eur Respir J. 2005;26:948-68. [PMID: 16264058]

Singh SJ, Puhan MA, Andrianopoulos V, Hernandes NA, Mitchell KE, Hill CJ, et al. An official systematic review of the European Respiratory Society/American Thoracic Society: measurement properties of field walking tests in chronic respiratory disease [Editorial]. Eur Respir J. 2014;44:1447-78. [PMID: 25359356] doi:10.1183/09031936.00150414

Airways Disease

Altenburg J, de Graaff CS, Stienstra Y, Sloos JH, van Haren EH, Koppers RJ, et al. Effect of azithromycin maintenance treatment on infectious exacerbations among patients with non-cystic fibrosis bronchiectasis: the BAT randomized controlled trial. JAMA. 2013;309:1251-9. [PMID: 23532241] doi:10.1001/jama.2013.1937

Bel EH, Wenzel SE, Thompson PJ, Prazma CM, Keene ON, Yancey SW, et al; SIRIUS Investigators. Oral glucocorticoid-sparing effect of mepolizumab in eosinophilic asthma. N Engl J Med. 2014;371:1189-97. [PMID: 25199060] doi:10.1056/NEJMoa1403291

Boulet LP, O'Byrne PM. Asthma and exercise-induced bronchoconstriction in athletes. N Engl J Med. 2015;372:641-8. [PMID: 25671256] doi:10.1056/NEJMra1407552

Daniels JM, Snijders D, de Graaff CS, Vlaspolder F, Jansen HM, Boersma WG. Antibiotics in addition to systemic corticosteroids for acute exacerbations of chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2010;181:150-7. [PMID: 19875685] doi:10.1164/rccm.200906-0837OC

Evensen AE. Management of COPD exacerbations. Am Fam Physician. 2010;81:607-13. [PMID: 20187597]

Fishman A, Fessler H, Martinez F, McKenna RJ Jr, Naunheim K, Piantadosi S, et al; National Emphysema Treatment Trial Research Group. Patients at high risk of death after lung-volume-reduction surgery. N Engl J Med. 2001;345:1075-83. [PMID: 11596586]

Gilljam M, Ellis L, Corey M, Zielenski J, Durie P, Tullis DE. Clinical manifestations of CF among patients with diagnosis in adulthood. Chest. 2004;126:1215-24. [PMID: 15486385]

Global Strategy for Asthma. Global Strategy for Asthma Web site. www.ginasthma.org. Accessed May 9, 2018.

Herth FJ, Gompelmann D, Ernst A, Eberhardt R. Endoscopic lung volume reduction. Respiration. 2010;79:5-13. [PMID: 19923881] doi:10.1159/000256510

Leuppi JD, Schuetz P, Bingisser R, Bodmer M, Briel M, Drescher T, et al. Short-term vs conventional glucocorticoid therapy in acute exacerbations of chronic obstructive pulmonary disease: the REDUCE randomized clinical trial. JAMA. 2013;309:2223-31. [PMID: 23695200] doi:10.1001/jama.2013.5023

Maguire G. Bronchiectasis—a guide for primary care. Aust Fam Physician. 2012;41:842-50. [PMID: 23145413]

McShane PJ, Naureckas ET, Tino G, Strek ME. Non-cystic fibrosis bronchiectasis. Am J Respir Crit Care Med. 2013;188:647-56. [PMID: 23898922] doi:10.1164/rccm.201303-0411CI

Most Recent Asthma Data. Centers for Disease Control and Prevention Web site. https://www.cdc.gov/asthma/most_recent_data.htm. Updated February 13, 2018. Accessed May 9, 2018.

Mulhall P, Criner G. Non-pharmacological treatments for COPD. Respirology. 2016;21:791-809. [PMID: 27099216] doi:10.1111/resp.12782

Ong T, Ramsey BW. Update in cystic fibrosis 2014. Am J Respir Crit Care Med. 2015;192:669-75. [PMID: 26371812] doi:10.1164/rccm.201504-0656UP

Pakhale S, Baron J, Dent R, Vandemheen K, Aaron SD. Effects of weight loss on airway responsiveness in obese adults with asthma: does weight loss lead to reversibility of asthma? Chest. 2015;147:1582-90. [PMID: 25763936] doi:10.1378/chest.14-3105

Prasad Kerlin M. In the clinic. Asthma. Ann Intern Med. 2014;160:ITC3 2-15; quiz ITC3 16-9. [PMID: 24737276] doi:10.7326/0003-4819-160-5-201403040-01003

Qaseem A, Wilt TJ, Weinberger SE, Hanania NA, Criner G, van der Molen T, et al; American College of Physicians. Diagnosis and management of stable chronic obstructive pulmonary disease: a clinical practice guideline update from the American College of Physicians, American College of Chest Physicians, American Thoracic Society, and European Respiratory Society. Ann Intern Med. 2011;155:179-91. [PMID: 21810710] doi:10.7326/0003-4819-155-3-201108020-00008

Scheinberg P, Shore E. A pilot study of the safety and efficacy of tobramycin solution for inhalation in patients with severe bronchiectasis. Chest. 2005;127:1420-6. [PMID: 15821224]

Skloot GS, Busse PJ, Braman SS, Kovacs EJ, Dixon AE, Vaz Fragoso CA, et al; ATS ad hoc Committee on Asthma in the Elderly. An official American Thoracic Society Workshop report: evaluation and management of asthma in the elderly. Ann Am Thorac Soc. 2016;13:2064-2077. [PMID: 27831798]

Tarlo SM, Lemiere C. Occupational asthma. N Engl J Med. 2014;370:640-9. [PMID: 24521110] doi:10.1056/NEJMra1301758

Teodorescu M, Broytman O, Curran-Everett D, Sorkness RL, Crisafi G, Bleecker ER, et al; National Institutes of Health, National Heart, Lung and Blood Institute Severe Asthma Research Program (SARP) investigators. Obstructive sleep apnea risk, asthma burden, and lower airway inflammation in adults in the severe asthma research program (SARP) II. J Allergy Clin Immunol Pract. 2015;3:566-75.e1. [PMID: 26004304] doi:10.1016/j.jaip.2015.04.002

The Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2017. Available from: goldcopd.org. Accessed May 25, 2018.

Vogelmeier CF, Criner GJ, Martinez FJ, Anzueto A, Barnes PJ, Bourbeau J, et al. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease 2017 Report. GOLD Executive Summary. Am J Respir Crit Care Med. 2017;195:557-582. [PMID: 28128970] doi:10.1164/rccm.201701-0218PP

Wechsler ME. Getting control of uncontrolled asthma. Am J Med. 2014;127:1049-59. [PMID: 24844737] doi:10.1016/j.amjmed.2014.05.006

Diffuse Parenchymal Lung Disease

Collard HR, Ryerson CJ, Corte TJ, Jenkins G, Kondoh Y, Lederer DJ, et al. Acute exacerbation of idiopathic pulmonary fibrosis. An international working group report. Am J Respir Crit Care Med. 2016;194:265-75. [PMID: 27299520] doi:10.1164/rccm.201604-0801CI

Fischer A, Antoniou KM, Brown KK, Cadranel J, Corte TJ, du Bois RM, et al; ERS/ATS Task Force on Undifferentiated Forms of CTD-ILD. An official European Respiratory Society/American Thoracic Society research statement: interstitial pneumonia with autoimmune features. Eur Respir J. 2015;46:976-87. [PMID: 26160873] doi:10.1183/13993003.00150-2015

Hansell DM, Bankier AA, MacMahon H, McLoud TC, Müller NL, Remy J. Fleischner Society: glossary of terms for thoracic imaging. Radiology. 2008;246:697-722. [PMID: 18195376] doi:10.1148/radiol.2462070712

Hutchinson JP, Fogarty AW, McKeever TM, Hubbard RB. In-hospital mortality after surgical lung biopsy for interstitial lung disease in the United States. 2000 to 2011. Am J Respir Crit Care Med. 2016;193:1161-7. [PMID: 26646481] doi:10.1164/rccm.201508-1632OC

Raghu G, Chen SY, Hou Q, Yeh WS, Collard HR. Incidence and prevalence of idiopathic pulmonary fibrosis in US adults 18-64 years old. Eur Respir J. 2016;48:179-86. [PMID: 27126689] doi:10.1183/13993003.01653-2015

Raghu G, Rochwerg B, Zhang Y, Garcia CA, Azuma A, Behr J, et al; American Thoracic Society. An official ATS/ERS/JRS/ALAT Clinical Practice Guideline: treatment of idiopathic pulmonary fibrosis. An update of the 2011 Clinical Practice Guideline. Am J Respir Crit Care Med. 2015;192:e3-19. [PMID: 26177183] doi:10.1164/rccm.201506-1063ST

Schwaiblmair M, Behr W, Haeckel T, Märkl B, Foerg W, Berghaus T. Drug-induced interstitial lung disease. Open Respir Med J. 2012;6:63-74. [PMID: 22896776] doi:10.2174/1874306401206010063

Tashkin DP, Elashoff R, Clements PJ, Goldin J, Roth MD, Furst DE, et al; Scleroderma Lung Study Research Group. Cyclophosphamide versus placebo in scleroderma lung disease. N Engl J Med. 2006;354:2655-66. [PMID: 16790698]

Tashkin DP, Roth MD, Clements PJ, Furst DE, Khanna D, Kleerup EC, et al; Sclerodema Lung Study II Investigators. Mycophenolate mofetil versus oral cyclophosphamide in scleroderma-related interstitial lung disease (SLS II): a randomised controlled, double-blind, parallel group trial. Lancet Respir Med. 2016;4:708-19. [PMID: 27469583] doi:10.1016/S2213-2600(16)30152-7

Travis WD, Costabel U, Hansell DM, King TE Jr, Lynch DA, Nicholson AG, et al; ATS/ERS Committee on Idiopathic Interstitial Pneumonias. An official

American Thoracic Society/European Respiratory Society statement: update of the international multidisciplinary classification of the idiopathic interstitial pneumonias. Am J Respir Crit Care Med. 2013;188:733–48. [PMID: 24032382] doi:10.1164/rccm.201308-1483ST

Weill D, Benden C, Corris PA, Dark JH, Davis RD, Keshavjee S, et al. A consensus document for the selection of lung transplant candidates: 2014—an update from the Pulmonary Transplantation Council of the International Society for Heart and Lung Transplantation. J Heart Lung Transplant. 2015;34:1-15. [PMID: 25085497] doi:10.1016/j.healun.2014.06.014

Occupational Lung Disease

Bacchus L, Shah RD, Chung JH, Crabtree TP, Heitkamp DE, Iannettoni MD, et al; Expert Panel on Thoracic Imaging. ACR appropriateness criteria review ACR appropriateness criteria® occupational lung diseases. J Thorac Imaging. 2016;31:W1-3. [PMID: 26656194] doi:10.1097/RTI.0000000000000194

Curti S, Sauni R, Spreeuwers D, De Schryver A, Valenty M, Rivière S, et al. Interventions to increase the reporting of occupational diseases by physicians. Cochrane Database Syst Rev. 2015:CD010305. [PMID: 25805310] doi:10.1002/14651858.CD010305.pub2

Laney AS, Weissman DN. The classic pneumoconioses: new epidemiological and laboratory observations. Clin Chest Med. 2012;33:745-58. [PMID: 23153613] doi:10.1016/j.ccm.2012.08.005

Sauler M, Gulati M. Newly recognized occupational and environmental causes of chronic terminal airways and parenchymal lung disease. Clin Chest Med. 2012;33:667-80. [PMID: 23153608] doi:10.1016/j.ccm.2012.09.002

Seaman DM, Meyer CA, Kanne JP. Occupational and environmental lung disease. Clin Chest Med. 2015;36:249-68, viii-ix. [PMID: 26024603] doi:10.1016/j.ccm.2015.02.008

Pleural Disease

Baumann MH, Strange C, Heffner JE, Light R, Kirby TJ, Klein J, et al; AACP Pneumothorax Consensus Group. Management of spontaneous pneumothorax: an American College of Chest Physicians Delphi consensus statement. Chest. 2001;119:590-602. [PMID: 11171742]

Bhatnagar R, Corcoran JP, Maldonado F, Feller-Kopman D, Janssen J, Astoul P, et al. Advanced medical interventions in pleural disease. Eur Respir Rev. 2016;25:199-213. [PMID: 27246597] doi:10.1183/16000617.0020-2016

Davies HE, Davies RJ, Davies CW; BTS Pleural Disease Guideline Group. Management of pleural infection in adults: British Thoracic Society Pleural Disease Guideline 2010. Thorax. 2010;65 Suppl 2:ii41-53. [PMID: 20696693] doi:10.1136/thx.2010.137000

Davies HE, Mishra EK, Kahan BC, Wrightson JM, Stanton AE, Guhan A, et al. Effect of an indwelling pleural catheter vs chest tube and talc pleurodesis for relieving dyspnea in patients with malignant pleural effusion: the TIME2 randomized controlled trial. JAMA. 2012;307:2383-9. [PMID: 22610520] doi:10.1001/jama.2012.5535

Feller-Kopman D, Light R. Pleural disease. N Engl J Med. 2018;378:740-751.

MacDuff A, Arnold A, Harvey J; BTS Pleural Disease Guideline Group. Management of spontaneous pneumothorax: British Thoracic Society Pleural Disease Guideline 2010. Thorax. 2010;65 Suppl 2:ii18-31. [PMID: 20696690] doi:10.1136/thx.2010.136986

Rahman NM, Maskell NA, West A, Teoh R, Arnold A, Mackinlay C, et al. Intrapleural use of tissue plasminogen activator and DNase in pleural infection. N Engl J Med. 2011;365:518-26. [PMID: 21830966] doi:10.1056/NEJMoa1012740

Rahman NM, Mishra EK, Davies HE, Davies RJ, Lee YC. Clinically important factors influencing the diagnostic measurement of pleural fluid pH and glucose. Am J Respir Crit Care Med. 2008;178:483-90. [PMID: 18556632] doi:10.1164/rccm.200801-062OC

Roberts ME, Neville E, Berrisford RG, Antunes G, Ali NJ; BTS Pleural Disease Guideline Group. Management of a malignant pleural effusion: British Thoracic Society Pleural Disease Guideline 2010. Thorax. 2010;65 Suppl 2:ii32-40. [PMID: 20696691] doi:10.1136/thx.2010.136994

Wilcox ME, Chong CA, Stanbrook MB, Tricco AC, Wong C, Straus SE. Does this patient have an exudative pleural effusion? The Rational Clinical Examination systematic review. JAMA. 2014;311:2422-31. [PMID: 24938565] doi:10.1001/jama.2014.5552

Pulmonary Vascular Disease

Galiè N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, et al; ESC Scientific Document Group. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Heart J. 2016;37:67-119. [PMID: 26320113] doi:10.1093/eurheartj/ehv317

Lung Tumors

Aberle DR, Adams AM, Berg CD, Black WC, Clapp JD, Fagerstrom RM, et al; National Lung Screening Trial Research Team. Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med. 2011;365:395-409. [PMID: 21714641] doi:10.1056/NEJMoa1102873

Gould MK, Donington J, Lynch WR, Mazzone PJ, Midthun DE, Naidich DP, et al. Evaluation of individuals with pulmonary nodules: when is it lung cancer? Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2013;143:e93S-e120S. [PMID: 23649456] doi:10.1378/chest.12-2351

Husain AN, Colby T, Ordonez N, Krausz T, Attanoos R, Beasley MB, et al; International Mesothelioma Interest Group. Guidelines for pathologic diagnosis of malignant mesothelioma: 2012 update of the consensus statement from the International Mesothelioma Interest Group. Arch Pathol Lab Med. 2013;137:647-67. [PMID: 22929121] doi:10.5858/arpa.2012-0214-OA

MacMahon H, Naidich DP, Goo JM, Lee KS, Leung ANC, Mayo JR, et al. Guidelines for management of incidental pulmonary nodules detected on CT images: from the Fleischner Society 2017. Radiology. 2017;284:228-243. [PMID: 28240562] doi:10.1148/radiol.2017161659

McWilliams A, Tammemagi MC, Mayo JR, Roberts H, Liu G, Soghrati K, et al. Probability of cancer in pulmonary nodules detected on first screening CT. N Engl J Med. 2013;369:910-9. [PMID: 24004118] doi:10.1056/NEJMoa1214726

Naidich DP, Bankier AA, MacMahon H, Schaefer-Prokop CM, Pistolesi M, Goo JM, et al. Recommendations for the management of subsolid pulmonary nodules detected at CT: a statement from the Fleischner Society. Radiology. 2013;266:304-17. [PMID: 23070270] doi:10.1148/radiol.12120628

Sholl LM. Biomarkers in lung adenocarcinoma: a decade of progress. Arch Pathol Lab Med. 2015;139:469-80. [PMID: 25255293] doi:10.5858/arpa.2014-0128-RA

Silvestri GA, Gonzalez AV, Jantz MA, Margolis ML, Gould MK, Tanoue LT, et al. Methods for staging non-small cell lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2013;143:e211S-e250S. [PMID: 23649440] doi:10.1378/chest.12-2355

Strollo DC, Rosado de Christenson ML, Jett JR. Primary mediastinal tumors. Part 1: tumors of the anterior mediastinum. Chest. 1997;112:511-22. [PMID: 9266892]

Strollo DC, Rosado-de-Christenson ML, Jett JR. Primary mediastinal tumors: part II. Tumors of the middle and posterior mediastinum. Chest. 1997;112:1344-57. [PMID: 9367479]

Sleep Medicine

Aurora RN, Chowdhuri S, Ramar K, Bista SR, Casey KR, Lamm CI, et al. The treatment of central sleep apnea syndromes in adults: practice parameters with an evidence-based literature review and meta-analyses. Sleep. 2012;35:17-40. [PMID: 22215916] doi:10.5665/sleep.1580

Caples SM, Rowley JA, Prinsell JR, Pallanch JF, Elamin MB, Katz SG, et al. Surgical modifications of the upper airway for obstructive sleep apnea in adults: a systematic review and meta-analysis. Sleep. 2010;33:1396-407. [PMID: 21061863]

Cowie MR, Woehrle H, Wegscheider K, Angermann C, d'Ortho MP, Erdmann E, et al. Adaptive servo-ventilation for central sleep apnea in systolic heart failure. N Engl J Med. 2015;373:1095-105. [PMID: 26323938] doi:10.1056/NEJMoa1506459

Kapur VK, Auckley DH, Chowdhuri S, Kuhlmann DC, Mehra R, Ramar K, et al. Clinical practice guideline for diagnostic testing for adult obstructive sleep apnea: an American Academy of Sleep Medicine clinical practice guideline. J Clin Sleep Med. 2017;13:479-504. [PMID: 28162150] doi:10.5664/jcsm.6506

Ramar K, Dort LC, Katz SG, Lettieri CJ, Harrod CG, Thomas SM, et al. Clinical practice guideline for the treatment of obstructive sleep apnea and snoring with oral appliance therapy: an update for 2015. J Clin Sleep Med. 2015;11:773-827. [PMID: 26094920] doi:10.5664/jcsm.4858

Sack RL. Clinical practice. jet lag. N Engl J Med. 2010;362:440-7. [PMID: 20130253] doi:10.1056/NEJMcp0909838

Xie W, Zheng F, Song X. Obstructive sleep apnea and serious adverse outcomes in patients with cardiovascular or cerebrovascular disease: a PRISMA-compliant systematic review and meta-analysis. Medicine (Baltimore). 2014;93:e336. [PMID: 25546682] doi:10.1097/MD.0000000000000336

High-Altitude–Related Illnesses

Ahmedzai S, Balfour-Lynn IM, Bewick T, Buchdahl R, Coker RK, Cummin AR, et al; British Thoracic Society Standards of Care Committee. Managing passengers with stable respiratory disease planning air travel: British Thoracic

Society recommendations. Thorax. 2011;66 Suppl 1:i1-30. [PMID: 21856702] doi:10.1136/thoraxjnl-2011-200295

Bärtsch P, Swenson ER. Clinical practice: acute high-altitude illnesses. N Engl J Med. 2013;368:2294-302. [PMID: 23758234] doi:10.1056/NEJMcp1214870

Hu X, Cowl CT, Baqir M, Ryu JH. Air travel and pneumothorax. Chest. 2014;145:688-694. [PMID: 24687705] doi:10.1378/chest.13-2363

Silverman D, Gendreau M. Medical issues associated with commercial flights. Lancet. 2009;373:2067-77. [PMID: 19232708] doi:10.1016/S0140-6736(09)60209-9

West JB; American College of Physicians. The physiologic basis of high-altitude diseases. Ann Intern Med. 2004;141:789-800. [PMID: 15545679]

Principles of Critical Care

Barr J, Fraser GL, Puntillo K, Ely EW, Gélinas C, Dasta JF, et al; American College of Critical Care Medicine. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. Crit Care Med. 2013;41:263-306. [PMID: 23269131] doi:10.1097/CCM.0b013e3182783b72

Connolly B, O'Neill B, Salisbury L, Blackwood B; Enhanced Recovery After Critical Illness Programme Group. Physical rehabilitation interventions for adult patients during critical illness: an overview of systematic reviews. Thorax. 2016;71:881-90. [PMID: 27220357] doi:10.1136/thoraxjnl-2015-208273

Girard TD, Alhazzani W, Kress JP, Ouellette DR, Schmidt GA, Truwit JD, et al; ATS/CHEST Ad Hoc Committee on Liberation from Mechanical Ventilation in Adults. An Official American Thoracic Society/American College of Chest Physicians Clinical Practice Guideline: Liberation from Mechanical Ventilation in Critically Ill Adults. Rehabilitation Protocols, Ventilator Liberation Protocols, and Cuff Leak Tests. Am J Respir Crit Care Med. 2017;195:120-133. [PMID: 27762595] doi:10.1164/rccm.201610-2075ST

Hermans G, Van den Berghe G. Clinical review: intensive care unit acquired weakness. Crit Care. 2015;19:274. [PMID: 26242743] doi:10.1186/s13054-015-0993-7

Schweickert WD, Pohlman MC, Pohlman AS, et al: Early physical and occupational therapy in mechanically ventilated, critically ill patients: A randomised controlled trial. Lancet 2009; 373:1874-1882. PMID 19446324

Taylor BE, McClave SA, Martindale RG, Warren MM, Johnson DR, Braunschweig C, et al; Society of Critical Care Medicine. Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.). Crit Care Med. 2016;44:390-438. [PMID: 26771786] doi:10.1097/CCM.0000000000001525

Common ICU Conditions

Briel M, Meade M, Mercat A, Brower RG, Talmor D, Walter SD, et al. Higher vs lower positive end-expiratory pressure in patients with acute lung injury and acute respiratory distress syndrome: systematic review and meta-analysis. JAMA. 2010;303:865-73. [PMID: 20197533] doi:10.1001/jama.2010.218

Brower RG, Matthay MA, Morris A, Schoenfeld D, Thompson BT, Wheeler A; Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med. 2000;342:1301-8. [PMID: 10793162]

Fan E, Del Sorbo L, Goligher EC, Hodgson CL, Munshi L, Walkey AJ, et al; American Thoracic Society, European Society of Intensive Care Medicine, and Society of Critical Care Medicine. An official American Thoracic Society/European Society of Intensive Care Medicine/Society of Critical Care Medicine clinical practice guideline: mechanical ventilation in adult patients with acute respiratory distress syndrome. Am J Respir Crit Care Med. 2017;195:1253-1263. [PMID: 28459336] doi:10.1164/rccm.201703-0548ST

Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2017. http://goldcopd.org. Accessed May 25, 2018.

Guérin C, Reignier J, Richard JC, Beuret P, Gacouin A, Boulain T, et al; PROSEVA Study Group. Prone positioning in severe acute respiratory distress syndrome. N Engl J Med. 2013;368:2159-68. [PMID: 23688302] doi:10.1056/NEJMoa1214103

National Heart, Lung and Blood Institute. National Asthma Education and Prevention Program. Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma. August 28, 2007: www.nhlbi.nih.gov/guidelines/asthma/asthgdln.pdf. Accessed May 25, 2018.

Papazian L, Forel JM, Gacouin A, Penot-Ragon C, Perrin G, Loundou A, et al; ACURASYS Study Investigators. Neuromuscular blockers in early acute respiratory distress syndrome. N Engl J Med. 2010;363:1107-16. [PMID: 20843245] doi:10.1056/NEJMoa1005372

Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, Fan E, et al; ARDS Definition Task Force. Acute respiratory distress syndrome: the berlin definition. JAMA. 2012;307:2526-33. [PMID: 22797452] doi:10.1001/jama.2012.5669

Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock: 2016. Crit Care Med. 2017;45:486-552. [PMID: 28098591] doi:10.1097/CCM.0000000000002255

Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). JAMA. 2016;315:801-10. [PMID: 26903338] doi:10.1001/jama.2016.0287

Wiedemann HP, Wheeler AP, Bernard GR, Thompson BT, Hayden D, deBoisblanc B, et al; National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network. Comparison of two fluid-management strategies in acute lung injury. N Engl J Med. 2006;354:2564-75. [PMID: 16714767]

Specific Critical Care Topics

Brooks DE, Levine M, O'Connor AD, French RNE, Curry SC. Toxicology in the ICU: part 2: specific toxins. Chest. 2011;140:1072-1085. [PMID: 21972388] doi:10.1378/chest.10-2726

Elmer J, Callaway CW. The brain after cardiac arrest. Semin Neurol. 2017;37:19-24. [PMID: 28147414] doi:10.1055/s-0036-1597833

Leon LR, Bouchama A. Heat stroke. Compr Physiol. 2015;5:611-47. [PMID: 25880507] doi:10.1002/cphy.c140017

Levine M, Brooks DE, Truitt CA, Wolk BJ, Boyer EW, Ruha AM. Toxicology in the ICU: Part 1: general overview and approach to treatment. Chest. 2011;140:795-806. [PMID: 21896525] doi:10.1378/chest.10-2548

Lieberman PL. Recognition and first-line treatment of anaphylaxis. Am J Med. 2014;127:S6-11. [PMID: 24384138] doi:10.1016/j.amjmed.2013.09.008

Rainer C, Scheinost NA, Lefeber EJ. Neuroleptic malignant syndrome. When levodopa withdrawal is the cause. Postgrad Med. 1991;89:175-8, 180. [PMID: 2008397]

Whelton PK, Carey RM, Aronow WS, Casey DE Jr, Collins KJ, Dennison Himmelfarb C, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: executive summary: A report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. Hypertension. 2018;71:1269-1324. [PMID: 29133354] doi:10.1161/HYP.0000000000000066

Pulmonary and Critical Care Medicine Self-Assessment Test

This self-assessment test contains one-best-answer multiple-choice questions. Please read these directions carefully before answering the questions. Answers, critiques, and bibliographies immediately follow these multiple-choice questions. The American College of Physicians (ACP) is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

The American College of Physicians designates MKSAP 18 Pulmonary and Critical Care Medicine for a maximum of 25 *AMA PRA Category 1 Credits*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Successful completion of the CME activity, which includes participation in the evaluation component, enables the participant to earn up to 25 medical knowledge MOC points in the American Board of Internal Medicine's Maintenance of Certification (MOC) program. It is the CME activity provider's responsibility to submit participant completion information to ACCME for the purpose of granting MOC credit.

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CME credits and MOC points are available from the publication date of December 31, 2018, until December 31, 2021. You may submit your answer sheet or enter your answers online at any time during this period.

Directions

*Each of the numbered items is followed by lettered answers. Select the **ONE** lettered answer that is **BEST** in each case.*

H

Item 1

A 52-year-old woman is evaluated in the emergency department for wheezing, dyspnea, and cough productive of clear sputum, which have worsened during the past 3 days despite use of her albuterol inhaler up to four times daily. She has no environmental triggers or recent respiratory infection. She smokes two packs of cigarettes per day and is unable to quit. History is notable for anxiety and a 20-year history of asthma. She has had two exacerbations in the past year and was hospitalized and briefly intubated for one of them. Her prescription for budesonide/formoterol controller inhaler ran out 2 weeks ago, and she has been unable to refill it. Other medications are albuterol, montelukast, and alprazolam.

On physical examination, temperature is 37.0 °C (98.6 °F), blood pressure is 140/82 mm Hg, pulse rate is 140/min, and respiration rate is 32/min with increased work of breathing. Oxygen saturation is 89% breathing ambient air. Chest examination demonstrates poor air movement with faint expiratory wheezing. The remainder of the examination is normal.

Chest radiograph demonstrates hyperinflation without infiltrates.

Albuterol improves her symptoms.

Which of the following is the most appropriate management?

(A) Admit patient to the hospital for inpatient management
(B) Begin prednisone and schedule outpatient follow-up
(C) Refill patient's prescription for budesonide/formoterol and schedule outpatient follow-up
(D) Refill patient's prescription for budesonide/formoterol, begin prednisone, and schedule outpatient follow-up

Item 2

A 37-year-old man is evaluated for a 1-month history of worsening cough and wheezing requiring use of rescue therapy several times per week, as well as increasing nasal congestion and rhinorrhea. He has a history of moderate persistent asthma and rhinitis since his early twenties. One month ago the patient underwent repair of a traumatic anterior cruciate ligament tear and has some residual daily knee pain. His medical history is notable for sinusitis. He has no symptoms of gastroesophageal reflux disease. Medications are albuterol, budesonide/formoterol, and ibuprofen.

On physical examination, vital signs are normal. Oxygen saturation is 97% breathing ambient air. Examination demonstrates conjunctival injection and nasal polyps in both nostrils. Chest examination reveals wheezing on expiration. The remainder of the examination is noncontributory.

Laboratory studies reveal IgE is 265 U/mL (265 kU/L). Complete blood count reveals a leukocyte count of 4000/µL (4×10^9/L) with 10% eosinophils.

Office spirometry demonstrates moderate airflow obstruction.

Which of the following is the most appropriate initial management?

(A) 24-Hour esophageal pH monitoring
(B) Add montelukast
(C) Discontinue ibuprofen, begin prednisone
(D) Nasal polypectomy

Item 3

A 69-year-old man is evaluated for a 3-year history of dyspnea and chronic productive cough. He was diagnosed with COPD 2 years ago after spirometry confirmed severe airflow obstruction. He discontinued smoking at that time but in the past year he was treated for three COPD exacerbations, one requiring hospitalization. Medications are tiotropium, fluticasone/salmeterol, and albuterol inhalers.

On physical examination, vital signs are normal; oxygen saturation is 92% on ambient air. He intermittently coughs during the examination. He has a prolonged expiratory phase. The remainder of the examination is unremarkable.

Chest radiograph shows the lungs to be clear.

Spirometry demonstrates a postbronchodilator FEV_1 of 45% of predicted.

Which of the following long-term treatments is most likely to reduce this patient's exacerbations of COPD?

(A) Prednisone
(B) Roflumilast
(C) Theophylline
(D) Trimethoprim-sulfamethoxazole

Item 4

A 57-year-old man is evaluated for a 6-month history of daytime sleepiness. His wife complains of his loud snoring and has observed breathing pauses; he sometimes awakens with a gasp. He has nocturia twice per night. He takes no medications.

On physical examination, vital signs are normal. Oxygen saturation is 96% breathing ambient air. BMI is 33. He has a crowded oropharynx with a low-lying soft palate; his neck is 46 cm (18 in) in circumference; he has trace edema at the ankles. Cardiovascular and neurologic examinations are normal.

Which of the following is the most appropriate management?

(A) Auto-adjusting positive airway pressure
(B) Home sleep testing
(C) Multiple sleep latency testing
(D) Overnight pulse oximetry

Item 5

A 72-year-old man is evaluated during a follow-up visit. He was evaluated in the emergency department 2 weeks ago for the sudden onset of chest pain. A CT scan was negative for

pulmonary embolism but demonstrated an 8-mm ground-glass nodule in the right upper lobe. He has had no recurrence of chest pain. His history is significant for hypertension treated with lisinopril.

Upon physical examination, vital signs are normal. The remainder of the physical examination is normal. The patient undergoes follow-up CT scans of his lung at 12 months and also at 2 years. The nodule is unchanged.

Which of the following is the most appropriate management of the lung nodule?

(A) Chest CT scans every 2 years for 5 years
(B) PET/CT scan
(C) Tissue sampling
(D) No further follow-up is needed

H Item 6

A 72-year-old man is hospitalized for progressive dyspnea and cough following a sore throat 3 weeks ago. Medical history is significant for idiopathic pulmonary fibrosis diagnosed 4 years ago that required 2 L/min of oxygen at rest. He is disabled because of his lung disease and is homebound. His only medication is pirfenidone.

On physical examination, blood pressure is 150/95 mm Hg, pulse rate is 105/min, and respiration rate is 28/min. Oxygen saturation is 89% on 6 L/min of oxygen. Lung examination demonstrates diffuse inspiratory crackles in all zones that are worse at the bases. He has clubbing and trace edema but no jugular venous distention.

Bronchoalveolar lavage is positive only for rhinovirus.

B-type natriuretic peptide is 20 pg/mL.

High-resolution CT scan with contrast demonstrates new bilateral ground-glass opacities on a background of basal predominant septal line thickening with traction bronchiectasis and honeycomb changes. CT angiography demonstrates no evidence of pulmonary embolism.

Which of the following is the most likely diagnosis?

(A) Acute exacerbation of idiopathic pulmonary fibrosis
(B) Acute heart failure
(C) Acute hypersensitivity pneumonitis
(D) Nonspecific interstitial pneumonia

H Item 7

A 32-year-old man is evaluated in the hospital for symptoms of persistent asthma. He was evaluated in the emergency department 2 days ago for dyspnea accompanied by wheezing, dysphonia, and upper chest and throat tightness. Symptoms persisted despite use of albuterol inhaler every 3 to 4 hours and intravenous methylprednisolone, and he was hospitalized. He was diagnosed with asthma in high school and generally requires several courses of prednisone per year. Current medications are albuterol and fluticasone/salmeterol inhalers, prednisone, and montelukast.

On physical examination, blood pressure is 130/85 mm Hg, pulse rate is 110/min, and respiration rate is 18/min. Oxygen saturation is 100% on 2 L/min of oxygen through nasal cannula. BMI is 25. Chest examination demonstrates monophonic wheezing on inspiration.

Laboratory studies, including complete blood count, metabolic panel, and IgE, are normal.

Chest radiograph is clear and bedside spirometry is normal.

Which of the following is the most appropriate management?

(A) CT scan of the sinuses
(B) Increase prednisone dosage
(C) Laryngoscopy
(D) Polysomnography

Item 8 H

A 56-year-old man hospitalized for respiratory failure is evaluated for new-onset confusion. He has acute respiratory distress syndrome secondary to community-acquired pneumonia. He has been in the critical care unit for 3 days. He is orally intubated and placed on mechanical ventilation. Current medications are ceftriaxone, azithromycin, and propofol for light sedation according to protocol.

On physical examination, temperature is 38.3 °C (100.9 °F), blood pressure is 100/45 mm Hg, pulse rate is 112/min, and respiration rate is 24/min. He cannot focus his attention, does not follow simple commands, and has demonstrated fluctuating mental status during the past 8 hours. The neurological examination is otherwise normal. He appears to be comfortable and shows no signs of pain.

Arterial blood gas studies show a pH of 7.41, a P_{CO_2} of 38 mm Hg (5.1 kPa), and a P_{O_2} of 62 mm Hg (8.2 kPa). Serum sodium, serum creatinine, and blood urea nitrogen are normal.

Chest radiograph shows multifocal opacities consistent with pneumonia and acute respiratory distress syndrome.

In addition to orientation strategies and promoting a normal sleep-wake cycle, which of the following is the most appropriate management?

(A) Add haloperidol
(B) Add lorazepam
(C) Early mobilization
(D) Increase propofol

Item 9

A 62-year-old man is evaluated during a general medical exam. He is a current smoker with a 42-pack-year history. He has a chronic cough but no shortness of breath or chronic health conditions.

On physical examination, vital signs and the remainder of the physical examination are normal.

Which of the following interventions is most likely to improve this patient's long-term survival?

(A) Annual chest radiograph
(B) Annual low-dose CT scan
(C) Annual sputum cytology
(D) Smoking cessation

H

Item 10

A 56-year-old man is hospitalized for hematemesis. He vomited 300 mL of bright red blood 15 minutes ago. He has a history of heavy alcohol use and cirrhosis. He takes no medications.

On physical examination, blood pressure is 99/50 mm Hg, pulse rate is 110/min, and respiration rate is 25/min. Oxygen saturation is 93% breathing ambient air. He is only responsive to painful stimuli. He is jaundiced. His breathing is shallow but without accessory muscle use. Lung examination reveals rhonchi. There are telangiectasias on his chest. Ascites is present. The remainder of the examination is unremarkable.

Laboratory studies reveal a hemoglobin level of 8 g/dL (80 g/L), total bilirubin of 6.8 mg/dL (116.3 µmol/L), aspartate aminotransferase of 154 U/L, and alanine aminotransferase of 54 U/L.

Two large-bore intravenous lines have been placed and crystalloid resuscitation has been initiated.

Which of the following should be done next?

(A) Administer a nonselective β-blocker
(B) Administer oxygen by nasal cannula
(C) Emergency upper endoscopy
(D) Initiate noninvasive bilevel positive airway pressure
(E) Insert an endotracheal tube

Item 11

A 30-year-old man presents for a refill on his albuterol inhaler. In the past he only needed albuterol once or twice a month, generally related to exercise. Over the last 4 to 5 months, he has noted that he needs his albuterol inhaler at least 3 or 4 times weekly for symptoms not associated with exercise. There are no apparent environmental triggers, symptoms of reflux, sinus symptoms, or recent respiratory infections. His medical and family history is otherwise unremarkable.

On physical examination, vital signs are normal. Oxygen saturation is 97% breathing ambient air. He has expiratory wheezing. Cardiac examination is normal.

Laboratory studies, including complete blood count and IgE level, are normal.

On spirometry FEV_1 is 82% of predicted and improves significantly following inhaled albuterol. His inhaler technique is excellent.

Which of the following is the most appropriate treatment?

(A) Beclomethasone
(B) Fluticasone/salmeterol
(C) Ipratropium
(D) Montelukast

H

Item 12

A 72-year-old man is evaluated for nonproductive cough and progressively worsening dyspnea on exertion during the past year. He has no history of dry eyes, dry mouth, Raynaud phenomenon, arthralgia, myalgia, or arthritis. He has a 30-pack-year smoking history and quit 15 years ago. Currently retired, he worked as a car insurance adjustor and reports no environmental exposures.

On physical examination, vital signs are normal. Oxygen saturation is 95% breathing ambient air. Findings on lung examination include late velcro inspiratory crackles at the bases. Bilateral clubbing is present. The remainder of the physical examination is normal.

Spirometry shows an FVC of 82% of predicted, an FEV_1 of 90% of predicted, an FEV_1/FVC ratio of 0.85, and a D_{LCO} of 65% of predicted.

Chest radiograph shows an increase in reticular markings at the lung bases. High-resolution CT scan shows bilateral peripheral and basal predominant septal line thickening with honeycombing at the bases.

Which of the following is the most likely diagnosis?

(A) Desquamative interstitial pneumonia
(B) Hypersensitivity pneumonitis
(C) Idiopathic pulmonary fibrosis
(D) Pulmonary Langerhans cell histiocytosis
(E) Respiratory bronchiolitis-associated interstitial lung disease

Item 13

H

A 38-year-old woman is evaluated for 24 hours of fever, myalgia, and confusion. She returned from a camping trip in the woods 5 days ago.

On physical examination, temperature is 39.0 °C (102.2 °F), blood pressure is 80/34 mm Hg, pulse rate is 125/min, and respiration rate is 24/min. Oxygen saturation is 95% breathing ambient air. She has right axillary lymphadenopathy. She is confused. The skin is warm and dry. Her right hand is erythematous and has a wound with purulent drainage. Lung examination reveals scattered basilar crackles. Cardiac examination shows no gallops, murmurs, or jugular venous distention. The remainder of the physical examination is noncontributory.

Which of the following is required to assess this patient's intravascular volume status before fluid administration?

(A) Central venous catheter measure of venous pressure
(B) Inferior vena cava collapsibility on echocardiography
(C) Pulmonary artery catheter measurements
(D) Pulse pressure variation
(E) No additional testing

Item 14

H

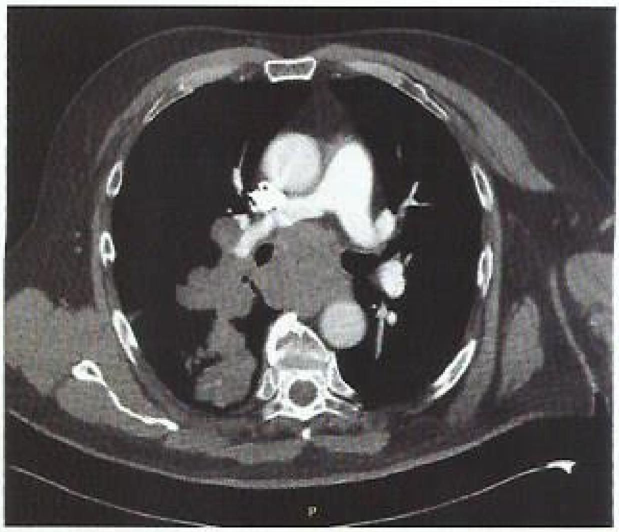
A 67-year-old man is evaluated in the emergency department with a 3-day history of weakness and nausea and a 2-week history of difficulty swallowing. He has lost 22.7 kg (50 lb) during the past year. He has no other symptoms. His history is significant for a 30-pack-year history of smoking. He quit smoking 4 years ago. He takes no medications.

On physical examination, vital signs are normal. Lung examination reveals decreased tactile fremitus above the lower portion of the right lung as well as dullness to percussion and decreased breath sounds. His neurologic examination is normal.

CONT.

Laboratory studies reveal a serum sodium concentration of 127 mEq/L (127 mmol/L).

A chest CT scan is shown.



Which of the following is the most likely diagnosis?

(A) Adenocarcinoma of the lung
(B) Malignant pleural mesothelioma
(C) Small cell lung cancer
(D) Squamous cell carcinoma of the lung

Item 15

A 62-year-old woman is evaluated in the emergency department for worsening dyspnea on exertion during the last 2 weeks. She has a history of severe COPD and an FEV_1 of 45% of predicted. She has a cough productive of yellow sputum and wheezing during the same time period. She has a 20-pack-year history of smoking but quit 10 years ago. Her albuterol inhaler and nebulizer have provided temporary relief at home. Current medications are umeclidinium/vilanterol, mometasone, and albuterol.

On physical examination, temperature is normal, blood pressure is 132/64 mm Hg, pulse rate is 110/min, and respiration rate is 30/min. Oxygen saturation is 90% on 6 L/min of oxygen by nasal cannula. Cardiopulmonary examination reveals tachycardia, tachypnea with accessory muscle use, and decreased breath sounds throughout with a prolonged expiratory phase and end expiratory wheezes. She has no jugular venous distention or edema.

Laboratory studies reveal an arterial Pco_2 of 46 mm Hg (6.11 kPa). Complete blood count, serum electrolytes, and blood glucose are normal.

A chest radiograph shows hyperinflated lungs with flattening of the diaphragms but no infiltrate.

Which of the following is the most appropriate next additional test?

(A) CT pulmonary angiogram
(B) Electrocardiogram
(C) Sputum culture
(D) Sputum Gram stain

Item 16

A 62-year-old man is evaluated for sleep apnea. He was recently hospitalized for atrial fibrillation with rapid ventricular rate. He sleeps 8 hours most nights but awakens feeling unrested. He is likely to doze off during the day while watching TV and reading the newspaper. He has hypertension and type 2 diabetes mellitus. Current medications are apixaban, lisinopril, metoprolol, and metformin.

On physical examination, blood pressure is 154/90 mm Hg and pulse rate is 82/min. Oxygen saturation is 98% breathing ambient air. BMI is 29. He has a low-lying soft palate, prominent tongue base, and an irregular heart rhythm. Cardiac examination reveals an irregular rhythm and variable intensity of S_1. There are no findings of heart failure.

Polysomnography demonstrates moderate obstructive sleep apnea (apnea-hypopnea index 18/hour).

Hemoglobin A_{1c} measurement is 7.5%.

Which of the patient's conditions is the strongest indication for positive airway pressure therapy?

(A) Atrial fibrillation
(B) Diabetes
(C) Excessive daytime sleepiness
(D) Hypertension

Item 17

A 39-year-old man with obesity hypoventilation syndrome is hospitalized for hypoxemia and altered mental status. Three hours ago he was placed on bilevel positive airway pressure (BPAP) with 50% oxygen. History is significant for obesity, diabetes, and obesity hypoventilation syndrome for which he is receiving home nocturnal BPAP ventilation and metformin. He has been unsuccessful in losing weight with diet and medications; he is being evaluated for bariatric surgery.

On physical examination, blood pressure is 150/78 mm Hg, pulse rate is 90/min, and respiration rate is 16/min. BMI is 42. Oxygen saturation is 96% on 50% oxygen. His respirations are shallow without wheezing. He is somnolent but awakens to light touch. He has an intact cough and gag reflex.

Chest radiograph shows small lung volumes, normal heart, and normal vascularization of the lung parenchyma.

Arterial blood gas studies on BPAP and 50% oxygen:

	3 Hours Ago	Now
Bicarbonate	29 mEq/L (29 mmol/L)	28 mEq/L (28 mmol/L)
pH	7.21	7.17
Po_2	114 mm Hg (15.1 kPa)	108 mm Hg (14.4 kPa)
Pco_2	74 mm Hg (9.8 kPa)	80 mm Hg (10.6 kPa)

Which of the following is the most appropriate treatment?

(A) Acetazolamide
(B) Endotracheal intubation
(C) Prednisone
(D) Theophylline

Item 18

A 42-year-old man is evaluated in the office for follow-up of progressive dyspnea of 2 years' duration. He first noted dyspnea with exercise but now has symptoms when walking up a flight of stairs. He has intermittent wheezing but no coughing or nocturnal respiratory symptoms. At the time of his initial evaluation 2 years ago, pulmonary function tests demonstrated moderate airflow obstruction. He has a 1-pack-year smoking history but has not smoked in 20 years. He has no environmental exposures. His father and uncle both have emphysema without a history of smoking. He takes no medications.

On physical examination, vital signs are normal. Oxygen saturation is 94% breathing ambient air. Examination reveals no clubbing or jugular venous distention, extra cardiac sounds, edema, pulmonary crackles, or wheezing.

A chest radiograph shows hyperinflation and diaphragmatic flattening.

Which of the following is the most appropriate test to perform next?

(A) α_1-Antitrypsin level
(B) Exhaled nitric oxide test
(C) High-resolution CT scan of the chest
(D) Vascular endothelial growth factor-D

Item 19

A 46-year-old man is evaluated for problems with autoadjusting positive airway pressure therapy that was prescribed 3 weeks ago for severe obstructive sleep apnea. He awakens with a sore throat, nasal congestion, and an occasional headache. Download from the device shows a residual apnea-hypopnea index of 3, which correlates with a decrease in his daytime sleepiness.

On physical examination, vital signs are normal. BMI is 33. He has a crowded oropharynx; low-hanging soft palate; 1+ tonsils; and boggy, erythematous nasal mucosa.

Which of the following is the most appropriate treatment?

(A) Bilevel positive airway pressure
(B) Eszopiclone
(C) Heated humidification
(D) Nasal fluticasone spray

Item 20

A 49-year-old woman is evaluated in the office following a recent hospitalization for an asthma exacerbation. Her symptoms have improved but she continues to have dyspnea and intermittent wheezing. She has had two other hospitalizations within the past year for asthma exacerbations despite the chronic use of oral glucocorticoids. Other than a 3-year history of asthma, her medical history is unremarkable. Medications are mometasone/formoterol, montelukast, albuterol, tiotropium, and prednisone.

On physical examination, vital signs are normal. Oxygen saturation is 95% on ambient air. Pulmonary examination reveals expiratory wheezes with good air movement. The remainder of the physical examination is unremarkable.

Laboratory studies reveal leukocyte count of 10,000/µL (10×10^9/L) with 650 eosinophils/µL (0.65×10^9/L). Serum IgE level is 12 U/mL (12 kU/L) (normal range, 0-90 U/mL [0-90 kU/L]).

FEV_1 is 56% of predicted.

Chest radiograph is normal.

Which of the following is the most appropriate treatment?

(A) Begin doxycycline
(B) Change mometasone/formoterol to fluticasone/salmeterol
(C) Initiate a trial of mepolizumab therapy
(D) Initiate a trial of omalizumab therapy

Item 21

H

A 79-year-old woman is brought into the emergency department after she was found unconscious in her apartment by a neighbor. She had been using a propane-fueled heater to heat her small apartment. No other medical history is available.

On physical examination, blood pressure is 100/64 mm Hg, pulse rate is 70/min, and respiration rate is 16/min. Pulse oximetry shows 100% oxygen saturation on mechanical ventilation using 50% oxygen. She is unresponsive to pain or voice but has intact normal deep tendon and brainstem reflexes.

Co oximetry shows a carboxyhemoglobin level of 50%. CT scan of the head shows no acute changes.

Which of the following is the most appropriate treatment?

(A) Continue current management
(B) Decrease oxygen to 30%
(C) Hydroxocobalamin administration
(D) Hyperbaric oxygen therapy

Item 22

H

A 55-year-old man with COPD is evaluated in the emergency department for worsening dyspnea. He was doing well until 3 days ago when he developed fever, myalgia, increased cough productive of yellow sputum, and progressive dyspnea. He has no headaches, hypersomnolence, tremors, or extremity edema. Pulmonary function tests obtained 4 months ago demonstrated severe obstruction with air trapping. Current medications are albuterol and umeclidinium/vilanterol.

On physical examination, temperature is 38.2 °C (100.9 °F), blood pressure is 142/82 mm Hg, pulse rate is 94/min, and respiration rate is 18/min. Oxygen saturation is 90% breathing ambient air. He has end-expiratory wheezing throughout. There is no jugular venous distention or extra cardiac sounds.

A complete blood count and comprehensive metabolic profile are normal.

Other than tachycardia, an electrocardiogram is normal. Chest radiograph shows the lungs to be clear.

Therapy for a COPD exacerbation is initiated.

Which of the following is the most appropriate next diagnostic test?

(A) Arterial blood gas analysis
(B) B-type natriuretic peptide measurement
(C) CT pulmonary angiography
(D) Echocardiogram

Item 23

A 35-year-old woman is evaluated for a 4-month history of exertional dyspnea and a 1-week history of chest pressure. She has no sputum production, cough, or wheezes. She has never smoked.

On physical examination, vital signs are normal. Oxygen saturation is 91% breathing ambient air. Cardiopulmonary examination reveals a widened split S_2 with a prominent pulmonic component and neck vein distention. Lungs are clear to auscultation.

Laboratory studies, including complete blood count and comprehensive metabolic profile, are normal.

Electrocardiogram is normal.

Chest radiograph shows clear lung fields and prominent hilae.

Which of the following is the most appropriate initial test?

(A) High resolution CT of the chest

(B) Pulmonary function testing

(C) Transthoracic echocardiogram

(D) Ventilation-perfusion ($\dot{V}/\dot{Q}$) scan

Item 24

A 58-year-old man is evaluated for follow-up of an asthma exacerbation with no clear trigger, which improved with oral glucocorticoids and a short-acting β_2-agonist in addition to his outpatient medications. The patient has a 30-year history of asthma and has had two previous exacerbations during the preceding 12 months. He has no environmental triggers, allergies, atopy, symptoms of reflux, sinus symptoms, snoring, or recent respiratory infections. A recent sleep study was negative for obstructive sleep apnea. Medications are albuterol, budesonide/formoterol, montelukast, tiotropium, and prednisone.

On physical examination, vital signs are normal. Oxygen saturation is 97% breathing ambient air. BMI is 36. Pulmonary examination reveals scattered expiratory wheezing. Cardiac examination is normal.

Bedside spirometry demonstrates moderate airflow obstruction; FEV_1 improves by 15% following inhaled albuterol.

Laboratory studies, including IgE level and complete blood count, are normal.

CT scan of the sinuses is normal.

Which of the following is the most appropriate management?

(A) Add beclomethasone

(B) Perform methacholine challenge testing

(C) Start mepolizumab

(D) Start omalizumab

(E) Supervised weight loss program

Item 25

A 71-year-old man is evaluated during a follow-up visit for sleep-related breathing pauses observed by the hospital staff when he was admitted for implantation of a cardioverter-defibrillator for ischemic cardiomyopathy (left ventricular ejection fraction of 30%). He has recently experienced dyspnea, a few episodes of which have awakened him from sleep. He has no insomnia or daytime sleepiness. He has dyslipidemia, stable coronary artery disease, and hypertension. Current medications are aspirin, atorvastatin, valsartan, metoprolol, and nitroglycerin as needed.

On physical examination, vital signs are normal. Oxygen saturation is 93% breathing ambient air. BMI is 23. Lung examination reveals bibasilar crackles, faint end-expiratory wheezing, neck vein distention, and 1+ ankle edema.

Polysomnography demonstrates central sleep apnea with a Cheyne-Stokes breathing pattern.

Which of the following is the most appropriate treatment of the patient's central sleep apnea?

(A) Adaptive servo-ventilation

(B) Auto-adjusting positive airway pressure

(C) Furosemide

(D) Supplemental oxygen

Item 26

A 60-year-old woman is evaluated during a follow-up visit. She has a lifelong history of intermittent asthma previously provoked by exertion and exposure to cold air. During the past 2 years her symptoms have progressed, and she now has dyspnea after walking one block or going up any incline. COPD was diagnosed 4 days ago after spirometry revealed an FEV_1 of 65% of predicted that was only partially reversible with bronchodilator therapy. She has no history of acute exacerbations. She has recently discontinued cigarette smoking. She currently takes albuterol as needed.

On physical examination, vital signs are normal; oxygen saturation is 95% breathing ambient air. Lungs are clear to auscultation.

Laboratory studies reveal normal hemoglobin concentration and leukocyte count with 8% eosinophils.

Chest radiograph shows clear lungs.

Which of the following is the most appropriate initial treatment?

(A) Chronic macrolide therapy

(B) Inhaled glucocorticoid and long-acting β_2-agonist

(C) Long-acting β_2-agonists

(D) Long-acting muscarinic agent and long-acting β_2-agonists

Item 27

A 68-year-old man develops abrupt, pleuritic, right-sided chest pain, and dyspnea 90 minutes into a flight from Nashville to Phoenix. He is on the second week of a prednisone taper for a recent COPD exacerbation in the setting of bullous emphysema. He is on supplemental oxygen at home at 2 L/min, which was augmented to 4 L/min for the flight. Current medications are a long-acting β_2-agonist, a long-acting muscarinic agent, and prednisone.

On physical examination, blood pressure is 138/78 mm Hg, pulse rate is 114/min, and respiration rate is 24/min. He appears moderately distressed. Lung examination reveals diminished breath sounds bilaterally, tympany to percussion bilaterally, and end-expiratory wheezing. He has

strong symmetric peripheral pulses but no neck vein distention. Cardiac examination is unremarkable.

Which of the following is the most likely diagnosis?

(A) Descending aortic dissection
(B) *Pneumocystis jirovecii* pneumonia
(C) Pneumothorax
(D) Pulmonary embolism

Item 28

A 58-year-old man with a history of severe COPD is evaluated for his chronic exertional dyspnea. He is taking his inhalers and medications as prescribed with excellent technique and has completed a pulmonary rehabilitation program within the last 6 months and is continuing his exercise program. He is using supplemental oxygen but despite adequate oxygenation still has significant exertional dyspnea. Current medications are umeclidinium/vilanterol, mometasone, and albuterol. He feels that his current quality of life is poor and would like other treatment options.

On physical examination, vital signs are normal. Oxygen saturation is 90% on 2 L/min of oxygen. BMI is normal. Pulmonary examination reveals decreased breath sounds throughout with a prolonged expiratory phase but no wheezing.

Spirometry demonstrates severe airflow obstruction. A recent chest CT shows heterogeneous emphysema without any nodules. A recent echocardiogram shows diastolic dysfunction but no evidence of pulmonary hypertension.

Which of the following is the most appropriate management?

(A) Add daily roflumilast
(B) Evaluation for lung volume reduction surgery
(C) Obtain a right heart catheterization
(D) Repeat pulmonary rehabilitation program

Item 29

A 58-year-old man is evaluated for a 2-year history of slowly progressive exertional dyspnea with intermittent wheezing and a cough that is occasionally productive of clear sputum. He has no chest pain, palpitations, or lower extremity edema. He has a 40-pack-year history of smoking but quit 3 years ago. He has a history of coronary artery disease. He currently takes aspirin, metoprolol, rosuvastatin, and lisinopril.

On physical examination, vital signs are normal; oxygen saturation is 94% on ambient air. Pulmonary examination reveals a prolonged expiratory phase. The remainder of the physical examination is normal.

Chest radiograph shows the lungs to be clear. Electrocardiogram is normal.

Which of the following is the most appropriate test to perform next?

(A) Echocardiogram
(B) Exercise stress test
(C) High-resolution chest CT
(D) Spirometry

Item 30

H

A 78-year-old woman is evaluated in the hospital for progressive dyspnea requiring increased oxygen. She was diagnosed with idiopathic pulmonary fibrosis 5 years ago. She was evaluated in the clinic 2 months ago; at that time she required 5 L/min of supplemental oxygen at rest and daily activities were limited to dressing and eating, both of which caused severe dyspnea. Currently, despite broad spectrum antibiotics and intravenous methylprednisolone, 1 g daily for 5 days, she is in severe respiratory distress requiring high-flow oxygen at 80%. She is alert and breathless, and understands her condition and treatment options.

On physical examination, blood pressure is 150/85 mm Hg, pulse rate is 110/min, and respiration rate is 36/min. Oxygen saturation is 88% on 80% high-flow oxygen. BMI is 24. Pulmonary examination reveals diffuse inspiratory crackles. She has clinical findings of pulmonary hypertension on cardiac examination, unchanged from 2 months ago. She has no edema or jugular venous distention.

Chest radiograph is unchanged.

Which of the following is the most appropriate management?

(A) Increase methylprednisolone
(B) Initiate albuterol
(C) Mechanical ventilation
(D) Palliative care

Item 31

A 41-year-old woman is evaluated for nonproductive cough with dyspnea on exertion for the past 6 months. Her medical history is significant for diffuse cutaneous systemic sclerosis, gastroesophageal reflux disease, and Raynaud phenomenon. Her medications are omeprazole, nifedipine, and lisinopril.

On physical examination, vital signs are normal. Oxygen saturation is 98% breathing ambient air at rest but drops to 93% with exertion. She has sclerodactyly. The lung examination is normal.

Pulmonary function tests demonstrate restriction with a total lung capacity of 70% of predicted and D_{LCO} of 65% of predicted.

Chest radiograph is normal.

Which of the following is the most appropriate diagnostic test to perform next?

(A) 6-Minute walk test
(B) Cardiopulmonary exercise testing
(C) High-resolution chest CT scan
(D) PET/CT scan

Item 32

A 62-year-old woman is evaluated for a 1-year history of cough. She works in an office and has no environmental exposures, and cannot recall any specific initiating event. Her cough seems to be triggered by temperature changes, exercise, laughter, and strong scents and perfumes. She has no sputum production, rhinitis, postnasal drip, wheezing,

or gastroesophageal reflux disease. She has recently been treated with intranasal fluticasone and oral antihistamines without significant improvement. She is not taking any medications currently.

On physical examination, oxygen saturation is 97% on ambient air. All vital signs and pulmonary and cardiac examinations are normal.

Laboratory studies, including complete blood count, are normal.

Chest radiograph is normal. Pulmonary function testing shows a normal FEV_1 and FEV_1/FVC ratio.

Which of the following is the most appropriate management?

(A) Begin daily inhaled budesonide and albuterol
(B) Obtain esophageal manometry and 24-hour pH monitoring study
(C) Obtain high-resolution CT scan of the chest
(D) Obtain methacholine challenge testing

H Item 33

A 45-year-old woman with hypovolemic shock is evaluated for rapid resuscitation in the ICU. She has sickle cell disease with recurrent pain and hemolytic crises, and osteoporosis.

On physical examination, temperature is 39 °C (102.3 °F), blood pressure is 70/40 mm Hg, pulse rate is 142/min and weak, and respiration rate is 22/min. Oxygen saturation is 99% breathing ambient air. There is a subcutaneous port in the right anterior chest wall.

Which of the following is the most appropriate type of venous access for this patient?

(A) Intraosseous port
(B) Peripheral wide-bore catheter
(C) Subcutaneous intravenous port
(D) Triple-lumen central catheter

H Item 34

A 66-year-old man is hospitalized in December for a 1-week history of increasing dyspnea on exertion, wheezing, and a nonproductive cough despite outpatient treatment with antibiotics and steroids. He now has awakenings with nocturnal dyspnea, which are only partially relieved by the use of his albuterol inhaler. He has started using his albuterol nebulizer four times a day, which provides only temporary relief. He does not have fever, headache, myalgia, runny nose, sputum production, chest pain, lower extremity edema, or palpitations. He has a history of COPD with an FEV_1 of 42% of predicted on spirometry obtained 3 months ago. In addition to albuterol, he takes umeclidinium and vilanterol and was started on azithromycin and prednisone 3 days ago.

On physical examination, temperature is 37.1 °C (98.8 °F), blood pressure is 135/80 mm Hg, pulse rate is 110/min, and respiration rate is 22/min. Oxygen saturation is 90% on ambient air. The patient is not using his accessory muscles. He has decreased breath sounds throughout, with diffuse end-expiratory wheezes. Other than tachycardia, the cardiovascular examination is normal without jugular venous distention or edema.

Laboratory studies, including complete blood count with differential, basic metabolic panel, B-type natriuretic peptide, and arterial blood gases, are unremarkable.

Electrocardiogram demonstrates sinus tachycardia, and a chest radiograph shows hyperinflation but no infiltrates.

Which of the following is the most appropriate diagnostic test to perform next?

(A) Bedside spirometry
(B) CT pulmonary angiography
(C) Polymerase chain reaction testing for influenza A and B
(D) Sputum culture

Item 35

A 72-year-old woman is evaluated during a routine visit. She has a 30-pack-year smoking history and quit 5 years ago. She has a history of mild COPD and breast cancer diagnosed 15 years ago, currently in remission. A chest radiograph from 5 years ago showed no signs of disease recurrence. Medications are albuterol and tiotropium inhalers.

On physical examination, vital signs are normal. Lung examination reveals prolonged expiration and diminished breath sounds throughout. The breast examination is unremarkable.

A screening low-dose chest CT scan shows a peripheral 9-mm solid pulmonary nodule in the left upper lobe and emphysema but no mediastinal or hilar lymphadenopathy and no pleural effusion. A PET/CT scan using fluorodeoxyglucose (FDG) is performed and the nodule is intensely hypermetabolic. There is no evidence of distant uptake.

Which of the following is the most appropriate management?

(A) Bronchoscopy with biopsy
(B) Serial chest CT scans
(C) Surgical wedge resection
(D) Transthoracic needle aspiration

Item 36

A 75-year-old man is evaluated for a 6-month history of dyspnea on exertion. He was a construction worker between 1972 and 1986. He notes that he was often in buildings with high levels of dust without respiratory protection. He finished his working career providing janitorial services for the public school system. He is an avid wood worker and has a shop in his garage. He has never smoked. He has no other medical problems and takes no medications.

On physical examination, vital signs are normal. Lung examination reveals inspiratory crackles at the lung bases bilaterally.

Spirometry shows an FVC of 80% of predicted, an FEV_1 of 85% of predicted, and a D_{LCO} of 75% of predicted. CT scan shows pleural plaques, peripheral and basal predominant septal line thickening without ground-glass opacities, micronodules, or honeycombing.

Which of the following is the most likely diagnosis?

(A) Asbestosis
(B) Chronic hypersensitivity pneumonitis
(C) Idiopathic pulmonary fibrosis
(D) Respiratory bronchiolitis-associated interstitial lung disease

H

Item 37

A 24-year-old woman is treated in the emergency department for an acute asthma exacerbation. She has received continuous albuterol and ipratropium nebulization and intravenous methylprednisolone. She has persistent wheezing and dyspnea. Her outpatient medications are inhaled albuterol and fluticasone/salmeterol.

On physical examination, blood pressure is 164/84 mm Hg, pulse rate is 121/min, and respiration rate is 28/min. Oxygen saturation is 95% on 4 L/min of oxygen through nasal cannula. Peak flow is less than 40% of her baseline. She is sitting upright and is using accessory muscles of respiration and can speak four words of a sentence. Lung examination demonstrates diffuse wheezing throughout both lungs.

Which of the following is the most appropriate treatment?

(A) Ketamine infusion
(B) Magnesium sulfate, intravenously
(C) Montelukast sodium
(D) Theophylline

H

Item 38

A 65-year-old woman is admitted to the ICU with sepsis. She has become increasingly hypotensive despite intravenous fluid resuscitation of 30 mL/kg and the administration of increasing doses of norepinephrine and a standard dose of vasopressin. She has an arterial catheter in place. Appropriate antibiotics have been administered.

On physical examination, temperature is 37.7 °C (100 °F), blood pressure is 88/45 mm Hg, pulse rate is 116/min. Oxygen saturation is 98% on 2 L/min of oxygen through nasal cannula. She is alert and oriented. Her skin is cool. The remainder of the examination is normal.

Telemetry shows premature ventricular complexes.

Which of the following is the most appropriate treatment?

(A) Change norepinephrine to dopamine
(B) Hydrocortisone
(C) Increase the vasopressin infusion rate
(D) Intravenous immune globulin

Item 39

A 73-year-old man is evaluated for a 6-month history of right-sided chest discomfort, fatigue, nonproductive cough, and progressive dyspnea. He has lost 9 kg (20 lb) during the last 6 months. His history is significant for COPD. He was a brake mechanic for 30 years. Medications are an albuterol inhaler as needed and tiotropium inhaler.

On physical examination, vital signs are normal. Lung examination reveals dullness to percussion and diminished breath sounds above the lower half of the right hemithorax. The physical examination is otherwise normal.

Laboratory studies, including complete blood count, are normal.

Chest radiograph shows a moderate right-sided loculated pleural effusion with pleural thickening.

A thoracentesis is performed that removes 600 mL of serosanguineous fluid.

Pleural fluid analysis:

Cytology	Atypical mesothelial cells, negative for malignancy
Gram stain	Negative
Lactate dehydrogenase	425 U/L
pH	7.35
Total protein	4.6 g/dL (46 g/L)

Which of the following is the most likely diagnosis?

(A) Empyema
(B) Heart failure
(C) Malignant pleural mesothelioma
(D) Rheumatoid pleuritis

Item 40

A 60-year-old woman is evaluated for a 2-year history of dyspnea on exertion. She has dyspnea and wheezing when walking up an incline, especially if she is carrying something, but no other symptoms. She quit smoking 5 years ago and has a history of hypertension. Current medications are hydrochlorothiazide and ramipril.

On physical examination, vital signs are normal; oxygen saturation is 95% on ambient air. Lungs are clear on auscultation. Cardiovascular examination is unremarkable.

Laboratory studies reveal normal hemoglobin.

Spirometry shows a postbronchodilator FEV_1 of 75% of predicted and an FEV_1/FVC ratio of 0.65. Electrocardiogram and chest radiograph are normal.

Which of the following is the most appropriate initial treatment?

(A) Roflumilast
(B) Short-acting and long-acting bronchodilator
(C) Short-acting bronchodilator
(D) Short-acting bronchodilator and inhaled glucocorticoid
(E) Short course of prednisone

Item 41

A 54-year-old man is evaluated during a follow-up visit 1 month after an emergency appendectomy. He was diagnosed with amyotrophic lateral sclerosis 9 months ago. He was placed on supplemental oxygen for 2 nights after surgery because of nocturnal oxyhemoglobin desaturations.

Arterial blood gas studies revealed a pH of 7.42, P_{CO_2} of 53 mm Hg (7.0 kPa), P_{O_2} of 53 mm Hg (7.0 kPa), and bicarbonate of 33 mEq/L (33 mmol/L).

On physical examination, vital signs are normal. Oxygen saturation is 92% breathing ambient air. He has no difficulty managing his secretions. Examination reveals upper limb weakness, muscle fasciculations, hyperactive deep tendon reflexes, and dysarthria. Lung examination is unremarkable.

In-office measurement of FVC is 49% of predicted.

Which of the following is the most appropriate management?

(A) Bilevel positive airway pressure
(B) Continuous positive airway pressure
(C) Hypoglossal nerve stimulation
(D) Supplemental oxygen
(E) Tracheostomy

H

Item 42

A 21-year-old man is hospitalized for sudden onset of dyspnea with chest pain that worsens with inspiration. He has a 3-pack-year history of smoking, but his medical history is otherwise unremarkable.

On physical examination, vital signs are normal. Oxygen saturation is 95% breathing ambient air. BMI is 18. Lung examination reveals reduced lung expansion, hyperresonance to percussion, and diminished breath sounds on the left side.

Chest radiograph demonstrates a large left-sided pneumothorax.

A thoracostomy tube is inserted that provides good lung reexpansion. Repeat chest radiograph is normal.

Avoidance of which of the following is the most appropriate measure to prevent long-term recurrence of pneumothorax?

(A) Air travel
(B) Mountain climbing
(C) Smoking
(D) Strenuous exercise

Item 43

A 32-year-old woman is evaluated for a 10-day history of severe cough with increased sputum production, fever, wheezing, and dyspnea. She has a 12-year history of recurrent abdominal pain with watery stools and poor weight gain, recurrent sinusitis, and chronic cough that is productive of foul sputum. She takes no medications chronically.

On physical examination, temperature is 38.2 °C (100.8 °F), blood pressure is 92/64 mm Hg, pulse rate is 101/min, and respiration rate is 24/min. Oxygen saturation is 91% on ambient air. BMI is 18.2. Pulmonary examination reveals wheezes. Additional findings include a scaphoid abdomen and clubbing.

Laboratory studies reveal a leukocyte count of 16,000/µL (16×10^9/L), hemoglobin of 10 g/dL (100 g/L), and serum creatinine of 0.7 mg/dL (61.9 µmol/L). Serum immunoglobulin levels are normal.

Pulmonary function testing reveals an FVC of 80% of predicted, an FEV_1 of 50% of predicted, and an FEV_1/FVC ratio of 0.55.

Chest radiograph is shown.

Which of the following is the most likely underlying diagnosis?

(A) Common variable immunodeficiency
(B) Complement component deficiency
(C) COPD
(D) Cystic fibrosis

Item 44

H

A 62-year-old woman with a history of moderate COPD is evaluated in the emergency department for increasing dyspnea, cough, and sputum production. She had been doing well until 4 days ago when she developed rhinorrhea and a cough productive of purulent sputum. During the past two days she has noted increasing dyspnea on exertion that responds transiently to her albuterol inhaler. This is the patient's first episode of this nature. She stopped smoking 18 months ago. Current medications are albuterol and tiotropium inhalers.

On physical examination, temperature is 38.1 °C (100.6 °F), blood pressure is 130/80 mm Hg, pulse rate is 102/min, and respiration rate is 22/min. Oxygen saturation is 90% on ambient air. The patient is tachypneic and catches her breath between sentences but improves after a treatment of albuterol. She has diffuse end-expiratory wheezing.

A chest radiograph shows the lungs to be clear but hyperinflated.

Arterial blood gases on 2L/min of oxygen through nasal cannula show a pH 7.38, a P_{CO_2} of 42 mm Hg (5.58 kPa), and a P_{O_2} of 70 mm Hg (9.31 kPa).

Which of the following is the most appropriate treatment?

(A) Azithromycin and prednisone
(B) Mometasone inhaler
(C) Noninvasive positive pressure ventilation
(D) Roflumilast

Item 45

A 62-year-old woman is evaluated for increasing exertional dyspnea during the past 6 months. She is a former smoker who was diagnosed with severe COPD 3 years ago (FEV_1 is 35% of predicted). For the past 18 months, she has used tiotropium and salmeterol; inhaled fluticasone was added 4 months ago, but without any perceived benefit. She takes no other medications.

On physical examination, blood pressure is 130/79 mm Hg, pulse rate is 88/min, and respiration rate is 18/min. Oxygen saturation is 89% breathing ambient air. Lung examination demonstrates diminished breath sounds. A prominent pulmonic sound is heard on cardiac examination.

Arterial blood gas studies breathing ambient air show a pH of 7.41, a PCO_2 of 43 mm Hg (5.7 kPa), and a PO_2 of 55 mm Hg (7.3 kPa).

Chest radiograph reveals hyperinflation. Echocardiography shows an estimated right ventricular systolic pressure of 58 mm Hg. Polysomnography showed an apnea-hypopnea index of 2 and a mean oxygen saturation of 87%.

Which of the following is the most appropriate treatment?

(A) Bilevel positive airway pressure
(B) Prednisone
(C) Sildenafil
(D) Supplemental oxygen

Item 46

A 46-year-old man is evaluated for 6 months of exertional dyspnea, fatigue, and ankle edema. Recently he experienced near-syncope walking up two flights of stairs. He has no other medical problems and takes no medications.

On physical examination, blood pressure is 106/70 mm Hg, pulse rate is 94/min, and respiration rate is 18/min. Oxygen saturation is 90% breathing ambient air. On cardiac examination, a prominent jugular venous *a* wave is present along with widened splitting of S_2. Lung examination is unremarkable.

A transthoracic echocardiogram demonstrates a normal size left ventricle with ejection fraction of 65% and right ventricular enlargement. The estimated pulmonary artery systolic pressure is 58 mm Hg. Spirometry, lung volumes, and ventilation-perfusion scan are unremarkable; DLCO is 42% of predicted. CT angiogram of the chest is negative for pulmonary embolism and interstitial lung disease. Right heart catheterization demonstrates a mean pulmonary arterial pressure of 36 mm Hg, with no change with inhaled nitric oxide. Pulmonary capillary wedge pressure is normal.

Which of the following is the most appropriate treatment?

(A) Bosentan
(B) Diltiazem
(C) Metoprolol
(D) Pirfenidone

Item 47

A 27-year-old woman is evaluated for concern about a 3-week history of a new chemical odor in her workplace. She has a history of mild asthma since childhood that is well-controlled with infrequent use of an albuterol inhaler. The plant safety manager at her job said there is no need for protective equipment, but she is experiencing increased cough and now uses her albuterol inhaler once daily.

On physical examination, vital signs are normal. Lungs are clear on auscultation with no wheeze.

Office spirometry shows an FVC of 98% of predicted, an FEV_1 of 93% of predicted, and an FEV_1/FVC ratio of 0.78 of predicted.

Which of the following is the most appropriate management?

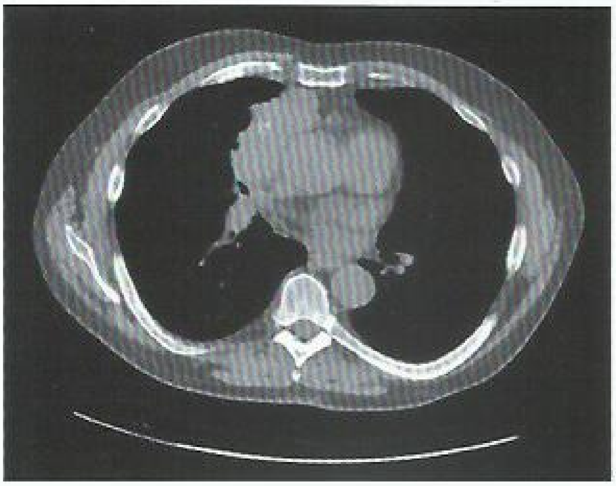
(A) Chest CT scan
(B) Obtain hair sample for toxic analysis
(C) Review employer Material Safety Data Sheet
(D) Transfer patient to other area of plant

Item 48

A 49-year-old man is evaluated for a 4-month history of cough, chest pressure, and double vision. He has no fever, night sweats, or weight loss. He has never smoked.

On physical examination, vital signs are normal. There is ptosis bilaterally. The remainder of the physical examination is normal.

A CT scan of the chest is shown.



Which of the following is the most appropriate test to perform next?

(A) Acetylcholine receptor antibody
(B) α-Fetoprotein
(C) β-Human chorionic gonadotropin
(D) Lactate dehydrogenase

Item 49

H

A 60-year-old woman is evaluated in the hospital for respiratory failure. She was hospitalized 3 weeks ago after a house fire. She suffered significant third-degree burns covering 40% of her body and mucosal burns to her nose. She was intubated, but was successfully liberated from the ventilator

H CONT.

last week. A surveillance bronchoscopy performed before extubation was unremarkable. Last night she became progressively dyspneic and hypoxic, eventually requiring reintubation. Current medications are topical antibiotics and subcutaneous heparin.

On physical examination, temperature is 37.9 °C (100.2 °F), blood pressure is 104/60 mm Hg, pulse rate is 95/min, and respiration rate is 26/min. Oxygen saturation is 91% breathing from a ventilator (FIO_2 of 0.6). Copious yellow sputum is present in the endotracheal tube when suctioned.

Laboratory studies reveal a leukocyte count of 16,000/µL (16×10^9/L), increased from 12,000/µL (12×10^9/L) yesterday.

A chest radiograph shows a focal consolidation in the lower left lobe.

Which of the following is the most appropriate treatment?

(A) Administer hydroxocobalamin
(B) Administer intravenous antibiotics
(C) Bronchoscopic airway stenting
(D) Insert a thoracostomy tube

H

Item 50

A 30-year-old man with a history of alcohol and drug abuse is brought to the emergency department. He was found unresponsive and on arrival he was intubated and placed on mechanical ventilation for poor respiratory effort. Witnesses confirmed that he had been drinking alcohol and had also taken drugs at a party.

On physical examination, vital signs are normal. Respiration rate is 14/min on mechanical ventilation. He is not triggering the ventilator. Oxygen saturation is 100% on 35% oxygen. He responds to pain only. His pupils are dilated and reactive to light. He shows no signs of trauma.

Blood toxicology screening is positive for alcohol; urine toxicology screening is positive for benzodiazepines. Arterial pH and electrolyte anion gap are normal.

Which of the following is the most appropriate management?

(A) Administer flumazenil
(B) Administer fomepizole
(C) Administer hemodialysis
(D) Monitor for signs of agitation

Item 51

A 22-year-old man is evaluated for acute onset of fever, chills, dyspnea, and nonproductive cough. He is a college student and spends summers using a combine to harvest wheat. He does not wear respiratory protective equipment. His symptoms start at the beginning of a work week, progress to the point that he must miss several days of work, and then the cycle begins again.

On physical examination, temperature is 37.8 °C (100.1 °F), blood pressure is 120/80 mm Hg, pulse rate is 98/min, and respiration rate is 22/min. Oxygen saturation is 94% breathing ambient air. Lung examination reveals diffuse crackles.

Chest radiograph demonstrates diffuse upper-lobe micronodular opacities.

Which of the following is the most appropriate treatment?

(A) Counsel the patient not to return to work
(B) Inhaled glucocorticoids
(C) Pirfenidone
(D) Sirolimus

Item 52

A 64-year-old woman is evaluated during a posthospital visit for severe COPD with an FEV_1 of 30% of predicted. She has been admitted three times during the last year with acute exacerbations characterized by cough, increased purulent sputum production, and dyspnea. She is now at baseline of her exertional dyspnea and has no cough. She has already participated in a pulmonary rehabilitation program. She currently takes tiotropium, budesonide/formoterol, and albuterol.

On physical examination, vital signs are normal. Oxygen saturation is 90% on 3 L/min of supplemental oxygen at rest and with exertion. Pulmonary examination reveals decreased breath sounds throughout. The remainder of the examination is noncontributory.

Which of the following is the most appropriate treatment to reduce this patient's COPD exacerbations?

(A) Chronic low-dose oral glucocorticoid
(B) Chronic macrolide therapy
(C) Increase supplemental oxygen
(D) Nebulized hypertonic saline

Item 53

H

A 52-year-old man is evaluated in the ICU for dyspnea that developed after aspiration of gastric contents during an upper endoscopy. The endoscopy was performed for evaluation of upper gastric bleeding due to peptic ulcer disease. His only medication is pantoprazole.

On physical examination, temperature is 37.3 °C (99.1 °F), blood pressure is 150/99 mm Hg, pulse rate is 110/min, and respiration rate is 28/min. Oxygen saturation is 90% on a 100% oxygen nonrebreather mask. He is awake, diaphoretic, and anxious. Lung examination reveals scant bilateral crackles and rhonchi as well as use of accessory muscles. The remainder of the physical examination is normal.

Arterial blood gas studies on a 100% oxygen nonrebreather mask show a pH of 7.35, a PCO_2 of 46 mm Hg (6.1 kPa), and a PO_2 of 55 mm Hg (7.3 kPa).

Chest radiograph reveals new bilateral opacities.

Which of the following is the most appropriate treatment?

(A) Continue current therapy
(B) High-flow humidified nasal cannula
(C) Intubation and mechanical ventilation
(D) Noninvasive mechanical ventilation

Item 54

A 38-year-old man is evaluated for a 6-month history of dyspnea on exertion. He has gastroesophageal reflux disease

and Raynaud phenomenon. He does not smoke and has no cough or wheezing. Current medications are lansoprazole and amlodipine.

On physical examination, vital signs are normal. Oxygen saturation is 91% breathing ambient air. He has scattered telangiectasias on the face and trunk and sclerodactyly. Lung fields are clear on auscultation.

The only abnormality on pulmonary function testing is a D_{LCO} of 43% of predicted.

High-resolution CT of the chest shows no evidence of parenchymal lung disease.

Which of the following is the most likely diagnosis?

(A) Cryptogenic organizing pneumonia
(B) Lymphangioleiomyomatosis
(C) Lymphoid interstitial pneumonia
(D) Pulmonary arterial hypertension

H

Item 55

A 58-year-old man is evaluated in the hospital for fever, hypotension, and altered mental status. He was hospitalized 2 days ago for an infected arm wound and was treated with intravenous piperacillin/tazobactam and vancomycin. This morning he developed new pain in the middle of his back and difficulty urinating. His medical history is significant for type 2 diabetes mellitus treated with metformin.

On physical examination, temperature is 39.1 °C (102.4 °F), blood pressure is 83/48 mm Hg, pulse rate is 109/min, and respiration rate is 21/min. Oxygen saturation is 98% breathing 2 L/min of oxygen through nasal cannula. He is somnolent but arousable and oriented when awake. There is erythema surrounding the wound on his right upper arm with no drainage or tenderness. There is tenderness to percussion in the middle of his back and a palpable bladder.

Laboratory studies reveal a blood serum leukocyte count of 22,000/µL (22×10^9/L), and plasma glucose of 160 mg/dL (8.88 mmol/L).

Chest radiograph is unremarkable.

Which of the following is the most appropriate next step in management?

(A) Intravenous fluid bolus
(B) Intravenous insulin
(C) MRI of the spine
(D) Surgical exploration of the arm wound

H

Item 56

A 72-year-old woman is evaluated in the hospital for a pneumothorax. The patient has severe, oxygen-dependent COPD complicated by several exacerbations. She was hospitalized 72 hours ago with abrupt onset of chest pain and dyspnea. Chest radiography confirmed the presence of a large left-sided pneumothorax and a thoracotomy tube was placed. She had 90% expansion of the lung following thoracostomy.

On physical examination, the patient is frail appearing but comfortable. Vital signs are normal. Oxygen saturation is 96% breathing 3 L/min of oxygen through nasal cannula. Pulmonary examination reveals diminished but present breath sounds bilaterally. A left thoracostomy tube is in place.

Chest radiograph demonstrates resolution of pneumothorax with a thoracostomy tube in place.

Which of the following is the most appropriate management?

(A) Clamp thoracostomy tube
(B) Place thoracostomy tube to high suction
(C) Pleurodesis
(D) Remove thoracostomy tube

Item 57

A 66-year-old man with a history of COPD is evaluated during a routine visit. He is able to walk one flight of stairs and one block before he develops dyspnea. He was last treated for two acute exacerbations of COPD within the last year, one of which required hospitalization. He recently completed a pulmonary rehabilitation program. His medical history is significant for hypertension and a 60-pack-year smoking history. He quit smoking 5 years ago. Current medications are hydrochlorothiazide, glycopyrrolate/formoterol, and albuterol.

On physical examination, vital signs are normal; oxygen saturation is 94% on ambient air. Pulmonary examination reveals a prolonged expiratory phase. The cardiac and remainder of the physical examination are unremarkable.

Spirometry today shows a postbronchodilator FEV_1 of 35% of predicted. Chest radiograph at the time of his last exacerbation shows hyperinflation and no other findings. An electrocardiogram is normal.

Which of the following patient characteristics places him at highest risk for a recurrent acute exacerbation?

(A) Enrollment in a pulmonary rehabilitation program
(B) Hypertension
(C) Previous COPD exacerbations and FEV_1 level
(D) Smoking history and use of COPD medications

Item 58

H

A 70-year-old man is hospitalized for a 4-week history of dyspnea, orthopnea, and daytime sleepiness. He was diagnosed with amyotrophic lateral sclerosis 6 months ago. His only medication is riluzole.

On physical examination, blood pressure is 128/73 mm Hg, pulse rate is 90/min, and respiration rate is 28/min. Oxygen saturation is 87% breathing ambient air. He has right hand atrophy, decreased mobility, and fasciculations. Lung examination reveals abdominal paradox with breathing, use of accessory breathing muscles, and shallow tachypnea. He is awake, alert, and interactive, but dozes off easily. His speech is clear with no secretions. He is able to move all extremities and shows no cranial nerve abnormality.

On arterial blood gas testing, pH is 7.30, P_{CO_2} is 76 mm Hg (10.1 kPa), P_{O_2} is 50 mm Hg (6.65 kPa), and bicarbonate is 36 mEq/L (36 mmol/L) on room air. The calculated alveolar-arterial oxygen gradient is normal.

Chest radiograph reveals bilateral basal opacities consistent with atelectasis and shallow inspiration.

H CONT.

Which of the following is the most appropriate treatment?

(A) Invasive mechanical ventilation
(B) Noninvasive ventilation with bilevel positive airway pressure
(C) Noninvasive ventilation with continuous positive airway pressure
(D) Oxygen administration through nasal cannula

H

Item 59

A 60-year-old man is evaluated in the emergency department for headache, nausea, vomiting, and confusion lasting 4 hours. He ran out of his hypertensive medications a few days ago. Current medications are lisinopril, metoprolol succinate, hydrochlorothiazide, and aspirin.

On physical examination, blood pressure is 230/140 mm Hg and pulse rate is 100/min. All other vital signs are normal. He is too uncooperative to perform a mental status examination or funduscopic examination. The cardiovascular examination is positive for an S_4 but otherwise normal.

Laboratory studies reveal normal electrolytes; serum creatinine is 1.6 mg/dL (141.4 µmol/L). It was 1.2 mg/dL (106 µmol/L) at his last outpatient appointment.

Electrocardiogram shows left ventricular hypertrophy and sinus tachycardia. Chest radiograph is normal. CT scan of the brain shows no acute findings.

Which of the following is the most appropriate treatment?

(A) Intravenous hypertensive therapy to lower systolic blood pressure (SBP) to 160 mm Hg within the first 6 hours
(B) Intravenous hypertensive therapy to lower SBP to 120 mm Hg within the first hour
(C) Intravenous hypertensive therapy to lower SBP to 160 mm Hg within the first 48 hours
(D) Resume usual oral antihypertensive regimen and observe

H

Item 60

A 30-year-old woman is evaluated in the emergency department after she was rescued from her home where her vinyl sofa caught fire. She is intubated and unconscious.

On physical examination, blood pressure is 108/78 mm Hg, pulse rate is 100/min, and respiration rate is 24/min. Oxygen saturation by pulse oximetry is 100% on mechanical ventilation using 50% oxygen. She is unresponsive. She has no visible burns on her skin, and her airway secretions are clear. Brainstem reflexes are all intact.

Laboratory studies:

Serum electrolytes:	
Sodium	140 mEq/L (140 mmol/L)
Potassium	4.4 mEq/L (4.4 mmol/L)
Chloride	99 mEq/L (99 mmol/L)
Bicarbonate	13.1 mEq/L (13.1 mmol/L)
Arterial blood gas studies:	
pH	7.29
Pco_2	28 mm Hg (3.7 kPa)
Po_2	233 mm Hg (31 kPa)
Carboxyhemoglobin	5%
Methemoglobin	2%
Lactate	11 mEq/L (1.2 mmol/L)

The oxygen is increased to 100%.

Which of the following is the most appropriate treatment?

(A) Hydroxocobalamin
(B) Hyperbaric oxygen therapy
(C) Methylene blue
(D) Sodium nitrite

Item 61

A 35-year-old man is evaluated for chronic cough productive of foul-smelling sputum. He has been treated with four courses of antibiotics in the last 12 months; several infections have been associated with *Pseudomonas* species. His symptoms have been present for many years and are also associated with chronic sinusitis. He was recently diagnosed with infertility.

On physical examination, all vital signs are normal. Oxygen saturation is 98% on ambient air. Clubbing is present. Pulmonary examination reveals rhonchi and wheezes in the upper lobes bilaterally.

Chest radiograph reveals bilateral upper-lobe bronchiectasis.

Laboratory studies reveal a negative sweat chloride test of 39 mEq/L (39 mmol/L).

Which of the following is the most appropriate management?

(A) Begin chronic ciprofloxacin therapy
(B) Begin tiotropium
(C) Repeat sweat chloride testing
(D) Test for α_1 antitrypsin deficiency

Item 62

A 62-year-old man undergoes routine follow-up evaluation. His medical history is significant for tobacco use (35 pack-year) and hypertension controlled with lisinopril. He quit smoking 3 months ago and does not have any cough, wheezing, or shortness of breath.

On physical examination, vital signs are normal. BMI is 31. Cardiopulmonary examination is normal.

Which of the following is the most appropriate test?

(A) 6-Minute walk test
(B) Chest radiograph
(C) Low-dose CT scan of the chest
(D) Office spirometry
(E) Urinary cotinine test

Item 63

H

A 22-year-old man is evaluated in the hospital for decreased responsiveness. He was hospitalized 4 days ago after a motor vehicle accident. He has multiple fractures and a chest contusion. He was intubated for respiratory distress in the emergency department and given morphine, propofol, and heparin. He is on volume-controlled continuous mandatory ventilation mode with an Fio_2 of 0.7.

On physical examination, temperature is 37.7 °C (99.9 °F), blood pressure is 124/65 mm Hg, pulse rate is 89/min, and

H CONT

respiration rate is 27/min. Oxygen saturation is 93% on mechanical ventilation. He is unresponsive to voice or pain, and his pupils are 3 mm and reactive; the neurological examination is otherwise nonfocal. He has external fixators in both lower extremities. There are bruises on the anterior chest wall. The remainder of the physical examination is noncontributory.

Which of the following is the most appropriate management?

(A) Change propofol to dexmedetomidine
(B) CT of the head
(C) Continuous electroencephalography
(D) Stop sedation and analgesia

H

Item 64

A 61-year-old man is evaluated in the emergency department after he collapsed on a hot and humid day. He was playing in a marching band and had to stand in the sun for 2 hours while wearing a heavy uniform. No other medical information is available.

On physical examination, temperature is 40 °C (104 °F), blood pressure is 90/45 mm Hg, pulse rate is 110/min, and respiration rate is 20/min. His face is flushed, he is somnolent, and although he is arousable, he is not coherent. There are no signs of trauma.

His clothing is removed.

Which of the following is the most appropriate treatment?

(A) Acetaminophen and a cooling blanket
(B) Continuous alcohol sponge bath with cooling fans
(C) Ice water immersion
(D) Intravenous dantrolene
(E) Sprayed water and cooling fans

H

Item 65

A 53-year-old man is evaluated in the emergency department after 4 days of cough, fever, chills, myalgia, and poor appetite. He currently has increased dyspnea and lightheadedness. His child was diagnosed with influenza 2 weeks ago.

On physical examination, temperature is 38.8 °C (101.8 °F), blood pressure is 82/40 mm Hg, pulse rate is 128/min, and respiration rate is 17/min. Oxygen saturation is 92% on ambient air. The cardiac examination reveals regular rhythm and tachycardia without an S_3 or jugular venous distention. Lungs are clear on auscultation and extremities are warm. The remainder of the examination is normal.

Laboratory studies:	
Hemoglobin	10 g/dL (100 g/L)
Lactate	4.6 mEq/L (4.6 mmol/L)
Leukocyte count	18,000/µL (18×10^9/L)
Arterial blood gases:	
pH	7.32
P_{CO_2}	32 mm Hg (4.3 kPa)
P_{O_2}	70 mm Hg (9.3 kPa)
Bicarbonate	16 mEq/L (16 mmol/L)

A chest radiograph shows basilar ground-glass opacities on the right. Electrocardiogram reveals sinus tachycardia but is otherwise normal.

Which of the following is the most appropriate initial treatment?

(A) 0.9% saline bolus
(B) Intravenous furosemide
(C) Norepinephrine
(D) Packed red blood cells

Item 66

H

A 19-year-old man is evaluated in the emergency department for cardiac arrest after he fell through the ice of a frozen lake. He was in the water for less than 10 minutes, but when he was pulled out onto the ice he was unresponsive and no pulse could be felt. Bystander cardiopulmonary resuscitation (CPR) was begun immediately and continued for 25 minutes until emergency medical services arrived. At the scene his rectal temperature was 27 °C (80.6 °F). He was intubated and bag ventilated and continued to receive CPR in the ambulance on the way to the emergency department.

On physical examination, temperature is 28 °C (82.4 °F). Oxygen saturation is 97% on mechanical ventilation with 65% oxygen. He is not responsive and shows no spontaneous movement or shivering. His heart rhythm on the monitor is ventricular fibrillation.

Which of the following is the most appropriate management?

(A) Continue CPR with active external rewarming
(B) Continue CPR with active internal (core) rewarming
(C) Continue CPR with passive external rewarming
(D) Discontinue CPR

Item 67

A 31-year-old man is evaluated near the end of a guided climb of a 3500 meter (11,482 feet) summit in the French Alps. He is confused and increasingly irritable. His only medication was prophylactic acetazolamide, which he discontinued due to bothersome nocturia.

On physical examination, pulse rate is 128/min and respiration rate is 22/min. In addition to confusion, his gait is ataxic. The neurological examination is otherwise nonfocal.

Supplemental oxygen is administered and arrangements are being made for descent.

Which of the following is the most appropriate additional treatment?

(A) Acetazolamide
(B) Dexamethasone
(C) Nifedipine
(D) Sildenafil

Item 68

H

A 42-year-old man was hospitalized 2 days ago with necrotizing fasciitis of the leg. He underwent extensive debridement and fasciotomy 2 hours earlier. He currently has severe pain in his leg wounds. He was well before this

H CONT.

illness. Current medications are imipenem, clindamycin, vancomycin, and a morphine infusion.

On physical examination, blood pressure is 150/99 mm Hg, pulse rate is 110/min, and respiration rate is 24/min. He is awake, anxious, grimacing, and wriggling in bed. The remainder of the examination is noncontributory.

Which of the following is the most appropriate treatment?

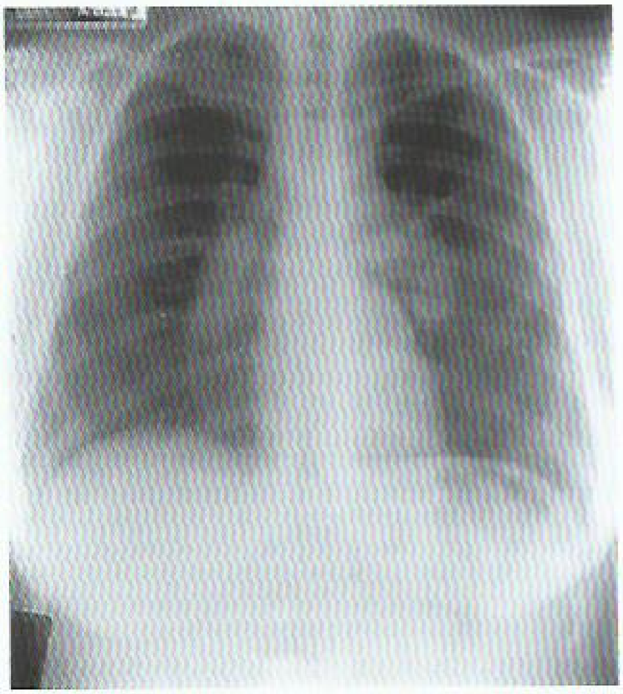
(A) Add gabapentin
(B) Epidural for regional analgesia
(C) Intravenous bolus of morphine
(D) Replace morphine with intravenous fentanyl

Item 69

A 24-year-old woman is evaluated during a follow-up visit. She was initially evaluated 6 weeks ago after a fall at work and had a chest radiograph performed for evaluation of pleuritic chest pain. This symptom has since resolved. She has no other symptoms and takes no medications.

Upon physical examination, vital signs are normal. The remainder of the physical examination is normal.

Chest radiograph is shown.



Which of the following is the most appropriate management?

(A) Endobronchial ultrasound and biopsy
(B) High-resolution CT scan of the chest
(C) Prednisone
(D) Observation

H Item 70

A 34-year-old male is hospitalized for acute respiratory failure following a heroin overdose and aspiration. Current medications are piperacillin/tazobactam, propofol, heparin, and pantoprazole.

On physical examination, temperature is 37.7 °C (99.9 °F), blood pressure is 114/77 mm Hg, pulse rate is 74/min, and respiration rate is 16/min. His ideal body weight is 63 kg (138 lb). Ventilator settings are in the volume-controlled ventilation mode with tidal volume of 630 mL, a positive end-expiratory pressure (PEEP) of 8 cm H_2O, and FIO_2 of 0.5.

Arterial blood gas studies on an FIO_2 of 0.5 show a pH of 7.33, a PCO_2 of 46 mm Hg (6.1 kPa), and a PO_2 of 76 mm Hg (10.1 kPa).

Chest radiograph shows bilateral opacities.

Which of the following is the most appropriate next step?

(A) Decrease PEEP
(B) Increase PEEP
(C) Increase respiration rate
(D) Reduce tidal volume

Item 71 H

A 51-year-old man is evaluated for fever, hypotension, and confusion. He was admitted to the ICU 8 days ago for observation after complications resulting from an outpatient surgical procedure. He had experienced unexpected bleeding in the recovery room and had a central venous catheter inserted emergently for blood transfusion. On the first postoperative day he was weaned from mechanical ventilation, vomited once but recovered, and has been receiving supplemental oxygen through nasal cannula. Today he developed a fever, hypotension, and confusion. His hemoglobin has remained stable.

On physical examination, temperature is 38.6 °C (101.5 °F), blood pressure is 89/50 mm Hg, pulse rate is 101/min, and respiration rate is 23/min. Oxygen saturation is 100% on 2L/min of oxygen through nasal cannula. Lung examination reveals clear breath sounds.

Laboratory studies reveal a leukocyte count of 15,000/µL (15×10^9/L) and a serum creatinine of 1.2 mg/dL (106.1 µmol/L).

An intravenous fluid bolus of 30 mL/kg of body weight is now infusing. Blood and respiratory cultures have been obtained and broad spectrum antibiotics are administered.

Which of the following is the most appropriate next step in management?

(A) Administer glucocorticoids
(B) Administer norepinephrine
(C) Obtain procalcitonin level
(D) Remove the central venous catheter

Item 72

A 31-year-old woman is evaluated for a 1-year history of daytime sleepiness. She falls asleep while watching TV, at the theater, and occasionally during a meal. She usually falls asleep between 10:00 PM and midnight and wakes during the workweek at 6:00 AM On weekends, she wakes at 9:00 AM. Her husband reports snoring but he hasn't observed breathing pauses. She has no

cataplexy or symptoms of restless leg syndrome. She takes no medications.

On physical examination, vital signs are normal. BMI is 24.5. The physical examination, including inspection of nasal passages and oropharynx, is normal.

Which of the following is the most appropriate management?

(A) Actigraphy
(B) Modafinil
(C) Multiple sleep latency testing
(D) Polysomnography

H

Item 73

A 43 year old man is evaluated in the emergency department for a 1 week history of cough, shortness of breath, chest pain, and night sweats. He has a 25-pack-year smoking history.

On physical examination, temperature is 38.8 °C (102 °F), blood pressure is 134/82 mm Hg, pulse rate is 142/min, and respiration rate is 30/min. Oxygen saturation is 88% breathing ambient air. There are decreased breath sounds at the right base and dullness to percussion. The remainder of the examination is noncontributory.

Laboratory studies reveal a leukocyte count of 29,000/µL (29.0×10^9/L).

Chest radiograph shows a large right pleural effusion with associated compressive atelectasis or consolidation, and consolidation in the right upper lobe.

The patient is prescribed broad-spectrum antibiotics and a diagnostic thoracentesis is performed that removes 100 mL of serous pleural fluid.

Pleural fluid studies:

pH	7.0
Lactate dehydrogenase	2310 U/L
Total protein	5.2 g/dL (52 g/L)
Glucose	42 mg/dL (2.3 mmol/L)
Gram stain	Negative

Which of the following is the most likely diagnosis?

(A) Complicated parapneumonic effusion
(B) Empyema
(C) Malignant effusion
(D) Uncomplicated parapneumonic effusion

Item 74

A 55-year-old woman is evaluated during a routine visit. She was previously diagnosed with spirometry-confirmed mild COPD for which she was prescribed a short-acting bronchodilator. She has a 20-pack-year history of cigarette smoking, but she quit 5 years ago. She is currently asymptomatic and has never received an influenza vaccination or pneumococcal vaccination. Her only medication is an albuterol inhaler.

On physical examination, vital signs are normal; oxygen saturation is 95% on ambient air. Lungs are clear to auscultation. The remainder of the physical examination is unremarkable.

Which of the following vaccinations should the patient receive at this time?

(A) High-dose influenza
(B) Pneumococcal polysaccharide (PPSV23) and standard influenza
(C) PPSV23 and pneumococcal conjugate (PCV13) and standard influenza
(D) PPSV23 and PCV13

Item 75

A 48-year-old woman is evaluated for recurrent pulmonary embolism. Her first episode was 18 months ago; she was treated with warfarin for 3 months. She was hospitalized 9 months ago for pulmonary embolism and has been treated with warfarin since then. She reports progressive exertional dyspnea. She has no chest pain, cough, hemoptysis, or wheezing. Her only medication is warfarin.

On physical examination, blood pressure is 108/68 mm Hg, pulse rate is 90/min, and respiration rate is 16/min. Oxygen saturation is 90% breathing ambient air. BMI is 36. The cardiovascular examination shows jugular venous distention, a prominent jugular venous *a* wave, and widened split S_2 with a prominent pulmonic component. Lung examination is unremarkable.

INR is 2.8.

Echocardiography reveals a normal left ventricle and dilated right ventricle with reduced function. Ventilation perfusion scan shows multiple mismatched defects. Right heart catheterization reveals a mean pulmonary arterial pressure of 58 mm Hg and a normal pulmonary capillary wedge pressure. Pulmonary angiography is remarkable for pulmonary artery webs, intimal irregularities, and abrupt narrowing of the major pulmonary arteries.

Which of the following is the definitive treatment?

(A) Apixaban
(B) Inferior vena cava filter
(C) Nifedipine
(D) Pulmonary thromboendarterectomy

Item 76

H

A 65 year old woman is evaluated for discontinuation of mechanical ventilation. She was placed on mechanical ventilation 5 days ago for respiratory failure secondary to an exacerbation of COPD. Ventilator settings are in the volume-controlled continuous mandatory ventilation mode, with a set respiration rate of 10/min, a tidal volume of 370 mL, an FIO_2 of 0.35, and a positive end-expiratory pressure of 5 cm H_2O. Current medications are albuterol/ipratropium, levofloxacin, prednisone, and fentanyl.

On physical examination, vital signs are normal. She is sleepy but arousable and can follow simple commands. Lung examination reveals distant breath sounds. The remainder of the examination is unremarkable.

Arterial blood gas studies show a pH of 7.46, PCO_2 of 47 mm Hg (6.25 kPa), and a PO_2 of 62 mm Hg (8.25 kPa). Other laboratory studies, including a leukocyte count, are normal.

Chest radiograph demonstrates hyperinflation but no infiltrates or evidence of heart failure.

H CONT.

Which of the following is the most appropriate test or evaluation to perform next?

(A) 30-Minute spontaneous breathing trial
(B) Cuff leak test
(C) Glasgow Coma Scale
(D) Measure negative inspiratory force

H

Item 77

A 48-year-old woman is hospitalized for a 2-week history of cough, sputum production, fever, and dyspnea.

On physical examination, temperature is 39.6 °C (103.3 °F), blood pressure is 110/63 mm Hg, pulse rate is 122/min, and respiration rate is 36/min. Oxygen saturation is 88% breathing ambient air. Lung examination reveals diminished breath sounds over the left base. Cardiac examination is notable only for tachycardia.

Chest radiograph reveals a small loculated effusion on the left.

A diagnostic thoracentesis is performed, which results in incomplete removal of the effusion.

Pleural fluid analysis:	
pH	6.8
Lactate dehydrogenase	3289 U/L
Total protein	3.7 g/dL (37 g/L)
Glucose	9 mg/dL (0.5 mmol/L)
Gram stain	Gram-positive cocci in chains

Appropriate intravenous antibiotics are initiated.

Which of the following is the most appropriate intrapleural treatment of the effusion?

(A) Antibiotics
(B) Streptokinase
(C) Tissue plasminogen activator-deoxyribonuclease
(D) No additional therapy required

Item 78

A 67-year-old woman is evaluated for history of rhinorrhea, pharyngitis, nonproductive cough, and associated intermittent dyspnea. Her symptoms began 12 weeks ago associated with low-grade fevers, rhinorrhea, and pharyngitis. The fever, rhinorrhea, and pharyngitis resolved but her other symptoms persist. She has no chest pain, palpitations, edema, fever, chills, or orthopnea, and she has never smoked. Her medical history is significant for hypertension treated with an angiotensin receptor blocker.

On physical examination vital signs are normal. Cardiac examination, including jugular venous pressure, is normal. Lung examination is normal.

Laboratory studies, including complete blood count, are normal.

Chest radiograph and spirometry are normal.

Which of the following is the most appropriate diagnostic test to perform next?

(A) Echocardiography
(B) Exhaled nitric oxide testing
(C) High-resolution chest CT scan
(D) Methacholine challenge testing
(E) Nasal swab for influenza polymerase chain reaction

Item 79

H

An 18-year-old woman is evaluated in the emergency department for lip swelling after eating at a neighborhood picnic. She has a history of peanut and tree nut allergies that have caused lip swelling, but she has never been hospitalized for a reaction. She currently takes no medications.

On physical examination, blood pressure is 100/64 mm Hg, pulse rate is 108/min, and respiration rate is 19/min. Oxygen saturation is 100% breathing ambient air. Bilateral lip swelling is evident that affects the upper lip more than the lower lip. She has no tongue swelling or stridor. Lungs are clear to auscultation. Urticaria is present on the hands and trunk.

Which of the following is the most appropriate immediate treatment?

(A) Diphenhydramine
(B) Epinephrine
(C) Intravenous fluid bolus
(D) Intravenous methylprednisolone

Item 80

H

A 62-year-old man was admitted 12 hours ago with severe acute respiratory distress syndrome (ARDS). Overnight, he developed fever and increasing respiratory distress, was intubated, and has had rapidly increasing ventilator requirements. Current ventilator settings are in the volume-controlled continuous mandatory ventilation mode, and he is receiving appropriate low tidal volume ventilation. Current medications are fentanyl, midazolam, heparin, piperacillin/tazobactam, and norepinephrine.

On physical examination, temperature is 38.4 °C (101.2 °F), blood pressure is 89/45 mm Hg, pulse rate is 110/min, and his spontaneous respiration rate is 35/min with a positive end-expiratory pressure of 16 cm H_2O and an F_{IO_2} of 1.0.

Arterial blood gases:	
pH	7.3
P_{CO_2}	51 mm Hg (6.8 kPa)
P_{O_2}	55 mm Hg (7.3 kPa)
Bicarbonate	24 mEq/L (24 mmol/L)

Chest radiograph shows diffuse, bilateral infiltrates throughout the lung fields.

Which of the following is the most appropriate management?

(A) Perform a recruitment maneuver
(B) Start inhaled nitric oxide
(C) Transition the patient to high-frequency oscillator ventilation
(D) Ventilate the patient in the prone position

Item 81

A 42-year-old man is evaluated in the office for chronic cough. He first developed a cough 3 years ago. It is productive of clear to yellow sputum that is occasionally blood-tinged. He has

taken antibiotics when his sputum production increases, after which his cough improves but never completely resolves. He has no dyspnea. He does not smoke cigarettes. He currently is taking no medications.

On physical examination, vital signs are normal. Oxygen saturation is 96% breathing ambient air. BMI is normal. Pulmonary examination reveals scattered inspiratory squeaks.

A chest radiograph shows ill-defined linear atelectasis and irregular peripheral opacities in the right and left lower lobes. A CT scan of the chest with contrast is shown below.

Which of the following is the most likely diagnosis?

(A) Bronchiectasis
(B) Centrilobular emphysema
(C) Chronic bronchitis
(D) Pulmonary Langerhans cell histiocytosis

H Item 82

A 35-year-old woman is evaluated in the emergency department for a 3-week history of worsening cough and dyspnea. She works as a sand mover operator at a hydraulic fracturing site and she notes that there is a large amount of dust that often clogs her respirator. She is otherwise healthy and has no history of fever, chills, sweats, or sick contacts. She has no current medications.

On physical examination, pulse rate is 110/min and respiration rate is 26/min. Other vital signs are normal. Oxygen saturation is 92% breathing ambient air. Lung examination reveals inspiratory crackles bilaterally. Cardiovascular examination is normal.

Chest radiograph shows patchy bilateral opacities with areas of consolidation in the lower lobes.

Bronchoalveolar lavage shows fluid with milky white return but no organisms; bacterial cultures are negative.

Which of the following is the most likely diagnosis?

(A) Acute interstitial pneumonia
(B) Acute silicosis
(C) Asbestosis
(D) Cryptogenic organizing pneumonia

Item 83 H

A 66-year-old woman is evaluated for difficult weaning from mechanical ventilation. She was hospitalized 8 days ago with septic shock due to pneumococcal pneumonia and bacteremia. She required mechanical ventilation and was treated with glucocorticoids and neuromuscular blockers. Pneumonia and sepsis have resolved, but she is unable to be weaned from ventilation. Current medications are fentanyl and heparin.

On physical examination, temperature is 37.3 °C (99.1 °F), blood pressure is 133/88 mm Hg, pulse rate is 70/min, and respiration rate is 14/min. Oxygen saturation is 100% on an F_{IO_2} of 0.35. She is awake and obeys commands but displays generalized weakness; she has decreased grip strength, distal lower extremity sensory loss, decreased tendon reflexes, and cannot raise her arms or legs.

Laboratory studies, including the complete blood count, metabolic profile, and electrolytes, are normal.

Which of the following is the most appropriate next step in the evaluation?

(A) Cervical spine MRI
(B) Electrodiagnostic testing
(C) Medical Research Council muscle scale
(D) Muscle biopsy

Item 84

A 36-year-old woman is evaluated for dry cough and progressive dyspnea that limits her ability to exercise. She initially presented 8 weeks ago with cough, fever, sputum production, and dyspnea. A chest radiograph at that time revealed left-lower-lobe opacities; she was diagnosed with pneumonia and treated with azithromycin but had little improvement in her symptoms. Her fever and sputum production have resolved. She is a nonsmoker.

On physical examination, vital signs are normal. Lungs are clear to auscultation.

Repeat chest radiograph reveals patchy opacities bilaterally and several nodular densities that are peripherally predominant in different locations than previous radiographs. High-resolution CT scan of the chest shows extensive ground-glass changes bilaterally with several areas of nodular consolidation that are peripherally predominant and along bronchovascular bundles.

Which of the following is the most likely diagnosis?

(A) Acute HIV infection
(B) Community-acquired pneumonia
(C) Cryptogenic organizing pneumonia
(D) Idiopathic pulmonary fibrosis

Item 85 H

A 56-year-old man is evaluated in the ICU for hypotension. He was admitted 3 hours ago for acute onset dyspnea. A CT angiogram performed upon admission showed a large, central pulmonary embolism. Treatment was started with subcutaneous low-molecular-weight heparin, and he was transferred to the ICU for monitoring. An hour later he became hypotensive.

Self-Assessment Test

H CONT.

On physical examination, blood pressure is 78/54 mm Hg, pulse rate is 120/min, and respiration rate is 28/min. Oxygen saturation is 93% on 4 L/min of oxygen through nasal cannula. Lungs are clear on auscultation. Cardiac examination reveals a grade 2/6 systolic murmur above the left lower sternal border. The second heart sound is persistently split.

Which of the following is the most appropriate treatment?

(A) Add recombinant tissue plasminogen activator (rtPA)
(B) Change to apixaban
(C) Change to intravenous unfractionated heparin infusion
(D) Continue low-molecular-weight heparin

H

Item 86

A 67-year-old woman is admitted to the ICU for abdominal distention, vomiting, and hypotension. She had a colectomy 3 weeks ago to treat recurrent diverticular bleeding, and postoperatively she had prolonged anorexia and nausea. She was discharged to an extended care facility on enteral nutrition through a small-bore nasogastric tube.

On physical examination, temperature is 36.8 °C (98.2 °F), blood pressure is 100/60 mm Hg, pulse rate is 109/min, and respiration rate is 19/min. BMI is 19. Preoperative BMI was 25. She has temporal wasting, colectomy wound with areas of dehiscence, lower extremity edema, decreased bowel sounds, and distended tympanitic abdomen.

Blood glucose is 65 mg/dL (3.6 mmol/L), albumin is 2.4 g/dL (24 g/L), creatinine is 0.6 mg/dL (53 µmol/L), and blood urea nitrogen is 6 mg/dL (2.14 mmol/L).

Radiograph and CT scan of the abdomen show dilated loops of small bowel. The nasogastric tube is in the proximal jejunum.

Intravenous fluid resuscitation is initiated and surgical consultation is obtained.

Which of the following is the most appropriate nutritional management?

(A) Maintain current enteral nutrition
(B) Measure gastric residual volume
(C) Start metoclopramide
(D) Switch to parenteral nutrition

Item 87

A 56-year-old woman is evaluated following screening for lung cancer with low-dose chest CT scan. She has a 35-pack-year history of cigarette smoking and continues to smoke. She has no symptoms.

On physical examination, vital signs and the remainder of the physical examination are normal.

Low-dose chest CT scan demonstrates diffuse centrilobular micronodules that are predominant in the midlung and upper lung. There is no evidence of septal line thickening, traction bronchiectasis, honeycombing, ground-glass opacities, or mediastinal or hilar lymphadenopathy.

Which of the following is the most likely diagnosis?

(A) Desquamative interstitial pneumonia
(B) Idiopathic pulmonary fibrosis
(C) Pulmonary Langerhans cell histiocytosis
(D) Respiratory bronchiolitis-associated interstitial lung disease

Item 88

A 73-year-old man is evaluated for a 3-month history of chronic productive cough, intermittent hemoptysis, night sweats, and 4.5 kg (10 lb) unintentional weight loss. He previously worked as a miner and has a history of chronic silicosis. He also has a 40-pack-year history of smoking, but quit 10 years ago.

On physical examination, vital signs are normal. He is thin and appears ill with temporal muscle wasting. Lung examination reveals bilateral upper-lobe crackles. Cardiac examination is unremarkable.

Chest radiograph reveals bilateral upper-lobe fibrosis with volume loss of the upper lobes and evidence of cavitation, traction of the hila upwards bilaterally, and bilateral calcified hilar lymphadenopathy.

Which of the following is the most appropriate management?

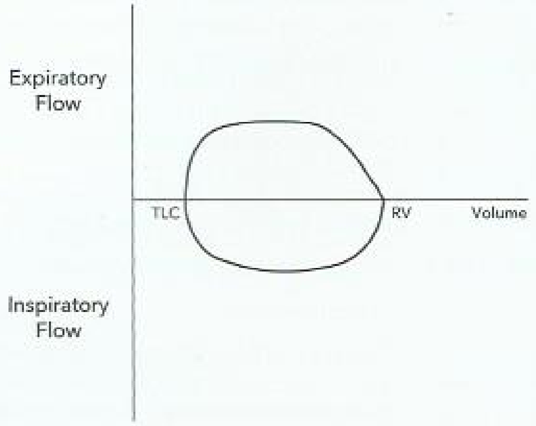
(A) Aspergillus IgG antibody test
(B) Bronchoscopy with transbronchial biopsy
(C) High-resolution CT scan of the chest
(D) Sputum sample for acid-fast bacillus

Item 89

A 32-year-old woman is evaluated for a 2-month history of gradually worsening dyspnea on exertion. She has difficulty climbing one flight of stairs, but has no wheezing or cough. She was hospitalized 6 months ago for a cholecystectomy complicated by sepsis, with a 2-week ICU stay requiring mechanical ventilation, but she recovered without difficulty. She uses an albuterol inhaler as needed, but this does not provide significant relief.

On physical examination, vital signs are normal. Oxygen saturation is 97% breathing ambient air. Cardiopulmonary examination is normal.

Chest radiograph is normal; spirometry is performed, and a flow-volume loop is shown.



Which of the following is the most likely diagnosis?

(A) Asthma
(B) COPD
(C) Fixed upper airway obstruction
(D) Normal lung function

Item 90

A 24-year-old woman is evaluated for recent onset of exertional dyspnea and chest tightness occurring three to four times weekly. She has a history of asthma since childhood that was previously well controlled with albuterol and budesonide. She is 14 weeks pregnant, and she stopped taking her medications 4 weeks ago out of concern for effects on the fetus. She has no other medical problems.

On physical examination, vital signs are normal. Oxygen saturation is 97% breathing ambient air. Chest examination shows good air movement with occasional expiratory wheezing. The remainder of the examination is normal.

Spirometry demonstrates mild airflow obstruction.

Which of the following is the most appropriate management?

(A) Begin fluticasone/salmeterol
(B) Begin low-dose prednisone
(C) Monitor serial peak flow measurements
(D) Restart previous medications

Item 91

A 78-year-old man is evaluated for an 8-month history of nonproductive cough and dyspnea on exertion, particularly when going up an incline. He has a 40-pack-year smoking history but quit 15 years ago. His sister had pulmonary fibrosis.

On physical examination, vital signs are normal. Clubbing is present. Lung examination reveals inspiratory crackles at the bases. Cardiac examination is normal. Pulmonary function testing shows an FVC of 75% of predicted and an FEV_1/FVC ratio of 0.85.

Chest radiograph demonstrates small lung volumes and interstitial opacities at the bases.

Which of the following is the most appropriate diagnostic test to perform next?

(A) Contrast-enhanced chest CT scan
(B) High-resolution chest CT scan
(C) Low-dose chest CT scan
(D) PET/CT imaging

Item 92

A 62-year-old man is evaluated for a 2-month history of nonproductive cough, progressive dyspnea, and fatigue. He reports a 6.8-kg (15-lb) weight loss during this time. He has a 30-pack-year history of smoking. He worked in a navy ship yard 32 years ago. His history is otherwise unremarkable.

On physical examination, vital signs are normal. Oxygen saturation is 94% breathing ambient air. Lung examination findings are consistent with a right pleural effusion. The remainder of the examination is normal. A complete blood count and metabolic profile are normal.

Chest radiograph shows a large right pleural effusion.

Thoracentesis is performed and removes 1200 mL of serosanguineous fluid.

Pleural fluid analysis:

Cytology	Negative
Glucose	89 mg/dL (4.9 mmol/L)
Lactate dehydrogenase	200 U/L
pH	7.36
Total protein	3.8 g/dL (38 g/L)

Laboratory studies:

Serum lactate dehydrogenase	235 U/L
Serum total protein	6.2 g/dL (62 g/L)

The patient returns 2 weeks later with a recurrent pleural effusion. CT scan of his chest demonstrates a moderate right pleural effusion with no parenchymal or pleural abnormalities noted. Thoracentesis is repeated; pleural fluid analysis is similar to the initial analysis, and cytology is again negative.

Which of the following is the most appropriate next step?

(A) Closed pleural biopsy
(B) Measure pleural fluid triglycerides
(C) Resend a pleural fluid specimen for cytology
(D) Thoracoscopy and pleural biopsy

Item 93

A 63-year-old man is evaluated for symptoms of gradually increasing dyspnea on exertion. Symptoms began about 2 years ago with activities such as golfing, and recently he notes dyspnea and occasional nonproductive cough with stair climbing in his home. He has no palpitations, chest pressure, wheezing, orthopnea, or systemic symptoms. History is significant for hypertension, 30-pack-year tobacco use (quit smoking 1 year ago), and obesity. He currently takes chlorthalidone.

On physical examination, vital signs are normal. Oxygen saturation is 92% on ambient air. BMI is 31. Pulmonary examination demonstrates basilar inspiratory crackles; cardiac examination is normal. The remainder of the examination is unremarkable.

Laboratory studies, including a basic metabolic panel and complete blood count, are normal.

Pulmonary function testing reveals an FEV_1 of 70% of predicted, an FVC of 65% of predicted, an FEV_1/FVC ratio of 0.78%, and a DL_{CO} of 63% of predicted. Total lung capacity is 70% of predicted.

Chest radiograph demonstrates diffuse interstitial reticulonodular infiltrates.

Which of the following is the most appropriate test to perform next?

(A) Bronchoscopy with transbronchial lung biopsy
(B) Cardiopulmonary exercise test
(C) High-resolution CT scan of the chest
(D) Methacholine challenge testing

Item 94

A 42-year-old man is evaluated for a 1-year history of disruptive snoring. His wife has not observed gasping, choking, or pauses in breathing. His normal sleep schedule is 10:30 PM to 6:30 AM. He awakens feeling refreshed and has no daytime sleepiness.

On physical examination, vital signs are normal. BMI is 34.6. He has a low-lying soft palate, his neck is 43 cm (17 in) in circumference, and he has patent nasal passages.

Which of the following is the most appropriate management?

(A) Home sleep testing
(B) Polysomnography
(C) Radiofrequency ablation of soft palate
(D) Weight loss program

Item 95

A 58-year-old woman is evaluated for 6 months of progressive dyspnea and cough. She was treated for breast cancer 10 years ago with a radical mastectomy on the left side, lymph node dissection, chemotherapy, and radiation. Her functional status is limited only by the dyspnea.

On physical examination, vital signs are normal. Oxygen saturation is 94% breathing ambient air. Lung examination is consistent with a left-side pleural effusion. The remainder of the physical examination is normal.

Chest radiograph shows moderate left-sided pleural effusion.

Thoracentesis is performed removing 1100 mL of serosanguineous fluid, providing significant relief of her symptoms. Cytology is positive for adenocarcinoma. The patient initiates therapy for metastatic breast cancer. During the next 2 weeks the patient requires repeated thoracentesis to remove large quantities of pleural fluid. Each thoracentesis provides significant relief of dyspnea for about 2 to 3 days.

Which of the following is the most appropriate management of the pleural effusions?

(A) Indwelling pleural catheter placement
(B) Pleurectomy
(C) Serial thoracentesis
(D) Talc pleurodesis

H Item 96

A 19-year-old man is brought to the emergency department after he attended a party with friends. He is anxious and tremulous. He has a history of depression. His only medication is fluoxetine.

On physical examination, he is alert and oriented. Temperature is 38.9 °C (102 °F), blood pressure is 136/79 mm Hg, pulse rate is 112/min, and respiration rate is 20/min. Oxygen saturation is 98% breathing ambient air. Physical examination is notable for slow, continuous, horizontal eye movements, tremor of extremities, hyperreflexia, and sustained ankle clonus and spontaneous myoclonus. The physical examination is otherwise normal.

Urine toxicology screening is pending.

Which of the following is the most likely diagnosis?

(A) Anticholinergic toxicity
(B) Malignant hyperthermia
(C) Neuroleptic malignant syndrome
(D) Serotonin syndrome

Item 97 H

A 62-year-old woman with alcoholic cirrhosis is evaluated for hypovolemic shock. She was hospitalized 24 hours ago with upper gastrointestinal bleeding. She underwent upper endoscopy, and a bleeding distal esophageal varix was controlled with epinephrine injection and banding. Gastric varices were also noted. Today she vomited 300 mL of bright red blood. Current medications are lactulose, rifaximin, pantoprazole, norfloxacin, and octreotide.

On physical examination, blood pressure is 79/54 mm Hg, pulse rate is 95/min, and respiration rate is 21/min. Oxygen saturation is 94% on 2 L/min of oxygen through nasal cannula. Ascites and splenomegaly are present.

Laboratory studies this morning reveal a hemoglobin level of 8 g/dL (80 g/L), platelet count of 74,000/µL (74×10^9/L), and an INR of 1.4.

Which of the following is the most appropriate immediate management?

(A) Packed red blood cell transfusion
(B) Recombinant factor VII infusion
(C) Transjugular intrahepatic portosystemic shunting
(D) Upper endoscopy

Item 98 H

A 45-year-old man is evaluated in the emergency department for alcohol intoxication, but the source and type of alcohol consumed are unknown. He has a history of heavy ethanol use and occasional isopropanol use.

On physical examination, vital signs are normal. Oxygen saturation is 97% on ambient air. He is somnolent but easily aroused.

Laboratory studies	
Bicarbonate	24 mEq/L (24 mmol/L)
Blood urea nitrogen	14 mg/dL (5 mmol/L)
Chloride	106 mEq/L (106 mmol/L)
Creatinine	1.6 mg/dL (141.4 µmol/L)
Ethanol	Negative
Glucose	90 mg/dL (5 mmol/L)
Osmolality, plasma	315 mOsm/kg H_2O
Potassium	4.1 mEq/L (4.1 mmol/L)
Sodium	139 mEq/L (139 mmol/L)

In addition to monitoring for signs of alcohol withdrawal, which of the following is the most appropriate treatment?

(A) Fomepizole
(B) Hemodialysis
(C) Levetiracetam
(D) Supportive care

Item 99

A 63-year-old man is evaluated in follow-up for a lung mass found during evaluation for a persistent cough. He is a current smoker with a 60-pack-year smoking history. His medical history is otherwise unremarkable, and he takes no medications.

Upon physical examination, vital signs are normal. The remainder of the physical examination is normal.

Laboratory studies, including liver chemistry tests, sodium, and calcium, are normal.

Chest radiograph shows a 2-cm nodule in the right upper lobe that was not seen on previous imaging. CT and PET scans demonstrate PET positivity of the lung lesion and in the mediastinal lymph nodes.

Which of the following is the most appropriate diagnostic procedure to perform next?

(A) CT-guided needle biopsy
(B) Endobronchial ultrasound and mediastinal lymph node biopsy
(C) Sputum cytology
(D) Thoracoscopic lung biopsy with lymph node dissection

H

Item 100

A 38-year-old woman is evaluated in the emergency department for unresponsiveness. On arrival she was minimally responsive with miotic pupils and a respiration rate of 4/min, but 5 minutes after administration of two doses of intravenous naloxone, her respiration rate is 15/min, and she is awake, oriented, and able to converse. She does not remember what happened before her admission, but her history is significant for heroin use.

On physical examination, vital signs are normal. Oxygen saturation is 99% breathing ambient air. The physical examination is unremarkable save for miotic pupils and signs of "needle tracks" on the arms.

Which of the following is the most appropriate management?

(A) Administer regular doses of naloxone starting now
(B) Continue to observe for several hours
(C) Discharge now with outpatient follow-up
(D) Elective endotracheal tube placement now

H

Item 101

A 74-year-old woman is evaluated in the hospital for loss of consciousness 1 day after total hip replacement. She suddenly became unresponsive and hypotensive while sitting in bed. Before this event she was doing well and discharge planning was under way. She has a remote history of penicillin allergy manifesting as hives. She received one dose of prophylactic cefazolin at the time of surgery. Her only medications are oxycodone and low-molecular-weight heparin.

On physical examination, blood pressure is 76/48 mm Hg, pulse rate is 116/min, and respiration rate is 26/min. Oxygen saturation is 80% on a 100% oxygen nonrebreather mask. The skin is cool and mottled but without rash. Cardiac sounds are soft, without murmur, but with persistent splitting of the second heart sound. Jugular venous distention is noted. The lungs are clear bilaterally.

Which of the following is the most likely diagnosis?

(A) Anaphylactic shock
(B) Opiate overdose
(C) Pulmonary embolism
(D) Tension pneumothorax

Item 102

A 56-year-old woman is evaluated in follow-up after polysomnography documented an apnea-hypopnea index of 6, a mean oxyhemoglobin saturation of 86.4%, and 38% of sleep time with an oxygen saturation of less than 90% of predicted. She has type 2 diabetes mellitus and hypertension. Current medications are metformin and lisinopril.

On physical examination, vital signs are normal. Oxygen saturation is 91% breathing ambient air. BMI is 44. Other than +1 ankle edema, the remainder of the physical examination, including neurological examination, is unremarkable.

Laboratory studies reveal a hemoglobin level of 16.9 g/dL (169 g/L). Arterial blood gas studies show a pH of 7.36, a P_{CO_2} of 58 mm Hg (7.7 kPa), and a P_{O_2} of 59 mm Hg (7.8 kPa).

Chest radiograph demonstrates clear lung fields.

Which of the following is the most likely diagnosis?

(A) Amyotrophic lateral sclerosis
(B) Central sleep apnea
(C) Obesity hypoventilation syndrome
(D) Severe obstructive sleep apnea

Item 103

A 54-year-old woman is evaluated in the office for an exacerbation of bronchiectasis characterized by low-grade fever, cough, and voluminous purulent sputum production progressing during the past 5 days. Her last exacerbation was 3 months ago and was treated with antibiotics. The results of the sputum culture from that episode are not available.

On physical examination, temperature is 38.0 °C (100.4 °F) and respiration rate is 18/min. All other vital signs are normal. Oxygen saturation is 96% breathing ambient air. Pulmonary examination reveals scattered inspiratory squeaks but no wheezes or crackles.

A chest radiograph does not show any infiltrates.

Sputum Gram stain shows gram-negative bacilli and a culture is pending.

Which of the following is the most appropriate empiric treatment?

(A) Amoxicillin
(B) Azithromycin
(C) Azithromycin and prednisone
(D) Inhaled tobramycin
(E) Levofloxacin

Answers and Critiques

H

Item 1 Answer: A

Educational Objective: **Treat an asthma exacerbation in the hospital.**

This patient should be hospitalized for further management. She has an asthma exacerbation and factors that increase her risk of asthma-related death, including several recent exacerbations, history of intubation for asthma, history of anxiety, and poor compliance with her controller medications. She also has worrisome clinical signs, including tachycardia and diminished oxygen saturation, increased work of breathing and decreased air movement on chest examination. These physical findings suggest a severe degree of airflow obstruction and risk for impending respiratory failure; therefore, the most appropriate site of care is the hospital.

Management should include close monitoring of dyspnea, work of breathing, and vital signs; frequent bronchodilator treatment; and systemic glucocorticoids. Pulse oximetry may be falsely reassuring because patients maintain normal oxygen levels despite high work of breathing, and hypoxemia is a late sign of pending respiratory failure. In patients who are at high risk or have lack of symptom resolution with initial therapies, arterial blood gas assessment is vital and should initially reveal hyperventilation with a low arterial P_{CO_2}. Normalization of the arterial P_{CO_2} could be an early indicator of respiratory muscle fatigue and impending respiratory arrest.

Outpatient treatment with prednisone and the patient's other medications would not be appropriate for this high-risk patient with severe asthma.

KEY POINT

- Patients with asthma exacerbations who have signs that indicate a severe attack should be hospitalized.

Bibliography

Prasad Kerlin M. In the clinic. Asthma. Ann Intern Med. 2014;160:ITC3 2-15; quiz ITC3 16-9. [PMID: 24737276]

Item 2 Answer: C

Educational Objective: **Recognize the role of NSAIDs in poor control of asthma.**

Treatment with ibuprofen should be discontinued for this patient, and therapy with prednisone should be started. This patient is presenting with signs of aspirin-exacerbated respiratory disease, triggered by his use of ibuprofen. This condition refers to upper and lower respiratory tract reactions to ingestion of substances inhibiting cyclooxygenase-1, which includes aspirin and many NSAIDs. Also known as aspirin-exacerbated respiratory disease or Samter's triad, aspirin-sensitive asthma includes severe persistent asthma, aspirin sensitivity, and hyperplastic eosinophilic sinusitis with nasal polyposis. Asthma is worsened by exposure to aspirin or other NSAIDs, likely because of the inhibition of cyclooxygenase and the resulting increase in leukotriene synthesis. Ingestion of cyclooxygenase-1-inhibiting substances can sometimes cause life-threatening bronchospasm, but patients can also have less severe symptoms, which often cause them to not recognize these substances as a trigger. In addition, the sensitivity to aspirin and other NSAIDs develops over time, generally after the onset of rhinosinusitis. Treatment consists of avoidance of aspirin or other NSAIDs along with typical asthma management. For patients who require aspirin use (such as those with coronary artery disease), an aspirin desensitization procedure can be performed. Successful desensitization down-regulates leukotriene receptors and modifies interleukin sensitivity, which may relieve asthma symptoms in some patients. For this reason, the addition of a leukotriene inhibitor such as montelukast or zafirlukast to an asthma maintenance regimen is helpful for most patients to modify the leukotriene dysregulation thought to contribute to the syndrome; however, addition of a leukotriene inhibitor alone would not be the appropriate next step for this patient.

24-Hour esophageal pH monitoring is helpful to diagnose gastroesophageal reflux disease, but the patient has no symptoms of this; moreover, a trial of empiric proton pump inhibitor therapy would be indicated before invasive testing.

A nasal polypectomy may be helpful in the long-term management of this syndrome, but it is not the initial step.

KEY POINT

- Treatment of aspirin-exacerbated respiratory disease consists of symptom treatment with glucocorticoids and removal of the exposure; treatment can also include a leukotriene receptor antagonist.

Bibliography

Ledford DK, Wenzel SE, Lockey RF. Aspirin or other nonsteroidal inflammatory agent exacerbated asthma. J Allergy Clin Immunol Pract. 2014;2:653-7. [PMID: 25439353] doi:10.1016/j.jaip.2014.09.009

Item 3 Answer: B

Educational Objective: **Treat chronic bronchitis and prevent frequent COPD exacerbations with roflumilast.**

Roflumilast is the most appropriate treatment. It is used primarily as add-on therapy in severe COPD associated with chronic bronchitis and a history of recurrent exacerbations despite other therapies; it has been shown to improve lung function and reduce risk and frequency of exacerbations in these individuals. However, it is not a bronchodilator, is expensive, and has not been shown to be effective in other groups of patients with COPD. Common side effects include

diarrhea, nausea, weight loss, and headache. Recently the FDA has raised concerns regarding psychiatric adverse events with roflumilast (anxiety, depression, insomnia). Roflumilast is contraindicated in patients with liver impairment and has significant drug interactions.

Oral glucocorticoids, such as prednisone, are reserved for limited periodic use in treating exacerbations of COPD and may provide some benefit in decreasing hospital readmission rates after exacerbation. Long-term oral glucocorticoid therapy has limited, if any, benefit in COPD and carries a high risk for other significant side effects (such as muscle weakness and decreased functional status) and is generally not recommended.

Methylxanthines such as theophylline have shown modest treatment benefit in COPD, likely due to a bronchodilating effect mediated by nonselective inhibition of phosphodiesterase. However, the potential toxicity of this class of drugs coupled with their reduced efficacy has led to increasingly limited use. Although they may be helpful in any classification of COPD, they tend to be used in selected patients with late-stage disease or for patients in whom other preferred therapies have proved ineffective for symptomatic relief; they may also be used when other medications are not available or affordable.

Clinical trials have demonstrated that chronic macrolide therapy is associated with a reduction in the rate of exacerbation in patients with moderate to severe COPD despite optimal maintenance inhaler therapy. Macrolide antibiotic therapy and roflumilast have not been directly compared in patients with frequent exacerbations of COPD and the choice among the two is informed by benefits and risks on an individual patient basis. Trimethoprim-sulfamethoxazole has not been shown to prevent exacerbations of COPD.

KEY POINT

- Roflumilast, a selective phosphodiesterase-4 inhibitor, is used as add-on therapy in severe COPD associated with chronic bronchitis and a history of recurrent exacerbations to reduce risk and frequency of exacerbations.

Bibliography

Chong J, Leung B, Poole P. Phosphodiesterase 4 inhibitors for chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2017;9:CD002309. [PMID: 28922692] doi:10.1002/14651858.CD002309.pub5

Item 4 Answer: B

Educational Objective: Evaluate a patient for obstructive sleep apnea.

The most appropriate next step is home sleep testing. This patient has signs (loud snoring, breathing pauses, gasping), symptoms (excessive daytime sleepiness, nocturia), and physical examination findings (BMI greater than 30, large neck size, crowded oropharynx, a low-lying soft palate) consistent with obstructive sleep apnea (OSA). Home sleep testing is the preferred diagnostic test when there is a high likelihood of OSA and an absence of significant comorbidities such as cardiopulmonary or neuromuscular disease. If OSA is confirmed, daytime sleepiness represents a strong indication for treatment. Polysomnography performed in a sleep laboratory is the preferred diagnostic test for OSA in patients with underlying cardiopulmonary or neuromuscular disease who might require advanced positive airway pressure modes (such as bilevel positive airway pressure) or supplemental oxygen but would not be indicated for this patient who has no evidence of such comorbidities.

Objective testing should occur before treatment of OSA is prescribed. Auto-adjusting positive airway pressure generally follows home sleep testing that confirms OSA.

Occasionally, multiple sleep latency testing (MSLT) is used to provide an objective measure of sleepiness. MSLT requires a series of brief nap opportunities during the course of a full day in a sleep laboratory to determine the average time to fall asleep and is time and labor intensive; however, it is necessary to establish the diagnoses of narcolepsy and idiopathic hypersomnia. A mean sleep latency of less than 5 minutes is a clear indicator of pathologic sleepiness, whereas more than 15 minutes is considered normal. If these additional sleep disorders were suspected in a patient with obstructive sleep apnea, MSLT would occur only after positive airway pressure treatment has been optimized.

There is no established role for overnight pulse oximetry as a screening or diagnostic tool in OSA. With limited sensitivity and specificity in the symptomatic patient with a high pretest probability of OSA, overnight oximetry is not likely to add diagnostic information beyond home sleep testing, nor will it alter the decision to treat.

KEY POINT

- Home sleep testing is the first test indicated in a patient with a high probability of obstructive sleep apnea without underlying cardiopulmonary or neuromuscular disease.

Bibliography

Kapur VK, Auckley DH, Chowdhuri S, Kuhlmann DC, Mehra R, Ramar K, et al. Clinical practice guideline for diagnostic testing for adult obstructive sleep apnea: an American Academy of Sleep Medicine clinical practice guideline. J Clin Sleep Med. 2017;13:479-504. [PMID: 28162150] doi:10.5664/jcsm.6506

Item 5 Answer: A

Educational Objective: Evaluate a subsolid solitary pulmonary nodule.

The most appropriate management of the pulmonary nodule is to perform follow-up chest CT scanning at 6-12 months and then every 2 years for 5 years, as recommended by the Fleischner Society Guidelines. Nodules are classified as solid or subsolid. Subsolid nodules are either pure ground glass nodules (no solid component) or part-solid nodules (both ground-glass and solid components). A ground-glass nodule is defined as a focal area of increased attenuation in the lung

through which normal parenchymal structures can still be seen. The classification of nodules helps in the assessment of malignant potential (for example, adenocarcinoma is more likely to present as a subsolid and part-solid nodule) and guides appropriate follow-up. This patient has a solitary pure ground-glass subsolid nodule that is larger than 6 mm. Earlier guidelines recommended initial follow-up at 3 months, but this was changed to 6-12 months because earlier follow-up is unlikely to affect the outcome of these characteristically indolent lesions. The average doubling time of subsolid, cancerous nodules typically is 3-5 years. Therefore, longer initial and total follow-up intervals are recommended for subsolid nodules than for solid nodules.

Evaluation with a PET/CT scan would be recommended for a solid nodule that is greater than 8 mm in size. This test most commonly uses fluorodeoxyglucose (FDG) as a metabolic marker to identify rapidly dividing cells such as tumor cells and, to a lesser degree, any inflammatory lesion. A nodule that demonstrates no FDG uptake is unlikely to be malignant. PET/CT imaging can also be used for staging a cancer by determining the presence or absence of metastatic disease.

Tissue sampling would not be appropriate at this stage because the vast majority of these lesions are not malignant.

KEY POINT

- Subsolid lung nodules 6-8 mm in size should be initially followed up at 6-12 months and then every 2 years for 5 years because of the slow rate of growth if such masses are malignant.

Bibliography

MacMahon H, Naidich DP, Goo JM, Lee KS, Leung ANC, Mayo JR, et al. Guidelines for management of incidental pulmonary nodules detected on CT images: from the Fleischner Society 2017. Radiology. 2017;284:228-243. [PMID: 28240562] doi:10.1148/radiol.2017161659

H

Item 6 Answer: A

Educational Objective: Diagnose an acute exacerbation of idiopathic pulmonary fibrosis.

The most likely diagnosis is an acute exacerbation of idiopathic pulmonary fibrosis (IPF). The clinical course of an acute exacerbation is acute to subacute onset (typically shorter than 30 days) of worsening dyspnea, and the medical evaluation does not reveal another cause for dyspnea such as infection, heart failure, or pulmonary embolism. High-resolution CT scan shows new-onset diffuse bilateral ground-glass opacities. Patients may develop frank respiratory failure due to an exacerbation or stabilize at a new, worsened baseline. The proposed criteria for an acute IPF exacerbation have recently changed and now include the possibility of a "trigger" and, therefore, the history of a viral prodrome and presence of rhinovirus no longer exclude this diagnosis. Evidence-based treatment options are limited. The role for mechanical ventilation in this population is often futile if there is not a reversible cause and particularly if there is not a path to lung transplantation. Glucocorticoids are often used in combination with broad spectrum antibiotics in the hopes of a clinical response. Many patients are now being treated for IPF with nintedanib or pirfenidone, although the value of continuing these antifibrotic therapies in the acute exacerbation phase of disease is currently unknown.

Heart failure does not fully explain the acute worsening of IPF because the B-type natriuretic peptide is low.

Hypersensitivity pneumonitis is the result of an immunologic response to repetitive inhalation of antigens and high-level exposure and will often be associated with fevers, flulike symptoms, cough, and shortness of breath, typically during a period of 48 hours. The most common sources of antigens are thermophilic actinomycetes, fungi, and bird droppings. High-resolution CT imaging of the chest shows findings of ground-glass opacities and centrilobular micronodules that are upper-lung and midlung predominant. The patient's history and radiological findings are not consistent with this diagnosis.

Nonspecific interstitial pneumonia (NSIP) is a disease that predominantly affects the lower lobes of the lung. Unlike IPF, NSIP tends to affect a younger patient population and is strongly associated with connective tissue disease. The ground glass opacities on this patient's CT scan indicate an acute exacerbation with a background of usual interstitial pneumonia and are not consistent with NSIP.

KEY POINT

- An acute exacerbation of idiopathic pulmonary fibrosis begins with an abrupt worsening during a few days to weeks in the absence of another cause for dyspnea such as infection, heart failure, or pulmonary embolism and is notable for new bilateral ground glass opacities superimposed on findings consistent with usual interstitial pneumonia on CT scan.

Bibliography

Collard HR, Ryerson CJ, Corte TJ, Jenkins G, Kondoh Y, Lederer DJ, et al. Acute exacerbation of idiopathic pulmonary fibrosis. An international working group report. Am J Respir Crit Care Med. 2016;194:265-75. [PMID: 27299520] doi:10.1164/rccm.201604-0801CI

Item 7 Answer: C

H

Educational Objective: Diagnose a patient with vocal cord dysfunction.

The most appropriate management is laryngoscopy. This patient has symptoms suggestive of vocal cord dysfunction, which is caused by paradoxical adduction of the vocal cords during inspiration, leading to functional upper airway obstruction. The diagnosis is suggested by dysphonia midchest or throat tightness with exposure to particular triggers such as strong irritants or emotions; difficulty breathing in; and symptoms that only partially respond to asthma medications. Patients may also experience midchest tightness, dyspnea, cough, and dysphonia, and stridor may be detected as inspiratory monophonic wheezing. Vocal cord dysfunction

H CONT.

is commonly misdiagnosed as asthma, leading to excessive health care use. Diagnosis is ideally made by visualization of the abnormal vocal cord adduction during laryngoscopy. It may also be diagnosed if spirometry happens to capture a flat inspiratory limb on the flow-volume loop. However, if patients are unable to tolerate laryngoscopy while symptomatic, empiric therapy should be started if there is a high clinical suspicion of vocal cord dysfunction. Treatment consists of speech therapy utilizing cognitive behavioral techniques.

Because disorders affecting the upper respiratory tract may affect the lower tract, sinus disorders may be associated with worsening control of asthma. Patients with frequent asthma exacerbations should be evaluated for occult sinus disease, as untreated upper airway inflammation may contribute to poor asthma control. However, CT scan of the sinuses is not appropriate because sinus disease cannot explain the patient's upper chest and throat tightness, dysphonia, inspiratory monophonic wheezing, or unresponsiveness to intensive asthma treatment.

Increasing the prednisone dose is not likely to improve the patient's symptoms, which are not likely or entirely due to airway inflammation and will expose the patient to more potential side effects of glucocorticoids.

Asthma has been associated with obstructive sleep apnea (OSA). In difficult-to-control asthma, OSA is a significant risk factor for frequent exacerbations. Treatment of OSA improves asthma symptoms. However, this patient has no obvious risk factors for OSA and OSA cannot explain the patient's upper chest and throat tightness, dysphonia, or inspiratory monophonic wheezing. Therefore polysomnography is not indicated.

KEY POINT

- The diagnosis of vocal cord dysfunction is suggested by midchest tightness with exposure to particular triggers such as strong irritants or emotions; difficulty breathing in; and symptoms that only partially respond to asthma medications.

Bibliography

Idrees M, FitzGerald JM. Vocal cord dysfunction in bronchial asthma. A review article. J Asthma. 2015;52:327-35. [PMID: 25365113] doi:10.3109/02770903.2014.982288

H

Item 8 Answer: C

Educational Objective: Treat a patient on mechanical ventilation for delirium using nonpharmacologic interventions.

Early mobilization with physical and occupational therapy and interruption of sedation should be used to decrease the duration of delirium. This patient has acute onset of cognitive dysfunction, impairment of attention, and fluctuating mental status, which are features of delirium. Increased or decreased psychomotor activity, disorganized thinking, disorientation, and perceptual disturbances are other supportive features. The use of a screening instrument (such as the Confusion Assessment Method) allows for improved recognition and diagnosis of delirium. Delirium contributes to length of ICU stay, morbidity, mortality, and post-intensive care cognitive impairment. A study of critically ill patients on mechanical ventilation demonstrated that an early physical and occupational therapy program reduced delirium by 2 days compared to controls.

Haloperidol is used to decrease hyperactive features of delirium. Currently, there is no strong evidence in favor of its use for treating delirium in critically ill patients.

Current guidelines for sedation in the ICU favor strategies that control pain, target lighter sedation, avoid benzodiazepines, and favor early mobility. The use of benzodiazepines is associated with an increased incidence of delirium, and would not be appropriate for this patient showing signs of delirium when compared with nonbenzodiazepine sedation strategies.

The practice of having all critically ill patients on mechanical ventilation receive continuous deep sedation is no longer followed, thus increasing the propofol dosage would not be appropriate. A practice-changing trial demonstrated that daily interruption of sedation decreased length of mechanical ventilation and stay in the ICU. Recent trials demonstrated that the use of a light sedation protocol had similar patient outcomes to daily interruption of sedation. Light levels of sedation using a protocol are associated with shorter length of mechanical ventilation and ICU stay.

KEY POINT

- Early mobilization with physical and occupational therapy and interruption of sedation should be used to prevent and treat delirium in critically ill patients.

Bibliography

Schweickert WD, Pohlman MC, Pohlman AS, et al. Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial. Lancet 2009; 373:1874-1882 PMID 19446324

Item 9 Answer: D

Educational Objective: Identify mortality benefits of smoking cessation.

Smoking cessation is the best way to prevent deaths and complications from lung cancer and other diseases. There is evidence of risk reduction within 5 years of quitting smoking. In addition, case-control studies have demonstrated an 80% to 90% relative risk reduction for lung cancer in former smokers who have been abstinent for 15 years.

Chest radiograph and sputum cytology are not recommended as screening tools for lung cancer. Several large-scale controlled clinical trials have been performed and none of them demonstrated a mortality benefit for screening with cytology or chest radiography.

Recently the national lung screening trial demonstrated that screening with low-dose CT (LDCT) reduced mortality in a high-risk population (based on age and smoking history) compared with screening by radiograph (relative

risk reduction of 20%). However, smoking cessation is still more likely to save a life than LDCT. The U.S. Preventive Services Task Force does recommend annual screening for lung cancer with LDCT in adults age 55-80 years who have a 30-pack-year smoking history and currently smoke or have quit within the past 15 years. Candidates for screening should take part in shared decision making, which includes a discussion of benefits and risks. Ideally it should take place in the context of a multidisciplinary program to ensure that it is properly performed and downstream testing is managed appropriately. Active smokers engaged in lung cancer screening should be counseled and assessed for smoking cessation at every opportunity.

KEY POINT

- Smoking cessation is the best way to prevent deaths and complications from lung cancer and other diseases.

Bibliography

Aberle DR, Adams AM, Berg CD, Black WC, Clapp JD, Fagerstrom RM, et al; National Lung Screening Trial Research Team. Reduced lung cancer mortality with low-dose computed tomographic screening. N Engl J Med. 2011;365:395-409. [PMID: 21714641] doi:10.1056/NEJMoa1102873

H

Item 10 Answer: E

Educational Objective: Prevent airway aspiration by establishing a secure airway in patients who are unable to protect their airway.

An endotracheal tube should be placed to establish a secure airway. This patient has upper gastrointestinal bleeding and several features of cirrhosis (telangiectasias, jaundice, ascites), and likely has an acute variceal bleed. Mortality in these patients is high and requires multidisciplinary management. Initial management of esophageal variceal bleeding includes placement of two large-bore intravenous lines, fluid resuscitation, and erythrocyte transfusion to a goal hemoglobin level of 7 g/dL (70 g/L) or greater. Up to 50% of patients with cirrhosis and gastrointestinal bleeding develop infections within 1 week, and prophylactic antimicrobial agents improve mortality rates. A splanchnic vasoconstrictor such as octreotide is recommended for 3 to 5 days. Upper endoscopy with band ligation should be performed urgently after the patient is stabilized, followed by addition of a nonselective β-blocker. For the 10% to 20% of patients with uncontrolled bleeding and those with early rebleeding, a transjugular intrahepatic portosystemic shunt (TIPS) should be placed. Early airway management to prevent aspiration is essential when a patient cannot protect the airway or is otherwise at risk for aspiration of blood or gastric contents. This patient has altered mental status and ongoing hemorrhage, both risk factors for airway aspiration.

A nonselective β-blocker is recommended as secondary prophylaxis against rebleeding after recovery from a variceal bleed, but it would not be warranted in the acute setting in this patient with hypotension.

Oxygen by nasal cannula is not indicated as the patient has adequate oxygenation; furthermore, additional oxygen though nasal cannula would not help establish a secure airway.

An upper endoscopy should be performed in this patient with presumed variceal hemorrhage, but only after his airway has been secured and he has been treated with standard pharmacotherapy (octreotide and antibiotics) and appropriately resuscitated to enable safe endoscopy.

Noninvasive bilevel positive airway pressure ventilation does not provide a secure airway and is contraindicated in patients with altered mental status or risk of vomiting because it can increase the risk of aspiration if the patient were to vomit into the mask.

KEY POINT

- In patients who cannot maintain a patent airway or protect the airway against aspiration, a secure airway should be established.

Bibliography

Long B, Koyfman A. The emergency medicine evaluation and management of the patient with cirrhosis. Am J Emerg Med. 2017 Dec 23. pii: S0735-6757(17)31049-5. doi: 10.1016/j.ajem.2017.12.047. [Epub ahead of print] [PMID:29290508]

Item 11 Answer: A

Educational Objective: Treat inadequately controlled mild persistent asthma by stepping up therapy.

This patient has mild persistent asthma (albuterol use more than twice weekly but no more than once per day, and FEV_1 greater than 80% predicted) and the most appropriate management is to begin low-dose inhaled glucocorticoids such as beclomethasone. An appropriate dosage would be 40 µg per puff with 1 inhalation twice daily. Patients with asthma who require a short-acting β_2 agonist more than twice per week for symptom control, rather than to prevent exercise-induced bronchospasm, are considered uncontrolled. The next step in treatment is the addition of low-dose inhaled glucocorticoids. An alternative would be to add montelukast but low-dose inhaled glucocorticoid therapy is preferred. Inhaler technique should be confirmed in all patients when beginning therapy and reviewed regularly.

When inhaled glucocorticoids alone do not achieve asthma control, the addition of a long-acting β_2-agonist (LABA) has proved to be effective as step-up therapy. Combination preparations that contain an inhaled glucocorticoid and a LABA are available, such as fluticasone/salmeterol. In addition to bronchodilation, LABAs appear to potentiate anti-inflammatory effects of inhaled glucocorticoids when taken together. However, beginning an inhaled glucocorticoid and a LABA combination is not appropriate, as this patient has mild persistent asthma and a combination inhaled glucocorticoid/LABA is indicated for moderate persistent asthma.

Anticholinergic agents dilate bronchial smooth muscle by decreasing the constrictive cholinergic tone in the

airways. Although it is less effective than β_2-agonists, the short-acting agent ipratropium can be used as adjunctive quick-relief therapy during asthma exacerbations. However, this patient has poorly controlled asthma and it is appropriate to start controller therapy, such as an inhaled glucocorticoid, to reduce airway inflammation from asthma.

Leukotriene receptor antagonists (LTRAs), such as montelukast, are not considered preferred first-line controller therapy in any asthma population. LTRAs may have a particular role in aspirin-sensitive asthma and a protective role in exercise-induced asthma; however, low-dose inhaled glucocorticoids are preferred in this patient with uncontrolled mild persistent asthma.

KEY POINT

- Patients with mild persistent asthma uncontrolled with a short-acting β_2-agonist should be stepped up to a controller medication; low-dose inhaled glucocorticoids are preferred.

Bibliography

McCracken JL, Veeranki SP, Ameredes BT, Calhoun WJ. Diagnosis and management of asthma in adults: a review. JAMA. 2017;318:279-290. [PMID: 28719697] doi:10.1001/jama.2017.8372

H Item 12 Answer: C

Educational Objective: Diagnose idiopathic pulmonary fibrosis.

The most likely diagnosis is idiopathic pulmonary fibrosis (IPF). Patients with IPF typically present with chronic shortness of breath on exertion and a dry cough. The prevalence of disease increases with increasing age and is rare in individuals younger than 50 years. Clubbing is common. A history of smoking is a risk factor for the development of IPF and is commonly seen in these patients. The finding of bilateral, peripheral, and basal predominant septal line thickening with honeycomb changes on CT scan is consistent with usual interstitial pneumonia pathologic pattern and can also be seen in connective tissue disease, asbestosis, and chronic hypersensitivity pneumonitis. However, the history is negative for symptoms suggestive of connective tissue disease and for significant environmental exposures. The exclusion of connective tissue diseases and environmental exposures combined with a definite usual interstitial pneumonia imaging pattern supports the diagnosis of IPF. Tobacco smoke is associated with the development of several diffuse parenchymal lung diseases (DPLDs), including IPF. There are also several disorders that generally develop only in individuals who are active smokers; these diseases are all subacute, evolving during weeks to months.

Desquamative interstitial pneumonia is due to extensive, diffuse macrophage filling of alveolar spaces and is accompanied by predominant cough and dyspnea symptoms and bilateral ground-glass opacities on chest imaging.

Hypersensitivity pneumonitis, in its chronic form, is the most common DPLD included in the differential diagnosis for patients with IPF. When fibrosis occurs with chronic hypersensitivity pneumonitis, it is typically in the midlung and upper-lung zones and is associated with an environmental exposure, which was not elicited in this patient. Although many patients with chronic hypersensitivity pneumonitis may no longer have an exposure to a causative antigen, the typical age of onset, history, and basal predominant CT scan abnormalities favor a diagnosis of IPF rather than hypersensitivity pneumonitis.

Pulmonary Langerhans cell histiocytosis is characterized by thin-walled cysts with accompanying nodules and is often associated with pulmonary hypertension. All of these diseases are subacute, evolving during weeks to months and present in active smokers.

Respiratory bronchiolitis-associated interstitial lung disease is used to describe disease in active smokers who have imaging findings of centrilobular micronodules with a pathologic finding of respiratory bronchiolitis on biopsy.

KEY POINT

- Idiopathic pulmonary fibrosis typically occurs in older individuals with nonproductive cough and progressive dyspnea on exertion; the diagnosis is supported by findings of usual interstitial pneumonitis on a high-resolution CT scan of the chest.

Bibliography

Raghu G, Collard HR, Egan JJ, Martinez FJ, Behr J, Brown KK, et al; ATS/ERS/JRS/ALAT Committee on Idiopathic Pulmonary Fibrosis. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. Am J Respir Crit Care Med. 2011;183:788-824. [PMID: 21471066] doi:10.1164/rccm.2009-040GL

Item 13 Answer: E H

Educational Objective: Assess intravascular volume status.

No further testing is required. The physical examination has several features that suggest she has decreased intravascular volume and reduced systemic vascular resistance. The presence of warm and vasodilated skin, a very low diastolic pressure, absent jugular venous distention, and tachycardia all suggest severe vasodilation. There are several invasive and noninvasive devices available to aid the clinician to confirm the clinical diagnosis; however, none of them alone can provide a definite answer. Integrating the physical examination and basic vital signs remains the best clinical method to define intravascular volume status and the type of shock.

Central venous catheter measurement of venous pressure can provide information that helps confirm the diagnosis of low central venous pressure; however, it is invasive, subject to technical issues, and the presence of spontaneous breathing needs to be considered when obtaining readings. Studies have demonstrated that a single measurement does not help define intravascular volume status or volume responsiveness. Thus the value must be taken in the context of the history and physical exam.

H CONT

Fullness of the vena cava as detected by ultrasonography is thought to correlate with increased right atrial pressure, whereas a collapsing inferior vena cava at the end of expiration suggests volume responsiveness. Volume responsiveness refers to an increase in cardiac output upon the administration of fluid. A common inference is that intravascular volume is high when the patient is not volume responsive; however, this would be a limited assumption as the response to volume also involves cardiac function and infusion volume. In addition, the presence of increased respiratory effort will make the measurements unreliable.

A pulmonary artery catheter will provide a plethora of information on the intravascular pressures (by inference, the volume status) and cardiac output of the patient. However, placing a pulmonary artery catheter in a patient with sepsis is invasive, does not improve management, increases complications, and has not demonstrated improved outcome.

Pulse pressure is the difference between systolic and diastolic arterial blood pressure during respiration induced by positive pressure ventilation. A low variation in pulse pressure is believed to be an indicator of unresponsiveness to a fluid challenge whereas a pulse pressure variation of at least 13% to 15% is associated with volume responsiveness. However, this measurement is only reliable in patients who are mechanically ventilated (and not spontaneously triggering the ventilator), receiving 8 mL/kg or more of tidal volume, and in sinus rhythm.

KEY POINT

- The most appropriate method to evaluate volume status remains the physical examination; several technologies can help confirm the assessment.

Bibliography

Teboul JL, Saugel B, Cecconi M, De Backer D, Hofer CK, Monnet X, et al. Less invasive hemodynamic monitoring in critically ill patients. Intensive Care Med. 2016;42:1350-9. [PMID: 27155605] doi:10.1007/s00134-016-4375-7

H

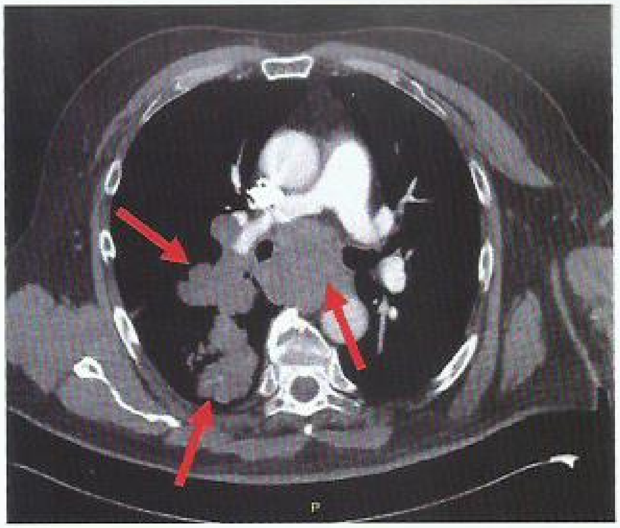
Item 14 Answer: C

Educational Objective: Diagnose small cell lung cancer.

The most likely diagnosis is small cell lung cancer (SCLC). SCLC is a neuroendocrine tumor that accounts for approximately 15% of all lung cancers and occurs predominantly in smokers.

This patient has signs and symptoms of hyponatremia and chest CT scan shows a large mediastinal right hilar mass and right-lower-lobe mass (arrows).

Imaging studies in SCLC commonly demonstrate a large hilar mass with bulky mediastinal lymphadenopathy; some patients may not have an obvious primary lesion. Signs and symptoms include cough, dyspnea, weight loss, and debility. Less commonly SCLC can present with endocrinologic or neurologic paraneoplastic syndromes. The



syndrome of inappropriate antidiuretic hormone secretion (SIADH) due to ectopic production of antidiuretic hormone (ADH) is most often due to a SCLC and is rarely seen with other lung tumors. It occurs in approximately 10% of patients and results in hyponatremia. The severity of symptoms is related to the degree of hyponatremia and rapidity of the decrease. They may include anorexia, nausea, and vomiting, but if the decrease is rapid, cerebral edema can occur and may result in irritability, restlessness, personality changes, confusion, coma, seizures, and respiratory arrest. SCLC is more aggressive than non-small cell lung cancer (NSCLC), is usually already disseminated at presentation, and requires prompt treatment; however, it is often initially more sensitive to chemotherapy and radiotherapy but typically relapses and becomes resistant to further treatment. Staging should not delay treatment.

NSCLC accounts for 80% of lung cancers, of which adenocarcinoma is the most common type, followed by squamous cell. Although NSCLC is in the differential diagnosis for this patient, hyponatremia and a large mediastinal mass are most consistent with SCLC.

Malignant pleural mesothelioma typically presents as a recurrent exudative pleural effusion with pleural thickening in a patient with exposure to asbestos. This patient did not present with a pleural effusion, which makes this diagnosis less likely.

KEY POINT

- Typical imaging findings in patients with small cell lung cancer (SCLC) include a large mediastinal mass; hyponatremia due to ectopic production of antidiuretic hormone is most often due to SCLC and is rarely seen with other lung tumors.

Bibliography

Jett JR, Schild SE, Kesler KA, Kalemkerian GP. Treatment of small cell lung cancer: diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2013;143:e400S-e419S. [PMID: 23649448] doi:10.1378/chest.12-2363

H

Item 15 Answer: B

Educational Objective: Evaluate an acute exacerbation of COPD.

An electrocardiogram should be obtained for this patient to evaluate other causes of her acute presentation, such as acute myocardial infarction, arrhythmia, and atrial fibrillation. The first steps in managing a patient with a presumed COPD exacerbation are to confirm the diagnosis. Studies helpful in the evaluation may include pulse oximetry to assess oxygenation or guide oxygen therapy; a chest radiograph to rule out an alternative diagnosis; a complete blood count to identify the presence of polycythemia, anemia, or leukocytosis; arterial blood gas studies; a biochemical panel to assess for electrolyte and glycemic abnormalities; and an electrocardiogram to evaluate tachycardia (as in this patient) and for other possible cardiac comorbidity. This patient has already had a chest radiograph and appropriate laboratory studies but an electrocardiogram is also indicated.

Patients with pulmonary embolism (PE) can present with symptoms similar to a COPD exacerbation. Because of this, pretest probability models such as the Wells criteria have been developed and validated to assist in clinical decision making. Patients who have a low pretest probability for PE using the Wells criteria, such as this patient, and who meet all Pulmonary Embolism Rule-Out Criteria do not need further testing to rule out PE. Physicians should obtain a D-dimer assay in patients with intermediate pretest probability for PE or for those with a low pretest probability for PE who do not meet all Pulmonary Embolism Rule-Out Criteria. In these patients, imaging studies should not be used for initial evaluation.

A sputum culture or Gram stain is not routinely used to assess COPD exacerbations as it rarely changes management. For patients with a confirmed COPD exacerbation with cough, increased sputum, and dyspnea, antibiotics are usually initiated regardless of the results of the sputum Gram stain or culture.

KEY POINT

- The first steps in managing a patient with a presumed COPD exacerbation are to confirm the diagnosis and to evaluate other causes of the acute presentation.

Bibliography

Holden V, Slack III D, McCurdy MT, Shah NG. Diagnosis and management of acute exacerbations of chronic obstructive pulmonary disease. Emerg Med Pract. 2017;19:1-24. [PMID: 28926214]

Item 16 Answer: C

Educational Objective: Identify the sequela of obstructive sleep apnea most responsive to therapy.

Excessive daytime sleepiness is the strongest indication for treatment of obstructive sleep apnea (OSA). Excessive daytime sleepiness is thought to result primarily from disruption of sleep architecture due to repetitive breathing events. Randomized trials and meta-analyses of systematic reviews show that positive airway pressure therapy reduces the frequency of respiratory events during sleep and is associated with reduction in daytime sleepiness and improved sleep-related quality of life.

Observational studies that suggest benefit from positive airway pressure therapy on the natural history of atrial fibrillation is yet to be proved in randomized trials. There is a similar lack of proved benefit in other important conditions, such as cardiovascular death. In addition, a recent large multicenter trial failed to show mortality benefit afforded by positive airway pressure therapy in those with OSA and cardiovascular disease.

Trials assessing various measures of glucose homeostasis (fasting glucose, insulin resistance, hemoglobin A_{1c}) in patients with OSA treated with positive airway pressure have shown inconsistent results. This patient requires adjustment of his medication with the goal of reducing the hemoglobin A_{1c} level.

Positive airway pressure therapy has been shown to modestly reduce blood pressure in those with OSA, but the effects are not always consistent. Those with excessive daytime sleepiness tend to be more responsive to these effects than those who are not sleepy. Also, comparative efficacy trials in those with OSA have shown greater reductions in blood pressure with antihypertensive drug therapy than positive airway pressure. This patient's antihypertensive medications should be adjusted with the goal of achieving the target blood pressure level recommended by the American College of Cardiology/American Heart Association of less than 130/80 mm Hg.

KEY POINT

- Excessive daytime sleepiness is the strongest indication for treatment of obstructive sleep apnea.

Bibliography

McEvoy RD, Antic NA, Heeley E, Luo Y, Ou Q, Zhang X, et al; SAVE Investigators and Coordinators. CPAP for prevention of cardiovascular events in obstructive sleep apnea. N Engl J Med. 2016;375:919-31. [PMID: 27571048] doi:10.1056/NEJMoa1606599

H

Item 17 Answer: B

Educational Objective: Treat a patient with obesity hypoventilation syndrome and hypercarbic respiratory failure who does not improve quickly with noninvasive ventilation.

The most appropriate treatment is endotracheal intubation. This patient has developed acute on chronic hypercapnic respiratory failure in the setting of obesity hypoventilation syndrome. In a patient who is able to protect the airway, the initial management of acute hypercapnic respiratory failure due to obesity hypoventilation syndrome includes noninvasive positive pressure ventilation. Because he has an intact gag and cough reflex and is arousable, noninvasive positive pressure ventilation was an appropriate initial choice. However,

H CONT.

when patients cannot protect their airway, do not tolerate bilevel positive airway pressure, or do not improve quickly, such as this patient, early intubation should be considered.

Respiratory stimulants such as acetazolamide have been considered adjunctive therapies of last resort for patients who chronically continue to have hypoventilation despite BPAP therapy and weight loss. Acetazolamide, by blocking carbon dioxide conversion to bicarbonate, can lower pH in the brain and theoretically increases central ventilatory drive. This patient already demonstrates significant acidemia with inadequate central respiratory drive. In addition, randomized trials demonstrating efficacy are lacking. Thus, acetazolamide is not recommended for either acute or chronic hypercapnic respiratory failure.

Although many patients with morbid obesity demonstrate features of obstruction or air trapping on pulmonary function testing, only a fraction have true reversible obstructive airways disease pathology. This patient has no clear evidence of obstruction on examination or chest radiograph and no history of asthma or other obstructive airways pathology. Therefore, prednisone use in this setting is not indicated.

Theophylline is a bronchodilator as well as a direct respiratory stimulant. Its use in obesity hypoventilation syndrome has never been studied and thus is not recommended for treatment of this or other hypercapnic states.

KEY POINT

- Early intubation is indicated for patients with obesity hypoventilation syndrome and hypercapnic respiratory failure who do not improve with noninvasive positive pressure ventilation.

Bibliography

Manthous CA, Mokhlesi B. Avoiding management errors in patients with obesity hypoventilation syndrome. Ann Am Thorac Soc. 2016;13:109-14. [PMID: 26512908] doi:10.1513/AnnalsATS.201508-562OT

Item 18 Answer: A

Educational Objective: Diagnose a patient with α_1-antitrypsin deficiency.

An α_1-antitrypsin level should be obtained. This patient is younger than the usual age of presentation of COPD, and he does not have a significant smoking history. In this situation it is prudent to rule out other causes of dyspnea, especially in a patient where a diagnosis of COPD is unexpected. White patients experiencing symptoms of COPD and who are younger than 45 years of age or have a strong family history of COPD should be tested for α_1-antitrypsin deficiency. Several guidelines even recommend that all patients with COPD regardless of age should be tested for α_1-antitrypsin deficiency after weighing the risks and benefits of testing. Patients with this disorder are often misdiagnosed with asthma for many years. They may have a modest smoking history and basilar emphysema (although they may present with any pattern of emphysema), and they may have concurrent liver disease. Patients with α_1-antitrypsin deficiency who never smoke may develop symptoms later in life. If the diagnosis of α_1-antitrypsin deficiency is confirmed, α_1-antitrypsin augmentation therapy may slow disease progression, although data on its efficacy are limited.

Nitric oxide promotes dilation of bronchial blood vessels and airways. The *fractional exhaled nitric oxide (FENO)* is a noninvasive test most commonly used in patients with severe airflow obstruction when other techniques are difficult to perform (for example, assessing airflow in a child or mentally impaired adult). High levels of FENO are typically associated with asthma and other inflammatory airway conditions. Measurement of FENO is not indicated as the next diagnostic test in this patient with a history strongly suspicious for α_1-antitrypsin deficiency.

High-resolution CT (HRCT) is indicated if diffuse parenchymal lung disease is suspected. HRCT can help narrow the differential diagnosis based on the distribution of the lung parenchymal abnormalities and the presence or absence of associated findings. Diffuse parenchymal lung disease should be suspected in the presence of restrictive or combined obstructive/restrictive diseases. HRCT is also diagnostically definitive for bronchiectasis, but this condition is typically characterized by cough and voluminous, often purulent, sputum production, which is not present in this patient.

A vascular endothelial growth factor-D level can help in the diagnosis of lymphangioleiomyomatosis (LAM). However, LAM is a cystic lung disease that mostly affects young women, so testing would not be indicated for this patient.

KEY POINT

- Measurement of α_1-antitrypsin level is indicated for white patients experiencing symptoms of COPD and who are younger than 45 years of age or have a strong family history of COPD.

Bibliography

American Thoracic Society. American Thoracic Society/European Respiratory Society statement: standards for the diagnosis and management of individuals with alpha-1 antitrypsin deficiency. Am J Respir Crit Care Med. 2003;168:818-900. [PMID: 14522813]

Item 19 Answer: C

Educational Objective: Treat a patient for side effects of positive airway pressure therapy.

The most appropriate treatment is heated humidification. A common complication of positive airway pressure therapy is desiccation of the nasopharyngeal mucosa by the forced air, often resulting in throat irritation and nasal congestion. In-line heated humidification, available on all positive airway pressure machines, is a simple intervention to mitigate mucosal irritation. Patients can control the temperature and degree of humidity. Although there is conflicting evidence that in-line humidification improves adherence to positive airway pressure therapy, it does mitigate upper airway symptoms.

Bilevel positive airway pressure is indicated for hypoventilation syndromes caused by severe COPD or neuromuscular weakness. There is no evidence that bilevel positive airway pressure is superior to continuous positive airway pressure for the treatment of obstructive sleep apnea without hypoventilation. This patient does not suffer from a hypoventilation syndrome, and he is improving on current therapy; therefore, a change in therapy is not indicated. Finally, bilevel positive airway pressure without humidification will not relieve his upper airway symptoms.

The role of hypnotics in promoting positive airway pressure adherence is controversial and not generally recommended. One study showed nightly eszopiclone (a benzodiazepine receptor agonist) administered to unselected patients during the first 2 weeks of continuous positive airway pressure treatment improved adherence as long as 6 months later. Its continued use beyond initiation of positive airway pressure treatment has not been studied and the risk of side effects may outweigh its benefit. Finally, eszopiclone will not relieve this patient's throat irritation or nasal congestion.

Topical nasal steroids are often prescribed to reduce these side effects of nasal congestion and rhinorrhea, but evidence supporting their effectiveness in reducing upper airway symptoms is sparse. A recent randomized clinical study failed to show a reduction in nasal symptoms or improved adherence to therapy in patients treated with nasal fluticasone compared to placebo.

KEY POINT

- In-line heated humidification is available on all positive airway pressure machines and is a simple intervention to mitigate mucosal irritation.

Bibliography

Sommer JU, Kraus M, Birk R, Schultz JD, Hörmann K, Stuck BA. Functional short- and long-term effects of nasal CPAP with and without humidification on the ciliary function of the nasal respiratory epithelium. Sleep Breath. 2014;18:85-93. [PMID: 23657665] doi:10.1007/s11325-013-0853-0

Item 20 Answer: C

Educational Objective: Treat a patient with eosinophilic asthma with mepolizumab.

The most appropriate treatment is initiation of a trial of mepolizumab therapy. This patient has signs and symptoms of severe persistent asthma that is uncontrolled (more than two exacerbations per year), despite treatment with a high-dose inhaled glucocorticoid, long-acting β_2-agonist, long-acting anticholinergic agent, leukotriene-receptor antagonist, and oral glucocorticoids, so her therapy should be stepped up. Biologic therapies that target atopic pathways of asthma are indicated in appropriate patients. Currently available agents are directed against either eosinophils or their products (IgE). Interleukin (IL-5) is a pro-eosinophilic cytokine that promotes eosinophil production and contributes to eosinophilic inflammation in the airways. Mepolizumab and reslizumab are monoclonal antibodies to IL-5 and both agents reduce exacerbations of severe asthma in patients who have blood eosinophil counts of 150/µL or 300/µL, respectively, or higher. Mepolizumab is administered subcutaneously every 4 weeks, whereas reslizumab is an infusion. Although these agents are expensive, patients with uncontrolled eosinophilic asthma treated with mepolizumab have reduced emergency department visits and hospitalizations, and both agents have reduced the requirement for inhaled and oral glucocorticoids. Use of these agents is contraindicated during acute asthma exacerbations.

Treatment with doxycycline is not indicated because there are no signs or symptoms of bacterial infection.

Changing from one inhaled glucocorticoid/long-acting β_2-agonist to another would not be expected to have a significant effect, as the inhaled glucocorticoid dose is similar and there is no apparent difference in the efficacy of the various combinations.

Omalizumab, a humanized monoclonal antibody directed at IgE, was the first biologic agent approved by the FDA for use in asthma. Administered subcutaneously every 2 to 4 weeks, omalizumab is indicated in patients with moderate to severe persistent asthma with the following characteristics: (1) symptoms inadequately controlled with inhaled glucocorticoids, (2) evidence of allergies to perennial aeroallergens, and (3) serum IgE levels between 30 and 700 U/mL (30-700 kU/L) (normal range, 0-90 U/mL [0-90 kU/L]). Omalizumab has been shown to reduce exacerbations and emergency department visits; it is not indicated for use in patients other than those meeting these treatment parameters.

KEY POINT

- In patients with moderate to severe uncontrolled asthma with the eosinophilic phenotype, treatment with mepolizumab can reduce emergency department visits, hospitalizations, and requirements for inhaled and oral glucocorticoids.

Bibliography

Israel E, Reddel HK. Severe and difficult-to-treat asthma in adults. N Engl J Med. 2017;377:965-976. [PMID: 28877019] doi:10.1056/NEJMra1608969

Item 21 Answer: D

Educational Objective: Treat severe carbon monoxide poisoning with hyperbaric oxygen therapy.

H

This patient should receive hyperbaric oxygen therapy. Inhaled carbon monoxide has a much higher affinity for hemoglobin binding sites than oxygen and readily forms carboxyhemoglobin, which is an ineffective oxygen transporter and results in reduced tissue oxygen content. Symptoms of carbon monoxide poisoning vary and include headache, confusion, nausea, vomiting, and, in severe cases, loss of consciousness. It is important to understand that carboxyhemoglobin does not lower oxygen saturation measured by standard pulse oximetry or reduce arterial P_{O_2} determined by blood gas analysis.

H CONT.

Co-oximetry, which measures carboxyhemoglobin levels, is used to make the diagnosis. She has severe carbon monoxide poisoning due to unvented combustion in a small, enclosed area. Cited indications for hyperbaric oxygen therapy include loss of consciousness, ischemic cardiac changes, neurological deficits, significant metabolic acidosis, or carboxyhemoglobin level greater than 25%. A carboxyhemoglobin level of 50% is critical and needs to be reduced as quickly as possible. Breathing 100% oxygen at normal atmospheric pressure, this patient will clear the carboxyhemoglobin with a half-life of 90 minutes, but hyperbaric oxygen therapy will lower the half-life to 30 minutes. Also, there is considerable risk of delayed neurocognitive impairment following a severe exposure such as this, and hyperbaric oxygen is believed to lower the risk of this long-term complication, although the strength of this evidence is disputed.

Maintaining the current ventilator settings of 50% oxygen or decreasing the oxygen to 30% will not clear the carboxyhemoglobin as rapidly as hyperbaric oxygen. If hyperbaric oxygen therapy is unavailable, or if the toxicity is less severe, administration of 100% oxygen is the most appropriate therapy. However, this patient has mental status changes and the carboxyhemoglobin level is 50%; hyperbaric treatment is clearly indicated.

Carbon monoxide poisoning resulting from smoke inhalation should prompt consideration of concomitant inhaled cyanide poisoning. Hydroxocobalamin effectively binds intracellular cyanide to form cyanocobalamin, which poses no harm. However, this patient's carbon monoxide poisoning is due to combustion of propane in an enclosed space, not a house fire; therefore, hydroxocobalamin is not indicated.

KEY POINT

- Cited indications for hyperbaric oxygen therapy include loss of consciousness, ischemic cardiac changes, neurological deficits, significant metabolic acidosis, or carboxyhemoglobin level greater than 25%.

Bibliography

Hampson NB, Piantadosi CA, Thom SR, Weaver LK. Practice recommendations in the diagnosis, management, and prevention of carbon monoxide poisoning. Am J Respir Crit Care Med. 2012;186:1095-101. [PMID: 23087025] doi:10.1164/rccm.201207-1284CI

H

Item 22 Answer: A

Educational Objective: Evaluate a patient who has an acute exacerbation of COPD with arterial blood gas analysis.

Arterial blood gas analysis is the most appropriate test for this patient with a COPD exacerbation. An exacerbation is considered mild when a change in the clinical condition is noted but no change in medication is necessary; moderate when medication changes are made; and severe if emergency department evaluation or hospitalization is required. A severe exacerbation can also be diagnosed if the patient has two of the three following symptoms: increased dyspnea, increased sputum volume, or increased sputum purulence. Studies helpful in the evaluation of a severe exacerbation may include pulse oximetry to assess oxygenation or guide oxygen therapy; a chest radiograph to rule out an alternative diagnosis; a complete blood count to identify the presence of polycythemia, anemia, or leukocytosis; a biochemical panel to assess for electrolyte and glycemic abnormalities; an electrocardiogram to evaluate for a possible cardiac comorbidity; and arterial blood gas analysis. Arterial blood gas analysis is recommended for patients with a severe exacerbation of COPD to assess for hypercapnia and hypoxemia. This information is helpful in determining site of care and the need for additional therapy such as noninvasive mechanical ventilation.

The patient has no signs or symptoms of heart failure or other cardiac disease to explain his presentation. Therefore, B-type natriuretic peptide measurement and echocardiogram are unlikely to change management at this time.

According to best practice advice from the Clinical Guidelines Committee of the American College of Physicians, patients who have a low pretest probability for pulmonary embolism (PE) using a validated clinical prediction rule (such as the Wells criteria for prediction of PE) and who meet all Pulmonary Embolism Rule-Out Criteria do not need further testing to rule out PE. Using the Wells criteria, this patient is a low risk for PE (0 points) and scores 2 points on the Pulmonary Embolism Rule-Out Criteria (fails to meet 2 criteria: age younger than 50 years and oxygen saturation greater than 94%). Additional evaluation for PE in this patient might include a D-dimer measurement as an initial test, but not an imaging study.

KEY POINT

- Arterial blood gas analysis is recommended for patients with a severe exacerbation of COPD to assess for hypercapnia and hypoxemia.

Bibliography

Qureshi H, Sharafkhaneh A, Hanania NA. Chronic obstructive pulmonary disease exacerbations: latest evidence and clinical implications. Ther Adv Chronic Dis. 2014;5:212-27. [PMID: 25177479] doi:10.1177/2040622314532862

Item 23 Answer: C

Educational Objective: Evaluate suspected pulmonary arterial hypertension with transthoracic echocardiography.

The next most appropriate initial test is transthoracic echocardiography. Pulmonary hypertension is easily overlooked because early signs and symptoms, such as exertional dyspnea and fatigue, are nonspecific. As the disorder progresses, right ventricular impairment may be heralded by exertional chest pain, syncope, and peripheral edema. Findings on physical examination depend on the severity of disease. The cardiovascular examination may show jugular venous distention, a prominent jugular venous *a* wave, parasternal heave, a widened split S_2 with a prominent pulmonic component,

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or murmurs of tricuspid regurgitation as the right ventricle dilates. Transthoracic echocardiography is a useful initial tool in the evaluation of suspected pulmonary hypertension as it allows an estimation of pulmonary artery pressures and right heart function as well as an assessment of the left heart. Because echocardiography may underestimate true pulmonary artery pressures, the evaluation should not end with an unrevealing echocardiogram if the index of suspicion for pulmonary hypertension is high. In such cases, right heart catheterization may be confirmatory. Once pulmonary hypertension is confirmed, further testing, guided by clinical history, helps determine identifiable causes. Left heart catheterization can assess coronary flow and left ventricular function. Diagnostic tests for respiratory diseases might include pulmonary function tests, chest imaging, ventilation-perfusion ($\dot{V}/\dot{Q}$) scanning, and overnight pulse oximetry.

High-resolution CT scanning of the chest allows a detailed assessment of the lung parenchyma and is useful in the evaluation of suspected interstitial lung diseases, but is unlikely to be helpful as an initial test in a patient with an unremarkable lung examination and clear lung fields on chest radiograph.

Pulmonary function testing is an important diagnostic test for suspected airways disease such as asthma, COPD, or interstitial lung disease. However, this patient has no symptoms or physical examination findings indicative of either obstructive or restrictive disease. In the patient with isolated pulmonary hypertension, pulmonary function tests demonstrate a reduction in diffusing capacity, which is a nonspecific finding.

$\dot{V}/\dot{Q}$ scanning is the diagnostic test of choice for suspected chronic thromboembolic pulmonary hypertension (CTEPH). Although CTEPH hasn't yet been excluded in this patient, $\dot{V}/\dot{Q}$ scanning would typically be performed after transthoracic echocardiography to first establish the presence of pulmonary hypertension.

KEY POINT

- Transthoracic echocardiography can estimate pulmonary artery pressures and is the preferred initial test if pulmonary hypertension is suspected.

Bibliography

Vonk Noordegraaf A, Groeneveldt JA, Bogaard HJ. Pulmonary hypertension. Eur Respir Rev. 2016;25:4-11. [PMID: 26929415] doi:10.1183/16000617.0096-2015

Item 24 Answer: E

Educational Objective: Manage obesity-related asthma with a supervised weight loss program.

This patient should be referred to a supervised weight loss program. He has poorly controlled asthma despite maximal medical therapy and in the absence of other factors known to exacerbate asthma (environmental triggers, uncontrolled gastroesophageal reflux disease, sinus disease, or obstructive sleep apnea). Obesity is associated with poor asthma control, and the incidence of asthma is 1.47 times greater in obese patients than nonobese patients. Weight loss in patients with obesity-related asthma improves asthma control, lung function, and quality of life; reduces asthma medication use; and should be considered an essential part of the treatment plan.

Addition of beclomethasone is not appropriate because this patient is already on adequate inhaled therapy and glucocorticoids; increasing the inhaled steroid dose is unlikely to be beneficial.

Between attacks and exacerbations of asthma, spirometry can be normal in patients with suspected but undiagnosed asthma. Therefore, a bronchial challenge test, such as a methacholine challenge, may be helpful for diagnosis if positive or make the diagnosis less likely if negative. Methacholine challenge testing is not necessary in this patient because spirometry confirms reversible airflow obstruction (with a 12% or greater improvement in FEV_1 or FVC of 200 mL after administration of a bronchodilator), supporting a diagnosis of asthma.

Mepolizumab is a monoclonal antibody to IL-5 that has been shown to reduce asthma exacerbations in patients with difficult-to-control asthma and elevated blood eosinophil counts. This patient's eosinophil count was normal; therefore, add-on therapy with mepolizumab is not indicated.

Although omalizumab can reduce hospitalizations when added to standard therapy, it is a monoclonal antibody used for treatment of allergic asthma, and it targets elevated levels of IgE. Because this patient does not have a history of allergies and his IgE level is normal, treatment with omalizumab would not be appropriate.

KEY POINT

- Weight loss in patients with obesity-related asthma improves asthma control, lung function, and quality of life; reduces asthma medication use; and should be considered an essential part of the treatment plan.

Bibliography

Pakhale S, Baron J, Dent R, Vandemheen K, Aaron SD. Effects of weight loss on airway responsiveness in obese adults with asthma: Does weight loss lead to reversibility of asthma? Chest. 2015;147:1582-1590. [PMID: 25763936] doi:10.1378/chest.14-3105

Item 25 Answer: C

Educational Objective: Treat heart failure in a patient with a Cheyne-Stokes breathing pattern.

Diuresis with furosemide is the most appropriate treatment option. This patient has central sleep apnea with Cheyne-Stokes breathing in the setting of decompensated heart failure, a state of ventilatory instability. Cheyne-Stokes breathing is an abnormal respiratory pattern characterized by cyclic crescendo-decrescendo respiratory effort during sleep (and sometimes during wakefulness), in the absence of upper airway obstruction. Apnea accompanying the decrescendo effort defines central sleep apnea. The degree of central sleep apnea tends to correlate with left ventricular dysfunction.

This patient has evidence on examination of volume overload (crackles and wheezing on lung exam, jugular venous distention, peripheral edema). Optimizing medical management of heart failure and improving fluid balance should precede other therapies for sleep apnea.

Adaptive servo-ventilation is a form of positive airway pressure therapy initially designed as a treatment of Cheyne-Stokes breathing. However, a large multicenter trial unexpectedly showed increased mortality in a subset of patients with systolic heart failure (left ventricular ejection fraction less than 45%) and central sleep apnea treated with adaptive servo-ventilation.

Auto-adjusting positive airway pressure is not an initial treatment for central sleep apnea. It is used to treat obstructive sleep apnea, where proprietary algorithms deliver varying pressure sufficient to prevent upper airway closure.

Supplemental oxygen is sometimes used in advanced heart failure where impaired gas exchange results in hypoxemia. This patient has preserved oxyhemoglobin saturation. Small trials have studied the use of nocturnal supplemental oxygen in the setting of central sleep apnea, with variable results. Such treatment would be premature before optimization of fluid status.

KEY POINT

- Initial treatment of central sleep apnea should target modifiable risk factors; medical optimization of heart failure has been shown to improve central sleep apnea and Cheyne-Stokes breathing and should precede other therapies for sleep apnea.

Bibliography

Hernandez AB, Patil SP. Pathophysiology of central sleep apneas. Sleep Breath. 2016;20:467-82. [PMID: 26782104] doi:10.1007/s11325-015-1290-z

Item 26 Answer: B

Educational Objective: Treat asthma-COPD overlap syndrome.

The most appropriate treatment is a combination inhaled glucocorticoid and a long-acting β_2-agonist. This patient has progressive symptoms, spirometry showing diminished FEV_1 that partially reversed with bronchodilation, and eosinophilia. Several diagnostic terms have been used to describe patients with both asthma and COPD, most including the word *overlap*, but there is no universally agreed upon term or defining diagnostic features for this condition. Given her progression of symptoms, her short-acting inhaler therapy should be augmented. Although a long-acting β_2-agonist is indicated in symptomatic patients with COPD and an FEV_1 of less than 60% of predicted, this may not be the best treatment for a patient with asthma. Patients with asthma are at increased risk of mortality when a long-acting bronchodilator is prescribed without a controller medication. Experts recommend that patients who have an asthma-COPD overlap syndrome who are receiving a long-acting bronchodilator should ideally also be prescribed an inhaled glucocorticoid. Combination therapy seems to mitigate the excess risk of mortality observed in patients with asthma treated with long-acting β_2-agonist monotherapy. Therefore, the patient should be started on a combination therapy of an inhaled glucocorticoid and a long-acting β_2-agonist.

Chronic macrolide therapy can reduce the incidence of acute exacerbations but this patient has not had any exacerbations to warrant starting a macrolide.

Using a long-acting β_2-agonist or a long-acting muscarinic agent/long-acting β_2-agonist combination inhaler is likely not indicated for this patient with asthma-COPD overlap syndrome based on current guidelines. Long-acting bronchodilators should only be used in combination with inhaled glucocorticoids in patients with a history of asthma. Using long-acting bronchodilators alone has been linked to increased risk of asthma-related deaths.

KEY POINT

- Patients with a history of asthma-COPD overlap syndrome should not be prescribed a long-acting β_2-agonist without concurrent therapy with an inhaled glucocorticoid because of the increased risk of mortality in patients with asthma who are prescribed long-acting β_2-agonist monotherapy.

Bibliography

GINA/GOLD Joint Report. 2015 asthma, COPD and asthma-COPD overlap syndrome (ACOS) [Internet] Bethesda: Global Initiative for Asthma; 2016. Available from: http://ginasthma.org/asthma-copd-and-asthma-copdoverlap-syndrome-acos/. Accessed May 1, 2018.

Item 27 Answer: C

Educational Objective: Diagnose pneumothorax in a patient with lung disease in the setting of air travel.

The most likely diagnosis is pneumothorax. An estimated 12% of in-flight medical emergencies involve a respiratory complaint. Commercial airline cabins are partially pressurized, typically to the equivalent of approximately 1400 to 2500 meters (4000 to 8000 feet) above sea level, limiting exposure to extreme hypobaric conditions. The risk of pneumothorax is therefore mitigated but it is most likely to occur at cruising altitude in patients with bullous lung disease, particularly those with a recent exacerbation of airways disease who are, therefore, more prone to air trapping. Pain is typically pleuritic; dyspnea may be present, depending upon the volume of trapped air. If tension physiology develops (hypotension, shock, altered mental status), needle thoracostomy using the on-board equipment can be life-saving. Descending to a lower altitude may also be beneficial, because cabin pressure is inversely related to the altitude of the aircraft.

Descending aortic dissection typically presents with acute, severe back pain. Although chest pain can occur, it is less common. Radiation of pain to the abdomen can occur with disruption of blood flow to the abdominal viscera. Hypertension is the most important risk factor and is

present in more than half of patients with descending aortic dissection. Pulse deficits are common. However, this patient does not have a history of hypertension and has normal peripheral pulses, making a diagnosis of descending aortic dissection unlikely.

Pneumocystis jirovecii pneumonia is unlikely to present in this manner. Although systemic glucocorticoids increase the risk for opportunistic lung infections such as *P. jirovecii* pneumonia, the risk is minimal during the course of a typical prednisone burst and taper used for a COPD exacerbation. In general, those taking prednisone dosage equivalents of at least 20 mg/day for more than 3 weeks should receive *P. jirovecii* pneumonia prophylaxis.

Air travel increases the risk of venous thromboembolism, though the risk is higher during relative immobilization on long flights and in those with other risk factors, such as cancer. The risk of pulmonary embolism does not really increase until the flight distance becomes greater than 5000 km (3000 miles). It is unlikely that a flight duration of only 90 minutes would heighten thrombotic risk in this patient.

KEY POINT

- During air travel, pneumothorax is most likely to occur at cruising altitude in patients with bullous lung disease, particularly those with a recent exacerbation of airways disease who are, therefore, more prone to air trapping.

Bibliography

Nable JV, Tupe CL, Gehle BD, Brady WJ. In-flight medical emergencies during commercial travel. N Engl J Med. 2015;373:939-45. [PMID: 26332548] doi:10.1056/NEJMra1409213

Item 28 Answer: B

Educational Objective: Evaluate a patient with upper-lobe emphysema and significant exercise limitations for lung volume reduction surgery.

Evaluation for lung volume reduction surgery is the most appropriate management for this patient with upper lobe emphysema, significant exercise limitation, and poor quality of life. Lung volume reduction surgery excises areas of emphysematous lung, improves the mechanical efficiency of respiratory muscles, and increases the elastic recoil of the lungs to improve expiratory flow and reduce exacerbations. The National Emphysema Treatment Trial (NETT) demonstrated that carefully selected patients with upper lobe predominant emphysema and significant exercise limitation despite participation in a pulmonary rehabilitation program had improved quality of life and survival with lung volume reduction surgery. Symptomatic improvement with the surgery appears to be durable.

Roflumilast is an oral selective phosphodiesterase-4 inhibitor. It is used primarily as add-on therapy in severe COPD associated with chronic bronchitis and a history of recurrent exacerbations despite other therapies; it has been shown to relieve symptoms and reduce risk and frequency of exacerbations in these individuals. However, it is not a bronchodilator, is expensive, and has not been shown to be effective in other groups of patients with COPD. It is not indicated in the treatment of primary emphysema and has not been shown to decrease exertional dyspnea and would not benefit this patient.

Although patients with chronic lung conditions can develop pulmonary hypertension, this patient had an unremarkable echocardiogram and has no evidence of pulmonary hypertension on examination. Therefore, proceeding with a right heart catheterization is unnecessary and unlikely to change management at this time.

This patient has already participated in a pulmonary rehabilitation program. Although it is helpful for patients to continue exercise, restarting a formal pulmonary rehabilitation program is unlikely to provide him with any more significant symptomatic improvement.

KEY POINT

- Lung volume reduction surgery improves quality of life and survival for patients with upper-lobe predominant emphysema and significant exercise limitations.

Bibliography

Ginsburg ME, Thomashow BM, Bulman WA, Jellen PA, Whippo BA, Chiuzan C, et al. The safety, efficacy, and durability of lung volume reduction surgery: a 10-year experience. J Thorac Cardiovasc Surg. 2016;151:717-724.e1. [PMID: 26670190] doi:10.1016/j.jtcvs.2015.10.095

Item 29 Answer: D

Educational Objective: Diagnose COPD with spirometry.

This patient's symptoms are consistent with a possible diagnosis of COPD and spirometry should be performed. Spirometric evaluation is required for the clinical diagnosis of COPD. Spirometry is warranted in any patient presenting with dyspnea, chronic cough, or sputum production. Screening for COPD with spirometry should not be performed in asymptomatic patients. For diagnosis of COPD, spirometry should be performed both before and after administration of an inhaled bronchodilator. A postbronchodilator FEV_1/FVC of less than 0.70 is diagnostic of airflow obstruction that is not completely reversible with bronchodilator therapy and is consistent with a diagnosis of COPD.

Diagnostic testing for structural heart disease should be based on a thorough history and physical examination. New murmurs or a change in examination findings or symptoms in a patient with known structural heart disease should prompt further evaluation. The patient's examination is not consistent with pulmonary hypertension, heart failure, or valvular disease. Therefore, an echocardiogram is unlikely to be helpful.

In patients with a previous history of coronary artery disease and worsening cardiac symptoms, stress testing is helpful to assess for possible recurrent or progressive disease. Given this patient's cough, which would be an unusual presentation of heart disease in the absence of volume

overload, a diagnosis of COPD is much more likely and should be investigated further. A cardiac stress test could be considered if his evaluation is otherwise unremarkable.

Although interstitial lung disease can present with similar symptoms, the absence of pulmonary crackles and normal chest radiograph do not support this diagnosis. Therefore, a high-resolution chest CT is currently not indicated.

KEY POINT

- A postbronchodilator FEV_1/FVC of less than 0.70 is diagnostic of airflow obstruction and is consistent with the diagnosis of COPD.

Bibliography

Qaseem A, Wilt TJ, Weinberger SE, Hanania NA, Criner G, van der Molen T, et al; American College of Physicians. Diagnosis and management of stable chronic obstructive pulmonary disease: a clinical practice guideline update from the American College of Physicians, American College of Chest Physicians, American Thoracic Society, and European Respiratory Society. Ann Intern Med. 2011;155:179-91. [PMID: 21810710] doi:10.7326/0003-4819-155-3-201108020-00008

H Item 30 Answer: D

Educational Objective: Manage a patient with progressive idiopathic pulmonary fibrosis with palliative care.

This patient should receive palliative care including morphine for the symptom of dyspnea. Idiopathic pulmonary fibrosis (IPF) is the most common idiopathic interstitial pneumonia. It occurs predominantly in older individuals. Prognosis is poor, and individuals diagnosed with IPF have an estimated average survival of 3 to 5 years. The most common cause of death in IPF is respiratory failure. Patients with IPF may experience an acute exacerbation of IPF, diagnosed when the chest radiograph shows new alveolar infiltrates and medical evaluation does not reveal another cause for dyspnea such as infection, heart failure, or pulmonary embolism. Despite maximal supportive care during the past 5 days, this patient has progressed and is now on the brink of respiratory failure. Lung transplantation has been shown to provide a survival advantage in select patients with IPF. This patient gives a history consistent with severe and prolonged deconditioning associated with chronic respiratory failure. She now presents with frank respiratory failure and rapid progression of IPF with an unclear trigger. Consideration for transplant typically includes a full assessment of the patient for evidence of additional organ disease and education regarding the risks and benefits of the procedure. This is best accomplished long before the development of an acute exacerbation. Because of this patient's age, functional status, and lack of previous assessment by a transplant center, lung transplantation is not a viable option for her. At this time, she remains awake and alert and is able to participate in her end-of-life decision making. Patients with this presentation and functional status do not typically respond favorably to intubation and mechanical ventilation and, as such, recommending palliative medicines and comfort measures is most appropriate.

Although high-dose glucocorticoids are often used for acute exacerbation, their efficacy remains unknown. This patient has already been treated with glucocorticoids without apparent improvement; this indicates that administration of additional glucocorticoids is not likely to be of benefit.

Albuterol is a bronchial vasodilator. Unfortunately, the limitation in patients with IPF that results in hypoxemia and dyspnea is at the level of the interstitium, and bronchial dilators have little effect on these symptoms.

For individuals who develop severe respiratory distress that has no underlying reversible cause, supportive mechanical ventilation is of little long-term benefit. Therefore, the most recent evidence-based consensus statement recommends against mechanical ventilation for individuals with acute respiratory failure due to either progression or an acute exacerbation of IPF. In these circumstances, the focus should be on palliation of the patient's underlying dyspnea.

KEY POINT

- For individuals with idiopathic pulmonary fibrosis who develop severe respiratory distress that has no underlying reversible cause, supportive mechanical ventilation is of little long-term benefit; in these circumstances, the focus should be on palliation of the patient's underlying dyspnea.

Bibliography

Raghu G, Collard HR, Egan JJ, Martinez FJ, Behr J, Brown KK, et al; ATS/ERS/JRS/ALAT Committee on Idiopathic Pulmonary Fibrosis. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. Am J Respir Crit Care Med. 2011;183:788-824. [PMID: 21471066] doi:10.1164/rccm.2009-040GL

Item 31 Answer: C

Educational Objective: Evaluate a patient with diffuse cutaneous systemic sclerosis for diffuse parenchymal lung disease.

This patient should receive a high-resolution CT (HRCT) scan of the chest. She has a history of diffuse cutaneous systemic sclerosis and has a chronic cough and dyspnea concerning for the possibility of scleroderma-associated interstitial lung disease. The most common cause of death from scleroderma is no longer kidney disease but progressive respiratory failure due to diffuse parenchymal lung disease. Among patients with the scleroderma spectrum disorders, patients with diffuse cutaneous systemic sclerosis and anti-Scl antibodies have the highest risk of interstitial lung disease. The most common pathologic finding in such patients is nonspecific interstitial pneumonia (NSIP). This patient has physiologic evidence of parenchymal lung disease with a mild restrictive defect and exercise-induced oxygen desaturation. Chest radiography can often miss mild disease and in these cases more advanced imaging is required. HRCT findings associated with NSIP include peripheral and basal predominant ground-glass opacities (cellular form) that spare the subpleural areas,

basal predominant septal line thickening, and traction bronchiectasis in the fibrotic form.

Results of a 6-minute walk test (6MWT) are helpful to assess disability and prognosis in chronic lung conditions. During a 6MWT, oxygen saturation, heart rate, dyspnea and fatigue level, and distance walked in 6 minutes are recorded. The 6MWT is routinely used before, during, and after pulmonary rehabilitation programs. It would not be helpful in this patient with probable interstitial lung disease.

Cardiopulmonary exercise testing is routinely performed to assess prognosis in patients being evaluated for transplantation. Patients with low oxygen consumption or a high ratio of ventilation-to-carbon dioxide production have a poor 1-year prognosis. It may also be helpful in detecting deconditioning as a cause of dyspnea of unclear cause. It would not be appropriate in this patient with known restrictive lung disease.

Patients with a pulmonary nodule or other findings suggestive of malignancy may require PET/CT. This test most commonly uses fluorodeoxyglucose as a metabolic marker to identify rapidly dividing cells such as tumor cells and, to a lesser degree, any inflammatory lesion. It has no role in the evaluation on this patient with probable interstitial lung disease.

KEY POINT

- Patients with diffuse cutaneous systemic sclerosis are at high risk for the development of diffuse parenchymal lung disease, which is the leading cause of death in these patients.

Bibliography

Suliman S, Al Harash A, Roberts WN, Perez RL, Roman J. Scleroderma-related interstitial lung disease. Respir Med Case Rep. 2017;22:109-112. [PMID: 28761806] doi:10.1016/j.rmcr.2017.07.007

Item 32 Answer: D

Educational Objective: Diagnose cough-variant asthma.

The most appropriate management is to perform methacholine challenge testing. This patient has a chronic cough with no cause identified by history or physical examination, and a normal chest radiograph. In such patients who are not taking ACE inhibitors and are not exposed to environmental irritants or tobacco smoke, the most common causes are asthma, gastroesophageal reflux disease (GERD), and rhinosinusitis. Cough-variant asthma refers to asthma in which the predominant manifestation is cough, without other typical asthma symptoms such as wheezing, breathlessness, and chest tightness. Although most patients with asthma have obstructive physiology on pulmonary function testing, in those patients with normal spirometry, methacholine challenge testing is indicated to evaluate for bronchial hyperreactivity, which supports a diagnosis of asthma. Bronchial challenge testing uses a controlled inhaled stimulus to induce bronchospasm in association with spirometry; a positive test is indicated by a drop in the measured FEV_1. Methacholine is a commonly used agent that induces cholinergic bronchospasm at low concentrations in patients with asthma; levels of exhaled nitric oxide may also be elevated. Positive methacholine testing is not specific enough to diagnose asthma; therefore, patients with cough and a positive methacholine challenge must also respond clinically to treatment with asthma therapies to be considered to have cough-variant asthma.

Although an empiric trial of asthma treatment with budesonide and albuterol could be considered, expert consensus indicates that it is preferable to first establish a diagnosis to avoid making an incorrect diagnosis and prescribing unnecessary or incorrect treatment.

Esophageal manometry and 24-hour pH testing would not be appropriate because the patient has no symptoms of GERD. Current guidelines suggest an empiric trial of diet and lifestyle modification for cough due to GERD before invasive testing for the disease.

A high-resolution CT scan of the chest would be indicated in some patients with chronic cough to evaluate for interstitial lung disorders or bronchiectasis, but the chest radiograph and physical examination findings are normal and the more common condition of asthma should be excluded first.

KEY POINT

- Cough-variant asthma refers to asthma in which the predominant manifestation is cough, and without other typical asthma symptoms; the diagnosis is supported by abnormal spirometry or methacholine challenge testing if spirometry is normal.

Bibliography

Kahrilas PJ, Altman KW, Chang AB, Field SK, Harding SM, Lane AP, et al; CHEST Expert Cough Panel. Chronic cough due to gastroesophageal reflux in adults: CHEST Guideline and Expert Panel Report. Chest. 2016;150:1341-1360. [PMID: 27614002] doi:10.1016/j.chest.2016.08.1458

Item 33 Answer: B

H

Educational Objective: Treat a patient with shock using a peripheral wide-bore catheter.

The most appropriate treatment is to insert a peripheral wide-bore central venous catheter. This patient is in shock with several possible causes. Flow of fluid through a catheter is inversely proportional to catheter length and proportional to the radius of the catheter to the fourth power. Therefore, the highest flow rates may be achieved through shorter, large-bore catheters. Peripheral intravenous (IV) catheters are shorter and larger than catheters used for central access or peripherally inserted central catheters and can deliver high volumes of fluid rapidly. For this reason, use of larger, shorter peripheral catheters is preferred for fluid resuscitation in patients requiring emergent treatment. However, peripheral IV catheters can sometimes be difficult to insert in patients in shock, and intraosseous ports and central venous catheters are the alternatives.

Intraosseous ports provide rapid access, but this patient has osteoporosis, which is a contraindication to this method.

H CONT.

When used, an initial dose of lidocaine is needed before infusing because pain levels are very high with initial flushes and infusion.

Subcutaneous intravenous ports are long and small bore, which makes them useful for blood draws and small-volume infusion administration but not for rapid, large-volume fluid resuscitation.

A triple-lumen central catheter is an acceptable alternative when no other intravenous access can be obtained; however, it takes longer to insert compared to a peripheral wide-bore central venous catheter. When used, care should be taken to choose wider-bore catheters to overcome the flow restriction from longer lengths.

KEY POINT

- Peripheral wide-bore venous catheters are the preferred method for rapid intravenous administration of large amounts of fluids.

Bibliography

Khoyratty SI, Gajendragadkar PR, Polisetty K, Ward S, Skinner T, Gajendragadkar PR. Flow rates through intravenous access devices: an in vitro study. J Clin Anesth. 2016;31:101-5. [PMID: 27185686] doi:10.1016/j.jclinane.2016.01.048

H

Item 34 Answer: B

Educational Objective: Diagnose pulmonary embolism as a potential trigger for acute COPD exacerbations.

This patient should undergo CT pulmonary angiography. Some COPD exacerbations thought to be of unknown cause may actually be due to other medical conditions, including a pulmonary embolism (PE). A meta-analysis suggests that the prevalence of PE in patients hospitalized for an acute COPD exacerbation is as high as 25%. Testing for PE is indicated for patients who are not responding to typical therapy for acute exacerbations unless the pretest probability for PE is unlikely. Other important entities in the differential diagnosis with high risk for mortality include heart failure and pneumonia. These entities are less likely in this patient because of the absence of fever, crackles, edema, normal chest radiograph, and normal B-type natriuretic peptide level.

Spirometry usually does not change management during an acute exacerbation. In addition, the patient may not be able to complete the testing given his symptoms and the increased work of breathing.

Evaluation for influenza may be useful in patients who present with compatible symptoms, including fever, headache, myalgia, pharyngeal irritation, and respiratory symptoms (nonproductive cough and nasal discharge), particularly during an influenza outbreak. During a confirmed local influenza outbreak, infection can be reliably diagnosed on the basis of clinical criteria alone. When confirmation is needed, polymerase chain reaction testing can be performed. Testing for influenza in this patient is not necessary in the absence of influenza symptoms.

Similarly, a sputum culture is usually not indicated as it infrequently changes management of COPD. An antibiotic is often added because infections are the most common triggers for an acute exacerbation.

KEY POINT

- Patients who are not responding to typical therapy for COPD exacerbations should be carefully evaluated for heart failure, pneumonia, and pulmonary embolism.

Bibliography

Aleva FE, Voets LWLM, Simons SO, de Mast Q, van der Ven AJAM, Heijdra YF. Prevalence and localization of pulmonary embolism in unexplained acute exacerbations of COPD: a systematic review and meta-analysis. Chest. 2017;151:544-554. [PMID: 27522956] doi:10.1016/j.chest.2016.07.034

Item 35 Answer: C

Educational Objective: Evaluate a solitary pulmonary nodule in a patient at high risk for malignancy.

Definitive treatment is recommended for this patient and, therefore, a surgical wedge resection is appropriate. She has several risk factors for malignancy, including age, size of the nodule, upper-lobe location of the nodule, smoking history, and history of malignancy. In addition, the PET/CT scan showed fludeoxyglucose avidity, confirming the high probability of malignancy but without evidence of distant metastasis. As with subcentimeter nodules, the availability of previous imaging of the chest to assess the stability or growth of these lesions is helpful. An enlarging or new pulmonary nodule warrants more aggressive evaluation with tissue diagnosis or excision depending on the nodule's pretest probability of malignancy. The first step when evaluating a solid pulmonary nodule that is larger than 8 mm is to estimate the probability of malignancy. This can be done either clinically or using quantitative models and should place the patient in one of three categories: low probability (less than 5%), intermediate probability (5% to 65%), or high probability (greater than 65%). This is most useful when nodules are 8-30 mm. If the lesion is larger than 30 mm, the likelihood of malignancy is so high that it typically is resected; in contrast, when the lesion is smaller than 8 mm, the likelihood of malignancy is low and the patient should undergo routine radiological surveillance with serial CT scans.

Biopsy of the nodule or a transthoracic approach is preferred when the probability of malignancy is intermediate (5% to 65%) and would not be appropriate for this patient with a hypermetabolic nodule on PET/CT scan suggesting a high probability of malignancy. Furthermore, the sampling procedure is chosen according to size and location of the nodule, availability, and local expertise. Typically, peripheral nodules are sampled using CT-guided transthoracic needle aspiration, and more central lesions are sampled using bronchoscopic techniques. This lesion is described as peripheral.

Radiologic surveillance with serial CT scans is preferred if the probability of malignancy is low (less than 5%).

This patient's lung nodule is highly suspicious for malignancy on CT/PET scan so sampling with CT-guided transthoracic needle aspiration is not indicated.

KEY POINT

- Patients with a solid indeterminate lung nodule larger than 8 mm and high probability of malignancy should be staged using a PET/CT scan followed by definitive management.

Bibliography

Gould MK, Donington J, Lynch WR, Mazzone PJ, Midthun DE, Naidich DP, et al. Evaluation of individuals with pulmonary nodules: When is it lung cancer? Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2013;143:e93S-e120S. [PMID: 23649456] doi:10.1378/chest.12-2351

Item 36 Answer: A

Educational Objective: Diagnose a patient with asbestosis.

The most likely diagnosis is asbestosis. Asbestosis refers to the pneumoconiosis caused by inhalation of asbestos fibers. Asbestos is a silicate mineral fiber previously used as an insulating material that is a major cause of lung disease. Workers in construction, naval shipyards, and the automotive service industries are particularly at risk for asbestosis, with duration and extent of exposure being the key risk factors for the development of disease. Although asbestos use in the United States has been virtually eliminated since its peak in the 1980s, asbestos-related diseases will persist well into this century owing to the long latency period between exposure and disease development (15 to 35 years). Parietal pleural plaques are the most common finding and differentiate asbestos-induced parenchymal disease from other interstitial lung diseases. Diffuse parenchymal lung disease (DPLD) due to asbestos is related to the extent of the fiber burden. The most common symptom is exertional dyspnea; cough and sputum production are unusual unless the patient is a cigarette smoker. The CT scan imaging of pleural plaques and DPLD combined with the exposure history is adequate to make the diagnosis of asbestosis.

Chronic forms of hypersensitivity pneumonitis are believed to be associated with more chronic low-level exposures to inhaled antigen. This patient's hobby is wood working and wood dust is a potential source of antigen exposure. Patients with chronic hypersensitivity pneumonitis will ultimately present with cough, dyspnea, malaise, and weight loss. High-resolution CT findings include centrilobular micronodules in upper-lung and midlung distribution, as well as evidence of septal line thickening and fibrosis. Pleural plaques are not found. This patient's symptoms and CT findings are not compatible with this diagnosis.

Although this patient has some CT scan findings consistent with idiopathic pulmonary fibrosis, that diagnosis can only be made in a patient who does not have another plausible cause for fibrosis. In addition, the finding of pleural plaques makes idiopathic pulmonary fibrosis unlikely.

Respiratory bronchiolitis-associated DPLD is a disease in active smokers who have imaging findings of centrilobular micronodules. The patient's negative smoking history and presence of pleural plaques on imaging excludes this diagnosis.

KEY POINT

- Parietal plaques are the most common radiologic finding in patients with asbestos exposure and are the features that differentiate asbestosis from other interstitial lung diseases.

Bibliography

Fishwick D, Barber CM. Non-malignant asbestos-related diseases: a clinical view. Clin Med (Lond). 2014;14:68-71. [PMID: 24532750] doi:10.7861/clinmedicine.14-1-68

Item 37 Answer: B

H

Educational Objective: Treat a patient for an acute asthma exacerbation with magnesium sulfate.

The most appropriate treatment is a single dose of magnesium sulfate. This patient is experiencing an acute asthma exacerbation. Treatment of acute asthma exacerbations can be difficult and requires prompt, aggressive management. The cornerstone of therapy in severe acute asthma exacerbation includes early administration of several doses of a short-acting β_2-agonist (SABA), a short-acting muscarinic antagonist (SAMA), and oral or intravenous glucocorticoids. In patients with a moderate to severe asthma exacerbation, combination therapy with a SAMA/SABA has been shown to reduce hospitalizations and improve lung function compared to SABA alone. Although use of a SAMA is not FDA-approved for treatment of an acute asthma exacerbation, several trials have demonstrated efficacy in both children and adults, and its use is supported by guidelines. Magnesium sulfate administration should also be considered early in the course of severe asthma exacerbation given its ability to relax bronchial smooth muscle tissue. A 2014 systematic review concluded that a single intravenous infusion of 1.2 g or 2 g of magnesium sulfate over 15 to 30 minutes reduces hospital admissions and improves lung function in adults with acute asthma who have not responded sufficiently to oxygen, nebulized SABAs and intravenous glucocorticoids.

Despite the theoretical bronchodilatory effect of intravenous ketamine, two randomized controlled trials have failed to demonstrate added bronchodilator effects when ketamine was compared to conventional management of asthma exacerbation.

Adjunct therapies such as a long-acting β_2-agonist, montelukast sodium, and theophylline have not demonstrated therapeutic benefit when used in the treatment of an acute asthma exacerbation and are not appropriate choices

H CONT.

for this patient. However, their efficacy as long-term options in the outpatient setting should be considered in the overall treatment of asthma once the patient has been stabilized and is ready for hospital discharge.

KEY POINT

- Intravenous magnesium sulfate reduces hospital admissions and improves lung function in adults with acute asthma who have not responded sufficiently to oxygen, nebulized short-acting β_2-agonists, and intravenous glucocorticoids.

Bibliography

Albertson TE, Sutter ME, Chan AL. The acute management of asthma. Clin Rev Allergy Immunol. 2015;48:114-25. [PMID: 25213370] doi:10.1007/s12016-014-8448-5

H

Item 38 Answer: B

Educational Objective: Treat septic shock that persists after adequate fluid resuscitation using glucocorticoids.

Hydrocortisone is the most appropriate treatment. There is controversy about the role of glucocorticoids in the treatment of septic shock, but the Surviving Sepsis Guidelines published in 2016 recommend that if glucocorticoids are used, they should be used in refractory shock with persistent hypotension after adequate fluid resuscitation and after vasopressor medications have been titrated to high dose, and that the dose should be no more than 200 mg of hydrocortisone in 24 hours.

It is unlikely that substituting norepinephrine with another catecholamine vasopressor (dopamine) will lead to increased blood pressure. Dopamine also has a higher risk of inducing cardiac arrhythmias, and in this elderly patient who already has sinus tachycardia and frequent ectopic beats, dopamine would be an inappropriate substitution. Dopamine might best be reserved for selected patients with hypoperfusion and relative bradycardia.

Vasopressin levels in septic shock have been reported to be lower than anticipated for a shock state. Low doses of vasopressin may be effective in raising blood pressure in shock refractory to other vasopressors. Guidelines suggest adding vasopressin (up to 0.03 U/min) to norepinephrine with the intent of raising blood pressure to target or to decrease norepinephrine dosage. Vasopressin is not titrated like other pressors. Higher doses of vasopressin lead to ischemic complications, which more than offset any hemodynamic benefit.

Guidelines currently recommend against the use of intravenous (IV) immunoglobulins in patients with sepsis or septic shock. The most recent systematic review and meta-analysis differentiated between standard polyclonal IV immunoglobulins and M-enriched polyclonal immunoglobulin. Studies included in the review had low to moderate certainty of results based on risk of bias and heterogeneity. After excluding low-quality trials, no survival benefit was discernable with either immune globulin preparation.

KEY POINT

- Glucocorticoids are indicated in patients with sepsis who have not achieved hemodynamic stability from intravenous fluid administration and vasopressor therapies.

Bibliography

Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, et al. Surviving Sepsis Campaign: international guidelines for management of sepsis and septic shock: 2016. Intensive Care Med. 2017;43:304-377. [PMID: 28101605] doi:10.1007/s00134-017-4683-6

Item 39 Answer: C

Educational Objective: Diagnose malignant pleural mesothelioma.

The most likely diagnosis is malignant pleural mesothelioma. Asbestos exposure is the primary risk factor for mesothelioma, which has a latency period of 20 to 40 years, and this patient likely has a history of asbestos exposure from working as a brake mechanic. Occupational exposure to asbestos is most common in miners, electricians, plumbers, brake mechanics, shipyard workers, home remodelers, and selected military personnel. Patients most commonly present with symptoms of chest pain and a slowly enlarging pleural effusion. Chest imaging typically shows a unilateral pleural effusion, but patients can also present with pleural thickening, calcification, nodules, or masses. If malignant pleural mesothelioma is suspected, a thoracentesis should be performed, including pleural fluid cytology. Additional evaluation includes a chest CT scan to determine the extent of disease and evaluate for pleural lesions. Confirmation of the diagnosis requires pleural biopsy. Video-assisted thoracoscopic biopsy or open thoracotomy is required when the diagnosis remains uncertain, as diagnosis of mesothelioma cannot be made using cytology alone.

Empyema often presents with unilateral loculated exudative pleural effusion; however, the patient would not have a 6-month history of symptoms in the absence of fever and with a normal complete blood count. Finally, the pleural fluid characteristics are not consistent with empyema (typically pleural fluid pH less than 7.2, purulent effusion, or positive Gram stain).

Although cough, dyspnea, and pleural effusion could occur in patients with heart failure, the lack of physical examination findings consistent with volume overload and findings of a serosanguineous exudative effusion on thoracentesis would not be consistent with a diagnosis of heart failure (transudative effusion).

Rheumatoid pleuritis would also present with an exudative pleural effusion, but the patient has no other signs or symptoms of rheumatoid arthritis.

KEY POINT

- Asbestos exposure is the primary risk factor for malignant pleural mesothelioma, and patients most commonly present with symptoms of chest pain and a slowly enlarging pleural effusion.

Bibliography

Scherpereel A, Astoul P, Baas P, Berghmans T, Clayson H, de Vuyst P, et al; European Respiratory Society/European Society of Thoracic Surgeons Task Force. Guidelines of the European Respiratory Society and the European Society of Thoracic Surgeons for the management of malignant pleural mesothelioma. Eur Respir J. 2010;35:479-95. [PMID: 19717482] doi:10.1183/09031936.00063109

Item 40 Answer: C

Educational Objective: Treat a patient with newly diagnosed mild COPD.

The most appropriate treatment is a short-acting bronchodilator. Two commonly used, evidence-based treatment schemes are available to guide therapy. The American College of Physicians, American College of Chest Physicians, American Thoracic Society, and European Respiratory Society classification and treatment scheme for stable COPD recommends an inhaled short-acting bronchodilator (anticholinergic or β_2-agonist) for patients with an FEV_1 between 60% and 80% of predicted. The Global Strategy for Diagnosis, Management and Prevention of COPD (GOLD) classification model allows for therapy for COPD based on spirometry, risk, and symptoms. According to the GOLD classification scheme, this patient is in group A (low risk, few symptoms, documented mild airflow obstruction with one or no exacerbations per year). Like the previous guideline, GOLD recommends a short-acting bronchodilator or a combination of short-acting bronchodilators.

Roflumilast is a phosphodiesterase-4 (PDE-4) inhibitor used as add-on therapy to reduce exacerbations in patients with severe COPD associated with chronic bronchitis and a history of recurrent exacerbations despite other therapies. Inhibition of PDE-4 decreases inflammation, which may be helpful in a limited number of patients with COPD in whom inflammation is a significant factor. Roflumilast has minimal bronchodilator activity and should always be used with at least one long-acting bronchodilator. This patient has no indication for roflumilast therapy and it should not be used as monotherapy.

If the patient's symptoms and airflow obstruction progress, both guidelines recommend the addition of a long-acting bronchodilator (either a long-acting β_2-agonist or long-acting muscarinic agent). If symptoms persist, either an inhaled glucocorticoid or long-acting muscarinic agent can be added to the regimen.

Because this patient has mild disease with minimal symptoms, it is not necessary to start an inhaled glucocorticoid at this time. Short prednisone bursts are used to treat patients with acute exacerbations but are not indicated for the management of mild chronic symptoms related to COPD.

KEY POINT

- Patients whose symptoms and spirometry are consistent with mild COPD can begin treatment with a short-acting bronchodilator as needed.

Bibliography

Qaseem A, Wilt TJ, Weinberger SE, Hanania NA, Criner G, van der Molen T, et al; American College of Physicians. Diagnosis and management of stable chronic obstructive pulmonary disease: a clinical practice guideline update from the American College of Physicians, American College of Chest Physicians, American Thoracic Society, and European Respiratory Society. Ann Intern Med. 2011;155:179-91. [PMID: 21810710] doi:10.7326/0003-4819-155-3-201108020-00008

Item 41 Answer: A

Educational Objective: Treat a patient with chronic hypoventilation due to neuromuscular disease with noninvasive ventilation.

Bilevel positive airway pressure is the most appropriate next step in management. This patient has chronic hypoventilation due to amyotrophic lateral sclerosis (ALS), as indicated by the elevated arterial P_{CO_2} and a compensatory metabolic alkalosis, resulting in a normal pH on blood gas testing. ALS is marked by hypoventilation during sleep and may be exacerbated by acute illness and anesthesia. Bilevel positive airway pressure therapy augments ventilation by providing pressure support, improves quality of life, and may prolong survival in patients with ALS. Ventilatory support should be started in the presence of respiratory symptoms or hypercarbia. It also is essential to discuss prognosis and establish goals of care with patients and families, thereby avoiding unnecessary diagnostic and therapeutic measures.

Continuous positive airway pressure is designed to maintain upper airway patency in obstructive sleep apnea (OSA) and would not be appropriate ventilatory support in the setting of chronic respiratory failure due to hypoventilation.

Hypoglossal nerve stimulation is a treatment of OSA that activates the tongue muscles to increase upper airway caliber and prevent collapse. It has no effect on the respiratory pump muscles weakened by ALS.

Supplemental oxygen should generally not be prescribed for patients with hypoventilation due to neuromuscular disease without adjunctive ventilatory support because supplemental oxygen may further impair ventilation in patients with respiratory muscle weakness.

Tracheostomy may be appropriate for some patients with advanced respiratory failure due to neuromuscular disease, particularly those who experience difficulty in managing secretions or who require support during the waking hours. However, this patient is not yet affected by those issues, and noninvasive therapy should be the initial choice.

KEY POINT

- Assisted breathing devices, such as bilevel positive airway pressure, can be prescribed to support gas exchange in patients with neuromuscular disorders and may prolong survival in amyotrophic lateral sclerosis.

Bibliography

Radunovic A, Annane D, Rafiq MK, Brassington R, Mustfa N. Mechanical ventilation for amyotrophic lateral sclerosis/motor neuron disease. Cochrane Database Syst Rev. 2017;10:CD004427. [PMID: 28982219] doi:10.1002/14651858.CD004427.pub4

Item 42 Answer: C

Educational Objective: Prevent recurrent spontaneous pneumothorax with smoking cessation.

Smoking cessation is the most effective measure to prevent recurrent pneumothorax. This patient has a primary spontaneous pneumothorax (PSP) (air in the pleural space in someone without underlying lung disease). Cigarette smoking is a significant risk factor for PSP, likely because of airway inflammation. The lifetime risk of pneumothorax for men who are lifelong heavy smokers is 12%, compared to 0.1% for men who have never smoked. Because of the strong association between smoking and occurrence of PSP, smoking cessation may help prevent recurrence. Other risk factors for PSP are family history of PSP and thoracic endometriosis. PSP usually develops when the patient is at rest, and presenting patients are typically in their early 20s. Symptoms include the sudden onset of dyspnea and pleuritic chest pain. Recurrence is estimated at 23% to 50% during the first 5 years. Interventions to prevent recurrence includes chemical and mechanical pleurodesis, which are recommended after the second occurrence of PSP on the ipsilateral side, or first occurrence if the patient has a high-risk occupation such as deep sea diver or airplane pilot.

Air travel should be discouraged until resolution of the pneumothorax, but it is not in itself a risk factor for developing a pneumothorax.

There is no association between mountain climbing and development of a pneumothorax.

There is no association between the onset of pneumothorax and physical activity, with the occurrence being as likely when the patient is sedentary as when active.

KEY POINT

- Patients with a primary spontaneous pneumothorax should be encouraged to stop smoking to prevent recurrence.

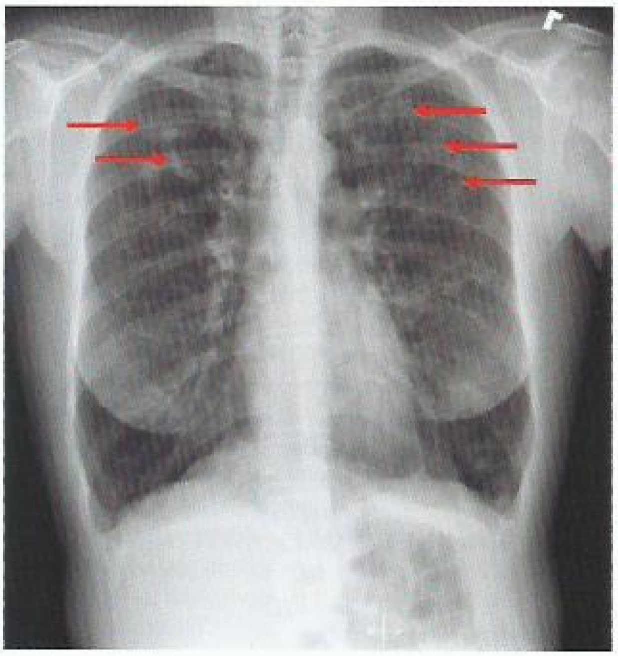
Bibliography

MacDuff A, Arnold A, Harvey J; BTS Pleural Disease Guideline Group. Management of spontaneous pneumothorax: British Thoracic Society Pleural Disease Guideline 2010. Thorax. 2010;65 Suppl 2:ii18-31. [PMID: 20696690] doi:10.1136/thx.2010.136986

Item 43 Answer: D

Educational Objective: Diagnose an adult with cystic fibrosis.

The most likely underlying diagnosis is cystic fibrosis. This patient has acute symptoms of increased cough, sputum production, fever, chills, wheezing, dyspnea, clubbing, and a chest radiograph (shown) with bilateral upper-lobe predominant bronchiectasis with mucoid impaction (arrows), as well as a history of chronic pulmonary and gastrointestinal disease. This constellation of signs and symptoms is most consistent with an acute exacerbation of bronchiectasis in a patient with cystic fibrosis.



Common variable immunodeficiency involves B- and T-cell abnormalities and results in clinically significant immune dysregulation. The primary manifestation is hypogammaglobulinemia, and adults present with recurrent respiratory infections. The gastrointestinal tract is frequently involved with malabsorption or chronic diarrhea. The diagnosis is made by confirming low levels of total IgG and IgA or IgM, as well as by a poor antibody response to vaccines. The patient's normal serum immunoglobulin levels exclude this diagnosis.

The most common of the early complement disorders is C2 deficiency; C6 deficiency is the most common of the late complement disorders. Patients lacking one of the early components usually present with a rheumatologic disorder. Those with late complement component deficiencies usually present with recurrent, invasive meningococcal or gonococcal infections. The patient's history and findings are not consistent with either early or late complement component deficiency.

Although the patient has obstruction on pulmonary function testing, her age and history of chronic sinus and gastrointestinal disease make a diagnosis of COPD less likely than cystic fibrosis.

KEY POINT

- Conditions suggesting the diagnosis of cystic fibrosis in adults include chronic asthma-like symptoms, chronic sinusitis, nasal polyposis, recurrent pancreatitis, infertility, and bronchiectasis.

Bibliography

Nick JA, Nichols DP. Diagnosis of adult patients with cystic fibrosis. Clin Chest Med. 2016;37:47-57. [PMID: 26857767] doi:10.1016/j.ccm.2015.11.006

H

Item 44 Answer: A

Educational Objective: Treat a patient with an acute exacerbation of COPD.

The most appropriate treatment of the COPD exacerbation in this patient is azithromycin and prednisone. Exacerbations are marked by increased breathlessness and are usually accompanied by increased cough and sputum production. The degree of exacerbation is considered mild when a change in the clinical condition is noted but no change in medication is necessary. An exacerbation is considered moderate when medication changes are made. A severe exacerbation results in hospitalization. Short-acting bronchodilator therapy is a mainstay of therapy for treating COPD exacerbation. Glucocorticoids, such as prednisone, have been shown to reduce recovery time, improve lung function and arterial hypoxemia, decrease risk of early relapse, decrease treatment failure, and decrease length of hospital stay. Guidelines recommend 40 mg of prednisone or an oral equivalent for 5 to 7 days. The most recent Global Initiative for Chronic Obstructive Lung Disease report recommends that antibiotics should be considered in patients with moderate or severe COPD and symptoms of increased dyspnea, increased sputum, and sputum purulence. Recent studies in patients with moderate COPD have demonstrated improved patient outcomes. Commonly used regimens include an advanced macrolide (such as azithromycin), a cephalosporin, or doxycycline.

This patient's COPD appears to be well-controlled at baseline, so the addition of an inhaled glucocorticoid such as mometasone is not indicated for long-term COPD management. An inhaled glucocorticoid is not an effective treatment of an exacerbation of COPD.

Noninvasive positive pressure ventilation (NIPPV) has a significant role in the management of patients with very severe COPD during an acute exacerbation and may be helpful to avoid intubation. NIPPV is strongly recommended in patients with acute COPD exacerbations who have respiratory acidosis. This patient does not have an indication for NIPPV.

Although roflumilast has been shown to decrease the frequency of recurrent exacerbations, there is no role for this agent in the treatment of an acute exacerbation. As this is a first exacerbation of COPD, chronic roflumilast therapy is not indicated.

KEY POINT

- An exacerbation of COPD is defined as a sustained worsening of symptoms, typically cough, dyspnea, and sputum production; standard treatment of moderate to severe exacerbations includes antibiotics and oral glucocorticoids.

Bibliography

Holden V, Slack III D, McCurdy MT, Shah NG. Diagnosis and management of acute exacerbations of chronic obstructive pulmonary disease. Emerg Med Pract. 2017;19:1-24. [PMID: 28926214]

Item 45 Answer: D

Educational Objective: Treat pulmonary hypertension secondary to chronic hypoxemia.

The most appropriate treatment is supplemental oxygen. The clinical assessment and echocardiographic findings are consistent with pulmonary hypertension in the setting of advanced COPD (Group 3 pulmonary hypertension [PH]). The mainstay of treatment of Group 3 PH targets the underlying lung disease. This patient is on maximal inhaler therapy for COPD. Hypoxemia during daytime rest and, in the setting of cor pulmonale or secondary polycythemia, hypoxemia during sleep, is an indication for supplemental oxygen, which has proved benefit in pulmonary hemodynamics and survival in this population.

Bilevel positive airway pressure is indicated in patients with hypercapnia in the setting of COPD. Furthermore, in patients with overlap of COPD and sleep disordered breathing, continuous positive airway pressure has been shown to increase quality of life and prolong survival. The arterial blood gas study shows this patient to be normocapnic, and polysomnography demonstrates hypoxemia but no sleep apnea. Therefore, positive airway pressure therapy is not indicated.

A short course of prednisone is indicated in acute exacerbations of COPD, which typically present with acute dyspnea, cough, and sputum production. The more insidious course of this patient's symptoms is not consistent with an acute exacerbation of COPD, and there is no role for systemic glucocorticoids in patients with PH due to COPD.

Therapy with a vasodilator such as sildenafil is generally not indicated in patients with pulmonary hypertension related to lung disease or hypoxemia. Such drugs may cause harm by worsening ventilation-perfusion matching and further impairing gas exchange.

KEY POINT

- Patients with pulmonary hypertension secondary to lung disease and associated hypoxemia should be treated with supplemental oxygen.

Bibliography

Continuous or nocturnal oxygen therapy in hypoxemic chronic obstructive lung disease: a clinical trial. Nocturnal Oxygen Therapy Trial Group. Ann Intern Med. 1980;93:391-8. [PMID: 6776858]

Item 46 Answer: A

Educational Objective: Treat pulmonary arterial hypertension.

The most appropriate treatment is bosentan. This patient has pulmonary hypertension most consistent with Group 1 (pulmonary arterial hypertension [PAH]), based upon the right heart catheterization demonstrating high pulmonary arterial pressures in the absence of left-sided heart failure, lung disease, and venous thromboembolic disease. Before administering advanced therapy for patients with PAH, vasoreactivity testing with nitric oxide is performed to identify those who

may respond to calcium channel blockers (CCBs). CCBs are desirable therapy because they are less expensive and have fewer side effects than other forms of advanced therapy. Failure to achieve a favorable hemodynamic response with nitric oxide predicts unresponsiveness to CCBs and the need for other advanced therapy. The endothelin receptor antagonist bosentan is one of many oral pulmonary vasoactive drugs that is indicated in PAH in patients with negative vasoreactivity testing, such as this patient, some of which have been shown to increase exercise capacity and improve echocardiographic parameters.

CCBs such as diltiazem may be used in the setting of PAH when a response to a vasodilator such as nitric oxide is demonstrated during right heart catheterization. When a response is not found, CCBs are not indicated.

β-Blockers such as metoprolol do not have a proved role specific to PAH, though they might be used as an adjunct agent for supraventricular tachyarrhythmias that are common in this population.

Pirfenidone is an antifibrotic agent indicated for the treatment of idiopathic pulmonary fibrosis. Pulmonary hypertension is frequently observed in patients with idiopathic pulmonary fibrosis, but pirfenidone would not be indicated for a patient with PAH without idiopathic pulmonary fibrosis.

KEY POINT

- Before administering advance therapy for patients with pulmonary arterial hypertension (PAH), particularly idiopathic PAH, vasoreactivity testing directs agent selection by identifying those who may respond to calcium channel blockers.

Bibliography

Galiè N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Respir J. 2015;46:903-75. [PMID: 26318161] doi:10.1183/13993003.01032-2015

Item 47 Answer: C

Educational Objective: **Evaluate a patient for occupational exposure using a Material Safety Data Sheet.**

The most appropriate management is to review the employer Material Safety Data Sheet (MSDS). This patient is concerned that an occupational exposure is causing new respiratory symptoms and potentially may worsen her asthma control. When an occupational lung disease is being considered, clinicians should request the MSDS, which details chemical properties and known health risks associated with substances within the workplace. The U.S. Occupational Safety and Health Administration (OSHA) requires that this information is available upon request for employees who work with potentially harmful materials. Establishing a clear causal link between this patient's symptoms of asthma and an occupational exposure is essential in diagnosis and management. Her history suggests a temporal relationship between the introduction of the new chemical and her cough. In addition, she feels the need to use her albuterol inhaler after exposure. Examples of known respiratory irritants include chlorine gas and sulfur dioxide, which are triggers of bronchospasm. Toluene diisocyanate is associated with allergic sensitization, cough, and bronchospasm that can develop weeks or months after initial exposure. Additional evaluation for occupational illness can include peak flow meter measurements before and after exposure, bronchoprovocation testing after prolonged time away from work and return to work, and, in select cases, specific inhalational challenges.

A chest CT scan is usually not needed for the evaluation of a patient with suspected occupational asthma. Exceptions to this rule include patients with abnormal chest radiography or suspected hypersensitivity pneumonitis. This patient has a normal lung examination, normal spirometry, and no symptoms compatible with acute hypersensitivity pneumonitis (fevers, flulike symptoms, cough, and shortness of breath). This patient has no indication for advanced imaging.

Although several commercial entities offer testing of hair samples for toxic chemicals, this testing is expensive, unlikely to be covered by insurance, and of questionable validity. It is, therefore, not recommended in the assessment of occupational exposure by primary care internists.

Supporting a patient's request to transfer work areas related to a health concern should be based on sound clinical assessment and judgment. A clinician's initial assessment should establish the presence of an occupational illness by assessing exposures, including known chemicals in the workplace, and establishing a temporal relationship between the introduction of the new chemical and symptoms.

KEY POINT

- When an occupational lung disease is being considered, clinicians should request a Material Safety Data Sheet detailing chemical properties and known health risks associated with substances within the workplace.

Bibliography

Friedman-Jimenez G, Harrison D, Luo H. Occupational asthma and work-exacerbated asthma. Semin Respir Crit Care Med. 2015;36:388-407. [PMID: 26024347] doi:10.1055/s-0035-1550157

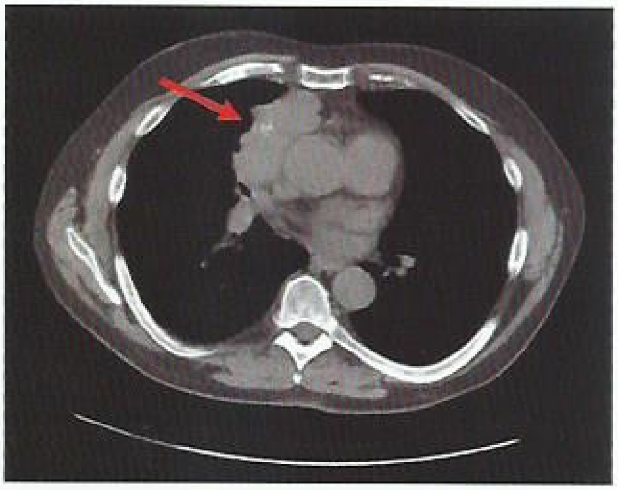
Item 48 Answer: A

Educational Objective: **Evaluate a patient with an anterior mediastinal mass and symptoms of myasthenia gravis.**

An acetylcholine receptor (AChR) antibody test should be ordered. The mediastinum can be divided into three separate compartments (anterior, middle, and posterior), which can help narrow the differential diagnosis of a mediastinal mass. Each compartment normally contains separate and distinct anatomic structures that can lead to development of a mass. Patients may be asymptomatic and are often diagnosed after obtaining a chest radiograph for another reason, whereas

others present with symptoms related to compression of adjacent structures. For example, they may present with dyspnea if the airway is compressed from a nearby mass or with upper extremity edema if vascular structures are compressed.

This patient has an anterior mediastinal mass (arrow) and neurologic symptoms. Masses in this location are usually remembered as the "terrible T's": thymoma, teratoma/germ cell tumor, "terrible" lymphoma, and thyroid. Additional considerations include thoracic aneurysm. Thymomas are the most common cause of an anterior mediastinal mass. Patients usually present as middle-age adults and may develop paraneoplastic syndromes. For example, myasthenia gravis can develop in 30% to 50% of patients with a thymoma. In comparison, only 10% to 15% of patients with myasthenia gravis have a thymoma. The second most common cause is lymphoma; these patients are typically younger at the time of presentation. Other less common paraneoplastic syndromes include pure red blood cell aplasia, nonthymic cancers, and acquired hypogammaglobulinemia.



Myasthenia gravis is an autoimmune disorder of the neuromuscular junction that is characterized by fatigable (or fluctuating) muscular weakness. Common symptoms are ptosis and diplopia, which this patient has. Diagnosis of myasthenia gravis is based on clinical findings, detection of disease-specific antibodies (acetylcholine receptor antibodies in 90% of patients and anti-muscle-specific kinase [MuSK] antibodies in another 5% [with 5% of patients remaining antibody negative]), and electromyography findings (such as a characteristic decremental response to repetitive stimulation). Thymectomy should be performed in all patients with thymoma.

α-Fetoprotein and β-human chorionic gonadotropin are commonly elevated in germ cell tumors, which are also part of the differential diagnosis of an anterior mediastinal mass. However, this patient also has symptoms of myasthenia gravis, which is not associated with germ cell tumors.

Lactate dehydrogenase is commonly elevated in lymphoma and seminomas but is not as specific as other tumor markers and will not help determine the cause of this patient's symptoms.

KEY POINT

- Masses in the anterior mediastinum are usually recalled as the "terrible T's": thymoma, teratoma/germ cell tumor, "terrible" lymphoma, and thyroid.

Bibliography

Strollo DC, Rosado de Christenson ML, Jett JR. Primary mediastinal tumors. Part 1: tumors of the anterior mediastinum. Chest. 1997;112:511-22. [PMID: 9266892]

Item 49 Answer: B

H

Educational Objective: Treat pneumonia in a patient with inhalational injury.

Administration of empiric intravenous antibiotics for presumed pneumonia is the most appropriate treatment. This patient suffered an inhalational injury as a result of her exposure to a house fire. Common acute complications of inhalational injury include systemic toxicity from carbon monoxide and hydrogen cyanide, upper airway obstruction from pharyngeal edema, mucosal sloughing, bronchial cast formation, bronchoconstriction, pneumonia, acute respiratory distress syndrome, and pulmonary edema. The most common complication following smoke inhalation injuries is pneumonia. Inhalational injury increases the risk for respiratory infections, especially from *Staphylococcus* and *Pseudomonas* species, because of several mechanisms, including impaired pulmonary macrophage activity, direct injury to the airway cilia and tracheobronchial mucosal epithelium, and impaired surfactant production. Although the patient is only borderline febrile, her increasing leukocyte count and the presence of a focal consolidation in her left lower lobe on chest radiograph increase the index of suspicion for pneumonia.

Acute cyanide poisoning primarily occurs through fire and occupational exposures. Although no reliable test for cyanide poisoning exists, patients suspected of cyanide poisoning should receive hydroxocobalamin. Because this patient's inhalational exposure occurred 3 weeks ago, it is unlikely that her acute respiratory failure is due to cyanide poisoning. Thus, hydroxocobalamin is not indicated.

Tracheobronchial stenosis is an infrequent but real complication of inhalational injury. However, it most commonly occurs several months postexposure. The patient's recent normal airway inspection also suggests stenosis is a less likely cause of her respiratory decline. Other long-term complications following smoke inhalation include vocal cord fixation, airway polyps, persistent dysphonia, bronchiolitis obliterans, and bronchiectasis.

Common indications for thoracostomy tube placement include empyema or pneumothorax. Although pneumothorax should be considered in a patient with acute respiratory failure, there is no pneumothorax on this patient's radiograph. A thoracentesis is indicated for any new unexplained pleural effusion. Observation and initiation of therapy without diagnostic thoracentesis is reasonable in the setting of a small parapneumonic effusion, as is seen in the left base of

H CONT.

this patient's radiograph. If an empyema or other small fluid collection requires evaluation, the initial investigation with needle thoracentesis is generally indicated before consideration of thoracostomy tube placement.

KEY POINT

- Secondary respiratory infections are common in patients with inhalational injuries, especially from *Staphylococcus* and *Pseudomonas* species, and are a major cause of morbidity and mortality.

Bibliography

Walker PF, Buchner MF, Wood LA, Boyer NL, Driscoll IR, Lundy JB, et al. Diagnosis and management of inhalation injury: an updated review. Crit Care. 2015;19:351. [PMID: 26507130] doi:10.1186/s13054-015-1077-4

H

Item 50 Answer: D

Educational Objective: Treat a patient at risk for alcohol withdrawal who has overdosed on benzodiazepines.

This patient should be kept on mechanical ventilation and monitored for signs of agitation. He shows signs of benzodiazepine overdose, combined with alcohol abuse. His airway is secure, and he is easily supported with mechanical ventilation, which can continue until he has metabolized the drug and his mental status has improved. Because of his history of alcohol abuse, he is at risk for alcohol withdrawal. Alcohol withdrawal occurs with chronic heavy alcohol use within hours to days after alcohol cessation. Early withdrawal symptoms occur within a few hours of abstinence and include agitation, anxiety, tremulousness, headache, and symptoms of autonomic hyperactivity (fever, diaphoresis, tachycardia, hypertension). Generalized tonic-clonic seizures may occur usually within 6 to 24 hours and should be treated with benzodiazepines because if left untreated, up to one third of patients may progress to delirium tremens.

Flumazenil, a γ-aminobutyric acid (GABA)-receptor antagonist, is the antidote for benzodiazepine toxicity, but reversing the benzodiazepine he took could put him at risk for seizures, especially if he is a chronic user. The short half-life of flumazenil makes it challenging to use in patients requiring sustained reversal of long-acting benzodiazepines, and given the overall low risk of benzodiazepine overdose, it is safer to allow his body to metabolize the benzodiazepine and eliminate it along with the alcohol.

Fomepizole inhibits alcohol dehydrogenase. It is used to block the metabolism of ethylene glycol and methanol into toxic metabolites when either of these alcohols is ingested. There is no reason to suspect either agent, especially in a patient with normal blood pH and a normal anion gap. Administration would therefore not be appropriate.

Dialysis would not be appropriate because there is no acute indication for this invasive and costly intervention. In principle, hemodialysis is indicated for drug intoxications when the clearance of the drug by hemodialysis is significantly shorter than metabolic clearance and the patient is deteriorating or when measured drug concentrations are predictive of a poor outcome without hemodialysis. Dialysis will remove alcohols effectively, but the patient is stable and does not require an invasive intervention.

KEY POINT

- Treatment for benzodiazepine overdose is supportive with assurance of adequate ventilation; flumazenil is generally not recommended for benzodiazepine overdose as it can precipitate seizures in chronic users and its short half-life makes it difficult to sustain reversal of long-acting benzodiazepines.

Bibliography

An H, Godwin J. Flumazenil in benzodiazepine overdose. CMAJ. 2016;188:E537. [PMID: 27920113]

Item 51 Answer: A

Educational Objective: Treat hypersensitivity pneumonitis.

This patient has acute hypersensitivity pneumonitis and should be counseled not to return to work. The acute form of hypersensitivity pneumonitis presents within 48 hours of a high-level exposure and will often be associated with fever, flu-like symptoms, cough, and shortness of breath. Radiographic imaging can demonstrate bilateral hazy opacities, whereas high-resolution CT imaging of the chest shows findings of ground-glass opacities and centrilobular micronodules that are upper- and midlung predominant. Symptoms typically wane within 24 to 48 hours after removal from the exposure. Recurrence of symptoms with exposure to the respiratory antigen is the hallmark of this disorder, and careful attention to the history will help identify the cause. Primary treatment of acute hypersensitivity pneumonitis is removal from the offending antigen. Studies indicate that pulmonary function can continue to gradually recover, with initial improvements in oxygen exchange followed by increased FVC and improved chest radiograph findings.

Although treatment of acute hypersensitivity pneumonitis with systemic glucocorticoids is appropriate for those with more severe disease, patient response is variable, and prolonged use is associated with significant side effects. There are no data to support the use of inhaled glucocorticoids for acute hypersensitivity pneumonitis and, again, the primary treatment is to remove the offending agent.

Idiopathic pulmonary fibrosis (IPF) is the most common idiopathic interstitial pneumonia. It occurs predominantly in older individuals; the diagnosis of IPF is rare in those younger than 50 years of age. Gradual onset of dyspnea and cough during months to years is typical. Pirfenidone is a novel therapeutic agent that regulates transforming growth factor β (TGF-β) and tumor necrosis factor α (TNF-α) activity through an unknown mechanism that is used in the treatment of idiopathic pulmonary fibrosis. Similarly, nintedanib is a tyrosine kinase inhibitor known to block pathways that lead to activation of the fibroblast. Although these therapies are an important step forward in the management of IPF,

they are not curative. This patient does not have IPF and treatment with pirfenidone is not indicated.

Lymphangioleiomyomatosis is a rare disorder that occurs sporadically in women or in association with tuberous sclerosis. It manifests as a diffuse cystic lung disease due to infiltration of smooth muscle cells into the pulmonary parenchyma. Genetic mutations within the cells lead to activation of the mechanistic target of rapamycin (mTOR) pathway. Diagnosis is based on imaging studies with diffuse thin-walled cysts as well as spontaneous pneumothorax and angiomyolipomas. Treatment is inhibition of the mTOR with sirolimus. Such treatment is not indicated in this patient with hypersensitivity pneumonitis.

KEY POINT

- Removal of the offending antigen is the most appropriate treatment of acute hypersensitivity pneumonitis.

Bibliography

Vasakova M, Morell F, Walsh S, Leslie K, Raghu G. Hypersensitivity pneumonitis: perspectives in diagnosis and management. Am J Respir Crit Care Med. 2017;196:680-689. [PMID: 28598197] doi:10.1164/rccm.201611-2201PP

Item 52 Answer: B

Educational Objective: Treat a patient with a macrolide antibiotic to reduce frequent COPD exacerbations.

The most appropriate guideline-recommended (grade 2A) treatment of this patient with severe COPD and frequent exacerbations is chronic macrolide therapy. Macrolide antibiotics have inflammatory and antimicrobial effects and may reduce the frequency of exacerbations when used long-term by patients with severe COPD. Several clinical trials to assess prophylactic use and benefit have demonstrated a reduction in the rate of exacerbation in patients with moderate to severe COPD with one or more moderate or severe exacerbations in the previous year despite optimal maintenance inhaler therapy. The duration and exact dosage of macrolide therapy are unknown. The primary concerns with long-term macrolide therapy are development of antibiotic resistance, including macrolide-resistant strains of nontuberculous mycobacteria. In addition, hearing loss and potentially fatal arrhythmias due to prolongation of the QT interval have occurred in association with azithromycin.

The long-term use of systemic glucocorticoids is avoided in the chronic management of COPD due to lack of demonstrated benefit and recognized increased risk of significant side effects such as diabetes, hypertension, muscle weakness, and decreased functional status.

The use of supplemental oxygen in patients with COPD and hypoxemia has been shown to improve quality of life and mortality in patients who have resting hypoxemia with an arterial Po_2 of 55 mm Hg (7.31 kPa) or lower, or oxygen saturation on pulse oximetry (Spo_2) of 88% or lower. This patient's Spo_2 is above 88% at rest and on exertion on her current level of supplemental oxygen. Increasing this further has not been shown to decrease the rate of acute exacerbations.

Mucolytics such as nebulized hypertonic saline and airway clearance maneuvers may provide some symptomatic relief in patients with significant sputum production, but this patient does not have cough or sputum production. Moreover, these interventions have not been shown to decrease the rate of acute exacerbations in patients with COPD.

KEY POINT

- In patients with severe COPD and frequent exacerbations, chronic macrolide therapy has been shown to decrease COPD exacerbations.

Bibliography

Criner GJ, Bourbeau J, Diekemper RL, Ouellette DR, Goodridge D, Hernandez P, et al. Prevention of acute exacerbations of COPD: American College of Chest Physicians and Canadian Thoracic Society Guideline. Chest. 2015;147:894-942. [PMID: 25321320] doi:10.1378/chest.14-1676

Item 53 Answer: C

H

Educational Objective: Treat a patient with acute hypoxemic respiratory failure with invasive mechanical ventilation.

The most appropriate treatment is intubation and mechanical ventilation. This patient has dyspnea, severe hypoxemia, bilateral opacities on chest radiograph, and acute hypoxemic respiratory failure after aspiration, all of which are diagnostic for acute respiratory distress syndrome (ARDS). ARDS is associated with heterogeneous but often widespread damage to the alveolar epithelium and vascular endothelium, as well as surfactant dysfunction leading to alveolar instability and collapse. The changes can severely reduce lung compliance, making adequate ventilation difficult and further worsening hypoxia. Most patients with ARDS require intubation and mechanical ventilation to ensure adequate delivery of high levels of inspired oxygen and positive end-expiratory pressure to stabilize alveoli.

Continuing oxygen through a face mask would not be appropriate. Although the patient is maintaining appropriate oxygen saturation, the presence of anxiety, diaphoresis, tachycardia, tachypnea, hypercapnia, and hypoxemia signal impending respiratory failure that should be treated with intubation and mechanical ventilation.

High-flow humidified nasal cannula devices decrease the work of breathing, provide heated and humidified air, provide a reliable Fio_2, and decrease dead space. Their initial application should occur in the critical care setting with close monitoring for tolerance and effectiveness. A recent trial demonstrated that in patients with acute hypoxemic respiratory failure, the use of high-flow nasal cannula led to decreased mortality compared to continuing face mask oxygen or noninvasive face mask ventilation; however, the study excluded patients with hypercapnia, such as this

H CONT

patient. This patient shows features of respiratory muscle fatigue, including rapid breathing, diaphoresis, use of accessory muscles of respiration, and an elevated arterial P_{CO_2}, all indications for mechanical ventilation.

Noninvasive positive pressure ventilation (NIPPV) is the delivery of positive airway pressure using a cushioned face mask or helmet or without the use of an invasive connection directly in a patient's airway. In patients with hypoxemic respiratory failure, the use of NIPPV is controversial. Select patients may benefit from short-duration NIPPV to avoid intubation and associated complications but some studies have demonstrated increased mortality, likely due to delay in the implementation of appropriate invasive mechanical ventilation. This patient with deteriorating ventilation should be intubated and mechanically ventilated.

KEY POINT

- Most patients with acute respiratory distress syndrome require intubation and mechanical ventilation to ensure adequate delivery of high levels of inspired oxygen and positive end-expiratory pressure to stabilize alveoli.

Bibliography

Wilson JG, Matthay MA. Mechanical ventilation in acute hypoxemic respiratory failure: a review of new strategies for the practicing hospitalist. J Hosp Med. 2014;9:469-75. [PMID: 24733692] doi:10.1002/jhm.2192

Item 54 Answer: D

Educational Objective: Diagnose pulmonary arterial hypertension in a patient with limited cutaneous systemic sclerosis and CREST syndrome.

The most likely diagnosis is pulmonary arterial hypertension. Pulmonary involvement is frequent (greater than 70%) in patients with systemic sclerosis and can be symptomatic and disabling. The two principal clinical manifestations are interstitial lung disease and pulmonary vascular disease. Pulmonary vascular disease leading to pulmonary arterial hypertension may occur secondary to interstitial lung disease (typically in diffuse cutaneous systemic sclerosis) or as an isolated process (typically in limited cutaneous systemic sclerosis). This patient has several features of limited cutaneous systemic sclerosis with CREST syndrome (a condition defined by calcinosis cutis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasias). Patients are usually asymptomatic in early disease but later develop dyspnea on exertion and diminished exercise tolerance. Severe disease can lead to right-sided heart failure. Chest imaging is often normal and pulmonary function tests demonstrate a reduced DLCO with normal lung volumes.

Organizing pneumonia is a patchy process that involves proliferation of granulation tissue within alveolar ducts, alveolar spaces, and surrounding areas of chronic inflammation. There are many known causes of this pattern, including acute infections and autoimmune disorders such as rheumatoid arthritis. The term *cryptogenic organizing pneumonia* (COP) is reserved for individuals who have this pattern but do not have a clear associated cause. Patients with COP will typically present with symptoms during 6 to 8 weeks that mimic community-acquired pneumonia. Evaluation typically demonstrates bilateral diffuse alveolar opacities on chest radiograph with normal lung volumes. This patient's presentation is not consistent with cryptogenic organizing pneumonia.

Lymphangioleiomyomatosis is a multisystem disease that almost exclusively affects young women. Pulmonary complications are prominent and include diffuse pulmonary cysts, pneumothorax, chylous pleural effusions, and obstructive airways disease. Lymphangioleiomyomatosis would be very unlikely in a patient with an unremarkable chest radiograph.

Lymphoid interstitial pneumonia is an interstitial lung disease characterized by lymphocytic infiltration of the pulmonary interstitium. It is observed in patients with Sjögren's syndrome and viral infections, especially HIV. Patients with lymphoid interstitial pneumonia often have crackles on the pulmonary examination, interstitial infiltrates on chest radiography, and decreased lung volumes and diffusing capacity on pulmonary function testing.

KEY POINT

- Pulmonary arterial hypertension is commonly associated with connective tissue diseases, such as limited cutaneous systemic sclerosis.

Bibliography

Kato M, Atsumi T. Pulmonary arterial hypertension associated with connective tissue diseases: A review focusing on distinctive clinical aspects. Eur J Clin Invest. 2018;48. [PMID: 29285766] doi:10.1111/eci.12876

Item 55 Answer: A

H

Educational Objective: Treat sepsis with immediate fluid resuscitation.

The most appropriate management is an intravenous fluid bolus of 30 mL/kg of body weight. Successful treatment of severe sepsis and septic shock depends on the rapid institution of hemodynamic support, empiric treatment of infection, and infection control. Crystalloid infusion (normal [0.9%] saline or lactated Ringer solution) to support circulating intravascular volume should be administered to all patients with severe sepsis and septic shock. The 2016 update to the Surviving Sepsis Guidelines recommends using an initial bolus of 30 mL/kg of body weight.

The 2018 American Diabetes Association Standards for Care recommend that insulin therapy be initiated for treatment of persistent hyperglycemia starting at a threshold of 180 mg/dL (10.0 mmol/L). Once insulin therapy is started, a target glucose range of 140 to 180 mg/dL (7.8-10.0 mmol/L) is recommended for most critically ill and noncritically ill patients. This patient's plasma glucose is not so high that it is an emergency; therefore, administration of insulin is a lower priority than treatment of shock.

H CONT.

This patient may have also have developed a paraspinous abscess (fever, new-onset back pain, difficulty urinating). This patient may need spine imaging but the more urgent priority is his hemodynamic instability, which requires fluid resuscitation before he can undergo any diagnostic imaging study.

Before this patient can be evaluated for surgical source control, he needs to be resuscitated. He is not showing signs of necrotizing fasciitis, which would be a surgical emergency, but even if he were suspected of this diagnosis, he would need aggressive fluid resuscitation while arrangements were made for urgent surgical debridement.

KEY POINT

- Patients with hypoperfusion due to sepsis should be managed with aggressive crystalloid fluid resuscitation using an initial bolus of 30 mL/kg of body weight.

Bibliography

Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, et al. Surviving Sepsis Campaign: international guidelines for management of sepsis and septic shock: 2016. Intensive Care Med. 2017;43:304-377. [PMID: 28101605] doi:10.1007/s00134-017-4683-6

H

Item 56 Answer: C

Educational Objective: Treat secondary spontaneous pneumothorax with chemical pleurodesis.

The most appropriate management of this patient with severe COPD and secondary pneumothorax is pleurodesis. Pneumothorax (air in the pleural space) can occur spontaneously, as a result of trauma, or iatrogenically. Spontaneous pneumothorax is further characterized as a primary spontaneous pneumothorax (PSP) in a person without underlying lung disease or a secondary spontaneous pneumothorax (SSP) in a person with underlying lung disease. Patients presenting with SSP are at higher risk for persistent air leak, further expansion of the pneumothorax, or pneumothorax recurrence due to their underlying lung disease. Intervention to prevent recurrence includes both chemical and mechanical pleurodesis, which is recommended in all patients with SSP and after the second occurrence of a PSP. In patients with SSP the cause of persistent air leak following pneumothorax is usually subpleural bullae or cysts. Additional interventions are required to close the leak. For patients who are surgical candidates, video assisted thoracoscopic surgery (VATS) is recommended to locate and staple or resect blebs followed by mechanical pleurodesis. Patients who cannot tolerate surgery are treated with blood patch or chemical pleurodesis. These procedures are designed to seal the leak and prevent recurrence of pneumothorax. A blood patch is performed by injecting a quantity of the patient's blood into the thoracostomy tube. Chemical pleurodesis is performed by instilling tetracycline or one of its derivatives or specialized talc powder through the thoracostomy tube. Success rate for chemical pleurodesis ranges from 60% to 90% but it is not as effective as mechanical pleurodesis using VATS.

Clamping or removing the thoracostomy tube would not be appropriate because the patient has a secondary spontaneous pneumothorax and the likelihood of recurrence is high.

Placing the thoracostomy tube to high suction would not be appropriate because high levels of suction can increase the risk for reexpansion and pulmonary edema; in addition, the pneumothorax has resolved so no additional suction is needed.

KEY POINT

- Recurrence prevention with pleurodesis is recommended after the first occurrence of secondary spontaneous pneumothorax.

Bibliography

MacDuff A, Arnold A, Harvey J; BTS Pleural Disease Guideline Group. Management of spontaneous pneumothorax: British Thoracic Society Pleural Disease Guideline 2010. Thorax. 2010;65 Suppl 2:ii18-31. [PMID: 20696690] doi:10.1136/thx.2010.136986

Item 57 Answer: C

Educational Objective: Identify risk factors of acute exacerbations of COPD.

The patient's previous COPD exacerbations and FEV_1 of 35% of predicted are most associated with high risk for recurrent acute exacerbations of COPD. In the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) prospective study, the best predictor of exacerbations was a history of exacerbations, regardless of COPD severity. In this study the number of exacerbations in the previous 12 months, degree of airflow obstruction, and number of hospitalizations for an exacerbation refined the risk estimate. A history of 0 or 1 exacerbation, FEV_1 of 50% or better, and no hospitalizations predicts a low risk of future exacerbations, whereas more than 1 exacerbation, FEV_1 less than 50% predicted, and hospitalization predicts a high future risk of exacerbation. Exacerbations of COPD can be prevented by optimizing treatment with appropriate interventions based on risk classification and overall disease management; this includes immunizations and lifestyle changes such as maintaining physical activity and addressing anxiety and depression.

Pulmonary rehabilitation is recommended for all symptomatic patients with an FEV_1 of less than 50% of predicted and specifically for those hospitalized with an acute exacerbation of COPD. Use of such a program is not causally linked with an increased risk of COPD exacerbation.

Several comorbidities are associated with an increased risk of acute exacerbation, including heart failure, ischemic heart disease, diabetes, kidney failure, and hepatic failure. However, hypertension has not been associated with an increased risk of acute COPD exacerbations.

Current tobacco use is an independent risk factor for the development of COPD. However, past tobacco use and significant pack-year history are not associated with an

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increased risk for acute exacerbation. Discontinuing maintenance COPD mediations is associated with COPD exacerbations, whereas the use of such medications is not.

KEY POINT

- Patients with COPD who have had two or more acute exacerbations within the last year, who have an FEV_1 of less than 50% of predicted, or who have ever been hospitalized for an acute exacerbation are considered to be at high risk for recurrent acute exacerbations.

Bibliography

Hurst JR, Vestbo J, Anzueto A, Locantore N, Müllerova H, Tal-Singer R, et al; Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) Investigators. Susceptibility to exacerbation in chronic obstructive pulmonary disease. N Engl J Med. 2010;363:1128-38. [PMID: 20843247] doi:10.1056/NEJMoa0909883

H **Item 58** **Answer: B**

Educational Objective: Treat a patient with neurologic disease and hypercapnic respiratory failure with bilevel positive airway pressure.

The use of bilevel positive airway pressure (BPAP) ventilation is the most appropriate treatment. This patient has features consistent with chronic hypercapnic respiratory failure secondary to neuromuscular disease. He has dyspnea and, more characteristically, orthopnea. The patient has chronic respiratory acidosis with a normal alveolar arterial (A-a) oxygen gradient. BPAP delivers both inspiratory positive airway pressure and expiratory positive airway pressure and improves survival and quality of life of patients with neuromuscular disease. The settings generate a pressure difference that augments the patient's own respiratory muscle activity, leading to an increase in the size of each breath. The P_{CO_2} level will decrease due to the increase in minute ventilation and efficiency of breathing.

Invasive mechanical ventilation (mechanical ventilation with airway intubation or tracheostomy) is a therapeutic option in the setting of acute hypercapnic respiratory failure due to neuromuscular disease. However, the patient is awake, has excellent bulbar control (swallows and gags), and has a chronic disease that responds well to noninvasive ventilation.

Continuous positive airway pressure (CPAP) delivers positive airway pressure at a level that remains constant throughout the respiratory cycle preventing upper airway collapse or narrowing during sleep. No additional pressure above the level of CPAP is provided and patients must initiate every breath. CPAP does not increase minute ventilation, and it is not helpful in patients with hypercapnic respiratory failure due to neuromuscular disorders.

The patient has a normal A-a oxygen gradient and hypercapnia, which confirm that the hypoxemia is secondary to hypoventilation rather than a ventilation-perfusion mismatch or shunt; therefore, oxygen administration should not be needed once his P_{CO_2} improves. More importantly, the administration of oxygen in the absence of supportive ventilation should be avoided in patients with neuromuscular disease and chronic hypercapnic respiratory failure; it has been associated with acute hypercapnia, in some cases leading to death.

KEY POINT

- Bilevel positive airway pressure ventilation improves survival and quality of life in patients with neuromuscular disease.

Bibliography

Gregoretti C, Pisani L, Cortegiani A, Ranieri VM. Noninvasive ventilation in critically ill patients. Crit Care Clin. 2015;31:435-57. [PMID: 26118914] doi:10.1016/j.ccc.2015.03.002

Item 59 **Answer: A** H

Educational Objective: Treat a patient with hypertensive encephalopathy.

The appropriate treatment is intravenous hypertensive therapy to lower the systolic blood pressure (SBP) to 160 mm Hg within the first 6 hours. Appropriate intravenous agents could include fenoldopam, nicardipine, or nitroprusside. Hypertensive emergency refers to elevation of SBP greater than 180 mm Hg, diastolic blood pressure (DBP) greater than 120 mm Hg, or both, that is associated with end-organ damage. Patients with hypertensive emergency require rapid, tightly controlled reductions in blood pressure that avoid overcorrection. Management typically occurs in an ICU with continuous arterial blood pressure monitoring and continuous infusion of antihypertensive agents. According to the 2017 American College of Cardiology/American Heart Association hypertension guidelines, for adults with a compelling condition (aortic dissection, severe preeclampsia or eclampsia, or pheochromocytoma crisis), SBP should be reduced to less than 140 mm Hg during the first hour and to less than 120 mm Hg in aortic dissection. For adults without a compelling condition, such as this patient, SBP should be reduced by no more than 25% within the first hour; then, if stable, to 160 mm Hg within the next 2 to 6 hours; and then cautiously to normal during the following 24 to 48 hours.

Because autoregulation of tissue perfusion is disturbed in hypertensive emergencies, reducing blood pressure too rapidly can result in ischemic organ damage. Therefore, targeting a blood pressure of 120/80 mm Hg during the first hour of treatment is inappropriate because it could result in further worsening of kidney injury, encephalopathy, or both.

Conversely, lowering the SBP to 160 mm Hg during 48 hours is likely too slow and not in keeping with current guidelines.

This patient's normal medication combined with observation is not aggressive enough. Eventually he will need a stable outpatient hypertension regimen with education on the importance of adherence to that regimen, but not in this acute setting.

Answers and Critiques

KEY POINT

- For adults with a hypertensive emergency and without a compelling condition (such as aortic dissection) systolic blood pressure should be reduced by no more than 25% within the first hour; then, if stable, to 160 mm Hg within the next 2 to 6 hours; and then cautiously to normal during the following 24 to 48 hours.

Bibliography

Whelton PK, Carey RM, Aronow WS, Casey DE Jr, Collins KJ, Dennison Himmelfarb C, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Hypertension. 2017. [PMID: 29133356] doi:10.1161/HYP.0000000000000065

H

Item 60 Answer: A

Educational Objective: Treat a patient for cyanide poisoning as a coexposure to carbon monoxide poisoning after a house fire.

This patient should be treated with intravenous hydroxocobalamin, which is the preferred antidote for cyanide poisoning. Cyanide toxicity is common in victims of house fires, with up to 90% of rescued victims having elevated cyanide levels and 35% having significantly elevated levels, which is higher than the rate of carbon monoxide poisoning among such victims. Cyanide disrupts oxidative phosphorylation, forcing cells to convert to anaerobic metabolism despite adequate oxygen supply. The result in severe cases is multiorgan failure with coma, seizures, and cardiovascular symptoms, including hypotension, bradycardia, heart block, and ventricular arrhythmias. Early manifestations are nonspecific. Diagnostic clues include lactic acidosis and inappropriately elevated central venous oxyhemoglobin saturation, which manifests as bright red venous blood. Cyanide levels are not readily available and because toxicity is rapidly fatal, prompt empiric treatment is imperative in suspected cases. Hydroxocobalamin avidly binds to cyanide to produce cyanocobalamin, which is soluble, nontoxic, and readily excreted. In addition, ongoing exposure, such as contaminated clothing, should also be eliminated. Hydroxocobalamin can affect accuracy of lab results for methemoglobin, lactate, and other tests, so it is important to obtain blood for these tests before administering the antidote, if possible.

Carbon monoxide is removed by competitive binding of oxygen to hemoglobin. The initial treatment is administration of 100% oxygen, which reduces the half-life of carboxyhemoglobin from 5 hours to 90 minutes. Hyperbaric oxygen therapy yields an even higher alveolar Po_2, thereby reducing the half-life to 30 minutes while substantially increasing the amount of oxygen directly dissolved in blood. However, hyperbaric oxygen therapy would not be appropriate because this patient's carboxyhemoglobin level is not high enough to suggest severe carbon monoxide poisoning. Hyperbaric oxygen is usually recommended for levels of 25% to 40% or higher, or for victims with lower levels who are pregnant.

Methylene blue would be recommended for toxic levels of methemoglobin, usually 20% to 30% or higher, but it is not indicated for this patient.

Although sodium nitrite is an antidote for cyanide poisoning, it is contraindicated in victims of smoke inhalation because it works by inducing methemoglobinemia, which would further impair oxygen delivery by additive or synergistic effects on oxygen binding and delivery in cases of carbon monoxide toxicity.

Sodium thiosulfate is also used as an antidote for cyanide toxicity and is safer than sodium nitrite, but has a slower onset of action. It is considered second-line therapy after hydroxocobalamin, but the two agents can be given to the same patient, possibly with synergistic effect. However, they should not be administered simultaneously or through the same intravenous catheter.

KEY POINT

- Hydroxocobalamin effectively removes cyanide from the mitochondrial respiration system and is the preferred antidote for cyanide poisoning.

Bibliography

Hamad E, Babu K, Bebarta VS. Case files of the University of Massachusetts Toxicology Fellowship: Does this smoke inhalation victim require treatment with cyanide antidote? J Med Toxicol. 2016;12:192-8. [PMID: 26831054] doi:10.1007/s13181-016-0533-0

Item 61 Answer: C

Educational Objective: Manage a patient with clinical signs of cystic fibrosis and a negative sweat chloride test.

The most appropriate next step is to repeat the sweat chloride testing. Diagnosis of cystic fibrosis (CF) is based on a combination of CF-compatible clinical findings in conjunction with either biochemical (sweat testing, nasal potential difference) or genetic (*CFTR* mutations) techniques. Genetic counseling should always occur before any genetic test is performed. The essential components of counseling include informing the patient of the test purpose, implications of diagnosis, and alternative testing options. Ultimately, the decision of whether or not to be tested rests with the patient. Use of the sweat test has been the mainstay of laboratory confirmation. Negative sweat chloride testing does not exclude the diagnosis of CF. This patient has many findings suggestive of CF upper-lobe predominant bronchiectasis, chronic sinus disease, colonization with *Pseudomonas*, clubbing, and infertility. Therefore, the index of suspicion for CF, as well as ciliary dyskinesia disorders, is extremely high for this patient. Because sweat chloride testing can give variable results, it is appropriate to repeat the testing and, if still negative, refer the patient to a center with expertise in CF or genetic testing.

Chronic oral macrolide antibiotics and inhaled antibiotic therapy are beneficial in patients with a confirmed diagnosis of CF. However, individuals with bronchiectasis are often exposed to several courses of antibiotics, and resistance to quinolones is common. Therefore, initiation of chronic ciprofloxacin therapy is not indicated.

In a recent phase 3 trial, tiotropium was well tolerated in patients with CF, but lung function improvements compared with placebo were not statistically significant and such treatment is not generally recommended.

Patients with α_1-antitrypsin deficiency can present with lung disease and liver disease. A characteristic radiographic finding of the emphysema associated with α_1-antitrypsin deficiency is bullous changes most prominent at the bases, which are not present in this patient. Additionally, α_1-antitrypsin deficiency cannot account for the patient's sinus disease or infertility. Therefore, α_1-antitrypsin deficiency testing would not be the most appropriate next diagnostic test in this patient with a clinical history suggestive of possible CF.

KEY POINT

- Negative sweat chloride testing does not exclude the *diagnosis of cystic fibrosis in patients with high pre-test probability of disease.*

Bibliography

Farrell PM, White TB, Ren CL, Hempstead SE, Accurso F, Derichs N, et al. Diagnosis of cystic fibrosis: consensus guidelines from the Cystic Fibrosis Foundation. J Pediatr. 2017;181S:S4-S15.e1. [PMID: 28129811] doi:10.1016/j.jpeds.2016.09.064.

Item 62 Answer: C

Educational Objective: Screen for lung cancer in a patient at high risk.

The most appropriate test is a low-dose CT scan of the chest. Annual low-radiation-dose CT has been shown to reduce lung cancer mortality (20% relative decrease in lung cancer deaths) among high-risk individuals and is now recommended by the U.S. Preventive Services Task Force and other expert groups. Patients recommended for screening are those aged 55 to 74-80 years (range differs among expert groups) with a greater than 30-pack-year history of tobacco use within the prior 15 years, and without signs or symptoms suggestive of lung cancer. This patient fulfills these criteria and is, therefore, an appropriate candidate for a low-dose CT scan of the chest. Patients must also receive in-office counseling regarding the potential benefits and harms of screening, and documentation of shared decision making.

Monitoring respiratory parameters during exertion with the 6-minute walk test (6MWT) is helpful to assess disability and prognosis in chronic lung conditions. During a 6MWT, oxygen saturation, heart rate, dyspnea and fatigue level, and distance walked in 6 minutes are recorded. This relatively simple maneuver quantifies exercise tolerance, determines effective interventions, and helps predict morbidity and mortality. This patient has no indication for a 6MWT.

Chest radiography has been shown to be ineffective in screening for lung cancer and is not indicated in an asymptomatic patient such as this one.

Spirometry is warranted in any patient presenting with dyspnea, chronic cough, or sputum production. Screening for lung disease with spirometry should not be performed in asymptomatic patients, even those with a history of smoking.

Urinary cotinine is a metabolite of nicotine that is excreted in the urine and can be measured to assess if patients are using tobacco products. It is sometimes used while patients are actively attempting to quit smoking to assess adequacy of nicotine replacement therapy and monitor abstinence. This patient is high risk and a candidate for screening regardless of his current smoking status, and this test is not indicated.

KEY POINT

- Patients recommended for lung cancer screening are those aged 55 to 74-80 years with a greater than 30-pack-year history of tobacco use within the previ*ous 15 years, and without signs or symptoms suggestive of lung cancer.*

Bibliography

Mazzone PJ, Silvestri GA, Patel S, Kanne JP, Kinsinger LS, Wiener RS, et al. Screening for lung cancer: CHEST guideline and expert panel report. Chest. 2018;153:954-985. [PMID: 29374513] doi:10.1016/j.chest.2018.01.016

Item 63 Answer: D

H

Educational Objective: Manage oversedation in a patient in the ICU.

The most appropriate management is to stop sedation and analgesia. Clinicians at the bedside may resist stopping sedation and analgesia in a patient with a clear need for both, or because of concerns with ventilator synchrony or oxygenation. Protocolized care can help guide nursing and respiratory therapy if these problems arise. In addition, daily protocolized interruptions of sedation and analgesia have been shown to decrease the incidence of delirium, the need for diagnostic testing, and the amount of time spent on mechanical ventilation and in the ICU. Stopping sedation and analgesia, rather than gradually decreasing them, allows for a faster return to awareness and titration of infusions to achieve the sedation and analgesia goal. Analgesia and sedation can be restarted, at lower doses, if the patient requires them later.

Dexmedetomidine has pharmacological properties that may benefit this patient (analgesia, allows arousal). However, there is currently no evidence that it is superior to appropriately titrated propofol.

Ordering a CT scan is not the most appropriate first step in management of an unresponsive patient with nonfocal physical examination findings currently being treated with propofol and morphine. Moreover, a CT would expose the patient to the risks of being moved while critically ill and

H CONT.

unnecessary radiation. The rate of serious events during transport is important enough to warrant careful determination of need.

Ordering an electroencephalogram to assess his unresponsiveness would be part of the diagnostic evaluation if interruption of sedation did not lead to improved mental status. Nonconvulsive status epilepticus has been reported in up to 20% of patients with unexplained unresponsiveness. Current recommendations suggest continuous electroencephalogram as the diagnostic test of choice.

KEY POINT

- Daily protocolized interruptions of sedation and analgesia have been shown to decrease the incidence of delirium, the need for diagnostic testing, and the amount of time spent on mechanical ventilation and in the ICU.

Bibliography

Barr J, Fraser GL, Puntillo K, Ely EW, Gélinas C, Dasta JF, et al; American College of Critical Care Medicine. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. Crit Care Med. 2013;41:263-306. [PMID: 23269131] doi:10.1097/CCM.0b013e3182783b72

H

Item 64 Answer: E

Educational Objective: Treat heat stroke with evaporative cooling techniques.

This patient should be sprayed with water, and fans should be used to lower his body temperature to a safe level (usually 38.5 °C (101 °F) through evaporative cooling. Heat stroke occurs with high ambient temperature and humidity and is defined by the presence of a temperature greater than 40.0 °C (104.0 °F) and encephalopathy. It is often associated with hypotension, gastrointestinal distress, and weakness. Patients with advanced heat stroke exhibit shock, multiorgan failure, rhabdomyolysis, and myocardial ischemia. Exertional heat stroke typically occurs in healthy individuals undergoing vigorous physical activity in warm conditions. In contrast, most patients with nonexertional heat stroke are older than 70 years of age or have chronic medical conditions that impair thermal regulation. Medications and recreational drugs with anticholinergic, sympathomimetic, and diuretic effects, including alcohol, pose added risk. The primary treatment of nonexertional heat stroke is evaporative, external cooling. This involves removing all clothing and spraying the patient with a mist of lukewarm water while continuously blowing fans on the patient. Evaporative and convective cooling techniques are generally the safest and most effective.

Acetaminophen and other centrally acting antipyretics are ineffective in the treatment of heat stroke. A cooling blanket could be used as an adjunct, but it is not as effective as evaporative cooling.

Alcohol would evaporate and provide cooling as effective as that from applying water, but it would also be absorbed through the vasodilated skin and could lead to alcohol toxicity similar to that observed in patients who have ingested alcohol and is therefore contraindicated.

Although ice water immersion is sometimes used in younger patients with exertional heat stroke to lower the body temperature rapidly, there is evidence for increased mortality when this method is used in older patients. Also, this patient's core temperature of 40 °C (104 °F) is not so severe that more aggressive measures need to be considered.

The muscle relaxant dantrolene is ineffective in the treatment of heat stroke. It is used for malignant hyperthermia and sometimes for neuroleptic malignant syndrome, although this is an off label application.

KEY POINT

- Patients with nonexertional heat stroke should be treated with evaporative cooling to lower their core temperature to a safe level.

Bibliography

O'Connor JP. Simple and effective method to lower body core temperatures of hyperthermic patients. Am J Emerg Med. 2017;35:881-884. [PMID: 28162872] doi:10.1016/j.ajem.2017.01.053

Item 65 Answer: A

H

Educational Objective: Treat septic shock with crystalloid infusion as the initial resuscitative therapy.

This patient should receive a 0.9% saline bolus. He has signs of septic shock from influenza (fever, tachycardia, hypotension, elevated leukocyte count, and exposure to influenza). In patients with septic or distributive shock, initial resuscitation efforts should be aimed at giving crystalloid fluids (0.9% saline, Ringer's lactate). The 2016 Surviving Sepsis guidelines recommend giving 30 mL/kg crystalloid solution within 3 hours of presentation in patients who demonstrate signs of tissue hypoperfusion. Judicious fluid administration is warranted thereafter, as intravascular volume overload can contribute to pulmonary edema and pleural effusions. This patient has several features of hypoperfusion, including hypotension, tachycardia, metabolic acidosis, and an elevated blood lactate.

Furosemide would be appropriate if the patient were in cardiogenic shock and presenting with signs of volume overload. The history, examination, and chest radiograph are not consistent with cardiogenic shock or volume overload. Therefore, furosemide is not recommended and would only promote further hypotension.

If hypotension does not rapidly correct with fluids, vasopressors should be titrated to maintain a mean arterial pressure of 65 mm Hg or greater. Norepinephrine is considered first-line therapy. This patient has not received crystalloid solution yet so initial therapy with norepinephrine is incorrect. However, in patients who are refractory to volume loading, vasopressor therapy is recommended to help improve hemodynamic stability.

In the absence of extenuating circumstances (myocardial ischemia, severe hypoxemia, or active hemorrhage), the

H CONT.

Surviving Sepsis guidelines recommend that red blood cell transfusion only be given if hemoglobin is less than 7 g/dL (70 g/L). Because this patient has a hemoglobin level above 7 g/dL, there is no direct role for packed red blood cell transfusion.

KEY POINT

- Initial treatment of septic or distributive shock should focus on aggressive fluid resuscitation with crystalloids within the first 3 hours of presentation.

Bibliography

Rochwerg B, Alhazzani W, Sindi A et al. Fluid resuscitation in sepsis: a systematic review and network meta-analysis. Ann Intern Med. 2014;161:347. [PMID 25047428]

H

Item 66 Answer: B

Educational Objective: Treat a patient in cardiac arrest due to accidental hypothermia with prolonged cardiopulmonary resuscitation and active internal rewarming.

Cardiopulmonary resuscitation (CPR) should be continued with active internal (core) rewarming. Conventional treatment of ventricular arrhythmias and asystole is often ineffective until the temperature is raised to greater than 30.0 °C (86.0 °F). Because severe hypothermia may appear clinically similar to death, aggressive rewarming is appropriate in all patients in the absence of obvious irreversible signs of death. A critical first step entails removing wet clothing and covering the patient with insulating material, especially the head and neck. For mildly hypothermic, healthy individuals capable of shivering, this strategy of passive external rewarming alone suffices. Active external rewarming using warm blankets or a forced heated air blanket is commonly used in hemodynamically stable patients with moderate hypothermia. Body cavity lavage with warm fluids is an option for patients with hypothermia that is severe or does not respond to external rewarming. The colon, bladder, and stomach are readily accessible for irrigation but have a small surface area for heat exchange. Rewarming by peritoneal or pleural space irrigation is supported by case reports. Extracorporeal support, including cardiopulmonary bypass, is recommended for patients in cardiac arrest because it maximizes the rewarming rate and can provide hemodynamic support.

Although this man has already received nearly an hour of CPR, there are reports of full recovery in patients with cardiac arrest in the setting of accidental hypothermia, sometimes even after CPR has been performed for many hours. Therefore, continued CPR is indicated until the patient can be rewarmed. Discontinuation of CPR is not appropriate because hypothermia prevents reaching a definite conclusion about the futility or possible effectiveness of continued resuscitation.

KEY POINT

- Cardiopulmonary resuscitation should be continued in patients with accidental hypothermia accompanied by cardiac arrest until the patient can be rewarmed.

Bibliography

Hilmo J, Naesheim T, Gilbert M. "Nobody is dead until warm and dead": prolonged resuscitation is warranted in arrested hypothermic victims also in remote areas—a retrospective study from northern Norway. Resuscitation. 2014;85:1204-11. [PMID: 24882104] doi:10.1016/j.resuscitation.2014.04.029

Item 67 Answer: B

Educational Objective: Treat high-altitude cerebral edema with dexamethasone.

The most appropriate treatment is dexamethasone. Hypoxia and hypocapnia associated with altitude alter cerebral blood flow and oxygen delivery to the brain. When autoregulatory mechanisms are overcome, symptoms may be mild, as with acute mountain sickness, or severe, as with life-threatening cerebral edema. Acute mountain sickness is characterized by nonspecific symptoms such as headache, fatigue, nausea, and vomiting, in addition to disturbed sleep. High-altitude cerebral edema is a more extreme manifestation of acute mountain sickness. Vascular leak leads to brain swelling, resulting in manifestations that range from confusion and irritability to ataxic gait to coma and death. Recognition of cerebral edema mandates immediate intervention. This patient is exhibiting signs and symptoms of encephalopathy indicative of high-altitude cerebral edema, the risk of which increases at more extreme elevations (higher than 3000 meters [9842 feet]). Although the most important intervention is descent to lower elevation, dexamethasone should be administered immediately upon recognition of high-altitude cerebral edema. Supplemental oxygen should also be administered.

High-altitude illness can be prevented by gradually ascending, which can generally be accomplished by spending one night at an intermediate altitude to allow acclimatization. Acetazolamide accelerates the acclimatization process to high altitude by inducing a slight metabolic acidosis to stimulate ventilation and enhance gas exchange; it can be used prophylactically in patients with a history of altitude illness. However, it isn't an effective treatment once symptoms develop; although it may be used as an adjunct to dexamethasone, it has no role in high-altitude cerebral edema as monotherapy.

Nifedipine is used as a preventive and therapeutic agent for high-altitude pulmonary edema.

Another vasodilator, sildenafil, may be used as an alternative to nifedipine in high-altitude pulmonary edema. However, neither is useful in the treatment of high-altitude cerebral edema.

KEY POINT

- Although the most important treatment of high-altitude cerebral edema is descent to lower elevation, dexamethasone should be administered immediately upon recognition of high-altitude cerebral edema.

Bibliography

Luks AM, Swenson ER, Bärtsch P. Acute high-altitude sickness. Eur Respir Rev. 2017;26. [PMID: 28143879] doi:10.1183/16000617.0096-2016

H

Item 68 Answer: C

Educational Objective: Treat a critically ill patient who has acute pain.

This patient should receive an intravenous push of morphine. He has acute postoperative pain of the leg and is experiencing severe pain despite a morphine infusion. Analgesia should be titrated to a specific pain management goal while preventing and monitoring for side effects. A bolus dose of morphine will reach therapeutic levels faster than changing rates of infusion. The bolus dose should be repeated until the patient achieves the therapeutic goal, a protocol limit is reached, or side effects occur. He should be monitored closely while receiving acute pain treatment. Common side effects include somnolence, depression of respiratory drive, urinary retention, and nausea and vomiting.

Adding gabapentin is a good strategy for patients with neuropathic pain. Enteral gabapentin added to parenteral opioids can reduce the doses of opiates needed and improve pain control in mechanically ventilated patients. However, this patient is experiencing acute nonneuropathic pain and an intravenous opioid is the drug class of choice.

Epidural analgesia is an effective means to control pain in critically ill patients. This has been demonstrated in patients with cardiac or thoracic surgery or in the setting of rib fractures. It can lead to a reduction of opiate dosing and improved pain control during dressing changes in patients such as this one; however, it takes time to implement and the patient should receive acute pain control before consideration of alternatives to improve his baseline pain control.

Changing the medication to fentanyl is not appropriate as all intravenously administered opioids have equi-analgesic efficacy and are associated with similar clinical outcomes when titrated to similar pain intensity end points. The choice of opiate should be based on pharmacological properties. Fentanyl has a shorter half-life than morphine, and this patient was not having any adverse effect or contraindication to morphine.

KEY POINT

- Intravenous opioids are the first-line drug class of choice to treat nonneuropathic pain in critically ill patients; all intravenously administered opioids have equi-analgesic efficacy and are associated with similar clinical outcomes when titrated to similar pain intensity end points.

Bibliography

Barr J, Fraser GL, Puntillo K, Ely EW, Gélinas C, Dasta JF, et al; American College of Critical Care Medicine. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. Crit Care Med. 2013;41:263-306. [PMID: 23269131] doi:10.1097/CCM.0b013e3182783b72

Item 69 Answer: D

Educational Objective: Manage an asymptomatic patient with stage I pulmonary sarcoidosis.

This patient should be managed with observation and clinical follow-up. She is incidentally discovered to have bilateral hilar lymphadenopathy likely representing pulmonary sarcoidosis.

Pulmonary sarcoidosis is classified based on the radiographic pattern: stage I, hilar lymphadenopathy with normal lung parenchyma; stage II, hilar lymphadenopathy with abnormal lung parenchyma; stage III, no lymphadenopathy with abnormal lung parenchyma; and, stage IV, parenchymal changes with fibrosis and architectural distortion. For patients such as this, a careful history and physical examination to rule out the possibility of lymphoma and infection are essential. In a series of 100 consecutive patients with bilateral hilar lymphadenopathy, none with either lymphoma or infection were asymptomatic. Furthermore, approximately 75% of patients with stage I pulmonary sarcoidosis, such as this patient, have spontaneous resolution of the hilar lymphadenopathy. Patients can, however, have extrapulmonary disease, and screening electrocardiography, assessment of serum calcium, and eye examination are appropriate initial tests in this population.

Endobronchial ultrasound is a bronchoscopic technique that involves the use of an ultrasound probe at the distal end of the bronchoscope. The ultrasound-tipped bronchoscope can identify mediastinal lymph nodes and increase the yield of a transbronchial needle aspiration by allowing direct visualization of the needle entering the lymph node. This can be used to visualize and biopsy structures adjacent to an airway. This patient has no need for endobronchial ultrasound and biopsy.

Obtaining a high-resolution CT of the chest in this patient may result in further findings of parenchymal lung disease; however, she is asymptomatic and the finding of parenchymal lung disease would not necessitate a change in management at this early stage.

Glucocorticoids are the mainstay of therapy for sarcoidosis. Treatment is usually limited to those with evidence of clinical symptoms from organ dysfunction. Because there is a high rate of spontaneous remission and stability, most treatment protocols favor a period of observation without therapy. The decision to initiate glucocorticoid therapy for sarcoidosis should be based on symptoms or physiologic impairment that is attributable to sarcoid disease. Therefore, treatment with prednisone is not indicated for this patient.

KEY POINT

- Treatment of pulmonary sarcoidosis should be based on symptoms rather than radiographic findings.

Bibliography

Baughman RP, Culver DA, Judson MA. A concise review of pulmonary sarcoidosis. Am J Respir Crit Care Med. 2011;183:573-81. [PMID: 21037016] doi:10.1164/rccm.201006-0865CI

H

Item 70 Answer: D

Educational Objective: Prevent ventilator-associated lung injury.

The most appropriate next step is to reduce the tidal volume. This patient fulfills the definition of acute respiratory

H CONT.

distress syndrome (ARDS) with presentation within 1 week of known insult, arterial Po_2/Fio_2 ratio of 300 with positive end-expiratory pressure (PEEP) of 5 cm H_2O or greater, and bilateral otherwise unexplained opacities seen on frontal chest imaging. Common pulmonary causes of ARDS include pneumonia (most common), aspiration, inhalational injury, near drowning, and drugs. Although ARDS mortality remains high, significant reductions in mortality have been attributed to the use of lung protective ventilation strategies. These strategies generally include limiting the tidal volume given in mechanical ventilation to 6 mL/kg of ideal body weight, limiting the plateau pressure in the respiratory cycle to no more than 30 cm H_2O, and use of adequate PEEP to prevent the collapse of unstable alveolar units in the expiratory phase of the cycle. In the 2000 ARMA trial, low tidal volume ventilation (LTVV) was associated with a 9% absolute reduction in mortality when patients were ventilated at a goal of 6-8 mL/kg of ideal body weight compared with more liberal tidal volumes of 10-12 mL/kg. However, implementation of LTVV remains challenging for several reasons. Among them, patients who receive LTVV often demonstrate signs of air hunger. This can lead to ventilator dyssynchrony and increased sedation requirements.

Current recommendations are to use a PEEP level that achieves adequate oxygenation with an Fio_2 of less than 0.6 and does not cause hypotension. These parameters are being met with the current level of PEEP; therefore, adjustment of PEEP is not the most appropriate next step.

If the respiration rate remains constant, a lower tidal volume will reduce the total minute ventilation and thus reduce CO_2 removal. This results in higher arterial Pco_2 and lower arterial pH. In the ARMA trial, LTVV-related hypercapnea was permitted, provided the arterial pH did not go below 7.3. In cases where the pH did drop below 7.3, respiration rate was increased to improve minute ventilation and decrease the Pco_2. The patient's Pco_2 and pH are acceptable and adjustment of the respiration rate is not the most appropriate next step.

KEY POINT

- The use of low tidal volume ventilation and positive end-expiratory pressure is associated with prevention of ventilator-associated lung injury and a reduction in mortality related to acute respiratory distress syndrome.

Bibliography

Thompson BT, Chambers RC, Liu KD. Acute respiratory distress syndrome. N Engl J Med. 2017;377:562-572. [PMID: 28792873] doi:10.1056/NEJMra1608077

H

Item 71 Answer: D

Educational Objective: Recognize an emergently placed central venous catheter as a potential source of sepsis.

The most appropriate management for this patient is removal of the central venous catheter. Morbidity and mortality in patients with sepsis are heavily influenced by the care delivered during the first several hours after sepsis onset. Once sepsis is recognized, interventions focus on adequate fluid resuscitation. Crystalloid is recommended at a volume of 30 mL/kg of body weight. In septic shock, mortality increases with each hour that appropriate antibiotic therapy is delayed. Two sets of blood cultures should be obtained before antibiotic infusion in addition to cultures from the suspected infection site. Empiric antimicrobial treatment should cover all suspected pathogens, with special attention to risk factors for resistant or opportunistic organisms, including methicillin-resistant *Staphylococcus aureus* and *Pseudomonas* species. Identification and control of the source of infection are critical steps in managing sepsis. This patient may have sepsis due to a central line-associated bloodstream infection. Removal of the emergently placed central venous catheter is the next critical management step.

Glucocorticoid administration is not recommended for patients without shock or who have responded to fluids and vasopressors because it offers no benefit. Some studies suggest that glucocorticoid therapy might benefit patients who remain hypotensive following adequate fluid resuscitation and vasopressor therapy. It is premature to consider administering glucocorticoids to this patient without first assessing the response to the initial resuscitation attempts.

If hypotension does not rapidly correct with fluids, vasopressors should be titrated to maintain a mean arterial pressure of 65 mm Hg or greater. Norepinephrine is considered first-line therapy. Because fluid resuscitation has just been initiated, it is premature to consider vasopressor therapy. If vasopressor therapy is needed, a new intravenous catheter should be placed rather than using the existing catheter, which is suspected as the source of infection.

The biologic marker procalcitonin may help differentiate between bacterial and nonbacterial pneumonia and help exclude a bacterial community-acquired pneumonia diagnosis in outpatients where there is already low suspicion. Procalcitonin level has no evidence-based role in the management of sepsis in the hospital.

KEY POINT

- Fluid resuscitation, administration of antibiotics, and infection source control are essential in the early sepsis management.

Bibliography

Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, et al. Surviving Sepsis Campaign: international guidelines for management of sepsis and septic shock: 2016. Crit Care Med. 2017;45:486-552. [PMID: 28098591] doi:10.1097/CCM.0000000000002255

Item 72 Answer: A

Educational Objective: Evaluate a patient with excessive daytime sleepiness with actigraphy.

The most appropriate management is testing with actigraphy. The initial step in the evaluation of the patient with excessive daytime sleepiness is to ensure adequate quantities (7 to 8 hours) of sleep on a regular basis. This patient's self-report

of a variable bedtime and restricted sleep schedule during the workweek raises the possibility of insufficient sleep syndrome. Wrist actigraphy measures movement and ambient light to estimate nightly sleep periods during a 1 to 2 week time frame. Actigraphy is more accurate than patient reports of sleep duration and is likely more accurate than sleep diaries. When actigraphy isn't available, a sleep diary can be a useful alternative. Insufficient sleep syndrome suggested by either actigraphy or sleep diary should prompt a trial of sleep extension.

Modafinil is a stimulant medication used in hypersomnia syndromes such as narcolepsy. It would not be appropriate therapy without first excluding insufficient sleep syndrome.

Multiple sleep latency testing can be useful in the evaluation of pathologic daytime sleepiness (for example, narcolepsy) and may help establish a diagnosis of narcolepsy, but it is resource intensive and expensive. It should be performed only after addressing insufficient sleep quantities and polysomnography has ruled out common sleep disorders such as sleep apnea.

Polysomnography or home sleep testing would be indicated if the clinical history strongly suggested a primary sleep disorder such as obstructive sleep apnea. However, obstructive sleep apnea is unlikely in a young woman who is not overweight and does not have obvious upper airway abnormalities. In addition, the patient is suspected of having a restricted sleep schedule that should be evaluated first with actigraphy.

KEY POINT

- The initial step in the evaluation of the patient with excessive daytime sleepiness is to ensure adequate quantities of sleep on a regular basis using either actigraphy or a sleep diary.

Bibliography

Watson NF, Badr MS, Belenky G, Bliwise DL, Buxton OM, Buysse D, et al; Consensus Conference Panel. Recommended amount of sleep for a healthy adult: a joint consensus statement of the American Academy of Sleep Medicine and Sleep Research Society. J Clin Sleep Med. 2015;11:591-2. [PMID: 25979105] doi:10.5664/jcsm.4758

H

Item 73 Answer: A

Educational Objective: Diagnose a complicated parapneumonic effusion.

This patient has community-acquired pneumonia and complicated parapneumonic effusion. A complicated parapneumonic effusion is defined as an effusion associated with a pneumonia that has a pH less than 7.2 and glucose less than 60 mg/dL (3.3 mmol/L). Complicated parapneumonic effusions occur when bacteria invade the pleural space. However, because bacteria may be cleared rapidly from the pleural space, the Gram stain is typically negative and cultures are usually sterile. Complicated parapneumonic effusions have a variable response to antibiotics alone. Pleural effusions greater than 10 mm in depth on chest radiograph and associated with a pneumonic illness should be sampled. In general, these require thoracostomy tube drainage when the pH is less than 7.2 or the pleural fluid glucose level is less than 60 mg/dL (3.3 mmol/L). The American College of Chest Physicians consensus guidelines concur as thoracostomy drainage speeds clinical recovery and hospital discharge.

An empyema is defined as a bacterial infection of the pleural space that results in frank pus on visual inspection of the pleural fluid or a positive Gram stain. A positive pleural fluid culture is not required for diagnosis as cultures are less sensitive than Gram stain in the detection of bacteria. The management of empyema includes early thoracic surgical consultation because thoracoscopic or open debridement and drainage is often required to successfully manage this condition. However, this patient's pleural fluid was described as serous and the Gram stain was negative making empyema an unlikely diagnosis.

Pleural fluid acidosis (pH less than 7.3) is seen in complicated parapneumonic effusions, tuberculous pleuritis, rheumatoid and lupus pleuritis, esophageal rupture, and malignancy. A low pleural fluid glucose level results from either increased utilization within the pleural space (bacteria, malignant cells) or decreased transport into the pleural space (rheumatoid pleurisy), and a concentration less than 60 mg/dL (3.3 mmol/L) narrows the differential diagnosis significantly. Although a malignant effusion can have a low pH and glucose, this patient's presentation is more consistent with a parapneumonic effusion.

An uncomplicated parapneumonic effusion is characterized by a pH greater than 7.2 and glucose greater than 60 mg/dL (3.3 mmol/L). These effusions do not require drainage and typically resolve with antibiotic therapy alone.

KEY POINT

- In general, parapneumonic effusions associated with a pH less than 7.2 or pleural fluid glucose level less than 60 mg/dL (3.3 mmol/L) require thoracostomy drainage in addition to antibiotics.

Bibliography

Colice GL, Curtis A, Deslauriers J, Heffner J, Light R, Littenberg B, et al. Medical and surgical treatment of parapneumonic effusions: an evidence-based guideline. Chest. 2000;118:1158-71. [PMID: 11035692]

Item 74 Answer: B

Educational Objective: Provide recommended vaccinations for patients with COPD.

This patient should receive the pneumococcal polysaccharide vaccine and an annual influenza vaccine. Influenza vaccination has been shown to reduce serious illness (such as lower respiratory tract infections that require hospitalization) and death in patients with COPD. These vaccines should be administered annually in all patients with COPD. There are currently three different types of influenza vaccine available in the United States:

inactivated influenza vaccine, live attenuated influenza vaccine, and recombinant trivalent influenza vaccine. Inactivated influenza vaccine is approved for use in all adults, including immunosuppressed persons and pregnant women.

A high-dose inactivated influenza vaccine is approved for use in adults age 65 years and older; it has been shown to be modestly more effective than the standard-dose inactivated influenza vaccine in this patient population.

Pneumococcal vaccination is indicated for all adults aged 65 years and older and for high-risk persons younger than 65 years. Two vaccines are currently available: pneumococcal polysaccharide vaccine (PPSV23) is composed of polysaccharide capsular material from 23 pneumococcal subtypes, whereas pneumococcal conjugate vaccine (PCV13) contains capsular material from 13 subtypes conjugated to a nontoxic protein, which increases its immunogenicity. For pneumococcal vaccine–naïve adults between the ages of 19 and 65 years with certain immunocompromising conditions or who are otherwise at high risk, a single dose of PCV13 should be given. These conditions include functional or anatomic asplenia, cerebrospinal fluid leaks, cochlear implants, and conditions causing immunosuppression. All patients should also receive the 13-valent pneumococcal conjugate vaccine at age 65 years, although the polysaccharide and conjugate vaccines should be given sequentially at least a year apart for immunocompetent adults over age 65 rather than together for optimal effect. COPD alone is not an indication for PCV13 vaccination.

PPSV23 has the same indications as the PCV13 vaccine, plus it is indicated in immunocompetent people with certain chronic medical conditions such as heart, liver, and lung disease (COPD, emphysema, asthma) and diabetes, as well as in cigarette smokers. PPSV23 revaccination should be given at age 65 years if 5 years have elapsed since the previous pneumococcal immunization. When possible, the PCV13 vaccine should be administered first, followed by a dose of PPSV23 at least 1 year later for most immunocompetent patients. Some patients with immunocompromising conditions, cochlear implants, or cerebrospinal fluid leaks should receive the dose of PPSV23 at least 8 weeks after the first dose of PCV13. If a patient has already received the PPSV23 vaccine, a single dose of PCV13 should be given at least 1 year after the administration of PPSV23.

KEY POINT

- Annual influenza vaccination and the pneumococcal polysaccharide vaccine are recommended for all patients with chronic lung disease (COPD, emphysema, asthma).

Bibliography

Kim DK, Riley LE, Hunter P; Advisory Committee on Immunization Practices. Recommended immunization schedule for adults aged 19 years or older, United States, 2018. Ann Intern Med. 2018;168:210-220. [PMID: 29404596]

Item 75 Answer: D

Educational Objective: Treat a patient with chronic thromboembolic pulmonary hypertension.

This patient has chronic thromboembolic pulmonary hypertension (CTEPH) and the preferred treatment is pulmonary thromboendarterectomy. There are two diagnostic criteria for CTEPH: (1) mean pulmonary artery pressure of 25 mm Hg or higher by right heart catheterization in the absence of left heart pressure overload and (2) compatible imaging evidence of chronic thromboembolism. CT pulmonary angiography (CT-PA) may demonstrate proximally located abnormalities such as vascular webs, intimal irregularities, and luminal narrowing but has limited sensitivity in more distal lesions. Ventilation-perfusion scanning is a more sensitive indicator of CTEPH and is generally the preferred first imaging modality. Once CTEPH is suggested by noninvasive testing, conventional pulmonary angiography should be performed to characterize the extent and distribution of organized thrombus and to determine suitability for surgical intervention. Surgical intervention is the only definitive therapy for CTEPH and can prevent irreversible remodeling of the pulmonary arterial vasculature. Surgical evaluation at an experienced center is warranted in all patients with CTEPH; however, only about half of patients will be surgical candidates and fewer than that will opt for surgery.

Lifelong anticoagulant therapy, traditionally with warfarin, is indicated in all patients to help prevent further thromboembolism. Experience with direct oral anticoagulants such as apixaban is limited in this patient population. Because this patient's INR is in the therapeutic range, there's no proved advantage of switching from warfarin to apixaban.

Inferior vena cava interruption is typically indicated in patients with venous thrombus for whom anticoagulation is ineffective or not tolerated. In patients with CTEPH and coexisting clot in the lower extremities, inferior vena cava interruption can be considered to help prevent further thromboembolism; however, its role in long-term outcomes is not known and of unclear benefit.

Calcium channel blockers such as nifedipine are used in the setting of pulmonary arterial hypertension when right heart catheterization reveals acute vasoreactivity. Their role in the treatment of CTEPH is unproved.

KEY POINT

- Surgical intervention is the only definitive therapy for chronic thromboembolic pulmonary hypertension (CTEPH), and most patients with CTEPH should be referred for evaluation at a specialty surgical center.

Bibliography

Edward JA, Mandras S. An Update on the management of chronic thromboembolic pulmonary hypertension. Curr Probl Cardiol. 2017;42:7-38. [PMID: 27989311] doi:10.1016/j.cpcardiol.2016.11.001

H

Item 76 Answer: A

Educational Objective: Evaluate readiness to liberate from mechanical ventilation in a patient with COPD.

A 30-minute spontaneous breathing trial (SBT) should be performed using low levels of pressure support (8 cm H_2O or less). Weaning from mechanical ventilation can start when the precipitating event or underlying condition that caused respiratory failure has resolved or is resolving. Patients should be assessed daily for their readiness to be removed from mechanical ventilation by performing an SBT. There are several methods used to assess if an SBT is successful. One criterion is the ability to tolerate a weaning trial for 30 minutes (in most patients, SBT failure will occur within approximately 20 minutes). 2-hour SBTs and 30-minute SBTs have a similar ability to recognize patients who are unable to breathe spontaneously. However a 30-minute trial has the benefits of less time on mechanical ventilation and less risk of respiratory muscle fatigue. If the patient successfully completes an SBT, the ability to follow commands, clear secretions, and a patent upper airway are other criteria that should be met to increase extubation success.

A "cuff leak" refers to measurable airflow around the endotracheal tube after the cuff of the endotracheal tube is deflated. Absent or minimal cuff leak following deflation of the cuff indicates reduced space between the endotracheal tube and the larynx. Minimal or absent cuff leak may be due to laryngeal edema, laryngeal stenosis, and thick secretions. The test is not standardized and not performed routinely and is not an initial routine test in the process of liberating a patient from mechanical ventilation. It might be considered in a patient who has a successful SBT but is at high risk for edema and stridor following extubation.

The Glasgow Coma Scale is pertinent to the actual extubation process, in which lack of awareness and ability to clear secretions and follow simple commands may increase the risk of aspiration and cooperation in the postextubation period. However, this patient should be placed on an SBT before being evaluated for extubation.

Negative inspiratory force has been used as a marker of inspiratory muscle strength to identify patients who will be able to be liberated from mechanical ventilation. However, there are technical issues that lead to variable predictive performance. A low negative inspiratory force by itself is not useful; however, serial measurements (for example, in patients with Guillain-Barré or myasthenia gravis) along with other measures (FVC, maximum tidal volume) may give a better picture of muscle strength recovery.

KEY POINT

- Patients should be assessed daily for their readiness to be removed from mechanical ventilation by performing a spontaneous breathing trial; one criterion for success is the ability to tolerate a spontaneous breathing trial for 30 minutes.

Bibliography

Schmidt GA, Girard TD, Kress JP, Morris PE, Ouellette DR, Alhazzani W, et al. Liberation from mechanical ventilation in critically ill adults: executive summary of an official American College of Chest Physicians/American Thoracic Society Clinical Practice Guideline. Chest. 2017;151:160-165. [PMID: 27818329] doi:10.1016/j.chest.2016.10.037

Item 77 Answer: C

H

Educational Objective: Treat a patient with empyema.

Instillation of intrapleural tissue plasminogen activator-deoxyribonuclease (tPA-DNase) is the most appropriate treatment to promote drainage. This patient has a community-acquired pneumonia complicated by an empyema. The diagnostic criterion for empyema is either visualization of frankly purulent pleural fluid or a positive Gram stain. The Gram stain supports the diagnosis of *group A pneumoniae* pneumonia. An empyema requires drainage to resolve the infection. A small-bore (14-Fr) tube can be placed to facilitate drainage. An empyema can become loculated (divided into small cavities or compartments) and will not resolve with simple thoracostomy drainage; loculated empyemas often require thorascopic or open surgical debridement. This patient has an incompletely drained empyema due to loculation. When performed twice daily for 3 days, intrapleural administration of tPA-DNase has been shown to decrease the radiographic pleural opacity, lower the rate of surgical intervention, and decrease hospital stay of patients with empyema (MIST-2 trial). It should be noted that the tPA-DNase has not been shown to decrease mortality. In addition, video-assisted thorascopic surgery has also been shown to effectively manage empyema in greater than 90% of cases, and a delay in surgery increases the risk of open thoracotomy. Given the lack of prospective data, a multidisciplinary discussion should be undertaken for any patient presenting with an empyema who is a good surgical candidate.

Instillation of intrapleural antibiotic solution may be used for postsurgical empyema but has no demonstrated efficacy in the initial management of a loculated empyema.

The MIST-1 trial compared the use of intrapleural instillation of streptokinase compared to saline and found no difference in mortality, need for surgery, radiographic outcome, or length of hospitalization. Consequently, use of fibrinolytics alone in empyema is not recommended.

Continued systemic antibiotic therapy without adequate drainage of the pleural space is inadequate therapy. Failure to adequately drain the pleural space of a complicated pleural effusion or empyema will result in failure to resolve the infection, increased morbidity, and the possibility of death by overwhelming infection.

KEY POINT

- Instillation of intrapleural tissue plasminogen activator-deoxyribonuclease has been shown to decrease the radiographic pleural opacity, lower the rate of surgical referral, and decrease hospital stay of patients with empyema.

Bibliography

Rahman NM, Maskell NA, West A, Teoh R, Arnold A, Mackinlay C, et al. Intrapleural use of tissue plasminogen activator and DNase in pleural infection. N Engl J Med. 2011;365:518-26. [PMID: 21830966] doi:10.1056/NEJMoa1012740

Item 78 Answer: D

Educational Objective: Diagnose asthma in a symptomatic patient with normal spirometry.

Methacholine challenge testing is the most appropriate test to perform next for this patient with persistent cough and wheezing following a presumed viral upper respiratory tract infection. These symptoms can be the initial presentation of asthma, which is common in patients older than 65 years, with a prevalence of 8.1%; this age group also has the highest mortality rate, particularly in low-income Hispanic and black women. However, asthma is currently underdiagnosed and undertreated in patients older than 65 years in the United States. In patients with clinical symptoms suggestive of bronchospastic disease (such as cough or unexplained dyspnea) but with normal spirometry, bronchial challenge testing may be diagnostically helpful. Bronchial challenge testing uses a controlled inhaled stimulus to induce bronchospasm in association with spirometry; a positive test is indicated by a drop in the measured FEV_1. This symptomatic patient's spirometry is normal; therefore, methacholine challenge testing to evaluate for bronchial hyperresponsiveness is indicated.

Echocardiography could help evaluate cardiac function but the patient does not have findings of heart murmur or heart failure so this test would not be indicated.

Exhaled nitric oxide testing is a noninvasive breath test. Nitric oxide is normally present in airways but is increased in certain types of airway inflammation (asthma, eosinophilic airway inflammation). When elevated, it supports the diagnosis of asthma in the appropriate clinical context. Other factors may affect nitric oxide values such as age, sex, atopy, and cigarette smoking so a normal level in an older adult would not rule out asthma. The sensitivity and specificity of exhaled nitric oxide in the diagnosis of asthma are not well defined, particularly in patients with confounding variables, and it is not the preferred next test for this patient.

High-resolution CT (HRCT) is indicated if diffuse parenchymal lung disease is suspected. HRCT can help narrow the differential diagnosis based on the distribution of the lung parenchymal abnormalities and the presence or absence of associated findings. HRCT scan of the chest would not help confirm a diagnosis of asthma.

Nasal swab for influenza polymerase chain reaction would not be indicated because the patient's symptoms of a viral infection have resolved; furthermore, influenza testing in immunocompetent adults should be performed within 5 days of symptom onset.

KEY POINT

- The diagnosis of asthma requires demonstrating reversible airflow obstruction; for a patient with symptoms of asthma and normal spirometry, methacholine challenge testing to evaluate for bronchial hyperresponsiveness is indicated.

Bibliography

Al-Alawi M, Hassan T, Chotirmall SH. Advances in the diagnosis and management of asthma in older adults. Am J Med. 2014;127:370-8. [PMID: 24380710] doi:10.1016/j.amjmed.2013.12.013

Item 79 Answer: B

H

Educational Objective: Treat a patient who has anaphylaxis with epinephrine.

This patient should be treated with epinephrine. Anaphylaxis is defined as a severe, potentially life-threatening allergic or hypersensitivity reaction that occurs within seconds to a few hours of allergen exposure, most commonly food, medication, or an insect sting. Classically, anaphylaxis occurs when allergen-specific IgE coating the surface of mast cells and basophils comes in contact with the triggering allergen, thereby precipitating cellular degranulation. The resulting abrupt systemic release of a host of mediators has various effects, including vasoconstriction, vasodilation, increased vascular permeability, and bronchoconstriction. The presentation is variable and findings may include flushing, urticaria, and angioedema (85%); wheeze, stridor, and respiratory distress (70%); and hypotension and tachycardia (less commonly bradycardia) (45%). Initial symptoms and findings may be mild but predicting the ultimate severity of the episode is difficult. The first step in treatment is immediate intramuscular or intravenous administration of epinephrine. There are studies showing increased mortality from anaphylaxis if epinephrine is delayed. The dose may be repeated after 5-15 minutes, or administered continuously as an intravenous solution (although at a lower concentration), until the effects are apparent. Patients can also be given supplemental oxygen and monitored for signs of airway compromise, which may require intubation to maintain airway patency. Following recovery, patients should maintain home access to an epinephrine auto-injector and may benefit from evaluation for anaphylactic triggers.

Diphenhydramine, a histamine$_1$-blocker, is often given because of its effect on itching and urticaria, but it has never been shown to effectively treat distributive shock, airway edema, or outcome in anaphylaxis. It is not a substitute for epinephrine.

Although intravenous fluids are often needed to manage anaphylaxis, they are reserved for use in cases where hypotension persists despite treatment with epinephrine.

Glucocorticoids are often given to reduce the risk of recurrent or persistent symptoms. However, there are no randomized controlled trials that confirm the effectiveness of glucocorticoids in preventing symptom recurrence.

H CONT

More clinically relevant, a study of emergency department patients with anaphylaxis treated with glucocorticoids did not demonstrate a reduction in return visits to the emergency department for recurrent symptoms.

KEY POINT

- Epinephrine is the appropriate initial treatment of anaphylaxis.

Bibliography

Commins SP. Outpatient emergencies: anaphylaxis. Med Clin North Am. 2017;101:521-536. [PMID: 28372711] doi:10.1016/j.mcna.2016.12.003

H

Item 80 Answer: D

Educational Objective: Treat a patient with severe acute respiratory distress syndrome using early prone positioning.

This patient should be ventilated in the prone position. In patients with acute respiratory distress syndrome (ARDS) low tidal volume ventilation (6-8 mL/kg ideal body weight) is optimal and is associated with significantly better outcomes than conventional, higher tidal volume ventilation (10-12 mL/kg). In patients with severe ARDS, several adjunctive therapies have been studied, but few have demonstrated additional improved outcomes beyond low tidal volume ventilation. However, in 2013, the PROSEVA trial evaluated patients with ARDS who had an arterial Po_2/Fio_2 ratio of less than 150 (defining severe ARDS) despite significant ventilator support. Patients were randomized to conventional therapy or low tidal volume ventilation plus prone positioning within 36 hours of developing ARDS and respiratory failure. The results suggested a 16.2% reduction in 28-day all-cause mortality in the prone-position group. The 2017 American Thoracic Society, European Society of Intensive Care Medicine, and Society of Critical Care Medicine (ATS/ESICM/SCCM) guideline makes a strong recommendation that all patients with ARDS receive ventilation with lower tidal volumes (4-8 mL/kg of predicted body weight). Patients with severe ARDS should be also ventilated in the prone position for at least 12 hours per day. Proning should be considered standard management for patients with severe ARDS, not a form of "rescue" or "salvage" therapy.

Recruitment is the application of a high level of continuous positive airway pressure to open up collapsed alveoli (for example, continuous pressure to 35 cm H_2O for 40 seconds). The ATS/ESICM/SCCM guideline provides a conditional recommendation for recruitment maneuvers based on low to moderate confidence in the small to moderate magnitude of its effect on mortality. The guideline cautions that recruitment should not be used in patients with preexisting hypovolemia or shock due to hemodynamic deterioration, which can occur during the maneuver. This patient is hypotensive and, therefore, not a candidate for recruitment maneuvers.

Nitric oxide (NO) selectively dilates the pulmonary vasculature when administered by inhalation. Its use in acute hypoxemic respiratory failure is based on the rationale that inhaled NO may improve ventilation-perfusion mismatch. Studies of inhaled NO in patients with severe ARDS have demonstrated temporary improvement in oxygenation but no improvement in survival.

In 2013 two large, prospective randomized trials demonstrated that compared to low tidal volume ventilation, high-frequency oscillator ventilation was either no different or harmful to patients with ARDS. In light of this, the ATS/ESICM/SCCM guideline strongly recommends against routine use of high-frequency oscillatory ventilation.

KEY POINT

- Patients with severe acute respiratory distress syndrome have a demonstrated mortality benefit from low tidal volume ventilation in the prone position.

Bibliography

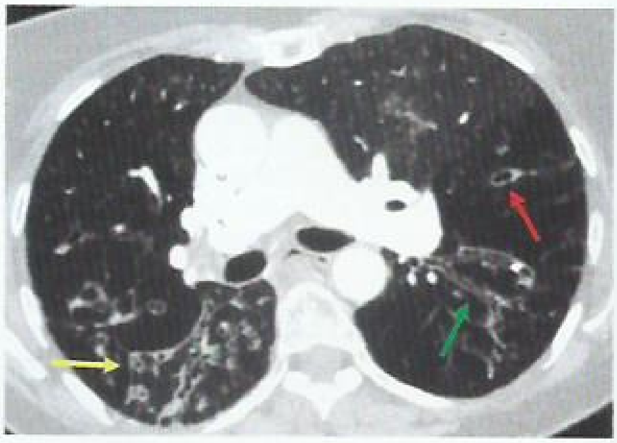
Fan E, Del Sorbo L, Goligher EC, Hodgson CL, Munshi L, Walkey AJ, et al; American Thoracic Society, European Society of Intensive Care Medicine, and Society of Critical Care Medicine. An official American Thoracic Society/European Society of Intensive Care Medicine/Society of Critical Care Medicine clinical practice guideline: mechanical ventilation in adult patients with acute respiratory distress syndrome. Am J Respir Crit Care Med. 2017;195:1253-1263. [PMID: 28459336] doi:10.1164/rccm.201703-0548ST

Item 81 Answer: A

Educational Objective: Diagnose bronchiectasis using chest CT imaging.

The most likely diagnosis is bronchiectasis. Bronchiectasis is irreversible pathologic dilation of the bronchi or bronchioles resulting from an infectious process occurring in the context of airway obstruction, impaired drainage, or abnormality in antimicrobial defenses. The pattern of lung involvement varies greatly with the underlying cause and may be focal or diffuse. Bronchiectasis causes a chronic or recurrent cough typically characterized by voluminous sputum production with purulent exacerbations. The vast majority of chest radiographs are abnormal, typically showing linear atelectasis, dilated and thickened airways, and irregular peripheral opacities. High-resolution CT (HRCT) of the chest is the definitive diagnostic test for bronchiectasis.

Typical findings (airway dilatation with lack of tapering [green arrow], bronchial wall thickening [yellow arrow], and cysts [red arrow]) may be seen on HRCT.



In addition to imaging, the cause of the bronchiectasis should be determined. This may involve testing for chronic bacterial or mycobacterial infections, assessing for the presence of connective tissue disease, and evaluating immune function. In selected patients, testing for cystic fibrosis or α_1-antitrypsin deficiency may be appropriate if suspected.

There is no evidence of emphysema on his chest CT imaging, which would typically appear as dilated airspaces, classified based on the distribution of abnormalities as centrilobular, panlobular, or paraseptal. Bullous or cystic changes may be seen.

Although the duration of his symptoms are consistent with chronic bronchitis, the chest CT scan shows evidence of bronchiectasis. In chronic bronchitis, the walls of the airways are thickened without dilation of the airways themselves.

Pulmonary Langerhans cell histiocytosis is a rare subacute interstitial lung disease of young, actively smoking adults. Patients may present with cough, fever, weight loss, and abnormal chest radiography. The chest CT findings include pulmonary nodules and cysts with midlung to upper-lung zone predominance and are not associated with bronchiectasis.

KEY POINT

- Chest CT is the definitive diagnostic study for bronchiectasis; typical findings are airway dilatation with lack of tapering, bronchial wall thickening, and cysts.

Bibliography

Milliron B, Henry TS, Veeraraghavan S, Little BP. Bronchiectasis: mechanisms and imaging clues of associated common and uncommon diseases. Radiographics. 2015;35:1011-30. [PMID: 26024063] doi:10.1148/rg.2015140214

H

Item 82 Answer: B

Educational Objective: Diagnose a patient with acute silicosis.

This patient most likely has acute silicosis, a fibrotic lung disease caused by the inhalation of silica dust. Silicosis is a spectrum of fibrotic lung diseases related to the inhalation of silica dust. Any occupation that disturbs the earth's crust involves potential risk. Workers in industries that process silica-containing rock or sand are also at risk. The typical disease course of simple silicosis can be accelerated (3 to 10 years after exposure) or latent (greater than 10 years after exposure). This patient has acute silicosis, a rare presentation characterized by onset of cough and dyspnea (but no fever) just a few weeks after intense exposure, patchy bilateral opacities on chest radiograph, and a milky effluent from bronchoalveolar lavage (BAL). Hydraulic fracturing, or fracking, is a process whereby large amounts of water and chemicals are injected into the ground; sand, which contains silica, is used to hold open the fissures created to enhance extraction of natural gas. Acute silicosis portends a poor prognosis, as there is little evidence that any therapies can alter disease course. However, removal from the environment and smoking cessation will prevent further lung injury.

Acute interstitial pneumonia develops rapidly during days to weeks and results in progressive hypoxemic respiratory failure. Radiographic examination reveals bilateral alveolar opacities consistent with pulmonary edema. The findings on BAL are nonspecific. This patient's findings are not compatible with acute interstitial pneumonia.

Workers in the mining industry are at risk for asbestos exposure, but the typical latency period for asbestosis is decades rather than weeks, making this diagnosis unlikely. In addition, the most common radiographic finding of asbestosis is pleural plaques, which are not present on this patient's radiograph.

Patients with cryptogenic organizing pneumonia typically present with cough, dyspnea, fever, and malaise during 3 to 4 weeks that mimic community-acquired pneumonia. The chest radiograph reveals bilateral, patchy or diffuse, consolidative or ground-glass opacities and BAL effluent is not milky opaque.

KEY POINT

- Patients who work in industries that expose them to silica dust are at risk for silicosis.

Bibliography

Esswein EJ, Breitenstein M, Snawder J, Kiefer M, Sieber WK. Occupational exposures to respirable crystalline silica during hydraulic fracturing. J Occup Environ Hyg. 2013;10:347-56. [PMID: 23679563] doi:10.1080/15459624.2013.788352

Item 83 Answer: C

H

Educational Objective: Diagnose ICU-acquired weakness in a critically ill patient using the Medical Research Council muscle scale.

Although rarely used in practice, the most appropriate initial test to perform is the Medical Research Council (MRC) muscle scale. This patient has symmetrical quadriparesis and distal sensory neuropathy after sepsis and should be evaluated for ICU-acquired weakness. ICU-acquired weakness is the presence of profound muscles weakness in the setting of a current or recent critical illness. The MRC scale is most appropriately used in awake and cooperative patients. In such a patient, muscle strength of each extremity can be tested and graded from 0 (no movement) to 5 (normal). Summing the maximum score for 3 movements of each upper extremity (shoulder abduction, elbow flexion, wrist extension) and each lower extremity (hip flexion, knee extension, ankle dorsiflexion) can result in a maximum score of 60. In the absence of other known causes of muscular weakness, a score less than 48 is considered diagnostic of ICU-acquired weakness. The MRC muscle scale has several limitations; however, it is universally available, easy to perform, and can guide management decisions.

H CONT.

Cervical spine MRI is an excellent imaging modality to detect a cervical epidural abscess in a patient with a history of bacteremia and supportive physical examination findings. However, the patient does not have numbness of the arms or increased tone and hyperreflexia of the lower extremities to support the diagnosis of a cervical myelopathy.

Electrodiagnostic testing can help establish the diagnosis of critical care polyneuropathy, critical care myopathy, or their combination, and provide clues to other causes of prolonged weakness (for example, acute inflammatory demyelinating polyneuropathy). However, the test is not universally available in all ICU centers, is invasive, may not affect management of patients with ICU-acquired weakness, and should not precede careful evaluation of the patient with the MRC scale.

Similarly, a muscle biopsy can also aid diagnosis of critical illness myopathy, especially in the setting of elevated serum creatine kinase levels, but it would not be an appropriate initial test.

KEY POINT

- Initial evaluation for ICU-acquired weakness can be done at the bedside using the Medical Research Council muscle scale.

Bibliography

Fan E, Cheek F, Chlan L, Gosselink R, Hart N, Herridge MS, et al; ATS Committee on ICU-Acquired Weakness in Adults. An official American Thoracic Society Clinical Practice guideline: the diagnosis of intensive care unit-acquired weakness in adults. Am J Respir Crit Care Med. 2014;190:1437-46. [PMID: 25496103] doi:10.1164/rccm.201411-2011ST

Item 84 Answer: C

Educational Objective: Diagnose cryptogenic organizing pneumonia.

The most likely diagnosis is cryptogenic organizing pneumonia. This patient has a subacute history of progressive dyspnea and persistent cough after an initial history consistent with community acquired pneumonia. Despite treatment with appropriate antibiotic therapy, she now has clear evidence of new opacities that are located in different areas, are peripherally predominant, and coalesce along bronchovascular bundles. These findings are consistent with a diagnosis of organizing pneumonia, which involves proliferation of granulation tissue within alveolar ducts, alveolar spaces, and surrounding areas of chronic inflammation. There are many known causes of this pattern, including acute infections and autoimmune disorders like rheumatoid arthritis. The term *cryptogenic organizing pneumonia* is reserved for individuals who have this pattern but do not have a clear associated cause. Patients with cryptogenic organizing pneumonia will typically present with a 6 to 8 week history of symptoms that mimic community-acquired pneumonia. Typically, an initial empiric treatment of infection is given but fails; subsequently, noninfectious causes are considered. This patient has a subacute illness that began with viral symptoms, persistent and progressive cough and dyspnea that are not responsive to past antibiotics, and radiographic findings typical of cryptogenic organizing pneumonia. Patients with cryptogenic organizing pneumonia respond well to glucocorticoids. Glucocorticoids are slowly tapered during the subsequent 6 months.

Acute HIV is unlikely in this patient who initially presented with symptoms of community acquired pneumonia and whose fever has resolved. Although acute HIV symptoms are not specific, the most common presentation includes persistence of symptoms including fever.

Recurrent community-acquired pneumonia is also unlikely in this patient who was appropriately treated with azithromycin and whose symptoms have partially improved with resolution of the fever and sputum production.

Idiopathic pulmonary fibrosis (IPF) is a disease that affects older patients (the mean age of presentation is in the mid- to late 60s) and presents with chronic (longer than 6 months) symptoms of dry cough and shortness of breath. This patient's presentation is not consistent with these criteria, making a diagnosis of IPF unlikely.

KEY POINT

- A typical presentation of cryptogenic organizing pneumonia includes cough, fever, and malaise for 6 to 8 weeks that does not respond to antibiotics; patchy opacities on chest radiograph; and ground-glass opacities on CT scan that are peripherally distributed; glucocorticoids are first-line therapy.

Bibliography

Lazor R, Vandevenne A, Pelletier A, Leclerc P, Court-Fortune I, Cordier JF. Cryptogenic organizing pneumonia. Characteristics of relapses in a series of 48 patients. The Groupe d'Etudes et de Recherche sur les Maladles "Orphelines" Pulmonaires (GERM"O"P). Am J Respir Crit Care Med. 2000;162:571-7. [PMID: 10934089]

Item 85 Answer: A

H

Educational Objective: Treat a patient with a hemodynamically unstable pulmonary embolism using thrombolytic therapy.

The most appropriate treatment is thrombolytic therapy with a recombinant tissue plasminogen activator (rtPA). This patient has a large pulmonary embolism and is most likely becoming hypotensive from acute right ventricular (RV) failure. RV failure is the leading cause of death among patients with acute pulmonary embolism. In patients with hemodynamic collapse, treatment with thrombolytics is associated with decreased mortality and improvement in clinical and echocardiographic parameters. Although this patient has no contraindications to rtPA, thrombolytics carry a significant side effect profile, including an up to 2% risk of intracranial hemorrhage, but this should be considered relative in patients with life-threatening, high-risk pulmonary embolism. In patients with contraindications to thrombolysis, and in those in whom thrombolysis has failed to improve the hemodynamic status, surgical or catheter-based embolectomy should be considered if surgical expertise and resources are available.

H CONT.

According to the Apixaban for the Initial Management of Pulmonary Embolism and Deep-Vein Thrombosis as First-line Therapy (AMPLIFY) study, apixaban is an equivalent option to conventional heparin therapy for the initial treatment of pulmonary embolism. In this patient with hemodynamic collapse, it would not be more beneficial than low-molecular-weight heparin (LMWH) and is less beneficial than rtPA therapy.

In patients with acute pulmonary embolism, unfractionated heparin, LMWH, a new oral anticoagulant such as apixiban, or fondaparinux (a factor Xa inhibitor) should be started immediately unless otherwise contraindicated. Because this patient is experiencing hemodynamic collapse despite therapy with LMWH, continuing that treatment alone would not be appropriate.

Treatment of patients with acute pulmonary embolism with unfractionated heparin infusion appears to be associated with increased risk of adverse effect compared to LMWH administration. The 2014 European Society of Cardiology guidelines for diagnosis and management of pulmonary embolism recommends LMWH or fondaparinux rather than unfractionated heparin in hemodynamically stable patients because they are associated with a lower risk of heparin-induced thrombocytopenia and major bleeding events. However, the guidelines caution that LMWH and fondaparinux have not been tested in the setting of hypotension and shock and thus are not preferred modes of initial anticoagulation in that patient population.

KEY POINT

- In patients with pulmonary embolism and hemodynamic collapse, treatment with thrombolytics is associated with decreased mortality and improvement in clinical and echocardiographic parameters.

Bibliography

Konstantinides SV, Torbicki A, Agnelli G, Danchin N, Fitzmaurice D, Galiè N, et al; Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology (ESC). 2014 ESC guidelines on the diagnosis and management of acute pulmonary embolism. Eur Heart J. 2014;35:3033-69, 3069a-3069k. [PMID: 25173341] doi:10.1093/eurheartj/ehu283

H

Item 86 Answer: D

Educational Objective: Treat a malnourished, critically ill patient using parenteral nutrition.

This patient should receive parenteral nutrition. Nutrition is an essential part of management for patients in the ICU and can be given enterally or parenterally, with the enteral route preferred. Initiation of enteral nutrition is recommended at 24 to 48 hours following admission if the patient is hemodynamically stable, with advancement to goal by 48 to 72 hours. Benefits include fewer infections and possibly reduced mortality. For patients with adequate nutritional status but who have contraindications to enteral nutrition or do not tolerate enteral nutrition, parenteral nutrition is delayed for 1 to 2 weeks based upon evidence that early parenteral nutrition may increase the risk of infection. For patients with inadequate nutrition (or who are at high risk for malnutrition) who have contraindications or intolerance of enteral nutrition, parenteral nutrition should be initiated as soon as possible. This practice is based on two meta-analyses showing early parenteral nutrition in poorly nourished patients is associated with fewer complications and decreased mortality. This patient has several features consistent with severe malnutrition (temporal wasting, edema, hypoglycemia, poorly healing wounds), as well as ileus and evidence of enteral nutrition intolerance (nausea, vomiting).

The patient is obviously not tolerating enteral nutrition, as evidenced by her clinical nutritional status, nausea, vomiting, and distended abdomen. Continuing enteral nutrition would not be appropriate.

Measurement of gastric residual volume is no longer recommended for routine monitoring of enteral nutrition because it does not affect outcomes. In this patient, it is clinically apparent that she is not tolerating enteral nutrition, and measurement of gastric residual volume will not add clinically useful information.

Metoclopramide improves enteral nutrition tolerance but does not affect patient outcomes and is associated with adverse events (diarrhea, QT prolongation, tardive dyskinesia, cardiac toxicity). Because of this patient's recent surgery, she should first be started on parenteral nutrition and evaluated for a mechanical cause of bowel obstruction. Metoclopramide and other prokinetic agents are contraindicated in the presence of mechanical small bowel obstruction.

KEY POINT

- Parenteral nutrition should be started as soon as possible for severely malnourished patients or those at high risk of malnutrition for whom enteral nutrition is not possible.

Bibliography

Taylor BE, McClave SA, Martindale RG, Warren MM, Johnson DR, Braunschweig C, et al; Society of Critical Care Medicine. Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.). Crit Care Med. 2016;44:390-438. [PMID: 26771786] doi:10.1097/CCM.0000000000001525

Item 87 Answer: D

Educational Objective: Diagnose respiratory bronchiolitis-associated interstitial lung disease.

The most likely diagnosis is respiratory bronchiolitis-associated interstitial lung disease (RB-ILD). Evidence of RB-ILD is found on approximately 5% to 25% of cancer-screening CT scans. RB-ILD is used to describe disease in active smokers who have imaging findings of centrilobular micronodules with a pathologic finding of respiratory bronchiolitis and tan-pigmented macrophages (smokers' macrophages) on biopsy. Patients with RB-ILD are often asymptomatic. Symptomatic patients are typically smokers presenting in their

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fourth and fifth decades of smoking with cough and dyspnea and bibasilar inspiratory crackles. There are two other disorders that generally only develop in individuals who have an active smoking history. These are desquamative interstitial pneumonia and pulmonary Langerhans cell histiocytosis. Pulmonary function tests usually reveal an obstructive pattern with a decreased D_{LCO} in individuals with more severe disease. For those with milder disease, pulmonary function tests can be normal, restrictive, or obstructive. Cessation of smoking is the primary management.

Desquamative interstitial pneumonia is due to extensive, diffuse macrophage filling of alveolar spaces with predominant cough and dyspnea symptoms and bilateral ground-glass opacities on chest imaging. This patient's symptoms and CT findings are not compatible with this disease.

CT scan findings of idiopathic pulmonary fibrosis include basal- and peripheral-predominant septal line thickening with traction bronchiectasis and honeycomb changes. This is the usual interstitial pneumonia pattern and can be seen in connective tissue disease, asbestosis, and chronic hypersensitivity pneumonitis; idiopathic pulmonary fibrosis is a diagnosis of exclusion. The CT scan findings are not consistent with this diagnosis.

Pulmonary Langerhans cell histiocytosis is characterized by middle and upper zone thin-walled cysts with accompanying nodules and is often associated with pulmonary hypertension. Patients tend to be young adults with cough and dyspnea. Thin-walled cysts are not present in this patient's CT scan, making this diagnosis unlikely.

KEY POINT

- Respiratory bronchiolitis–associated interstitial lung disease is found in active smokers who have chest CT scan findings of centrilobular micronodules.

Bibliography

Chung JH, Richards JC, Koelsch TL, MacMahon H, Lynch DA. Screening for lung cancer: incidental pulmonary parenchymal findings. AJR Am J Roentgenol. 2017:1-11. [PMID: 29231759] doi:10.2214/AJR.17.19003

Item 88 Answer: D

Educational Objective: Manage a patient with chronic silicosis and likely tuberculosis infection.

The most appropriate management is a sputum sample for acid-fast bacillus. This patient has constitutional symptoms that include night sweats, unintentional weight loss, hemoptysis, and upper-lobe cavitary disease on chest radiograph. Reactivation tuberculosis most commonly involves the apical-posterior segments of the upper lobe; cavitation is present in up to 40% of cases. Tuberculosis should be strongly considered when a patient with silicosis develops constitutional symptoms, worsening respiratory impairment, hemoptysis, or changes in the chest radiograph, particularly cavities. Chronic silicosis adversely affects macrophage function and is clearly associated with the development of infection with tuberculosis. Concomitant silicosis and tuberculosis is associated with a substantially increased risk of mortality. Therefore, a high index of suspicion for this complication of chronic silicosis is essential to ensure early and appropriate medical therapy.

Aspergilloma is generally a consequence of colonization of a preexisting pulmonary cavity or cyst or in areas of devitalized lung. Symptoms include cough, hemoptysis, dyspnea, weight loss, fever, fatigue, and chest pain. Radiographic images show a round mass within a pulmonary cavity or cyst. Sputum cultures or IgG antibody are usually positive. This patient's chest radiograph is not consistent with an aspergilloma, and aspergillosis IgG antibody testing is not necessary.

Mine workers are often exposed to radon and several kinds of dust, and they have high rates of tobacco use; however, the development of silicosis is also an independent risk factor for the development of lung cancer. Nevertheless, bronchoscopy with transbronchial biopsy would not be appropriate for this patient. Although he has a substantially increased risk of lung cancer, the chest radiograph does not clearly demonstrate a target for biopsy. Furthermore, pursuing bronchoscopy without first ensuring there is not an active tuberculosis infection potentially places health care workers at risk for infection.

A high-resolution CT scan of the chest may identify additional findings not visible on the chest radiograph, but it will not change the need to rule out tuberculosis, which is a common comorbidity of chronic silicosis.

KEY POINT

- Tuberculosis should be strongly considered when a patient with silicosis develops constitutional symptoms, worsening respiratory impairment, hemoptysis, or changes in the chest radiograph, particularly cavities.

Bibliography

Nasrullah M, Mazurek JM, Wood JM, Bang KM, Kreiss K. Silicosis mortality with respiratory tuberculosis in the United States, 1968-2006. Am J Epidemiol. 2011;174:839-48. [PMID: 21828370] doi:10.1093/aje/kwr159

Item 89 Answer: C

Educational Objective: Diagnose upper airway obstruction using a flow-volume loop.

The most likely diagnosis is fixed upper airway obstruction. Flow-volume loops graphically plot pulmonary airflow during exhalation and inspiration, with characteristic patterns associated with specific clinical conditions. The normal expiratory portion of the flow-volume loop (above the x-axis) is characterized by a rapid rise to the peak flow rate, followed by a nearly linear fall in flow as the patient exhales. The inspiratory curve (below the x-axis) appears as a semicircle. Flattening of both the inspiratory and expiratory curve of the flow-volume loop suggests this patient has a fixed intrathoracic lesion, such as tracheal stenosis, which can be seen postintubation.

Spirometry is relatively insensitive to all but severe (greater than 71%) intrathoracic airway obstruction. Therefore, if intrathoracic airway obstruction is suspected, appearance of a normal flow-volume loop should not discourage further evaluation.

Patients with asthma would be expected to have this obstructive pattern, although patients without active symptoms can have a completely normal loop.

Patients with COPD demonstrate an obstructive pattern of the flow-volume loop. This is typically manifested by a fairly normal initial portion of the expiratory flow loop, with increased concavity of the terminal portion, indicating airway narrowing during exhalation.

The flow-volume loop demonstrates reduced inspiratory and expiratory volumes, and not the normal pattern described above.

KEY POINT

- Flattening of both the inspiratory and expiratory curve of the flow-volume loop suggests a fixed intrathoracic lesion; direct examination of the airways is indicated to confirm the finding and identify the cause.

Bibliography

Murgu SD, Egressy K, Laxmanan B, Doblare G, Ortiz-Comino R, Hogarth DK. Central airway obstruction: benign strictures, tracheobronchomalacia, and malignancy-related obstruction. Chest. 2016;150:426-41. [PMID: 26874192] doi:10.1016/j.chest.2016.02.001

Item 90 Answer: D

Educational Objective: Treat asthma during pregnancy.

This patient's previous medications of albuterol and budesonide should be restarted. Asthma management during pregnancy should consist of optimization of anti-inflammatory therapy, management of gastroesophageal reflux, and smoking cessation. Inhaled glucocorticoids are considered safe in pregnancy, and abundant long-term safety evidence exists for budesonide. With the exception of zileuton, most leukotriene receptor antagonists are also considered safe in pregnancy. The treatment of asthma in pregnancy is very similar to treatment in nonpregnant patients. This patient has mild persistent asthma, with symptoms more than twice weekly, and use of low-dose inhaled glucocorticoids plus a short-acting β_2-agonist is the recommended therapy. The risks to the fetus of untreated asthma are significantly greater than the risks of asthma medications. Maternal asthma increases the risk of perinatal mortality, preterm birth, low-birth-weight infants, and preeclampsia. Budesonide is the preferred inhaled glucocorticoid to use in pregnant asthma patients because there are more data available concerning budesonide use in pregnancy than the other inhaled glucocorticoid formulations. However, there are no studies indicating that other inhaled glucocorticoid formulations are unsafe in pregnancy, so if a patient's asthma is well controlled on another inhaled glucocorticoid, it is not necessary to change to budesonide during pregnancy.

Combination fluticasone/salmeterol is not the recommended treatment regimen for mild persistent asthma and would be inappropriate for this patient.

Prednisone is used to treat asthma exacerbations, and all patients with asthma should have a written asthma action plan to manage an exacerbation and begin self-treatment. Therefore, although prednisone may be part of this patient's asthma management plan, it is not indicated for treatment of her current symptoms of mild persistent asthma.

This patient is experiencing frequent symptoms of asthma and would benefit from treatment. Therefore, peak flow monitoring alone is not appropriate without initiation of pharmacotherapy.

KEY POINT

- Treatment of asthma during pregnancy is similar to treatment in nonpregnant patients.

Bibliography

Bonham CA, Patterson KC, Strek ME. Asthma outcomes and management during pregnancy. Chest. 2018;153:515-527. [PMID: 28867295] doi:10.1016/j.chest.2017.08.029

Item 91 Answer: B

Educational Objective: Evaluate a patient with diffuse parenchymal lung disease using high-resolution chest CT scan.

High-resolution CT (HRCT) scan of the chest is the most appropriate test. The choice of imaging modality in the evaluation of pulmonary disease is dependent on the information being sought based on the differential diagnosis. HRCT scan is indicated if diffuse parenchymal lung disease (DPLD) is suspected. The diagnostic approach to DPLD is grounded in the predominant pattern of abnormalities, distribution of disease, and associated findings (pleural plaques, calcifications, effusions, lymphadenopathy). HRCT scan provides more detail than either chest radiography or conventional CT scanning and can more accurately assess the pattern and distribution of DPLD. This patient's history, physical findings, pulmonary function tests, radiography results, and family history strongly suggest the diagnosis of idiopathic pulmonary fibrosis. An HRCT scan will allow for better characterization of pattern and distribution of the opacities on chest radiograph and will help diagnose the underlying disease.

Contrast-enhanced chest CT scan may be added to the study to better evaluate the mediastinal structures (for example, to assess for lymphadenopathy). However, there is no suggestion of mediastinal abnormality on the chest radiograph; rather, the patient's history, physical examination findings, and chest radiograph more strongly suggest DPLD, and HRCT is the preferred imaging modality in that situation.

Patients who meet criteria for lung cancer screening should undergo imaging with low-dose chest CT scan to minimize radiation exposure. Low-dose chest CT images utilize a lower total radiation dose than standard CT chest

protocols. The lower dose of radiation decreases the radiation to patients and is as effective as standard-dose CT in imaging lung nodules owing to the high inherent contrast between lung tissue and air. Low-dose CT scan is a good modality to screen for pulmonary nodules but not a good modality to assess DPLD.

Patients with a pulmonary nodule or other findings suggestive of malignancy may require PET/CT imaging. This test most commonly uses fluorodeoxyglucose (FDG) as a metabolic marker to identify rapidly dividing cells such as tumor cells. A nodule that demonstrates no FDG uptake is unlikely to be malignant. Any disease with metabolic activity, including infection, inflammation, and malignancy, can cause an FDG-avid nodule. PET/CT imaging would not be helpful in the evaluation of DPLD.

KEY POINT

- High-resolution chest CT scan is the preferred advanced imaging modality for suspected diffuse parenchymal lung disease; it can help narrow the differential diagnosis based on the character and distribution of the lung parenchymal abnormalities.

Bibliography

Walsh SL, Hansell DM. High-resolution CT of interstitial lung disease: a continuous evolution. Semin Respir Crit Care Med. 2014;35:129-44. [PMID: 24481766] doi:10.1055/s-0033-1363458

Item 92 Answer: D

Educational Objective: Evaluate recurrent unilateral exudative effusion for malignancy.

This patient should be referred for thoracoscopy and pleural biopsy. He has a recurrent exudative pleural effusion. The characterization of pleural fluid as a transudate or exudate helps narrow the differential diagnosis and direct subsequent investigations. An effusion is considered an exudate if any of the following criteria are met: pleural fluid total protein/serum total protein greater than 0.5; pleural fluid lactate dehydrogenase (LDH)/serum LDH greater than 0.6; pleural fluid LDH greater than 2/3 the upper limit of normal for serum LDH. This patient has an exudate. Despite the negative chest radiograph and CT scan, this exudate is concerning for malignancy considering his age, smoking history, and work in a shipyard with potential exposure to asbestos. The cytology of the pleural fluid was negative, but cytology is only 60% sensitive for malignancy.

Closed pleural biopsy is less sensitive than cytology and should not be performed.

A chylous effusion can be suspected by its milky appearance (seen in 50% of patients) and is associated with traumatic and nontraumatic etiologies. Nontraumatic chylous effusion is most commonly due to malignancy (lymphoma, chronic lymphocytic leukemia, metastatic cancer). Traumatic chylous effusions are most commonly associated with thoracic surgical procedures. A pleural fluid triglyceride level greater than 110 mg/dL (1.24 mmol/L) is characteristic of a chylothorax. There is no reason to suspect a chylothorax at this point; thoracoscopic pleural biopsy will be of higher diagnostic yield.

The yield of sending more than two cytology specimens taken on different occasions is low. If cytology is negative and malignancy is still suspected, thoracoscopy with pleural biopsy allows for direct visualization of the pleural surface and has greater than 90% sensitivity for the diagnosis of malignancy.

KEY POINT

- For patients with negative cytology in whom malignancy is suspected, thoracoscopy with pleural biopsy allows for direct visualization of the pleural surface and has a diagnostic sensitivity for malignant disease of greater than 90%.

Bibliography

Hooper C, Lee YC, Maskell N; BTS Pleural Guideline Group. Investigation of a unilateral pleural effusion in adults: British Thoracic Society Pleural Disease Guideline 2010. Thorax. 2010;65 Suppl 2:ii4-17. [PMID: 20696692] doi:10.1136/thx.2010.136978

Item 93 Answer: C

Educational Objective: Diagnose interstitial lung disease with a high-resolution CT scan of the chest.

This patient should receive a high-resolution CT (HRCT) scan of the chest. He has symptoms of progressive dyspnea on exertion, inspiratory crackles, restrictive pulmonary function tests, and a chest radiograph demonstrating diffuse parenchymal lung disease. This constellation of findings suggests interstitial lung disease. Plain chest radiography findings may be highly variable in patients with diffuse parenchymal lung disease. Chest films may show increased interstitial reticular or nodular infiltrates in different patterns of distribution, but they may be normal in up to 10% of patients. Characteristics on HRCT of the chest have pulmonary pathology correlates that can help narrow the differential diagnosis. HRCT provides detailed resolution of the pulmonary parenchymal architecture. HRCT, clinical presentation (including time course of symptoms), physical findings, and, when necessary, lung biopsy and histopathology allow clinicians to reach selected diagnoses from an extensive list of diffuse parenchymal lung diseases.

In selected cases, bronchoscopic lung biopsy can provide enough tissue to demonstrate specific histopathologic features diagnostic of several specific disease processes, including carcinoma, sarcoidosis, and eosinophilic pneumonia. Bronchoalveolar lavage can provide additional diagnostic information, including culture, cytology, and cell differential. However, a lung biopsy and bronchoalveolar lavage would not be indicated until imaging studies confirmed the presence of diffuse parenchymal lung disease and have narrowed the differential diagnosis to entities that might be assessed with biopsy or bronchoalveolar lavage.

Cardiopulmonary exercise testing includes assessment of respiratory gas exchange during treadmill or bicycle exercise

for a more detailed assessment of functional capacity and differentiation between potential causes of exercise limitation (cardiac, pulmonary, or deconditioning, versus volitional). It would not be the most appropriate next choice in a patient with increasing exercise limitation, pulmonary crackles, an abnormal chest radiograph, and restrictive findings on pulmonary function testing.

Methacholine challenge testing is used to evaluate bronchial hyperreactivity in patients with normal pulmonary function tests, and this patient's testing is abnormal, with a restrictive pattern, so such testing would not be indicated.

KEY POINT

- High-resolution CT scan of the chest is standard care for evaluating parenchymal opacities seen on a plain radiograph.

Bibliography

Meyer KC. Diagnosis and management of interstitial lung disease. Transl Respir Med. 2014;2:4. [PMID: 25505696] doi:10.1186/2213-0802-2-4

Item 94 Answer: D

Educational Objective: **Treat disruptive snoring with weight loss.**

The most appropriate next step in management is a trial of weight loss. In this obese but otherwise healthy patient without other sleep-related symptoms, weight loss is a reasonable first step that often relieves snoring. Obesity is the strongest risk factor for snoring and obstructive sleep apnea (OSA). Snoring occurs as the upper airway narrows during sleep, when inspired air collides with redundant soft tissue. Further airway collapse leads to OSA. Other treatments for snoring can include limiting time spent in the supine position (postural therapy) and curbing alcohol intake.

Home sleep testing should be reserved for patients with a high probability of moderate to severe apnea in whom positive airway pressure therapy is being considered. Although OSA hasn't been ruled out in this patient, his bed partner hasn't observed classic signs such as gasping or choking, nor does he exhibit strong indications for positive airway pressure therapy, such as excessive daytime sleepiness.

In-laboratory polysomnography allows more detailed analysis of the possible underlying sleep-related breathing disorder than out-of-center methods. Once the type of apnea is clarified during the diagnostic portion of the in-laboratory study, the technician may also then utilize the most appropriate mode of positive airway pressure therapy and assess the response to treatment. However, for this patient, testing of any kind should be preceded by a conservative approach that includes weight loss.

Upper airway surgical procedures, such as radiofrequency ablation of soft palate, are sometimes used to treat snoring and OSA but are variably effective and not considered first-line therapy.

KEY POINT

- Obesity is the strongest risk factor for snoring and obstructive sleep apnea, and in obese but otherwise healthy patients without other sleep-related symptoms, weight loss is a reasonable first step that often relieves snoring and improves mild obstructive sleep apnea.

Bibliography

Balachandran JS, Patel SR. In the clinic. Obstructive sleep apnea. Ann Intern Med. 2014;161:ITC1-15; quiz ITC16. [PMID: 25364899] doi:10.7326/0003-4819-161-9-201411040-01005

Item 95 Answer: A

Educational Objective: **Manage a malignant pleural effusion.**

This patient should be referred for an indwelling pleural catheter placement. Her diagnosis of a malignant pleural effusion signifies advanced disease and overall poor prognosis and the goal of management is the relief of symptoms. Several therapeutic options are available and should be made based on symptoms, prognosis, degree of lung reexpansion, and patient performance status. She has rapid reaccumulation of fluid and, therefore, should be offered more definitive management. Indwelling pleural catheters with intermittent drainage provide significant symptom relief, and 50% to 70% of patients achieve spontaneous pleurodesis after 2 to 6 weeks. In a recent randomized trial indwelling pleural catheters were found to be noninferior to talc pleurodesis, and patients who had an indwelling pleural catheter had a shorter hospital stay and less dyspnea at 6 months.

Pleurectomy is another management option but is rarely performed because it is invasive, associated with long recovery times, and appears to be no more effective than less invasive options.

Repeat therapeutic thoracentesis is appropriate for patients with poor prognosis (less than 3 months) and slow reaccumulation of fluid; given this patient's good performance status and rapid reaccumulation of pleural fluid, serial thoracentesis is not indicated.

Chemical pleurodesis refers to obliteration of the pleural space with a sclerosing agent (typically talc). Talc can be introduced through a thoracostomy tube (talc slurry) or during a thoracostomy or thoracotomy (talc poudrage). Talc pleurodesis is very effective, with a success rate of 60% to 90%, depending on the degree of lung reexpansion; however, it is associated with increased pain and longer initial hospital stay, so an indwelling pleural catheter would be preferable at this time.

KEY POINT

- For patients with a malignant pleural effusion and rapid reaccumulation of fluid, indwelling pleural catheters provide significant symptom relief, and 50% to 70% of patients achieve spontaneous pleurodesis after 2 to 6 weeks.

Bibliography

Feller-Kopman D, Light R. Pleural disease. N Engl J Med. 2018;378:740-751. doi: 10.1056/NEJMra1403503. [PMID: 29466146]

Item 96 Answer: D

Educational Objective: Diagnose serotonin syndrome.

The most likely diagnosis is serotonin syndrome. The features of hyperthermia, tremor, hyperreflexia, ocular clonus (slow, continuous, horizontal eye movements), other clonus (spontaneous or induced), and anxiety are classic features of this syndrome. Hyperreflexia and clonus help distinguish serotonin syndrome from other hyperthermic syndromes and toxic ingestions. This patient's history supports the diagnosis, which usually occurs after coingestion of several serotonergic medications—for example, fluoxetine and methylenedioxymethamphetamine ("ecstasy"). Treatment is mainly supportive, using benzodiazepines as needed to keep the patient calm and to control blood pressure and heart rate. Physical restraint can lead to agitated exertion and worsen hyperthermia. Autonomic instability is common, so close monitoring is recommended. Only in very severe cases of agitation or hyperthermia do patients need to be deeply sedated, intubated, paralyzed, and sometimes treated with cyproheptadine.

Anticholinergic toxicity is unlikely in this patient because he has no signs of mydriasis, dry mucus membranes, or urinary and bowel retention. He does exhibit hyperthermia and agitation, but has clonus and hyperreflexia, which are not associated with anticholinergic toxicity.

Malignant hyperthermia would be very unlikely without a history of inhaled anesthesia agents or neuromuscular blockade. Clinical features of malignant hyperthermia usually include higher fever, muscle rigidity, and, occasionally, hemorrhage but not hyperreflexia or clonus.

Neuroleptic malignant syndrome would be very unlikely without a history of neuroleptic medications, such as haloperidol. It usually develops subacutely during days or weeks, whereas serotonin syndrome typically develops within hours. Rigidity with hyporeflexia is more common, rather than hyperreflexia and myoclonus in serotonin syndrome. Hyperthermia, altered mental status, and rigidity are features of both syndromes. Neuroleptic malignant syndrome usually takes many days to resolve, whereas serotonin syndrome usually resolves within 24 hours.

KEY POINT

- Classic features of serotonin syndrome include hyperthermia, tremor, hyperreflexia and clonus; treatment is mainly supportive, using benzodiazepines as needed to keep the patient calm and to control blood pressure and heart rate.

Bibliography

Dobry Y, Rice T, Sher L. Ecstasy use and serotonin syndrome: a neglected danger to adolescents and young adults prescribed selective serotonin reuptake inhibitors. Int J Adolesc Med Health. 2013;25:193-9. [PMID: 24006318] doi:10.1515/ijamh-2013-0052

Item 97 Answer: A

Educational Objective: Treat a patient with acute hemorrhagic shock using volume resuscitation with blood products.

The most appropriate management for this patient is a transfusion of packed red blood cells. Clinicians should base decisions on blood transfusion on the full clinical picture, recognizing that overtransfusion may be as damaging as undertransfusion. A restrictive transfusion policy aiming for a hemoglobin level of 7 to 8 g/dL (70 to 80 g/L) is suggested in hemodynamically stable patients. More liberal blood transfusion thresholds lead to increased portal pressures and risk of further bleeding. This patient most likely is experiencing hemorrhagic shock from a recurrent variceal bleeding episode. Because the patient is hemodynamically unstable, initial guideline-based management includes volume resuscitation, and transfusion of blood products is the best method for achieving this. In patients who are bleeding and have a platelet count less than 50,000/µL (50×10^9/L) or who have an INR greater than 1.5, transfusion of platelets or fresh frozen plasma, respectively, is indicated.

Historically, uncontrolled variceal bleeding offered a compelling rationale for use of recombinant factor VII, but a 2014 meta-analysis of almost 500 patients from two randomized clinical trials evaluated the role of factor VII following variceal bleed. In both trials, there was no indication that factor VII improved outcomes. Therefore, it would not be appropriate for this patient.

Emergent upper endoscopy and consideration of placing a transjugular intrahepatic portosystemic shunt are indicated in this patient, but are pursued after initial resuscitation efforts are completed. Because this patient is hemodynamically unstable and these procedures take time to coordinate, they would not supersede initial resuscitative efforts with blood products.

KEY POINT

- In patients with hemorrhagic shock, initial management includes volume resuscitation with blood products to stabilize the patient.

Bibliography

Tripathi D, Stanley AJ, Hayes PC, Patch D, Millson C, Mehrzad H, et al; Clinical Services and Standards Committee of the British Society of Gastroenterology. U.K. guidelines on the management of variceal haemorrhage in cirrhotic patients. Gut. 2015;64:1680-704. [PMID: 25887380] doi:10.1136/gutjnl-2015-309262

Item 98 Answer: D

Educational Objective: Treat a patient intoxicated with isopropyl alcohol.

The most appropriate management is supportive care. Calculation of the plasma osmolal gap is helpful in assessing the presence of unmeasured solutes, such as ingestion of certain toxins (for example, methanol or ethylene glycol). The plasma osmolal gap is the difference between the measured

H CONT.

and calculated plasma osmolality. Plasma osmolality can be calculated using the following formula:

$$\text{Plasma Osmolality (mOsm/kg } H_2O) = 2 \times \text{Serum Sodium (mEq/L)} + \text{Plasma Glucose (mg/dL)}/18 + \text{Blood Urea Nitrogen (mg/dL)}/2.8.$$

When the measured osmolality exceeds the calculated osmolality by greater than 10 mOsm/kg H_2O, the osmolal gap is considered elevated. This patient does not have an increased anion-gap metabolic acidosis, thus eliminating methanol and ethylene glycol poisoning. An elevated osmolal gap of 27 and absent blood ethanol support the diagnosis of isopropyl alcohol ingestion (rubbing alcohol), which does not cause a metabolic acidosis. It is metabolized by alcohol dehydrogenase (ADH) to acetone, which can cause a fruity odor on the patient's breath. There are no other toxic metabolites, and the main effect of isopropyl alcohol ingestion is central nervous system depression by both the isopropyl alcohol and the acetone.

There is no need to block the action of ADH with fomepizole. Administration of fomepizole would be advised for treatment of methanol or ethylene glycol ingestion, because these alcohols both have toxic metabolites that can lead to blindness, kidney failure, or death. Inhibiting ADH in patients who have ingested isopropyl alcohol only prolongs its elimination.

Hemodialysis is not normally needed to clear isopropyl alcohol from the blood, although it is a highly effective modality for eliminating all ingested alcohols. The risks of initiating hemodialysis in this patient who is inebriated but otherwise stable would not be justified.

Seizure prophylaxis with levetiracetam is not indicated for isopropyl alcohol ingestion, and this patient shows no clinical signs of withdrawal, a prelude to seizures. As long as he is closely monitored and treated appropriately with benzodiazepine medication for signs of withdrawal, antiepileptic medication should not be needed.

KEY POINT

- Patients with isopropyl alcohol poisoning can be treated effectively using supportive care.

Bibliography

Beauchamp GA, Valento M. Toxic alcohol ingestion: prompt recognition and management in the emergency department. Emerg Med Pract. 2016;18:1-20. [PMID: 27538060]

Item 99 Answer: B

Educational Objective: Evaluate potential lung cancer with the optimal diagnostic procedure.

The most appropriate diagnostic test for this patient with a lesion highly suspicious for lung cancer and PET-positive mediastinal lymphadenopathy is bronchoscopy with endobronchial ultrasound-guided transbronchial needle aspiration. The evaluation of a patient with suspected lung cancer aims to confirm whether the patient indeed has lung cancer, to determine the pathology (non-small cell lung cancer versus small cell lung cancer), and to assess the stage at presentation. Most patients undergo chest CT scan as the first imaging modality, either after an abnormal chest radiograph or in evaluation of a symptom. The findings on the chest CT scan determine whether a PET/CT scan is necessary. A PET/CT scan can help in staging and therefore also help guide where to biopsy. For example, if a patient has a solitary pulmonary nodule, a PET/CT scan may help determine if any lymph node involvement is present that was not visible on the chest CT scan.

The next step is to obtain tissue diagnosis. The choice of initial diagnostic testing should be aimed first at identifying potential lymph node involvement or metastatic disease. Tissue diagnosis should then be targeted at the lesion that would result in the highest potential staging. In this patient, sampling the mediastinal lymph nodes is critical to both diagnose and stage the patient and will affect the clinical decision making for this patient. Endobronchial ultrasound-guided transbronchial needle aspiration is a minimally invasive way and preferred to more invasive surgical techniques. Endobronchial ultrasound-guided transbronchial needle aspiration can sample most mediastinal and some hilar lymph node stations, although some of the more posterior lymph nodes are not accessible with this technique.

CT-guided needle biopsy has a high accuracy for diagnosis of lung cancers, but has higher risks of procedural complications than endobronchial ultrasound-guided transbronchial needle aspiration (mainly pneumothorax), and the patient would require a second procedure to sample the mediastinum if the lung lesion is a non-small cell lung cancer.

Sputum cytology has a lower sensitivity than endobronchial ultrasound-guided transbronchial needle aspiration for diagnosis of lung cancer, does not produce sufficient sample material for molecular studies, and will not provide needed staging information.

Thoracoscopic lung biopsy with lymph node dissection is less preferable than a minimally invasive approach, due to cost and risks of complications.

KEY POINT

- Endobronchial ultrasound-guided transbronchial needle aspiration is the procedure of choice for diagnosing and staging mediastinal and hilar lymphadenopathy in patients with suspected thoracic malignancy.

Bibliography

Silvestri GA, Gonzalez AV, Jantz MA, Margolis ML, Gould MK, Tanoue LT, et al. Methods for staging non-small cell lung cancer: diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2013;143:e211S-e250S. [PMID: 23649440] doi:10.1378/chest.12-2355

Item 100 Answer: B

H

Educational Objective: Treat acute opioid overdose with naloxone.

The most appropriate management is continued observation for signs of recurrent respiratory failure. Patients with opioid overdose have findings that suggest the diagnosis including:

H CONT.

miosis, respiratory depression, lethargy, confusion, hypothermia, bradycardia, and hypotension. An early empiric trial of the opioid antagonist naloxone is warranted when opioid overdose is suspected. It is important to remember that naloxone has a very short half-life, and its antidote effects will usually wear off before the opioid effects are gone. Naloxone is given at higher doses to apneic patients, such as 2 mg intravenously (IV), which is larger than the typical starting dose of 0.4 mg IV usually given to overdose patients who are still breathing. The dose of naloxone is titrated to a respiration rate of at least 12/min, not to a normal mental status. Chronic opioid users require close monitoring for withdrawal.

Serial escalating doses of naloxone may be necessary in some patients, and patients who respond to serial dosing may require a continuous naloxone infusion. However, there is no immediate need for more naloxone because this patient has normal breathing and mentation. During the period of observation, more naloxone may be needed if her respiration rate slows or stops.

This patient cannot be discharged until it is known that her respiratory suppression will not return when the naloxone wears off. Patients should be observed for at least 60 minutes after the last dose of naloxone. Drug addiction resources should be accessed for this patient. It is also appropriate after overdose to rule out suicidal ideation or intent and refer the patient to a psychiatric clinician if needed.

Endotracheal intubation would not be appropriate because the patient is protecting her airway and is not in respiratory distress or failure. Intubation is required for patients whose respiratory suppression cannot be quickly reversed with naloxone.

KEY POINT

- In the treatment of opioid overdose the antidote effects of naloxone will usually wear off before the opioid effects are gone; observation and repeated dosing are often necessary.

Bibliography

Willman MW, Liss DB, Schwarz ES, Mullins ME. Do heroin overdose patients require observation after receiving naloxone? Clin Toxicol (Phila). 2017;55:81-87. [PMID: 27849133] doi:10.1080/15563650.2016.1253846

H

Item 101 Answer: C

Educational Objective: Diagnose pulmonary embolism as the cause of acute hypoxemic respiratory failure and shock.

This patient most likely has a pulmonary embolism. This patient has hypoxemic respiratory failure and shock. Severe hypoxemia is generally defined as an arterial Po_2 of 60 mm Hg (8.0 kPa) or less or an oxygen saturation of 89% or less while breathing ambient air. The most common causes of hypoxemic respiratory failure are conditions that lead to mismatch between the ventilation of inspired air in the alveoli and perfusion of adjacent alveolar capillaries by blood (called ventilation-perfusion [$\dot{V}/\dot{Q}$] mismatch). Conditions such as pulmonary embolism lead to $\dot{V}/\dot{Q}$ mismatch. Hypoxemia due to $\dot{V}/\dot{Q}$ mismatch should resolve with oxygen therapy. However, extremes of $\dot{V}/\dot{Q}$ mismatch (known as a shunt) do not fully resolve with supplemental oxygen because inspired gas does not interface with the shunted blood in the lungs. In addition, this patient has evidence of cardiogenic shock, including hypotension, elevated jugular venous pressure, fixed splitting of the second heart sound, and cool, mottled skin. Although cardiogenic shock can occur for many reasons, in this patient, it is the result of the pulmonary embolism causing a mechanical blockage in the pulmonary circulation, leading to impaired cardiac output from the right ventricle. Fat emboli following long-bone fractures can mimic pulmonary emboli.

Anaphylactic shock is a type of distributive shock, as might occur if a patient with an allergy to penicillin were given either penicillin or a related agent to which she reacted. Anaphylaxis is an IgE-mediated reaction and manifests within minutes to 1 hour after exposure to the implicated antigen. Anaphylactic shock would result in hypotension and warm extremities, typically with hives or rash. The patient is hypotensive, but does not have a rash. Respiratory failure could be present but would be associated with wheezing or stridor.

Opioid overdose can cause hypercapnic respiratory failure with hypoxemia occurring as the result of hypoventilation. Although the hypoxemia improves with oxygen, it does not improve the hypercapnea. Opioid overdose cannot account for the findings of obstructive shock.

Tension pneumothorax can cause respiratory failure and cardiogenic shock as a result of poor right ventricular filling. It should be suspected in patients with hypotension, diminished breath sounds on the affected side, distended neck veins, and tracheal deviation away from the affected side. Risk factors for tension pneumothorax include trauma, recent pulmonary procedure, mechanical ventilation, and underlying cystic lung disease. The patient has no risk factors for tension pneumothorax, and her lung findings do not support this diagnosis.

KEY POINT

- The most common causes of hypoxemic respiratory failure are conditions that lead to ventilation-perfusion mismatch or shunt; hypoxemia due to ventilation-perfusion mismatch with shunting does not improve with supplemental oxygen.

Bibliography

Wagner PD. The physiological basis of pulmonary gas exchange: implications for clinical interpretation of arterial blood gases. Eur Respir J. 2015;45:227-43. [PMID: 25323225] doi:10.1183/09031936.00039214

Item 102 Answer: C

Educational Objective: Diagnose obesity hypoventilation syndrome.

The most likely diagnosis is obesity hypoventilation syndrome. Obesity hypoventilation syndrome is characterized

by daytime hypercapnia (arterial P_{CO_2} greater than 45 mm Hg [5.9 kPa]) that is thought to be a consequence of diminished ventilatory drive and capacity related to extreme obesity. Persons with a BMI of 35 or higher are considered at risk for obesity hypoventilation syndrome; it's estimated that more than half of patients with a BMI of 50 or higher have this condition. This patient's BMI of 44, compensated hypercapnic respiratory failure, hypoxemia during wakefulness but more pronounced during sleep, and polycythemia are all consistent with obesity hypoventilation syndrome. Positive airway pressure therapy (continuous positive airway pressure or bilevel positive airway pressure), sometimes with supplemental oxygen, is first-line therapy.

Neuromuscular diseases that can affect the respiratory system must be considered in the differential diagnosis of hypoventilation syndromes. Amyotrophic lateral sclerosis (ALS) often leads to hypercapnic respiratory failure. However, this patient has an unremarkable neurologic examination and none of the typical features of ALS, such as muscle weakness and fasciculations and hyperactive deep tendon reflexes.

Central sleep apnea (CSA) is defined by intermittent reduced central drive to breathe but is not a hypoventilation syndrome. In fact, the tendency to hyperventilate, as seen with the cyclic ventilatory pattern of Cheyne-Stokes breathing, is a key underlying mechanism of CSA. Patients with CSA are generally normocapnic or slightly hypocapnic on blood gas testing.

An apnea-hypopnea index (AHI) of 5 to 15 is indicative of mild obstructive sleep apnea (OSA). This patient has mild OSA based upon an AHI of 6. OSA is typically encountered on sleep testing in those with obesity hypoventilation syndrome, with upper airway collapse superimposed on obesity-related hypoventilation. Severe OSA is defined as an AHI of at least 30; OSA severity is not defined by degree or duration of hypoxemia.

KEY POINT

- Obesity hypoventilation syndrome is characterized by daytime hypercapnia, defined as an arterial P_{CO_2} greater than 45 mm Hg that is thought to be a consequence of diminished ventilatory drive and capacity related to extreme obesity.

Bibliography

Randerath W, Verbraecken J, Andreas S, Arzt M, Bloch KE, Brack T, et al. Definition, discrimination, diagnosis and treatment of central breathing disturbances during sleep. Eur Respir J. 2017;49. [PMID: 27920092] doi:10.1183/13993003.00959-2016

Item 103 Answer: E

Educational Objective: Treat an acute exacerbation of bronchiectasis with antibiotics.

The most appropriate treatment of this patient is levofloxacin. Oral antibiotic treatment is appropriate for clinically stable patients with an acute exacerbation of bronchiectasis. The choice of antibiotic therapy can be based on previous sputum culture results, if available. If not available, a reasonable empiric antibiotic choice is a respiratory fluoroquinolone such as levofloxacin or moxifloxacin. Although duration of therapy is not well defined, most experts treat for 10 to 14 days.

Amoxicillin or a macrolide such as azithromycin is a reasonable choice for patients in the absence of β-lactamase-positive *Haemophilus influenzae* or *Pseudomonas*. Initial empiric therapy can also be deescalated to amoxicillin based on the results of sputum culture and sensitivity. However, in the absence of bacteriologic data from sputum culture, amoxicillin is an inadequate choice for empiric therapy in patients with recurrent acute exacerbations previously treated with antibiotics due to the high risk of β-lactamase-producing organisms and *Pseudomonas*.

For similar reasons, azithromycin is not an appropriate empiric antibiotic for this patient. There is likely a role for long-term azithromycin therapy to prevent recurrent exacerbations of bronchiectasis. The salutary effect on chronic macrolide therapy in these situations may not be entirely due to its antimicrobial properties but rather its well-known antiinflammatory properties. However, the development of antibiotic resistance is a potential risk.

Oral or inhaled glucocorticoids would seem to be reasonable adjunctive therapy for patients with acute exacerbation of bronchiectasis, but supporting evidence for their use is sparse. Some experts may employ glucocorticoids in patients with coexistent asthma and wheezing or allergic bronchopulmonary aspergillosis, but the risk of routine use is related to immunosuppression and promotion of bacterial and fungal colonization and is not recommended.

Inhaled aerosols of antibiotics, including inhaled tobramycin solution, are not recommended for an acute exacerbation of bronchiectasis. This recommendation is based on a multicenter randomized trial that demonstrated the addition of inhaled tobramycin to ciprofloxacin was not superior to ciprofloxacin alone but was associated with more wheezing. There may be a role of inhaled antibiotics in the prophylaxis of acute exacerbations of bronchiectasis.

KEY POINT

- If previous data on bronchiectasis exacerbations are not available, a fluoroquinolone should be started to ensure *Pseudomonas* coverage until the sputum culture is completed.

Bibliography

Smith MP. Diagnosis and management of bronchiectasis. CMAJ. 2017;189: E828-E835. [PMID: 28630359] doi:10.1503/cmaj.160830

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10 (A) (B) (C) (D) (E)	55 (A) (B) (C) (D) (E)	100 (A) (B) (C) (D) (E)	145 (A) (B) (C) (D) (E)
11 (A) (B) (C) (D) (E)	56 (A) (B) (C) (D) (E)	101 (A) (B) (C) (D) (E)	146 (A) (B) (C) (D) (E)
12 (A) (B) (C) (D) (E)	57 (A) (B) (C) (D) (E)	102 (A) (B) (C) (D) (E)	147 (A) (B) (C) (D) (E)
13 (A) (B) (C) (D) (E)	58 (A) (B) (C) (D) (E)	103 (A) (B) (C) (D) (E)	148 (A) (B) (C) (D) (E)
14 (A) (B) (C) (D) (E)	59 (A) (B) (C) (D) (E)	104 (A) (B) (C) (D) (E)	149 (A) (B) (C) (D) (E)
15 (A) (B) (C) (D) (E)	60 (A) (B) (C) (D) (E)	105 (A) (B) (C) (D) (E)	150 (A) (B) (C) (D) (E)
16 (A) (B) (C) (D) (E)	61 (A) (B) (C) (D) (E)	106 (A) (B) (C) (D) (E)	151 (A) (B) (C) (D) (E)
17 (A) (B) (C) (D) (E)	62 (A) (B) (C) (D) (E)	107 (A) (B) (C) (D) (E)	152 (A) (B) (C) (D) (E)
18 (A) (B) (C) (D) (E)	63 (A) (B) (C) (D) (E)	108 (A) (B) (C) (D) (E)	153 (A) (B) (C) (D) (E)
19 (A) (B) (C) (D) (E)	64 (A) (B) (C) (D) (E)	109 (A) (B) (C) (D) (E)	154 (A) (B) (C) (D) (E)
20 (A) (B) (C) (D) (E)	65 (A) (B) (C) (D) (E)	110 (A) (B) (C) (D) (E)	155 (A) (B) (C) (D) (E)
21 (A) (B) (C) (D) (E)	66 (A) (B) (C) (D) (E)	111 (A) (B) (C) (D) (E)	156 (A) (B) (C) (D) (E)
22 (A) (B) (C) (D) (E)	67 (A) (B) (C) (D) (E)	112 (A) (B) (C) (D) (E)	157 (A) (B) (C) (D) (E)
23 (A) (B) (C) (D) (E)	68 (A) (B) (C) (D) (E)	113 (A) (B) (C) (D) (E)	158 (A) (B) (C) (D) (E)
24 (A) (B) (C) (D) (E)	69 (A) (B) (C) (D) (E)	114 (A) (B) (C) (D) (E)	159 (A) (B) (C) (D) (E)
25 (A) (B) (C) (D) (E)	70 (A) (B) (C) (D) (E)	115 (A) (B) (C) (D) (E)	160 (A) (B) (C) (D) (E)
26 (A) (B) (C) (D) (E)	71 (A) (B) (C) (D) (E)	116 (A) (B) (C) (D) (E)	161 (A) (B) (C) (D) (E)
27 (A) (B) (C) (D) (E)	72 (A) (B) (C) (D) (E)	117 (A) (B) (C) (D) (E)	162 (A) (B) (C) (D) (E)
28 (A) (B) (C) (D) (E)	73 (A) (B) (C) (D) (E)	118 (A) (B) (C) (D) (E)	163 (A) (B) (C) (D) (E)
29 (A) (B) (C) (D) (E)	74 (A) (B) (C) (D) (E)	119 (A) (B) (C) (D) (E)	164 (A) (B) (C) (D) (E)
30 (A) (B) (C) (D) (E)	75 (A) (B) (C) (D) (E)	120 (A) (B) (C) (D) (E)	165 (A) (B) (C) (D) (E)
31 (A) (B) (C) (D) (E)	76 (A) (B) (C) (D) (E)	121 (A) (B) (C) (D) (E)	166 (A) (B) (C) (D) (E)
32 (A) (B) (C) (D) (E)	77 (A) (B) (C) (D) (E)	122 (A) (B) (C) (D) (E)	167 (A) (B) (C) (D) (E)
33 (A) (B) (C) (D) (E)	78 (A) (B) (C) (D) (E)	123 (A) (B) (C) (D) (E)	168 (A) (B) (C) (D) (E)
34 (A) (B) (C) (D) (E)	79 (A) (B) (C) (D) (E)	124 (A) (B) (C) (D) (E)	169 (A) (B) (C) (D) (E)
35 (A) (B) (C) (D) (E)	80 (A) (B) (C) (D) (E)	125 (A) (B) (C) (D) (E)	170 (A) (B) (C) (D) (E)
36 (A) (B) (C) (D) (E)	81 (A) (B) (C) (D) (E)	126 (A) (B) (C) (D) (E)	171 (A) (B) (C) (D) (E)
37 (A) (B) (C) (D) (E)	82 (A) (B) (C) (D) (E)	127 (A) (B) (C) (D) (E)	172 (A) (B) (C) (D) (E)
38 (A) (B) (C) (D) (E)	83 (A) (B) (C) (D) (E)	128 (A) (B) (C) (D) (E)	173 (A) (B) (C) (D) (E)
39 (A) (B) (C) (D) (E)	84 (A) (B) (C) (D) (E)	129 (A) (B) (C) (D) (E)	174 (A) (B) (C) (D) (E)
40 (A) (B) (C) (D) (E)	85 (A) (B) (C) (D) (E)	130 (A) (B) (C) (D) (E)	175 (A) (B) (C) (D) (E)
41 (A) (B) (C) (D) (E)	86 (A) (B) (C) (D) (E)	131 (A) (B) (C) (D) (E)	176 (A) (B) (C) (D) (E)
42 (A) (B) (C) (D) (E)	87 (A) (B) (C) (D) (E)	132 (A) (B) (C) (D) (E)	177 (A) (B) (C) (D) (E)
43 (A) (B) (C) (D) (E)	88 (A) (B) (C) (D) (E)	133 (A) (B) (C) (D) (E)	178 (A) (B) (C) (D) (E)
44 (A) (B) (C) (D) (E)	89 (A) (B) (C) (D) (E)	134 (A) (B) (C) (D) (E)	179 (A) (B) (C) (D) (E)
45 (A) (B) (C) (D) (E)	90 (A) (B) (C) (D) (E)	135 (A) (B) (C) (D) (E)	180 (A) (B) (C) (D) (E)

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18

Pulmonary and Critical Care Medicine

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MKSAP 18 Made Easy

Gastroenterology and Hepatology

Gastroenterology and Hepatology

High Value Care Recommendation: A recommendation to choose diagnostic and management strategies for patients in specific clinical situations that balance clinical benefit with cost and harms with the goal of improving patient outcomes. Below are the High Value Care Recommendations for the Gastroenterology and Hepatology section ofMKSAP 18.

• In patients with gastroesophageal reflux symptoms without alarm features, empiric proton pump inhibitor therapy is the first therapeutic and diagnostic step.

• Attempts to stop or reduce long-term proton pump inhibitor therapy for uncomplicated gastroesophageal reflux disease should be considered at least annually (see Item 59).

• Women with gastroesophageal reflux disease do not require screening for Barrett esophagus.

• Patients 60 years and older with dyspepsia should undergo upper endoscopy.
• Patients younger than age 60 years with dyspepsia should be tested and treated for *Helicobucter pylori* infection.
• Enteral nutrition is preferred in patients with acute pancreatitis (see Item 26).
• Same-admission cholecystectomy reduces rates of gallstone-related complications for patients with mild gallstone pancreatitis (see Item 20).
• Asymptomatic patients with walled-off necrosis of the pancreas require no intervention (see Item 95).
• Biopsy and endoscopic retrograde cholangiopancreatography are not indicated in the diagnosis of chronic pancreatitis.
• Evaluation with imaging, endoscopy, and other testing is not indicated for irritable bowel syndrome or functional diarrhea.
• Irritable bowel syndrome can often be managed with reassurance, lifestyle modifications, and dietary modifications.
• The evaluation for centrally mediated pain syndrome does not require extensive laboratory testing or imaging.
• Acute diverticulitis usually does not require abdominal imaging.
• Patients with small hyperplastic polyps should undergo repeat colonoscopy no sooner than 10 years (see Item 11).
• Patients with uncomplicated diverticulitis should be treated with oral antibiotics (see Item 74).
• Ultrasonography is the most effective means of diagnosing ascites.
• Asymptomatic hepatic cysts require no follow-up.
• Focal nodular hyperplasia does not require follow-up.
• Incidentally diagnosed gallstones do not require cholecystectomy.
• The diagnosis of acute cholecystitis can be made by ultrasonography.
• In patients with upper gastrointestinal bleeding, a transfusion threshold of less than 7 g/dL (70 g/L) with a target hemoglobin level of7-9 g/dL (70-90 g/L) is associated with decreased mortality and length of hospital stay (see Item 83).

TABLE 1. Causes of Dysphagia

Condition	Diagnostic Clues
	Oropharyngeal Dysphagia
Structural disorders	
Cervical osteophytes	High dysphagia, degenerative joint disease
Cricoid webs	High dysphagia, iron deficiency
Pharyngoesophageal (Zenker) diverticulum	Aspiration, neck mass, and regurgitation of foul-smelling food
Goiter	Neck mass
Neurologic/myogenic disorders	
Amyotrophic lateral sclerosis	Upper and lower motoneuron signs, fasciculations
Central nervous system tumor	Headache, vision changes, nausea, seizures, balance problem
Stroke	Focal neurologic deficits
Muscular dystrophy	Slow progression of muscular weakness over years
Myasthenia gravis	Weakness with repetitive activity
Multiple sclerosis	Episodes of neurologic dysfunction with variable degrees of recovery
Parkinson disease	Bradykinesia, rigidity, tremor
Dementia	Altered cognition
Sjögren syndrome	Dry mouth, dry eyes
	Esophageal Dysphagia
Structural disorders	
Dysphagia lusoria (vascular dysphagia)	Vascular extrinsic compression on the esophagus on imaging
Epiphrenic/traction diverticulum	Outpouching of the esophagus at any level on imaging
Esophageal strictures	Intermittent dysphagia, especially for solid food; history of reflux
Eosinophilic esophagitis	Food impactions, atopic history, rings or strictures on endoscopy
Esophageal webs or rings	Upper esophageal webs may be associated with iron deficiency anemia
Neoplasms	Rapidly progressive dysphagia for solids, then liquids; anorexia; weight loss
Motility disorders	
Achalasia	Concomitant liquid and solid dysphagia
Diffuse esophageal spasm	Chest pain
Systemic sclerosis	Tight skin, telangiectasias, sclerodactyly, gastroesophageal reflux disease, Raynaud phenomenon

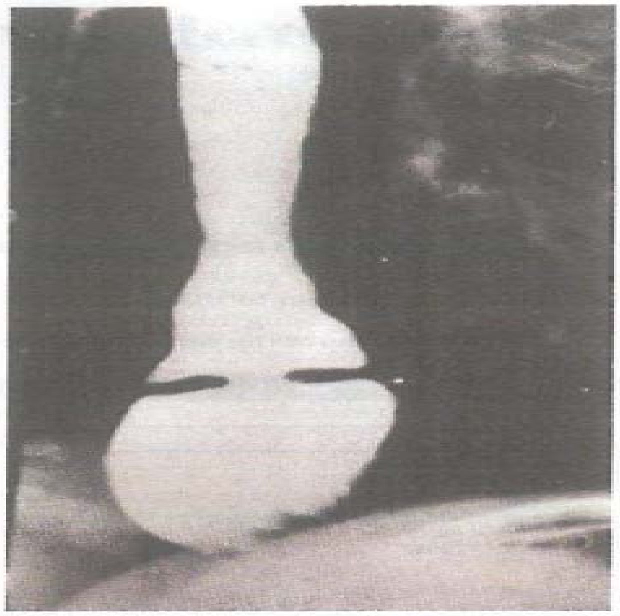

FIGURE 1. Barium esophagram showing a Schatzki ring, a subtype of esophageal ring located at the squamocolumnar junction and a common cause of dysphagia.

KEY POINTS

- Oropharyngeal dysphagia occurs when the patient is unable to transfer the food bolus from the mouth into the upper esophagus by swallowing and should be evaluated with a modified barium swallow.
- Esophageal dysphagia occurring with solids alone suggests a mechanical obstruction, whereas dysphagia with either liquids alone or the combination of liquids and solids favors a motility disorder.
- Upper endoscopy is diagnostic and may be therapeutic for esophageal dysphagia.
- Chest pain is common in patients with gastroesophageal reflux disease, but a cardiac cause of chest pain must be ruled out first.

TABLE 2. Factors Associated with Reflux

Category	Factor
Lifestyle	Cigarette smoking
	Obesity
Eating habits	Eating large meals
	Eating late at night
	Lying supine shortly after eating
Foods and beverages	Alcohol
	Chocolate
	Citrus fruits and juices
	Coffee
	Fatty and fried foods
	Onions
	Peppermint
Medications	Anticholinergic agents
	Aspirin and NSAIDs
	Calcium channel blockers
	Nitrates
	Progesterone
	Opioids (due to delayed gastric emptying)
Body position	Bending over, exercising (both result in increased intra-abdominal pressure)
Other	Pregnancy
	Tight-fitting clothing
	Hiatal hernia

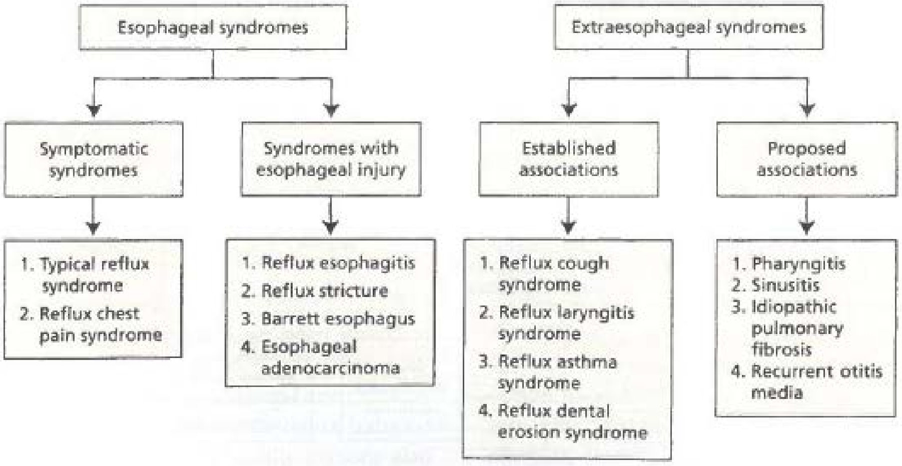

FIGURE 2. Classification of gastroesophageal reflux disease and its subsets.

Reprinted with permission from Vakil N, van Zanten SV, Kahrilas P, Dent J, Jones R; Global Consensus Group. The Montreal definition and classification of gastroesophageal reflux disease: a global evidence-based consensus. Am J Gastroenterol. 2006;101:1900-20; quiz 1943. [PMID: 16928254]. Copyright 2006, Springer Nature.

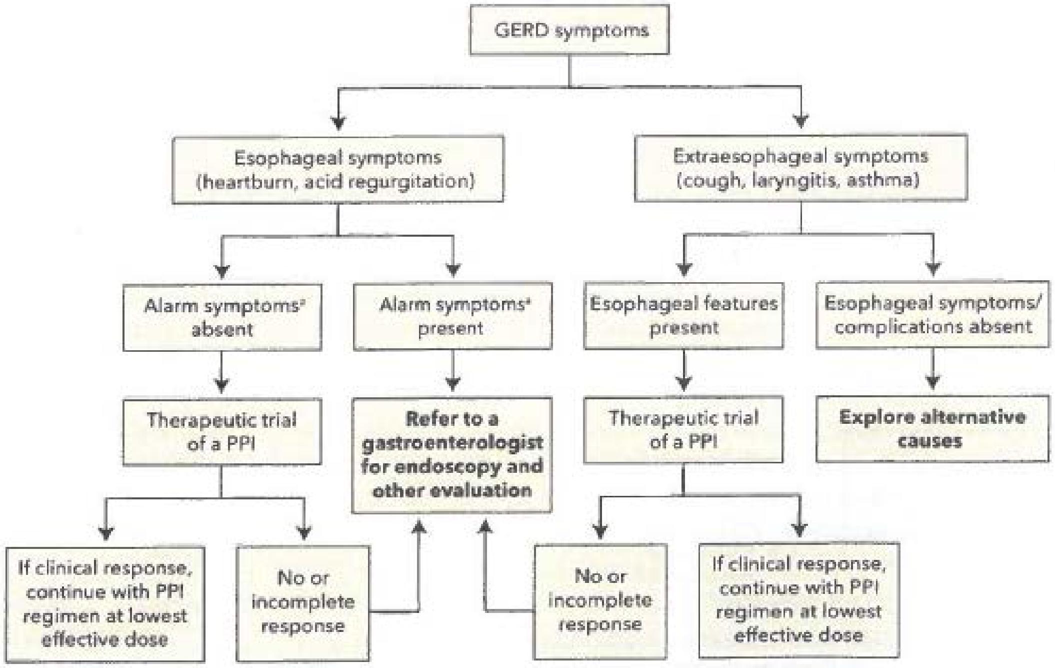

FIGURE 3. Management of gastroesophageal reflux disease.

GERD = gastroesophageal reflux disease; PPI = proton pump inhibitor.

[a]Alarm symptoms include dysphagia, unintentional weight loss, hematemesis, and melena.

TABLE 3. Adverse Effects of Proton Pump Inhibitors

Common	Unusual	Proposed Associations
Headache	Vitamin B_{12} deficiency	Kidney injury
Diarrhea	Hypomagnesemia	Dementia
Dyspepsia	Community-acquired pneumonia	
	Clostridium difficile infection	
	Hip fracture	

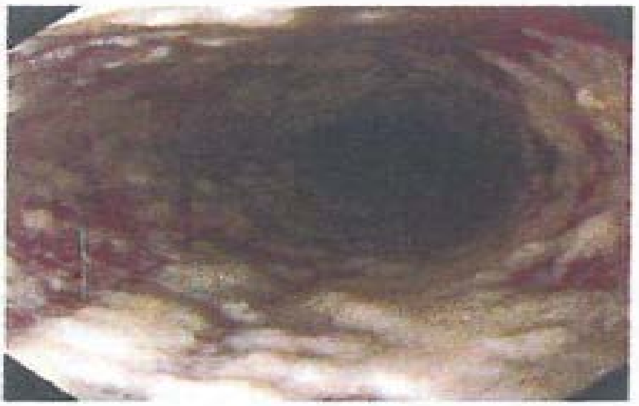

FIGURE 4. Upper endoscopy showing white adherent plaques suggestive of *Candida* esophagitis.

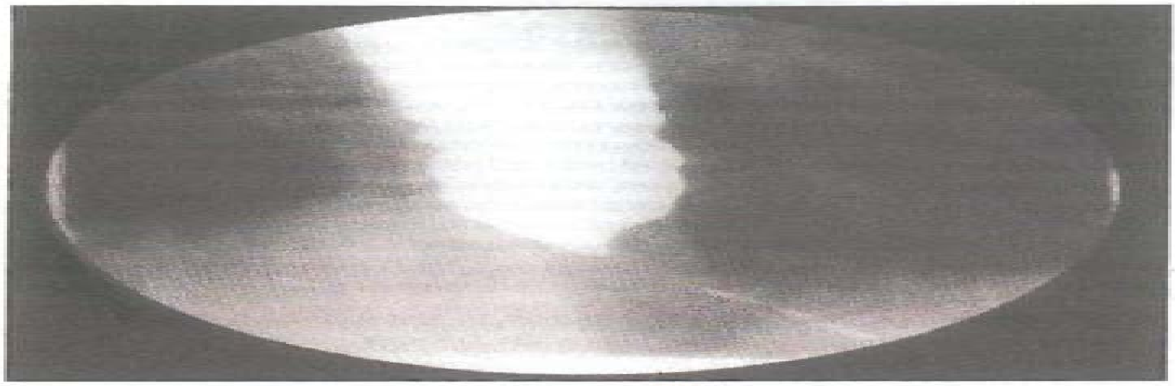

FIGURE 5. Barium esophagram showing the typical appearance of a dilated esophagus and "bird's beak" narrowing at the gastroesophageal junction in a patient with achalasia.

FIGURE 6. Findings of a "corkscrew esophagus" (caused by multiple simultaneous contractions) on esophagography are typical of diffuse esophageal spasm.

KEY POINTS

- In patients with symptoms of gastroesophageal reflux disease but without alarm features, an empiric trial of a proton pump inhibitor can relieve symptoms and confirm the diagnosis.
- Most patients with gastroesophageal reflux disease do not require surgery; indications include failure of optimal proton pump inhibitor therapy, wanting to stop medication, and intolerable medication side effects.
- The diagnostic criteria for eosinophilic esophagitis are esophageal symptoms (most commonly dysphagia), esophageal biopsies showing persistent counts of 15 eosinophils/hpf or greater despite a trial of proton pump inhibitor therapy, and exclusion of other causes of eosinophilia.
- Odynophagia and dysphagia are the most common presenting symptoms of infectious esophagitis.
- To prevent pill-induced esophagitis, patients should drink water with medication and remain upright for at least 30 minutes after ingestion.

FIGURE 7. Upper endoscopic view of Barrett mucosa, with salmon-colored mucosa representing Barrett mucosa compared with the normal pearl-colored squamous mucosa.

TABLE 4. Practice Guidelines for Endoscopic Surveillance of Barrett Esophagus

Dysplasia Grade	Recommendation
None	If no dysplasia is present, repeat upper endoscopy every 3 to 5 years
Indefinite	Start or adjust proton pump inhibitor therapy, then repeat endoscopy in 3 to 6 months
	If still present, then repeat endoscopy in 1 year
Low-grade	Confirmation by expert pathologist, then proceed to endoscopic eradication therapy (surveillance endoscopy in 12 months is an alternative)
High-grade	Confirmation by expert pathologist
	Endoscopic eradication therapy is preferred

Adapted with permission from Shaheen NJ, Falk GW, Iyer PG, Gerson LB; American College of Gastroenterology. ACG clinical guideline: diagnosis and management of Barrett's esophagus. Am J Gastroenterol. 2016;111:30-50; quiz 51. [PMID: 26526079] doi:10.1038/ajg.2015.322.

KEY POINTS

- Barrett esophagus is a premalignant condition caused by longstanding gastroesophageal reflux disease.
- Women with gastroesophageal reflux disease do not require routine screening for Barrett esophagus.
- Patients with Barrett esophagus should receive proton pump inhibitor therapy with dosing based on symptom relief and healing of erosive esophagitis.
- Dysphagia with solid foods is the most common presenting symptom of esophageal cancer.

TABLE 5. Organic Causes of Dyspepsia

Gastroesophageal	Gastroesophageal reflux disease, peptic ulcer disease, *Helicobacter pylori* gastritis, gastric cancer/lymphoma, gastric amyloidosis, Ménétrier disease, gastroparesis
Small bowel	Celiac disease, Crohn disease
Pancreatic	Pancreatitis, pancreatic cancer
Infectious	*Giardia lamblia, Strongyloides stercoralis*, tuberculosis, syphilis
Common medications	NSAIDs, aspirin, iron, antibiotics (erythromycin, ampicillin), narcotics, estrogens and oral contraceptives, theophylline, levodopa, digitalis
Other systemic conditions	Coronary artery disease, kidney disease, thyroid dysfunction, adrenal insufficiency, hyperparathyroidism, pregnancy

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TABLE 6. Rome 4 Diagnostic Criteria for Functional Dyspepsia

One or more of the following:[a]

- Bothersome postprandial fullness
- Bothersome early satiation
- Bothersome epigastric pain
- Bothersome epigastric burning

No evidence of structural disease (including upper endoscopy) that is likely to explain the symptoms

[a]Criteria fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis.

Reprinted with permission from Stanghellini V, Chan FK, Hasler WL, Malagelada JR, Suzuki H, Tack J, et al. Gastroduodenal disorders. Gastroenterology. 2016;150:1380-92. [PMID: 27147122] doi:10.1053/j.gastro.2016.02.011. Copyright 2016, The AGA Institute.

TABLE 7. Rome 4 Diagnostic Criteria for Postprandial Distress Syndrome

Criteria[a]	Supportive Remarks
Must include one or both of the following at least 3 days per week: Bothersome postprandial fullness (i.e., severe enough to affect usual activities) Bothersome early satiation (i.e., severe enough to prevent finishing a regular-sized meal) No evidence of organic, systemic, or metabolic disease that is likely to explain the symptoms on routine investigations (including upper endoscopy)	Postprandial epigastric pain or burning, epigastric bloating, excessive belching, and nausea can also be present Vomiting warrants consideration of another disorder Heartburn is not a dyspeptic symptom but may often coexist Symptoms that are relieved by evacuation of feces or gas should generally not be considered as part of dyspepsia Other individual digestive symptoms or groups of symptoms, such as from gastroesophageal reflux disease and irritable bowel syndrome, may coexist

[a]Criteria fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis.

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TABLE 8. Rome 4 Diagnostic Criteria for Epigastric Pain Syndrome

Criteria[a]	Supportive Remarks
Must include the following symptoms at least 1 day per week: Bothersome epigastric pain and/or burning (i.e., severe enough to affect usual activities) No evidence of organic, systemic, or metabolic disease that is likely to explain the symptoms on routine investigations (including upper endoscopy)	Pain may be induced by ingestion of a meal, relieved by ingestion of a meal, or may occur while fasting Postprandial epigastric bloating, belching, and nausea can also be present Persistent vomiting suggests another disorder Heartburn is not a dyspeptic symptom but may often coexist The pain does not fulfill biliary pain criteria Symptoms that are relieved by evacuation of feces or gas should generally not be considered as part of dyspepsia Other individual digestive symptoms or groups of symptoms, such as from gastroesophageal reflux disease and irritable bowel syndrome, may coexist

[a]Criteria fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis.

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KEY POINTS

- For patients with dyspepsia, routine upper endoscopy to exclude malignancy is reserved for patients older than age 60 years.
- Upper endoscopy should be considered for patients with alarm features such as a family history of gastric cancer, immigration from a region with increased risk for gastric cancer, or severe symptoms, regardless of age.
- Patients younger than age 60 years with dyspepsia symptoms should be tested and treated for *Helicobacter pylori* infection.

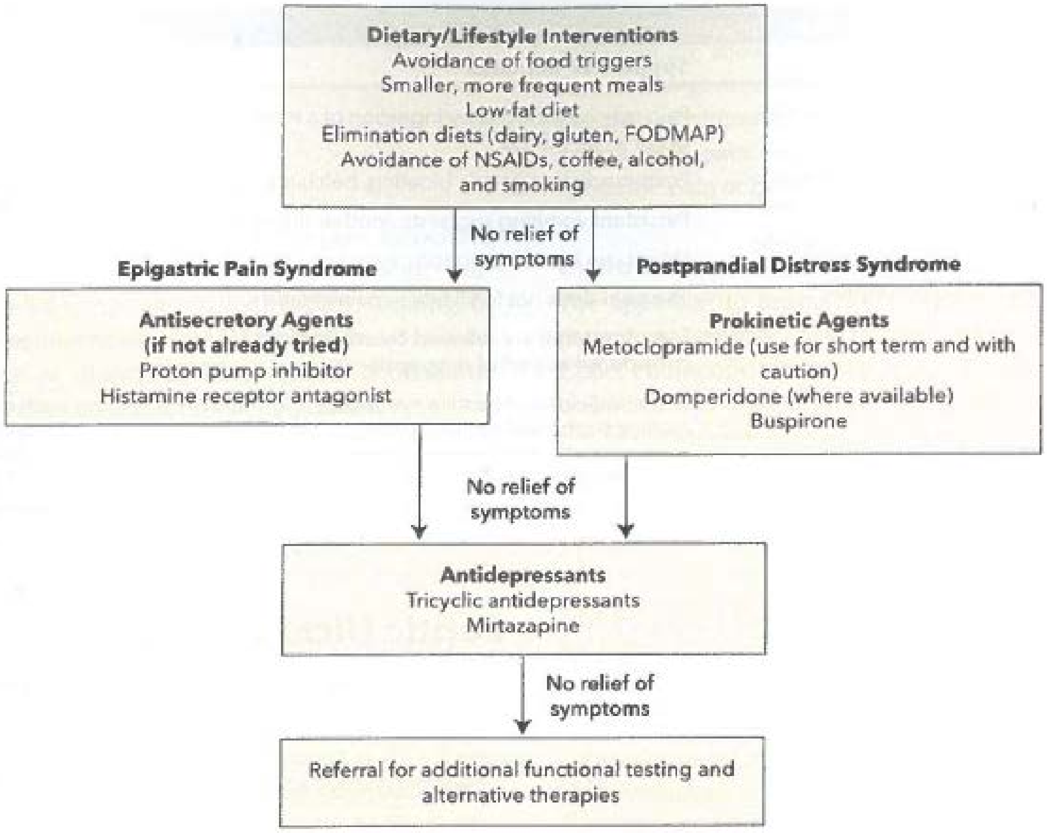

FIGURE 8. Treatment of functional dyspepsia.

FODMAP = Fermentable Oligosaccharides, Disaccharides, Monosaccharides, And Polyols.

KEY POINTS

- NSAIDs and *Helicobacter pylori* infection are the two most common causes of peptic ulcer disease.
- Upper endoscopy is the diagnostic test of choice for peptic ulcer disease.
- Repeat upper endoscopy is reserved for patients with persistent symptoms after 8 to 12 weeks of therapy, ulcers of unknown cause, or if gastric ulcer biopsy was not performed during the initial upper endoscopy.

KEY POINTS

- Patients with active peptic ulcer disease, history of peptic ulcer disease without documented cure of *Helicobacter pylori* infection, gastric mucosa-associated lymphoid tissue lymphoma, or history of endoscopic resection of early gastric cancer must be tested for *H. pylori* and treated if positive.
- Gastric biopsies during upper endoscopy or noninvasive testing methods, including ^{13}C-urea breath and stool antigen testing, can confirm the presence of *H. pylori* infection; negative serologic testing can exclude infection, but a positive serologic result requires confirmation.
- Treatment regimens for *H. pylori* consist of a minimum of three agents, including two antimicrobial agents and one antisecretory agent; treatment duration is 14 days in most cases.
- Testing for eradication of *H. pylori* is performed using a ^{13}C-urea breath test, fecal antigen test, or biopsies obtained during upper endoscopy at least 4 weeks after completion of eradication therapy.

TABLE 9. First-Line Treatment Options for *Helicobacter pylori* Infection

Treatment Regimen	Duration of Therapy	Clinical Indicators
PPI, standard[a] or double dose twice daily (esomeprazole, once daily only) Clarithromycin, 500 mg twice daily Amoxicillin, 1 g twice daily	14 days	*H. pylori* clarithromycin resistance is known to be <15% No previous history of macrolide exposure for any reason
PPI, standard or double dose twice daily Clarithromycin, 500 mg twice daily Metronidazole, 500 mg three times daily	14 days	*H. pylori* clarithromycin resistance is known to be <15% No previous history of macrolide exposure for any reason Penicillin allergy
PPI, standard dose twice daily Bismuth subcitrate, 120-300 mg or subsalicylate, 300 mg four times daily Tetracycline, 500 mg three times daily Metronidazole, 250 mg four times daily or 500 mg three times daily	10-14 days	Previous macrolide exposure Penicillin allergy
PPI, standard dose twice daily Clarithromycin, 500 mg twice daily Amoxicillin, 1 g twice daily Nitroimidazole, 500 mg twice daily	10-14 days	May be an alternative to standard clarithromycin triple therapy Not validated in North America
PPI, standard dose twice daily Levofloxacin, 500 mg twice daily Amoxicillin, 1 g twice daily	10-14 days	May be an alternative to standard clarithromycin triple therapy Not validated in North America

PPI = proton pump inhibitor.

[a]Standard dose PPIs: esomeprazole, 40 mg; lansoprazole, 30 mg; omeprazole, 20 mg; pantoprazole, 40 mg; rabeprazole, 20 mg.

Adapted with permission from Chey WD, Leontiadis GI, Howden CW, Moss SF. ACG clinical guideline: treatment of *Helicobacter pylori* infection. Am J Gastroenterol. 2017;112:212-239. [PMID: 28071659] doi:10.1038/ajg.2016.563.

TABLE 10. Second-Line Treatment for *Helicobacter pylori* Infection after Failure of Initial Treatment

Treatment Regimen	Duration of Therapy	Clinical Indicators
PPI, standard dose twice daily Bismuth subcitrate, 120-300 mg, or subsalicylate, 300 mg four times daily Tetracycline, 500 mg three times daily Metronidazole, 250 mg four times daily, or 500 mg three times daily	14 days	Failure of clarithromycin-based or levofloxacin-based therapy
PPI, standard dose twice daily Levofloxacin, 500 mg twice daily Amoxicillin, 1 g twice daily	14 days	Failure of bismuth-based or clarithromycin-based therapy
PPI, standard or double dose twice daily Clarithromycin, 500 mg twice daily Amoxicillin, 1 g twice daily	14 days	Failure of bismuth-based therapy
PPI, standard or double dose twice daily Clarithromycin, 500 mg twice daily Metronidazole, 500 mg three times daily	14 days	Failure of bismuth-based therapy Penicillin allergy

PPI = proton pump inhibitor.

Adapted with permission from Chey WD, Leontiadis GI, Howden CW, Moss SF. ACG clinical guideline: treatment of *Helicobacter pylori* infection. Am J Gastroenterol. 2017;112:212-239. [PMID: 28071659] doi:10.1038/ajg.2016.563.

KEY POINTS

- Autoimmune atrophic gastritis is associated with pernicious anemia, iron deficiency, small intestinal bacterial overgrowth, and gastric cancer.
- *Helicobacter pylori* is associated with upper gastrointestinal conditions other than peptic ulcer disease including environmental metaplastic atrophic gastritis, gastric intestinal metaplasia, and, rarely, lymphocytic gastritis.

TABLE 11. Risk Factors for NSAID-Related Upper Gastrointestinal Complications

History of upper gastrointestinal bleeding
History of peptic ulcer disease
Helicobacter pylori infection
Age older than 65 years
Hemodialysis or peritoneal dialysis
Use of high-dose or multiple NSAIDs
Concomitant use of aspirin (even low-dose), nonaspirin antiplatelet agents, anticoagulants, oral glucocorticoids, selective serotonin reuptake inhibitors

KEY POINTS

- Upper gastrointestinal complications, such as bleeding, are common with the use of NSAIDs (both short- and long-term) and low-dose aspirin.
- Proton pump inhibitors are the preferred agent for the prevention and treatment of NSAID-related (including aspirin-related) upper gastrointestinal complications.
- In high-risk individuals without cardiovascular disease, including those with previous NSAID-induced gastrointestinal bleeding, the combination of a selective cyclooxygenase-2 inhibitor plus a proton pump inhibitor provides the best gastrointestinal protection if avoidance of NSAIDs is not possible.

TABLE 12. Strategies for Prevention of NSAID-Related Ulcer Complications

	No GI Risk Factors[a]	One to Two GI Risk Factors[a,b]	More than Two GI Risk Factors[a]
No aspirin	NSAID	NSAID plus PPI	Ideally, avoidance of NSAIDs If no alternative to NSAIDs, then a selective COX-2 inhibitor plus a PPI
Low-dose aspirin (81 mg/d) for cardiovascular prophylaxis	Naproxen plus PPI	Naproxen plus PPI	Avoid selective COX-2 inhibitors and use alternative analgesic

COX-2 = cyclooxygenase-2; GI = gastrointestinal; NSAID = nonsteroidal anti-inflammatory drug; PPI = proton pump inhibitor.

[a]GI risk factors: history of GI bleeding; history of peptic ulcer disease; concurrent use of NSAIDs and aspirin (including low-dose aspirin), nonaspirin antiplatelets, anticoagulants, or glucocorticoids; age older than 65 years; any chronic, debilitating illness.

[b]With no prior NSAID-related upper GI bleeding.

Adapted with permission from Lanza FL, Chan FK, Quigley EM; Practice Parameters Committee of the American College of Gastroenterology. Guidelines for prevention of NSAID-related ulcer complications. Am J Gastroenterol. 2009;104:728-38. [PMID: 19240698] doi:10.1038/ajg.2009.115.

TABLE 13. Causes of Gastroparesis	
Common causes	Diabetes mellitus (40% in long-standing type 1 diabetes mellitus, 20% in type 2 diabetes mellitus)
	Postsurgical (e.g., Nissen fundoplication, bariatric surgery, pancreatic surgery)
	Idiopathic (e.g., postviral)
Infrequent causes	Connective tissue disease (e.g., systemic sclerosis)
	Neurologic disease (e.g., Parkinson disease)
	Eating disorders
	Hypothyroidism
	Amyloidosis
	Paraneoplastic syndromes (e.g., small cell lung cancer)
	Mesenteric ischemia
	Medications (e.g., opiates, anticholinergic agents)

KEY POINTS

- Gastroparesis is a heterogeneous clinical syndrome with three components to the diagnosis: the presence of specific symptoms, absence of mechanical outlet obstruction, and objective evidence of delay in gastric emptying into the duodenum.
- Initial management of gastroparesis includes correction of dehydration and electrolyte abnormalities; nutritional support; small, frequent meals that are low in fat and soluble fiber; and improved glycemic control in patients with diabetes mellitus.
- Metoclopramide is a prokinetic drug that improves gastric emptying but is associated with dystonia, tardive dyskinesia, and Parkinsonism.

TABLE 14. Diagnostic Tests Assessing Gastric Emptying

Test Modality	Advantages	Disadvantages	Clinical Pearls
Gastric scintigraphy	Considered the gold standard	Radiation exposure (technetium radiolabeled meal) Requires specially trained personnel Cost	4-Hour study is most accurate Assesses solid emptying (liquid emptying is less accurate) Blood sugar should be less than 275 mg/dL (15.3 mmol/L)
Wireless motility capsule	Can also assess small bowel, colon, and whole gut transit No radiation Ambulatory study	Cost Can't be used with pacemaker or defibrillator Risk for capsule retention	Consider in a patient with suspected global motility problem Stop antisecretory agents as study relies on measurement of pH
Gastric emptying breath test	Low cost	Only recently commercially available Efficacy and accuracy limited to clinical trials	—

KEY POINTS

- Polyps in the stomach include fundic gland polyps, which have no malignant potential; hyperplastic polyps; and, less commonly, adenomas, which should be resected.
- Gastrointestinal stromal tumors should be evaluated with endoscopic ultrasonography and excised if symptoms or high-risk features are present.
- Carcinoid tumors are well-differentiated neuroendocrine tumors that can occur throughout the gastrointestinal tract, including the stomach.

KEY POINTS

- In countries with a low incidence of gastric cancer, screening for gastric cancer should be reserved for patients with genetic cancer syndromes.
- The primary nongenetic risk factor for gastric cancer is *Helicobacter pylori* infection.
- Upper endoscopy with biopsy is the diagnostic test of choice for gastric cancer.

KEY POINTS

- Patients who undergo partial gastrectomy for malignancy require lifelong surveillance for recurrence of cancer.
- Dumping syndrome results from rapid gastric emptying after gastric surgery; first-line treatment is smaller, more frequent meals with liquids taken following meals.

TABLE 15. Causes of Acute Pancreatitis
Common
Biliary disease
Gallstones
Microlithiasis (1- to 2-mm stones that are not detected by imaging studies)
Alcohol use
Post-endoscopic retrograde cholangiopancreatography
Occasional
Medications
Furosemide
Didanosine
Asparaginase
Mesalamine
Hydrochlorothiazide
6-Mercaptopurine/azathioprine
Simvastatin
Hypertriglyceridemia
Hypercalcemia
Choledochocele
Rare
Autoimmune
Infectious
Viral (mumps, coxsackie B virus, cytomegalovirus)
Parasitic (*Toxoplasma* species, *Ascaris lumbricoides*)
Ischemia
Trauma
Neoplasia
Celiac disease
Genetic (only if attacks are recurrent)

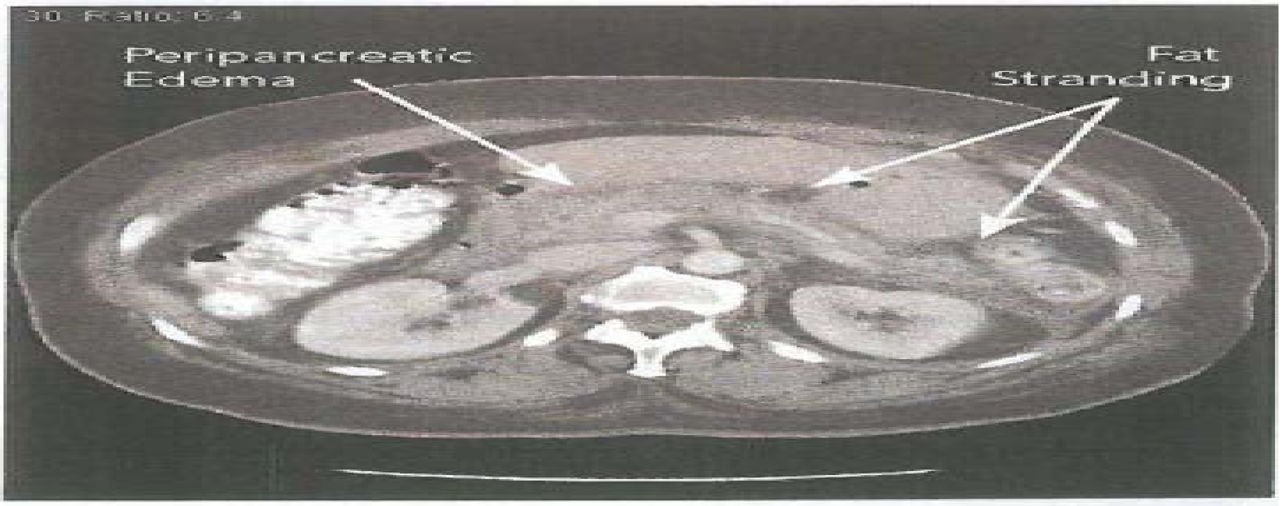

FIGURE 9. CT scan showing acute pancreatitis with peripancreatic fat stranding and inflammation. The hazy appearance of the mesenteric fat surrounding the pancreas in this image is called fat stranding, and the blurring of the margins of the pancreas is consistent with peripancreatic edema, features seen with inflammatory changes of acute pancreatitis.

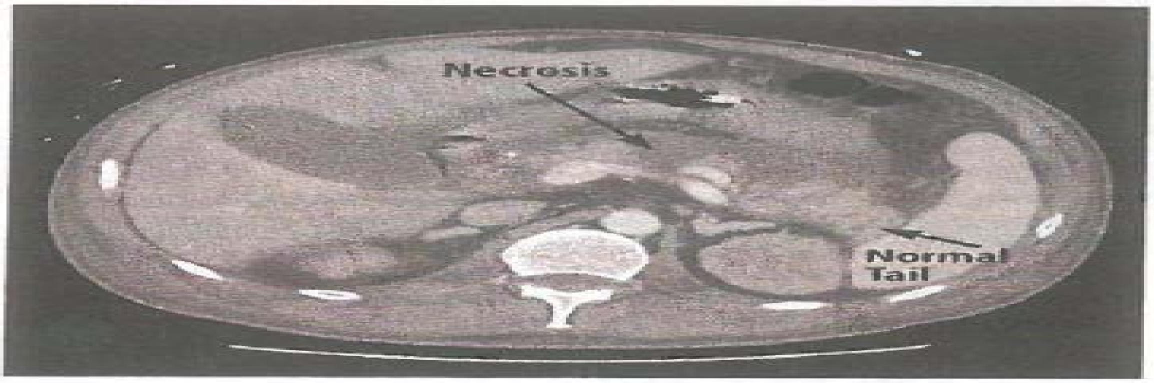

FIGURE 10. CT scan showing acute pancreatitis with hypoperfusion of the body of the pancreas as indicated by lack of enhancement following intravenous contrast infusion (necrosis) and normal perfusion of the pancreatic tail.

FIGURE 11. CT scan showing maturation and liquefaction of pancreas necrosis of nearly the entire pancreas over 4 weeks in duration with a well-defined rim or wall (*arrows*), known as walled-off necrosis.

KEY POINTS

- Biliary disease, such as gallstone or microlithiasis, is the most common cause of acute pancreatitis.
- Diagnosis of acute pancreatitis requires two of three criteria: (1) acute-onset upper abdominal pain, (2) serum lipase or amylase levels elevated at least three times greater than the upper limit of normal, and (3) characteristic findings on imaging.
- Patients with acute pancreatitis should undergo transabdominal ultrasonography to evaluate for biliary disease.
- Patients with acute pancreatitis should be hospitalized for fluid administration and close monitoring of cardiovascular, respiratory, and kidney status.

TABLE 16. Causes of Chronic Pancreatitis

Toxic or metabolic
Alcohol, tobacco, hypercalcemia, hypertriglyceridemia, chronic kidney disease
Genetic
Mutations or polymorphisms of the *CFTR*, *PRSSI*, *SPINKI*, *CTRC*, *CASR*, *CLDN2* genes
Recurrent and severe acute pancreatitis
Vascular disease/ischemia
Obstructive
Pancreatic tumor, intraductal papillary mucinous neoplasm
Posttraumatic (pancreatic duct stricture)
Autoimmune (type 1 and type 2)
Idiopathic

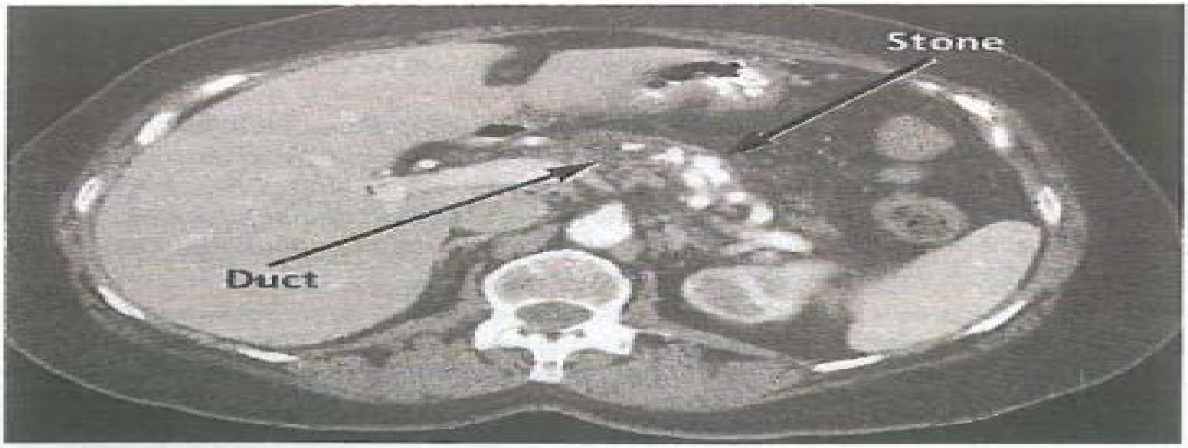

FIGURE 12. CT scan showing chronic calcific pancreatitis with multiple stones in the main duct and side branches of the pancreas.

KEY POINTS

- Abdominal pain, which may occur as intermittent attacks or as ongoing, daily pain, is the most common symptom of chronic pancreatitis.
- Pancreatic biopsy and endoscopic retrograde cholangiopancreatography are not indicated in the diagnosis of chronic pancreatitis.
- Symptomatic management is the cornerstone of treatment for chronic pancreatitis, including patients with refractory pain.
- Patients with chronic pancreatitis should be counseled to avoid alcohol and tobacco use.

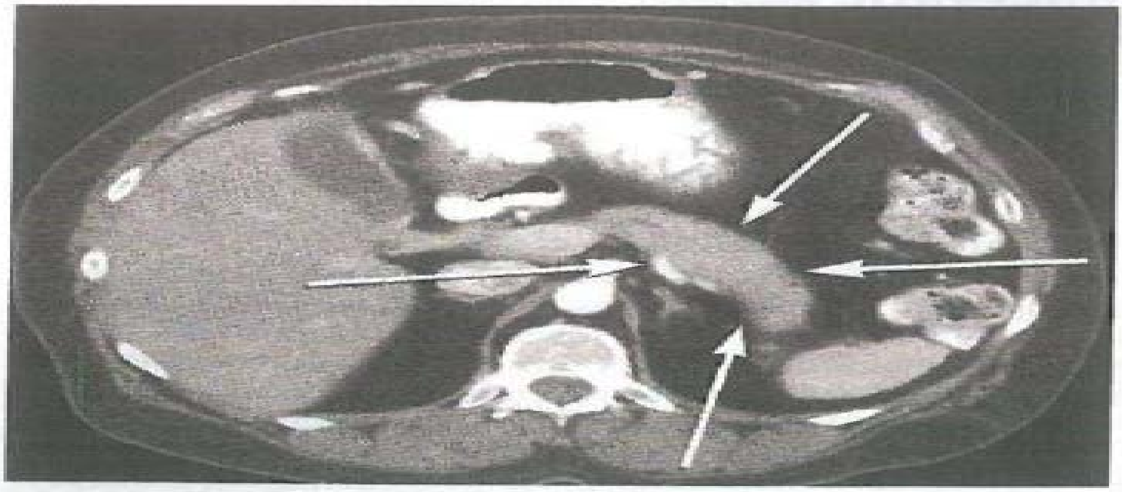

FIGURE 13. CT scan showing the homogeneous, hypodense "sausage-shaped" swelling (*arrows*) seen in autoimmune pancreatitis.

KEY POINTS

- Diagnosis of autoimmune pancreatitis requires the presence of a narrowed main pancreatic duct and parenchymal swelling ("sausage-shaped" pancreas) on imaging and disease response to glucocorticoids.
- Type 1 autoimmune pancreatitis is characterized by elevated numbers of IgG4-positive cells in pancreatic tissue; most patients also have a significant elevation of IgG4 in serum.
- Patients with type 2 autoimmune pancreatitis have normal IgG4-positive cell counts.
- Types 1 and 2 autoimmune pancreatitis are treated with glucocorticoids, with a relapse rate of up to 60%.

KEY POINTS

- Diagnosis of pancreatic cancer is suggested by weight loss, abdominal pain, jaundice, and new-onset diabetes mellitus; pancreas protocol CT or MRI help support the diagnosis and delineate the extent of disease.
- Endoscopic ultrasound-guided fine-needle aspiration of the pancreas is recommended to provide histological confirmation of cancer.

KEY POINTS

- Most pancreatic cysts never become malignant, with the exception of intraductal papillary mucinous neoplasms involving the main pancreatic duct.
- Cystic lesions are managed with surveillance and surgical resection of high-risk cysts.

KEY POINTS

- Ten to twenty-five percent of pancreatic neuroendocrine tumors are functional and hypersecrete hormones, most commonly gastrin or insulin.
- Genetic testing for inherited tumor syndromes should be considered based on patient age and history.

TABLE 17. Types of Chronic Diarrhea

Diarrhea Type	Causes (examples)
Osmotic	Medications (laxatives)
	Undigested sugars (lactose, fructose, sorbitol, mannitol)
Secretory	Medications (nonosmotic laxatives, antibiotics)
	Endocrine (carcinoid, gastrinoma, VIPoma, adrenal insufficiency, hyperthyroidism)
	Bile salt malabsorption (ileal resection, cholecystectomy)
	Noninvasive infections (giardiasis, cryptosporidiosis)
	Small intestinal bacterial overgrowth
Steatorrhea	Maldigestion (decreased bile salts, pancreatic dysfunction)
	Malabsorption (celiac disease, tropical sprue, giardiasis, Whipple disease, chronic mesenteric ischemia, short bowel syndrome, bacterial overgrowth, lymphatic obstruction)
Inflammatory	Inflammatory bowel disease (ulcerative colitis, Crohn disease, microscopic colitis)
	Malignancy (colorectal cancer, lymphoma)
	Invasive infections (*Clostridium difficile*, cytomegalovirus, *Entamoeba histolytica*, tuberculosis)
	Ischemia
	Radiation colitis/enteritis
Motility	Postsurgical (vagotomy, dumping)
	Endocrine (diabetes mellitus, hyperthyroidism)
	Scleroderma
Miscellaneous	Irritable bowel syndrome
	Functional diarrhea[a]
	Factitious
	Overflow
	Fecal incontinence

[a]Frequent or loose or watery stools without abdominal discomfort in the absence of other identifiable causes.

Adapted with permission from Schiller LR, Pardi DS, Spiller R, Semrad CE, Surawicz CM, Giannella RA, et al. Gastro 2013 APDW/WCOG Shanghai working party report: chronic diarrhea: definition, classification, diagnosis. J Gastroenterol Hepatol. 2014;29:6-25. [PMID: 24117999] doi:10.1111/jgh.12392.

TABLE 18. Medications that Cause Diarrhea

Common
Antacids, proton pump inhibitors
Chemotherapy
Antibiotics
Colchicine
Metformin
NSAIDs, mesalamine
Cholesterol-lowering drugs
Rarer
ACE inhibitors
Angiotensin receptor blockers
β-adrenergic receptor antagonists
Carbamazepine
Lipase inhibitors
Lithium
Prostaglandin
Vitamin/mineral supplements

Adapted with permission from Schiller LR, Pardi DS, Spiller R, Semrad CE, Surawicz CM, Giannella RA, et al. Gastro 2013 APDW/WCOG Shanghai working party report: chronic diarrhea: definition, classification, diagnosis. J Gastroenterol Hepatol. 2014;29:6-25. [PMID: 24117999] doi:10.1111/jgh.12392.

KEY POINTS

- Acute diarrhea (of less than 2 weeks' duration) is usually caused by infectious agents; chronic diarrhea (of more than 4 weeks' duration) is most commonly noninfectious.
- Maintaining hydration is the primary goal of treatment for acute diarrhea.
- The primary causes of chronic diarrhea are irritable bowel syndrome with predominant diarrhea, functional causes, and medications.
- Evaluation with imaging, endoscopy, and additional testing should be reserved for patients whose symptoms do not suggest irritable bowel syndrome or a functional cause of chronic diarrhea.

TABLE 19. Sources of FODMAP Carbohydrates

Fructose: honey, apples, pears, peaches, mangos, fruit juice, dried fruit
Lactose: milk, custard, ice cream, yogurt, soft cheeses
Fructans: wheat, rye, onions, leeks, zucchini
Galactans: legumes
Sugar alcohols: xylitol, sorbitol, maltitol, mannitol

FODMAP = Fermentable Oligosaccharides, Disaccharides, Monosaccharides, And Polyols.

FIGURE 15. Dermatitis herpetiformis, a manifestation of celiac disease, is characterized by pruritic papules and transient, almost immediately excoriated blisters on the elbows, knees, and buttocks.

KEY POINTS

- The best initial test for celiac disease is testing for IgA tissue transglutaminase antibodies.
- Up to 40% of the general population carries the *HLA-DQ2* or *HLA-DQ8* mutation, so genetic testing alone cannot be used to diagnose celiac disease.
- The treatment of celiac disease is lifelong avoidance of gluten.
- The most common cause of refractory celiac disease symptoms is gluten exposure.

KEY POINTS

- Small intestinal bacterial overgrowth is caused by various conditions, including impaired motility, strictures, or blind loops, and is treated with antibiotic therapy.
- Short bowel syndrome is defined by a small-intestine length of less than 200 cm, resulting in maldigestion, malabsorption, and malnutrition.
- Lactose malabsorption is common, with symptoms occurring when lactose is ingested and subsiding with exclusion of lactose from the diet.

TABLE 20. Features of Ulcerative Colitis and Crohn Disease

Feature	Ulcerative Colitis	Crohn Disease
Depth of inflammation	Mucosal	Transmural
Pattern of disease	Contiguous and symmetric	Skips areas and asymmetric
Location	Colorectum	Mouth to anus
Rectal involvement	Nearly 100%	Less common
Ileal disease	Backwash ileitis (15%)	Common
Fistulas, abscess, and strictures	Rare	Common
Perianal disease	Rare	Common
Granulomas	Unlikely	In approximately 30%
Overt rectal bleeding	Common	Less common
Tobacco use	Protective	Exacerbates

FIGURE 16. Erythema nodosum, a manifestation of inflammatory bowel disease, typically appears as ill-defined erythema overlying subcutaneous, tender nodules most commonly symmetrically located on the anterior shins.

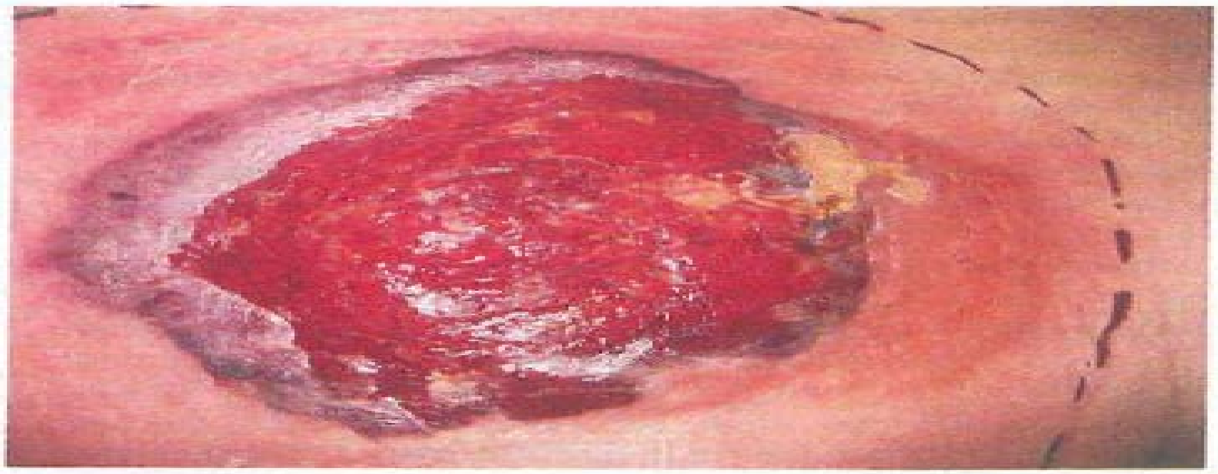

FIGURE 17. Pyoderma gangrenosum, a manifestation of inflammatory bowel disease, typically begins as a small pustule or red nodule that rapidly expands with an edematous, infiltrated, actively inflamed border and a painful, exudative wet ulcer. The border is characteristically violaceous with an edge that overhangs the ulcer.

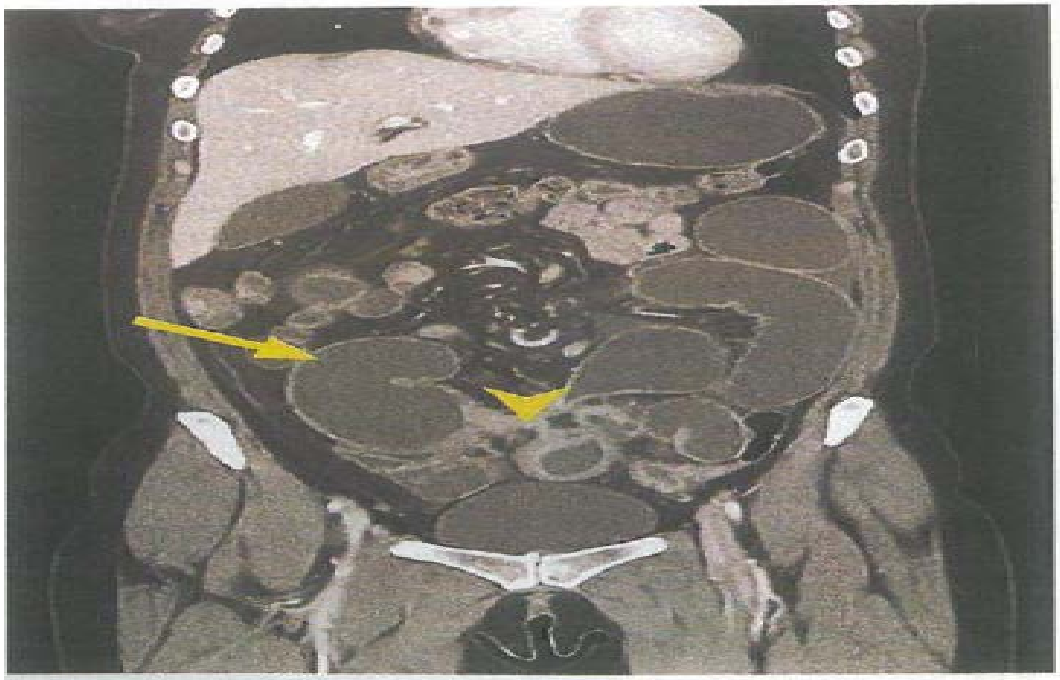

FIGURE 18. CT scan of the abdomen and pelvis in a patient with Crohn disease, showing small-bowel obstruction with dilated loops of small intestine (*arrow*) and matted loops of bowel (*arrowhead*) in the pelvis.

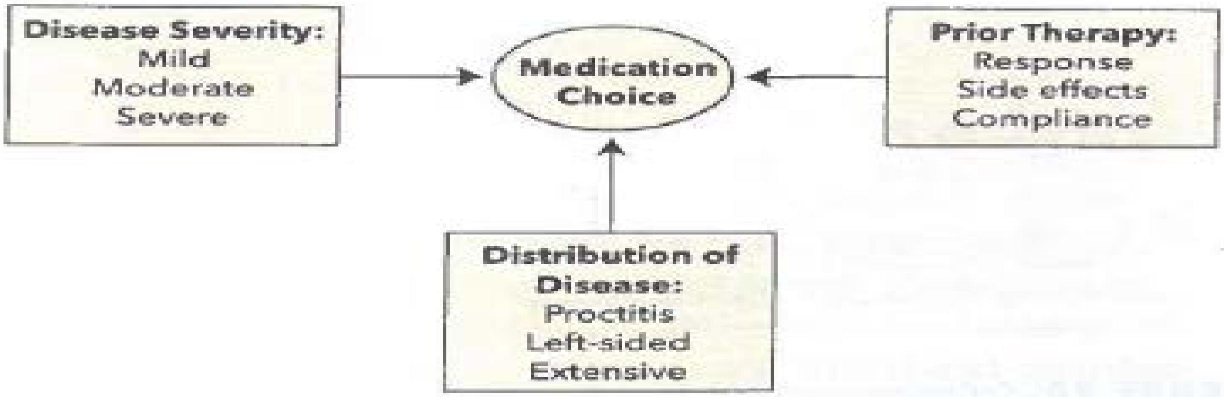

FIGURE 19. Factors to consider when choosing medical therapy for ulcerative colitis.

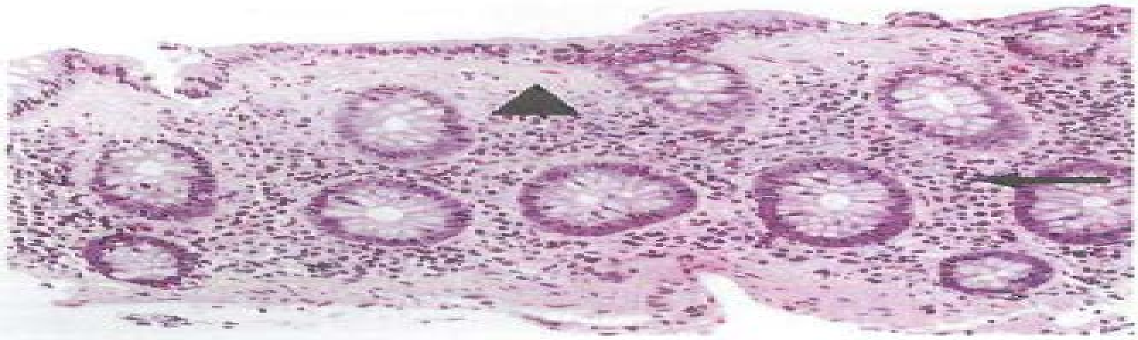

FIGURE 20. Collagenous colitis: colon mucosal biopsy showing a pink, abnormal subepithelial collagen band (*arrowhead*) and lamina propria expanded by inflammatory cells (*arrow*).

KEY POINTS

- The major symptoms of ulcerative colitis include diarrhea, abdominal discomfort, rectal bleeding, and tenesmus, with a slow onset of symptoms.
- Fistula, abscess, and stricture are characteristic complications of Crohn disease.
- Endoscopy with biopsy is needed to help make the diagnosis of inflammatory bowel disease.
- The goals of therapy are to induce and maintain remission of inflammatory bowel disease, and to prevent disease- and treatment-related complications.
- Unlike patients with Crohn disease or ulcerative colitis, patients with microscopic colitis are not at increased risk for colorectal cancer.

TABLE 21. Secondary Causes of Constipation
Medications
Opioids
Antidiarrheals
Anticholinergics (antispasmodics, antiparkinsonian drugs, tricyclic antidepressants, antipsychotics)
Antihistamines
NSAIDs
Iron supplements
Calcium supplements
Bismuth
Antihypertensives (calcium channel blockers, diuretics, clonidine)
Serotonergic antagonists (ondansetron)
Mechanical Causes
Colorectal cancer
Rectocele
Rectal intussusception
Rectal prolapse
Sigmoidocele
Enterocele
Anastomotic stricture
Anal stenosis/stricture
Extrinsic compression from pelvic/abdominal process
Systemic Illnesses
Endocrinologic
Diabetes mellitus
Hypothyroidism
Panhypopituitarism
Pheochromocytoma
Glucagonoma
Neuropathy/myopathy
Altered Physiologic State
Hypercalcemia
Hypokalemia
Pregnancy
Porphyria
Heavy-metal poisoning (arsenic, lead, mercury)
Psychosocial
Depression
Cognitive impairment
Immobility

TABLE 22. Treatments for Constipation

Intervention	Mechanism of Action	Considerations
Bulk Laxative Soluble fiber (psyllium, methylcellulose, calcium polycarbophil, wheat dextrin) Insoluble fiber (bran, rye, flax seed)	Increases ability of stool to retain water Bulks stool Speeds movement of stool through colon	Start with a low dose and increase slowly Soluble fiber works better than insoluble fiber Bloating, distension, flatulence, and cramping may be limiting
Stool Softener Docusate sodium, docusate calcium	A detergent that allows water to penetrate the stool	Minimal effectiveness in clinical trials Only role is in mild constipation symptoms Well tolerated Few side effects
Osmotic Laxative Polyethylene glycol 3350 Lactulose Magnesium hydroxide/magnesium citrate Sorbitol	Poorly absorbed compounds Creates an osmotic gradient Water moves into the bowel lumen	Polyethylene glycol 3350 and lactulose improve stool frequency and consistency; others have not been tested in clinical trials Bloating and gas can be limiting Caution with use of magnesium in renal insufficiency
Stimulant Laxative Anthraquinones (senna, cascara) Diphenylmethanes (bisacodyl, sodium picosulfate)	Irritates the colon wall, increasing contractions Stimulates sensory nerves lining the colon May inhibit water absorption in the colon	Quickest acting (works within 8-12 hours of ingestion) Senna can cause melanosis coli (benign pigmentation of the colon) Diarrhea, cramping, bloating, and nausea can be limiting
Secretagogue Lubiprostone Linaclotide Plecanatide	Lubiprostone activates type-2 chloride channels on enterocytes lining the gut lumen, causing chloride ions to move into the colonic lumen with sodium and water following the ionic gradient Linaclotide and plecanatide activate guanylate cyclase C receptors on enterocytes, leading to chloride channel activation through a series of processes within the cell	Lubiprostone improves stool form and frequency, straining, and abdominal pain; nausea is a common side effect Linaclotide and plecanatide improve stool form and frequency, straining, bloating, and abdominal pain; diarrhea is a common side effect
Serotonergic Agent Prucalopride	Increases intestinal contractions Increases intestinal secretion	Not available in the United States Available in Canada and Europe
Neuromuscular Reeducation (biofeedback)	Retrains the skeletal muscle involved in defecation (abdominal wall, pelvic floor, anorectal) Corrects altered rectal sensation	Effective for dyssynergic defecation Requires a specially trained physical therapist

KEY POINTS

- The most common cause of secondary constipation is medication.
- Treatment strategies include dietary and lifestyle modification, addressing causes of secondary constipation, and various pharmacologic agents.

KEY POINTS

- Irritable bowel syndrome is diagnosed based on clinical criteria and is no longer a diagnosis of exclusion.
- Many cases of irritable bowel syndrome can be effectively managed with reassurance, lifestyle modifications, and dietary modifications.
- Pharmacotherapy should target predominant symptoms and be used if conservative treatment is not effective.

KEY POINTS

- The evaluation for centrally mediated pain syndrome in the setting of chronic abdominal pain requires a detailed medical and psychosocial history and physical examination with limited laboratory testing.
- Narcotic bowel syndrome, also known as opiate-induced gastrointestinal hyperalgesia, is characterized by the paradoxical increase in abdominal pain with increasing doses of narcotics.

KEY POINTS

- Diverticulitis is the consequence of a diverticulum becoming blocked, trapping bacteria, and subsequently developing inflammation.
- The main presenting symptom of diverticulitis is colicky abdominal pain that is relieved with flatus or a bowel movement.
- Acute diverticulitis is often a clinical diagnosis, usually not requiring abdominal imaging.

KEY POINTS

- Acute abdominal pain out of proportion to physical examination findings should immediately raise suspicion for early acute mesenteric ischemia.
- CT angiography is the recommended imaging method for the diagnosis of acute mesenteric ischemia.
- The classic symptom triad of chronic mesenteric ischemia is postprandial abdominal pain, sitophobia (fear of eating), and weight loss.
- Colonic ischemia is the most common form of ischemic bowel disease, and most cases resolve spontaneously and rapidly.

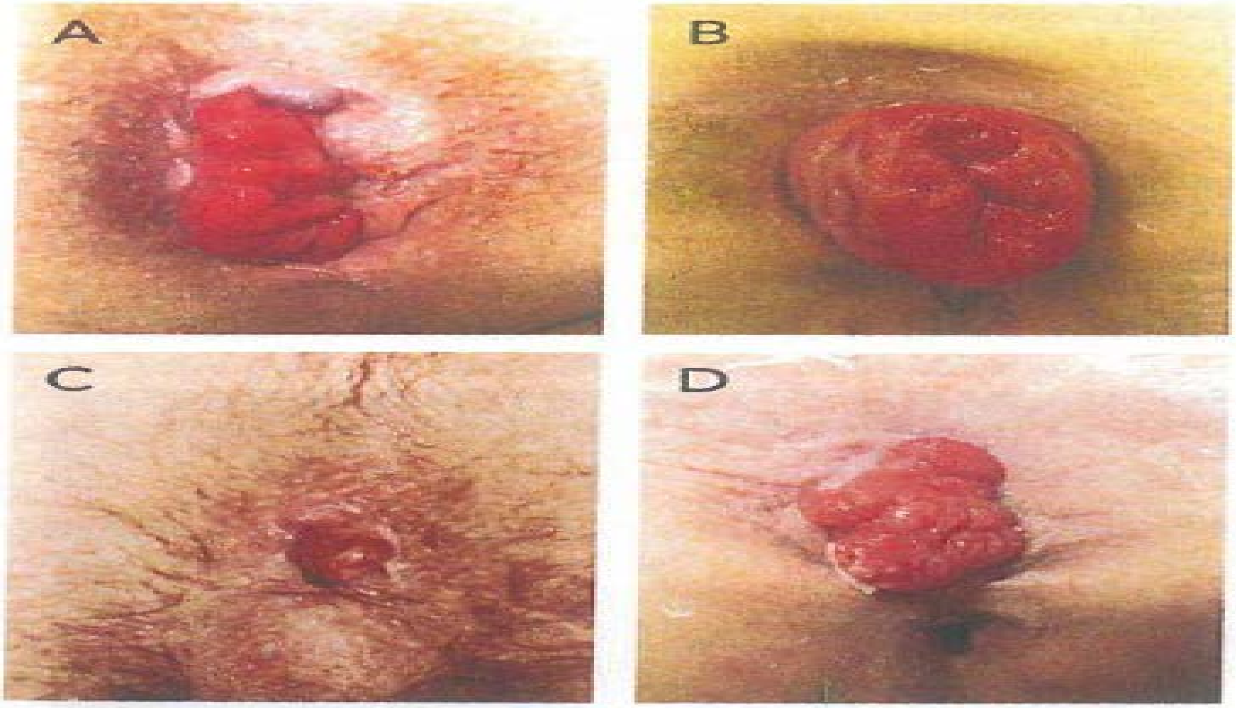

FIGURE 22. Hemorrhoids are vascular cushions that support the muscles of the anal sphincter by swelling up as needed to maintain stool continence. Prolapsed hemorrhoids (*A*) are internal hemorrhoids that protrude out of the rectum. The hallmark of rectal prolapse (*B*) is the identification of concentric rings of the rectum protruding through the anus. Prolapsed polyps (*C, D*) present as mucosa-covered globular masses protruding from the anus.

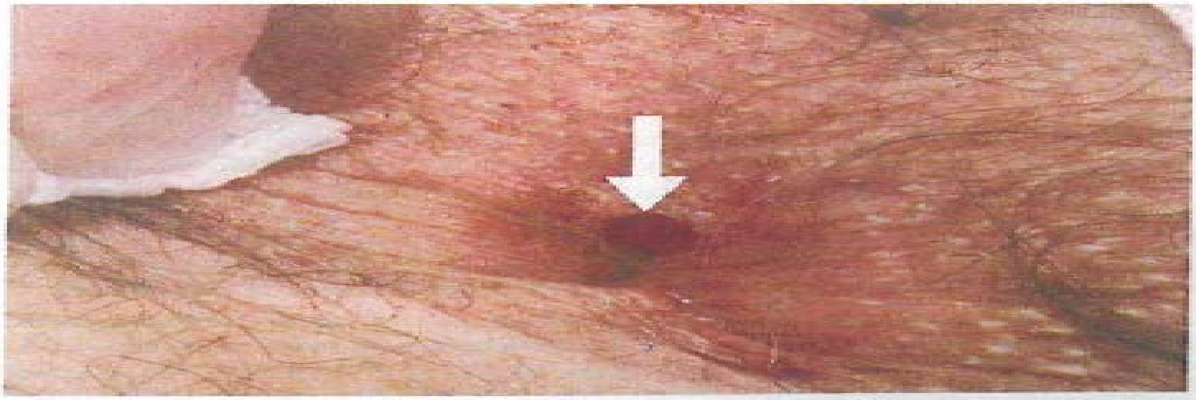

FIGURE 23. Anal fissures are painful longitudinal mucosal tears in the anal canal.
Image courtesy of Richard E. Burney, MD, Professor of Surgery, Michigan Medicine at the University of Michigan.

FIGURE 24. Anal cancer presenting as an ulcerated mass protruding from the anal canal. The presentation of anal cancer can vary from an obstructing anal mass to a nonprotruding polyp or flat growth in the anal canal.
Image courtesy of Richard E. Burney, MD, Professor of Surgery, Michigan Medicine at the University of Michigan.

KEY POINTS

- First-line therapy for hemorrhoids includes increased fiber intake, adequate liquid intake, and avoidance of straining.
- Fecal incontinence is grossly underreported due to embarrassment, and health care providers should inquire about it during clinic visits, particularly in patients at risk.
- Presenting symptoms of anal cancer may include bleeding, pain, or pruritus; however, 25% of cases present without any anorectal symptoms.
- Patients with Crohn disease with longstanding perianal disease are particularly at risk for anal cancer.

KEY POINT

- Colorectal cancer is the third most common cancer and second most common cause of cancer-related mortality among men and women in the United States.

KEY POINT

- Chromosomal instability is the most common mechanism responsible for the development of colorectal cancer, accounting for 85% of cases.

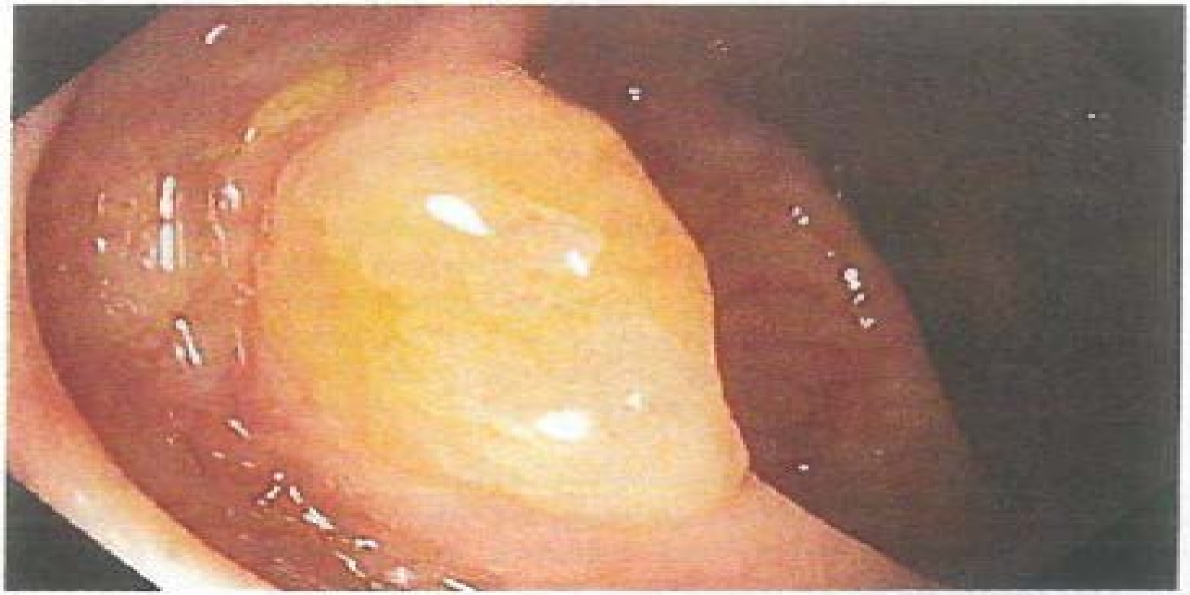

FIGURE 25. A serrated polyp in the ascending colon, showing flat morphology that can make these polyps difficult to identify on colonoscopy.

KEY POINTS

- Nonmodifiable risk factors for colorectal cancer include age (50 years and older), male sex, black race, and a personal or family history of colorectal cancer.
- Modifiable risk factors for colorectal cancer include diets high in red and processed meat; low intake of fruits, vegetables, fiber, and dairy; use of alcohol and tobacco; type 2 diabetes mellitus; sedentary lifestyle; and obesity.
- Longstanding inflammatory bowel disease (both ulcerative colitis and Crohn disease) is associated with increased risk for colorectal cancer.

KEY POINT

- The U.S. Preventive Services Task Force recommends the use of low-dose aspirin for preventing colorectal cancer and cardiovascular disease in individuals aged 50 and 59 years who are at increased risk for cardiovascular disease.

KEY POINTS

- Screening for colon cancer should be individualized in patients at increased risk.
- The risk for colon cancer depends on the size of the adenoma, degree of villous histology, and presence of dysplasia.

TABLE 23. Screening for Colorectal Cancer in Individuals at Increased Risk

Risk Category	Criteria	Screening Recommendations (age; modality; interval)
Increased	Family history of CRC:	
	CRC diagnosed in FDR <60 years old or two or more FDRs at any age	Begin at age 40 years or 10 years earlier than age of youngest FDR at diagnosis, whichever comes first; colonoscopy; repeat every 5 years[a]
	CRC diagnosed in FDR >60 years old	Begin at age 50 years; any modality; repeat every 10 years[a]
	Personal history of CRC	Perform at time of diagnosis; colonoscopy; repeat at 1 year, 3 years, and, if normal, every 5 years thereafter until the benefit of continued screening is outweighed by risks
High	Familial adenomatous polyposis	Begin at age 10-12 years; flexible sigmoidoscopy or colonoscopy; repeat every 1-2 years until colectomy
	Lynch syndrome	Begin at age 20-25 years or 10 years earlier than youngest cancer in family; colonoscopy; repeat every 1-2 years
	Inflammatory bowel disease (Crohn disease or ulcerative colitis)	Begin after 8 years of chronic colitis; colonoscopy with biopsies; repeat every 1-2 years

CRC = colorectal cancer; FDR = first-degree relative (parent, sibling, or child).

[a]If baseline examination is normal.

Data from Rex DK, Johnson DA, Anderson JC, Schoenfeld PS, Burke CA, Inadomi JM; American College of Gastroenterology. American College of Gastroenterology guidelines for colorectal cancer screening 2009 [corrected]. Am J Gastroenterol. 2009;104:739-50. [PMID: 19240699] doi:10.1038/ajg.2009.104; Rubenstein JH, Enns R, Heidelbaugh J, Barkun A; Clinical Guidelines Committee. American Gastroenterological Association Institute Guideline on the Diagnosis and Management of Lynch Syndrome. Gastroenterology. 2015;149:777-82; quiz e16-7. [PMID: 26226577] doi:10.1053/j.gastro.2015.07.036; Syngal S, Brand RE, Church JM, Giardiello FM, Hampel HL, Burt RW; American College of Gastroenterology. ACG clinical guideline: Genetic testing and management of hereditary gastrointestinal cancer syndromes. Am J Gastroenterol. 2015;110:223-62; quiz 263. [PMID: 25645574] doi:10.1038/ajg.2014.435.

KEY POINTS

- The diagnosis of colorectal cancer is usually made by colonoscopy with biopsy.
- Staging of colon cancer is based on tumor size and extent of invasion into local tissues, lymph node involvement, and evidence of metastasis.

TABLE 24. Classification of Colorectal Polyps

Adenomatous Polyps*
Tubular adenoma
Tubulovillous adenoma
Villous adenoma
Serrated Polyps
Hyperplastic polyp
Sessile serrated polyp with or without cytologic dysplasia
Traditional serrated adenoma
Other
Hamartomatous polyp
Inflammatory polyp

*With or without high-grade dysplasia.

TABLE 25. Surveillance for Colorectal Cancer After Screening or Polypectomy

Adenomatous Polyps	Interval to Next Colonoscopy
1-2 tubular adenomas <10 mm in size	5-10 years
3-10 adenomas ≥10 mm in size, villous histology, or high grade dysplasia	3 years
≥10 adenomas on single examination	<3 years; a genetic cause of disease should be investigated
Serrated Polyps	**Interval to Next Colonoscopy**
Rectosigmoid hyperplastic polyps <10 mm in size	10 years
SSP <10 mm in size	5 years
SSP ≥10 mm in size or SSP with dysplasia or TSA	3 years
Serrated polyposis syndrome	1 year

SSP = sessile serrated polyps; TSA = traditional serrated adenomas.

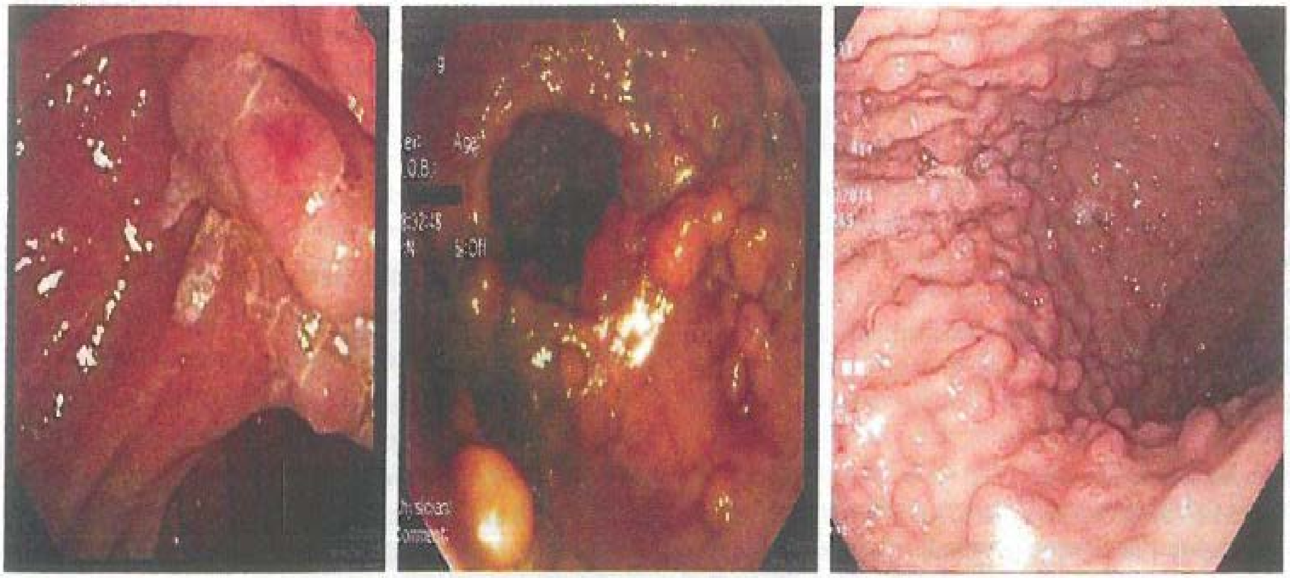

FIGURE 26. Intestinal features of familial adenomatous polyposis (FAP). Patients with FAP can develop polyps throughout the gastrointestinal tract. Adenomatous polyps always develop in the colon. Duodenal adenomas can also develop in patients with FAP, especially involving the ampulla of Vater. Regular upper endoscopic surveillance is indicated to remove polyps larger than 10 mm (*left*). If a patient with FAP has had surgery and has an ileorectal anastomosis, that patient must continue to be surveyed regularly because rectal polyps can develop in the remaining rectum (*center*). Numerous fundic gland polyps of the stomach can develop in FAP (*right*).

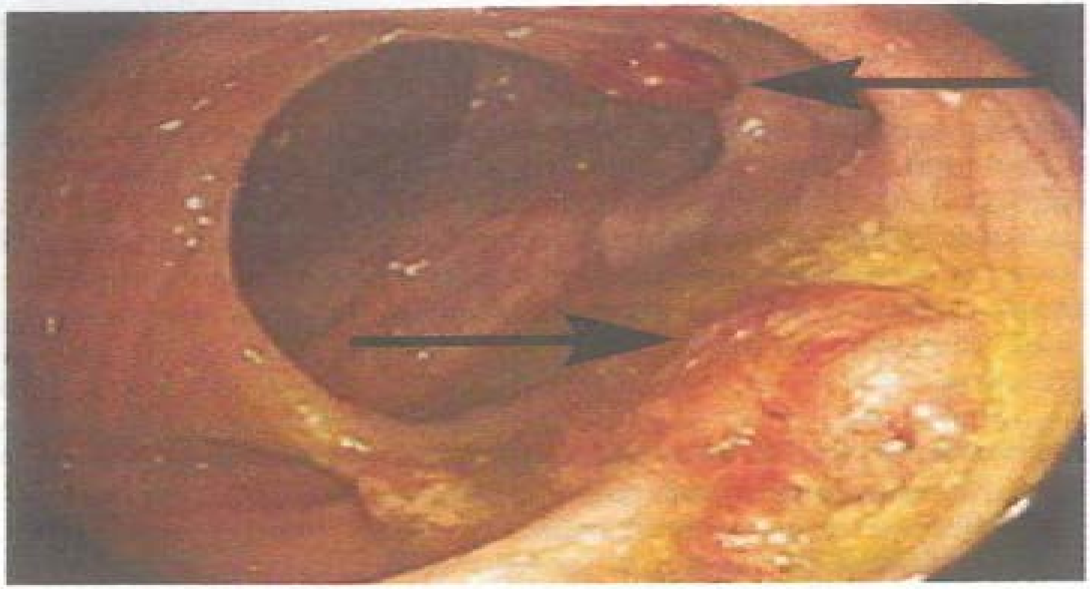

FIGURE 27. Juvenile polyps in the colon of a patient with juvenile polyposis syndrome, on endoscopy. Juvenile polyps can have an erythematous and waxy appearance.

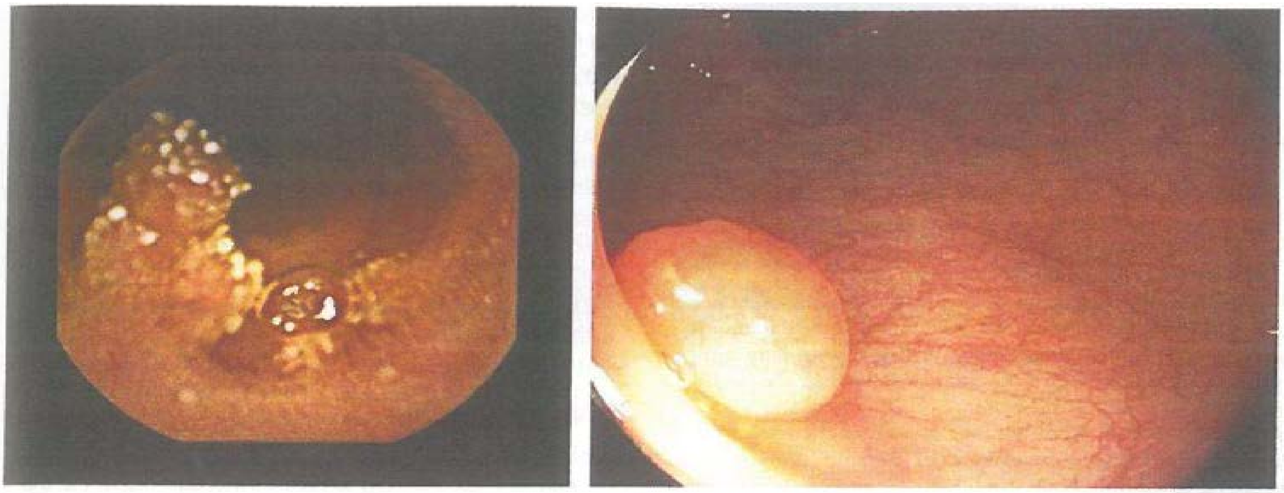

FIGURE 28. Peutz-Jeghers syndrome (PJS) polyps. Capsule endoscopy showing a PJS hamartomatous polyp in the small intestine (*left*); polyps in the small intestine can cause bleeding and/or obstructions. Colonoscopy showing a hamartomatous polyp in the colon of a patient with PJS (*right*).

FIGURE 29. Peutz-Jeghers syndrome is associated with multiple hamartomatous polyps in the gastrointestinal tract and distinctive mucocutaneous pigmentations. The pigmented lesions occur most commonly on the lips and perioral region but can also occur on the nose, perianal area, and genitals.

KEY POINTS

- Lynch syndrome is caused by germline mutations in the mismatch repair genes and carries a lifetime risk for colorectal cancer of 50% to 80%.
- Syndromes that predispose persons to multiple adenomatous polyps in the colon include familial adenomatous polyposis, *MutYH*-associated polyposis, and polymerase proofreading-associated polyposis.
- Hamartomatous polyposis syndromes are associated with increased risk for multiple cancers, including colon cancer.

KEY POINTS

- Elevations of aspartate aminotransferase and alanine aminotransferase levels represent hepatic parenchymal inflammation; alanine aminotransferase levels are more specific for hepatic inflammation.
- Elevations in alkaline phosphatase and bilirubin levels result from inflammation of the biliary tree or bile flow abnormalities.
- The prothrombin time and serum albumin levels reflect the synthetic function of the liver.

TABLE 26. Typical Liver Chemistry Studies in Common Hepatobiliary Disorders

Disease	AST	ALT	ALP	Bilirubin	Other Features
Acute viral hepatitis	↑↑↑	↑↑↑	Normal to ↑	Normal to ↑↑↑	Exposure history, fatigue, nausea
Chronic viral hepatitis	↑	↑↑	Normal to ↑	↑ if advanced	History of exposure to infected blood or body fluids
Nonalcoholic steatohepatitis	↑	↑	Normal to ↑	Normal	Metabolic syndrome
Alcoholic hepatitis	↑↑	Normal or ↑	↑	Normal to ↑↑↑	Excess alcohol intake
Acute autoimmune hepatitis	↑↑↑	↑↑↑	Normal to ↑	Normal to ↑↑	Autoantibodies
Chronic autoimmune hepatitis	↑	↑↑	Normal to ↑	Normal	Autoantibodies
Wilson disease	↑	↑	Low	↑ and often unconjugated	Hemolysis if acute, neurologic symptoms if chronic
α_1-Antitrypsin deficiency	↑	↑	Normal	↑ if advanced	May have pulmonary disease
Hemochromatosis	Normal	Normal	Normal	Normal	Joint symptoms, family history, other organ involvement
Primary biliary cholangitis	↑	↑	↑↑↑	↑ if advanced	Female, sicca symptoms, antimitochondrial antibody
Primary sclerosing cholangitis	↑	↑	↑↑↑	↑ if advanced or dominant stricture is present	Ulcerative colitis, abnormal cholangiogram
Large duct obstruction	↑ (↑↑ if acute)	↑ (↑↑ if acute)	↑↑	↑↑	Pain if acute, dilated ducts on imaging
Infiltrative liver disease	↑	↑	↑↑↑	Normal	Features of malignancy, sarcoid, amyloid, or mycobacterial or fungal infection
Hepatic ischemia	↑↑↑	↑↑↑	Normal	Normal	AST >5000 U/L, history of hypotension
Celiac disease	Normal or ↑	Normal or ↑	Normal or ↑	Normal	Usually other features of celiac disease

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase.

TABLE 27. Risk Factors Requiring Testing for Hepatitis B Virus

Individuals born or raised in regions with high rates of hepatitis B virus infection, including Asia, Africa, the South Pacific, European Mediterranean countries, Eastern Europe, most of South America, Honduras, Guatemala, and the Middle East (except Israel and Cyprus)
U.S.-born persons not vaccinated as infants whose parents were born in endemic areas
Household or sexual contact with hepatitis B surface antigen-positive persons
Intravenous drug use
Multiple sex partners or history of sexually transmitted infection
Men who have sex with men
History of incarceration
History of hepatitis C virus or HIV infection
Hemodialysis
Pregnancy
Elevated aminotransferase levels of unknown cause

TABLE 28. Interpretation of Hepatitis B Virus Test Results

Clinical Scenario	HBsAg	Anti-HBs	IgM anti-HBc	IgG anti-HBc	HBeAg	Anti-HBe	HBV DNA (IU/mL)
Acute hepatitis B; occasionally reactivation of chronic hepatitis B	+	−	+	−	+	−	>20,000
Resolved previous infection	−	+	−	+	−	+/−	Undetected
Immunity due to previous vaccination	−	+	−	−	−	−	Undetected
False positive anti-HBc or resolved previous infection	−	−	−	+	−	−	Undetected
Immune-tolerant chronic hepatitis B (perinatally acquired, age <30 years)	+	−	−	+	+	−	>1 million
Inactive chronic hepatitis B	+	−	−	+	−	+	<10,000
HBeAg-positive immune-active chronic hepatitis B	+	−	−	+	+	−	>10,000
HBeAg-negative immune-reactive chronic hepatitis B	+	−	−	+	−	+	>10,000

Anti-HBc = hepatitis B core antibody; anti-HBe = hepatitis B e antibody; anti-HBs = hepatitis B surface antibody; HBeAg = hepatitis B e antigen; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus.

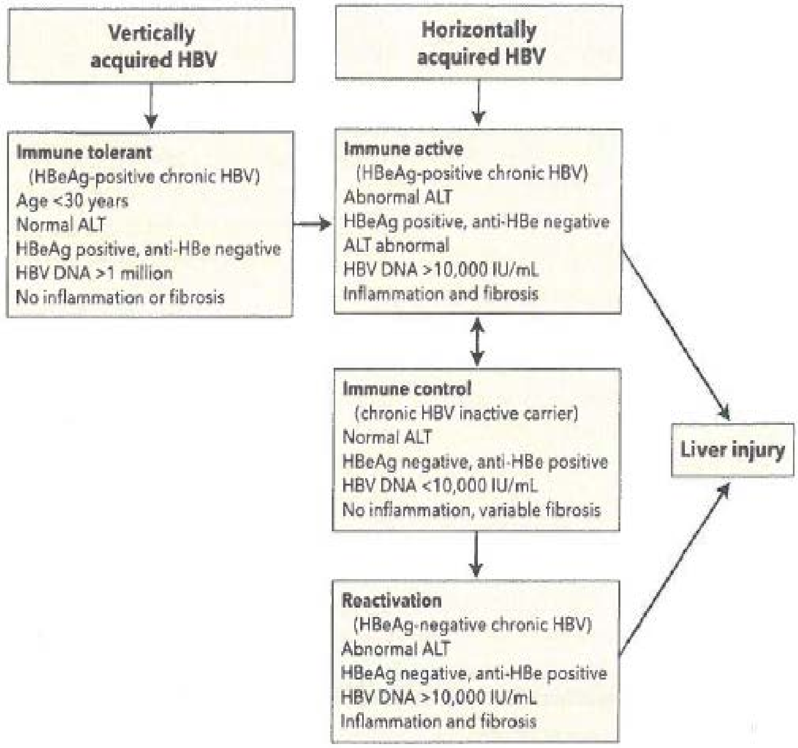

FIGURE 30. Phases of chronic hepatitis B infection. It is assumed that patients progress through the phases in sequence, although not all patients develop HBeAg-negative chronic hepatitis B, and only patients with vertical transmission of hepatitis B have a clinically recognized immune-tolerant phase. All phases have positive HBsAg, negative anti-HBs, and positive IgG anti-HBc.

ALT = alanine aminotransferase; anti-HBc = hepatitis B core antibody; anti-HBe = hepatitis B e antibody; anti-HBs = hepatitis B surface antibody; HBeAg = hepatitis B e antigen; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HBV DNA = hepatitis B virus DNA.

TABLE 29. Risk Factors for Developing Cirrhosis or Hepatocellular Carcinoma in Patients with Chronic Hepatitis B Virus Infection
Age older than 40 years
Hepatitis B virus DNA level >2000 IU/mL
Elevated alanine aminotransferase level
Genotype C infection
Heavy alcohol use
Development of hepatitis B e antigen-negative reactivation phase of chronic hepatitis B virus infection
HIV infection
Hepatitis C virus or hepatitis D virus infection

TABLE 30. Conditions Requiring Testing for Hepatitis C Virus
Birth year 1945-1965
Injection-drug use or intranasal illicit-drug use (ever)
Long-term hemodialysis (ever)
Percutaneous/parenteral exposures in an unregulated setting (nonsterile technique)
Needlesticks, sharps, or mucosal exposure to hepatitis C virus-infected blood
Children born to women infected with hepatitis C virus
Receipt of blood or blood-components transfusion or organ transplantation before 1992
Receipt of clotting-factor concentrates produced before 1987
History of incarceration
HIV infection
Sexually active persons about to start preexposure prophylaxis for HIV
Undiagnosed chronic liver disease
Elevated alanine aminotransferase level
Living organ donors, before donation

TABLE 31. Treatment Regimens for Hepatitis C Virus Infection

Drug Treatment Regimens
Grazoprevir[a] + elbasvir[b]
Paritaprevir[a] + ombitasvir[b] + dasabuvir[c]
Simeprevir[a] + sofosbuvir[d]
Daclatasvir[b] + sofosbuvir[d]
Ledipasvir[b] + sofosbuvir[d]
Velpatasvir[b] + sofosbuvir[d]

[a]Drug class: NS3/4A protease inhibitor (-previr)

[b]Drug class: NS5A inhibitor (-asvir)

[c]NS5B non-nucleoside polymerase inhibitor (-buvir)

[d]NS5B nucleotide polymerase inhibitor (-buvir)

KEY POINTS

- Treatment of hepatitis A virus infection is supportive, and 90% of patients or more recover fully within 3 to 6 months of infection.
- Treatment of hepatitis B virus infection is advised for patients with acute liver failure, infection in the immune-active phase or the reactivation phase, cirrhosis, and in immunosuppressed patients.
- Individuals born between 1945 and 1965 require one-time testing for hepatitis C virus.
- Up to 95% of patients with hepatitis C virus infection can be cured with direct-acting antiviral agents.

KEY POINTS

- Diagnosis of autoimmune hepatitis is made based on the presence of elevated aminotransferase levels, positive antinuclear antibody and smooth-muscle antibody, elevated levels of IgG, and compatible findings on liver biopsy.
- Wilson disease, viral hepatitis, and drug-induced liver injury need to be excluded before making the diagnosis of autoimmune hepatitis.

KEY POINTS

- The Alcoholic Liver Disease/Nonalcoholic Fatty Liver Disease Index score can be helpful in distinguishing alcoholic liver disease from nonalcoholic fatty liver disease.
- Manifestations of alcoholic hepatitis include fever, jaundice, tender hepatomegaly, and leukocytosis.
- Severity of alcoholic hepatitis is determined by the Maddrey discriminant function score; patients with a score of 32 or greater or with hepatic encephalopathy may be considered for prednisone therapy.

KEY POINTS

- Acetaminophen, antibiotics (particularly amoxicillin-clavulanate), and antiepileptic agents (phenytoin and valproate) are the most common causes of drug-induced liver injury.
- Liver injury typically resolves after discontinuation of the offending drug.

TABLE 32. Causes of Acute Liver Failure
Acetaminophen
Hepatitis A virus
Herpes simplex virus
Autoimmune hepatitis
Other medications (antituberculosis drugs, sulfa-containing antimicrobial agents, antifungal agents, and herbal supplements)
Hepatitis B virus
Amanita phalloides mushrooms
Acute fatty liver of pregnancy

KEY POINTS

- The most common cause of acute liver failure in the United States is acetaminophen overdose.
- The diagnosis of acute liver failure requires immediate referral to a liver transplant center.

KEY POINTS

- Nonalcoholic fatty liver disease is the commonest cause of liver disease in the world.
- Management of nonalcoholic liver disease is focused on weight loss through dietary and lifestyle modification.
- α_1-Antitrypsin deficiency is an autosomal recessive genetic disorder that results in accumulation of a variant protein in the liver; homozygosity can result in liver injury and cirrhosis.
- Hereditary hemochromatosis is a condition characterized by excessive iron absorption that results in accumulation of iron in the liver and the development of cirrhosis.
- Wilson disease is a rare autosomal recessive disorder that causes accumulation of copper in the liver.

KEY POINTS

- In patients with primary biliary cholangitis, ursodeoxycholic acid treatment results in histologic improvement, better survival rates, and diminished need to for liver transplantation.
- Primary sclerosing cholangitis is associated with inflammatory bowel disease in about 85% of cases; these patients have an increased risk for colorectal cancer and require surveillance colonoscopy every 1 to 2 years.
- Primary sclerosing cholangitis often requires liver transplantation and has the highest case-based mortality rate among the autoimmune liver diseases.

TABLE 33. Child-Turcotte-Pugh Score[a]

	1 Point	2 Points	3 Points
Encephalopathy	None	Grade I-II	Grade III-IV
Ascites	None	Mild/moderate	Severe
Bilirubin	<2 mg/dL (34.2 µmol/L)	2-3 mg/dL (34.2-51.3 µmol/L)	>3 mg/dL (51.3 µmol/L)
Albumin	>3.5 g/dL (35 g/L)	2.8-3.5 g/dL (28-35 g/L)	<2.8 g/dL (28 g/L)
Prothrombin time/INR	<4 s/<1.7	4-6 s/1.7-2.3	>6 s/>2.3

[a]5-6 points = Child-Turcotte-Pugh class A; 7-9 points = Child-Turcotte-Pugh class B; 10-15 points = Child-Turcotte-Pugh class C.

KEY POINT

- The Model for End-Stage Liver Disease-sodium formula accurately predicts 3-month mortality and is used for liver transplant allocation.

TABLE 34. Management of Esophageal Varices in Patients with Cirrhosis

Findings	Management
No varices	Repeat upper endoscopy in 3 years (unless decompensation occurs)
Small varices (<5 mm)	Repeat upper endoscopy in 2 years (unless decompensation occurs)
Small varices with red wale marks (erythematous raised areas)	Initiate nonselective β-blocker therapy (propranolol, nadolol, or carvedilol)
Large varices (>5 mm)	Initiate nonselective β-blocker therapy or endoscopic variceal ligation
Varices in patients unable to tolerate β-blockers	Endoscopic variceal ligation

TABLE 35. Hepatic Encephalopathy Classification

Severity of Encephalopathy	Description	Findings
Minimal	Detected only on neuropsychiatric testing	Few or absent clinical manifestations
Grade 1	Mild lack of awareness, sleep disturbances	Oriented to time and place, but with psychomotor slowing
Grade 2	Lethargic, disoriented, and with personality change	Disoriented to time, with asterixis
Grade 3	Somnolence, confusion, and significant disorientation	Disoriented to time, place, and situation, with asterixis
Grade 4	Coma	Lack of response even to painful stimuli

Adapted with permission from Vilstrup H, Amodio P, Bajaj J, Cordoba J, Ferenci P, Mullen KD, et al. Hepatic encephalopathy in chronic liver disease: 2014 practice guideline by the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver. Hepatology. 2014;60:715-35. [PMID: 25042402] doi:10.1002/hep.27210.

TABLE 36. Characteristics of Ascites

	SAAG	Ascitic Fluid Total Protein Level	Other Characteristics
Cirrhosis	High[a]	Low[c]	Clear, straw-colored
Heart failure	High[a]	High[d]	—
Chylous ascites	Low[b] or high[a]	High[d]	High triglycerides
			SAAG can be high if caused by portal hypertension
			SAAG is low if caused by lymphatic disruption
Tuberculosis	Low[b]	High[d]	Peritoneal biopsy may be required to confirm diagnosis of tuberculosis
Malignancy	Low[b]	High[d]	Positive cytology
Nephrotic syndrome	Low[b]	Low[c]	Proteinuria and edema

SAAG = serum-ascites albumin gradient.

[a]≥1.1 g/dL (11 g/L)

[b]<1.1 g/dL (11 g/L)

[c]<2.5 g/dL (25 g/L)

[d]≥2.5 g/dL (25 g/L)

KEY POINTS

- Upper endoscopy should be performed on all patients with cirrhosis to assess for the presence of varices; primary prophylaxis to prevent bleeding includes nonselective β-blocker therapy (propranolol, nadolol, or carvedilol) or endoscopic variceal ligation.
- Precipitating causes of hepatic encephalopathy may include infection, sedating medications, volume depletion, or gastrointestinal bleeding; treatment involves addressing the precipitating cause and lactulose.
- Ultrasound is the most effective means of ascertaining the presence of ascites; the serum-ascites albumin gradient and total protein levels in ascitic fluid assist in determining the cause of ascites.
- The management of ascites involves a sodium-restricted diet and diuretic therapy with spironolactone.
- An ascitic-fluid neutrophil count of 250/µL or greater confirms the diagnosis of spontaneous bacterial peritonitis; patients who develop this condition have a high mortality rate and should be considered for liver transplantation.
- Hepatopulmonary syndrome should be suspected in patients with portal hypertension who have symptoms of dyspnea and evidence of hypoxia; the diagnosis is confirmed by demonstrating intrapulmonary shunting with agitated saline administration during echocardiography.

KEY POINTS

- Patients with cirrhosis should avoid alcohol, sedating drugs including opioids, and raw shellfish.
- Patients with cirrhosis should be screened for osteoporosis; confirmed osteoporosis should be treated with either oral or intervenous bisphosphonates.
- Patients with chronic liver disease should be vaccinated against hepatitis A and B viruses and should receive annual influenza vaccination and recommended pneumococcal vaccinations.

KEY POINTS

- Asymptomatic hepatic cysts are benign and require no follow-up.
- Focal nodular hyperplasia, a common incidental finding, does not have malignant potential or a risk for bleeding, and does not require follow-up.
- Hepatic adenomas 5 cm in size or smaller can be managed with serial imaging; hepatic adenomas larger than 5 cm in size should be considered for surgical resection.
- Patients with cirrhosis and high-risk patients with hepatitis B virus infection require hepatocellular carcinoma surveillance using liver ultrasound with or without α-fetoprotein measurement every 6 months.

KEY POINT

- Referral to a transplant center is indicated for patients with acute liver failure or for patients with cirrhosis with a Model for End-Stage Liver Disease score of 15 or greater or decompensated cirrhosis.

KEY POINTS

- Measures to reduce vertical transmission of hepatitis B virus include administration of hepatitis B virus immune globulin to newborns and immediate vaccination of newborns.
- The most serious liver complications of pregnancy occur in the third trimester and include HELLP (Hemolysis, Elevated Liver enzymes, and Low Platelets) syndrome and acute fatty liver of pregnancy; both are managed in high-risk obstetrical units and with early delivery.

KEY POINTS

- Portal vein thrombosis is common in patients with decompensated cirrhosis and is a consequence of poor flow through the portal veins.
- The classic presentation of Budd-Chiari syndrome includes hepatomegaly, ascites, and right-upper-quadrant abdominal pain.

KEY POINT

- Gallstones that are found incidentally do not typically cause any symptoms, and cholecystectomy is generally not recommended because most stones remain asymptomatic.

KEY POINT

- Patients with typical biliary colic symptoms and gallstones on imaging should undergo cholecystectomy.

KEY POINTS

- The diagnosis of acute cholecystitis can be made by ultrasonography showing gallbladder wall thickening and/or edema and sonographic Murphy sign.
- Treatment of acute cholecystitis includes pain control, intravenous antibiotics with gram-negative and anaerobic coverage, and cholecystectomy during the initial hospitalization in good candidates for surgery.

KEY POINTS

- Acalculous cholecystitis typically occurs in critically ill patients and is a result of gallbladder ischemia that can be complicated by enteric bacterial infection.
- Left untreated, the mortality rate for acalculous cholecystitis is as high as 75%.

KEY POINTS

- Endoscopic retrograde cholangiopancreatography is the preferred therapeutic method for relieving obstruction due to a common bile duct stone.
- Cholangitis (heralded by the onset of fever, jaundice, and right-upper-quadrant abdominal pain) is potentially life-threatening; antibiotic therapy targeting gram-negative *Enterobacteriaceae* should be administered, and identified common bile duct stones should be removed urgently.

KEY POINT

- Gallbladder polyps greater than 1 cm in size and those associated with gallbladder stones or primary sclerosing cholangitis are more likely to be neoplastic.

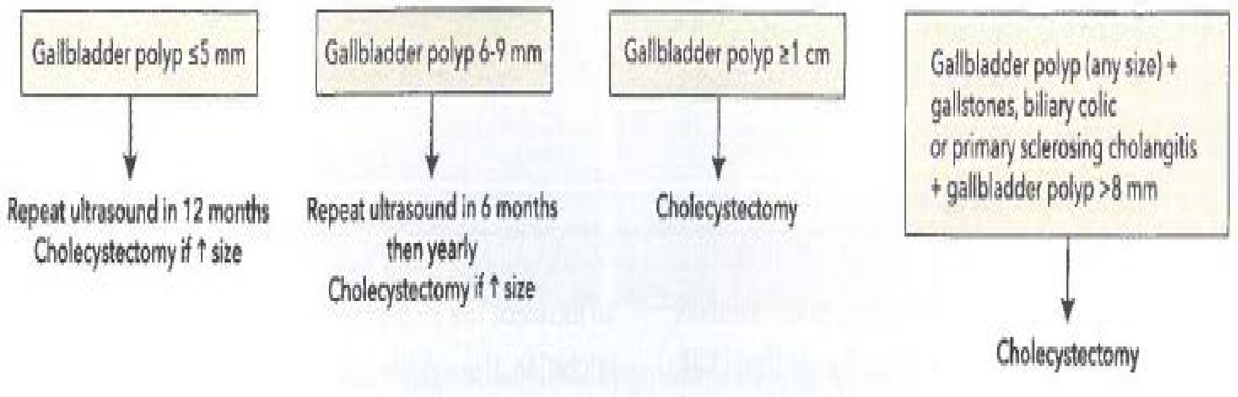

FIGURE 32. Management of gallbladder polyps.

KEY POINTS

- Resection is first-line treatment for cholangiocarcinoma.
- Selected patients with unresectable hilar cholangiocarcinoma smaller than 3 cm in size and without extrahepatic spread may be candidates for liver transplantation.

KEY POINT

- Upper gastrointestinal bleeding is more common, more severe, and has a higher mortality rate than lower gastrointestinal bleeding.

TABLE 37. Less Common Causes of Upper Gastrointestinal Bleeding

Lesion	Pathogenesis	Presentation	Treatment
Cameron erosion	Mechanical trauma to mucosal folds of hiatal hernia	Typically chronic GI bleeding presenting as iron deficiency anemia	Includes medical therapy with PPI and iron, and surgical repair of hiatal hernia
Dieulafoy lesion	Dilated, aberrant submucosal vessel	Included in differential diagnosis of recurrent, often massive bleeding without clear source	Endoscopic
Gastric antral vascular ectasia	Most idiopathic; associated with cirrhosis and systemic sclerosis	Acute bleeding or iron deficiency anemia	Endoscopic
Aortoenteric fistula	Direct communication between aorta and GI tract	"Herald" bleed followed by massive exsanguination	Surgical
Hemosuccus pancreaticus	Erosion of pancreatic pseudocyst or tumor into a vessel with bleeding into pancreatic duct	Upper GI bleeding in setting of pancreatic disease	Mesenteric angiography with coil embolization
Hemobilia	Bleeding from the hepatobiliary tract often caused by arteriobiliary fistula from trauma or liver biopsy	Triad of jaundice, biliary colic, and GI bleeding	Angiography or surgical
Upper GI tumors	Benign or malignant neoplasms	Slow or massive hemorrhage	Palliative radiographic and endoscopy for malignant tumors, surgical resection for benign tumors

GI = gastrointestinal; PPI = proton pump inhibitor.

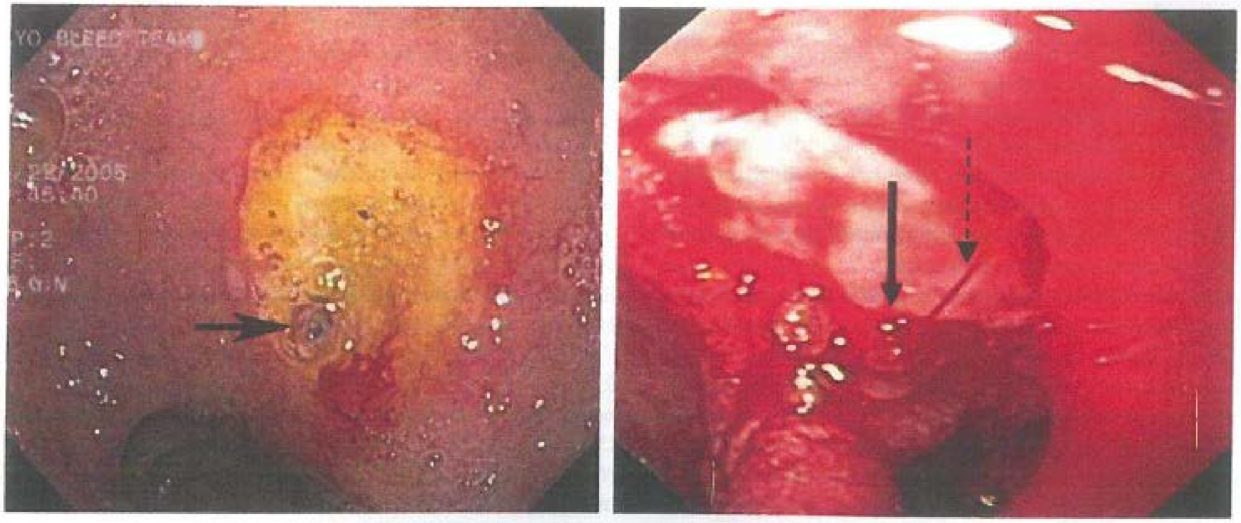

FIGURE 33. *Left:* Duodenal ulcer with nonbleeding visible vessel (*arrow*) that is at high risk for rebleeding and must be treated endoscopically. *Right:* Active arterial spurting (*dotted arrow*) from a duodenal ulcer (*solid arrow*). This lesion is at the highest risk for rebleeding and must be treated endoscopically.

Courtesy of Louis M. Wong Kee Song, MD, Mayo Clinic.

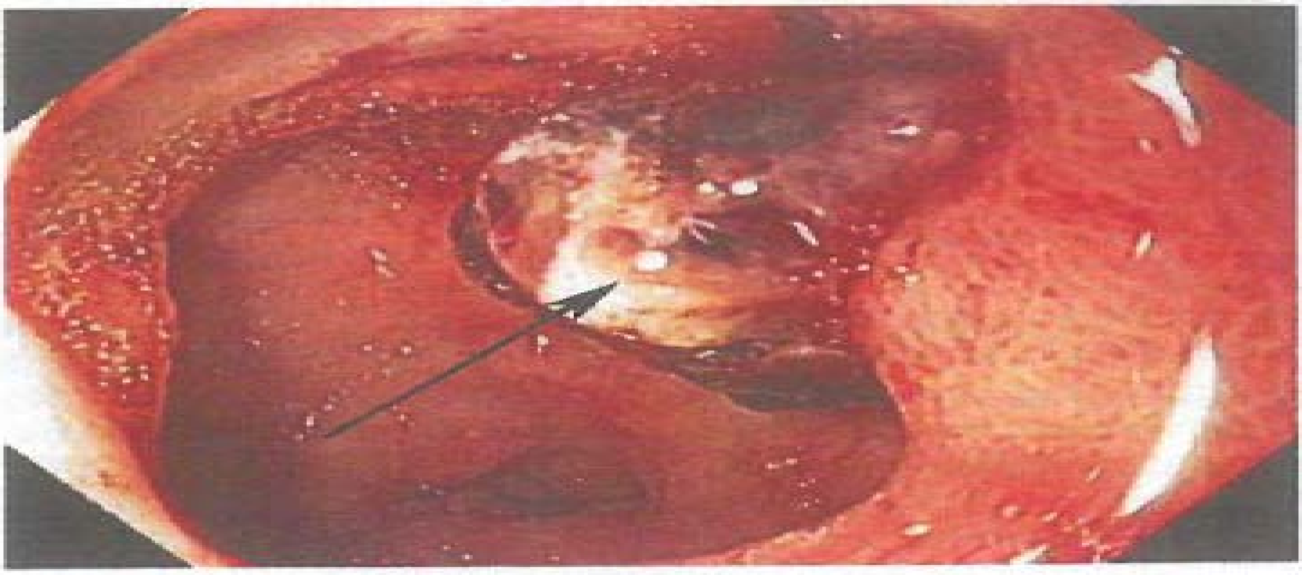

FIGURE 34. Duodenal ulcer with adherent clot (*arrow*) that is at risk for rebleeding. This can be treated medically or by clot removal and endoscopic therapy in addition to standard medical therapy.

Courtesy of Louis M. Wong Kee Song, MD, Mayo Clinic.

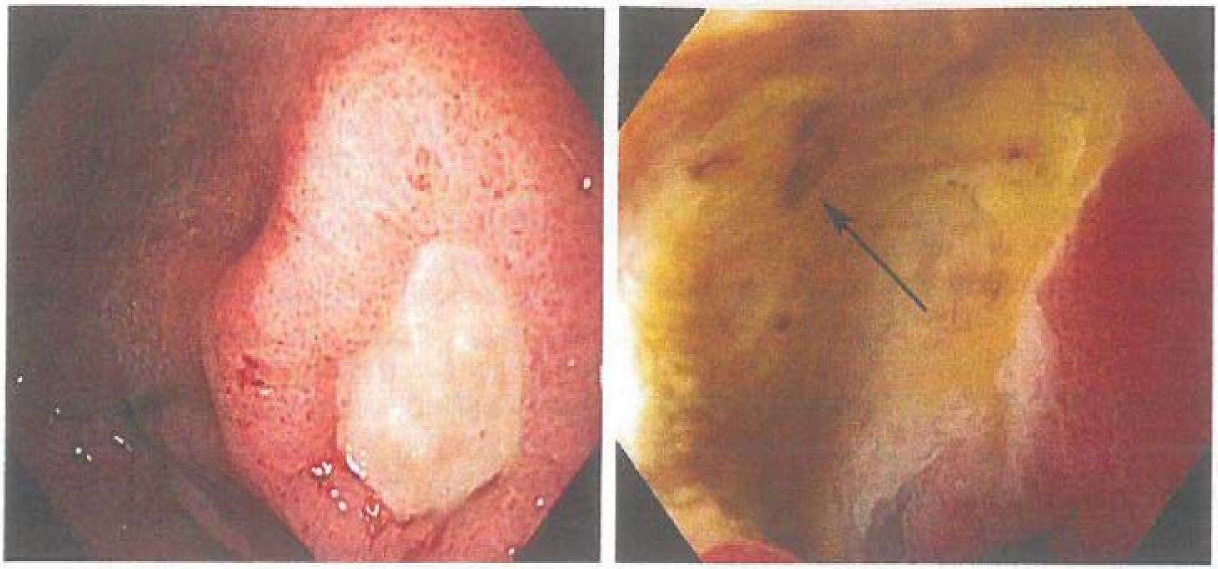

FIGURE 35. Ulcers at low risk for rebleeding, for which endoscopic therapy is not indicated. *Left:* Clean-based gastric ulcer with no blood vessels, pigmented spots/protuberances, or clots noted in the base. *Right:* Nonprotuberant pigmented spot (*arrow*) in a duodenal ulcer bed.

Courtesy of Louis M. Wong Kee Song, MD, Mayo Clinic.

FIGURE 36. Mallory-Weiss tear. A superficial linear mucosal tear (*arrow*) seen on endoscopic retroflexion in the proximal stomach.

Courtesy of Louis M. Wong Kee Song, MD, Mayo Clinic.

FIGURE 37. Acute esophageal variceal hemorrhage. A varix in the distal esophagus is seen spurting bright red blood.

KEY POINTS

- The most common causes of upper gastrointestinal bleeding include peptic ulcer disease, gastroesophageal varices, and Mallory-Weiss tear.
- Tachycardia (pulse rate >100/min), hypotension (systolic blood pressure <100 mm Hg), age older than 60 years, and major comorbid medical conditions are all associated with increased risk for rebleeding and death in patients with upper gastrointestinal bleeding.
- Upper endoscopy is the primary diagnostic modality for evaluating upper gastrointestinal bleeding.
- Management of an ulcer depends on the endoscopic appearance and risk for rebleeding.

TABLE 38. Causes of Severe Lower Gastrointestinal Bleeding

Diverticulosis
Aortoenteric fistula
Colonic or rectal varices
Dieulafoy lesions
Neoplasm
Colitis
Ischemic
Inflammatory bowel disease
Infectious
Intussusception
Meckel diverticulum
Angiodysplasia

KEY POINTS

- Patients with lower gastrointestinal bleeding usually present with sudden onset of hematochezia (maroon or red blood per rectum).
- Most cases of lower gastrointestinal bleeding stop spontaneously and have good outcomes; however, higher rates of morbidity and mortality are seen in older patients and in those with comorbid conditions.
- Colonoscopy identifies a source of lower gastrointestinal bleeding in two thirds of patients.

TABLE 39. Causes of Small-Bowel Gastrointestinal Bleeding

Differential Diagnosis	Patient Age (Years)	Clinical Clues
Angiodysplasia	>60	Intermittent, usually occult bleeding; may also occur in the colon
Peutz-Jeghers syndrome	<20	Perioral pigmentation, obstructive symptoms
Meckel diverticulum	20-60	Possible abdominal pain
Hemangioma	<20	Possible cutaneous hemangiomas
Malignancy	>50	Weight loss, abdominal pain
Hereditary hemorrhagic telangiectasia	>50	Mucocutaneous telangiectasias

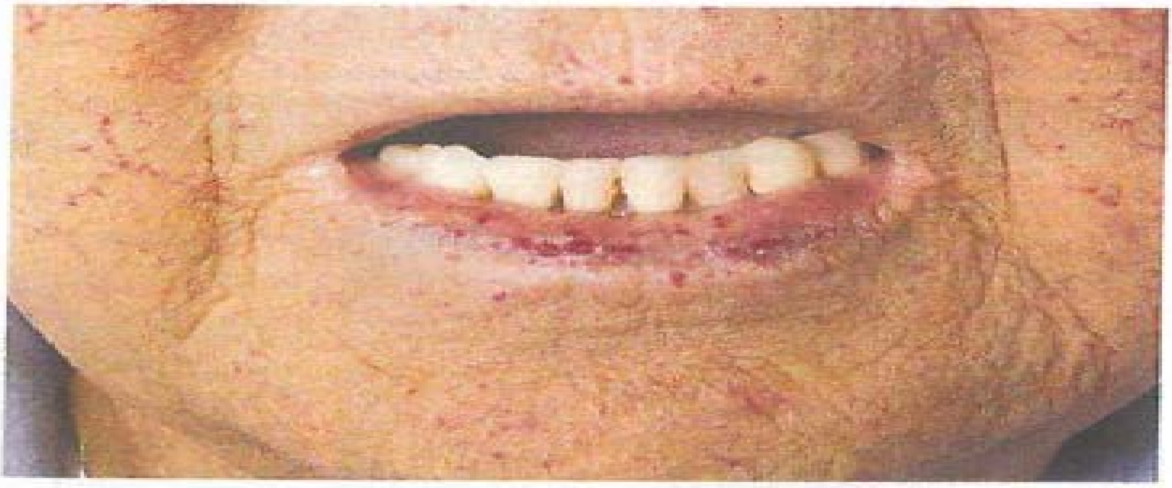

FIGURE 39. Hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu syndrome) is a disorder of development of the vasculature characterized by telangiectases and arteriovenous malformations in specific locations. It is one of the most common monogenic disorders, but affected individuals are frequently not diagnosed. The most common features of the disorder—nosebleeds and telangiectases on the lips, hands, and oral mucosa—are often quite subtle.

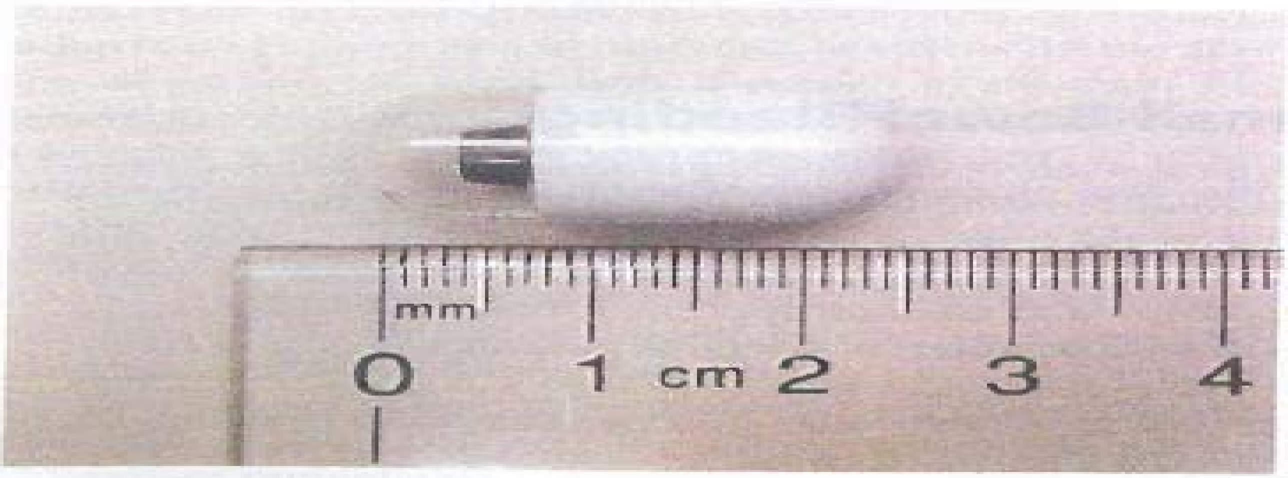

FIGURE 40. Endoscopy capsule.
Courtesy of Elizabeth Rajan, MD, Mayo Clinic.

KEY POINTS

- Capsule endoscopy is the preferred test for evaluating stable patients for small-bowel bleeding after normal results on endoscopy and colonoscopy.
- After achieving hemodynamic stabilization, therapy for small-bowel bleeding is guided by the underlying source of bleeding.

Item 1

Educational Objective: Treat opioid-induced constipation.

KEY POINT

- Oral naloxegol is a peripherally acting μ-opioid receptor antagonist that is FDA-approved for the treatment of opioid-induced constipation in adults with chronic noncancer pain.

Item2

Educational Objective: Manage the immune-tolerant phase of hepatitis B viral infection.

KEY POINT

- Patients with hepatitis B infection in the immune-tolerant phase require serial monitoring of aminotransferase levels.

Item 3

Educational Objective: Manage aspirin use before and after polypectomy.

KEY POINT

- Aspirin for secondary prophylaxis in patients with established cardiovascular disease should be continued after colonoscopy with polypectomy.

Item4

Educational Objective: Diagnose nonalcoholic fatty liver disease.

KEY POINT

- Nonalcoholic fatty liver disease is the most common cause of abnormal liver test results in the United States.

Items5

Educational Objective: Diagnose pseudoachaJasia.

KEY POINT

- Pseudoachalasia is caused by a tumor at the gastroesophageal junction infiltrating the myenteric plexus causing esophageal motor abnormalities; symptoms, barium-imaging and manometric findings, and endoscopic appearance are similar to achalasia.

Item6

Educational Objective: Treat diarrhea-predominant irritable bowel syndrome.

KEY POINT

- A low-FODMAP (Fermentable Oligosaccharides, Disaccharides, Monosaccharides, And Polyols) diet can reduce abdominal pain and bloating and improve stool consistency, frequency, and urgency in patients with diarrhea-predominant irritable bowel syndrome.

Item7

Educational Objective: Diagnose a Zenker diverticulum.

KEY POINT

- Patients with dysphagia associated with regurgitation of undigested food should be evaluated with a barium esophagram for the presence of a Zenker diverticulum.

Items 8

Educational Objective: Diagnose hepatopulrnonary syndrome.

KEY POINT

- The diagnosis of hepatopulmonary syndrome is made by demonstrating an arterial oxygen tension less than 80 mm Hg (10.7 kPa) breathing ambient air, or an alveolar-arterial gradient of 15 mm Hg (2 kPa) or greater, along with evidence of intrapulmonary shunting on echocardiography with agitated saline or macroaggregated albumin study.

Item 9

Educational Objective: Treat acalculous cholecystitis.

KEY POINT

- Acalculous cholecystitis can present with biliary colic symptoms in the alert patient or with unexplained leukocytosis, sepsis, and jaundice in the critically ill patient.

Item 10

Educational Objective: Prevent recurrent NSAIDrelated peptic ulcer disease.

KEY POINT

- In patients requiring NSAIDs, an evidence-based treatment strategy to prevent recurrent NSAID-induced peptic ulcers is the use of a cyclooxygenase-2 selective NSAID plus a proton pump inhibitor.

Item 11

Educational Objective: Manage follow-up colonoscopy for hyperplastic polyps.

KEY POINT

- Patients with small (<10 mm) hyperplastic polyps on baseline colonoscopic examination should undergo surveillance colonoscopy in 10 years.

Item 12

Educational Objective: Treat acute cholangitis with biliary obstruction.

KEY POINT

- Patients who have cholangitis with evidence of biliary obstruction should be treated with antibiotic therapy and biliary decompression with endoscopic retrograde cholangiopancreatography.

Item 13

Educational Objective: Treat an esophageal stricture.

KEY POINT

- Esophageal stricture in patients with eosinophilic esophagitis requires treatment with endoscopic dilation when symptoms do not respond to medical therapy.

Item 14

Educational Objective: Treat toxic megacolon.

KEY POINT

- Toxic megacolon is defined by the presence of toxicity and evidence of colonic dilation; it requires prompt surgical treatment.

Item 15

Educational Objective: Diagnose microscopic colitis.

KEY POINT

- Microscopic colitis is a cause of nonbloody, watery diarrhea in older adults and is diagnosed by colonoscopy with random biopsies from multiple colonic segments.

Item 16

Educational Objective: Treat autoimmune pancreatitls.

KEY POINT

- Almost all patients (>90%) with autoimmune pancreatitis enter clinical remission in response to glucocorticoids.

Item 17

Educational Objective: Treat acute fatty liver of pregnancy with immediate delivery of the fetus.

KEY POINT

- The fetus should be delivered immediately upon recognition of acute fatty liver of pregnancy.

Item 18

Educational Objective: Treat a gallbladder polyp.

KEY POINT

- The finding of a gallbladder polyp larger than 1 cm in size, or a polyp of any size associated with gallstones, is an indication for cholecystectomy even if the patient is asymptomatic.

Item 19

Educational Objective: Evaluate for *Heltcobacter pylori* eradication following treatment.

KEY POINT

- After eradication therapy for *Helicobacter pylori* infection, eradication should be confirmed using the urea breath test or fecal antigen test.

Item 20

Educational Objective: Treat gallstone pancreatitis with prompt cholecystectomy.

KEY POINT

- Same-admission cholecystectomy reduces rates of gallstone-related complications compared with cholecystectomy after hospital discharge for patients with mild gallstone pancreatitis.

Item 21

Educational Objective: Treat cholangitis using endoscopic retrograde cholangiopancreatography.

KEY POINT

- Indications for endoscopic retrograde cholangiopancreatography in patients with primary sclerosing cholangitis are bacterial cholangitis, increasing jaundice, increasing pruritus, or a dominant stricture on imaging.

Item 22

Educational Objective: Evaluate rectal bleeding in a young patient.

KEY POINT

- Red-flag symptoms such as rectal bleeding with iron deficiency anemia, abdominal pain, and weight loss should prompt evaluation by colonoscopy for colorectal cancer regardless of the patient's age or the presence of bleeding hemorrhoids.

Item 23

Educational Objective: Diagnose narcotic bowel syndrome.

KEY POINT

- Narcotic bowel syndrome, also known as opiate-induced gastrointestinal hyperalgesia, is a centrally mediated disorder of gastrointestinal pain characterized by a paradoxical increase in abdominal pain with increasing doses of opioids.

Item 24

Educational Objective: Treat pain in chronic pancreatitis.

KEY POINT

- Mild hepatitis B virus–related polyarteritis nodosa is treated with antiviral agents.

Item 25

Educational Objective: Treat hepatitis B virus-related polyarteritis nodosa,

KEY POINT

- Mild hepatitis B virus–related polyarteritis nodosa is treated with antiviral agents.

Item 26

Educational Objective: Treat acute necrotic pancreatitis with enteral feeding.

KEY POINT

- Enteral nutrition is preferred in patients with acute pancreatitis because of the benefit of maintaining a healthy gut mucosal barrier to prevent translocation of bacteria.

Item 27

Educational Objective: Prevent spontaneous bacterial peritonitis.

KEY POINT

- Primary prophylactic antibiotic therapy is indicated for patients at high risk for the development of spontaneous bacterial peritonitis, including patients with very low ascitic-fluid protein levels and those with advanced liver failure.

Item 28

Educational Objective: Diagnose dumping syndrome after gastrojejunostomy.

KEY POINT

- Rapid gastric emptying of hyperosmolar chyme into the small intestine after partial gastric resection can lead to postprandial vasomotor symptoms, abdominal pain, and diarrhea, collectively known as dumping syndrome.

Item 29

Educational Objective: Treat chronic idiopathic constipation unresponsive to first-line treatment.

KEY POINT

- Linaclotide is a peripherally acting guanylate cyclase-C receptor agonist that is FDA approved for the treatment of chronic idiopathic constipation in adults with symptoms refractory to first-line therapies.

Item 30

Educational Objective: Prevent vertical transmission of hepatitis B viral infection.

KEY POINT

- Pregnant women who have hepatitis B virus DNA levels greater than 200,000 IU/mL at 24 to 28 weeks' gestation should be treated with tenofovir to prevent vertical transmission during delivery.

Item 31

Educational Objective: Diagnose pancreatic cancer.

KEY POINT

- Pancreatic neoplasm must be considered as a cause of acute pancreatitis in patients older than age 40 years when no other cause has been identified and/or when worrisome features, such as weight loss or new onset of diabetes mellitus, are present.

Item 32

Educational Objective: Manage antithrombotic therapy after gastrointestinal bleeding.

KEY POINT

- Once endoscopic hemostasis has been achieved in a patient with gastrointestinal bleeding, anticoagulation should be reinitiated, and in most cases, this can be done on the same day as the procedure.

Item 33

Educational Objective: Diagnose celiac disease.

KEY POINT

- Anti-tissue transglutaminase IgA antibody testing is the best screening test for celiac disease.

Item 34

Educational Objective: Monitor for colorectal neoplasia after colon cancer resection.

KEY POINT

- After treatment of colon cancer, patients should undergo surveillance colonoscopy 1 year after diagnosis.

Item 35

Educational Objective: Treat main-duct intraductal papillary mucinous neoplasm of the pancreas.

KEY POINT

- Surgical resection is the best management option for high-risk cystic lesions of the pancreas, such as intraductal papillary mucinous neoplasms that involve the main duct.

Item 36

Educational Objective: Diagnose the cause of hematochezia.

KEY POINT

- Hematochezia associated with hemodynamic instability in a young patient is likely due to an upper gastrointestinal source.

Item 37

Educational Objective: Diagnose secretory diarrhea.

KEY POINT

- Patients with secretory diarrhea may pass liters of stool daily, causing severe dehydration and electrolyte disturbances, with persistent stooling despite fasting.

Item 38

Educational Objective: Diagnose Crohn disease.

KEY POINT

- Colonoscopy results in Crohn disease show patchy distribution of mucosal inflammatory changes with "skip areas" of normal intervening mucosa, and biopsy results for involved mucosa show features of chronicity (distorted and branching colonic crypts).

Item 39

Educational Objective: Manage follow-up colonoscopy after uncomplicated diverticulitis.

KEY POINT

- Patients with uncomplicated diverticulitis should undergo colonoscopy 1 to 2 months after the episode of acute diverticulitis, when colonic inflammation has resolved.

Item40

Educational Objective: Diagnose atrophic gastritis.

KEY POINT

- Patients with newly diagnosed pernicious anemia should be evaluated for gastric adenocarcinoma and gastric carcinoid with upper endoscopy and gastric biopsy.

Item 41

Educational Objective: Treat acute anal fissure.

KEY POINT

- The most effective treatment approach for anal fissure is daily warm-water sitz baths and the use of the bulk laxative psyllium.

Item42

Educational Objective: Diagnose familial adenomatous polyposis

KEY POINT

- Patients with multiple fundic gland polyps found at a young age should be evaluated for familial adenomatous polyposis.

Item43

Educational Objective: Diagnose primary sclerosing cholangitis.

KEY POINT

- Approximately 5% of patients with inflammatory bowel disease will develop primary sclerosing cholangitis during the course of their disease, typically presenting as cholestatic liver injury with a characteristic imaging study showing bile duct strictures and dilations ("string of beads").

Item44

Educational Objective: Treat gastroesopbageal reflux disease

KEY POINT

- Patients with a clinical diagnosis of gastroesophageal reflux disease should start an empiric trial of a proton pump inhibitor in conjunction with lifestyle and dietary changes, with no further testing.

Item45

Educational Objective: Screen for osteoporosis in a patient with cirrhosis.

KEY POINT

- Patients with cirrhosis are at increased risk for the development of osteoporosis and should be screened using bone densitometry.

Item 46

Educational Objective: Prevent venous thromboembolism in **a hospitallzed patient with inflammatory bowel disease.**

KEY POINT

- All hospitalized patients with inflammatory bowel disease should be given pharmacologic venous thromboembolism prophylaxis with subcutaneous heparin.

Item47

Educational Objective: Diagnose Lynch syndrome.

KEY POINT

- Patients with a family history suggesting Lynch syndrome (three family members are affected with a Lynch syndrome–associated cancer, at least two successive generations are affected, one of the affected family members is a first-degree relative of the other two affected family members, and at least one cancer was diagnosed in a family member younger than age 50 years) should be referred for genetic counseling.

Item 48

Educational Objective: Evaluate persistent gastroesophageal reflux disease.

KEY POINT

- Medications that decrease kidney perfusion, including NSAIDs, ACE inhibitors, and angiotensin receptor blockers, should be discontinued in patients with ascites.

Item49

Educational Objective: Treat ascites caused by portal hypertension.

KEY POINT

- Medications that decrease kidney perfusion, including NSAIDs, ACE inhibitors, and angiotensin receptor blockers, should be discontinued in patients with ascites.

Item 50

Educational Objective: Treat acute liver failure.

KEY POINT

- Acute liver failure is an indication for immediate referral to a liver transplantation center.

Item 51

Educational Objective: Treat left-sided ulcerative colitis.

KEY POINT

- Combined mesalamine therapy (oral and topical) is superior for induction of remission in mild to moderately active ulcerative colitis compared with oral or topical therapies alone.

Item 52

Educational Objective: Evaluate dyspepsia

KEY POINT

- Patients younger than age 60 years presenting with dyspepsia should first undergo a noninvasive test for *Helicobacter pylori* followed by eradication therapy if testing is positive.

Item 53

Educational Objective: Treat amebic liver abscess.

KEY POINT

- The mainstay of therapy for amebic liver abscesses is antibiotic therapy, such as metronidazole, plus a luminal agent, such as paromomycin, to eradicate the coexisting intestinal infection.

Item 54

Educational Objective: Diagnose ulcerative colitis

KEY POINT

- Chronic bloody diarrhea and abdominal discomfort arc typical presenting symptoms of inflammatory bowel disease; endoscopic findings help distinguish ulcerative colitis from Crohn disease.

Item 55

Educational Objective: Test for Wilson disease.

KEY POINT

- Wilson disease should be considered in all patients younger than age 40 years who have unexplained liver disease.

Item 56

Educational Objective: Treat achalasia with botulinum toxin injection.

KEY POINT

- Patients with achalasia who are at high surgical risk should be treated with endoscopic botulinum toxin injection.

Item 57

Educational Objective: Recognize atypical chest pain and evaluate before starting treatment for gastroesophageal reflux disease.

KEY POINT

- In patients with atypical chest pain, a cardiac cause must be ruled out before starting treatment for gastroesophageal reflux disease.

Item 58

Educational Objective: Diagnose the relapsing, remitting variant of hepatitis A viral infection.

KEY POINT

- The relapsing, remitting variant of hepatitis A viral infection is characterized by multiple clinical or biochemical relapses with spontaneous improvement within months to 1 year without intervention.

Item 59

Educational Objective: Manage chronic proton pump inhibitor therapy.

KEY POINT

- Long-term proton pump inhibitor (PPI) therapy for uncomplicated gastroesophageal reflux disease should be given at the lowest effective dose possible, and consideration should be given to reducing or stopping PPI therapy at least once a year.

Item 60

Educational Objective: Treat intrahepatic cholestasis of pregnancy with ursodeoxychollc acid

KEY POINT

- The mainstay of therapy for intrahepatic cholestasis of pregnancy is ursodeoxycholic acid, which is associated with alleviated symptoms, improved fetal outcomes, and improved liver test abnormalities.

Item 61

Educational Objective: Evaluate isolated right-colon ischemia.

KEY POINT

- Isolated right-colon ischemia may be a warning sign of acute mesenteric ischemia caused by embolism or thrombosis of the superior mesenteric artery and should be evaluated using CT angiography.

Item 62

Educational Objective: Diagnose medication-induced enteropathy.

KEY POINT

- Olmesartan causes medication-induced enteropathy that can mimic refractory celiac disease.

Item 63

Educational Objective: Manage a patient with Barrett esophagus with low-grade dysplasia

KEY POINT

- Barrett esophagus with low-grade dysplasia should be treated with endoscopic ablation therapy in patients without significant comorbidities.

Item 64

Educational Objective: Diagnose *Gtardla lamblia* infection.

KEY POINT

- *Giardia lamblia* infection is a common parasitic infection that occurs most often among children, child care workers, and backpackers or campers who drink untreated water from lakes, rivers, or wells.

Item 65

Educational Objective: Diagnose gastroparesls,

KEY POINT

- The diagnosis of gastroparesis requires the presence of specific symptoms, absence of mechanical outlet obstruction, and objective evidence of delay in gastric emptying into the duodenum.

Item 66

Educational Objective: Treat bleeding esophageal varices.

KEY POINT

- The mainstay of therapy for variceal hemorrhage is endoscopic therapy, and adjunctive therapies such as antibiotic therapy improve outcomes.

Item 67

Educational Objective: Manage hepatic encephalopathy.

KEY POINT

- Up to 80% of patients with hepatic encephalopathy have a precipitating factor, most commonly infection or gastrointestinal bleeding.

Item68

Educational Objective: Screen for colorectal cancer in a high-risk individual.

KEY POINT

- Individuals with a first-degree relative with colon cancer or an advanced adenoma diagnosed at an age younger than 60 years, or two or more first-degree relatives with colon cancer or advanced adenoma diagnosed at any age, should begin colon cancer screening at age 40 years (or 10 years earlier than the youngest age at which colon cancer was diagnosed in a first-degree relative, whichever is first).

Item 69

Educational Objective: Treat hepatocellular carcinoma with liver transplantation.

KEY POINT

- Patients with cirrhosis and who meet the Milan criteria (up to three hepatocellular carcinoma tumors ≤3 cm or one tumor ≤5 cm) are best treated with liver transplantation and have excellent 5-year survival rates.

Item 70

Educational Objective: Diagnose eosinophilic esophagitis.

KEY POINT

- Eosinophilic esophagitis typically presents in young men with symptoms of dysphagia and in patients with a history of food allergies, eczema, and asthma.

Item 71

Educational Objective: Manage asymptomatic gallstones.

KEY POINT

- Incidentally found gallstones with no associated symptoms and no complications require no further intervention.

Item 72

Educational Objective: Diagnose aortoenteric fistuJa.

KEY POINT

- Gastrointestinal bleeding occurring in patients following aortic graft surgery should raise the possibility of aortoenteric fistula; CT with contrast is the initial test in appropriate patients.

Item 73

Educational Objective: Manage lower gastrointestinal bleeding.

KEY POINT

- Colonoscopy is the recommended initial diagnostic test after hemodynamic resuscitation in most patients with significant lower gastrointestinal bleeding.

Item 74

Educational Objective: Treat uncomplicated diverticulitis.

KEY POINT

- Patients with uncomplicated diverticulitis should be treated conservatively with oral antibiotics.

Item 75

Educational Objective: Manage a patient with Barrett esophagus that is indefinite for dysplasia.

KEY POINT

- Patients whose Barrett esophagus is indefinite for dysplasia should begin optimized antisecretory medical therapy and undergo a repeat endoscopy.

Item 76

Educational Objective: Evaluate fecal incontinence in an elderly patient.

KEY POINT

- Fecal loading (excess stool in the colon) with resultant overflow diarrhea is a common cause of fecal incontinence in elderly patients, particularly those who are hospitalized or have degenerative neurologic disorders.

Item 77

Educational Objective: Diagnose ischemic colitis.

KEY POINT

- Ischemic colitis is a low-flow state of the colon occurring most frequently in the left colon and characterized by moderate, left-sided, cramping abdominal pain followed by bloody diarrhea.

Item 78

Educational Objective: Treat ileal Crohn disease.

KEY POINT

- Anti–tumor necrosis factor agents such as infliximab are effective in inducing and maintaining remission in moderate to severe Crohn disease.

Item 79

Educational Objective: Manage Lynch syndrome.

KEY POINT

- Patients with Lynch syndrome should begin screening colonoscopy between ages 20 and 25 years or 2 to 5 years before the earliest age of colorectal cancer diagnosis in the family, whichever comes first, and colonoscopy should be repeated every 1 to 2 years if the baseline examination is normal.

Item 80

Educational Objective: Diagnose hereditary diffuse gastric cancer.

KEY POINT

- A history of multiple family members with gastric cancer, particularly before age 50 years, or multiple family members with lobular breast cancer with or without gastric cancer, suggest the possibility of hereditary diffuse gastric cancer and the need for upper endoscopy and testing for mutations of the *CDH1* gene.

Item 81

Educational Objective: Manage drug-induced liver injury.

KEY POINT

- In patients with well-preserved liver function, drug-induced liver injury should be managed with discontinuation of the offending medication and observation until resolution of symptoms occurs.

Item 82

Educational Objective: Treat centrally mediated abdominal pain syndrome.

KEY POINT

- Centrally mediated abdominal pain syndrome is characterized by near-constant abdominal pain lasting longer than 6 months, involving a large anatomic distribution, and without initiating triggers or alarm features.

Item 83

Educational Objective: Treat upper gastrointestinal bleeding.

KEY POINT

- In patients with upper gastrointestinal bleeding, a restrictive transfusion strategy (transfusion threshold of less than 7 g/dL [70 g/L] with a target hemoglobin level of 7-9 g/dL [70-90 g/L]) is associated with decreased mortality, length of hospital stay, and transfusion-related adverse events compared to a liberal transfusion strategy.

Item 84

Educational Objective: Screen for duodenal cancer in a patient with familial adenomatous polyposis syndrome.

KEY POINT

- Upper-endoscopy screening for duodenal cancer in patients with familial adenomatous polyposis should begin at onset of colonic polyposis or at age 25 to 30 years, whichever comes first.

Item 85

Educational Objective: Manage colonoscopy surveillance following polypectomy.

KEY POINT

- Patients with three or more adenomas on screening colonoscopy should undergo surveillance colonoscopy in 3 years.

Item 86

Educational Objective: Treat functional dyspepsia.

KEY POINT

- First-line treatment for functional dyspepsia is once-daily omeprazole for at least 4 weeks; if symptoms do not respond, a tricyclic antidepressant is the next recommended treatment.

Item 87

Educational Objective: Treat cryoglobulinemia in a patient with chronic hepatitis C viral infection.

KEY POINT

- Mixed cryoglobulinemia arising from chronic hepatitis C viral infection resolves after treatment and eradication of the virus.

Item 88

Educational Objective: Treat microscopic colitis.

KEY POINT

- The first step in the management of microscopic colitis is to discontinue a potentially causative medication, after which supportive treatment with antidiarrheal agents such loperamide can be tried, with budesonide recommended for patients whose symptoms do not respond.

Item 89

Educational Objective: Manage hepatic adenoma.

KEY POINT

- For women with asymptomatic hepatic adenomas smaller than 5 cm in size, estrogen-containing oral contraceptive agents should be discontinued, and follow-up liver imaging is recommended every 6 months for at least 2 years.

Item90

Educational Objective: Evaluate the small bowel for a source of gastrointestinal bleeding

KEY POINT

- Capsule endoscopy is the most appropriate test to evaluate patients for causes of small-bowel bleeding after negative upper endoscopy and colonoscopy.

Item 91

Educational Objective: Treat chronic hepatitis B viral infection In Its immune-active, hepatitis B e antigen positive phase.

KEY POINT

- Chronic hepatitis B viral infection in the immune-active, hepatitis B e antigen–positive phase should be treated with tenofovir or entecavir to decrease hepatic inflammation and the risk for progression to fibrosis.

Item 92

Educational Objective: Treat irritable bowel syndrome with predominant constipation.

KEY POINT

- Polyethylene glycol 3350 is a first-line treatment for patients whose symptoms meet the criteria for irritable bowel syndrome with predominant constipation.

Item 93

Educational Objective: Treat *Helicobacter pylori* infection persisting after treatment.

KEY POINT

- For *Helicobacter pylori* infection that persists after eradication therapy, the salvage therapy regimen should consist of different antibiotics from those used in the initial, unsuccessful regimen.

Item 94

KEY POINT

- In patients with end-stage liver disease and portal hypertension, hepatorenal syndrome is characterized by the development of oliguric kidney failure, bland urine sediment, and marked sodium retention (edema, ascites, low urinary sodium).

Item 95

Educational Objective: Manage walled-off necrosis after acute pancreatitis.

KEY POINT

- Asymptomatic patients with walled-off necrosis of the pancreas require no intervention.

Item *96*

Educational Objective: Screen for hepatocellular carcinoma in a patient with cirrhosis.

KEY POINT

- Patients with hepatitis C viral infection who achieve sustained virologic response have a reduced risk for hepatocellular carcinoma; regardless of virologic response, ultrasonographic surveillance is recommended for patients with stage 3 or stage 4 fibrosis.

M-K-S-A-P

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TABLES

RHEUMATOLOGY

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TABLE 1. Features of Inflammatory Versus Noninflammatory Pain		
Feature	**Inflammatory Pain**	**Noninflammatory Pain**
Physical examination findings	Erythema; warmth; soft-tissue swelling; joint effusions; reduced ROM is frequent	Minimal or no warmth; no soft-tissue swelling; bony enlargement and joint effusions may occur in osteoarthritis; reduced ROM may occur
Morning stiffness	>60 min; worsens with immobility	<30 min
Constitutional symptoms	Fever; fatigue; malaise	Generally absent
Synovial fluid	Leukocyte count >2000/µL (2.0×10^9/L), predominantly neutrophils in acute inflammation and monocytes in chronic inflammation	Leukocyte count between 200-2000/µL ($0.2\text{-}2.0 \times 10^9$/L), predominantly monocytes
Other laboratory findings	Elevated inflammatory markers (ESR, CRP); anemia of chronic disease	Inflammatory markers usually normal or minimally elevated

CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; ROM = range of motion.

TABLE 2. Dermatologic Manifestations of Rheumatologic Disease

Rheumatologic Disease	Dermatologic Manifestations
Systemic lupus erythematosus	Butterfly (malar) rash; photosensitive rash; discoid lupus erythematosus; subacute cutaneous lupus erythematosus; oral ulcerations (on the tongue/hard palate; usually painless); alopecia; lupus panniculitis (painful, indurated subcutaneous swelling with overlying erythema of the skin)
Dermatomyositis	Gottron papules (erythematous plaques on extensor surfaces of MCP and PIP joints); photodistributed poikiloderma, including shawl sign (over the back and shoulders) and V sign (over the posterior neck/back or neck/upper chest); heliotrope rash (violaceous rash on the upper eyelids); mechanic's hands (hyperkeratotic, fissured skin on the palmar and lateral aspects of fingers); nailfold capillary abnormalities; holster sign (poikilodermic rash along lateral thigh); can occur in the absence of myositis (amyopathic dermatomyositis)
Systemic sclerosis	Skin thickening and hardening; nailfold capillary changes
Vasculitis	Palpable purpura; cutaneous nodules; ulcers; necrosis
Behçet syndrome	Painful oral and genital ulcers; erythema nodosum; acne/folliculitis; pathergy (skin inflammation/ulceration from minor trauma)
Sarcoidosis	Erythema nodosum; infiltrated plaques; maculopapular and papular lesions; nodules; soft infiltrates of the nose (lupus pernio); on blanching with a glass slide, sarcoid skin lesions reveal "apple jelly" discoloration
Psoriatic arthritis	Plaque psoriasis typically on extensor surfaces, umbilicus, gluteal fold, scalp, and behind ears; pustular psoriasis on palms and soles; nail pitting; onychodystrophy
Reactive arthritis	Keratoderma blennorrhagicum (psoriasiform rash on soles, toes, palms); circinate balanitis (psoriasiform rash on penis)
Adult-onset Still disease	Evanescent, salmon-colored rash on trunk and proximal extremities
Rheumatic fever (secondary to streptococcal infection)	Erythema marginatum (annular pink to red nonpruritic rash with central clearing)
Lyme disease	Erythema chronicum migrans (slowly expanding, often annual lesion with central clearing)

MCP = metacarpophalangeal; PIP = proximal interphalangeal.

TABLE 3. Ocular Manifestations of Systemic Inflammatory Disease

Systemic Inflammatory Disease	Ocular Manifestations
Ankylosing spondylitis, reactive arthritis, and inflammatory bowel disease (anterior chamber); sarcoidosis and Behçet syndrome (anterior and/or posterior chamber); granulomatosis with polyangiitis (posterior chamber)	Uveitis (inflammation of the anterior and/or posterior chamber and/or retina)
Rheumatoid arthritis; spondyloarthritis; systemic vasculitis	Episcleritis
Rheumatoid arthritis; relapsing polychondritis; inflammatory bowel disease; systemic vasculitis	Scleritis
Systemic vasculitis; antiphospholipid syndrome	Retinal ischemia
Sjögren syndrome	Dryness of the eyes (keratoconjunctivitis sicca)
Giant cell arteritis	Anterior/posterior ischemic optic neuropathy; central retinal artery occlusion; loss of vision
Sarcoidosis; granulomatosis with polyangiitis	Exophthalmos/retrobulbar inflammatory infiltrate
Reactive arthritis	Conjunctivitis

TABLE 4. Internal Organ Involvement in Rheumatologic Disease

Organ	Disease	Type of Involvement
Heart		
	Kawasaki disease	Coronary artery vasculitis
	Systemic sclerosis	Arrhythmia; myocardial fibrosis
	SLE	Pericarditis; valvular disease; myocarditis
	RA	Pericarditis; myocarditis
	Rheumatic fever; antiphospholipid syndrome	Valvular disease
	GCA	Aortic aneurysm/dissection; aortitis; large-vessel obstruction
Lung		
	RA	Serositis; ILD; rheumatoid nodules
	SLE; CTDs; Henoch-Schönlein purpura	Serositis; pneumonitis; pulmonary hemorrhage from vasculitis
	AAV	Pulmonary hemorrhage; cavitary nodules
	Diffuse cutaneous systemic sclerosis	ILD; pulmonary hypertension
	Limited cutaneous systemic sclerosis	Pulmonary hypertension
	Antiphospholipid syndrome	Pulmonary embolism
	Sarcoidosis	Hilar lymphadenopathy; ILD
	Goodpasture syndrome	Pulmonary hemorrhage
Kidney		
	SLE; CTDs; AAV; systemic vasculitis (except PAN)	Glomerulonephritis
	PAN	Renal artery vasculitis; pseudoaneurysms
	Antiphospholipid syndrome	Renal infarct; renal vein thrombosis
	Sjögren syndrome	Acute interstitial nephritis/renal tubular acidosis
	Goodpasture syndrome	Glomerulonephritis
Gastrointestinal System		
	PAN	Mesenteric vasculitis
	Henoch-Schönlein purpura	Intestinal vasculitis and ulcerations
	Diffuse and limited cutaneous systemic sclerosis	Esophageal and small bowel hypomotility
	Behçet syndrome	Mucosal ulcerations
	Familial Mediterranean fever	Peritonitis
Nervous System		
	SLE; CTDs; AAV; systemic vasculitis	Mononeuritis multiplex; peripheral neuropathy
	PACNS	CNS vasculitis

AAV = ANCA-associated vasculitis; CNS = central nervous system; CTD = connective tissue disease; GCA = giant cell arteritis; ILD = interstitial lung disease; PACNS = primary angiitis of the central nervous system; PAN = polyarteritis nodosa; RA = rheumatoid arthritis; SLE = systemic lupus erythematosus.

TABLE 5. Autoantibodies in Rheumatologic Disease

Autoantibody	Rheumatologic Disease	Sensitivity/Specificity	Comments
ANA	SLE; also SSc, Sjögren, MCTD	SLE: >95% sensitivity, poor specificity; indirect IFA is the most appropriate methodology	Does not correlate with disease activity
Anti-double-stranded DNA	SLE	SLE: 50%-60% sensitivity, >95% specificity; *Crithidia* IFA or Farr assays more specific than ELISA	Found in more severe disease, especially kidney disease; antibody levels commonly follow disease activity and are useful to monitor
Anti-Smith	SLE	SLE: 30% sensitivity, 99% specificity	Most specific test for SLE; does not correlate with disease activity
Anti-U1-RNP	MCTD; SLE	High sensitivity for MCTD	High titer seen in MCTD (>1:10,000); does not correlate with disease activity
Anti-Ro/SSA; anti-La/SSB	Sjögren; SLE; RA; SSc	Sjögren: 70% sensitivity; SLE: 20% sensitivity	Sicca symptoms; in SLE, associated with photosensitive rash; offspring of mothers who are positive for anti-Ro/SSA or anti-La/SSB are at increased risk for neonatal lupus erythematosus (rash and congenital heart block)
Antiribosomal P	SLE	15% sensitivity	Associated with CNS lupus and lupus hepatitis
Anti-Scl-70 (antitopoisomerase-1)	DcSSc	10%-30% sensitivity	Seen more often in patients with DcSSc who have pulmonary fibrosis
Anticentromere	LcSSc (CREST)	10%-30% sensitivity	Patients with LcSSc with this antibody are more likely to develop pulmonary arterial hypertension
c-ANCA (antiproteinase-3)	GPA	90% sensitivity when disease is active; high specificity in classic presentations	Correlation with disease activity is unclear
p-ANCA (antimyeloperoxidase)	MPA; EGPA	MPA: 80% sensitivity; EGPA: 60% sensitivity; less specific than c-ANCA	Atypical p-ANCA (antimyeloperoxidase negative) can be seen in inflammatory bowel disease and with positive ANA
Anti-Jo-1	Polymyositis	20%-30% sensitivity	Associated with antisynthetase syndrome, including lung inflammation
Rheumatoid factor	RA; Sjögren; cryoglobulinemia	RA: 70% sensitivity; limited specificity, especially in patients without a classic disease presentation	RF is common in multiple other diseases (e.g., hepatitis C, endocarditis, SLE); 30% with RA are RF negative but may become positive later in RA course
Anti-cyclic citrullinated peptide	RA	RA: 70% sensitivity; 95% specificity	Can be positive in RF-negative RA patients; often present before RF becomes positive; associated with erosions; predicts disease progression in undifferentiated arthritis
Antihistone	DILE	95% sensitivity; poor specificity	Also seen in primary SLE
Cryoglobulins	Vasculitis; hepatitis C; myeloma; SLE; RA	Type II or III cryoglobulins seen in cryoglobulinemic vasculitis	May be present in connective tissue diseases in the absence of vasculitis

ANA = antinuclear antibodies; CNS = central nervous system; CREST = calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia; DcSSc = diffuse cutaneous systemic sclerosis; DILE = drug-induced lupus erythematosus; EGPA = eosinophilic granulomatosis with polyangiitis; ELISA = enzyme-linked immunosorbent assay; GPA = granulomatosis with polyangiitis; IFA = immunofluorescence assay; LcSSc = limited cutaneous systemic sclerosis; MCTD = mixed connective tissue disease; MPA = microscopic polyangiitis; RA = rheumatoid arthritis; RF = rheumatoid factor; RNP = ribonucleoprotein; SLE = systemic lupus erythematosus; SSc = systemic sclerosis.

TABLE 6. Radiographic Findings of Common Rheumatologic Diseases

Rheumatologic Disease	Radiographic Findings
Rheumatoid arthritis	Bony erosions; periarticular osteopenia; subluxations; soft-tissue swelling; MCP, PIP, and wrist involvement
Osteoarthritis	Asymmetric joint-space narrowing; osteophytes; subchondral sclerosis and cystic changes; degenerative disk disease with collapse of disks; degenerative joint disease with facet joint osteophytes; spondylolisthesis (anterior/posterior misalignment of the spine); kyphosis
Diffuse idiopathic skeletal hyperostosis	Calcification of the anterior longitudinal ligament; bridging horizontal syndesmophytes; usually seen in the thoracic spine and more prominent on the right side of the spine
Ankylosing spondylitis	Sacroiliitis; squaring of the vertebral bodies; bridging vertical syndesmophytes; shiny corners; ankylosis does not skip vertebrae
Psoriatic arthritis	Destructive arthritis with erosions and osteophytes; DIP involvement is common; pencil-in-cup deformity on hand radiograph; arthritis mutilans; syndesmophytes
Gout	Punched-out erosions with sclerotic borders and overhanging edges; periarticular soft-tissue swelling with calcifications in tophaceous deposits
Calcium pyrophosphate deposition	Chondrocalcinosis, most commonly of the knees, shoulders, wrists, pubic symphysis; osteoarthritis, including in locations atypical for primary osteoarthritis (MCPs, wrists, shoulders)

DIP = distal interphalangeal; MCP = metacarpophalangeal; PIP = proximal interphalangeal.

TABLE 7. Synovial Fluid Analysis

	Normal	Noninflammatory	Inflammatory	Crystal Induced	Infectious	Hemorrhagic
Appearance	Clear/yellow/ transparent	Clear/yellow/ transparent	Yellow/white/ translucent/ opaque	Yellow/white/ translucent/ opaque	Yellow/white/ opaque	Red/opaque
Leukocyte count	<200/µL (0.2×10^9/L)	200-2000/µL ($0.2\text{-}2.0 \times 10^9$/L)	2000-20,000/µL ($2.0\text{-}20 \times 10^9$/L) (may be higher)	10,000-50,000/µL ($10\text{-}50 \times 10^9$/L) (may be higher)	>50,000/µL (50×10^9/L) (may be lower)	—
Other studies	Negative Gram stain; negative culture	Negative Gram stain; negative culture	Negative Gram stain; negative culture	Negative Gram stain; positive crystals[a]	Positive Gram stain[b]; positive culture[c]	Negative Gram stain; negative culture

[a]Crystal description: Urate crystals are needle shaped and bright. Viewed under polarized light, they are negatively birefringent; they appear yellow when parallel to the axis of the polarized field and blue when perpendicular to the axis. Calcium pyrophosphate crystals are rhomboid, pale, and weakly (not as vividly) positively birefringent; they appear blue when parallel to the axis and yellow when perpendicular.

[b]Gram stain sensitivity for infection is approximately 30% to 50%.

[c]Nearly all cultures are positive except for infection caused by *Neisseria gonorrhoeae*, which may be positive in 50% or fewer cases.

TABLE 8. Potential Toxicities of NSAID Use	
Category	**Toxicity**
Cardiovascular	Myocardial infarction; exacerbation of heart failure
Hemostatic	Platelet dysfunction
Gastrointestinal	Dyspepsia; reflux; peptic ulcer disease; gastrointestinal bleeding
Obstetric/Gynecologic	Bleeding; delayed labor; premature ductus arteriosus closure
Pulmonary	Asthma exacerbation
Renal	Hypertension; decreased glomerular filtration; increased salt and water retention; increased renin production; uncommonly, allergic interstitial nephritis or acute tubular necrosis

TABLE 9. Nonbiologic Disease-Modifying Antirheumatic Drugs

Agent	Mechanism	Indications	Common Monitoring Parameters
Methotrexate	Low dose: anti-inflammatory agent via up-regulation of adenosine A_{2A} signaling High dose: antimetabolite/folate antagonist used in neoplastic disease	RA; psoriasis; psoriatic arthritis; IBD; SLE (arthritis only); reactive arthritis; DM; PM; vasculitis	Baseline: chest radiography, hepatitis screening, CBC, LCTs, serum creatinine Thereafter: CBC, LCTs, serum creatinine after the first month, then approximately every 2-3 months[a]
Hydroxychloroquine	Uncertain; appears to involve stabilization of lysosomal vacuoles, leading to inhibition of antigen processing and/or inhibition of Toll-like receptor activation	SLE; RA	Baseline: CBC, LCTs, serum creatinine Retinal examinations at baseline and annual examination after 5 years of therapy to evaluate for retinopathy
Sulfasalazine	Unknown; the prodrug is broken down into 5-amino salicylic acid (active metabolite in the gastrointestinal tract) and sulfapyridine (exerts systemic action)	RA; SpA; IBD	Baseline: CBC, LCTs, serum creatinine Thereafter: CBC, LCTs, serum creatinine every 3-6 months
Leflunomide	Inhibits the mitochondrial enzyme dihydroorotate dehydrogenase to block pyrimidine synthesis (decreasing lymphocyte production); antiproliferative	RA	Baseline: hepatitis screening, CBC, LCTs, serum creatinine Thereafter: CBC, LCTs, serum creatinine after 4 weeks, then every 3 months
Azathioprine	A prodrug of 6-mercaptopurine; purine analogue; inhibits DNA synthesis essential for proliferating T- and B-lymphocytes	SLE; DM; PM; vasculitis; IBD	Baseline: CBC, LCTs, serum creatinine Thereafter: CBC, LCTs, serum creatinine every 3 months[a]
Cyclophosphamide	Alkylating agent; blocks DNA synthesis and causes cell death, especially of T cells	Severe and life-threatening disease in SLE, DM, PM, and vasculitis; may be used when other agents fail	Close monitoring clinically and measuring CBC, chemistries, LCTs, urinalysis every 4-8 weeks
Mycophenolate mofetil	Active metabolite (mycophenolic acid) inhibits purine synthesis; preferentially inhibits T- and B-lymphocytes	SLE (especially lupus nephritis); vasculitis (maintenance therapy); DM; PM; SSc	Baseline: CBC, LCTs, serum creatinine Thereafter: CBC, LCTs, serum creatinine after 4 weeks and then every 3 months[a]
Cyclosporine	Inhibits calcineurin (a transcription activating factor); preferentially targets T cells	SLE; psoriasis; RA	Baseline: CBC, LCTs, serum creatinine Thereafter: CBC, LCTs, serum creatinine every 2-3 months[a]
Tofacitinib	Janus kinase inhibitor	RA	Baseline: CBC, LCTs, creatinine, lipid panel Thereafter: CBC, LCTs, creatinine every 8 weeks, lipids after 8 weeks and then every 6 months
Apremilast	Inhibits phosphodiesterase 4	Psoriasis; psoriatic arthritis	Baseline: weight Thereafter: weight, neuropsychiatric effects

CBC = complete blood count; DM = dermatomyositis; IBD = inflammatory bowel disease; LCTs = liver chemistry tests; PM = polymyositis; RA = rheumatoid arthritis; SLE = systemic lupus erythematosus; SpA = spondyloarthritis; SSc = systemic sclerosis.

[a]Recommended monitoring interval is for a stable dose but may be shorter after initiation or in the case of abnormal results and must be individualized to the patient's risk of toxicity.

TABLE 10. Tumor Necrosis Factor α Inhibitors[a]

Agent	Agent Structure	Indications
Adalimumab	Humanized monoclonal antibody	RA; psoriatic arthritis; ankylosing spondylitis; IBD
Etanercept	Fusion protein made of two p75 TNF-α receptors linked to IgG Fc segment	RA; psoriatic arthritis; ankylosing spondylitis
Certolizumab pegol	Fab' segment of humanized monoclonal antibody attached to polyethylene glycol strands	RA; psoriatic arthritis; ankylosing spondylitis
Golimumab	Humanized monoclonal antibody	RA; psoriatic arthritis; ankylosing spondylitis
Infliximab	Chimeric (mouse-human) monoclonal antibody	RA; psoriatic arthritis; ankylosing spondylitis; IBD

IBD = inflammatory bowel disease; RA = rheumatoid arthritis; TNF = tumor necrosis factor.

[a]Common monitoring parameters for TNF-α inhibitors include tuberculosis, fungal, and other infections as well as complete blood count, serum creatinine, and liver chemistry tests at baseline and thereafter every 3 to 6 months.

TABLE 11. Other Biologic Disease-Modifying Antirheumatic Drugs[a]

Agent	Agent Structure	Target	Indications	Comments
Abatacept	Soluble CTLA4 receptor/IgG Fc segment chimera	CD80/CD86; blocks T-cell costimulation	RA	Preferred for those with history of severe infection; relatively contraindicated in COPD
Rituximab	Chimeric (mouse-human) monoclonal antibody	CD20⁺ B cells	RA; ANCA-associated vasculitis; occasionally for SLE (off-label); hyper-IgG4 syndrome	Given as an intravenous infusion over several hours; has a higher risk of infusion reactions than other biologic DMARDs; can cause hypogammaglobulinemia
Tocilizumab	Humanized monoclonal antibody	IL-6 receptor	RA; JIA; Castleman disease; GCA	Can cause transaminitis, hyperlipidemia, leukopenia, thrombocytopenia; avoid in those with history of diverticulitis because of an attendant risk of bowel perforation
Belimumab	Human monoclonal antibody	BLyS/BAFF	SLE	Phase III trials showed a small but statistically significant improvement versus standard therapy alone, with a glucocorticoid-sparing effect
Ustekinumab	Human monoclonal antibody	IL-12/IL-23	Psoriasis; psoriatic arthritis	Injectable; less robust effect than other biologic DMARDs
Secukinumab	Human monoclonal antibody	IL-17a	Psoriatic arthritis; ankylosing spondylitis	Phase III trials suggest equal efficacy to TNF-α inhibitors; can cause flares of IBD
Anakinra	Recombinant receptor antagonist	IL-1β receptor	RA; CAPS[b]; AOSD (off-label); acute gouty arthritis (off-label)	Rarely used in RA because efficacy is inferior to other biologic DMARDs; reversible neutropenia can develop
Canakinumab	Human monoclonal antibody	IL-1β	CAPS[b]	Newer, more expensive IL-1 inhibitor
Rilonacept	Dual IL-1β receptors chimerically attached to IgG Fc segment	IL-1	CAPS[b]; refractory gout	Newer, more expensive IL-1 inhibitor

AOSD = adult-onset Still disease; BAFF = B-cell-activating factor; BLyS = B-lymphocyte stimulator; CAPS = cryopyrin-associated periodic syndromes; DMARD = disease-modifying antirheumatic drug; GCA = giant cell arteritis; IBD = inflammatory bowel disease; IL = interleukin; JIA = juvenile idiopathic arthritis; RA = rheumatoid arthritis; SLE = systemic lupus erythematosus; TNF = tumor necrosis factor.

[a]Prior to initiating any biologic, tuberculosis screening must be performed. Complete blood counts should be performed every 3 to 6 months for all biologics, and aspartate aminotransferase/alanine aminotransferase and a lipid panel should be checked every 2 to 3 months for tocilizumab.

[b]The cryopyrin-associated periodic syndromes (CAPS) include familial cold autoinflammatory syndrome, Muckle-Wells syndrome, and neonatal-onset multisystem inflammatory disease (chronic infantile neurologic, cutaneous, articular syndrome).

TABLE 12. Rheumatologic Medications and Pregnancy[a]

Medication/Class	Comments
Anti-Inflammatory Agents	
NSAIDs	May impede implantation and may be associated with a small increased risk of miscarriage when used before 20 weeks' gestation. Use of NSAIDs after 30 weeks' gestation can lead to premature closure of the ductus arteriosus.
Glucocorticoids	When taken in the first trimester, can increase the risk of fetal cleft palate, and can raise the risk of maternal gestational diabetes throughout the pregnancy.
	Useful in the management of active autoimmune disease in pregnancy. Non-fluorinated glucocorticoids (e.g., prednisone, prednisolone, methylprednisolone) have limited ability to cross the placenta and are preferred, except when treating the fetus (e.g., neonatal lupus erythematosus).
Colchicine	Should be used only if the potential benefit justifies the potential risk to the fetus.
Analgesics	
Acetaminophen	Generally considered safe at standard dosing, but does cross the placenta.
Opiates	Some opiates/opioids cross the placenta; may cause fetal opioid withdrawal at birth.
Tramadol	Should be used only if the potential benefit justifies the potential risk to the fetus; postmarketing reports suggest the possibility of neonatal seizures, withdrawal syndrome, and stillbirth.
Topical agents	Topical use may limit serum levels; individual agents should be reviewed for pregnancy impact prior to use.
Nonbiologic DMARDs	
Methotrexate	Highly teratogenic and abortifacient; must be discontinued at least 3 months before pregnancy.
Hydroxychloroquine	Relatively safe in pregnancy and should not be discontinued if needed.
Sulfasalazine	Relatively safe during pregnancy.
Leflunomide	Extremely teratogenic; must not be used before/during pregnancy; upon discontinuation, cholestyramine administration is required to remove the drug from the body in all women of childbearing potential and specifically in those wishing to become pregnant; should be followed up with measurement of leflunomide and its metabolite levels to ensure removal of the drug.
Azathioprine	Routine use in pregnancy is not recommended; however, azathioprine may be safer than some other DMARDs and may be used if an immunosuppressive agent is imperative.
Cyclophosphamide	Not used in pregnancy unless absolutely necessary.
Mycophenolate mofetil	Teratogenic; should not be used in pregnancy; discontinue for 3 months before attempting pregnancy.
Cyclosporine	May be used in pregnancy only if benefits outweigh the risks.
Tofacitinib	May be teratogenic at high doses.
Biologic DMARDs	
TNF-α inhibitors	Accumulating retrospective data suggest low risk in pregnancy, but evidence is limited; can be continued if absolutely needed; different agents may have different considerations regarding crossing the placenta.
Ustekinumab; anakinra; secukinumab	Should be used only if the potential benefit justifies the undefined risk to the fetus.
Abatacept; belimumab; canakinumab; rilonacept; rituximab; tocilizumab	Should be used only if the potential benefit justifies the potential risk to the fetus.
Urate-Lowering Therapy (rarely needed in premenopausal women)	
Allopurinol	Should be used only if the potential benefit justifies the potential risk to the fetus.
Febuxostat	Should be used only if the potential benefit justifies the potential risk to the fetus.
Probenecid	No current evidence for adverse impact on pregnancy.
Pegloticase	Should be used only if the potential benefit justifies the potential risk to the fetus.

DMARD = disease-modifying antirheumatic drug; TNF = tumor necrosis factor.

[a]See MKSAP 18 General Internal Medicine for information on the FDA pregnancy categories.

TABLE 13. The 2010 American College of Rheumatology/European League Against Rheumatism Classification Criteria for Rheumatoid Arthritis

Criteria	Score[a]
Joint Involvement[b]	
1 large joint (shoulders, elbows, hips, knees, ankles)	0
2-10 large joints	1
1-3 small joints (MCPs, PIPs, wrists, 2-5 MTPs)	2
4-10 small joints	3
More than 10 small joints	5
Serology	
Negative RF or anti-CCP antibodies	0
Low-positive RF or anti-CCP antibodies (under 3 times the upper limit of normal)	2
High-level RF or anti-CCP antibodies (above 3 times the upper limit of normal)	3
Acute Phase Reactants	
Normal CRP or ESR	0
Abnormal CRP or ESR	1
Duration	
Less than 6 weeks	0
More than 6 weeks	1

CCP = cyclic citrullinated peptide; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; MCP = metacarpophalangeal; MTP = metatarsophalangeal; PIP = proximal interphalangeal; RF = rheumatoid factor.

[a]Six points needed for classification as rheumatoid arthritis.

[b]At least one joint with definite clinical synovitis that is not better explained by another disease.

From Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO 3rd, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum. 2010 Sep;62(9):2569-81. doi: 10.1002/art.27584. [PMID: 20872595] Copyright 2010, American College of Rheumatology. Adapted with permission from John Wiley & Sons, Inc.

TABLE 14. Consequences of Persistent Inflammation on Joints and Supporting Structures

Joint Area	Implications
C1-C2 articulation and transverse ligament	Laxity of the transverse ligament results in increased posterior motion of the dens on C2; with neck flexion, the dens can impact the midbrain and other vital neurologic structures
Shoulder and rotator cuff tendons	Restricted range of motion of the glenohumeral joint and rotator cuff tears
Elbow joint	Elbow contractures and difficulty with hand pronation and supination
Wrist carpal joints and finger tendons	Restricted range of motion of wrist; carpal tunnel syndrome; rupture of finger extensor tendons, especially the fourth and fifth
MCPs and surrounding structures	Ulnar deviation and subluxation of MCPs
PIPs and surrounding structures	Swan neck or boutonniere deformity due to inflammatory disruption of periarticular support structures
Hip joint	Axial migration of the femoral head in the acetabulum (protrusio acetabuli)
Knee joint	Tricompartmental joint-space narrowing
Ankle and mid-foot joints and tendons	Restricted range of motion of ankle; progressive pronated flat foot deformity
MTPs and surrounding structures	Fibular deviation of MTPs; cock-up deformities; skin ulceration underneath subluxed MTP heads

MCP = metacarpophalangeal; MTP = metatarsophalangeal; PIP = proximal interphalangeal.

TABLE 15. Secondary Causes of Osteoarthritis

Secondary Cause	Joint(s) Typically Involved
Hemochromatosis	Second/third MCP joints
Calcium pyrophosphate deposition	MCP joints; wrists; knees; hips; shoulders; atlanto-axial joint
Alkaptonuria/ochronosis	Spine; hips; knees
Acromegaly	Knees; shoulders; spine
Hyperparathyroidism	Wrists; MCP joints
Joint injury	Knees

MCP = metacarpophalangeal.

TABLE 16. Comparison of the 1990 ACR Classification Criteria and the 2010 ACR Diagnostic Criteria for Fibromyalgia

1990 ACR Classification Criteria	2010 ACR Preliminary Diagnostic Criteria
Widespread pain by self-report	Widespread pain by the Widespread Pain Index (WPI; 19-point scale) assessing the number of regions in which the patient has pain[a,b]
≥11 tender points on digital palpation or using a dolorimeter	Symptom severity by the Symptom Severity (SS) Scale (12-point scale) assessing 1) fatigue; 2) nonrestorative sleep; 3) cognitive symptoms[a,b]
	Duration of symptoms ≥3 months
	No other disorder explaining the pain

ACR = American College of Rheumatology.

[a]Fibromyalgia is diagnosed in the setting of WPI ≥7 plus SS score ≥5, or WPI ≥3 plus SS score ≥9.

[b]The Widespread Pain Index and the Symptom Severity Scale can be viewed at https://www.rheumatology.org/Portals/0/Files/2010%20Fibromyalgia%20Diagnostic%20Criteria_Excerpt.pdf.

TABLE 17. Clinical Features of Spondyloarthritis

	Ankylosing Spondylitis	Psoriatic Arthritis	IBD-Associated Arthritis	Reactive Arthritis
Musculoskeletal				
Axial involvement	Axial involvement predominates; initially symmetrically involves the SI joints and lower spine, progressing cranially; does not skip regions	May occur at any level; may start in the cervical spine; may skip regions	May be asymptomatic but can follow a course similar to ankylosing spondylitis; SI involvement often asymmetric; axial arthritis does not parallel IBD activity	Less common than in other forms of spondyloarthritis
Peripheral involvement	Enthesitis; may have asymmetric large-joint oligoarthritis, including hips and shoulders; hip involvement can cause significant functional limitation; dactylitis uncommon	Five subtypes (symmetric polyarthritis; asymmetric oligoarthritis; DIP-predominant; spondyloarthritis; arthritis mutilans); also, enthesitis, dactylitis, and tenosynovitis	Acute polyarticular peripheral arthritis: especially knee; early; can parallel IBD activity Chronic polyarticular peripheral arthritis: of PIPs, MCPs, wrists, elbows, shoulders, knees, ankles, and MTPs; does not parallel IBD; dactylitis; enthesitis	Enthesitis and asymmetric large-joint oligoarthritis; usually self-limited; nonerosive; some patients experience recurrent or persistent arthritis; may develop features of other forms of spondyloarthritis
Dermatologic	Skin findings not characteristic, but psoriatic-like lesions may occasionally occur	Psoriasis typically precedes joint involvement; nail pitting; onychodystrophy	Pyoderma gangrenosum; erythema nodosum	Keratoderma blennorrhagicum (psoriasiform rash on soles, toes, palms); circinate balanitis (psoriasiform rash on penis)
Ophthalmologic	Anterior uveitis (unilateral, recurrent)	Conjunctivitis more common than anterior uveitis (can be bilateral, insidious, or chronic)	Anterior uveitis (can be bilateral, insidious, or chronic); conjunctivitis, keratitis, and episcleritis are rare	Conjunctivitis more common than anterior uveitis
Gastrointestinal	Asymptomatic intestinal ulcerations (rare)	—	Crohn disease; ulcerative colitis	Prior GI infection in some patients
Genitourinary	Urethritis (rare)	—	Nephrolithiasis	Prior GU infection in some patients; sterile urethritis; prostatitis; cervicitis; salpingitis
Cardiovascular	Aortic valve disease; aortitis; conduction abnormalities; CAD	Association with traditional CAD risk factors	Thromboembolism	—
Pulmonary	Restrictive lung disease from costovertebral rigidity; apical fibrosis (rare)	—	—	—
Bone quality	Falsely elevated bone mineral density from syndesmophytes; increased risk of spine fracture	Increased risk of fracture (multifactorial)	High risk for vitamin D deficiency, low bone density, and fracture	Localized osteopenia

CAD = coronary artery disease; DIP = distal interphalangeal; GI = gastrointestinal; GU = genitourinary; IBD = inflammatory bowel disease; MCP = metacarpophalangeal; MTP = metatarsophalangeal; PIP = proximal interphalangeal; SI = sacroiliac.

TABLE 18. American College of Rheumatology Criteria for the Classification of Systemic Lupus Erythematosus

Criteria[a]	Definition
Malar rash	Fixed erythema, flat or raised, over the malar eminences
Discoid rash	Erythematous, circular, raised patches with keratotic scaling and follicular plugging; atrophic scarring may occur
Photosensitivity	Rash after exposure to ultraviolet light
Oral ulcers	Oral and nasopharyngeal ulcers (observed by physician)
Arthritis	Nonerosive arthritis of ≥2 peripheral joints, with tenderness, swelling, or effusion
Serositis	Sterile pleuritis, pericarditis, or peritonitis (documented by electrocardiogram, rub, or evidence of effusion or ascites)
Kidney disorder	Urinalysis: 3+ protein or urine protein >500 mg/24 h; cellular casts
Neurologic disorder	Seizures or psychosis (without other cause)
Hematologic disorder	Hemolytic anemia or leukopenia (<4000/µL [4.0×10^9/L]) or lymphopenia (<1500/µL [1.5×10^9/L]) or thrombocytopenia (<100,000/µL [100×10^9/L]) in the absence of offending drugs
Immunologic disorder	Anti-double-stranded DNA, anti-Smith, and/or antiphospholipid antibodies
ANA	An abnormal titer of ANA by immunofluorescence or an equivalent assay at any point in the absence of drugs known to induce ANA

ANA = antinuclear antibodies.

[a]Any combination of 4 or more of the 11 criteria, well documented at any time during a patient's history, makes it likely that the patient has systemic lupus erythematosus (specificity and sensitivity are 95% and 75%, respectively).

From Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum. 1997;40(9):1725. [PMID: 9324032] Copyright 1997, American College of Rheumatology. Adapted with permission from John Wiley & Sons, Inc.

TABLE 19. Common Autoantibodies in Systemic Lupus Erythematosus

Autoantibody	Frequency in SLE	Comments
Antinuclear	>95%	Useful as an initial screening test; assesses multiple antigens simultaneously
Anti-double-stranded DNA	50%-60%	Found in more severe disease, especially kidney disease; antibody levels commonly follow disease activity and are useful to monitor
Anti-Ro/SSA	30%	Associated with photosensitive rashes, discoid lupus erythematosus, and neonatal lupus erythematosus; also common when secondary Sjögren syndrome is present
Anti-U1-ribonucleoprotein	35%	Associated with Raynaud phenomenon and esophageal dysmotility; also seen in MCTD
Anti-Smith	30%	Specific for SLE; often associated with more severe disease
Anti-La/SSB	20%	Common in Sjögren syndrome; less common in SLE and neonatal lupus erythematosus
Antiribosomal P	15%	Associated with CNS lupus and lupus hepatitis

CNS = central nervous system; MCTD = mixed connective tissue disease; SLE = systemic lupus erythematosus.

TABLE 20. Medications Commonly Associated with Drug-Induced Lupus Erythematosus

Medication	Antibodies Detected	Comments
Procainamide	ANA (75%); antihistone	20% develop DILE; fever; arthritis; serositis
Hydralazine	ANA (20%); antihistone	5%-8% develop DILE; fever; arthritis; rare vasculitis and kidney disease
Minocycline	ANA; ANCA; anti-dsDNA rare	Arthritis; vasculitis; autoimmune hepatitis
Antithyroid drugs	ANA; ANCA; antihistone	Vasculitic rash; rare pulmonary and kidney disease
Statins	ANA; antihistone; anti-dsDNA	SLE, SCLE, dermatomyositis, and polymyositis all reported
Calcium channel blockers	ANA; anti-Ro/SSA; antihistone rare	SCLE
Thiazide diuretics	ANA; anti-Ro/SSA; antihistone rare	SCLE
ACE inhibitors	ANA; anti-Ro/SSA; antihistone rare	SCLE
TNF-α inhibitors	ANA (23%-57%); chromatin and anti-dsDNA common; antihistone rare	DILE most common with infliximab, uncommon for etanercept; SLE, SCLE, DLE all reported

ANA = antinuclear antibodies; DILE = drug-induced lupus erythematosus; DLE = discoid lupus erythematosus; dsDNA = double-stranded DNA; SCLE = subacute cutaneous lupus erythematosus; SLE = systemic lupus erythematosus; TNF = tumor necrosis factor.

TABLE 21. Medications Commonly Used to Treat Systemic Lupus Erythematosus

Medication	Common Uses in SLE	Important Side Effects
NSAIDs	Arthritis; pain; fever	Hypertension; GI bleeding; AKI
Prednisone	Used for all manifestations in varying doses	Hypertension; glucose intolerance; weight gain; infection; osteonecrosis
Hydroxychloroquine	Used in all patients; especially useful for skin involvement and to prevent disease flares	GI intolerance; rash; blurry vision; retinopathy; vacuolar myopathy
Mycophenolate mofetil	Moderate to severe disease; as effective as cyclophosphamide for remission induction for nephritis	Bone marrow suppression; elevation of liver enzymes; infection
Azathioprine	Moderate to severe disease	Bone marrow suppression; elevation of liver enzymes; hematologic malignancy
Cyclophosphamide	Severe organ or life-threatening disease	Bone marrow suppression; hemorrhagic cystitis; infection; malignancy; infertility
Belimumab	Add-on therapy for moderate to severe disease	Infusion reactions; infections

AKI = acute kidney injury; GI = gastrointestinal; SLE = systemic lupus erythematosus.

TABLE 22. Extraglandular Clinical Manifestations of Sjögren Syndrome

Site/Organ	Manifestation/Frequency
General	Fatigue (70%), fever (6%)
Skin	Dry skin (xerosis), cutaneous vasculitis: 10%-16%
Joint	Arthralgia/arthritis: 36%
Lung	Interstitial pneumonitis: 5%-9%
Kidney	Interstitial nephritis, distal (type 1) renal tubular acidosis, glomerulonephritis: 5%-6%
Neurologic	Central nervous system (CNS): demyelinating disease, myelopathy, cranial nerve neuropathy Peripheral nervous system: small-fiber neuropathy, mononeuritis multiplex, peripheral neuropathy 8%-27% for CNS and peripheral
Gastrointestinal	Autoimmune hepatitis, primary biliary cirrhosis: 3%-20%
Hematologic	Lymphoma, cytopenia: 2%
Other	Systemic vasculitis (7%), cryoglobulinemia (4%-12%), Raynaud phenomenon (16%), thyroid disease (10%-15%)

TABLE 23. American College of Rheumatology/European League Against Rheumatism Classification Criteria for Primary Sjögren Syndrome[a]

The presence of a subjective finding of Sjögren syndrome (e.g., sicca complaint) plus any combination of the following resulting in a score of ≥4:

Item	Score
Salivary gland biopsy with ≥1 foci of lymphocytic infiltrate/4 mm^2	3
Anti-Ro/SSA autoantibodies	3
Ocular staining score ≥5 in at least one eye	1
Schirmer test ≤5 mm/5 min in at least one eye	1
Unstimulated whole saliva flow rate ≤0.1 mL/min	1

[a]Exclusion criteria include prior head/neck radiation and history of active hepatitis C virus infection, AIDS, sarcoidosis, amyloidosis, graft-versus-host disease, and IgG4-related disease.

From Shiboski CH, Shiboski SC, Seror R, Criswell LA, Labetoulle M, Lietman TM, et al; International Sjögren's Syndrome Criteria Working Group. 2016 American College of Rheumatology/European League Against Rheumatism Classification Criteria for Primary Sjögren's Syndrome: A Consensus and Data-Driven Methodology Involving Three International Patient Cohorts. Arthritis Rheumatol. 2017 Jan;69(1):35-45. doi: 10.1002/art.39859. [PMID: 27785888]. Copyright 2016, American College of Rheumatology. Adapted with permission from John Wiley & Sons, Inc.

TABLE 24. Differential Diagnosis of Myopathy

Myopathy	Common Examples	Comments
Inflammatory myopathies	Dermatomyositis (DM); polymyositis (PM); immune-mediated necrotizing myopathy (IMNM); inclusion body myositis (IBM)	DM and PM: acute-subacute onset, symmetric, proximal; DM: pathognomonic rash; IMNM: acute onset, symmetric, proximal; IBM: insidious onset, proximal and distal
Systemic rheumatologic disease	Systemic lupus erythematosus; systemic sclerosis; mixed connective tissue disease	Prominent extramuscular features typical of underlying disorder
Muscular dystrophies	Duchenne muscular dystrophy; Becker muscular dystrophy	Childhood onset; cardiomyopathy possible
Metabolic myopathies	Glycogen storage diseases; carnitine palmitoyltransferase deficiency	Exercise intolerance
Mitochondrial myopathies	Kearns-Sayre syndrome; Leigh syndrome	Variable age of presentation and features; isolated myopathy or with neurologic, multisystem disease
Endocrine disorders	Hypothyroidism; hyperthyroidism; adrenal insufficiency	Prominent myalgia
Infection induced	Bacterial: pyomyositis; viral: influenza; parasitic: trichinosis	Prominent myalgia; sometimes accompanied by fever

TABLE 25. Drug-Induced Myopathies

Drug	Time Course	Clinical Presentation
Alcohol	Increased with long-term use	Asymptomatic elevations of serum creatine kinase; chronic muscle atrophy; acute, severe rhabdomyolysis with kidney failure
Antimalarials	Can occur after prolonged use	Infrequent elevation of serum creatine kinase (30%); muscle weakness (50%); myopathic electromyogram findings (100%); cardiomyopathy can occur
Cocaine	Can occur after single use	Asymptomatic elevations of serum creatine kinase; acute, severe rhabdomyolysis with kidney failure
Colchicine	Usually months to years; increased risk with coadministration of cytochrome P450 inhibitors	Proximal muscle weakness with elevations of serum creatine kinase; mild sensory symptoms; reduced reflexes
Glucocorticoids	Increased with long-term use	Proximal muscle weakness in the absence of elevations of serum creatine kinase
Statins	Usually weeks to months but can occur at any time; increased risk with preexisting neuromuscular disease, hypothyroidism, kidney failure, and/or coadministration of cytochrome P450 inhibitors; may also trigger immune-mediated necrotizing myopathy	Elevations of serum creatine kinase with myalgia and weakness
Zidovudine	Variable; may be more common after long-term use	Elevations of serum creatine kinase with myalgia and weakness

TABLE 26. Cutaneous Manifestations of Dermatomyositis

Cutaneous Sign	Location	Clinical Appearance
Gottron rash (Gottron papules and Gottron sign)	Metacarpophalangeal and proximal interphalangeal joints; occasionally on distal interphalangeal joints, elbows, knees	Erythematous to violaceous papules; occasional scale; can ulcerate; atrophic scars may occur
Heliotrope rash	Eyelids	Subtle pink to deep purple or brown discoloration; may be associated with edema of eyelids or periorbital edema
V sign	V of neck	Erythematous to violaceous papules to patches
Shawl sign	Base of posterior neck to upper back	Erythematous to violaceous papules to patches
Fixed erythema	Malar area (may cross nasolabial folds); flanks of trunk	Erythematous to violaceous papules to patches
Nail area changes	Periungual area; cuticles	Periungual erythema; capillary dilatation and dropout; cuticular hypertrophy; cuticular infarcts
Mechanic's hands	Lateral aspects of digits and palms	Hyperkeratotic fissuring of the palmar and lateral surfaces of the fingers resembling the hands of a laborer

TABLE 27. Autoantibodies in Inflammatory Myopathies

Autoantibody	Disease Association	Clinical Association
Antinuclear	DM; PM	Seen in up to 80%; nonspecific
Anti-aminoacyl-tRNA synthetase; most commonly anti-Jo-1 (anti-histidyl tRNA synthetase)	DM	Antisynthetase syndrome (ILD, Raynaud phenomenon, nonerosive arthritis, mechanic's hands)
Anti-cytoplasmic 5′-nucleotidase 1A	IBM	Insidious onset
Anti-HMG Co-A reductase	IMNM	Typically but not always in the setting of statin exposure; may also be seen in patients with statin exposure without IMNM
Anti-Mi 2	DM	Seen in up to 30%; associated with acute onset, typical rash
Anti-signal recognition protein	IMNM	Severe, treatment-resistant disease and myofiber necrosis but little to no inflammation on muscle biopsy

DM = dermatomyositis; IBM = inclusion body myositis; ILD = interstitial lung disease; IMNM = immune-mediated necrotizing myopathy; PM = polymyositis.

TABLE 28. American College of Rheumatology/European League Against Rheumatism Classification Criteria for Systemic Sclerosis

Manifestation	Additional Manifestations	Weight/Score[a]
Skin thickening of fingers of both hands extending proximal to the MCPs	—	9
Skin thickening of the fingers (count higher score only)	Puffy fingers	2
	Sclerodactyly of fingers distal to the MCPs but proximal to PIPs	4
Fingertip lesions	Digital tip ulcers	2
	Fingertip pitting scars	3
Telangiectasia	—	2
Abnormal nailfold capillaries	—	2
Pulmonary hypertension and/or interstitial lung disease (maximum score is 2)	Pulmonary hypertension	2
	Interstitial lung disease	2
Raynaud phenomenon	—	3
SSc-related autoantibodies (maximum score is 3)	Anticentromere	3
	Anti-Scl-70 (antitopoisomerase-1)	3
	Anti-RNA polymerase III	3

MCP = metacarpophalangeal; PIP = proximal interphalangeal; SSc = systemic sclerosis.

[a]A score of 9 or more equates to definite systemic sclerosis.

From van den Hoogen F, Khanna D, Fransen J, Johnson SR, Baron M, Tyndall A, et al. 2013 classification criteria for systemic sclerosis: an American College of Rheumatology/European League Against Rheumatism Collaborative Initiative. Ann Rheum Dis 2013;72:1747-55. doi: 10.1136/annrheumdis-2013-204424. [PMID: 24092682] Copyright 2013, American College of Rheumatology. Adapted with permission from BMJ Publishing Group Ltd.

TABLE 29. Common Manifestations/Features of the Scleroderma Spectrum Disorders

Disorder	Manifestation/Feature	Comments
Systemic Sclerosis		
Diffuse cutaneous systemic sclerosis (DcSSc)	Distal and proximal skin thickening (chest, abdomen, arms proximal to wrists); commonly has visceral organ involvement	Skin involvement is extensive and is commonly accompanied by internal organ fibrosis and ILD
Limited cutaneous systemic sclerosis (LcSSc)	Distal (face, neck, hands), but not proximal, skin thickening; typically not accompanied by internal organ fibrosis	More likely to develop PAH and Raynaud phenomenon early in the disease and more likely to display features of the CREST syndrome
Systemic sclerosis sine scleroderma	Fibrosing organ involvement without skin thickening	Difficult to diagnose; prognosis may be similar to LcSSc
Localized Scleroderma		
Morphea	Focal plaques of skin thickening, generally on the trunk	Systemic manifestations or Raynaud phenomenon is extremely rare
Linear scleroderma	Streaks/lines of thickened skin	Same as morphea
Scleroderma-like Conditions[a]		
Eosinophilic fasciitis	Orange peel induration (peau d'orange) of proximal extremities with sparing of hands and face; peripheral eosinophilia; skin retraction over the superficial veins may be more apparent with elevation of an affected limb	Full-thickness skin biopsy demonstrates lymphocytes, plasma cells, and eosinophils infiltrating the deep fascia; glucocorticoids are the mainstay of treatment
Nephrogenic systemic fibrosis	Secondary to gadolinium in patients with kidney disease; brawny, wood-like induration of extremities, sparing the digits	Skeletal muscle fibrosis with contractures and/or cardiac muscle involvement can occur, with cardiomyopathy and increased mortality; changes in use and formulation of gadolinium have reduced incidence
Scleredema	Indurated plaques/patches on back, shoulder girdle, and neck	Typically seen in long-standing diabetes mellitus
Scleromyxedema	Waxy, yellow-red papules over thickened skin of face, upper trunk, neck, and arms; deposition of mucin with large numbers of stellate fibroblasts in the dermis	Associated with paraproteinemia (IgGλ) and may therefore occur in the setting of multiple myeloma or AL amyloidosis; more frequent in men
Chronic graft-versus-host disease	Lichen planus–like skin lesions, or localized or generalized skin thickening	Occurs most commonly after hematopoietic stem cell transplantation; may occasionally be seen after blood transfusion in an immunocompromised host
Drug and toxin exposure	Can produce scleroderma-like tissue changes	Examples: bleomycin, docetaxel, pentazocine, L-tryptophan, organic solvents

CREST = calcinosis cutis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia; ILD = interstitial lung disease; PAH = pulmonary arterial hypertension.

[a]Scleroderma-like skin changes may also occur as a manifestation of systemic endocrine, kidney, or infiltrative disorders.

TABLE 30. Autoantibodies and Their Associations in Systemic Sclerosis

Autoantibody	Clinical Associations	Comments
Antinuclear antibodies	DcSSc; LcSSc	Overall prevalence in SSc: 70%; not associated with specific manifestations
Anticentromere (kinetochore proteins)	LcSSc ± PAH	Overall prevalence in SSc up to 30%; highly associated (>90%) with CREST variant of LcSSc
Anti-Scl-70 (DNA topoisomerase-1)	DcSSc; ILD	Overall prevalence in SSc: up to 30%; highly associated with DcSSc
Anti-RNA polymerase III	DcSSc; scleroderma renal crisis	Useful in DcSSc with negative anti–Scl-70
Anti-U3-RNP (fibrillarin)	DcSSc; PAH; myositis	Associated with poor outcome; more common in black men
Anti-PM-Scl	Myositis	Associated with overlap syndrome and polymyositis
Anti-Ku	Myositis	Rare occurrence
Anti-Th/To	LcSSc; PAH	Rare occurrence

CREST = calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia; DcSSc = diffuse cutaneous systemic sclerosis; ILD = interstitial lung disease; LcSSc = limited cutaneous systemic sclerosis; PAH = pulmonary arterial hypertension; RNP = ribonucleoprotein; SSc = systemic sclerosis.

TABLE 31. Treatment Options for Common Manifestations of Systemic Sclerosis

Manifestations	Treatment
Cutaneous manifestations	Methotrexate, mycophenolate, cyclophosphamide, and rituximab have been shown to improve skin scores; for pruritus, antihistamines can be tried; low-dose prednisone can also help; laser therapy can used for telangiectasias.
Musculoskeletal manifestations	NSAIDs, intra-articular or low-dose prednisone, hydroxychloroquine, or methotrexate can be used for arthralgia/arthritis; methotrexate, azathioprine, or mycophenolate can be used for significant myositis.
Raynaud phenomenon	Cold avoidance; gloves; central warmth
	Calcium channel blockers
	Sildenafil; losartan; prazosin
	Topical nitrates; low-dose aspirin
	Digital sympathectomy
Gastroesophageal reflux disease	Avoid eating close to bed time; head of bed elevation
	H_2 blockers; proton pump inhibitors
	Surgical fundoplication
Gastrointestinal dysmotility	Metoclopramide (avoid long-term use); domperidone (limited access program)
	Erythromycin; cisapride (limited access program)
Gastric antral vascular ectasia	Ablation laser therapy
Small intestine bacterial overgrowth	Rotating antibiotics
	If fat malabsorption, cholestyramine
Pseudo-obstruction	A promotility agent such as domperidone can be tried
	If resistant, octreotide may be useful
Constipation	Fiber; stool softeners
	Polyethylene glycol
Scleroderma renal crisis	ACE inhibitors (typically captopril)
	Dialysis
Interstitial lung disease	Mycophenolate mofetil
	Cyclophosphamide
	Lung transplantation
Pulmonary arterial hypertension	Supplemental oxygen; treat right-sided heart failure
	Prostanoids; endothelin receptor antagonists; phosphodiesterase-5 inhibitors; soluble guanylate cyclase inhibitors
	Combination therapy
	Lung transplantation

TABLE 32. Comparison of Mixed Connective Tissue Disease, Undifferentiated Connective Tissue Disease, and Overlap Syndrome

Condition	Typical Clinical Features	Diagnosis	Treatment
Mixed connective tissue disease	Raynaud phenomenon; arthritis; puffy fingers; sclerodactyly; serositis; esophageal dysmotility; myositis; interstitial lung disease; PAH	Positive anti-U1-RNP antibodies Fulfills criteria for at least two of the following: SSc, PM, and SLE	Disease/organ involvement specific Anti-inflammatories for symptoms; DMARDs and/or immunosuppressives for arthritis or other major organ disease Vasodilators for PAH and Raynaud phenomenon PPI for esophageal disease
Undifferentiated connective tissue disease	Variable; most common include Raynaud phenomenon, arthralgia, skin rash, cytopenia, and serositis	Insufficient criteria for any specific connective tissue disease	Same as mixed connective tissue disease
Overlap syndrome	Variable; will have features satisfying two distinct autoimmune diseases (such as SLE, RA, PM, and SSc)	Fulfills criteria for two distinct autoimmune diseases	Same as mixed connective tissue disease

DMARD = disease-modifying antirheumatic drug; PAH = pulmonary arterial hypertension; PM = polymyositis; PPI = proton pump inhibitor; RA = rheumatoid arthritis; RNP = ribonucleoprotein; SLE = systemic lupus erythematosus; SSc = systemic sclerosis.

TABLE 33. Causes of Hyperuricemia

Primary renal uric acid underexcretion (hereditary, renal tubular basis)
Chronic kidney disease of any cause (secondary uric acid underexcretion)
Uric acid overproduction due to primary defect in purine metabolism: PRPP synthetase overactivity; HPRT deficiency
Conditions of increased cell turnover leading to purine/urate generation: leukemia/lymphoma; psoriasis; hemolytic anemia; polycythemia vera
Drug-induced hyperuricemia (agents reducing renal glomerular filtration and/or tubular urate excretion): thiazide and loop diuretics; cyclosporine; low-dose salicylates; ethambutol; pyrazinamide; lead ingestion/toxicity
Diet-induced hyperuricemia (agents high in purines or inducing purine/urate biosynthesis): alcohol; shellfish; red meat; high-fructose corn syrup-sweetened beverages and foods; impact on serum urate generally is limited in the absence of other causes

HPRT = hypoxanthine-guanine phosphoribosyltransferase; PRPP = phosphoribosylpyrophosphate.

TABLE 34. Differential Diagnosis of Acute Gouty Arthritis

Condition	Comments
Infectious arthritis	Presentation may be identical to gout. Infectious arthritis is usually monoarticular but can be polyarticular. Onset may be less acute than gout. Gout and infectious arthritis can coexist.
Acute calcium pyrophosphate crystal arthritis (pseudogout)	Pseudogout is less likely to present in the great toe, but acute presentations may otherwise be identical to gout. Synovial fluid analysis can distinguish these entities. Gout and pseudogout can coexist.
Basic calcium phosphate deposition	Basic calcium phosphate deposition in articular cartilage and periarticular tissues. Because of their small size, basic calcium phosphate crystals are unlikely to be seen in synovial fluid on light microscopy except as aggregates stained with alizarin red.
Trauma	Trauma can lead to local pain and swelling, with or without a fracture, and can also trigger a gout attack.
Other forms of inflammatory arthritis (e.g., reactive arthritis, rheumatoid arthritis, psoriatic arthritis, acute rheumatic fever)	Clinical context, affected joints, and pattern of arthritis are all helpful in distinguishing these entities. Synovial fluid analysis is particularly important when there is diagnostic uncertainty.

TABLE 35. Management of Calcium Pyrophosphate Deposition

Clinical Presentation	Treatment/Comments
Cartilage calcification (chondrocalcinosis)	No specific treatment
Acute calcium pyrophosphate crystal arthritis (pseudogout)	Local treatment: joint aspiration, followed by intra-articular glucocorticoid injection, intramuscular glucocorticoid injection; joint immobilization; ice packs
	Systemic treatment: NSAIDs; colchicine; glucocorticoids (oral or parenteral)
	Prophylaxis if recurrent attacks (three or more annual attacks): low-dose colchicine or daily NSAIDs (with gastrointestinal protection)
Chronic calcium pyrophosphate crystal inflammatory arthritis	Low-dose colchicine or daily low-dose NSAIDs (with gastrointestinal protection); low-dose glucocorticoids
Osteoarthritis with calcium pyrophosphate deposition (CPPD)	Same treatment as osteoarthritis without CPPD (e.g., physical therapy; pain control; local glucocorticoids)

TABLE 36. Risk Factors for Infectious Arthritis in Adults
General Risk Factors
Age >80 years
Alcoholism
Cutaneous ulcers or skin infections
Diabetes mellitus
End-stage kidney disease
History of intra-articular glucocorticoid injection
Injection drug use
Low socioeconomic status
Malignancy
Patients receiving immunosuppressive agents
Preexisting arthritis or joint damage (e.g., rheumatoid arthritis or osteoarthritis)
Prosthetic joint or recent joint surgery
Sickle cell disease
Risk Factors for Gonococcal Arthritis
Younger, sexually active patients
Risk Factors for Lyme Arthritis
Travel or residence in an endemic area
Documented tick bite or erythema chronicum migrans
Risk Factors for Mycobacterial or Fungal Arthritis
Patients with HIV infection or other immunosuppression
Patients receiving tumor necrosis factor α inhibitors
Travel or residence in an endemic area
Risk Factors for Viral Arthritis
Chronic viral infection (HIV, hepatitis B, hepatitis C)
Exposure to infectious agent or vaccine (e.g., rubella)
Travel or residence in an endemic area
Exposure to affected children (parvovirus, rubella)

TABLE 37. Infectious Arthritis Treatment Based on the Suspected Pathogen

Likely or Identified Pathogen	First-Line Therapy	Second-Line Therapy	Comments
Gram-Positive Cocci			
If MRSA is a concern (risk factors or known MRSA carrier)	Vancomycin	Clindamycin; daptomycin; linezolid	—
MSSA	Nafcillin or cefazolin	—	Narrow treatment to MSSA coverage based on sensitivity data.
Gram-Negative Bacilli			
Enteric gram-negative bacilli	Third generation cephalosporin (e.g., ceftriaxone or cefotaxime)	Fluoroquinolones	—
Pseudomonas aeruginosa	Ceftazidime; cefepime; piperacillin-tazobactam	Carbapenems; aztreonam; fluoroquinolones	—
Gram-Negative Cocci			
Neisseria gonorrhoeae	IV ceftriaxone for at least 7 days plus 1 gram of oral azithromycin x one dose	Fluoroquinolones (only if culture sensitivities confirm susceptibility)	In the absence of specific culture sensitivity data, "stepping down" to oral therapy of any type is no longer recommended due to increasing resistance of *N. gonorrhoeae* to commonly used oral agents.
Gram Stain Unavailable or Inconclusive			
Likely pathogen depends on patient risk factors: consider MRSA, and gram-negative organism if immunocompromised, at risk for gonococcal infection, or with joint trauma; also consider community patterns of infection.	Vancomycin, or vancomycin + third generation cephalosporin, or antipseudomonal antibiotic if pseudomonas suspected	—	Appropriate to start with broad antibiotic coverage and narrow coverage if culture data become available.
Borrelia burgdorferi (Lyme arthritis)	Oral doxycycline or amoxicillin × 28 days	—	If inadequate response or concurrent neurologic findings, IV ceftriaxone × 28 days.
Mycobacterium tuberculosis	3- to 4-drug treatment (e.g., isoniazid, pyrazinamide, rifampin, ethambutol, streptomycin)	—	Duration may vary from 6 months or longer depending on drug regimen (shorter treatment if rifampin is used).
Fungal infections	Amphotericin B, echinocandin, or azoles (fluconazole, itraconazole, voriconazole, posaconazole), depending on suspected organism or culture data	—	Prolonged treatment courses of several months may be needed; maintenance therapy may be required in high-risk patients.

IV = intravenous; MRSA = methicillin-resistant *Staphylococcus aureus*; MSSA = methicillin-sensitive *Staphylococcus aureus*.

TABLE 38. Causes of Secondary Vasculitis
Medications
Common causes: antimicrobial agents (e.g., minocycline, sulfadiazine); antithyroid agents (mostly propylthiouracil [80%-90%], methimazole, carbimazole, and benzylthiouracil [10%-20%]); other cardiovascular drugs (hydralazine); tumor necrosis factor α inhibitors Rare causes: vaccines; antiepileptic agents; antiarrhythmic agents; diuretics; anticoagulants; antineoplastic agents; hematopoietic growth factors; NSAIDs; psychotropic drugs; sympathomimetic agents; allopurinol; interferon alfa; levamisole (associated with cocaine)
Infections
Hepatitis A, B, and C viruses; HIV; bacterial endocarditis; parvovirus B19
Neoplasms
Hairy cell leukemia (associated with polyarteritis nodosa); other hematologic and solid malignancies
Autoimmune Diseases
Systemic lupus erythematosus; rheumatoid arthritis; Sjögren syndrome; inflammatory myopathies; systemic sclerosis; relapsing polychondritis; inflammatory bowel disease; primary biliary cirrhosis

TABLE 39. Differential Diagnosis (Mimics) of Vasculitis	
Disease	**Comments**
Infection (sepsis; endocarditis; hepatitis)	Rash and/or musculoskeletal symptoms can occur.
Drug toxicity/poisoning	Cocaine, amphetamines, ephedra alkaloids, and phenylpropanolamine may produce vasospasm, resulting in ischemia.
Coagulopathy	Thrombotic diseases (disseminated intravascular coagulation; antiphospholipid syndrome; thrombotic thrombocytopenic purpura) can produce ischemic symptoms.
Malignancy	Paraneoplastic vasculitis is rare. Any organ system may be affected, but the skin and nervous system are the most common. Vasculitic symptoms may precede, occur simultaneously with, or follow diagnosis of cancer. Lymphoma occasionally may involve the blood vessels and mimic vasculitis. Consider malignancy in patients with incomplete or no response to therapy for idiopathic vasculitis.
Atrial myxoma	Classic triad of symptoms is embolism, intracardiac obstruction leading to pulmonary congestion or heart failure, and constitutional symptoms (fatigue; weight loss; fever). Skin lesions can be identical to those seen in leukocytoclastic vasculitis. Atrial myxomas are rare but are the most common primary intracardiac tumors. Myxomas can also occur in other cardiac chambers.
Cholesterol emboli	Typically seen in patients with severe atherosclerosis. Embolization may occur after abdominal trauma, aortic surgery, or angiography. May also occur after heparin, warfarin, or thrombolytic therapy. Patients may have livedo reticularis, petechiae and purpuric lesions, and localized skin necrosis.

TABLE 40. Clinical Features of Polyarteritis Nodosa

Organ System	Symptoms	Frequency	Comments
Constitutional	Fever; malaise; weight loss	65%	—
Musculoskeletal	Arthralgia; myalgia	55%	—
Skin	Purpura; nodules; necrotic ulcers	50%-60%	—
Neurologic	Mononeuritis multiplex; peripheral neuropathy	79%	Wrist drop; foot drop
Kidney	Hypertension; hematuria; proteinuria	40%	Renal artery microaneurysms with tissue infarct/hematoma; no glomerulonephritis
Gastrointestinal	Mesenteric ischemia; intestinal perforation; pancreatitis; cholecystitis; appendicitis; gastrointestinal bleeding	38%	One third of gastrointestinal cases manifest as acute abdomen
Testicular	Orchitis	17%	Usually unilateral, due to testicular artery involvement
Other	Sensorineural hearing loss	Case reports	Bilateral; symmetric; sudden onset; rapidly progressive
Laboratory	Elevated erythrocyte sedimentation rate in 82%; elevated C-reactive protein; leukocytosis; anemia; thrombocytosis; increased liver chemistry tests in 33%	—	—

TABLE 41. Clinical Features of ANCA-Associated Vasculitis Diseases

	Granulomatosis with Polyangiitis	Microscopic Polyangiitis	Eosinophilic Granulomatosis with Polyangiitis
ANCA	c-ANCA (antiproteinase-3 antibodies) (>95%)	p-ANCA (antimyeloperoxidase antibodies) (50%-75%)	p-ANCA (antimyeloperoxidase antibodies) (~50%)
Vascular Histology	Pauci-immune necrotizing granulomatous vasculitis	Pauci-immune nongranulomatous necrotizing vasculitis	Pauci-immune necrotizing granulomatous vasculitis with eosinophilic infiltration of vessel walls and tissues; extravascular granulomas
Cardiac	Pericarditis; myocarditis; conduction disorder (<10%)	—	Pericarditis; endomyocarditis; conduction disorder; heart failure (27%-47%)
Ears/Nose/Throat	Crusting; rhinorrhea; sinusitis; otitis media; chondritis of ears and nose with saddle nose deformity; septal perforation (70%-100%)	Sinusitis; sensorineural hearing loss (9%-30%)	Nasal polyps; rhinitis; sinusitis (prodromal)
Gastrointestinal	Ulceration; perforation (5%-11%)	Abdominal pain; bleeding (30%-58%)	Abdominal pain; bleeding
Kidney	Pauci-immune necrotizing glomerulonephritis (40%-100%)	Pauci-immune necrotizing glomerulonephritis (80%-100%)	Pauci-immune necrotizing glomerulonephritis (25%)
Lung	Alveolar hemorrhage; nodules; tracheal/subglottic stenosis (50%-90%)	Alveolar hemorrhage; pulmonary infiltrates; pulmonary fibrosis (25%-55%)	Asthma (prodromal, >90%); nodular opacities; infiltrates (25%-86%)
Ocular	Scleritis; episcleritis; retinal vasculitis; retro-orbital pseudotumor; dacryoadenitis (14%-60%)	—	—
Skin	Palpable purpura; nodules; pyoderma gangrenosum; mucosal ulcerations (10%-50%)	Palpable purpura; livedo reticularis; nodules; necrotic skin ulcers (30%-60%)	Palpable purpura; nodules (60%)
Neurologic	Mononeuritis multiplex, sensorimotor peripheral neuropathy (33%) Central nervous system involvement (pachymeningitis) (<5%)	Distal symmetric polyneuropathy; mononeuritis multiplex (37%-72%) Central nervous system pachymeningitis; cerebral hemorrhage; infarcts (<20%)	Sensorimotor peripheral neuropathy, mononeuritis multiplex (70%)

TABLE 42. International Criteria for Behçet Disease

Manifestations	Points[a]
Oral ulcers	2
Genital ulcers	2
Pathergy	1
Skin lesions (pseudofolliculitis; skin ulcers; erythema nodosum)	1
Eye lesions (anterior uveitis; posterior uveitis; retinal vasculitis)	2
Central nervous system lesions	1
Vascular lesions (arterial thrombosis; large vein thrombosis; phlebitis)	1

[a]Four or more points are needed for the diagnosis of Behçet syndrome.

TABLE 43. Yamaguchi Criteria for the Diagnosis of Adult-Onset Still Disease

Major Criteria[a]	Approximate Frequency
Daily spiking fever to 39.0 °C (102.2 °F)	99%
Arthralgia/arthritis >2 weeks	85%
Nonpruritic salmon-colored macular/maculopapular rash on trunk or extremities	85%
Leukocyte count >10,000/µL (10×10^9/L), >80% neutrophils	90%
Minor Criteria	**Approximate Frequency**
Sore throat	66%
Lymphadenopathy and/or splenomegaly	65%/50%
Elevated AST, ALT, or LDH	70%
Negative ANA and RF	—

ALT = alanine aminotransferase; ANA = antinuclear antibodies; AST = aspartate aminotransferase; LDH = lactate dehydrogenase; RF = rheumatoid factor.

[a]Diagnosis requires five criteria with at least two major criteria included.

Adapted with permission from Yamaguchi M, Ohta A, Tsunematsu T, Kasukawa R, Mizushima Y, Kashiwagi H, et al. Preliminary criteria for classification of adult Still's disease. J Rheumatol. 1992 Mar;19(3):424-30. [PMID: 1578458] Copyright 1992, the Journal of Rheumatology.

TABLE 44. Features and Treatment of Select Autoinflammatory Diseases

	FMF[a]	TRAPS	FCAS[b]	MWS[b]	NOMID/ CINCA[b]	Schnitzler Syndrome
Inheritance	AR	AD	AD	AD	AD	Acquired
Gene	*MEFV*	*TNFRSF1A*	*NLRP3*	*NLRP3*	*NLRP3*	Unknown
Protein	Pyrin	TNF receptor type 1	Cryopyrin	Cryopyrin	Cryopyrin	MGUS (hallmark but not proven causal)
Age at Onset	65% <10 years of age; 90% <20 years of age	50% <10 years of age; up to fifth decade	<1 year of age	Childhood	Neonatal period	Adult (51 ± 10 years)
Ethnicity	Mediterranean	All	European	European	All	Caucasian/European
Clinical Manifestations						
Attack Duration	12-72 h	Days to weeks	12-24 h	1-2 days	Continuous	Daily
Abdominal	Pain; serositis	Pain; serositis	Nausea	Pain	—	—
Pleuritis	Common	Common	—	Rare	Rare	—
Musculoskeletal	Monoarthritis of lower extremities	Large joints	Arthralgia	Arthralgia; oligoarthritis	Epiphyseal overgrowth; contractures	Arthralgia; arthritis; bone pain
Rash	Erysipeloid on lower legs	Migratory with underlying myalgia	Cold-induced; urticaria-like	Urticaria-like	Urticaria-like	Urticarial rash; neutrophilic
Other	High risk for amyloidosis	Conjunctivitis; periorbital edema	Conjunctivitis; headache; amyloidosis; sensorineural deafness	Sensorineural deafness; conjunctivitis; amyloidosis	Sensorineural deafness; aseptic meningitis; mental retardation; amyloidosis	Leukocytosis; lymphadenopathy; hepatosplenomegaly; MGUS (usually IgM kappa); may later develop Waldenstrom macroglobulinemia
Treatment	Colchicine	Glucocorticoids; TNF-α inhibitors	IL-1β inhibition	IL-1β inhibition	IL-1β inhibition	IL-1Ra or IL-1β inhibition

AD = autosomal dominant; AR = autosomal recessive; CINCA = chronic infantile neurologic, cutaneous, articular syndrome; FCAS = familial cold autoinflammatory syndrome; FMF = familial Mediterranean fever; IL = interleukin; IL-1Ra = interleukin-1 receptor antagonist; MGUS = monoclonal gammopathy of uncertain significance; MWS = Muckle-Wells syndrome; NOMID = neonatal-onset multisystem inflammatory disease; TNF = tumor necrosis factor; TRAPS = tumor necrosis factor receptor-associated periodic syndrome.

[a]FMF is the most common autoinflammatory disease.

[b]The cryopyrin-associated periodic syndromes (CAPS) include familial cold autoinflammatory syndrome, Muckle-Wells syndrome, and neonatal-onset multisystem inflammatory disease (chronic infantile neurologic, cutaneous, articular syndrome).

TABLE 45. Findings and Management of Genetic Diseases of Connective Tissue						
	Ehlers-Danlos Syndrome				Marfan Syndrome	Osteogenesis Imperfecta
	Hypermobility	Classic	Kyphoscoliotic	Vascular		
Genetic Testing Available	Gene is unknown	*COL5A1*; *COL5A2*	*PLOD1*	*COL3A1*	*FBN1*	*COL*
Inheritance	AD	AD	AR	AD	AD	AD or AR
Clinical Findings						
Musculoskeletal	Joint laxity; joint instability; musculoskeletal pain; early osteoarthritis	Hypermobility; joint dislocations; pes planus	Hypermobility; progressive scoliosis; marfanoid habitus	Hypermobility; joint dislocations	Hypermobility; tall stature; dolichostenomelia[a]; arachnodactyly; pectus excavatum/carinatum; scoliosis	Bone fractures; short stature
Skin	Easy bruising; mild laxity	Smooth, velvety; easy bruising; hyperextensible; striae atrophicae (widened stretch marks)	Easy bruising; hyperextensible	Thin; translucent; easy bruising	Hyperextensible	—
Cardiovascular	No risk of organ rupture or dissection	Mitral/tricuspid valve prolapse; aortic root dilation (rare); arterial rupture (rare)	Medium-size arterial rupture; mitral/tricuspid valve prolapse	Arterial rupture; aneurysm; dissection	Aortic aneurysm/dissection; mitral valve prolapse	—
Other	—	Muscular hypotonia; delayed motor development	Muscular hypotonia; scleral fragility with risk of globe rupture; restrictive lung disease; recurrent pneumonia; heart failure	Organ rupture (uterus, bowel, rarely spleen, liver); pneumothorax; gingival recession	Myopia (most common feature [60%]); ectopia lentis; high arched palate; pneumothorax; blue sclerae	Dentinogenesis imperfecta[b]; hearing loss; blue sclerae
Management[c]	Joint protection; supportive care	Joint protection; echo/vascular monitoring; preconception counseling	Joint protection; echo/vascular monitoring; preconception counseling; physical therapy; bracing	Joint protection; echo/vascular monitoring; preconception counseling	Annual ophthalmic examination; periodic aortic arch imaging; β-blockers[d]; joint protection; pregnancy counseling/monitoring	Bisphosphonates; audiology assessments; joint and bone protection; dental evaluations

AD = autosomal dominant; AR = autosomal recessive.

[a]Dolichostenomelia describes when the extremities are disproportionately long for the size of the trunk.

[b]Dentinogenesis imperfecta is defined as discolored (blue/gray or yellow/brown), translucent, weak teeth prone to breakage.

[c]Genetic consultation is appropriate for all listed conditions.

[d]Slow rate of aortopathy.

TABLE 46. Select Conditions Associated with IgG4-Related Disease

Condition	Organ Involved
Hypertrophic pachymeningitis	Dura mater
Lymphocytic hypophysitis	Pituitary gland
Idiopathic orbital inflammatory disease	Periorbital often with involvement of the ocular adnexal tissues
Mikulicz disease	Parotid glands
Dacryoadenitis	Lacrimal glands
Küttner tumor	Submandibular glands
Riedel thyroiditis	Thyroid
Inflammatory aortitis/vasculitis	Aorta/arteries
Autoimmune pancreatitis	Pancreas
Ormond disease (retroperitoneal fibrosis)	Periaortic mass
Tubulointerstitial nephropathy	Kidneys
Sclerosing cholangitis	Biliary tract

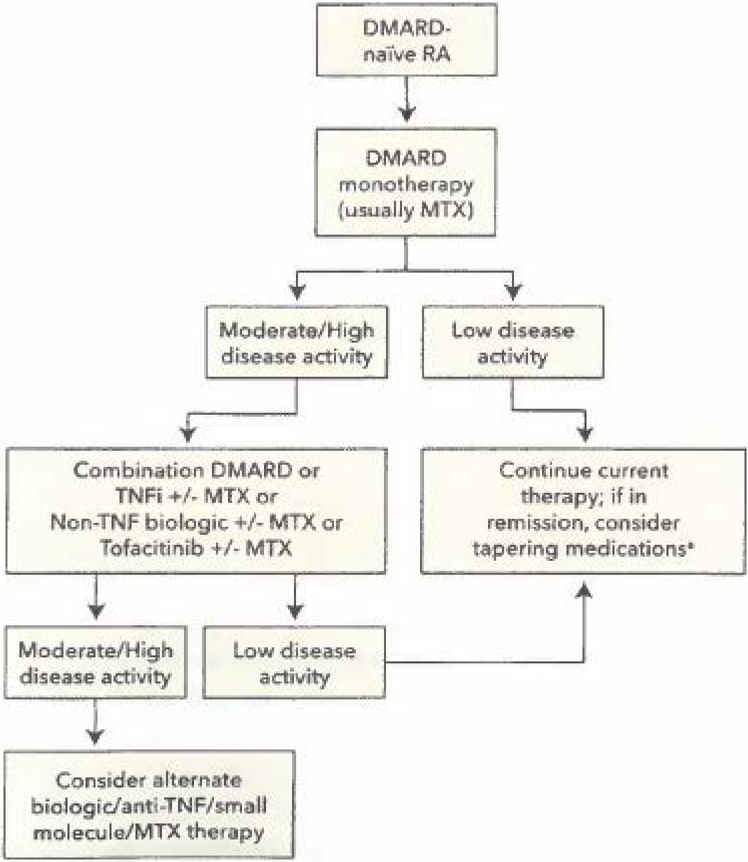

FIGURE 6. A simplified algorithm presenting an initial approach to the treatment of both early and established rheumatoid arthritis (RA). All patients with RA should receive a disease-modifying antirheumatic drug initially and be advanced to more aggressive and/or combination therapy as needed to control disease. Disease activity should be assessed, wherever possible, using a formal, validated, and consistent disease activity index. Refer to the American College of Rheumatology RA treatment guidelines for more complex algorithms accounting for differences between agents and patient-specific complexities. DMARD = disease-modifying antirheumatic drug; MTX = methotrexate; RA = rheumatoid arthritis; TNFi = tumor necrosis factor inhibitor.

*Do not discontinue all RA treatments.